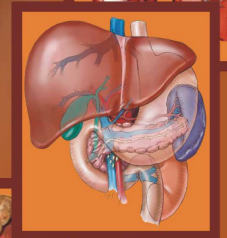
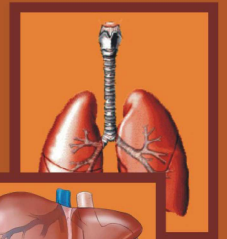


# MEDICAL DISORDERS IN PREGNANCY



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# MEDICAL DISORDERS IN PREGNANCY

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## **PREFACE**

Almost all medical disorders can affect a pregnant person as in case of non-pregnant. Normal physiological changes peculiar to pregnancy can mimic or aggravate the clinical course of the disease process. Some diagnostic approaches such as radiography and CT scanning are not advised due to danger of radiation exposure to the foetus. Invasive tests pose extra challenge to the attending physician. The physician involved in practice of obstetrics must be an extra ordinarily competent person. He should be knowledgeable in internal medicine, cardiology, endocrinology, immunology, hematology, neonatology and perinatology. One can hope that this volume will adequately cover the medical disorders commonly seen complicating pregnancy. The students can benefit from this extra reading. Current methods of diagnosis have been dealt in a simple manner. Multi specialty input by competent contributors will hopefully add to the knowledge in treating various medical conditions. The idea of compiling this manuscript year after my retirement reflects my desire to share the experience of life time practice with my fellow colleagues and students. I hope they will find this useful in their practice to deal with ailing humanity.

**Mohammed S. Akhter. MD**

## Foreword

The author has served as a devoted teacher in the field of reproductive medicine. His academic contributions in England, Sweden, Canada, USA and Lahore Pakistan stretch over a period of 40 good years. He is a medical graduate with multiple Fellowships from England, Canada, USA and Pakistan. He is a Ph.D., in Humanities, and has held prestigious positions as Vice Chancellor, Dean of Science and Professor of Obstetrics and Gynecology both in England, Canada, USA and Pakistan. He has served almost every major teaching hospital in Lahore. He continues to contribute in science, education and scientific research. He is fellow of our National Academy, (Pakistan Academy of Sciences) Islamabad. He received distinguished scientist Award in Health Sciences form the Pakistan Academy of Sciences Islamabad.

This book covers in detail the complications of General Medical disorders such as Diabetes, Heart Disease and Hypertension along with problems specific to Pregnancy such as Pre-Eclampsia Eclampsia, High Risk pregnancy, due to early rupture of fetal membranes, Anemia nutritional and endocrine gland problems, accidental Hemorrhage, prolonged pregnancy and unexplained fetal death in utero during pregnancy. I am impressed with the scientific approach adopted by the author in providing guidelines for management of difficult and serious medical problems. The book provides easy reading for students, teachers, consultants and medical scientists. I commend the author for his scholarly work and wish him well.

### **Prof. Dr. Atta-ur-Rahman,**

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Pakistan.

## **Dedication**

This manuscript is dedicated to all my students, who have chosen the field of obstetrics as their specialty. My youngest son Ahmed Murad Akhter, who is a close friend and motivator, has done a great job by leaving Stanford and coming back to settle in Pakistan. He constantly reminded me to document and publish my experience in the literature for present and future generations. I kept on reading, improved my knowledge and ultimately compiled this book. I owe my special gratitude to my father and my other two children Waseem and Natasha, who are both medical doctors and specialists in their fields of interest-one is a cardiologist and the other is endocrinologist, they have both contributed in the preparation of this book. My son in law, Dr. Kamran Mahmood, equally deserves my appreciation for contributing in his field of interest (Pulmonology). The driving force, which kept me going and revising various chapters of this book, has been my wife Dr. Ismat Salim Akhter and grand children whom I adore and love. I am therefore dedicating this book to all of them. This book describes a number of important subjects and procedures all of which can, if practiced wisely, ensure a healthy and better life for mother and her newborn baby.

**Mohammed. S. Akhter MD**

## **Acknowledgement**

I wish to thank my staff officer and incharge Shadman Hospital and Shadman Education Trust affairs Miss Kausar Chaudhry. I must thank Prof Dr. Zafar Ullah Chaudhry, Prof. Dr. Asad Aslam, Madam Saadia Rashid, Prof. Dr. Brig. Naseem A. Khan, Prof Dr. Javed Iqbal, Prof. Dr. Naved-ul-Zafar, Dr. Humaira Durani , Dr. Mahlika Fawad , Dr. Zia ud Din, Dr. Perveen Akhter and Dr. Diyyali Gul for their constant encouragement. My personal staff officers Miss Farah Sarwer, Mr. Hassan Jameel and Miss Mahwish Hummayun, who composed this manuscript with great patience and dedication must be thanked. I am most grateful to Dr. Atta-ur-Rehman for writing the Foreword for this book. It will be appropriate for me to acknowledge help and support of Pakistan Academy of Sciences Islamabad, Higher Education Commission of Pakistan and Shadman Education Trust for sponsoring publication and distribution of this book. The encouragement and help, I received from Prof. Dr. M.D. Shami, Prof. Dr. G.A. Miana and Senator S. M. Zafar, Chancellor, Hamdard University, deserve special gratitude and thanks.

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## Chapter No: 1

# ANAEMIA IN PREGNANCY

### Anaemia in pregnancy:

The increase in plasma volume causes hemodilution in a pregnant woman which can give artificially low haemoglobin. The WHO advice that haemoglobin levels should not fall below 11.0g/dl and certainly haemoglobin concentrations of less than 10.5g/dl should be regarded as abnormal.

When the hemoglobin falls below 10 grams per hundred milliliters of blood during pregnancy, true anemia is said to be present. A fall in hemoglobin level without a concomitant fall in the mean corpuscular hemoglobin concentration is considered to be due to hemodilution. But when reduction in hemoglobin as well as mean corpuscular hemoglobin concentration occurs, this is always due to real anaemia.

### Physiological hemodilution:

This can reduce the hemoglobin level to as low as 80 per cent or 10 grams per cent. The total mass of circulating hemoglobin is not diminished by this physiological dilution process. If the bone marrow is provided with sufficient amounts of iron.

It can then produce more red cells, and hemoglobin will increase in proportion to the increase in plasma volume. The mass of circulating hemoglobin is greater than in normal non pregnant woman.

Whether this is advantageous to the patient is not clear, but it appears to do no harm, therefore iron supplementation during pregnancy remains an accepted

sound practice. The student is referred to consult Chapter on nutrition in pregnancy concerning value of routine iron supplementation.

<b>Mild anaemia</b>	<10 – 11.9 gm%
<b>Moderate anaemia</b>	< 7 - 9.9 gm%
<b>Severe anaemia</b>	< 7 gm%
<b>Infants 6-12 months &amp; children</b>	
<b>1-2 years</b>	< 11 gm%
<b>Adolescent girls</b>	< 12 gm%
<b>Pregnant women</b>	< 11 gm%
<b>Lactating women</b>	< 12 gm%
<b>Women in reproductive age group</b>	< 12 gm%
<b>Adult men &amp; boys</b>	< 13 gm%

### Haemoglobin cut off levels for Anaemia as per who guidelines

### Changes in blood components:

There is considerable increase in plasma volume. Leukocytes are also increased, a figure of 10,000 to 15,000 per cubic mm is usual.

This change is quite obvious during second half of pregnancy. Poly-morph nuclear leucocytes may reach 20,000 to 30,000 per cubic mm during labour.

There is no change in the number of platelets during pregnancy, but they increase after delivery, and may reach a figure as high as 600,000 per cubic mm around the tenth day of the Puerperium Erythrocyte sedimentation rate increases and may reach about 60 mm in an hour during the last trimester. This returns to

normal in four to six weeks after delivery.

### **Epidemiology:**

Body of a healthy adult woman contains 3,500-4,500mg iron of which 75% is in red blood cells as hemoglobin, 20% as ferritin in bone marrow and reticulo-endothelial system and 5% in muscles and enzyme systems. Nearly all of iron in red blood cells is recycled as they are replaced every 100-120 days. Normal loss is 1mg iron from death of epithelial cells plus an average of 1mg daily from monthly menstrual loss. Average woman's diet in developed world provides 12mg iron daily, of which 14-20% is absorbed so a balance is maintained.

However, in developing countries with a mainly vegetarian diet iron levels are low because of the relative lack of iron in the diet and the ability of phytate in cereals to interfere with iron absorption. Also, in many countries, very high level of infestation with hookworm, which causes considerable fecal blood loss? Presence of occult blood in coeliac disease in pregnancy has a strong association with anaemia.

The bone marrow aspirate shows normoblastic reaction with a slight increase in the number of plasma cells and megakaryocytes.

### **Clinical features:**

Features which are common to all anemias of pregnancy include tiredness, listlessness, headache and bouts of giddiness. There may also be anorexia and indigestion, due to hypochlorhydria which develops secondary to nutritional

deficiency states. Cardiac output is increased and systolic ejection murmur can be heard over the base of the heart. A third heart sound can sometimes be heard at the apex in these cases. This sound is due to rapid diastolic filling of the left ventricle. In patients with organic heart disease, there may be signs of cardiac failure. Ectopic beats are a frequent phenomenon which is often noted as palpitations. Slight edema of the ankles may be present, when severe anemia with megaloblastic picture is present. This may sometimes be accompanied by hypertension and mild albuminuria, which disappears when the anemia is corrected. Incidence of premature labor is more in these cases. If anemia is severe, fetal anoxia may result in intrauterine death of the fetus.

### **Iron deficiency Anaemia**



**Anaemia**

**Normal Blood**

**Fig 1.1: Shows hypochromic anaemic red cells in the left picture and normal red cells in the right picture**

It has been reported that uterine inertia may be increased and labor prolonged, but the reason for this is not known. Incidence of puerperal infection and venous thrombosis is increased.

### **Common symptoms:**

#### **Mild Anaemia:**

Decreases capacity to do physical and mental work. Reduces concentration, attention and, memory affecting school

performance. Tiredness, listlessness, lethargy and fatigue.

**Moderate or severe Anaemia:** Pallor of nails eyes and tongue Breathlessness or fainting increased susceptibility to infection and recurrent illnesses.

### **Iron deficiency Anaemia:**

This type of anaemia is most common in Pakistan. The reason for this is the eating habits and deficiency of Iron intake by our child bearing women.

**Iron metabolism:** Iron deficiency 85% of all cases. Un common causes folic acid deficiency, sickle cell disease, haemoglobin SC, beta thalassanemia (more common in patients from South East Asia, Southern Europe and Africa).  $\beta$ -Thalassemia major,  $\alpha$ -thalassemia, vitamin B12 deficiency, chronic hemolysis (hereditary spherocytosis), paroxysmal nocturnal hemoglobinuria, leukanemia, GI bleeding. HB  $<10.5$ g/dl and serum ferritin and mean cell volume low indicate iron deficiency anaemia. Iron exists in the body as a trace element. In an adult man there is about 4.5 gm of iron. Three fourth of this iron exists in complex pigments and enzymes i.e. (hemoglobin, myoglobin and heme enzymes). The remainder exists in inorganic form and is protein bound.

Iron in the body is found in four different forms, the blood hemoglobin in this about 2.5 gm of the metal is present. Myoglobin (myohemoglobin) is present in red muscles, in varying amount. Intracellular enzymes such as cytochrome, cytochrome oxidase, catalase, and peroxidase contain less than 0.1 gm of iron in this form. Iron is bound with a special tissue protein called

apoferritin. This forms the tissue iron storage compound, called ferritin. When this is fully saturated with iron, ferritin may contain nearly 23 per cent of its dry weight as iron. This so called "storage" iron may amount to 1.5 gm in all.

**Causes of iron deficiency:** Inadequate food, intake poor women consume only 1400-1800 kcal/day, Poor iron absorption due to phytate and tannins, Diet poor in iron content Average dietary intake of 20-25 mg of Iron/day meets only 45% of requirement, Low absor-bable iron content - only 70% is absor-bable. Low ascorbic acid in diet also retards absorption.

**Blood iron:** Iron in the blood is present in two forms as hemoglobin and as plasma iron. Normally hemoglobin in the red blood cells is 15 gm per 100 ml of blood. This corresponds to 50 mg of inorganic iron. Hemoglobin consists of a protein globin which is united with the pigment called heme. This is an iron-containing porphyrin known as iron-protoporphyrin. The hemoglobin has the property of combining loosely and reversibly with oxygen. This depends upon the ferrous ( $Fe^{++}$ ) atoms of the heme. Each  $Fe^{++}$  atom combines with one molecule of  $O_2$  when reduced or oxygenated. The  $Fe^{++}$  in it is oxidized to ferric ( $Fe^{+++}$ ) form of iron.

**Functions:** Hemoglobin is essential for oxygen carriage. It also plays an essential part in the transport of  $CO_2$ , and in the regulation of blood reaction.

**Varieties:** There are two main varieties of hemoglobin. These are the normal adult hemoglobin (HbA), and the fetal hemoglobin (HbF) which forms 94 per cent of the total hemoglobin at 20th

week of pregnancy, 80 per cent at birth, 50 per cent at 2 months postnatal and 10 per cent at 4 months of age.

### **Plasma iron:**

This is the form in which iron transport takes place. Plasma iron is in the ferric form and is bound with beta globulin.

This plasma protein is capable of carrying a maximum of 300 mg of iron per 100 ml. normally it is only 30 per cent saturated.

Plasma (serum) iron is increased in conditions where red cell formation is depressed as it occurs in cases of aplastic anaemia and pernicious anaemia.

This is lowered when the absorption of iron is decreased or when red cell formation is rapid, as it occurs after hemorrhage. Substantial rise in serum iron takes place after ingestion of therapeutic doses of iron salts, but under ordinary conditions of food intake the fluctuations in serum iron are slight.

### **Storage:**

Iron is stored in the tissues such as liver, spleen, bone marrow, and lymph glands and in the reticulum cells.

When there is excess blood destruction, hemosiderin which is probably a polymer of the ferritin may accumulate and become visible microscopically as small brownish granules in the tissues.

**Ferrous and ferric iron:** Iron in the food stores, within the body, and in the process of transport through the plasma, exists in the ferric form. It penetrates the intestinal mucosa in the ferrous form,

and moves in and out of the cells in the ferrous form.

### **Iron requirements in pregnancy: (without considering losses at delivery):**

COMPARTMENT	TOTAL mg
Daily in tegumental losses (0.8 mg/d)	≈ 220
Fetal and placental iron	≈ 300
Maternal increment (20%) in total hemoglobin	≈ 320
<b>GRAND TOTAL</b>	≈ 820
Desirable iron reserves (mg)	> 300
In this case, total iron needs become	< 520?
Needs during 2nd and 3 <sup>rd</sup> trimesters:	2.9 mg/d, or 20.3mg/wk.
Food iron absorption ≈ 1 mg/d. Supplemental iron needs	1.9 mg/d, or 13.3 mg/wk.

**Iron in food** - The iron in food varies according to the amount of blood and ferritin. Animal foods contain only minute amounts of iron. It is generally not recognized that liver and lentils are a rich source of iron in our diet.

**Iron balance:** The iron content of hemoglobin is only 0.33 per cent. One hundred milliliter blood contains 15 gm of hemoglobin which is equal to only 50 mg of iron in a normal person. The red cells live for about 100 days. About one per cent of total blood hemoglobin which is contained in 50 ml of blood is destroyed daily, releasing 25 mg of iron. An adult woman needs more iron than man because there is regular loss of blood during monthly menstruation and there is drain on iron stores during

pregnancy and labour. The monthly blood loss in women averages 50 ml corresponding to 25 mg of hemoglobin iron. There is considerable iron loss during child bearing in spite of abeyance in menstruation.

The main iron demands of the mother start in the last two months of pregnancy when the fetus and placenta are growing rapidly, this is followed by the blood loss during labor. Anaemia for lack of iron commonly develops during pregnancy.

### **Iron absorption:**

Very little is known about the changes which food iron undergoes in the alimentary canal. It is believed that inorganic iron is split off from ferritin, (Tissue iron storage compound) but the digestive juices cannot release the iron which is bound with the porphyrin molecule in the heme compounds of food.

Iron is absorbed in the ferrous form possibly in the stomach and certainly in the duodenum and upper small intestine.

The presence of bile salts does not promote iron absorption. The iron is taken up by the cells of the intestinal mucosa and combines with apoferritin there to form ferritin, which releases its contained iron into the circulation when required for hemoglobin formation. It is found clinically that a total iron food intake of 10 to 15 mg daily is sufficient to maintain a normal state of the blood in all physiological states in women and children and is well above the minimal requirements of normal man. Normal gastric acidity is important in favoring the absorption. Iron is absorbed in the

first portion of the duodenum chiefly as the ferrous salt. At the low pH of the stomach the colloidal ferric iron of food is changed to monomolecular ferric iron, and is then reduced by foodstuffs to the more soluble ferrous state for absorption. Once in the mucosal epithelial cell, most is again oxidized to the ferric state. The mechanisms which control the rate of absorption are still somewhat controversial. One of the most widely accepted views, the mucosal block theory, postulates that the rate of absorption depends upon the degree of unsaturation of the apoferritin in the duodenal lining epithelium. Iron is absorbed into the intestinal mucosa cells after reduction to the ferrous state, and conjugates there with apoferritin to form ferritin. When the apoferritin is completely saturated and totally transformed to ferritin, further absorption is blocked. The various body needs are supplied by the release of the iron from the ferritin complex, thus producing more unsaturated apoferritin available for combination with iron.

The release of iron from the ferritin complex appears to be a function of the oxygen carrying capacity of the blood. When the hemoglobin level of the blood is low, the oxygen level is depressed, and more iron is transferred from the ferritin molecule in the cells of the intestinal mucosa to siderophilin (Tran's ferritin) in the serum. This mechanism permits further absorption of iron into the mucosal cells, to desaturate the newly released apoferritin. It is also suggested that there may be a direct transfer of iron through the mucosal cells, dependent upon oxidation reduction potentials in these cells. This direct transfer is particularly operative in anaemic states where the anaerobic state

of the cells favors the reduction of the intracellular ferric iron to the soluble ferrous form and its direct diffusion out of the mucosal cell into the blood.

**Iron excretion:** The excretion of iron occurs in very minute amounts, chiefly through the urine (0.4 mg daily) and stools (0.8 mg daily). Excretion through bile, desquamation of skin cells and sweat is very minute. The average diet contains quite excesses of iron. The losses are also minimal in health therefore iron deficiency states almost never occur in the males. When there is abnormal loss of blood or iron or deficient diet is consumed for longer periods. Anaemia may occur. In the female the situation is quite different as there can be excessive loss of menstrual blood and the depletion of iron stores by pregnancy and lactation.



**Fig 1.2: Shows normal red blood corpuscles**

**Clinical features:** When iron deficiency occurs, lassitude and exhaustion are quite early manifestations. These result due to failure of enzyme systems in the body.

**Presentation symptoms:**

Often asymptomatic but fatigue, dyspnea and Signs: of Pallor.

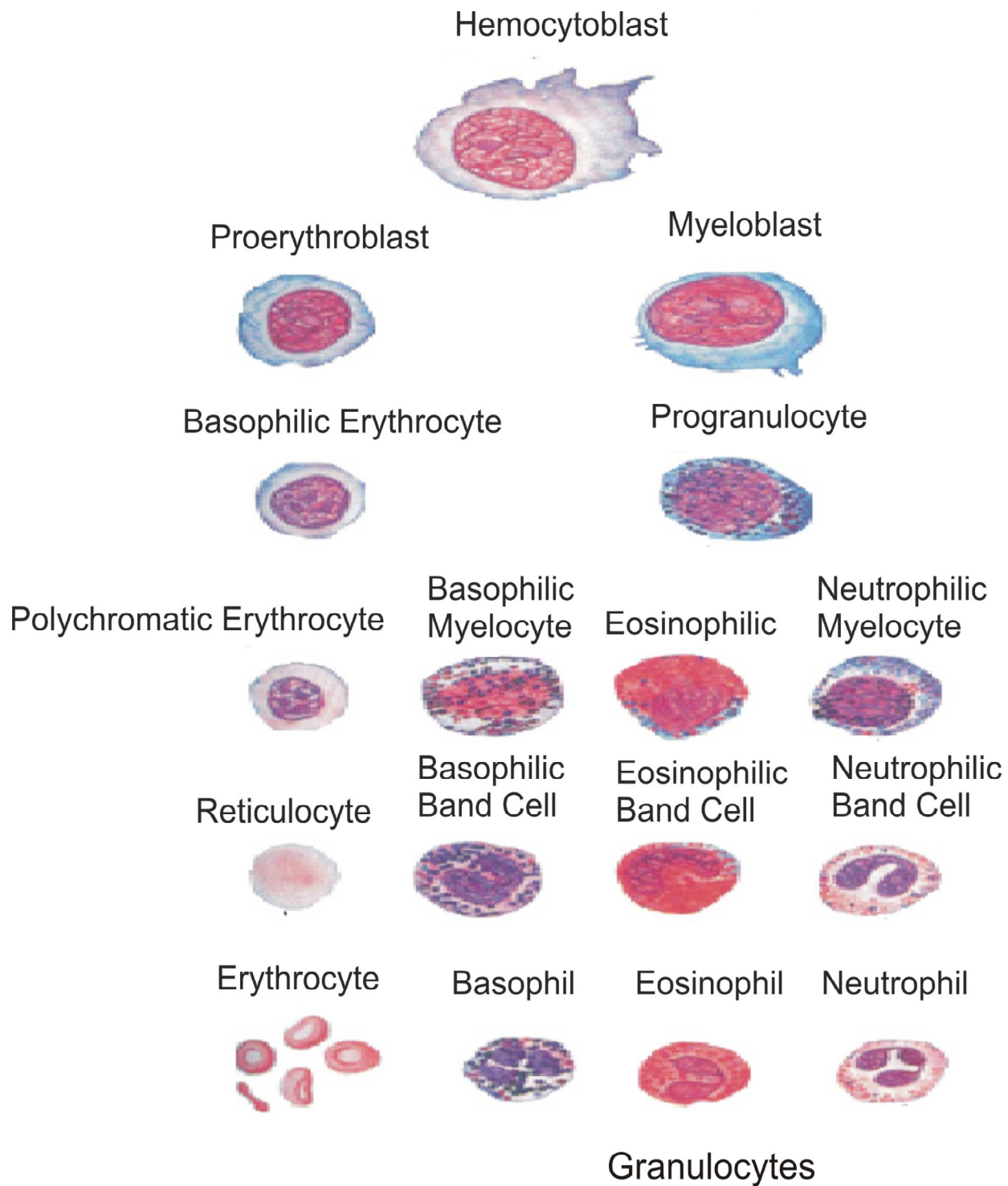
Can be present Investigations Hb <11.0g/dl 3 MCV (mean cell volume): if

<76fl then probable cause is iron deficiency but if lower than concomitant with other signs of anaemia and RBC count raised, then suggests possible thalassemia (estimate HbA2 and use Hb electrophoresis). Normal MCV (76-96fl) with low Hb is typical of pregnancy. Serum ferritin 10-50µg/l needs monitoring and <10µg/l requires treatment in later stages the symptoms are common to any other form of anemia which include restless-ness, headache, giddiness, anorexia and indigestion. Systolic ejection murmur at the base and third heart sound at the apex can be heard. This variety of anaemia often starts at the end of the first trimester and if untreated progresses steadily and gets worst around thirtieth week when the level of hemoglobin begins to fall more sharply. Normally a reduction in plasma volume takes place during the last month of pregnancy. The red cell mass however continues to increase. Hemodilution becomes less and the anaemia appears to improve spontaneously. This is erroneous and does not mean that mean corpuscular hemoglobin has increased; therefore the student is advised to keep these physiological changes in mind while interpreting levels of hemoglobin during antenatal check ups.

**Management:**

Iron deficiency at or before 36 weeks gestation, if Hb > 6.5g/dl give oral iron. Healthy patients on a normal mixed diet do not normally require iron supplements during first half of pregnancy.

However, women on a restricted diet (e.g. vegetarians, vegans) and women in developing countries need iron supplementation.



**Fig 1.3: Shows developmental stages of blood corpuscles**



In industrialized countries, women should receive 85mg elemental iron daily and in developing countries 120-140mg/day, because of increased severity of absorption.

**Thalassemias** Inherited blood disorders with reduced or absent production of alpha or beta chains of the globin content of haemoglobin. Women who are carriers of thalassemia, may be asymptomatic when not pregnant but more anaemic than usual during pregnancy. MCV <80fl requires investigation with an HbA2 >3.5 being positive for  $\beta$  thalassemia. In these cases, the father of the child should be tested and the couple offered genetic counselling. Chorionic villus sampling in the 1st quarter of pregnancy and fetal cord blood sampling under ultrasound guidance in the 2nd quarter can be used to detect  $\beta$  thalassemia major and termination of pregnancy offered.

**Sickle cell anaemia** is genetic defect which causes production of abnormal haemoglobin with a red blood cell life of <15 days. In a sickle cell crisis, RBC destruction causes severe hemolytic anaemia and bone pain. Commonest form is haemoglobin S but mainly affects people from East and West Africa. Where suspected, women should receive folate 15mg/day with frequent Hb counts. If Hb falls <6g/dl, need transfusion. Use of regular prophylactic transfusions reduced number of transfusions required but was associated with more pain crises. May give prophylactic antibiotics during childbirth and afterwards. If crisis occurs, give heparin, measure Hb every 2 hours and if falls >2g give exchange transfusion. Spontaneous abortion can occur in up to 25% of women affected by sickle cell

anaemia with mortality also often associated with pre-term delivery and low birth weight (30% <2500g). Stillbirth rates of 8-10% have been seen and thorough antenatal fetal testing is required to assess growth including ultrasound of the umbilical artery for systolic/diastolic ratio.

Frequent urinary tract infections are common and require prompt treatment. Pregnancy associated hypertension is also more common and may affect almost 1/3 of pregnancies. Folate supplements of 1mg/day minimum should be given from confirmation of pregnancy although iron supplements are not needed unless serum iron and ferritin levels are reduced. If given routinely, can reduce iron overload leading to hemochromatosis. **Complications** Women with anaemia have a mortality rate 3-5 times higher than normal and still birth rate 6 times normal.

#### **Laboratory investigations:**

The circulating blood cells are deficient in number, and show poor staining properties. There is also anisocytosis and microcytosis. The hemoglobin level is below 10 grams per cent. Serum iron is around 60 milligram per cent. Bone marrow aspirate shows normoblastic reaction. Sometimes iron deficiency is combined with folic acid deficiency. This type of anemia then does not respond to iron therapy.

**Diagnosis** - This can be easily made by laboratory investigations and review of the clinical features.

**Treatment** - This can be discussed under two separate headings; the prophylactic and therapeutic.

Prophylactic this includes routine administration of iron during pregnancy and lactation. Iron supplementation should start after the sixteenth week of pregnancy in order to avoid increase in the early vomiting of pregnancy. If the patient's initial hemoglobin level is over 90 per cent or 11 gram per cent then she requires only a single dose of 200 mgm of ferrous sulphate. Each tablet of 200 mgm of ferrous sulphate contains 60 mg of elemental iron. If the hemoglobin level is less than 90 per cent she should receive 180mg. of elemental iron, which can be given daily in divided doses after meals.

When ferrous sulphate or gluconate is not tolerated well by the patient, ferrous succinate or ferrous fumarate may be tried. A number of preparations such as fefol, feospan and autrin are available in the market; some of these have been in use for many decades without any side effects and therefore can be safely prescribed. Amino-acids are an essential part of the hemoglobin molecule, therefore all pregnant women should be encouraged to drink milk and eat meat.

### **Therapeutic:**

Iron in therapeutic doses can be administered by oral, intramuscular or intravenous route. Oral route is preferred in treatment of outdoor cases, while intramuscular injections are recommended in patients where rapid increase in hemoglobin is needed.

Some patients are unable to tolerate iron by mouth, they also need intramuscular therapy. Some of the commonly used iron preparations for intramuscular administration include the following.

### **Iron sorbitol citric acid complex (Jectofer):**

This preparation contains 50 mg of elemental iron in one milliliter solution. Each injection of 2 ml. of Jectofer may be expected to raise the hemoglobin by about 0.3 gram per hundred milliliters of blood.

**Imferon:** Iron can also be given by intravenous route. Imferon is an iron dextran complex which is available in 5 ml ampoules and contains 100 mg of iron. In pregnant patients each 100 mg of iron can raise the hemoglobin by about 0.3 per cent. Total dose of iron required to meet deficiency of hemoglobin can be mathematically calculated by using the formula shown in table (31). This compound must not be allowed to leak outside the vein as it is extremely irritant and can cause thrombophlebitis.

The total dose of iron, as iron dextran, is mixed with 1000 ml of normal saline solution, 8,000 units of heparin are added in this to discourage venous thrombosis. The drip should be run at a rate of 10 drops per minute for fifteen minutes and then, at 45 drops a minute until the infusion is completed, and this should take about five hours. The drip should be stopped on the slightest evidence of adverse reaction and 50 mgm of Phenergan along with 100 mgm of hydrocortisone should be given to avert exacerbation of reactions.

When iron is administered intravenously, a shower of renal casts and leucocytes often appears in the maternal urine.

Intravenous total dose iron therapy should be avoided in patients who have a

history of asthma, hay fever or any form of allergy. In such patients iron may produce shock.

### **Reactions:**

The use of intravenous iron should not be taken lightly since in about 5 per cent patients quite unpleasant reactions may occur. These reactions include vomiting, diarrhoea, and pain in the loins, pyrexia and urticaria. Some times symptoms such as tachycardia, flushing of face, fall of blood pressure and syncope may develop. Most of these reactions usually occur during injection or within half an hour of its completion. The student should realize that expected rise in hemoglobin is usually not observed until about a week after the parenteral administration of iron.

### **Placental transfer of iron:**

It has been reported that some iron dextran crosses the placenta. These appear to have no ill effect on the fetus.

Intravenous transfusion can also cause cardiac failure by overloading a circulation which is already greatly increased by hemodilution in cases of high output cardiac failure. In such cases where generalized edema is also present exchange transfusion may be required.

### **Exchange transfusion:**

In this procedure about 1,000 ml of packed cells are run slowly into a vein in one arm, whilst 1,500 ml of blood are re-moved by venesection from the other arm. We prefer to lower the circulating blood volume by giving 40 mg of Lasix intravenously three hours prior to the commencement of intravenous infusion.

### **Protein deficiency anaemia:**

Hemoglobin production requires a constant supply of essential amino acids. If women's diet is deficient in amino acids, especially lysine and methionine, then she can not produce protein fraction of hemoglobin adequately. This results in anaemia in spite of adequate supply of iron.

**Clinical features** - These include Hepato and splenomegaly, blood picture is microcytic but normochromic, mean corpuscular hemoglobin concentration is normal and bone marrow biopsy shows normoblastic reaction. These patients also show changes in the liver biopsy and may even proceed to cirrhosis. Hepatic cirrhosis is considered to be secondary to the long standing dietary lack of lipotropic factors, which may be accentuated by the demands of pregnancy. This type of anaemia is refractory to iron, folic acid, liver extract and vitamin B12 therapy. Daily extra supplements of high quality protein can be very effective in such cases.

**Megaloblastic anaemia:** In this type of anaemia, the bone marrow shows megaloblastic cellular activity and results from deficiency of folic acid in child bearing age. The growing fetus requires large amounts of folic acid. Multipara gets no chance to replenish their exhausted stores due to continued demand posed by successive and rapid child bearing. The folic acid deficiency produces maturation arrest in the bone marrow and thus interrupts the normal course of erythropoiesis. The marrow is filled with megaloblast, these cells can neither carry out the functions of mature cell nor can they be transformed to normoblast or erythrocytes. Maturation of

granulocytes and thrombocyte is also adversely effected.

**Metabolism of folic acid:** Folic acid is pteroylmonoglutamic acid which can be prepared synthetically. Conjugates of this substance are present in most green vegetables.

**Daily requirements** - The normal requirements of folic acid are about 50 micrograms in the non pregnant patient. The requirements increase to about 300 mcg daily during pregnancy. Average diet of women in this country cannot meet this extra demand of folic acid. Routine supplementation of the diet is therefore a sound practice. The normal range of serum folate is 6 to 30 ng per ml. This can fall during pregnancy to level as low as 2.0 ng per ml. The serum B12 level is closely linked with that of folate level and may fall from the normal figure of 150 to 350 mcg per ml. to under 100 mcg per ml. during pregnancy, especially when folic acid deficiency is present.

#### **Causes of folate deficiency:**

The causes of folate deficiency in women are poor intake or impaired absorption. This usually results from frequent child bearing which does not allow the woman time to replenish her stores before the next pregnancy begins. Whenever there is rapid turn over of red cells as is the case in hemolytic anemia, the demand for folic acid increases greatly. Folate deficiency is a common feature in all cases of anemia due to hemoglobinopathies.

A pregnant woman who is suffering from malaria also needs increased amount of folic acid as hemo-

lysis is produced by the parasite. Patients who have been on long term therapy with sulphonamides or anticonvulsant drugs can become deficient in folic acid and require supplements of this vitamin in their daily diet.

**Incidence** - Megaloblastic anaemia occurs in 2.8 per cent of cases. The condition is more common in multigravida and in multiple pregnancies than in primigravida.

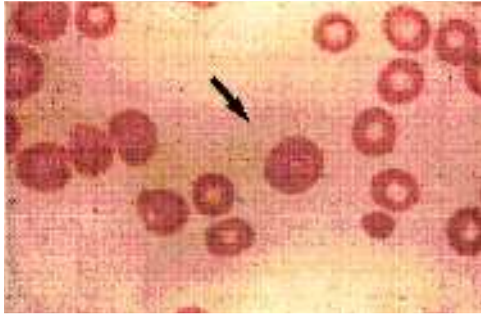
**Clinical picture** - In contrast to iron deficiency anemia the folic acid deficiency develops late in pregnancy. Sometimes mild hypertension and albuminuria may develop. When the patient complains of soreness of tongue, anor-exia, vomiting or diarrhoea, the Physi-cian should suspect folic acid deficiency occasionally this type of anaemia, may present as pyrexia of unknown origin in the puerperium.

Preeclampsia is nearly five times more commonly encountered in patients with megaloblastic anaemia. It has been reported that folic acid deficiency is sometimes associated with accidental hemorrhage. The cause and effect relationship of this deficiency have not been proven as yet. The hemoglobin level can fall very low i.e. 3 to 4 gram per cent, while the pack cell volume can fall to 13-14 per cent. The MCV is raised but M.C.H.C. is normal.

#### **Blood picture:**

The stained blood film shows anisocytosis and poikilocytosis. Megaloblast may be seen on examination of the buffy coat. Granulocytes will be low in number. The neutrophil polymorphs with four or five

lobed nuclei are common finding in these cases.



**Fig 1.4: Shows blood picture 9 different size and shape cells with few granulocytes**

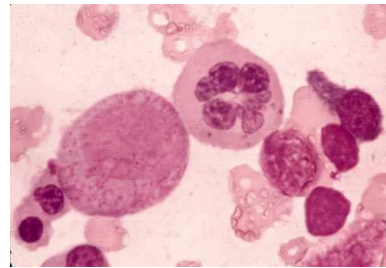
**Bone marrow biopsy** - The bone marrow aspirate will show megaloblast, intermediate megaloblast and giant metamyelocyte.

**Diagnosis** - The condition can be diagnosed by analysis of clinical features and cellular details of blood film and bone marrow aspirate. Folic acid deficiency can sometimes be demonstrated by the FIGLU test which is based on the increased level of formiminoglutamic acid. When an oral dose of histidine is given to a normal person it is almost entirely converted to glutamic acid and then to urea. If the patient is deficient in folic acid. The metabolism of histidine is stopped at the stage of formiminoglutamic acid and this product is then excreted in abnormally large amounts in the urine. The value of this substance (FIGLU) can be estimated from the urine of the patient.

**Serum Folate** - Serum folates will be found below 2 ng per ml in cases of severe folic acid deficiency.

**Refractory anaemia** - This type of anaemia is very rarely seen in

pregnancy. When the bone marrow has been depressed by the action of drugs such as gold, arsenic, phenacetin or chloram-phenicol or by physical agents such as radium or deep X-ray therapy. Anaemia results. Some cases are caused by a combination of iron and folic acid deficiency.



**Fig 1.5: Shows granulocyte in blood picture**

Chronic diseases such as tuberculosis, rheumatoid arthritis, nephritis, and leukemia may also depress the bone marrow. Anemia caused by bone marrow depression is usually very refractory and will not respond to treatment unless the causative factor has been removed. When all these cases have been excluded, there remains a small, unexplained group of patients whose anaemia remains refractory to all treatments during pregnancy, but recovers spontaneously within a few months of delivery.

### **Hemoglobinopathies:**

Anaemia due to the presence of abnormal quality or quantity of hemoglobin is not common in pregnancy. In most of these disorders the amount of normal hemoglobin A (adult hemoglobin) in the red blood cells is diminished, either because the body cannot manufacture the globin necessary to form hemoglobin A, as in thalassemia

or because the hemoglobin A is replaced by an abnormal hemoglobin, as in sickle cell disease. The abnormalities in hemoglobin formation are genetically determined.

**Sickle cell Anaemia** - The hemoglobin molecule consists of two pairs of polypeptide chains which are attached to the haem group. Abnormal hemoglobins are formed when there is substitution of specific amino acids in either  $\alpha$  or the  $\beta$  chain. In all cases the haem portion of the molecule remains unaltered and the oxygen-binding power of the hemoglobin is therefore unaffected. The most common abnormal hemoglobin is 'S' which is produced by substitution of valine for glutamic acid radical in  $\beta$  chain of the normal hemoglobin. In hemoglobin C the same glutamic acid radical in the  $\beta$  chain is replaced by lysine. Sickle cell disease - This disorder is inherited through an autosomal dominant gene transmitted equally by males and females. The reduced form of Hb. S has only about one hundred the solubility of Hb-S. It crystallizes out of solution, when the oxygen tension in the tissues is lowered to 35 to 40 mm Hg. When crystallization of hemoglobin occurs the red cells become distorted and assume the typical sickle shape. When sickling takes place the blood becomes increasingly viscid and multiple intracapillary thrombi are produced. This causes sludging of the affected cells, particularly in the bones, spleen, alimentary tract and the kidneys where the effected Islands of cells may die, due to break of blood supply and oxygenation. The survival time of red blood cells is about one fifteenth that of normal erythrocytes. These cells are destroyed at a great speed by the phagocytes of the reticuloendothelial

system. The end result of these changes is chronic hemo-lytic anemia. Incidence the incidence of sickle cell anaemia (5-5) among the Negroes of the United States is about one in 600, the sickle cell trait (A-S), is present in about 8 per cent of the Negro population.

In heterozygous patients where genetic pattern is (A-S) only 20 to 30 per cent of the hemoglobin is in the S form, while the remaining 70 per cent hemoglobin is adult type. In these patients sickling does not occur at the normal oxygen tension in the body, therefore there is no anemia. When these patients are subjected to abnormal anoxia which may occur during anesthesia or in the non pressurized air craft, sickling can easily occur and result in severe crisis.

### **Clinical features**

Sickle cell Anaemia (Homozygous 5-5) Variant. The patients with this disease are relatively infertile. They also die in very early life from recurrent infection.

**Heterozygous A-S disease** - This is usually asymptomatic but hematuria and pyelonephritis may occur in this condition. These changes are produced by infarction of the medullary pyramids. Hyperosmolarity of the papillary tips predisposes to sickling and sludging of the red cells. Sickle cell hemoglobin C disease. This is quite mild and is first suspected during a hemolytic crisis in the course of pregnancy. The patients are often chronically ill. Mild attacks of hemolytic anaemia occur every now and then. There are often hemolytic or painful crisis which may be precipitated by deoxygenation or an acid PH. These changes are often associated with infection or stasis of the blood flow.

These patients have long extremities and may suffer from chronic ulceration of the legs. Spleen is usually enlarged but may occasionally be small. Some patients may even have pelvic deformities due to softening of the bones.

**Blood picture** - The red cells show normocytic and orthochromic characteristics. There is constant presence of reticulocytoses. This may exceed 30 per cent during the crisis. In long standing cases the anaemia may become megaloblastic due to shortage of folic acid. The red cells may also show sickling when tested. The majorities of patients are well adjusted to their anaemia and remain free from symptoms with their hemoglobin level reading as low as 7 or 8 gram per cent.

#### **The sickle cell disease crisis:**

The two types generally described are the hemolytic and painful crisis. Hemolytic crisis in this the anemia develops with great rapidity. There is a polymorphonuclear leukocytosis, and jaundice. The patient is pyrexial and fever up to 39.44 Celsius has been recorded. This type of crisis may be precipitated by infection anywhere in the body.

#### **Painful crisis:**

This condition is due to sludging of sickled cells in various organs of the body, which in turn results in thrombosis of capillaries and infarctions in the affected tissues. The pain may be in the lower part of the back, the long bones and abdomen. There may be history of severe vomiting or hematuria. Hemoptysis can result from pulmonary

infarction which is caused by fat. Death may result from heart failure or infarction during these crises.

#### **Effect on pregnancy:**

##### **Homozygous (5-5) Sickle cell Anaemia**

- Patients with sickle cell anaemia (5-5) have low fertility. Somehow this does not hold true for sickle cell hemoglobin C disease. There is considerably increased incidence of intrauterine growth retardation. The utero decidual vessels get blocked by sludging and lead to placental insufficiency. The Sickle Cell Trait A-S - This has no ill effect on pregnancy or the foetus.

**Effect of disease on pregnancy** - Both hemolytic and painful crises are more during the last trimester and before delivery. Hemolytic crisis can be dealt with repeated blood transfusions.

**Diagnosis** - Different genetic types of hemoglobin can be identified by paper electrophoresis. In sickle cell disease the two genetic variants of hemoglobin 5 and C, exist together in the red cells and can also be diagnosed by this method. The diagnosis must be made on carefully evaluating the history and clinical features of the patient. The presence of an orthochromic and normocytic blood picture with reduction of the granulocyte series and platelets should be confirmed. There should be no evidence of hemolysis. The hypoplastic bone marrow must show a diminution in all cellular elements but there should be no infiltration of bone marrow with cancer cells.

**Blood picture** - In such cases the blood picture shows orthochromic, normocytic cells with normal M C H C. and serum

iron. Decrease in the number of granulocytes and platelets may also accompany these changes. The bone marrow is normoblastic with hypoplasia of the red cell precursors. The ratio of red cell series to white cells falls from the normal 1: 3 or 1:4 to 1:6.

**Treatment:** The student should realize that Iron deficiency is not a feature of sickle cell disease therefore administration of iron will not influence the anemia. Folic acid deficiency is a common feature therefore supplementation with 5 mgm of this vitamin will go a long way in combating with this condition. Blood transfusion should not be given unless the hemoglobin falls below 6 g per cent.

When painful infarct ive crisis are present, sodium bicarbonate in divided doses should be given. Intr-avenous injection of 2 ml of 50 per cent magnesium sulphate four hourly will usually relieve this pain. When infarction in any organ or tissue is suspected heparinization should be carried out without delay.

### **Thalassemia:**

In this disorder there is a failure in the synthesis of either the or peptide chains from which the globin of adult hemoglobin (A) is formed. Depending on which chain is affected, two types of thalassemia are recognized i.e. the alpha thalassemia and Beta thalassemia. In the homozygous patient the disease presents as thalassemia major, where the pigment in the red cell is totally hemoglobin F or the fetal form of hemoglobin and thalassemia minor where adult hemoglobins A and A2 are present.

**Clinical features** - In this condition the life span of the red cells is greatly shortened therefore these patients present with severe hemolytic anemia. They are physically stunted, their spleen is enlarged and they have great tendency to acute infection. A few patients live be-yond the age of adolescence therefore pregnancy is very rarely seen amongst these women.

**Thalassemia minor** - This is the heterozygous form of the disease. In this disorder some hemoglobin A is present with hemoglobin F and A2 in the red cells. The A2 hemoglobin does not normally exceed 2 to 3 per cent of the total pigment. Sometimes this may increase up to 10 per cent. Sickle cell trait and thalassemia minor may coexist in the same patient.

**Blood picture-** The red cells are hypochromic unusually thin and mechanically fragile. This results in hemolytic anemia. Although hypochromia is present there is no iron deficiency. Serum iron is usually normal. If there is chronic blood loss from any cause then iron deficiency may exist. The hypochromia is due to failure to manufacture sufficient hemoglobin A. There is vigorous cellular activity of the bone marrow. The reaction is normoblastic. This activity may lead to depletion of the body's stores of folic acid. The cells are hypochromic, microcytic and show anisocytosis and poikilocytosis.

### **Treatment:**

Treatment with blood transfusion is given when there is history of acute blood loss otherwise folic acid in large doses is usually sufficient. Iron is



generally useless because the patient is usually not deficient in iron.

### **Management options:**

#### **Thrombocytopenia:**

#### **Gestational:**

Exclude pathological causes, Monitor platelet count, No specific management if  $>100 \times 10^9/l$  if rapid fall or count below  $50 \times 10^9/l$  reevaluate for pathological causes, cord blood at delivery and ensure maternal count returns to normal

#### **Autoimmune thrombocytopenia (AITP) Pre pregnancy:**

Optimize management, consider splenectomy. If all therapy fails counsel regarding risks in pregnancy

#### **Prenatal:**

Serial platelet counts. Treat if platelet count  $<20 \times 10^9/l$  nor hemorrhagic Complications. From 36 weeks aim to maintain count  $>50 \times 10^9/l$ . For delivery options for treatment. Steroids IVIg. Splenectomy Azathioprine if all else fails

#### **Labor and delivery:**

Avoid traumatic delivery, fetal scalp electrodes and Fetal scalp blood sampling, platelets available if count  $<50 \times 10^9/l$  regional anesthesia safe if count  $>80 \times 10^9/l$  prompt perineal repair.

**Postnatal:** Cord blood for fetal platelet evaluation pediatrician at delivery, consider daily neonatal FBC if thrombocytopenic (nadir day 2-5).

### **Secondary Autoimmune:**

**Thrombocytopenia:** Antiphospholipid syndrome/systemic lupus erythematosus Manage thrombocytopenia as for AITP Screening, diagnosis and management of other complications HIV thrombocytopenia, platelet counts improved by IVIg, Zidovudine, and corticosteroids.

(But secondary infection risk), cesarean section will need to be covered by IV Platelets if refractory thrombocytopenia

Drug-induced thrombocytopenia stop drug and choose alternative. Alternatives for heparin-induced thrombocytopenia include danaparoid.

#### **Non-immune platelet consumption:**

Disseminated intravascular coagulation, Preeclampsia/HELLP.

#### **Thrombotic thrombocytopenic purpura:**

Plasma exchange is first line treatment fresh frozen plasma infusion is second line treatment. Avoid platelet transfusion

#### **Management options acute leukemia: Hematological malignancies:**

#### **Pre pregnancy:**

Counsel about prognosis, Advise against conception until in remission and not on chemotherapy.

**Prenatal:** Start chemotherapy as for non pregnant supportive therapy (blood, platelets, antibiotics, etc.). Careful counseling, especially if treatment commenced in first trimester. Monitor fetal growth and health.

**Labor/delivery:** Expedite for normal obstetric indications. Ideally when mother in remission and fetus mature. Steroids if preterm delivery contemplated.

**Postnatal:**

Contraceptive advice, counseling about long-term prognosis, avoid breastfeeding if on active cytotoxic treatment) Examination and follow up of newborn

**Chronic granulocytic leukemia:**

**Pre pregnancy:**

Counsel about prognosis both for pregnancy and in long term. Give contraceptive advice.

**Prenatal:**

Regular hematological monitoring consider leukopheresis, control with busulphan, hydroxyurea or alpha interferon (avoid cytotoxics in first trimester) manage accelerated phase and blast crisis as for non pregnant patient and expedite delivery if possible (to allow possibility of bone marrow transplantation).

**Postnatal:**

As for acute leukemia.

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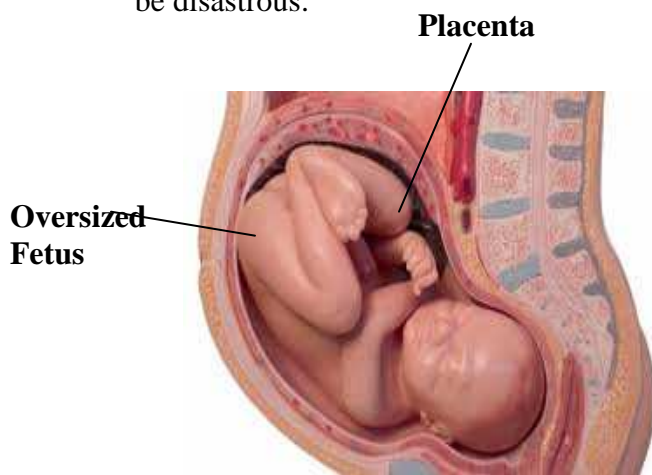
## Chapter No: 2

# DIABETES MELLITUS IN PREGNANCY

Diabetes is a state of carbohydrate metabolism derangement and is considered to be present when there is lack of effective insulin to maintain a normal blood sugar on presenting adequate carbohydrate load to the body.

**Historic perspective** - Prior to the introduction of insulin in 1921, most diabetic women were sterile. When conception took place, the pregnancy frequently ended in spontaneous abortion, or it precipitated diabetic acidosis and coma. The relatively few diabetics who carried pregnancy to term frequently produced stillbirths, abnormal infants, or infants who died from undetermined causes during the neonatal period.

If diabetes is uncontrolled, it affects reproductive mechanisms so adversely that it makes successful child bearing virtually impossible. Unless the disease can be carefully controlled and the metabolic disturbances cured, effect of diabetes on the mother and the infant can be disastrous.



**Fig2.1: Shows section of uterus with oversized fetus**

There is no consensus about the definition or management of gestational diabetes. It occurs when those who were not formerly diabetic develop the disease in pregnancy and suffer many of the problems that are common with established diabetes in pregnancy. A number of the hormones of pregnancy raise blood glucose. There are often other factors that predispose to impaired glucose tolerance.

**Gestational diabetes mellitus (GDM)** - This is characterized by an abnormality of carbohydrate metabolism identified during gestation and found to be absent on repeat glucose tolerance testing some time beyond the sixth postpartum week.

**Incidence** - It has been reported that between 1 to 3 per cent of all pregnant women suffer from gestational diabetes 1:250 pregnancies are complicated by all types of diabetes.

Renal blood flow and glomerular filtration rate (GFR) rise in pregnancy with the result that the renal threshold for glycosuria is reduced. Glucose tolerance tests may be unreliable especially as gastric emptying is delayed in pregnancy.

Having had gestational diabetes in a previous pregnancy does not necessarily mean that it will recur in future pregnancies. A study from Japan looked at those with previous GDM and also those with one previous abnormal feature of an oral glucose tolerance test. About two thirds of those with previous gestational diabetes and around 40% of those with one previous abnormal value developed the condition.

**Risk factors:**

The risk of GDM increases with increasing age, and high BMI before pregnancy, Smoking doubles the risk of gestational diabetes Increase in weight between pregnancies, Short interval between pregnancies, previous unexplained stillbirth, previous macrosomia and Family history of GDM, also increases risk of developing GDM.

**Screening:**

Because the condition may be asymptomatic but have serious consequences that can be reduced by treatment the patient should be screened. There is lack of consensus about who to screen and the criteria for diagnosis. Urine should be checked for glucose at every antenatal visit and if it is present at ++, further investigation is required. The World Health Organization advice that a 75 g oral glucose tolerance test (OGTT) should be conducted if the blood glucose exceeds 5.5 mmol/l at 2 hours or more after food, or exceeds 7 mmol/l within 2 hours of food. The criteria recommended for diagnosis of GDM are fasting venous plasma glucose over 5.5 mmol/l or 2 hours after OGTT over 9mmol/l. Screen-ing will detect 50% or more of all cases which means that up to half will not be screened or detected. Hence vigilance is required during antenatal care, especially if there is glycosuria.

**Causes of diabetes:** There is increased level of hormones such as cortisol, and human growth hormone during pregnancy. These hormones are insulin inhibitor. Hypertension coexists with type II in about 40% at age 45 rising to 60% at age 75. 70% of type II patients

die from cardio-vascular disease and at least 60% of patients will require 2 or 3 antihypertensive agents to achieve tight control.

Critical balance which is maintained between these hormones during normal health is upset during pregnancy.

The student will realize that insulin is released from pancreatic islet cells in response to hyperglycemia and hyperaminoacidemia. The blood level of the insulin is maintained by both synthesis and transport of the hormone. In cases of output failure, insulin dependent diabetes results. The primary output failure may be due to inherent deficiency in pancreas. The secondary output failure may be due to destruction of islets, pancreatitis, and pancreatic replacement with tumor, hemochromatosis and exhaustion of pancreas associated with increased requirements. The pancreatic release of insulin may be blocked by drugs such as Thiazide and Epinephrine. The failure may also be idiopathic or secondary to known antagonist of insulin like cortisol, epinephrine and human growth hormone (HGH). The half life of insulin is 10 minutes.

**Classification:** There are number of classifications reported in the literature. These are shown below. Some of these are based on history of the patient while the other on laboratory findings and clinical symptoms.

From obstetrical point, classification presented by Priscilla Whites is considered to be most useful and practical.

- A. Glucose tolerance test abnormal; no symptoms, euglycemia

- Maintained with treatment by appropriate diet but without insulin.
- B. Adult onset (age 20 or older and Short duration (less than 10 years).
  - C. Relatively young onset (age 10-19) or relatively long duration (10-19 years).
  - D. Very young onset (age less than 10) or very long duration (20 years or more) or evidence of background retinopathy.
  - E. Pelvic vascular disease determined by X-Ray.
  - F. Renal disease.
  - G. Multiple failures in pregnancy.
  - H. Arteriosclerotic heart disease.
  - R. Proliferative retinopathy.

**R F Both renal disease and Proliferative retinopathy:**

- T. Pregnancy after renal transplantation.

**Other classifications:**

- I. Pre gestational diabetes, that diabetes which began before conception and continues after the pregnancy.
- II. Gestational diabetes, that diabetes which starts during pregnancy and goes away after the pregnancy.
- III. Pre gestational diabetes complicated by vascular disease, retinopathy, nephropathy, pelvic

vessels or peripheral vascular disease.

**Advantages of priscilla whites classification in obstetrics:**

This classification has an edge over others as it guides the physician about the time of delivery, as well as the mode of delivery.

Classes A delivers between 38 to 40 weeks.

Classes B deliver between 37 to 38 weeks.

Classes C deliver between 36 to 37 weeks.

Classes D deliver between 35 to 36 weeks.

Classes E deliver between 34 to 35 weeks.

Classes F deliver between 34 to 35 weeks.

Class A, B and C according to Priscilla white's classification diabetics are delivered normally and by vaginal route while class D.E.F.G.H. is delivered by caesarean section. In cases of class R, the pregnancy is contraindicated as it aggravates the disease process quite rapidly.

**Pathophysiology:**

This can be discussed under two separate headings i.e. the effect of pregnancy on diabetes and the effect of diabetes on pregnancy and its outcome.

**Effect of diabetes on pregnancy** - The effect of diabetes on pregnancy depends

to a large extent on the measure of control of diabetes. If properly controlled, the fetal complications may be eliminated.

1. Women should be encouraged and supported to monitor their blood glucose levels regularly and to adjust their insulin dosage, in order to maintain their blood glucose levels within the normal (non diabetic) range. The aim should be for the woman to maintain her HbA1c below 7.0%. Evidence Level = IV/C [Diabetes NSF – Intervention details] 28% of women who had a glycol ate hemoglobin (HbA1c) measurement before pregnancy had a value of less than 7%. 38% had HbA1c <7% in the first trimester 65% had HbA1c <7% from 18 weeks onwards this reflects the poor level of preparation for pregnancy (seen with regard to preconception care and folic acid supplementation)

The incidence of spontaneous abortion or premature delivery is slightly increased; preeclampsia and eclampsia are greatly increased. While only 6 to 8% of normal pregnant patients show toxemia, about 25% of diabetic pregnant patients demonstrate the complication.

The frequency of hydramnios is about 20% in diabetic pregnancies, as compared with 0.5 to 1% in normal pregnancies. Perinatal mortality is considerably increased. This can be reduced to approximately 15% with excellent care. The presence of renal vascular disease, hypertension, or retinopathy increases the perinatal mortality to 25 to 37%. Hydramnios further increases this mortality. However without conscientious prenatal care or meticulous diabetic management, the mortality rate rises to 50 per cent. Considerable fetal loss occurs in the last

four weeks of pregnancy. This observation has led to the empiric practice of artificial termination of pregnancy between the 36th and 37th gestational week.

Interruption of pregnancy between the 37th and 40th week results in an 11% perinatal loss while interruption between the 34th and 36th week results in 26% perinatal loss. Neonatal mortality before the 34th gestational week is so great that interruption before that time is contraindicated.

#### **Pregnancy complications:**

#### **Maternal include the following in order of frequency:**

Abortions 3.78%, Stillbirths 9.8%, Preeclampsia 20.7%. Polyhydramnios 7.5%, Preterm delivery 27.12% and operative delivery 45.8%.

#### **Fetal complications include the following:**

Neonatal deaths 5.1% and macrosomia 21.9%.

#### **Fetal risks:**

Poorly controlled pre-existing diabetes increases the risk of serious birth defect (heart defect, neural tube defect (NTD) etc). Miscarriage and stillbirth. Macrosomia (> 10 lbs birth weight) injuries during birth breathing difficulties, hypoglycemia and jaundice in neonatal period.

**Gestational diabetes:** Has not shown to have increased risk of birth defects. Increased risk for babies to develop obesity and diabetes (36%) as teens or young adults.

**Infant** - There is an increase in rate of intrauterine as well as neonatal death. Neonatal morbidity increases due to prematurity, birth trauma, congenital anomalies, respiratory distress syndrome and hyperbilirubinemia. Carbohydrate metabolism alteration is associated with increased glucose environment in utero and sudden withdrawal of glucose at delivery produces subsequent hypoglycemia in the neonate with blood sugar less than 20 mgm per cent. Apneic spells, neuromuscular irritability and sepsis are common.

**The effect of pregnancy on diabetes:**

The most obvious change is the increase in endocrine activity. There is hyperactivity of the pituitary, adrenal, thyroid, parathyroid, pancreatic, ovarian and placental hormones. There are also alterations in hepatic chemistry which maintain the appropriate energy transformations, release of intermediary metabolites, and regulation of proper levels of circulating hormones. These metabolic adjustments induced by pregnancy are similar to the adaptive changes which occur when any urgent requirement for energy is presented to the body.

**The effect of diabetes on pregnancy can be summarized as follows:**

**Mother** - There is increased abortion rate which varies with duration of diabetes mellitus and vascular lesions. Hydramnios favors premature rupture of membranes, and incidence of premature delivery is increased, toxemia is also increased, and control of diabetic becomes considerably difficult during pregnancy.

Ordinarily, most energy needs are provided by normal carbohydrate metabolism. However, demands of pregnancy

require addition of glucogenic mechanisms. These include increased secretion of adrenocorticoid trophic, growth, and thyroid hormones, as well as adrenal glucocorticoids. These factors may be regarded as glucogenic, ketogenic, and glycosuric in their activity and are therefore contra insulin in their effects.

In the normal individual, the increase in contra-insulin factors is compensated by an increase in the secretion of insulin, as evidenced by the hypertrophy of the pancreas which occurs in the pregnant state. However, the individual with an inherent defect of the pancreas cannot adapt to the increased demand for insulin to counteract the effect of elevated contra insulin factors. As a result a reduced capacity for adjustment will be manifested by glycosuria and a reduction of glucose tolerance. The most obvious effect of pregnancy is the response of the diabetic to insulin. In the first trimester, sensitivity to insulin increases, and hypoglycemia readily occurs. The warning signs and symptoms diminish in intensity, and the patient fails to recognize reactions which may progress to unconscious state.

With growth of the placenta, increasing quantities of antagonists to insulin are produced and degradation of insulin by the placenta becomes increasingly more effective. Fatty acid production increases and additional binding of insulin may occur. The average insulin requirement rises by 50 to 60% of the pre-pregnancy dosage. Exceptions occur with diabetic nephropathy. The shorter the duration of diabetes, the greater the insulin need during pregnancy. In pregnancy, short term diabetics are more susceptible to ketoacidosis than the growth onset patient. This state may be precipitated by the loss of carbohydrate through

vomiting, or through intercurrent infections.

**Role of fetus** - The rate of fetal growth is in inverse ratio to the duration of diabetes. Prediabetes and chemical diabetics usually have large fetuses. This indicates that hyperglycemia is not the most important cause of fetal obesity. Excess of growth hormone, free fatty acids and insulin like activity have been found in prediabetes and these appear to promote the excessive fetal growth. The long term diabetic, with pan vascular lesions have smaller babies.

**Role of placenta** - Insulin degradation has been shown to be progressively influenced by the placenta as it increases in size. An enzymatic substance has been isolated from human placentas which destroyed insulin at a relatively rapid rate. This enzyme action could be competitively inhibited by large quantities of such protein hormones as glucagon and ACTH.

#### **Complications of diabetes:**

**Retinopathy** - Occurs in 15-30% of diabetic patients who become pregnant. The commonest and the earliest change of diabetic retinopathy is the appearance of small red dots in the region of the posterior pole of the eye. These may be either microaneurysm or small hemorrhages.

A later finding is a waxy exudate, which takes the form of small, discrete, glistening, yellow white plaque, generally located in groups in the retina. This state is termed central punctate retinopathy. Dilatation of retinal veins occurs in an aneurysmal fashion.

A full retinal assessment should be undertaken in all women with preexisting diabetes during the first trimester or at

booking if this is later, accompanying this venous disease is the development of new vessels and connective tissue (retinitis proliferans).

All women with diabetes should be referred promptly for T1 US to accurately date pregnancy. All should be offered detailed anomaly US 18-22 w and serial US during the third trimester to monitor fetal growth.

These vessels may bleed into the retina, and large hemorrhages may occur which break into the vitreous humor. The occurrence and recurrence of such bleeding usually leads to permanent damage of the vision in the diabetic patient. Advancing retinopathy may be considered a contraindication to pregnancy, because of this complication.

#### **Kimmelstiel Wilson's disease:**

This complication occurs in the most advanced state of diabetes, and is manifested by hypertension, renal disease and edema.

Kimmelstiel Wilson's disease, in the non pregnancy state consists of the symptom complex which is found in toxemia of pregnancy, therefore it is difficult to differentiate between the two conditions, when they exist together.

If delivery is indicated before 34 weeks, administration of corticosteroids should be considered to prevent neonatal respiratory distress syndrome.

The specific lesion found in the kidney is intercapillary glomerulosclerosis. Pathologically there is a nodular subintimal deposition of hyaline material in the glomerular tuft. The material deposited in this lesion is a glycoprotein



related to the intercellular ground substance. It does contain some lipids but its basic composition is entirely different from that of the pathologic lesions of atherosclerosis. The juvenile diabetic (developing diabetes before age 16) frequently has significant renal vascular disease after 10 years, and almost definitely after 20 years.

Asymptomatic bacteriuria in diabetic pregnancies is twice or three times as common as in nondiabetic and it is likely that the incidence of pyelonephritis, premature delivery and renovascular complications is proportionately increased.

Patients with renal disease secondary to diabetes should be discouraged to get pregnant. If they do so, and signs of renal failure such as azotemia develop, the pregnancy should be terminated and tubal ligation advised.

If the OGTT is performed at or before 16 weeks gestation, a negative result does not necessarily exclude future problems and if the results are border line the test should be repeated between 32 and 34 weeks. Early diagnosis of GDM is associated with poor maternal and fetal outcome. Rather than suggesting that management is counterproductive, this probably means that the more severe cases present earlier. Treatment of gestational diabetes reduces serious perinatal morbidity and may also improve the woman's health related quality of life.

### **Management:**

If there is gross abnormality of blood sugar this must be corrected as a matter of urgency an ultrasound examination should be performed to assess for

macrosomia. This is usually taken as dimensions above the 95<sup>th</sup> percentile for that period of gestation. If it is present dietary management is required but it may also be necessary to use insulin to obtain suitable glucose levels. This management causes a modest but consistent reduction in the weight of the baby. Measurement of abdominal circumference of the baby can exclude macrosomia and reduce the need for insulin without impairing outcome. A paper from the USA described the use of glyburide (glibenclamide in UK) in GDM with some benefit but possibly an increased risk of preeclampsia. This is unusual as Sulphonylurea are usually used in type 2 diabetes and such drugs are usually avoided in pregnancy. Lispro has also been used with possible benefit. If there is no macrosomia but glucose levels are in the diabetic range, intensive therapy is required as in diabetes. If, after dietary advice, fasting glucose levels exceed 6mmol or 1 and 2 hours post-prandial the figure is over 7mmol or 1, then intensive therapy is required if there is no macrosomia, and glucose levels are not grossly abnormal, intensive therapy should be avoided as it may be counterproductive.

If the fetus is small for dates in women on intensive therapy, the outcome for the baby is poorer than if the baby is normal or large. This is probably a reflection of placental inadequacy if there is no macrosomia and after dietary advice the blood glucose levels before and after meals are normal, treat as normal. Prognosis: GDM is a variable disease with different criteria for diagnosis and different degrees of severity. Hence it is impossible to be clear about prognosis but some features do seem apparent. The risk to mother and baby are similar to those with known diabetes. This is

largely related to the problems of a large baby with shoulder dystocia and obstructed labor although sudden intrauterine death, placental insufficiency and neonatal hypoglycaemia can all occur. The traditional pride of a new father to a very large baby is misplaced. A large baby is an unhealthy baby.

Most women will apparently recover after the pregnancy but with a 2 in 3 chance of recurrence in a future pregnancy. However, the chance of developing overt diabetes, usually type 2, at some stage is much greater than in those who did not have it. During pregnancy, the highest fasting glucose level, followed by the severity of glucose

#### **Management of diabetic pregnancy:**

The successful management of pregnancy in a diabetic patient depends on the close cooperation of a team of the obstetrician, the internist, pediatrician, and most importantly, the patient. The main objective in the management of diabetes complicated by pregnancy is rapid control of the disease. The obstetrician has the unique opportunity of looking after the interest of the fetus in utero by meticulous control of maternal disease.

#### **Diagnosis –**

The diagnosis of diabetes mellitus may be difficult to make during pregnancy, especially by testing urine sugar alone. Lactosuria of 100 mgm% or more will produce a positive test for reducing substances in the urine. It is commonly found between 6 and 8 weeks before delivery, but is rare before that time. A sugar free urine test does not exclude

diabetes. The most accurate screening test is a two hour after meal blood glucose.

When values over 145 mgm per cent are found, a glucose tolerance test should be done after three days of adequate carbohydrate load. When glucose tolerance test described above is carried, diabetes is considered present if any two or more of the following values are exceeded; fasting blood sugar of 90 mgm per cent) one hour after glucose, blood value is 190 mgm per cent. The values obtained from plasma sugar are interpreted differently. Similarly different investigators have used different values. If a laboratory is not available in a village where the physician is practising, 5 mL of blood to which a sodium fluoride tablet has been added, can be sent to a nearby government or private laboratory and reliable results can be obtained even after 96 hours.

The usual renal threshold for glucose is 160 to 180 mgm per cent. This is lowered in pregnancy to 120 to 160 mgm per cent. This excessive loss of solute such as carbohydrates produces osmotic diuresis. The loss of fluids and electrolytes may reach considerable proportions. The vomiting may further aggravate this and provoke acidosis readily.

Intolerance and earlier gestational diabetes are the best predictors for postpartum diabetes. Impaired glucose tolerance in the first few months after delivery is associated with a high risk of diabetes in the near future. Children whose mothers had GDM are more likely to be obese but this does not necessarily imply a genetic or intrauterine effect. The parents tend to

be obese too and families eat together and acquire similar attitudes to food. The problem may simply be behavioral.

**Advice after gestational diabetes:** A woman who has had GDM should be given the following advice: You are at risk of developing diabetes and so: Achieve and maintain a satisfactory BMI Take regular exercise Do not smoke Do not have pregnancies in rapid succession. Whereas combined oral contraceptives and hormone replacement therapy do not seem to increase the risk of developing diabetes, further pregnancy does a lower renal threshold for glucose develops early in pregnancy and some women have glucosuria with levels of blood sugar below 100 mg%. Diabetic as well as non diabetic patients may show physiologic glucosuria, and this must be considered in making the diagnosis. It is generally accepted that the renal threshold in pregnancy is lowered partly due to the increased renal plasma flow and increased glomerular filtration rate. Partly due to decreased reabsorption of glucose from the renal tubules as a result of increased output of adrenocorticotrophic and adrenocortical hormones. There is no proof of the exact incidence of the lowered renal threshold in normal pregnancy, for it does not always occur, even in the diabetic patient. However, Fine claims that if efficient methods are used, there is a uniform finding of glucosuria in pregnancy. An intravenous glucose tolerance test may be a more reliable index of islet cell function than the oral test because of variations in gastrointestinal absorption and motility during pregnancy, but misleading results occur, Welsh subjected a series of patients to oral and intravenous tests and found that approximately 3/4 of those showing abnormal oral test had normal

intravenous test. The introduction of the intravenous tolbutamide test and the cortisone glucose tolerance test has been added in addition to the venous tolbutamide test because of its lack of sensitivity. In any case these tests can not be done in pregnancy.

**Antenatal care** - On the initial visit a complete history is taken, a thorough physical examination is performed, and routine laboratory work scheduled. The patient is then seen every two weeks until the 26th week of gestation and every week thereafter ideally, at each subsequent visit, the patient is evaluated both medically and obstetrically by an obstetrician and an internist together. The urine is examined at each visit for glucose, acetone and albumin. Weight and blood pressure are checked and the patient examined for signs of edema and polyhydramnios.

Hemoglobin determination is carried out monthly and the ocular fundus examined frequently if the patient shows evidence of fluctuating carbohydrate tolerance, early toxemia or infection, she is admitted to hospital for further evaluation and strict diabetic control.

**Fetal age assessment** - The clinician assesses fetal maturity with difficulty in the diabetic mother. The menstrual cycle is frequently irregular in diabetic women, so the calculation may be erroneous from the start. The fundal height may be misleading due to the large fetal size or the presence of hydramnios. In mothers with cardiovascular or renal disease the infants may be smaller than average for gestational age. A combination of gestational date estimation, fundal height, and fetal size radiological evidence of the presence of the distal

femoral epiphyses can help in assessment of fetal maturity.

In the multiparous patient, with the fetal head dipping in the pelvis and the cervix favorable, induction of labour with oxytocin may be used. If the patient is primiparous, cesarean section is usually chosen. The best perinatal results, are obtained when cesarean section is done for gigantic size baby. Difficult and prolonged labors only make diabetic control difficult.

The availability of serial urinary estriol measurement can provide the clinician with an objective assessment of the integrity of the fetoplacental unit. In the non-pregnant female, the ratio of estriol/estrone/estradiol is 3/3/1 respectively. In pregnancy the ratio is 30/2/1, illustrating very considerable increase in the estriol fraction during pregnancy. Estriol is produced in the placenta, but production is dependent on an adequate supply of precursors from the fetal adrenal glands.

In normal pregnancy urinary secretion levels of estriol exceed 12 mg/24 hours. Values less than 10 mg/24 hours signify impending fetal jeopardy, while values below 4 mg/24 hours are compatible with fetal death. These values are less significant in the earlier weeks of gestation, but absolutely true in the last four week and relatively true in the last eight to ten weeks. As there is individual variation, plus a 25% range of error, single laboratory determinations maybe inconclusive. Significance should be attached to the trend with repeat estriol determinations and not to a single high or low value.

#### **Self monitoring:**

#### **Pre existing diabetes and GDM:**

4 times/day: before breakfast and 2 hours post meal Pre-meal monitoring may also be necessary in many patients Nocturnal monitoring ( $\gg$ 3 AM) may be necessary on intermittent basis Fasting urine ketones. In the diabetic patient, daily estriol levels can give an index for predicting impending intrauterine death.

#### **Diabetes monitoring and visits:**

The only diabetes medication currently used during pregnancy is insulin. Endocrinology visits every 1-4 weeks. At each visit, review results of urine analyses perform blood pressure, urine protein and ketones by dipstick. Hb A1C level every 4-8 weeks. Education by counseling as needed. Ophthalmology exam early in first trimester; follow up depending on findings of this exam.

Measurement of Biparietal diameter by ultrasonography can be very helpful, diameter measuring 9.1 to 9.2 cm implies that the fetus is greater than 36 weeks. Amniotic fluid analysis for orange cells percentages, creatinine and lecithin sphingomyelin ratio can also provide an index of fetal maturity and help physician in close follow up of his patient.

Greater than 20 per cent orange cells implies fetal maturity, similarly greater than 2 mgm per cent creatinine implies maturation of fetal kidneys while lecithin sphingomyelin ratio of greater than 2:1 indicates fetal lung maturity. None of these values should be singly used to decide about the time for interruption of pregnancy.

There is considerable variation in absolute values of these substances in diabetic mothers. It is the total progress of pregnancy which the clinician must consider in conjunction with these

special tests to decide about the mode and timing of delivery.

**Diet** - At first visit, the diabetic meal plan is worked out. While working out diet for a diabetic patient total number of calories needed should be kept in mind. A reasonably accurate estimate of calories can be worked out by providing 30 calories per kilogram of body weight and adding 200 extra calories. Caloric requirements for 60 kilogram women would be  $30 \times 60 + 200 = 2000$  calories. These calories should come from carbohydrate, protein and fats. Carbohydrate- $30 \times 1/10$ th of the body weight i.e.  $30 \times 6 = (180 \text{ grams})$ , proteins =  $30 \times 1/120$ th of the body weight i.e.  $30 \times 3 = (90 \text{ grams})$  and the rest should come from fats.

These 2000 calories can be split as  $1/7$ th of total at breakfast  $2/7$ th at lunch,  $1/7$ th at afternoon snack,  $2/7$ th at dinner, and  $1/7$ th at late night snack. The time table can be useful for the dietician or the relatives and physician of the patient to plan menu.

#### **Tools to estimate food intake:**

24 hours recall, Diet diary, Food charts Weekly visits to or dietician endocrinologists, Serum glucose monitoring and Hb A1C An ideal weight gain in pregnancy should be one tenth of the ideal body weight, 10 calories per pound is provided; 30 to 40 per cent is added for activity and fetal growth. The diet should be planned to permit a weight gain of 15-20 pounds; the obese patient may, however, need to have the weight reduced, but she should not be restricted to fewer than 1400 calories per day. Majority of early diabetics can be controlled on diet and do not require

insulin but those who need this should have a properly planned therapy.

#### **Oral hypoglycemic agents:**

Oral agents are a pragmatic alternative to insulin therapy in pregnancy because they are easy to administer and noninvasive and therefore user friendly. Since the original study in 2000, many experts and authoritative organizations in the United States (e.g., the Fifth International Workshop on Gestational Diabetes and the North American Diabetes in Pregnancy Study Group) have endorsed the use of glyburide (a sulfonylurea) as an alternative pharmacological therapy to insulin during pregnancy. The introduction of any new drug in pregnancy will raise concerns about fetal and maternal safety. The ultimate proof that a drug cannot affect the fetus during pregnancy is founded on its inability to cross the placenta. The majority of drugs used in pregnancy cross the placenta. Thus, even if a new drug crosses the placenta, it remains to be proven that it will cause a teratogenic effect on the fetus in utero. If there is no adverse effect on the fetus, the drug can be used. Glyburide does not cross the placenta. Our original observations have been re-confirmed by several studies. Glyburide has been safely used in pregnancy without adverse effects on the fetus. In contrast, metformin, rosiglitazone, and pioglitazone freely cross the placenta. We await further evidence on safety when fetuses are exposed to these drugs. In the case of metformin with patients who have polycystic ovary syndrome, data from retrospective studies give us hope for its safe use. The ongoing Metformin in Gestational Diabetes study from Australia and New Zealand is evaluating

in a randomized design the efficacy of metformin versus insulin use. Because there is no clinical study to date reporting on the use of thiazolidinediones in pregnancy, these agents should not be prescribed.

Glyburide is the most common oral agent used in GDM and is wholeheartedly endorsed by authoritative organizations. The drug increases insulin secretion and diminishes insulin resistance by lowering glucose toxicity. Its onset of action is 4 hours, and its duration of action is 10 hours.

Thus, after achieving the targeted therapeutic level, glyburide covers the basal requirement as well as postprandial glucose excursions.

The starting dose is 2.5 mg orally in the morning. If the targeted level of glycemia is not attained, add 2.5 mg to the morning dose. If indicated (after 3–7 days), add 5 mg in the evening. Thereafter, increase the dose in 5/mg increments to a maximum of 20 mg/day. If the patient does not achieve targeted levels of glycemic control, add long-acting insulin to the regimen or assign the patient to insulin therapy alone. In one randomized study in 2000, they enrolled 440 women between 11 and 33 weeks' gestation with singleton pregnancies that had GDM requiring treatment (failed oral glucose tolerance test and fasting plasma glucose level of 95–140 mg/dl). Patients were randomly assigned to receive either glyburide ( $n = 201$  initial dose 2.5 mg orally, increasing by 5 mg to a total of 20 mg) or insulin ( $n = 203$ ; initial dose 0.7 units/kg subcutaneously 3 times/daily, increasing each week as necessary) for glycemic control. Subjects were required to measure

### **Insulin:**

It is not the type of insulin used which matters; instead it is the quality of metabolic control, and supervision of the patient which is of utmost importance. The urine must be kept free of acetone, and heavy precipitates of sugar in the urine are undesirable.

The most significant guide to therapy with insulin and diet is the two hours post prandial blood sugar level. The target should be to maintain this level between 100 to 120 mg. per cent. Pregnant women usually require insulin where diabetes was discovered before pregnancy, or before 20 weeks of gestation and when blood glucose levels are over 150 mgm per cent after meals, and in patients taking blood glucose lowering agents before pregnancy.

### **Actions:**

Insulin is responsible for translocation of glucose and amino acids, and transfer of potassium in muscles. In liver it also helps in translocation of glucose and amino acids, as well as incorporation of amino acids into peptides. The enzyme glucokinase increases due to the action of insulin. In adipose tissue it is responsible for translocation of glucose and escape of free fatty acids.

**Lente insulin or NPH:** This has a maximum blood glucose lowering effect from 8 to 14 hours after injection with decreasing action over night to 24 hours. The dose should be assessed by the 4.00 p.m. blood sugar and by urine tests done before supper, at bedtime and before breakfast. If this blood glucose test is over 145 mgm% or urine tests done are over a trace at supper, bedtime and before breakfast for two days, the dose is increased by 10% the following

morning. If the blood glucose is less than 60 mgm% at 4.00 p.m. or if there is an insulin reaction before supper or in the evening, the dose is reduced by 10% on the following morning. Every effort should be made to avoid insulin reactions in pregnant patient.

**Semi Lente insulin or Toronto insulin:**

This has a maximum blood glucose lowering effect from 3 to 5 hours after injection.

The dose can be assessed by the before noon urine test (on the second voiding after breakfast) and by 11.00 a.m. blood glucose. If the blood glucose is over 145 mgm% or the urine test is over a trace at noon for two days, the Semi Lente dose is increased by 2 units on the following morning. If the blood glucose is below 60 mgm% at 11.00 a.m. or there is an insulin reaction before the noon meal, the Semi-Lente dose is reduced by 2 units the following morning.

**Ultra Lente insulin:** It has a maximum blood glucose lowering effect from 12 to 24 hours after injection with lessening action up to 36 hours. When given at bedtime it serves as a "basis" for stabilizing blood sugar throughout the day, because of slow release.

**Dose regimen:** The starting dose of insulin averages 1/10th of the blood glucose level given as Lente or NPH before breakfast. If the dose required is over 20 units, a short acting insulin, such as Semi Lente or Toronto insulin is mixed in a 2/1 ratio and given before breakfast.

Patient should be trained to adjust the dose herself on the basis of her urine tests done before meals and at bed time,

this however, can only be done in educated and highly motivated patient. Blood glucose tests are to be preferred and should be done at 11.00 a.m. and 4.00 p.m. every one or two weeks. Patients should be advised to contact their doctor frequently concerning glycosuria, hyperglycemia or insulin reactions so that insulin dosage could be adjusted without delay. Blood sugar measurements are a better and preferable method of monitoring control of diabetes in pregnancy, since glucosuria due to lowered renal threshold can not interfere with this method.

**Method and timing of delivery:**

All diabetic gravidas should be admitted to hospital four weeks prior to term. Diabetics who have only abnormal glucose tolerance curve and do not receive insulin may be allowed to deliver normally, unless a death in utero has occurred during the last four weeks of a previous pregnancy. In this case delivery at 36 to 37th week should be accomplished. All other pregnant diabetic women should be delivered before the date of confinement. Even well controlled diabetic patients should be delivered by the 37th or even the 38th week of pregnancy. If toxemia supervenes, some diabetic patients may have to be delivered as early as 35th week. Prior to this time the dangers of prematurity are too great, and may result in neonatal death easily.

**Management on day of delivery:**

The mode and timing of delivery should be determined on an individual basis, aiming to realize a spontaneous vaginal delivery by no later than 40 weeks of gestation if possible induction of labour oral feedings are withheld. One quarter

of the previous day's dose of insulin is given at 8.00 I.V. glucose, totalling 200 Grams per day is started at 8.00 a.m. i.e. (2000 mL 5% dextrose in water and 1000 mL of 10% dextrose in water run for 12 hours). No analgesia or sedation is given. After delivery, another dose of one quarter of the previous day's insulin is given.

Continuous electronic fetal heart monitoring should be offered to all women with diabetes during labor and fetal blood sampling should be available if indicated.

One day after delivery half of the Pre partum insulin dose is given. A diabetic fluid diet totalling 200 gms, carbohydrate is offered. In the event of nausea or vomiting, oral fluids are stopped, and 1000 mL 10% Dextrose in water is given.

#### **Cesarean section:**

8.00 a.m. blood glucose is done. Insulin is withheld; narcotic premedication is withheld, I.V. Glucose totalling 200 Gms.

Per day is started at 8.00 a.m. For example, 1500 mL of 10% dextrose in water are run during operation, and 1500 mL of 10% Dextrose in water are run in 6 hours. Postoperatively half of the daily dose of insulin is given. If blood is required, it is given in a separate infusion to avoid possible hypoglycemia.

#### **One day after operation:**

At 8.00 a.m. blood glucose is done. Half of the predelivery dose of Lente insulin is given. I V. Glucose totalling 200 gms is given with 5-10 units of Semi Lente insulin. Per flask depending on the

morning blood glucose. On Second Post Op. Day - the total dose of Lente and Semilente insulin required on the previous day is given at 8.00 a.m.

#### **The neonate:**

The newborn of the diabetic mother should be treated as a premature infant, irrespective of his gestational age. There is increased incidence of respiratory distress syndrome, congenital anomalies, and neonatal hyperbilirubinemia, in these babies. Anomalies such as tracheo-esophageal fistula, diaphragmatic hernia, malrotation of the bowel, and imperforate anus occur more frequently. Intravenous dextrose and insulin should be administered during labour and delivery following an agreed multi-disciplinary protocol. The weight of the diabetic infant is similar to that of a nondiabetic infant up to 220 days of gestation, but in the last 60 days of gestation there is a significant increase in weight. It is known that there is hypertrophy of the islet tissue of the pancreas in the infant of both the established diabetic and the pre diabetic mother there is also a direct correlation between the amount of islet cell hypertrophy and the fetal weight. There is no increase in the total body water content, but an increase in skeletal growth does take place. It is likely that the fetal gigantism is due to the anabolic and lipogenic effects of fetal hyperinsulinism and this must be operative in the pre diabetic as well as the diabetic phase. The four possible reasons for fetal hyperinsulinism are maternal hyperglycemia increase in pituitary growth hormone, maternal adrenal glucocorticoids and the action of insulin antagonists. The care of these infants should be undertaken by a pediatrician who is familiar with the



special problems of the sick, premature and full term newborn. The infant should be placed in an incubator and receive oxygen therapy. Special care should be taken to clear the airway at birth and treat hypoglycemia, Hyperbilirubinemia or hypocalcemia w-hich may be present.



**Fig2.2: The looks of diabetic baby**

Constant nursing care is required during the first four days of life. Oral feedings are postponed until the infant is vigorous, and can start taking feeds without any problem. Babies blood glucose test < 4–6 hours before a feed [Diabetes NSF – Intervention details] Hypoglycemia diagnosed with ward based glucose electrode or laboratory method (not reagent strip) Babies should remain with mothers unless specific medical indication NNICU admission. [Diabetes NSF – Intervention details] Feed babies ASAP after birth & all should receive first feed <4 h, unless medical contraindications [Diabetes NSF Intervention details] Breastfeeding recommended but mothers should be supported in feeding method of their choice.

### **Conclusion:**

The lasting beneficial effects of breast-feeding appear to be life long for the offspring, Careful attention should be paid to the glucose control of the postpartum woman with diabetes or

GDM if she breastfeeds, •Waiting until diabetes is diagnosed at the 6 week postpartum visit is too late and weight gain in the offspring of women with diabetes should be closely monitored regardless of feeding method.

### **Recommendations:**

Breastfeeding is the best way to nurture healthy newborns of healthy mothers, Prevention of overweight and diabetes is only one of many benefits of breast-feeding and AAP recommends breast-feeding  $\geq 1$ st year.

### **Quick Review**

#### **Management options: Diabetes mellitus and gestational i diabetes:**

**Pre pregnancy:** explain general risks and management of diabetes in pregnancy evaluate any additional risks with appropriate specialist referral (e.g. renal, ophthalmologic) optimize blood glucose control, discuss effective contraception until good glucose control (? avoid estrogen containing-preparations with vascular disease). Folate supplementation (4-5 mg daily) for at least 2 months before and during first trimester

#### **Prenatal:**

screen for gestational diabetes ideally in all pregnancies (controversy over which test and whether just at 24-28 weeks): is diagnostic test, regular capillary glucose series, avoid oral hypoglycemic agents, appropriate diet, amend insulin regimen to keep capillary glucose, values as normal as possible (see table 38.5) "0 instruct, partners/relatives in glucagon use for hypoglycemic attacks, baseline renal and possibly cardiac function, randomized trials of low dose aspirin in

women with vascular disease are awaited, regular ophthalmologic review, monitor for hypertensive disease, fetal surveillance, normality, growth, well-being (nst, bps), umbilical artery blood flow gestational diabetics: initially try to control with diet rather than insulin; otherwise, as for established diabetics.

### **Labor/delivery**

Timing: can be delayed until term if diabetes is well-controlled and pregnancy uncomplicated, method: will depend on complications in mother (e.g. hypertension, ophthalmic) and/or fetus (e.g. macrosomia, acute fetal compromise) when cesarean section more likely), Maintain good perinatal glucose control Postnatal, Reduced insulin requirements, Continue capillary glucose monitoring >- Encourage breastfeeding: Give contraceptive advice.

### **Postnatal:**

Reduced insulin requirements continue capillary glucose monitoring, Encourage breastfeeding. Give contraceptive advice.

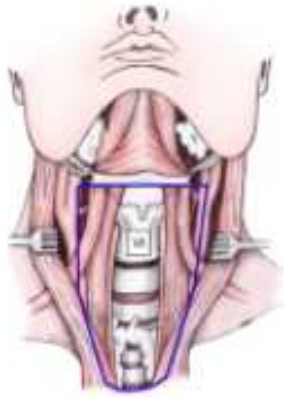
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## Chapter No 3

# THYROID DISEASE IN PREGNANCY



**Fig3.1: shows dissected view of space for thyroid gland in neck**

Thyroid dysfunction in pregnancy is not a very common complication. The problem of fertility can arise both from hyper function as well as hypofunction of the gland. Hyperthyroidism in severe form is rarely encountered in pregnancy, since this causes amenorrhea and infertility.

The incidence reported in the literature varies between 0.02 to 0.04 per cent (Hawed and Francis, 1962). Mild cases of hyperthyroidism are difficult to diagnose due to hemodynamic and metabolic changes normally produced in pregnancy. The physiological changes mimic clinical features of thyrotoxicosis to some extent.

### **Effect of pregnancy on disease:**

Hyperthyroidism is usually affected by pregnancy; In fact pregnancy sometimes has beneficial effect on this condition.

Thyrotoxicosis even in its severest form can be controlled by current therapy and is therefore not an accepted indication for termination of pregnancy.

**Effects of disease on pregnancy -** Severe hyperthyroidism may produce' abortion or premature labor in some cases. The incidence of pre eclampsia is increased in patients with this complication. In cases of mild hyperthyroidism there is little if any effect on the course of pregnancy.

**Effect on infant:** It is generally accepted that thyroxine does not cross the placenta under normal circumstances. Recently it has been reported that small amounts of thyroxine may some-time cross the placenta.

This does not appear to harm the fetus in utero. Hyperthyroidism in the infant can however result from secondary over-activity of the fetal gland wh-en excessive secretion of maternal TSH is present. This is however not permanent. The clinical changes usually disappear in two to three months after birth.

### **Clinical features:**

The changes in cardiovascular system include tachycardia, ectopic beats, full bounding pulse, high pulse pressure, warm skin, sweating and occasional fibrillation of the heart. Central nervous system changes are manifested by, emotional instability of the patient, which is often quite marked and should not be missed. There are also fine tremors of the hands. The eyes may

show marked evidence of exophthalmos, which will make the diagnosis easy for the student. The patient often presents with history of diarrhoea. This is due to hypermotility of the gastro intestinal tract.

**Diagnosis** - This can be usually made by analysis of history, clinical features and appropriate laboratory investigations.

This complication affects various systems in the body.

#### **Laboratory investigations:**

**Protein bound iodine** - This will be increased in hyperthyroid state. The estrogens increase many fold during normal pregnancy and in turn increase the capacity of thyroxine binding globulin.

In non-pregnant cases protein bound iodine ranges from 4 to 8 microgram percent while in pregnancy it increases up to 8 to 11 microgram percent. When values more than 11 microgram percent are discovered, the diagnosis of hyperthyroidism can be made with confidence.

#### **Red cell uptake of radioactive Iodine:**

This is quite a reliable test for diagnosing hyperthyroidism. The non thyrotoxic pregnant patient gives a value in the hypothyroid range while the thyrotoxic pregnant patient gives value in normal or toxic range. The other advantage of this test is that, radioiodine is not given to the patient, and it is done in vitro.

#### **Radioactive iodine 131 uptake test:**

Iodine 131 has a half life of two to three hours. It is contraindicated during pregn-

ancy because of risk of fetal thyroid irradiation.

**Serum T3 and T4** - These hormones can be measured by employing radio immunoassay. Since these tests are done in vitro there is no danger to the fetus. However caution is needed for interpretation of results.

#### **Free thyroxine and free Triiodotyrosine Levels:**

(FT 4' FT 3) the student should note that the above mentioned conventional thyroid functions tests have been replaced by free thyroxine and free triiodothyronine tests. The normal range of these hormones is 8.8 - 23.2 Pico moles per litre and 3.0 - 8.6 Pico moles per litre respectively. These hormone assays can be carried out by radio immuno assay for which commercial kits are readily available in developed countries. It is strongly recommended that these two tests instead of the others should be carried out in assessing the thyroid function tests during pregnancy.

#### **Management:**

The important feature in the treatment of thyroid disease during pregnancy is to avoid over-treatment of the mother.

This is serious matter and can lead to hypothyroidism with its serious consequences such as, abortion, premature labor, fetal goitre and even mental retardation which may be permanent. It is very important that the treatment chosen should maintain eu-thyroid state of the mother throughout pregnancy.

**General measures** - These should include bed rest and sedation. Sedative

such as phenobarbitone 30 mg given orally at 8 hourly intervals is quite useful.

**Medical treatment** - The physician treating thyroid disease should do so in collaboration with an internist who is especially interested in obstetrical problems.

The drugs commonly used reduce the production of thyroxine and include Carbimazole or (nimorazole), Methyl thiouracil and potassium perchlorate. THE first two drugs prevent incorporation of Iodine into Tyrosine nucleus by inhibiting the required enzymes, while the third or last drug interferes with Iodine trapping mechanism of the thyroid gland. These drugs can cross the placental barrier and therefore produce fetal goitre. This goitre usually disappears in 1 to 2 weeks after birth. The fetal goitre may result in respiratory obstruction. Hypothyroidism can result from over treatment with these drugs and this may lead to mental retardation in the neonate.

Initial dose of carbimazole is 15 milligram 8 hourly by mouth. When the symptoms are controlled, the dose is reduced to 10 milligrams, and finally 5 mgs twice daily, until she becomes euthyroid.

Initial dose of methylthiouracil is 100 mgs hourly by mouth. When symptoms are relieved 50 mgs 8 hourly is given and finally 50 mgs daily, till patient is euthyroid.

Initial dose of Potassium Perchlorate is 250 mgs 8 hourly. When the patient is euthyroid then 300 mgs daily is given as a maintenance dose. Side effects such as fever, rashes on skin, sore throat, agran-

ulocytosis etc, may occur. Occasionally medication may have to be stopped due to side effects.

It is important that the physician treating hyperthyroidism in pregnancy constantly monitors the thyroid status during treatment. The PBI tests are not reliable, therefore, T3, T4 and 1131 red cell uptake tests should be done. It has been demonstrated that if the mother is kept euthyroid, no harm can result to the fetus by the use of antithyroid drugs. There may be slight thyroid enlargement, but this disappears within two weeks after birth. Some physicians prefer to give 0.1 mg of sodium L-thyroxine at the same time the antithyroid drug is being given. The rational is to avoid the risk of hypothyroidism in the infant. The fetus starts to produce its own thyroxine around 20th week of gestation. A critical level of thyroxine is necessary for normal development of the fetus. If this is not available proper brain development cannot occur, and the damage produced in utero cannot be reversed by giving thyroid hormone after birth.



**Fig3.2: Shows thyroidectomy being carried out surgically.**

**Thyroidectomy** - Some Physicians prefer surgery over medical treatment. Hawe and Francis in (1962) reported good results with partial thyroidectomy

during pregnancy. The advantages they described in their study include and no increased danger to the mother.

There was no danger of abortion or premature labor. It also prevents the danger of hypothyroidism in the fetus. The mothers could also breast feed. Antithyroid drugs are secreted in the mother's milk. Therefore breast feeding is avoided in these cases.

The disadvantages of surgery are that physiological enlargement of thy-roid occurs in pregnancy and this makes it difficult to assess how much of the gland should be removed.

#### **Quick Review:**

#### **Management options:**

#### **Hypothyroidism:**

#### **Pre pregnancy:**

Consider hypothyroidism in differential diagnosis of infertility and/or menstrual disorders. Delay pregnancy until maintenance drug levels are achieved

**Prenatal:** Continue full thyroid hormone replacement Serial (every trimester) thyroid function studies )<sup>1</sup>- Watch for evidence of myxedema

#### **Labor and Delivery:**

No specific considerations necessary

**Postnatal:** Watch for exacerbation of subclinical thyroid disease, which may present with transient hyperthyroidism.

#### **Management options:**

#### **Hyperthyroidism:**

**Pre pregnancy:** Establish the diagnosis of hyperthyroidism prior to pregnancy so that a complete diagnostic workup can be performed and therapy instituted. Counsel regarding the need to continue therapy during pregnancy, the potential perinatal risk, and the need for serial thyroid function studies

#### **Prenatal:**

Continue thio amide therapy to maintain the patient clinically euthyroid and ensure that the laboratory parameters remain in the acceptable ranges for pregnancy (Table 40.1). Use beta-blockers for symptomatic complaints (i.e. tachycardia, palpitations).

Thyroid function studies should be obtained every 1-3 months. Serial ultrasonography of the fetus should be obtained to rule out fetal growth retardation and/or fetal goiter. The recognition and management of thyroid storm (Table 40.3)

#### **Labor and delivery:**

No specific management needs are associated with the intrapartum process

#### **Postnatal:**

Watch for worsening of symptoms if autoimmune etiology is suspected.

Adjust thio amide therapy according to laboratory parameters and symptoms.

Complete the diagnostic evaluation of hyperthyroidism, and when appropriate institute definitive therapy. Evaluate the neonate for evidence of goiter and transient hyperthyroidism.

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## Chapter No 4

# HYPERTENSIVE DISEASE IN PREGNANCY

### Introduction

**Hypertension** - is considered present when diastolic B.P. is greater than 90 mm Hg or the increase is greater than 15 mm Hg over pre-pregnancy pressure, or Systolic B.P. is greater than 140 mm Hg or the increase is greater than 30 mm Hg over pre-pregnancy level. "The increase in pressure should manifest on two occasions more than 6 hours apart.

### Checking blood pressure



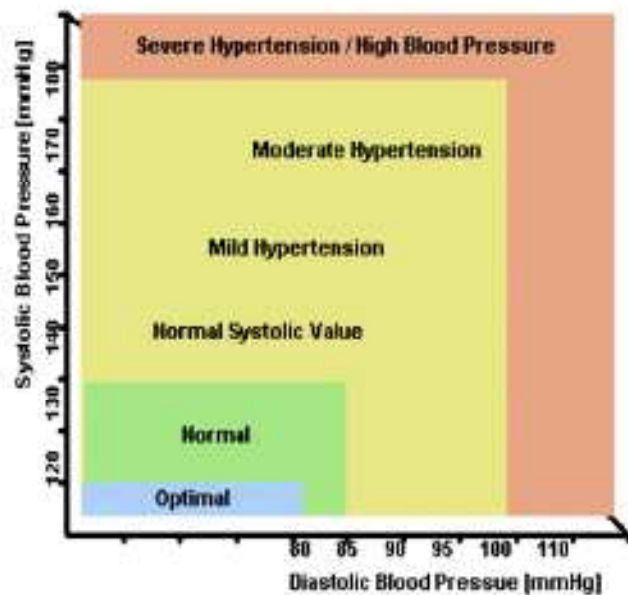
**Fig 4.1: Shows position of blood pressure measuring cuff zero point at zero pressure in chest**

Zero Pressure is found in right atrium the level of right atrium of the heart should be kept in mind while applying blood pressure measuring cuff.

**Gestational hypertension** - This is defined as blood pressure elevated at gestational age greater than 20 weeks or within 24-hour of delivery (most likely it is a variant of pre-eclamptic toxemia.

The designation of hypertensive states of pregnancy is usually limited to pre-eclampsia, eclampsia, and chronic hypertensive vascular disease with superi-

mposed preeclampsia or eclampsia. The available clinical criteria



**Fig 4.2; Shows various types of hypertension**

### Classification:

The student must realize that diagnosis based on clinical features alone is not always valid. The diagnosis of some of these conditions can only be possible by retrospective analysis, there-fore the classification presented here is only an arbitrary one. The disease can be divided into four groups for descriptive purposes.

### Pregnancy induced hypertension:

Chronic hypertension preceding pregnancy. Chronic hypertension with superimposed toxemia Latent or transient hypertension.

**Incidence** - Its incidence varies according to geographical location, socioeconomic status, racial origin and nutritional status of the patient. The increase in frequency of eclampsia in areas where dietary deficiencies are common, such as China, the Philippines and Pakistan is suggestive but not conclusive. The proof of dietary deficiency as causative factor is not very clear.

**Etiology** - The etiology of pregnancy induced hypertension is entirely unknown. Functioning trophoblastic tissue is required for its initiation and maintenance, but the presence of a fetus is not apparently essential. Classically, it is a disease of the young Primigravida and characteristically, it occurs in the third trimester. Twins and hydatidiform mole are predisposing factors.

#### **Classification of hypertension:**

In order to classify blood pressure the guide lines for both systolic and diastolic blood pressure are provided. It is considered normal when BP recording is found Systolic 90-119 mmHg and 60-79 mmHg diastolic while it is considered that Prehypertension is present when BP systolic is recorded as 120-139 mmHg and diastolic as 80-89 mmHg. Stage 1 hypertension is considered as present when systolic BP is recorded as 140-159 mmHg and diastolic as 90-99 mmHg. Stage 2 hypertension is considered present when systolic BP is recorded as 160 mmHg and diastolic as 100 mmHg. This classification is based on guidelines provided by American Heart Association.

#### **Other classification used in literature:**

Primary 90-95% of cases also termed "essential" or "idiopathic".

- Secondary – about 5% of cases
  - Renal or renovascular disease
  - Endocrine disease
    - Pheochromocytoma
    - Cushing's syndrome
    - Conn's syndrome
    - Acromegaly
    - hypothyroidism
  - Coarctation of the aorta
  - Iatrogenic
- Hormonal / oral contraceptive
- NSAIDs

High chorionic gonadotrophin levels are occasionally seen in these patients, but the levels are not related to the severity of the disease process.

A number of reversible biological changes occur in preeclampsia. These indicate that there are widespread aberrations in cellular function, and strongly suggest that it is a metabolic disease.

Hypertension in pregnancy is a disease of many theories.

**Theories** - A number of hypotheses have been expressed concerning the etiology of preeclampsia. None so far has been able to explain the reasons for its predisposition in primigravidas, in multiple pregnancy and hydatidiform mole. Similarly other factors such as its appearance in certain geographic areas and in poor populations, its appearance late in pregnancy, and its tendency not to recur in subsequent pregnancies and its improvement after fetal death remain unexplained.

**Theory of uterine ischemia** - This hypothesis at present is greatly favored. It is postulated that mechanical factors in or about the uterus fail to allow the

blood flow to adapt to the requirements of the uterus and the products of conception. Reduced uterine blood flow provides a situation which favors increase in production of pressor polypeptides, such as thromboplastin or thromboplastin like substances. These are produced by the ischemic placenta or by ischemia induced degeneration of decidual tissue. These substances are responsible for the clinical manifestations of preeclampsia.

Factors which have been implicated to increase uterine ischemia include the following. Increased Myometrial Tension in multiple pregnancies or in the course of labour and excessive amounts of trophoblast as seen in the presence of hydatidiform mole.

In primi gravidas, deficient vascular hypertrophy and hyperplasia have been reported as causes of the failure of circulatory adaptation. It is also believed that arteriolar sclerosis depresses adequate circulatory adjustment in patients with acute preeclampsia super imposed on chronic hypertensive disease.

These hypothetical changes are suggested as the basis for exacerbation of chronic renal and vascular diseases during gestation, the high incidence of pre-eclampsia in primi gravidas and in patients with twins and with hydatidiform moles, and for the failure of the disorders to recur in subsequent pregnancies after the first. A decrease of 40 per cent in uterine blood flow has been measured in hypertensive patients by Assail and his colleagues. Hunter and Howard reported finding of pressor polypeptides in blood, amniotic fluid and decidua of patients with acute preeclampsia.

**Theory of disseminated intravascular coagulation** - MacKay, on reviewing the evidence supported the contention that disseminated intravascular coagulation is a major mechanism in eclampsia. He reported that Pathologic evidence is available in the form of platelet fibrin thrombi in the microcirculation of various organs, including the brain, kidney, heart, lung and placenta. Clinical signs and symptoms of consumptive coagulopathy has been shown to be quite similar to the manifestations of eclampsia, including secondary hypertension, bleeding tendency, oliguria, anuria, hematuria, convulsions, coma, abdominal pain, dyspnea and cyanosis, which further supports that DIC may be the causative factor in some cases.

#### **The immunological theory:**

According to this theory some immuno active substances in the primigravida patient produce these changes. Scott and Beer in (1976) reviewed the immunological aspects of pregnancy and suggested that the increase in the number of antigenic cells transferred to the maternal circulation during pregnancy are increased in size along with the size of placenta (hyperalimentosis) in diabetes, Twins and molar pregnancy. This alters the maternal immune state and produces the problem.

#### **Nutritional or metabolic theory:**

There is little evidence confirming this theory. There is evidence that good nutrition prevents Pre eclamptic toxemia. Good nutrition implies adequate caloric intake and adequate protein intake.

**Renin angiotensin IL theory:** Speraff in 1975 summarized the theory con-

cerning the disturbance in the Renin angiotensin II aldosterone disruption by coupling it with his own theory of the role of prostaglandins. His theory postulates that an imbalance is found between the systemic vasodilatory mechanisms and the effect of Renin and Angiotensin II which produces vasoconstrictive effect.

Plasma renin levels are higher in pregnant normotensive women than in non pregnant normotensive women although there is some overlap in values. Angiotensinogen levels are markedly elevated in pregnancy probably in response to estrogen.

The entire Renin angiotensin aldosterone mechanism is increased but the reason for this is not clear. It may be that the system is increased to produce the required increase in blood volume associated with increased vascular capacity in pregnancy. As such the elevated aldosterone levels are not a cause of excessive sodium retention but may represent a compensatory response. The usual physiological changes affecting renal renins do not affect uterine renin. The uterine renin is probably manufactured mostly in the chorion.

Chronic Uterine ischemia results in hypertensive hypernatremic proteinuric dogs (Hodari 1976), toxemia was associated with a 40 to 60% reduction of blood flow in the utero-placental unit.

Gant (1974) has however demonstrated an increase in Dehydro epiandrosterone Sulphate clearance early in the pregnancy of hypertensive patients, reducing to less than normal prior to the development of the clinically evident pre

eclamptic toxemia. This and other studies have suggested that there is a declining placental blood flow.

Reduction in Uterine blood flow results in outpouring of renin into uterine vein (in pregnant rabbits) •. Angiotensin-II infusions acutely elevate B.P. in Rh monkeys and PgE<sub>2</sub> in uterine veins and this is associated with an increase in blood flow to the uterus. There seems to be a problem with autoregulation of blood flow which produces such systemic effects.

**Definitions** - The definitions presented here are those adopted by the Adhuc Committee of the American College of Obstetricians and Gynecologists.

**Gestational edema** - This is defined as more than one plus of edema after 12 hours of bed rest or weight gain of 5 pounds or more in one week.

**Gestational proteinuria** - This is defined as proteinuria in pregnancy without evidence of hypertension, renal disease (vascular or infective) or edema.

**Proteinuria:** This is an important sign of pre-eclampsia. Proteinuria is usually defined as the presence of 500 mg or more of protein found in 24 hour urine collection or a protein measurement of 2+ or greater in a random urine specimen.

It is important to note that the degree of proteinuria may fluctuate widely over any 24 hours period even in severe cases. Random sampling is thereby somewhat less accurate.

**Pre eclampsia** - This is defined as hypertension with proteinuria and/or edema

induced by pregnancy greater than 20 weeks gestation (or earlier if extensive hydatidiform change is present in the placenta).

**Eclampsia:** This is defined as disease in which fits occur with pre eclampsia.

**Chronic hypertensive disease:** Chronic hypertensive disease is the presence of persistent hypertension, of whatever cause, before pregnancy or before the twentieth week of gestation, or persistent hypertension beyond the forty second postpartum day.

**Superimposed preeclampsia or eclampsia:**

Superimposed preeclampsia or eclampsia is the development of preeclampsia or eclampsia in a patient with chronic hypertensive vascular or renal disease. When the hypertension antedates the pregnancy, a rise in the systolic pressure of 30 mm Hg, or a rise in the diastolic pressure of 15 mm Hg, and the development of proteinuria, edema or both are required during pregnancy to establish the diagnosis.

**Unclassified hypertensive disorders:**

Unclassified hypertensive disorders are those in which information is insufficient for classification.

**Pre eclampsia:**

Gestational hypertension is the second most common cause of maternal mortality. The prognosis for mother can be considerably improved by adopting proper preventive measures during pre-natal, natal and post natal period. The fetal health however is placed in considerable jeopardy in most cases.

In normal circumstances, this condition is unique to human pregnancy and is common in the primigravida. When it occurs in multigravida there are usually other underlying predisposing factors, such as diabetes mellitus, multiple pregnancy, fetal hydrops, hydatidiform mole and chronic vascular disease.

**Incidence:** The incidence of preeclampsia is about six to seven percent among obstetric patients admitted to hospitals in the United States, while eclampsia is encountered once in every 2000 pregnancies.

There were 600 cases of preeclampsia (20 percent) and ten cases of Eclampsia in 3000 deliveries at Lahore General Hospital over three years period. These figures show that standards of obstetrical care in Pakistan need considerable improvement.

**Pathological changes:**

**Uteroplacental changes:** There is decrease in perfusion at the utero placental junction. Radiosodium disappears more slowly from myometrium and is typically prolonged in late pregnancy in hypertensive women implying diminished perfusion.

**Myometrium:** This is more active both spontaneously and in response to oxytocin therefore induction is more likely to be successful and hyperstimulation is also more likely.

**Placental function:** The decrease in placental perfusion may cause retarded fetal growth. The placental infarcts which are usually present are probably vascular rather than a primary placental event.

**Renal function:** In normal pregnant patients, the urea clearance is 102 to 104 percent of normal in contrast to an average range of 50 to 70 per cent for patient with pre eclampsia. In severe cases, there is decrease in renal blood flow and glomerular filtration rate. Glomerular filtration fraction is also lowered. The resistance of the afferent glomerular arteries is increased. The tubular capacity for reabsorption of sodium appears to be increased. Unless there is tubular or cortical necrosis which may occur in very severe cases. The azotemia is mild and regresses quite rapidly after delivery. Nitrogen retention occurs only when there is oliguria or anuria.

**Renal changes:** During normal pregnancy, both glomerular filtration rate and renal perfusion are elevated above normal non pregnant levels. In pre-eclamptic toxemia, the levels are reduced proportional to the severity of the disease. Usually creatinine and uric acid are slightly elevated. Blood Urea levels are not much affected and have been reported to be of no prognostic or diagnostic value in this disease. However uric acid concentrations have been found to relate better than B.P. level to fetal prognosis.

Sheehan in (1950) described the histology of renal lesion, he reported, "that the glomeruli are 20 per cent enlarged and pointing into tubules. The capillary loops are variably dilated or swollen endothelial cells are swollen with fibrinous deposits. On Electron Microscopy, there is marked vascularization and swelling of capillary endothelial cells without changes elsewhere. Occasional small subendothelial deposits of fibrinoid material may be

seen. IgG and IgM are thought to be present in these deposits along with fibrin and complement material. This is similar to deposits elsewhere e.g. placenta and liver. Tubular lesions are either due to degeneration or precipitation of escaped protein in the tubules. These changes are common but not diagnostic of pre-eclampsia. Casts and haemoglobin in urine are also seen in this disorder.

**Hepatic changes:** What happens to blood flow pattern is not known, but definite changes occur in hepatic function especially with pre-eclampsia and eclampsia. There is delay in brom-sulphthalein (BSP) excretion, and S GOT. Levels are elevated. Hyperbilirubinemia is uncommon. Alkaline phosphatase is elevated but this is placental in origin and does not signify liver damage.

Hemorrhagic necrosis in the periphery of liver lobule is characteristic lesion in fatal cases but biopsy of non fatal cases has also shown the lesion to be present. The lesion is characteristically variable in extent and severity "Periportal necrosis" and subcapsular hemorrhage may occur and are associated with high mortality.

#### **Brain:**

There is no general blood flow reduction but there may be focal hypoperfusion or hyper perfusion. EEG. Shows nonspecific abnormalities for some time following eclampsia. There is a higher familial incidence of EEG abnormalities suggesting a congenital predisposition to eclampsia. Autopsy findings reported in fatal cases include edema, hyperemia, focal anaemia, thrombosis and hemorrhage.

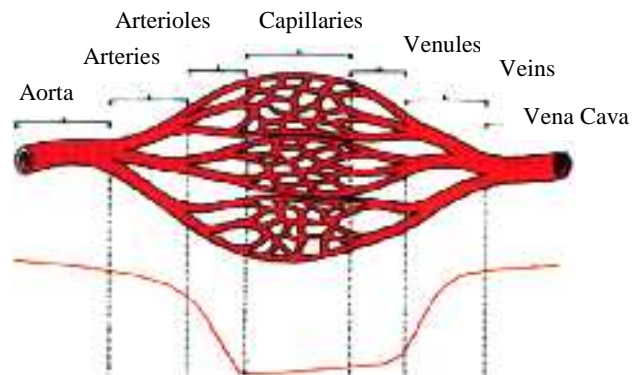
**Pulmonary changes:** Eclamptic fits produce lactic acidemia, Hypercarbia, and consequently hyperventilation. Pulmonary edema is common in fatal cases; heart failure may occur due to circulatory overload. Aspiration of gastric contents may result in pulmonary edema or bronchopneumonia.

**Endocrine changes:** The elevation of renin angiotensin aldosterone system has been reported to occur in case of PET. The aldosterone levels have been postulated to be elevated to combat natriuretic effects of progesterone, but other investigators have found no change in aldosterone levels when compared with progesterone suggesting that this is probably not true.

HCG levels are inconstantly elevated while HPL is inconstantly reduced. Pituitary necrosis has been documented in fatal cases of eclampsia, but this is very rare.

**Blood chemistry:** In pre-eclampsia, serum potassium, sodium, calcium and chloride are usually within the normal range. Although serum sodium may fall below 130 mEq. Per liter, osmolality is normal and the relative sodium level per liter of diminished serum water is essentially normal patients do not have physiologic hyponatremia. Blood sugar, plasma bicarbonate and pH are within the limits of normal pregnancy. The pH is often reduced immediately after a convulsion, but tends to return to normal when adequate ventilatory exchange is re-established. Uncompensated acidosis may ensue when there are repeated convulsions. Increase in the tubular reabsorption of urate is the result of decreased clearance and causes hyperuricemia in patients with pre-ecl-

ampsia. The concentrations of creatine and creatinine are normal. Total serum protein, the albumin-globulin ratio and the osmotic pressure of the plasma are reduced in normal pregnancy and tend to be further reduced in preeclampsia except in the most severe cases when hemoconcentration occurs. In normal term pregnancy there is a substantial increase in the concentration of plasma fibrinogen. In patients with pre-eclampsia, levels of fibrinogen are further increased. Coagulation time, which is usually shortened in normal pregnancy, is decreased further in preeclampsia. Clotting times of less than one minute have been observed in some patients with eclampsia. Electrolyte levels are normal except in cases where vigorous diuretic therapy has been given, sodium has been restricted or high water load with oxytocin has been given which promotes an antidiuretic effect. Bicarbonate is reduced in cases of eclampsia where the body attempts to compensate metabolic acidosis produced during the eclamptic fit.



**Fig4.3: Shows arterio venous anastomosis at peripheral level (Capillary)**

**Hematological changes:** In normal pregnancy both circulating plasma and red cell volumes are increased. But with

severe pre eclampsia and eclampsia there is reduction in the plasma volume. The hypervolemia is reduced following both vasoconstriction and perhaps to some extent, hypoproteinemia. This means that values in hypertensive patients are significantly depressed when compared to normotensive patients. There is a decrease in RBC mass but only in cases of severe hypertension.

**Alterations in coagulation:  
mechanism:**

Changes suggestive of disseminated intravascular coagulation and red cell destruction occur at times in preeclampsia. The rate of RBC destruction varies and evidence of hemolysis usually clears promptly after delivery.

**Clinical features:** The symptoms in pre-eclamptic toxemia are generally a late occurrence, therefore early detection is necessary to prevent progression of this disease further. The symptoms include headache, visual disturbances, puffiness of eyelids and fingers.

**Edema:**

Most normal pregnant women can be shown to have postural edema of the lower extremities. This disappears after bed rest or merely by elevating the legs for a brief interval. A weight gain exceeding 500 gm (0.5 Kg) in one week signifies acute water retention and may be a manifestation of occult edema.

Pitting edema of the abdominal wall, face, hands and sacral area indicates abnormally excessive retention of water. Sudden and excessive weight gain is an important sign. Gain of 0.5 Kg per week is accepted as normal but excess of 1 Kg

per week or 3 Kg per month is considered abnormal. Steady weight gain is acceptable in most instances but sudden increase should be evaluated carefully. The fluid retention occurs before the development of edema.

Dependent edema of the lower extremities appears to be universal in pregnancy and is based on mechanical factors relating to gravity, increased venous pressure, and lymphatic obstruction. These factors do not apply for edema appearing in face and the hands.

**Proteinuria** - Great variations in patient to patient and hour to hour suggest that the problem is related to vasospasm and may be absent or minimal in early pre-eclampsia. This almost always follows hypertension but can follow excessive weight gain. In many normal pregnant women, there is a trace or more of protein in voided specimens of urine. This is associated with orthostatic albuminuria or contamination of the specimen by vaginal discharge. Determinations of total protein in 24 hour collections are required for accurate evaluation. Although limits of normal are arbitrarily designated, it is generally agreed that the maximum daily excretion of protein should not exceed 300 mg in normal gravidas. Appearance of protein in the urine is the most common manifestation of renal disease, there is general clinical agreement that proteinuria in pregnancy is ominous. However, as noted above, protein may be found in the urine of normal gravidas. The quantity of protein in the urine fluctuates widely and rapidly with time. Certain circumstances tend to enhance the amount of protein that appears in the urine, including violent exercise, hard work, and exposure to cold, cold



showering and in a number of autoimmune and hypersensitive states. Orthostatic or postural proteinuria occurs in 5 to 20 per cent of young adults. Vaginal discharge or bleeding readily contaminates urine specimens that are obtained casually and will yield falsely high levels of protein. The need for clean, midstream voided or a catheterized specimen is therefore strongly advocated. This can help in avoiding erroneous result due to contamination. However, when protein in excess of 500 mg is discovered in 24-hour urine specimen the protein urea is considered pathologic.

### **Hypertension:**

An elevation of 30 mm. Hg or more in the systolic and 15 mm. Hg or more in the diastolic pressure is considered abnormal in pregnancy regardless of the absolute levels observed. Levels in excess of 140 mm. Hg systolic and/or 90 mm. Hg diastolic by convention are hypertensive levels in pregnant women. The blood pressure must be abnormal on at least two occasions with at least a six-hour interval between the two determinations, before a diagnosis of hypertension in pregnancy is definitely made.

### **Stages of preeclampsia:**

The disease may be mild, moderate and severe. The differentiation of mild, moderate and severe is not always possible. However the student will come across three distinct groups. One in which the disease can remain mild, second in which the disease can be checked by therapy and third in which the disease is only checked by delivery. This is the reason why boundaries between mild, moderate and severe form

of disease continue to remain blurred and purely arbitrary.

### **Severe pre eclampsia:**

Pre eclampsia is regarded severe when one or more of the following features are detected.

1. Blood pressure of at least 160 mm Hg systolic or 110 mm Hg diastolic on two occasions at least 6 hours apart while the patient is at bed rest.
2. Proteinuria of at least 5g per 24-hours, or 3+ to 4+ by semi-quantitative assay.
3. Oliguria (24-hour urinary output less than 400 ml). Cerebral or visual disturbances such as altered consciousness, headache, scotoma, or blurred vision.
5. Pulmonary edema or cyanosis.
6. Epigastric Pain.

These criteria for defining severe pre-eclampsia were adopted by both the Committee on Terminology of the American College of Obstetricians and Gynecologists and the American Committee on maternal Welfare.

In practice, however, we do not wait six hours between diastolic blood pressure readings of greater than 100 mm Hg before taking action, to reduce the blood pressure for presumed severe PET.

**Headache:** This is a late sign and often forerunner of eclampsia. Headache is often frontal but may be occipital. It is often resistant to analgesic agents.

**Epipastic pain:**

It is also a late symptom produced by stretching of the liver capsule due to hemorrhage under neath it. Imminent convulsions can occur in these patients. These may be due to hemorrhage but central origin of these convulsions can not be ruled out.

**Visual disturbances** - These vary from slight blurring of vision to blindness. Probably "retinal arteriolar spasm, ischemia, edema, and perhaps even retinal detachment occur. Generally the prognosis as regards recovery of vision is good. Hemorrhage and exudates are rare and usually indicate underlying chronic hypertensive disease.

**Diagnosis** - This is usually made by analysis of clinical features and laboratory investigations.

**Differential diagnosis:**

This condition must be carefully differentiated from the chronic renal disease, non gestational hypertension and other incidental causes such as adrenal, thyroid and vascular problems. The incidental causes will be discussed first.

**Pheochromocytoma:**

This is a tumor of the chromaffin tissue, which secretes catecholamines. Nor adrenaline is the main hormone produced, however adrenaline is also produced.

This is a tumor of adrenal gland, but sometimes it may occur at any site along the sympathetic chain. It is responsible for hypertensive disease in pregnancy in less than 0.5 per cent of all cases.

The characteristic features which distinguish this condition from gestational hypertension include; paroxysmal or sustained hypertension which is accompanied by palpitations, sweating, pallor and headache. Diagnosis is usually based on history of paroxysmal hypertension, and its association with multiple neuro fibromatosis. Clinically abdominal examination may reveal a supra renal mass. Radiologically kidney may be found displaced and intravenous pyelography may also be helpful. In laboratories where retro peritoneal air insufflation or aortography can be done, diagnosis can be made with the help of these measures. However, the most reliable means of diagnosis is based on the measurement of level of free catecholamines in the urine. Similarly urinary metabolites such as Venyl Mandelic Acid can help to make the diagnosis. These values are elevated.

The management of pregnancy complicated with pheochromocytoma depends upon period of gestation. If the pheochromocytoma is discovered when the fetus is 36 weeks, the tumor should be removed in conjunction with elective cesarean section. However, if the tumor is found earlier in pregnancy, surgical removal after adequate cortisol coverage is the treatment of choice.

Considerably high maternal and fetal mortality is associated with this condition.

**Coarctation of the aorta** - Coarctation of the aorta is commonly found distal to the origin of left subclavian artery. Physiological changes produced by coarctation are, decrease in pulse pressure below the site of lesion, while

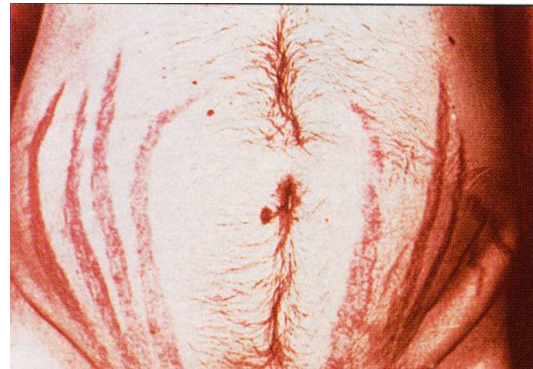
increase in blood pressure above the coarctation. The blood pressure in the upper half of the body is raised, while the pressure in the femoral vessels is diminished. When pregnancy is complicated with this lesion, it can be associated with a very high perinatal mortality. Maternal mortality is not significantly affected. Diagnosis can be made by noting the pulse in radial and femoral arteries at the same time. The pulse wave in the femoral artery is considerably varied when compared with the radial. The pressure recorded in femoral artery is considerably less than the brachial. The blood vessels in the interscapular region are easily visible, they are collateral vessels. A bruit may be heard over the collateral vessels. Similarly a murmur can be heard in the scapular region.

Chest x-ray can confirm the diagnosis. The shadow of double aortic knuckle seen on X ray is due to dilated subclavian artery and descending aorta. If aortography is available, it can also be helpful. Coarctation of the aorta can be corrected surgically during pregnancy. Only an experienced vascular surgeon can help in dealing with this situation and lowering the perinatal mortality considerably.

#### **Renal artery stenosis:**

This is not a common condition. When all other causes of hypertension have been excluded, renal artery stenosis should be suspected; especially if the patient has wide spread arterial disease and a bruit is heard on the abdomen or loin. Causes of this condition include atherosclerosis, dissecting aneurysm of the aorta or fibro muscular hyperplasia. Pressure from neighboring tumors or

cysts can also produce renal artery stenosis. Similarly thrombosis or embolism of the renal artery may be responsible. Diagnosis can be made by intravenous pyelography. The affected kidney will be smaller. The contrast medium in the affected kidney is very dense because its excretion is delayed. For definite diagnosis, aortography or renal arteriography, both of which are contraindicated in pregnancy, can be very helpful.



**Fig4.4: Shows stria marks on the abdominal wall.**

**Cushing's syndrome** - It results from excess of glucocorticoids produced by the adrenal tumor. This could also be due to pituitary dysfunction where excessive ACTH is produced. Diagnosis can be made from detection of characteristic features.

The patient presents with central obesity, round moon face, buffalo neck, hirsutism, and acne. Purplish striae are present on the abdomen. The masculinizing features are due to excessive androgens.

Laboratory investigations such as increased levels of cortisol and 17 hydroxy steroids, along with abnormal glucose tolerance test, confirm the diagnosis. These patients often have amenorrhea and infertility, therefore pregnancy

rarely occurs. However, if pregnancy does occur adrenalectomy should be performed during pregnancy.

### **Thyrotoxicosis:**

Pregnancy associated with this condition can be differentiated from other causes of hypertension by careful history and physical examination. Patient may present with goitre, exophthalmos and pre-tibial myxedema.

This syndrome is often described as Grave's disease, sometime thyroid carcinoma or TSH secreting pituitary adenoma can produce such changes. There is often history of weakness, fatigue, insomnia, weight loss, palpitation, dyspnea, increase in appetite and diarrhoea.

Patient gives anxious look, her skin is hot and moist, eyes appear prominent, and thyroid is usually en-larged. Systolic bruit may be heard over the gland. Systolic murmur is usually audible. Diagnosis can be made by measuring the free T 3 and T 4 in serum as discussed in thyroid disease in pregnancy. "

### **Chronic renal disease:**

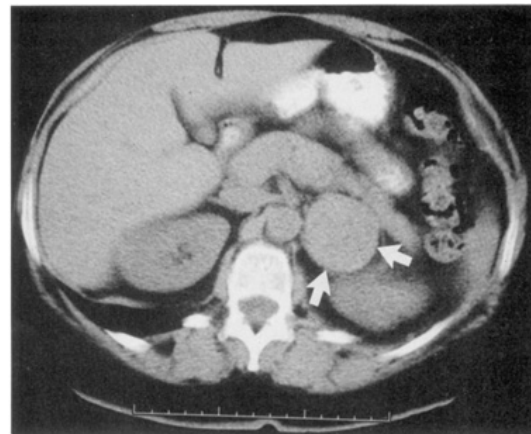
The association between preeclampsia and chronic renal disease is strong. The renal function is frequently altered in these patients and the clinical diagnosis is not usually difficult to establish.

Marked decline in glomerular filtration rate, elevation of plasma creatinine and urea nitrogen levels, and the presence of significant proteinuria or casts in analysis of urinary sediment are all helpful in establishing the diagnosis of chronic renal disease.

The diagnostic criteria for preeclampsia have already been outlined. The student is advised to use great care in separating these two conditions with widely different etiology and prognosis.

### **Chronic hypertension:**

Chronic hypertensive disorders, whatever their cause may be, probably predispose to the development of superimposed pre-ec-lampsia and can create a difficult problem for differential diagnosis and management, especially if the woman first presents herself for obstetric care after the 20th week of gestation.



**Fig4.5: -Shows Ct scan section showing Kidney disease**

The diagnosis of chronic hypertension can be based on either of the following criteria.

1. A history of hypertension (140/90 or greater) antedating pregnancy.
2. Discovery of hypertension (140 /90 or greater) before the 20th week of gestation and/or its persistence indefinitely following delivery. Additional suggestive

historical factors that can help make the presence of hypertension in a previous pregnancy.

When the patient is not seen until after the 20th week of gestation, the diagnosis of chronic hypertension may be difficult to make because of the well documented decrease in blood pressure that may occur during the middle and early third trimesters of pregnancy in normotensive as well as in the majority of chronically hypertensive pregnant women. A patient with chronic hypertension who is seen for the first time at the 20th week of pregnancy may appear normal, early in the third trimester. However, the patient's blood pressure often returns to its former hypertensive level, presenting a diagnostic problem for the physician who is called on to differentiate this chronic hypertensive state from acute pre-eclampsia. Some clinical findings that might suggest the presence of underlying chronic hypertension and thus help in differentiation are;

1. Hemorrhages and Exudates seen 'on fundoscopic examination.
2. Blood urea nitrogen levels above 20 mg/100 ml.
3. Plasma creatinine levels above 1 mg/100 ml.
4. Presence of chronic disease such as diabetes mellitus and connective tissue disease.

In chronic hypertension, one must consider the following variety of underlying conditions, i.e. normal renin

hypertension, low renin hypertension, high renin hypertension, and renal vascular disease, coarctation of the aorta,

primary aldosteronism and pheochromocytoma. A number of renal lesions such as; Glomerulonephritis which may be acute or chronic, nephrotic syndrome which may occur in several other diseases, Pyelonephritis may again be acute or chronic, lupus erythematosus, with glomerulitis or with glomerulonephritis, scleroderma with renal involvement, polyarteritis nodosa with renal involvement, acute renal insufficiency, polycystic disease of the kidney and diabetic nephropathy, should be kept in mind as factors responsible for hypertension. It must be remembered that chronic hypertension is a dangerous disease whether the patient is pregnant or not as it may lead to associated cardiovascular diseases such as cardiac decompensation and cerebrovascular accidents. Intrinsic renal damage may also result from chronic hypertensive disease, or the hypertension itself may be the result of underlying chronic pyelonephritis or chronic glomerulonephritis.

Additional dangers to the patient who has chronic hypertension include the risk of developing superimposed preeclampsia and the risk of abruptio placentae. Placental abruptio has been reported to occur in 5 to 10% of all chronically hypertensive pregnant women. The fetus of the patient with chronic hypertension is also subjected to additional risks, including growth retardation and unexplained intrauterine death.

**Angiotensin test:** An angiotensin II infusion might also help in

differentiating between chronic hypertension and pregnancy induced hypertension when a patient becomes hypertensive in the early third trimester. Patients, who require less than 7 mg of angiotensin II per kilogram of body weight per minute to elicit a pressure response at this time, can be diagnosed as case of preeclampsia. The student must be cautioned here that in normal clinical practice such tests can not be done, therefore no attempt should be made to perform this test. Such cases should be referred to a referral centre equipped with these diagnostic facilities.

### **Chronic hypertension with superimposed pre eclampsia:**

Chronic hypertension with superimposed pre-eclampsia is the result of acute aggravation of the already existing underlying hypertension, with the rapid development of edema and proteinuria. The fundoscopic findings showing re-tinal sheen, hemorrhages, and exudates may become more prominent. There is often a quick progression to eclampsia, which may develop before the 30th week of gestation. Strict diagnostic criteria are sometimes difficult to establish but depend on the following.

When documented evidence is available that the patient had chronic hypertension along with the evidence of a superimposed acute process, as demonstrated by elevation of systolic blood pressure by 30 mm Hg or diastolic blood pressure by 15 to 20 mm Hg above the base line on two occasions at least 6-hours apart. Proteinuria and or edema as observed in women with pre-eclampsia are also present. The development of any one of the three signs of superimposed preeclampsia, that

is, worsening hyper-tension, proteinuria, or edema, may al-one if severe enough, justify the diagnosis of superimposed preeclampsia. However, the diagnosis should re-quire the presence of accelerated hyper-tension accompanied by at least one of the two other signs.

If the gravida with chronic hypertension requires less than 7 mg/kg/minute of angiotensin II to elicit a 20 mm Hg increase in diastolic blood pressure, it is likely that she has superimposed pre-eclampsia.



**Fig4.6: Shows brain vessels exposed.**

### **Latent or transient hypertension:**

The category of 'Intent or transient hypertension includes only those patients whose transient elevations of blood pressure are observed during labor or in the early puerperium.

Their illnesses may range widely from mild preeclampsia to latent or early vascular hypertension.

### **Management of pregnancy induced hypertension:**

The management includes prevention and therapeutic treatment.

**Prevention** - The student must realize that there is very high fetal and maternal mortality associated with this complication, especially if eclampsia is allowed to develop. Eclampsia is preventable if the disease process leading to this complication can be identified early and treated in very early stages. The disease is asymptomatic in its early stages therefore one must look for clues of pre-eclampsia in the high risk group of patients such as the primi gravidas, those with family history of eclampsia/pre-eclampsia. Women with family history of chronic hypertensive disorders, in multiple pregnancies and those with molar pregnancy. Rapid weight gain in the latter half of pregnancy and an upward trend of blood pressure should forewarn the physician, that the patient may develop pregnancy induced hypertension. Good antenatal care, where such screening is constantly reinforced can reduce the incidence of severe pre-eclampsia and should be able to abolish the development of eclampsia altogether. The main objectives of modern therapy are to prevent convulsions and to deliver a healthy baby, inflicting minimal trauma to the mother and prevent residual hypertension.

A number of studies in the literature have shown that attempts to improve nutrition have resulted in decreasing PET, prematurity and peri-natal mortality rates. Excessive weight gain alone is not associated with a high complication rate and pregnancy is surely not the time to carry out weight reduction programmes. Insufficient protein intake is harmful both to the fetus and the mother. 2,200 calories usually satisfy the needs of both and less than this can be dangerous in some cases. Weight gain has been shown to

positively correlate with birth weight of the baby. Inadequate caloric intake exposes the fetus at risk to hypoglycemia and ketosis in the mother.

#### **Ambulatory treatment:**

There is little place for ambulatory treatment in any but the mildest degrees of pre eclampsia. Bed rest is mandatory; patient should be advised to lie in left lateral position. It is best accomplished in well controlled hospital surroundings. Sedation is an important adjuvant to bed rest. It relieves anxiety component and reduces physical and neural activity. In addition to the potential of lowering arterial pressure, bed rest may also reduce extravascular fluid volume by its natriuretic and saluretic effect and increase uteroplacental blood flow by decreasing the demands of activity related organs and structures. In a number of instances a sharp increase in plasma estriol concentrations with bed rest alone has been reported.

**Bed rest** - The patient is encouraged to lie in left lateral position, high protein and caloric diet should be given.

**Sedation** - There are a number of sedatives available in the market but the time honored barbiturate, the Phenobarbitone remains the drug of choice in our centre.

**Phenobarbitone** - This drug is most commonly used. Its long term use has shown that it is safe to give during pregnancy. The dosage is 120 to 240 mg per day in mild to moderately severe cases of PET. Adverse effects of this drug include sleepy babies and sleepy mothers. There is a reduction of Vitamin K dependent coagulation factors in some

fetuses. Recent studies indicate that it is useful in preventing neonatal jaundice since it helps in early induction of liver enzyme system necessary for conjugation of bilirubin.

### **Monitoring of pregnancy and delivery:**

Constant evaluation of fetal growth, his wellbeing and maturation should be carried out routinely in all cases. Monthly sonograms for increase in fetal biparietal diameter can be reassuring. Similarly estriol should be measured. Weekly oxytocin challenge tests and the use of amniocentesis may also provide important information regarding intrauterine status of the fetus. Amniocentesis for both the presence of meconium and lung maturation should be started by the 35th week and delivery accomplished as soon as lung maturity is confirmed.

### **Hospital management:**

When B P. is greater than 140/90; or when there is increase of 30 mm Hg. in pre-pregnancy systolic blood pressure and 15 mm Hg in the diastolic, the patient should be admitted to hospital for treatment. She should be weighed on admission and then daily, to note trend of fluid retention. Blood pressure should be recorded four hourly daily. The urine should be screened for protein, quantitative analysis in 24 hour urine specimen is better. Creatinine clearance should be checked if renal involvement is suspected.

Management generally varies with severity of disease, similarly course in hospital depends on duration of gestation and condition of the cervix. The underlying disease process does not

abate until after delivery, but in general three groups emerge; (1) those who settle on bed rest. (2) Those needing antihypertensives before settling. (3) Those who settle only after delivery. The two most important aspects of management of this complication include control of convulsions and conduct of delivery as soon as control is obtained. The patients with hypertension can be broadly divided into 3 groups.

**Group I:** The recognition of hypertensive, prior to 36 weeks means, at least several weeks of medical management in anticipation of delivery. There fore treat the patient as in ambulatory management.

### **Group II:**

When hypertensive syndrome develops at 36 weeks or later, it presents a different type of challenge to the obstetrician. The objectives of therapy in these patients should be rapid stabilization, confirmation of fetal maturity and delivery. If the diastolic pressure with bed rest is persistently over 110 mm Hg, an antihypertensive drug should be added very early in the management. The most frequently used antihypertensive agent is methyldopa (Aldomet) this is quite practical agent for long term therapy, but for the short term acute management of hypertension, hydralazine (Apresoline) is given parenterally. It is also relatively easy to titrate its dose and maintain its effect. If long term therapy is indicated, oral hydralazine may be equally effective. Recently hydralazine has been added to Propranolol beta blocking agent for its independent hypotensive action and to relieve some of side effects of hydralazine. This therapeutic meddling is



counterproductive to the overall management objectives. Propranolol blocks the positive inotropic and chronotropic effect of hydralazine upon the heart and the combined therapy prevents increase in uterine blood flow. A less satisfactory alternative antihypertensive agent is the rauwolfia compound, Reserpine, which can be given both parenterally and orally with good effect. The side effects such as nasal congestion in the neonate are manageable with good neonatal nursery care. The maternal risk of catecholamine depletion in the event of a general anaesthetic is also manageable in competent hands.

**Group III:** The emergency management of an acute hypertensive crisis presents the greatest challenge to the obstetrical team. The patient with diastolic pressure of 115 mm Hg may very well present with massive peripheral edema and impending or frank pulmonary edema. In these patients aggressive medical management in an intensive care setting is directed toward maternal survival and prevention of fetal sequelae. Management may progress on several fronts at the same time hydralazine in appropriate doses should be started at once by intravenous route. Pulmonary edema should be treated by aggressive management such as intra-venous infusion of frusemide, in doses of 40 to 80 mg. The fetal prognosis in these acute situations is generally very poor. The rapid lowering of the arterial pressure, for maternal indication, may further compromise uteroplacental perfusion.

**Fulminating disease** - When the B.P is more than 160/110 and edema and proteinuria along with headache and epigastric pain are present, the danger of oliguria and imminent convulsions

becomes very real, therefore anti-convulsant drugs should be given to avoid convulsions. Antihypertensive agents to avoid intracranial hemorrhage and delivery should be planned without delay to deliver live infant in such cases.

#### **Follow-up:**

For patients with BP stabilized by management, follow up should normally be three monthly (interval should not exceed 6 months), at which the following should be assessed by a trained nurse:

- \* Measurement of BP and weight
- \* Reinforcement of non-Pharmacological advice
- \* General health and drug side-effects.
- \* Test urine for proteinuria (annually)

High risk pregnancy units which are equipped with intensive care facilities for mother and the neonate can help improve results of maternal morbidity and neonatal survival.

Usually rapid improvement in patient's blood pressure occurs following delivery but occasionally there may be transient worsening. Fits may occur within 24 hours of delivery but rarely thereafter, therefore, the patient must be observed and treated at least for 24 hours after delivery.

#### **Termination of pregnancy:**

It may be justified in milder cases to temporize with premature babies. The chance of survival of low birth weight fetus is greater in neonatal intensive care unit than if left in utero. If it is decided

to procrastinate all available methods of rapid digitalization. Liberal use of pethidine, oxygen and suction is needed for such patients and should be administered judiciously. Foley's catheter should be introduced and fluid and electrolyte balance maintained.

Fetal well being assessment should be employed. The time of induction will depend upon fetal maturity and state of cervix. One may be inclined to induce a labour earlier if the cervix is favorable. In cases with unfavorable cervixes the dangers of caesarean section should be weighed against continuation of the pregnancy.

**Thiazide diuretics** - These drugs are potent diuretics. The antihypertensive action of these drugs has been ascribed to an initial reduction in extracellular and plasma volume and total exchangeable sodium with a concomitant reduction in cardiac output. The limited hypotensive effect achieved, however, may be blocked subsequently by either salt administration or plasma volume expansion. In pregnancy the use of diuretics carries an increased risk of sodium and potassium depletion. Its use is associated with elevated plasma renin levels and reduced placental clearance of dehydro epiandrosterone sulfate. Common maternal side effects are hyperuremia, hypokalemia, alteration in glucose metabolism and acute pancreatitis. Fetal side effects reported are hyponatremia and thrombocytopenia.

**Hypotensive agents:**

**methyldopa (Aldomet)** - Methyldopa interferes with chemical neural transmission at the post ganglionic nerve endings and results in reduced peripheral arteriolar resistance. This is accom-

plished by the drug acting as a competitive inhibitor in the synthesis of catecholamines its conversion to alpha methyl norepinephrine and subsequent displacement of norepinephrine stores at the adrenergic post ganglionic nerve endings and alteration of the norepinephrine binding sites. Its release in place of norepinephrine acts as a false transmitter, thereby impairing the intended pressor effects. The end result is a lowering of the diastolic and systolic pressure in both the standing and supine positions. Regional blood flow to the kidneys and uterus appear to be maintained in the presence of the hypotensive action despite the fact that a reduction in cardiac output has been reported. Methyldopa has been observed to reduce plasma renin levels. The major side effects are sedation, sodium retention, depression and a reported 20% positive direct Comb's test. Methyldopa is a good choice for long-term antihypertensive therapy in pregnancy.

**Hydralazine (Apresoline)** - This drug reduces arteriolar resistance. Hydralazine may also elicit a central effect at the vasomotor centre resulting in reduced sympathetic tone. The predominant effect of the drug is on the arterioles rather than veins. This results in a greater diastolic than systolic reduction in arterial pressure and produces minimal postural hypotension.

In addition to its hypotensive effect, hydralazine also has a positive inotropic and chronotropic effect upon the heart, which results in an increased heart rate and stroke volume. Hydralazine produces increase in cardiac output and blood flow to the cerebral, coronary, splanchnic, renal and uterine circulations. The direct vascular effect of hydralazine,

along with the augmentation in cardiac output and uterine blood flow, makes it a good selection for the treatment of gestational Hypertension.

If the diastolic blood pressure exceeded 110 mm Hg, Hydralazine (Apresoline) can be administered as follows. A test dose of 5 mg is injected as a bolus intravenously and the blood pressure monitored every 5 minutes. If the diastolic pressure is not lowered to about 100 mm Hg in 20 minutes, a 10 mg dose is similarly administered, and its effects are monitored. This dose can be repeated until the diastolic blood pressure is lowered to about 100 mm Hg.

#### **Rauwolfia compounds (Reserpine) –**

The rauwolfia compounds interfere with chemical neurotransmission at the post ganglionic adrenergic nerve endings and results in decreased peripheral vascular resistance. The peripheral effect is a result of depletion of terminal post ganglionic catecholamine stores and reduced catecholamine uptake, leading to maximum catecholamine depletion in 24 hours. A second, though less effective, hypotensive mechanism may be a direct action on the vasomotor center of the brain, secondary to depletion of CNS catecholamines. Because of the slow restoration rate of tissue catecholamines, the antihypertensive effect of Reserpine may last several days after the final dose.

Increased parasympathetic activity can result in bradycardia, nasal congestion, increased salivation, cramps and diarrhea. Other maternal side effects are depression, increased water and sodium retention, sedation and decreased plasma renin levels. The major fetal com-

plication is neonatal respiratory difficulty secondary to nasal congestion. Despite the side effects and the anesthetic risks of catecholamine depletion, Reserpine is a good alternative antihypertensive agent for both long-term and acute management of gestational hypertension.

**Propranolol (Inderal)** - Inderal is a beta adrenergic blocking agent which decreases the force and frequency of myocardial contractions. This results in reduction in cardiac output and an initial elevation in peripheral vascular resistance, which decreases with continued drug usage. Chronic administration of propranolol can cause a reduction in plasma renin, possibly due to its direct effect upon the kidneys. The result of treatment is a decrease in systolic and diastolic pressure, without orthostatic hypotension. Reported maternal side effects have been nightmares and drowsiness. Use of propranolol in asthmatic patients may lead to aggravation of bronchospasm.

Beta blockade and the lowering of cardiac output, have no place in the management of hypertension during pregnancy.

**Eclampsia** - This is defined as disease in which fits occur with pre eclampsia.

**Clinical features** - In this condition both clonic and tonic convulsions occur, there is often severe hypertension present. The condition may occur during antepartum, intrapartum or postpartum period. Most frequently the complication occurs in the last trimester and near term. Almost all cases of postpartum eclampsia occur within 24 hours after delivery 24 hours is the usual limit given though some

cases are said to occur up to 1 week after delivery. Frequently, poor antenatal care and ignoring of premonitory symptoms i.e. apprehension, excitability, hyperreflexia precede convulsion. The description of the fit is typically like grand mal epilepsy. It is followed by coma of varying duration. Fits may recur at short or long intervals. Status epilepticus picture may supervene. Coma or, more usually, rapid convulsive episodes may terminate fatally. Tachypnea with acidosis and pyrexia up to 39.44 Celsius is often present. Proteinuria, oliguria or even anuria may result in some cases. Hemoglobinuria, passage of casts due to renal involvement can also occur. Edema is usually massive. Diuresis after delivery is usually a good prognostic sign. Edema and proteinuria disappear within a week after delivery. Blood pressure usually returns to normal within 2 to 6 weeks from delivery. Persistence of high blood pressure beyond this time suggests chronic hypertension. In antepartum eclampsia, labour may be precipitated similarly, intrapartum eclampsia may shorten labor. "Inter current eclampsia" has been described where the patient does not go into labour but returns to normality. Recurrent eclampsia is also a strong possibility and can occur. Fatalities usually result from pulmonary edema which must be considered a grave prognostic sign. Other signs of cardiac failure are rising pulse rate, cyanosis, and falling blood pressure. Massive cerebral hemorrhage may result in hemiplegia. Post eclamptic psychosis rarely occurs and remains for 1 to 2 weeks. Post-eclamptic visual problem such as blindness is usually the result of retinal edema but has good prognosis, since complete recovery often takes place.

### **Differential diagnosis of eclampsia -**

Convulsions and coma are common features in eclampsia and a number of other medical disorders, completely unrelated to pregnancy. It is important that it should be differentiated from other clinical disorders where convulsions and coma occurs. Convulsions result due to central nervous system dysfunction. They are usually sudden in onset and commonly followed by state of unconsciousness. Epilepsy, encephalitis, cerebral tumor, acute porphyria, ruptured cerebral aneurysm, uremia, diabetic coma or even hysteria may simulate this condition.

Post epileptic coma may last for few minutes after a single epileptic attack or persist for hours between repeated attacks of status epilepticus. Past history of epilepsy is helpful. Vital signs and blood pressure are usually normal.

### **Sub arachnoid hemorrhage:**

This usually occurs in young adults from rupture of the congenital aneurysm. The onset is sudden and there is history of severe headache, neck stiffness, nausea and vomiting. Examination of spinal fluid obtained by lumbar puncture will reveal the presence of blood.

**Hysterical fits:** These occur in the hysterical subject in the presence of the audience. The tongue is not bitten, similarly there is no incontinence of urine. The Plantar response is flexor in contrast to extensor. These features can help differentiate this condition from epilepsy.

**Epilepsy:** This condition is characterized by a premonitory aura. There is loss or disturbance of

consciousness, tonic and/or clonic movements of extremities, trunk and face and incontinence of urine and feces. The family history or patient's past history may be helpful in separating this from eclampsia. The signs such as oedema, proteinuria and hypertension are distinctly absent in cases of epilepsy.

**Cerebral tumour** - When convulsions are reported with previous history of headache, nausea and projectile vomiting; presence of papilloedema and raised cerebrospinal pressure are very suggestive features of cerebral tumor. Final diagnosis will depend on demonstrating the mass by C.T. or other type of brain scan.

#### **Head injury:**

Inspection and palpation may reveal bruises and depression of the skull. There may be leakage of spinal fluid from nose or ear.

Sub conjunctival hemorrhage usually indicates the fracture of anterior or middle fossa. Radio-logical evidence of fracture of skull will confirm the diagnosis.

#### **Vascular accidents:**

Cerebral thrombosis is a common cause of coma. There is usually some indication of a local lesion such as facial asymmetry deviation of eyes or undue flaccidity of arm and leg on one side.

Cerebral Hemorrhage usually results in fatal coma. The blood pressure is usually high, the pulse is slow, the left ventricle is enlarged and hypertensive retinopathy may be present.

#### **Intracranial infections**

**Meningitis** - Any form of meningitis can cause convulsion. High grade fever, headache nausea and vomiting with neck rigidity are highly suggestive. When leucocytes and organisms are found in the CSF, the diagnosis is definite.

Fulminating Meningococcal Meningitis may cause coma and death within 24 hours. The temperature is usually elevated, stiffness of neck and fine purpuric rash is common. Diagnosis is made by lumbar puncture which reveals cloudy fluid containing organism and polymorph leucocytes.

**Cerebral malaria** - This tropical disease can cause convulsions, coma and fever. The diagnosis will depend on the history of exposure to the disease and presence of parasites in the peripheral blood film.

Cerebral malaria is an important cause of sudden coma. The temperature may be normal or high. The spleen may or may not be enlarged.

#### **Tetanus:**

In cases where there is previous history of abrasions or wound of skin, tetanus needs to be ruled out. The earliest manifestation in tetanus is trismus or tonic spasm of the masseter muscles. This is followed by tetanic spasm of other muscles and finally leads to episthotonos and risus sardonicus. During the interval of tetanic spasms, the muscles are rigid.

**Hypoglycemic convulsions:** These convulsions tend to occur in the early hours of the day, when a meal has been missed or unwanted physical exertion

has been carried out. There can be history of over dosage with insulin in these cases. Blood and urine sugar and ketone bodies will help in differentiating this condition from eclampsia.

In diabetic, coma the patient is dehydrated and collapsed. Acetone will be smelt in the breath and urine will contain sugar and ketones.

Hypoglycemic coma is marked by collapse, low blood pressure, sweating and low blood sugar. It is result of over dosage of insulin. Careful search of skin for signs of hypodermic injection is essential.

**Uremic coma** - This is marked by dehydration, dyspnea, high blood pressure, hypertensive retinopathy and presence of albumin in urine. The specific gravity of urine is usually in the region of 1010. The blood urea will be much elevated.

**Hepatic coma** - This usually follows a period of prolonged illness. In pre-coma stage, there may be psychosis which is accompanied by flapping tremor. Other features of liver disease such as foetor hepaticus, jaundice or ascites may be present.

**Hypocalcemic convulsion (tetany)** - In this condition, there is paroxysmal tonic spasm of the hands and feet. Hands assume conical attitude with fingers extended at the inter phalangeal joints. They are adducted and slightly flexed at the metacarpophalangeal joints. The thumb is adducted and the palm hollowed. The toes are flexed towards the sole. There is planter flexion and the foot is inverted. When such a convulsion can be produced by arresting the circulation in a limb for 3 to 4 minutes (Trousseau's

sign) or by percussion of the superior motor or facial nerve which will produce spasm (Chvostek's sign) the diagnosis of hypocalcemic convulsion can be confirmed.

### **Poisoning:**

Any type of poisoning may result in coma and convulsions. This may be common finding in countries where quacks and traditional birth attendants use herbal medicines and powders to relieve labour pain. Carbon Monoxide is present in the coal gas and in the fumes given off by any fire or explosion. It unites with blood to form carboxy-hemoglobin, which is cherry red and imparts this hue to complexion of the patient. Spectroscopic examination of blood will confirm diagnosis. Strychnine is an alkaloid which is obtained from nux vomica seeds. This has powerful stimulant effect on the spinal cord. When convulsions are of sudden onset with previous history of good health, poisoning should be suspected. In strychnine poisoning the contractions are violent and are first clonic, later tonic. The whole body is arched backward or bends forward or to the side. It does not commence in the lower Jaw muscles as it does in tetanus. Similarly during the interval, the muscles are relaxed.

**Alcoholism:** The coma is not so deep, there is marked pallor, sweating, and stertorous breathing present. The pupils are dilated; smell of alcohol may be present. Examination of blood will show alcohol content in excess of 300 mg percent.

**Heat stroke** - Hyperpyrexia and absence of sweating are diagnostic features of coma due to heat stroke. Pregnant

women may have to work under the scorching sun in certain countries with very hot climate and they may be brought to hospital in coma. Therapy is directed at eclampsia but the above should be excluded before a firm diagnosis is made.

**Treatment** - This primarily depends on the frequency and number of fits the woman had. Fetal maturity and well-being plays a secondary and minor role in deciding about the time and mode of therapy. When the patient is having fits or had multiple fits, then active intervention is required on emergency basis, irrespective of fetal maturity. In our unit, the patient is admitted to the eclampsia room, which is located at a fairly quiet corner in the ward and equipped with suction apparatus, oxygen cylinder, nasal tubing, face mask, respirator, mouth gag and tongue depressor, oximeter and cardiac monitor. A trolley containing all life saving emergency drugs is also available at the bed side of the patient. At the time of admission, a complete and detailed history is taken. A thorough general physical, systemic and obstetrical examination is rapidly completed. Vital signs which include pulse, temperature, respiratory rate, blood pressure and joint reflexes are recorded at regular intervals. Level of consciousness is assessed by response of the patient to the examiner's questions, brisk and sluggishness of reflexes and reaction of pupils to light. Fetal heart rate and regularity is established. An intravenous line is started with five per cent dextrose solution and blood is drawn for studies such as grouping, cross matching, hemoglobin, hematocrit, sugar and electrolytes including blood urea and serum creatinine. Indwelling Foley's catheter is passed into the bladder and

complete accountancy of intake and output is maintained. Urine is analyzed for albumen, sugar, ketone, red cells and casts.

#### **Therapy for control of convulsion-**

One hundred mg of pethidine are given intravenously as a stat dose; this is followed by phenobarbitone, 90 to 120 mg given by intramuscular route, every 4 to 6 hours depending upon the level of consciousness of the patient, her reflexes, respiratory rate, and urinary output. If the convulsions are not controlled with this regime within 6 to 8 hours then 2 gram of magnesium sulphate is injected in each buttock by deep intramuscular route, while 10 grams are added in 1000 ml of 5 per cent dextrose in water and given slowly by intravenous route. The rate of administration is controlled by its effect on reflexes and respiratory rate which is never allowed to go below 12 per minutes.

**Paraldehyde:** This drug can be used as an alternative to the above regime 10 ml of paraldehyde are mixed in one ounce of olive oil and given rectally. The patient is strictly observed for depression of respiration. As soon as the convulsions are controlled, the membranes are ruptured and Syntocinon drip started to induce the labor. However, if convulsions are not controlled within 12 hours, induction is carried out irrespective of fetal maturity. In most cases, delivery is completed rapidly. However, in some cases Cesarean Section may have to be performed, especially when labor fails to proceed after rupturing of the membranes. The patient is carefully observed and her vital signs monitored in the

intensive care room for the next 48 hours.

### **Magnesium sulfate:**

**Activity** - The action of magnesium sulfate is primarily at the neuromuscular junction, causing a reduction in liberated acetylcholine and reducing muscle fibre excitability. Its use is also associated with occasional reduction in arterial pressure. This slight lowering of peripheral vascular resistance is due either to peripheral vasodilation or secondary to high initial magnesium concentrations in the vasomotor center of the brain. Increases in renal and uterine blood flow have been reported. Therapeutic plasma levels of 6 to 8m eq/L are recommended for prevention of seizure activity. Adequate monitoring to prevent magnesium intoxication should include frequent evaluation of deep tendon reflexes, respiratory rate and urinary output. Magnesium sulfate is cleared by the kidneys and excreted unchanged in the urine. Maternal side effects include depressed myometrial and cardio-respiratory activity. Confusion and agitation may also occur. The woman's confusion and agitation when she regains consciousness can be minimized by having a member of the immediate family at the bedside and by avoiding bright light, loud noises and number of people in the room. If respiratory depression develops, 10 ml of a 10 per cent solution of calcium gluconate may be given intravenously over 3 minutes. Fetal side effects are negligible, though some newborns may initially show some degree of hypotonia.

**Prognosis** - This is potentially a serious condition. Considerably increased maternal and fetal mortality is associated with

this complication. Maternal mortality associated with these complications has fallen markedly from 52.2 per 100,000 live births in 1940 to 6.2 per 100,000 in 1970. The change is attributable to improved antepartum care, early detection, and aggressive management. Other factors of general health, nutrition and socio-economic status for the gravid population at large, have also played a major role. The incidence of both pre-eclampsia and eclampsia in this country has remained high in spite of improvement in the nutritional status of masses. This sad state of affairs reflects the failure of both Government and private agencies such as population planning, maternal and child health welfare organizations and a couple of societies of obstetricians and gynecologists of this country to introduce adequate antenatal screening in this country.

### **Management options:**

#### **Pre pregnancy:**

Establish the etiology, if possible, and the severity of the hypertension. Evaluate renal function. The patient with mild to moderate disease should be taken off antihypertensive medication or switched to medication known to have few fetal side effects. Patients difficult to control with severe diseases may need to remain on pre-pregnancy medications, despite potential fetal risks. Encourage early prenatal care in an appropriate setting.

**Prenatal:** Early and frequent prenatal care is crucial to optimize maternal and fetal outcome, Antihypertensive medication can be discontinued, unless the maternal, diastolic pressure exceeds 100-110 mmHg. Oral medications



(methyldopa, hydralazine or 0 calcium channel blockers) are used in severe hypertensives and in those with mild hypertension. Complicated by known risk factors, Laboratory studies include 24 h urine collection, for creatinine clearance and quantitative protein, uric acid, blood sugar, electrolytes and, where appropriate, antinuclear antibody, serum complement studies and antiphospholipid antibodies Fetal surveillance should include serial ultrasonography evaluations for fetal growth, umbilical artery Doppler recording and Biophysical Profile Testing beginning about 26 weeks in women with severe hypertension and/or risk factors (perhaps later in women with mild, uncomplicated hypertension), Vigilance for superimposed pre-eclampsia.

### **Labor/Delivery:**

Continuous electronic fetal monitoring is necessary to evaluate the fetus who may be compromised by long-standing growth restriction and hypoxemia. Antihypertensive medications are employed to maintain blood pressures below 160/110 mmHg and Monitor for potential complications including superimposed pre-eclampsia, and abruptio placenta.

**Postnatal:** Close monitoring in the first 48 h postpartum is needed to anticipate the development of hypertensiveencephalopathy, pulmonary edema or renal failure, Oral or intravenous medication (methyldopa, hydralazine, Or 13/calcium channel blockers) is used to control hypertension, Evaluation in the postpartum period for deterioration in cardiac or renal status, Although detectable in breast milk in minute

amounts, most antihypertensives are not contraindicated in breastfeeding mothers. Thiazide diuretics should be avoided in this group.

### **Quick Review:**

#### **Management options:**

#### **Pre eclampsia:**

**Pre pregnancy:** Advice early prenatal care, pre-pregnancy diabetic and hypertension control, good nutrition for those at risk

**Prenatal Prediction:** Increased risk with pre-existing hypertension, renal disease, connective tissue disorders, diabetes mellitus, previous pre eclampsia.

**Prevention:** Dietary supplementation, diuretics, Antihypertensives and low dose aspirin are all controversial in their efficacy.

**Early detection:** Roll over test', angiotensin II, plasma cellular fibronectin, platelet angiotensin II receptors, platelet intracellular calcium when exposed to arginine vasopressin, urinary calcium excretion, fasting insulin levels, mean arterial pressure, isometric exercise test, serum uric acid, microalbuminuria, platelet • count, hematocrit, Doppler velocimetry, have all been studied but none fulfill the criteria of a good predictive test.

### **Management:**

Diagnosis at term mandates delivery Mild pre-eclampsia remote from term can be managed conservatively with bedrest, fetal and maternal surveillance and monitoring for disease progression (Table 37.4).

Severe pre eclampsia at or remote from term requires delivery of the fetus (Tables 37.5 and 37.6). Expectant management under these circumstances is unusual, and requires careful patient and family counseling. Laboratory studies utilized during expectant management include 24 hours urine collections for quantitative protein and creatinine clearance, platelet counts, liver function tests, serum fibrinogen, PT and PTT

### **Labor/delivery:**

The judicious use of fluid therapy and careful, frequent assessment of maternal vital signs is critical. Continuous electronic fetal heart rate monitoring is necessary to evaluate fetal status. Magnesium sulfate is the drug of choice for seizure prophylaxis (Tables 37.7 and 37.8). Antihypertensive medications are employed to maintain blood pressures below 160/110 mmHg (Table 37.9). Potential complications include oliguria, pulmonary edema, HELLP syndrome and seizures. Invasive hemodynamic monitoring is infrequently needed. It should be employed to provide specific hemodynamic data to effect management decisions in patients who are unstable or in whom the volume status is uncertain

### **Postnatal:**

Continue seizure prophylaxis in pre-eclamptic approximately 24 h postpartum. In patients who have severe disease in the MID trimester, eclampsia or HELLP syndrome, slow resolution of the disease process may dictate close monitoring and continuation of seizure prophylaxis for 2-4 days. Patients who still require antihypertensive medication on discharge from the hospital should be evaluated weekly. A full work-up should be initiated for those persistently

hypertensive at/or more than 6 weeks postpartum.

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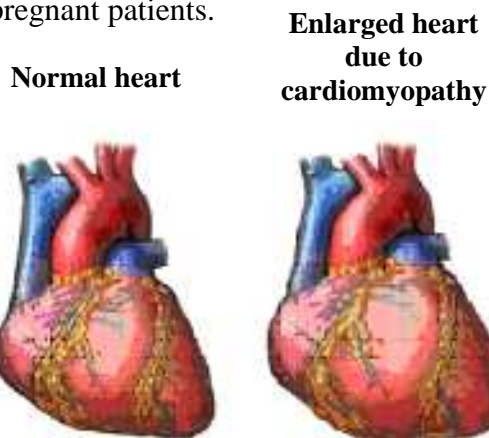
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## Chapter No: 5

# HEART DISEASE IN PREGNANCY

Heart disease is one of the major causes of maternal mortality. Its incidence varies between 1 to 3.7 per cent of all pregnancies. The complication is more frequent in areas where predisposing factors such as rheumatic fever syphilis and other diseases which can affect the cardiovascular system are more prevalent. The most common variety of heart disease encountered during pregnancy is the rheumatic heart disease; this is responsible for about 85 per cent of all cases, 75 per cent of which include involvement of the mitral valve alone while 10 to 15 per cent involve both the mitral and the aortic valves. A small number of cases are due to lesions of the aortic and the tricuspid valves. Congenital heart disease is responsible in about 1 to 3 per cent cases. These lesions include septal defects, tetralogy of Fallot and heart block. Hypertensive heart disease accounts for 1 to 2 per cent of total cases. Coronary heart disease, coarctation of the aorta, bacterial endocarditis and arteriosclerotic heart disease are rarely encountered in pregnant patients.



**Fig5.1: Shows Human heart both normal and enlarged in size**

### Physical adjustments in the cardiovascular system:

The heart is pushed upward and to the left by elevation of the diaphragm, making the heart appear larger than normal.

Its volume is increased by nearly 10 per cent of the normal base value. The increase in volume is due to hypertrophy of the cardiac muscle and increase in volume of blood available for filling the heart. There is a slight increase in heart rate during pregnancy.

**Blood Pressure** - Both the systolic and diastolic blood pressure decrease around mid term. These decreases in pressure never exceed more than 10 mm of Hg in normotensive patients. Patients who have essential hypertension can show a significant decrease in pressure earlier in pregnancy but a considerable increase later in pregnancy.

Age of Woman	Blood Pressure
15-19	117/77mmHg
20-24	120/79mmHg
25-29	121/80mmHg
30-34	122/81mmHg
35-39	123/82mmHg
40-44	125/83mmHg
45-49	127/84mmHg
50-54	129/85mmHg
55-59	131/86mmHg
60-64	134/87mmHg

**Fig5.2: Shows women average of blood pressure**

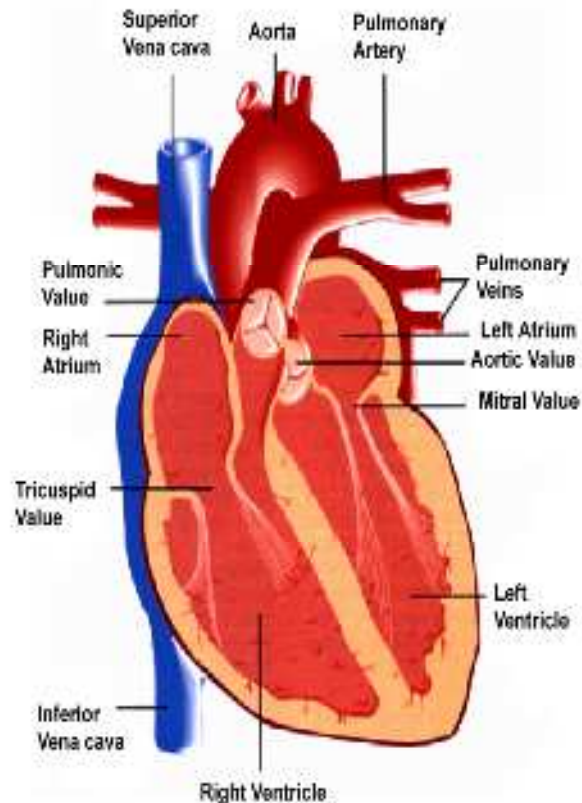
**The Stroke Volume** - This increases considerably during pregnancy. The change becomes maximum between 19th to 20th weeks. From 20 weeks until term the stroke volume increase remains constant. The difference in results reported by various authors is probably due to the position of the patient when stroke volume and cardiac output was measured. Some authors in the past had reported a decrease in stroke volume near term, but this is not now accepted as correct by most authorities.

**Cardiac Output** - There is 40 per cent increase in cardiac output above normal by the 28th week. The increase starts early in the first trimester, and continues gradually during the second trimester, it reaches its peak around 28 weeks, and then remains at this level till term. Most authorities in the past reported a decline in cardiac output in the last trimester. This difference is due to the position of the patient. When the patient is lying in supine position, pressure on the inferior vena cava produces a decrease in the venous return to the right heart and thus lowers the cardiac output. These workers made their measurements while the patient was lying in the lateral position. An additional increase in cardiac output occurs during labour. It is due to an increase in stroke volume caused by uterine contractions which can squeeze an extra 400ml of blood into the general circulation.

#### **Blood vessels -**

There is generalized vasodilatation due to decrease in tone of the smooth muscles during pregnancy. This helps in peripheral vasodilatation and thus produces a great increase in the peripheral blood flow. The veins are easily dis-

tended and therefore there is an increase in the incidence of varicosities. The incidence of hemorrhoids is also considerably increased.



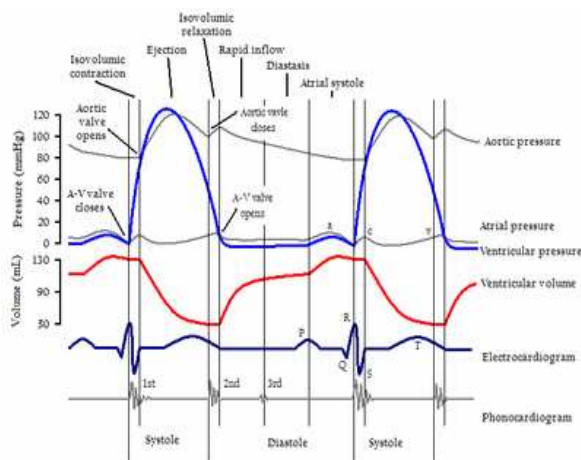
**Fig 5.3: Shows inside heart structures**

**Blood volume** - This is markedly increased, reaching its peak around the end of the second trimester where it can be as much as 48 per cent above the baseline. There is only a slight increase during the third trimester. This increase in volume is quite disproportionate to the red cell mass increase. In the first half of pregnancy the increase is more in the volume while in the second half red cell mass increases more than the plasma. The net result is a fall in the hematocrit value, from 41 per cent in the non-pregnant stage to 37 per cent, earlier in

pregnancy. The increase in volume is probably due to increased production of aldosterone which occurs in normal pregnancy. Estrogens also play some part in increasing this volume.

**Blood corpuscles** - The white cells increase from 4000 to 10,000 per cu mm. The increase is mainly in polymorphonuclear cells. There is also an increase in the platelet count which may rise from 150,000 to 500,000/cu mm.

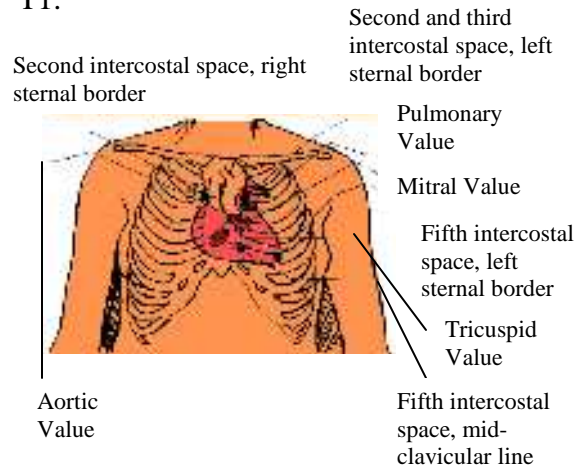
**Heart sounds** - It is important for the student of obstetrics to review normal functioning of the heart in the non-pregnant state. He must familiarize himself with various heart sounds which are produced by opening and closure of various heart valves. In my opinion it is not possible to appreciate abnormal heart sounds and murmurs unless the student is adequately familiar with normal heart sounds and physiological changes which occur in the blood volume and shapes of the heart and cardiac output during pregnancy.



**Fig5.4: Shows two cardiac cycles opening and closing of valves produce sounds.**

## Heart sounds

The closing of the mitral and tricuspid valves (known together as the atrioventricular valves) at the beginning of ventricular systole cause the first part of the "lubb-dub" sound made by the heart as it beats. Formally, this sound is known as the First Heart Tone, or  $S_1$ . This first heart tone is created by the closure of mitral and tricuspid valve and is actually a two component sound,  $M_1$ ,  $T_1$ .



**Fig5.5: Shows principal areas for auscultation for heart sounds.**

The second part of the "lub-dubb" (the Second Heart Tone, or  $S_2$ ), is caused by the closure of the aortic and pulmonary valves at the end of ventricular systole. As the left ventricle empties, its pressure falls below the pressure in the aorta, and the aortic valve closes. Similarly, as the pressure in the right ventricle falls below the pressure in the pulmonary artery, the pulmonary valve closes. The second heart sound is also two components,  $A_2$  and  $P_2$ . The aortic valve closes earlier than the pulmonary valve and they are audibly separated from each other in the second heart sound. This "splitting" of  $S_2$  is only audible during inhalation. However, some cardiac conduction ab-

normalities such as left bundle branch block (LBBB) allow the P2 sound to be heard before the A2 sound during expiration. With LBBB, inhalation brings A2 and P2 closer together where they cannot be audibly distinguished.

#### **Normal non pregnant state:**

**First Heart sound** - This sound is produced by closure of the mitral and the tricuspid valves. The first heart sound can be heard and its character appreciated over the left sternal border. The student should remember that in this area lie both the mitral and the tricuspid valves. The intensity of the heart sound depends on the mobility of the leaflets of the valve and the distance which separates the valve cusps. The valve cusps are moved by the flow of the blood during atrial systolic contraction which occurs just before ventricular contraction. In normal adolescents the first heart sound may be heard with some splitting. The important thing to recognize is that this splitting is not influenced by respiration. Conditions where the first heart sound is increased are; mitral stenosis, systemic hypertension and hyperthyroidism. Those conditions where first heart sound is decreased include myocarditis, myocardial infarction, fibrosis, hypothyroidism, aortic insufficiency and pericarditis with effusion.

**Second Heart sound** - The second heart sound is produced by the closure of the pulmonary and the aortic valves. The aortic valve closes slightly before the pulmonary valve, therefore unlike the first heart sound the closure of the valves in the second heart sound is not synchronized. The important point to note for student is that the closure of the aortic

valve maintains a relatively fixed relation with first heart sound. During inspiration the blood flow through the right heart is transiently increased, therefore the closure of the pulmonary valve is further delayed, so splitting of the second heart sound is heard in the second and the third left intercostal spaces. (Areas where the aortic and the pulmonary valves are present). In cases of atrioseptal defect the right side of the heart is overloaded and the pulmonary valve closure is very much delayed in both phases of respiration. The student will find that the splitting of the second heart sound is fixed in such cases.

In cases where ventricle conduction or emptying time of the heart is delayed, the closure of the aortic valve is so much delayed that it synchronizes with the pulmonary valve closure in inspiration. The pulmonary valve closure sound is more close to the first heart sound during inspiration. This type of splitting of the second heart sound is called paradoxical splitting of the second heart sound and is always pathological. Conditions where the aortic component of the second heart sound is increased include coarctation of the aorta and systemic hypertension; lesions in which the aortic component of the second heart sound is decreased include aortic stenosis. Conditions where pulmonary component of the second heart sound is increased include pulmonary hypertension.

**Third Heart sound** - This is heard in older age group of patients and is rarely found before 30 years of age. When it is heard it indicates stress and is first sign of the left ventricular failure. It is best heard over ventricular area. Occasionally it can be heard in children and adolescents that are normal.

**Fourth Heart sound** - This is rarely heard and is thought to be caused by very strong atrial contraction which occurs against strong resistance. It is not heard in normal heart.

**Diastolic and Presystolic gallop** - When third heart sound is heard with heart rate of more than 100 per minute, the rhythm of heart is called diastolic gallop. While presystolic gallop is produced when fourth heart sound is heard with a heart rate of more than 100 per minute.

It can only be shown by Phono-Cardiogram that a gallop rhythm is due to intensification of the true 3rd or true 4th heart sound. They are heard most frequently in severe cardiac disease and may in fact be due to continuation of both increased 3rd and 4th sound (summation gallop).

**Ejection click** - This occurs due to increased blood pressure. The increased pressure distends stiff walls of the aorta or the pulmonary artery, and dilates these stiff vessels and thus produce ejection click.

**Heart sounds in pregnancy** - All sounds usually increase in intensity. A short systolic murmur is best heard at the apex of the pulmonary area during normal pregnancy. The murmur is usually of ejection type, and is probably produced by increase in blood volume and blood flow through the heart. This murmur is physiologically normal, starts around 12 weeks of pregnancy and automatically disappears within a week after delivery. A number of murmurs can be found in pathological heart conditions one of which is mitral regurgitation. Various diagnostic murmurs may be

greatly decreased or even not heard during pregnancy due to decrease in peripheral resistance. The student should realize that when heart disease is severe the prognosis for the fetus is worst.

Cardiac disease and childbearing ordinarily do not shorten the life expectancy of the mother or cause permanent cardiac ~status deterioration. When maternal heart disease is congenital, pregnancy may result in increased incidence of fetal congenital heart disease.

In cases of heart disease the most important factor in their management is to prevent heart failure. This increases the hemodynamic burden and causes decompensation of the heart, which usually causes death. The danger of death is greatest when the hemodynamic burden is severe.



**Fig5.6: Shows radiograph with enlarged heart**

#### **Valvular lesions:**

The mitral valve can be Stenosed or incompetent, which in turn can be mild, moderate or severe.

**Mild mitral stenosis** - The valve between the left atria and left ventricle is narrowed. Most women will give a history of past rheumatic fever. Until



there is 60 per cent reduction in function of the valve no significant hemodynamic changes will be evident.

The Left atrial pressure is increased which is necessary to overcome the obstruction of stenosed valve. This increased pressure is reflected in the pulmonary bed veins, arteries and capillaries with symptoms of congestion, and is characterized by dyspnea, cough, hemoptysis, and pulmonary edema.

When the orifice of the mitral valve is only one third of its normal size the left auricular pressure rise cannot overcome this resistance and eventually leads to right ventricular hypertrophy. The cardiac output falls, as a result. In mitral valve disease there is an increase in blood volume which causes increase in venous return and cardiac output. When mitral disease is long standing it leads to pulmonary artery sclerosis. This increases the pulmonary artery pressure out of proportion to the increase in left atrial pressure and eventually leads to right heart failure.

#### Severe mitral stenosis:

When stenosis of the mitral valve is severe left atrial and pulmonary hypertension develops. This is further aggravated by pregnancy, because of increase in the cardiac output, blood volume, and the circulation time. When cardiac output is increased in the presence of severe stenosis the pressure behind the stenosed valve increases further.

#### Classification:

Various classifications have been advanced to grade the severity of heart

disease. The most common one used today is the New York classification. This is based on the functional status of the patient. It takes into consideration etiological factors, anatomical status of the lesions, physiological state of the patient and functional capacity of the heart.

Classification of blood pressure	
Category DBP MMHG	SBP MMHG
Normal	<120 and <80
Prehypertension	120-139 or 80-89
Hypertension Stage 1	140-159 or 90-99
Hypertension Stage 2	≥ 160 and ≥100
Key: SBP = systolic blood pressure      DBP = diastolic blood pressure	

**Fig5.7: Shows classification of blood pressure**

According to this classification, the disease can be divided into four classes.

**Class I-** In this class cardiac disease is present, but there is no limitation of physical activity. Ordinary physical exertion does not cause fatigue to the patient. Palpitation dyspnea and anginal pain are usually not present.

**Class II-** Cardiac disease is present and there is only slight limitation of the physical activity. The patient is comfortable, especially when she is at rest, while ordinary physical exertion causes fatigue, palpitation, anginal pain and dyspnea.

**Class III** – With cardiac disease present the patient requires marked limitation in physical activity, to become comfortable. Less than ordinary activity also causes fatigue, palpitation dyspnea and anginal pain.

**Class IV** - The patient has cardiac disease and is unable to carry on any physical activity without discomfort. Symptoms of angina or coronary insufficiency may be present at rest. Discomfort increases with exertion.

**Management:**

This can be achieved by using better diagnostic methods, proper antibiotics for the treatment of rheumatic fever and sub acute bacterial endo-carditis.

**Diagnosis:**

**History:**

The student must establish that his patient has had heart disease before the pregnancy.

When past history of rheumatic fever, with the presence of heart murmur is discovered and a history of previous treatment for heart disease is available a concerted effort should be made to note symptoms antedating pregnancy.

During normal pregnancy dys-pnea, pedal edema and limitation of physical activity is a routine finding in the absence of heart disease. In a number of cases, history of past pregnancy is useful to provide information regarding cardiac complications which may have occurred during the previous pregnancy. Chest X-ray taken prior to pregnancy if available should be reviewed.

Some adjustments in the car-diovascular system occur in patients with heart disease. These are especially marked in pregnancy. The changes include decompensation which starts by third month of pregnancy and increases slightly in the fourth, fifth, sixth and seventh month. This is followed by a slight decrease in the decompensatory mechanism in the eighth and ninth month. However, over all decompensation at terms is still higher than in the third month.

During pregnancy tachycardia can lead to a decrease in diastolic blood flow through the mitral valve and results in increased demand for retro valvular pressure to maintain cardiac output. Similarly hypervolemia can lead to increased congestion and hypertension in the pulmonary circulation.

It is because of this change that severe congestive heart failure in pregnancy complicated with mitral stenosis is manifested by pulmonary edema. Sometimes these factors become responsible for the first episode of congestive heart failure. Congestive heart failure or pulmonary edema is the commonest cause of maternal mortality in cases of mitral stenosis.

Acute cor pulmonale may occur due to massive intra or extra pulmonary vascular obstruction or due to venous air embolism, fibrin emboli or acid aspiration. This is usually fatal for the patient. Signs and symptoms of congestive heart failure in pregnancy are always of left sided failure. Persistent basal rales, cough and dyspnea on exertion are common. There is also decrease in vital capacity. The circulation time is however prolonged.

When heart disease is severe the patient may get a fulminating pulmonary edema which is frequently intractable. This is most frequently seen in cases of mitral stenosis. Cause of death is congestive heart failure in 80% of these cases. Acute heart failure may also develop during pregnancy in the previously "normal heart".

Detailed scrutiny of clinical features, history and special investigations can help a great deal in diagnosing the exact cause.

Women who have cardiac diseases often present with a diastolic murmur and an enlarged heart. It has already been stated that even in normal patient there may be 10 per cent increase in the size of the heart due to diaphragmatic elevation and rotation of heart on its long axis.

Systolic murmur of grade III intensity may be heard. Sometimes the murmur in the beginning of auscultation appears to be of grade II and is described as slight murmur, but it is actually grade V and can be audible with the rim of the stethoscope when placed on the chest. The student should realize that a "coarse or musical murmur" is of greater significance than a "blowing" one.

The probability that a systolic murmur indicates organic heart disease increases as the murmur's intensity increases. When severe arrhythmias are present, they can lead to atrial flutter or complete heart block. Occasionally one may find pericardial friction rub as one would see in cases of pericarditis. Diastolic gallop rhythm, pulsus alternans or anginal pain can be noted in case of myocardial pain. Persistent bacteraemia may be associated

with heart murmur. Notching of the lower margin of the ribs is seen on X-ray in cases of coarctation of the aorta.

**Importance of past history** - Absence of cardiac murmurs is regarded as prime evidence against the more common cardiac disorders. If a history of rheumatic fever is present and no evidence of heart lesion is discovered one or more years later then one may accept that no significant cardiac damage has occurred.

When there is no evidence of heart disease, but predisposing factor such as rheumatic fever is present, the patient should be treated as a high risk patient.

The significance of cardiac disease is based mainly on the occurrence of pulmonary edema, as 88% of antepartum cardiac deaths and 37% of postpartum deaths occur as a result of pulmonary edema.

A detailed account of previous pregnancies is very useful because severe cardiac failure associated with mitral stenosis is likely to reoccur in successive pregnancies. However absence of congestive heart failure in one pregnancy does not guarantee that it will not occur in a subsequent pregnancy.

### **Physical examination and auscultation of the Heart:**

The physical examination should be carried out vigilantly. If pedal edema is discovered, it should be thoroughly evaluated and differentiated from edema of normal pregnancy.

**Innocent cardiac murmurs** - Systolic flow murmurs may be hard to

differentiate from hemodynamically significant murmurs if the patient has not been examined before. If the murmur is loud and transmitted to the axilla or neck vessels, and its association with a palpable thrill is established, it is abnormal without exception. It is conventional to grade murmurs according to their intensity. The grades vary from one to six. The grade I murmur can be heard with special effort only. The grade II murmur is very faint but is recognizable with some experience. The grade III murmur is prominent but is not so loud; a grade IV murmur is much louder. The grade V murmur is also loud while the grade VI murmur is the loudest and can even be heard with stethoscope while it is barely in contact with the chest wall. In the absence of heart disease a pregnant patient should have no murmur louder than grade II. Blood flow murmurs associated with pregnancy are heard along the left sternal border in nearly 90 per cent of pregnant women. They do not usually radiate to the axilla, and are not associated with thrills of any sort. The diastolic murmur of aortic regurgitation is usually faint and some times, inaudible during pregnancy. This murmur is heard while the patient is squatting or performing strenuous work.

Diastolic cardiac murmurs in pregnancy always indicate cardiac pathology. A diastolic bruit originating in the internal mammary artery may be misinterpreted as being cardiac in origin.

A murmur which originates from the breast vasculature can be heard in about 10 per cent pregnant women, during the third trimester.

**Heart sounds and murmurs** - A parasternal systolic murmur is heard in most cases and is due to increase in

blood volume which occurs in normal pregnancy.

This is the murmur of organic mitral regurgitation and careful interpretation is necessary since the presence of an S3 gallop signifies left ventricular failure. More than 80 per cent of women develop a third heart sound at some time during pregnancy.

The frequency parallels the increase in cardiac output. Systolic murmurs increase in intensity during pregnancy. This is due to increased blood flow across normal cardiovascular valves. This is particularly so in murmurs arising in the pulmonic and aortic areas. Systolic murmurs produced by mitral regurgitation usually become softer during pregnancy, because systemic arterial resistance falls.

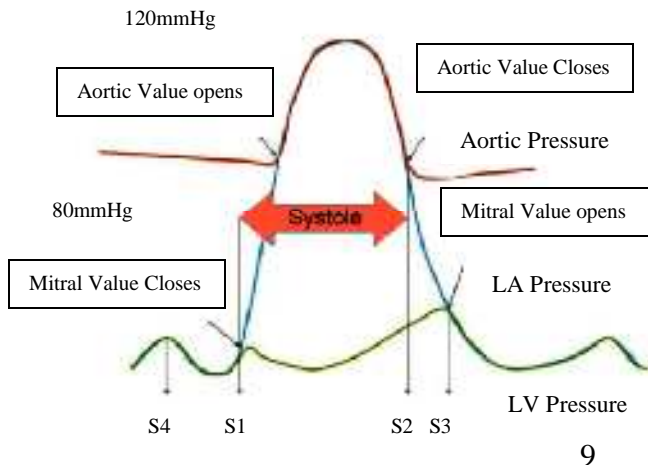
#### **Murmur in mitral valve prolapse syndrome:**

In this syndrome an apical systolic murmur is noted and is preceded by a mid systolic click. The majority of patients with a mitral valve prolapse syndrome have uneventful gestation.

These patients are susceptible to subacute bacterial endocarditis and should be protected with antibiotics at delivery.

#### **Chest X-ray:**

A chest X-ray is useful to assess the degree of enlargement of the heart. Similarly, enlargement of a particular chamber of the heart can be detected and the presence of pulmonary overcirculation diagnosed. It is wise not to expose the fetus to radiation, unless it is absolutely necessary.

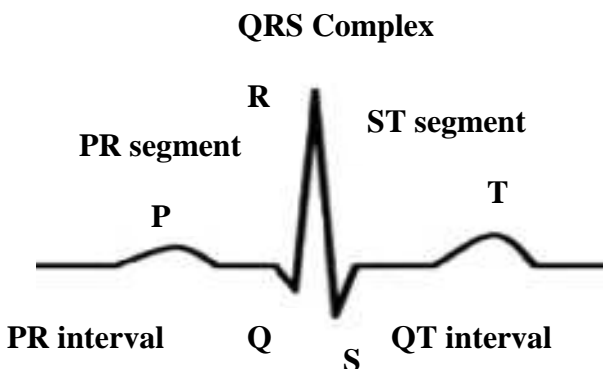


**Fig5.8: Shows heart sounds.**

### Electrocardiography:

The mean QRS axis shifts to the left in the frontal plane of the electrocardiogram. A "Q" wave may develop in lead III, but disappear on deep inspiration.

The electrocardiogram is quite useful in assessing the presence or absence of ventricular hypertrophy and atrial enlargement. (LBBB) allow the P2 sound to be heard before the A2 sound during expiration. With LBBB, inhalation brings A2 and P2 closer together where they cannot be audibly distinguished.



**Fig5.9: Shows ECG.**

**Normal adult 12-lead ECG:** The diagnosis of the normal electrocar-

diogram is made by excluding any recognized abnormality. Its description is therefore quite lengthy.

### Normal sinus rhythm:

Each P wave is followed by a QRS, P waves normal for the subject, P wave rate 60 - 100 bpm with <10% variation, rate <60 = sinus bradycardia, rate >100 = sinus tachycardia and variation >10% = sinus arrhythmia.

Normal QRS axis, normal P waves, height < 2.5 mm in lead II and width < 0.11 s in lead II for abnormal P waves see right atrial hypertrophy, left atrial hypertrophy, atrial premature beat, hyperkalemia, normal PR interval and 0.12 to 0.20 s (3 - 5 small squares) for short PR segment consider Wolff-Parkinson-White syndrome or Lown-Ganong-Levine syndrome (other causes - Duchenne muscular dystrophy).

Type II glycogen storage disease (Pompe's), HOCM), for long PR interval see first degree heart block and 'trifascicular' block, normal QRS complex, < 0.12 s duration (3 small squares), for abnormally wide QRS consider right or left bundle branch block, ventricular rhythm, hyperkalemia, etc. No pathological Q waves, no evidence of left or right ventricular hypertrophy and normal QT interval. Calculate the corrected QT interval (QTc) by dividing the QT interval by the square root of the preceding R - R interval. Normal = 0.42 s. Causes of long QT interval, myocardial infarction, myocarditis, diffuse myocardial disease, hypocalcaemia, hypothyroidism, subarachnoid hemorrhage, intracerebral hemorrhage, drugs (e.g. sotalol, amiodarone), hereditary, Romano Ward syndrome (autosomal

dominant). Jervell + Lange Nielson syndrome (autosomal recessive) associated with sensorineural deafness, normal ST segment, no elevation or depression and causes of elevation include acute MI (e.g. anterior, inferior), left bundle branch block, normal variants (e.g. athletic heart, Ed Eiken pattern, high-take off), and acute pericarditis.

Causes of depression include myocardial ischemia, digoxin effect, ventricular hypertrophy, acute posterior MI, pulmonary embolus, left bundle branch block, normal T wave, causes of tall T waves include hyperkalemia, hyperacute myocardial infarction and left bundle branch block. Causes of small, flattened or inverted T waves are numerous and include ischemia, age, race, hyperventilation, anxiety, drinking iced water, LVH, drugs (e.g. digoxin), pericarditis, PE, intraventricular conduction delay (e.g. RBBB) and electrolyte disturbance and normal U wave.

### **Echocardiography:**

This is quite useful in confirming the presence of the mitral valve prolapse syndrome. It also helps in assessing the degree of mitral stenosis and in excluding the presence of hypertrophic cardiomyopathy. Both aortic valve disease and a reliable measurement of left atrial size can be assessed by this method block and a slow ventricular rate, a transvenous pacemaker can be inserted with no great risk. The student must note

### **Cardiac complications and management in pregnancy:**

**Dysrhythmias:** Paroxysmal atrial tachycardia is a common feature during pregnancy. Premature beats, atrial or

ventricular can also occur without heart disease. When heart disease is present, any attack of atrial fibrillation, with rapid ventricular rate can pose a serious problem. Direct current countershock conversion has been used in pregnancy with no evidence of any serious effect on the fetus. In patients with complete heart block that if a pregnant patient with tight mitral stenosis goes from normal sinus rhythm into atrial fibrillation, the rapid control the ventricular rate. This will allow adequate period of ventricular filling and thus prevent the rapid development of pulmonary edema. Ventricular rate may be lethal. Proper digitalization can reduce the chance of developing atrial fibrillation and also

**Drugs** - Both quinidine or procainamide can be used during pregnancy to control dysrhythmias. However, propranolol should be avoided. When administered during pregnancy it can produce post-natal bradycardia, hypoglycemia and impair responsiveness of the fetus to anoxic stress. Propranolol administered to the mother crosses the placenta. This drug is strongly bound to albumin and tissues, and may continue to be released from such binding sites over a 2 to 3 day period. Severe hypoglycemia in the neonate where mothers had been given propranolol has been reported, with blood sugar levels of 11 to 30 MG dl and persisting for about 8 to 24 hours after delivery. Treatment of hypoglycemia consists of administering a 10 per cent dextrose solution to the baby. Beta blockade impairs the ability of the fetus to develop a rebound tachycardia in response to transient anoxia. This is possibly the explanation for impaired responsiveness to anoxic stress. The depressed state of the fetus at birth, with delay in onset of sustained breathing,

may require vigorous resuscitation and administration of atropine and isoproterenol for treatment of such bradycardia. Babies born to mothers who have been on propranolol may be small for gestation age and may have a small placenta.

The student may be interested to note that small doses such as 10 mg of propranolol four times a day have been associated with significant neonatal bradycardia, hypoglycemia, and respiratory distress. These findings suggest a cumulative effect of the drug on the fetus. Therefore it is advised to avoid using this drug during pregnancy.

**Congestive heart failure** - Moist rales are usually audible at the bases of the lungs. The lungs may also become atelectatic due to the elevated diaphragm, which is pushed upward by the gravid uterus. Peripheral edema may result due to compression of the inferior vena cava by the gravid uterus. The heart size may be difficult to assess clinically because of the lateral displacement of the apex by the elevated diaphragm.

**Management** - Once it has been established that the patient is in congestive cardiac failure, and then management should include digitalization, salt restriction, and judicious use of diuretics. The use of diuretics in pregnancy is not recommended unless they are absolutely necessary. Diuretics can cross the placental barrier and cause fetal electrolyte and water depletion. In the case of thiazide diuretics, neonatal jaundice and severe thrombocytopenia may result.

**Prevention of Endocarditis:** Patients with heart disease are at a greater risk of

contracting subacute bacterial endocarditis from bacteremia, which can even occur during delivery; therefore it is important to give these patients prophylactic antibiotics.

An uncomplicated vaginal delivery may not be associated with bacteremia. Current regimen advocated is aqueous penicillin G 2,000,000 units intramuscularly or intravenously, or ampicillin, 1.0 gm intramuscularly or intravenously plus gentamycin 1.5 mg/kg (not to exceed 80 mg) intramuscularly or streptomycin 1.0 gm intramuscularly.

The initial dose should be given 30 minutes to 1 hour prior to delivery. If gentamycin is used, a similar dose of Genta- mycin and penicillin or ampicillin should be given every 8 hours for two additional doses. If streptomycin is used, then a similar dose of streptomycin and penicillin or ampicillin should be given every 12 hours for two additional doses.

### **Thromboembolic complications:**

Patients with heart valve replacement are often advised to take anticoagulants throughout their life. When they conceive, only two out of three pregnancies have a chance of normal outcome. These patients should be informed of the risk and advised against pregnancy.

### **Coumarin anticoagulants:**

These agents cross the placental barrier, and have been reported to be associated with fetal abnormalities. The abnormalities which develop are referred to as warfarin embryopathy. They include a hypoplastic saddle type nose and bone abnormalities, the most

striking of which is stippling seen on X-rays of the newborn infants.

Stippling may not be evident after the first year of life, however calcific stippling is incorporated into epiphyses during the second and third trimester of pregnancy. It has also been associated with such anomalies as mental retardation, blindness, deafness, seizures, scoliosis, and occasionally, congenital heart disease.

**Management** - These cases should preferably be treated with low doses of subcutaneous heparin therapy throughout pregnancy, labor and delivery. The heparin molecule (molecular weight 15,000 - 30,000) does not cross the placental barrier and can therefore be safely given during pregnancy. The effectiveness of low dose subcutaneous heparin in the prevention of thromboembolic complications of heart valve replacement has not been fully established. Chronic (over 6 months) heparin administration had led to the development of osteoporosis, therefore prolonged use of this drug should be planned with caution.

Hall et al reviewed cases in which heparin was used during gestation, comparing the outcome of pregnancy in these cases with that of pregnancies in which coumarin derivatives were used. They noted that although heparin does not cross the placental barrier the likelihood of a normal outcome of the pregnancy is, amazingly similar to that in the group treated with coumarin anticoagulants. They calculated that when heparin was used during pregnancy one eighth of the pregnancies would end in stillbirth and one fifth would be premature. The regimen of

anticoagulants described below is for the guidance of the student. Coumarin derivatives are used in non pregnant states. In the New York Lying in hospital obstetrical cardiac clinic, during the first trimester anticoagulation is switched from coumarin to heparin which is administered subcutaneously in doses of 5,000 units every 12 hours. The coumarin anticoagulants are meant to allow enough time for the necessary coagulation factors in the fetus to return to normal. Since all oral anticoagulants are actively excreted in the breast milk, breast feeding should be prohibited when the mother is on oral anticoagulants. A major advantage of heparin administration in puerperium is that breast feeding can be allowed. With patients who are at high risk for thromboembolic complications, prophylactic subcutaneous heparin administration should be continued for 2 or 3 weeks following delivery. Such patients would include those with previous history of thrombophlebitis or with a past history of pulmonary embolism.

**Management during labour and delivery** - Nearly 80 per cent of pregnant women with heart disease are in Class I or Class II. They should be allowed to reach term and spontaneous delivery should be the aim. Second stage may be shortened with timely application of forceps or vacuum extractor. Complete bed rest is important after delivery. Infections especially upper respiratory tract should be avoided. The physician must be alert to recognize congestive heart failure. The majority of cases where cardiac decompensation occurs are acute but sometimes this may occur gradually. The signs of cardiac failure are persistent basal rales after deep breathing, cough and decreased



ability to carry on household task. Hemoptysis may be the only warning sign in some cases.

**During labour** - Hospitalization at least two weeks prior to term especially in Class II cardiac cases should be mandatory. Prophylactic antibiotics should be given during labor and puerperium. Labour should be conducted in a semi-recumbent position. An increase in pulse rate to 115 per minute and a respiratory rate of 28 per minute associated with dyspnea indicate impending congestive cardiac failure.

If the cervix is not fully dilated any attempt to deliver the baby will precipitate congestive heart failure, therefore, the patient should be sedated with morphine, and properly digitalized.

If the cervix is fully dilated and decompensation of heart occurs then immediate delivery by forceps is indicated to avoid bearing down. The patient should be sitting up if possible and caudal anesthesia administered, which is safer.

Sudden collapse of cardiac patients after delivery can occur due to engorgement of splanchnic vessels, Treatment is sedation, digitalization, extremity tourniquet and abdominal binder.

In normal patients a rise of about 30 per cent in cardiac output occurs after labor and continues for about four days. Rarely there is congestive heart failure within the first 24 hours or after 4 to 5 days postpartum. Bed rest for 2 weeks during postpartum period and contraception advise which should be given to these patients.

### **Class III and IV:**

These patients constitute nearly 12 per cent of the total pregnancies complicated with cardiac disease. They can go into congestive cardiac failure easily, and anytime through the pregnancy. For Class IV patient's delivery by vaginal or surgical method carries the risk of maternal mortality in nearly 50 per cent of the cases. The physician should recommend against pregnancy in both Class III and IV type of cardiac patients. However if he finds the patient in advanced stage of pregnancy he should hospitalize her and plan for vaginal delivery. The heart disease alone is never an indication for caesarean section. Surgery in pregnancy complicated with rheumatic heart disease carries 30 per cent maternal mortality. These patients tolerate surgery and anesthesia rather poorly especially spinal anesthesia. Cardiac patients are known to have a super normal hypotensive response to sympathetic paralysis.

Indications for caesarean section are obstetrical complications, coarctation of the aorta, aneurysm, and sub arachnoid hemorrhage.

**Vaginal delivery** - This should be favored over caesarean section for most patients. The majority of patients can be handled with regional anesthesia (Pudendal or epidural block). Hypotension should be avoided. When vaginal delivery is planned, the patient should be in hospital, with all precautions taken to protect her from respiratory infection. She should be provided with complete bed rest, liberal use of oxygen and digitalized. The use of ergometrine is not recommended during management of third stage of labour. These agents

increase venous pressure and burden the already failing heart. Syntocinon is relatively safer to use in these cases.

Shortening the second stage of labour by the use of forceps is favored. Adequate analgesics to relieve pain and thereby decrease the hemodynamic burden are important. Synthetic oxytocin is preferable to the natural product because it is less likely to be contaminated by pressor agents. Close cooperation between the cardiologist and the obstetrician during pregnancy, delivery and postpartum is essential for successful outcome.

### **Indications for termination of pregnancy:**

Nearly one third of patients who are in Class III and IV undergo cardiac decompensation. Where previous history of congestive heart failure is present, nearly 65 per cent can undergo decompensation. This is a very serious complication and cause of maternal death in most cases.

Patients with severe pulmonary arterial hypertension usually present with a history of hemoptysis, loud pulmonary sound, left parasternal lift, and right ventricular hypertrophy on the electrocardiogram. These patients carry very high risk during delivery and the early postpartum period. Mortality in the range of 27 to 50 per cent even in women, who are asymptomatic before pregnancy, has been reported therefore one is justified to recommend termination of pregnancy in these cases. Similarly patients with tight mitral stenosis are usually advised not to become pregnant. These patients should undergo

mitral valvotomy before entertaining pregnancy.

Therapeutic abortion may be seriously considered if the patient has severe heart disease, size of the heart is enlarged, and atrial fibrillation is present. When other complications such as renal and cerebral are associated with heart disease termination of pregnancy is most definitely indicated. The termination of pregnancy is a life-saving or even life lengthening procedure in some cases. If abortion is to be done it must be done by 15 weeks and not later than 20th week. The student should realize that some surgical procedures carry risk which may be more severe than allowing the pregnancy to continue. The patient must have the best cardiac status before termination is carried out. Sterilization for class I and II can be done as in non-cardiac patients and should be done within the first 24 hours after delivery while in Class III and IV it should not be done prior to the fifth postpartum day. Indications for sterilization are, moderately advanced cardiac patients or any significant cardiac difficulty during pregnancy.

### **Pregnancy in women with heart disease: the typical patient journey:**

All women with heart disease should be assessed at the time of puberty (typically around the age of 12–15 years) by clinicians with expertise in the management of pregnancy complicated by heart disease. They should be given an estimate of their risks which is as accurate as possible, and this risk should be reassessed every five years (or more often if their condition deteriorates significantly).

They should be advised whether specialist care from a high-risk

pregnancy with heart disease team is advisable in the event of pregnancy. If so, they should be advised to see the appropriate high risk team as soon as a pregnancy is confirmed, which will usually be by a urinary pregnancy test within two weeks of the missed period?

Women who present initially to their general practitioner or community/local hospital midwifery service, and give a history of heart disease should be referred promptly to an appropriate high-risk pregnancy and heart disease team. At the initial assessment by the high risk multidisciplinary team, a full clinical examination should be carried out and all recent investigations reviewed. Usually, an echocardiogram will be ordered to assess cardiac function. An electrocardiogram should be taken and kept in the notes for future reference, in the event that there is any change in cardiac status. The special antenatal notes should be started. The woman should be asked to carry her notes with her at all times, in case of any emergencies. It is important to offer the woman a fetal nuchal translucency scan, as this is a significant indicator of recurrent cardiac disease in the fetus. It is usually carried out at 12 weeks of gestation. Once this scan has confirmed a viable fetus without obvious abnormalities, a standard fetal anomaly scan at approximately 20 weeks of gestation, and a fetal cardiac scan at approximately 22 weeks of gestation, should be organized. Depending on her cardiac status, the woman should be seen by an appropriately experienced consultant obstetrician every two to four weeks until 20 weeks of gestation, then every two weeks until 24 weeks of gestation, and then weekly thereafter. Continuity of care is of particular importance, because this makes it much

easier to detect any deterioration in the woman's condition. If the woman threatens to go into labour before 34 weeks of gestation, immediate assessment by the multidisciplinary team is important to assess the best management. In pregnancies that are progressing satisfactorily, a multidisciplinary team assessment at 32–34 weeks of gestation is important to plan care around the time of delivery and to establish optimum management. The delivery plan Performa should be completed. The woman should be given clear instructions about how to recognize the onset of labour.

Once labour begins, she should immediately ring the labour ward to alert them that she is coming. She needs to make sure that they appreciate she is a cardiac patient so that they do not give her advice to wait at home, go for a bath, etc. On arrival at the labour ward, the woman should make herself known immediately to the labour ward staff. They should inspect the delivery plan and take action accordingly. This is likely to include informing senior staff, usually consultants, of the woman's admission. The majority of women with significant lesions will have epidural anaesthesia during labour, and a significant number will have an assisted vaginal delivery. All anaesthetics should be given by senior staff that are familiar with the delivery plan and have experience of pregnant women with cardiac disease. Following delivery, the woman should be transferred to a high dependency area where she can be monitored closely for anything between 12 and 48 hours. She should not be transferred to a normal labour ward until she has been reviewed by senior staff (preferably consultants) who can

determine whether she will be safe in an area where monitoring will be less intensive.

**Prognosis** - Heart disease in pregnancy carries an overall maternal mortality rate of 0.8 to 5 per cent. In patients with Class IV disease, the mortality is markedly increased and may become as high as 50 per cent. It is further increased where inadequate medical advice is obtained and the patient received no treatment. The prime factor in seriousness of the disease is the presence or absence of cardiac decompensation. Class I and II, as a rule, do well with pregnancy. Prognosis is worse in women over the age of 35 years. Congestive heart failure may predispose to premature labour because of congestion of the uterus with blood which has less than normal oxygen content.

#### **Fetal mortality –**

Fetal mortality in Class I is 7 per cent while in Class II it is 13 per cent. In Class III it is 35 per cent and in Class IV it is 54 per cent.

#### **Quick Review**

#### **Management Options:**

##### **Cardiac Disease: general**

##### **Pre pregnancy:**

Obstetrician and cardiologist in collaboration, Discussion of maternal or fetal risks, Discussion of effective/safe contraception, Obtain update on cardiac status, Optimize medical and surgical management, advise against pregnancy with certain conditions.

##### **Prenatal:**

Assess functional class of heart disease (see Table 39.2) Termination is an option with a few conditions S joint management with cardiologist Optimize medical management Avoid/minimize aggravating factors An coagulation for certain conditions (? Stop warfarin and change to subcutaneous heparin: see Chapter 50) Prophylactic antibiotics with certain conditions (see Table 39.4 and 39.5) Fetal surveillance: Growth and umbilical artery Doppler (especially if left to right shunt) Detailed fetal cardiac ultrasonography if maternal congenital heart disease.

**Labor/delivery:** Elective induction may be necessary for maternal and fetal indications. Prophylactic antibiotics with certain conditions (see Tables 39.4 and 39.5) Avoid mental and physical stress (?epidural) Labor in left lateral or upright position, Monitor electrocardiogram: more invasive monitoring with certain conditions Administer extra oxygen with certain conditions, Full resuscitation facilities available, Continuous fetal heart rate monitoring, Assisted second stage with certain conditions, Avoid ergometrine for third stage.

##### **Postnatal:**

Vigilance for cardiac failure, Avoid fluid overload, Continued high dependency care and discuss effective/safe contraception.

**Management options:** Cardiac murmur, Echocardiography for significant history or pathological, murmur (late systolic, pansystolic, diastolic), Cardiological referral if abnormal echocardiography.

**Mitral valves prolapse:** Cardiological and echocardiographic evaluation prenatally for mitral regurgitation, Surveillance and treatment of arrhythmias in pregnancy. ? Antibiotic prophylaxis for delivery if regurgitation.

#### **Atrial septal defect:**

Pre pregnancy: screen for arrhythmias and/or pulmonary hypertension (PH); manage accordingly both before and during pregnancy (if undertaken) Prenatal routine except if arrhythmias and/or PH Labor Delivery: Screen for arrhythmias, monitor BP, avoid fluid overload Postnatal: encourage early mobilization

#### **Patent ductus arteriosus:**

Pre pregnancy: screen for PH and manage accordingly before and during pregnancy (if undertaken), Prenatal: screen for PH, Labor/delivery/postnatal: monitor BR attention to normal fluid balance, antibiotic prophylaxis except for normal deliveries.

#### **Coarctation of the aorta:**

Pre pregnancy: screen for aneurysms and/or aortic valve disease and manage appropriately prior to conception. Prenatal? Consider termination with severe uncorrected disease Labor/delivery/postnatal: avoid hypertension, antibiotic prophylaxis except for normal delivery, screen newborn for congenital heart disease (CHD).

#### **Ventricular septa! defect:**

Pre pregnancy: screen for PH and manage accordingly, Consider repair of

uncorrected lesions, counseling about CHD risks, Prenatal: serial echocardiography and manage accordingly, Labor/delivery: avoid hypertension, antibiotic prophylaxis except for normal delivery Postnatal: careful fluid balance, early ambulation

#### **Primary pulmonary hypertension:**

Pre pregnancy: counsel against pregnancy; sterilization requested Prenatal: consider termination, obstetric and cardiological joint care, early anesthesiologist consultation, Thromboembolism prophylaxis, consider hospital admission, and monitor SaO<sub>2</sub>, fetal surveillance labor/delivery: high dependency setting (degree of invasive monitoring varies); dilemma over induction (end pregnancy) versus spontaneous (shorter labor) onset of labor, oxytocic or E series prostaglandins safe, O<sub>2</sub> at 5-6 l/min, monitor SaO<sub>2</sub> continuously, monitor BR maintain fluid balance. Epidural analgesic. Preferable (? reduce/stop anticoagulation for a few hours for delivery).

**Postnatal:** Maintain high dependency monitoring, O<sub>2</sub> therapy and throm-Bo embolism prophylaxis, vigilance for fluid retention and consequences, consider sterilization

#### **Eisenmenger's complex:**

As for primary pulmonary hypertension Echocardiography may be helpful.

**Tetralogy of Fallot:** Pre pregnancy: surgical correction, evaluation of cardiac status after, corrective surgery, Prenatal: consider termination with uncorrected lesions, monitor maternal Sao<sub>2</sub> and exercise tolerance, and consider rest and

supplemental O<sub>2</sub>. Fetal surveillance  
 Labor/delivery: careful fluid management, monitor BR SaO<sub>2</sub>, electrocardiogram (EKG). Epidural use requires careful preloading. ?need to shorten second stage, fetal monitoring  
 Postnatal: maintain maternal monitoring, discuss effective contraception.

**Rheumatic heart disease: general**  
 Principles, Prevent heart failure and prevent bacterial endocarditis.

**Mitral stenosis:**

Pre pregnancy: assess cardiac function, optimize medical therapy, and consider surgical correction. Prenatal: avoid excess weight gain. Tachycardia, serial echocardiography, treats tachycardia or arrhythmias, surgery for symptomatic severe disease, fetal surveillance.

**Labor/delivery:** High dependency or intensive care setting, consider central invasive monitoring, epidural analgesia has benefits, antibiotic prophylaxis for complicated deliveries, fetal surveillance.

**Mitral regurgitation:** Pre pregnancy: as for stenosis, Prenatal: restrict activity, serial echocardiography, adjust medical control, consider surgery for symptomatic severe disease, fetal surveillance.

**Labor/delivery/postnatal:**

Avoid fluid overload and hypertension, maternal cardiac monitoring. Endocarditic prophylaxis for complicated deliveries

**Aortic regurgitation: Pre pregnancy:**  
 As for mitral disease.

**Prenatal:** Surveillance for cardiac failure, surgery for failed medical therapy. Fetal surveillance.

**Labor, delivery or postnatal:** avoid fluid overload, invasive monitoring usually unnecessary, epidural beneficial, fetal surveillance

**Prosthetic valves:**

**Pre pregnancy:** assess cardiac status, counseling about valve function and warfarin risks

**Prenatal:** biosynthetic valves, adequate anticoagulation.

**Labor/delivery:** adjust anticoagulation, endocarditis prophylaxis.

**Postnatal:** Re adjust anticoagulation.

**Marfan syndrome:**

**Pre pregnancy:** genetic counseling, echocardiography (especially aortic root)? Counsel against pregnancy.

**Prenatal:** serial aortic root echocardiography. ?beta-blocker, avoid hypertension. Encourage rest? Surgery in extreme cases.

**Labor, delivery or postnatal:**

Epidural beneficial, avoid hypertension, ensure adequate oxygenation, short second stage, vigilance for aortic root dissection for at least 8 weeks postnatal.

**Dilated cardiomyopathy:** Pre pregnancy? Counsel against pregnancy. If history of peripartum cardiomyopathy. Prenatal:? Termination of pregnancy

with abnormal echo-cardiogram, medical therapy if symptomatic, anticoagulation.

### **Labor/delivery:**

Monitor for heart failure, avoid fluid overload, care with invasive monitoring. Postnatal: avoid fluid overload, discuss contraception.

### **Cardiac arrhythmias:**

Pre pregnancy: investigate and rest. Prenatal, labor, delivery or postnatal: maintenance of therapy to control arrhythmia, cardio conversion can be used

### **Myocardial infarction:**

Pre-pregnancy: assess cardiac function (especially echocardiography and stress test), counsel for pregnancy on basis of results, low dose aspirin.

Prenatal: avoid strenuous activity, surveillance for failure and arrhythmias, management as for non-pregnant, surgery can be carried out in pregnancy, thrombolytic therapy has been used.

Labor/delivery: monitor ECG, supplementary oxygen, epidural beneficial.

Postnatal: avoid fluid overload and exertion, discuss contraception (avoid combination oral preparations)

### **Idiopathic hypertrophic subaortic stenosis**

Pre-pregnancy: genetic counseling if parents have condition

Prenatal: limit activity: beta blockers for symptomatic parents.

Labor/delivery/postnatal: Avoid dehydration hypotension, beta-blockers for tachycardia, endocarditis prophylaxis for complicated deliveries.

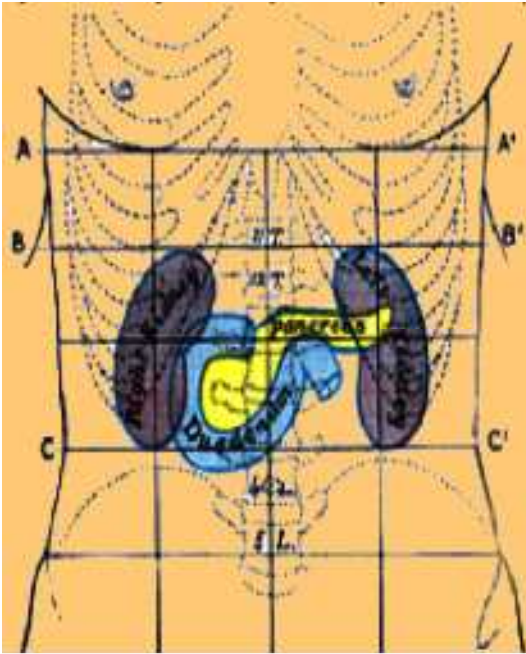
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## Chapter No: 6

**RENAL DISEASE IN PREGNANCY**

**Fig6.1: Shows locations of kidneys and its relations with pancreas**

**In pregnancy**, physiological and anatomical changes in the urinary tract occur in response to a variety of factors. Knowledge of these changes is important for the understanding and management of the various disease entities that occur in the genitourinary system of the pregnant patient.

**Major physiological changes in the urinary tract in pregnancy** - The increased blood flow to the kidney during pregnancy, which approximates 50% above normal, begins early in pregnancy and by the second month is well established. As a result of the increased renal blood flow both in the erect and supine positions, changes occur in many of the fundamental physiological functions of the kidney, they include. Glomerular filtration rate

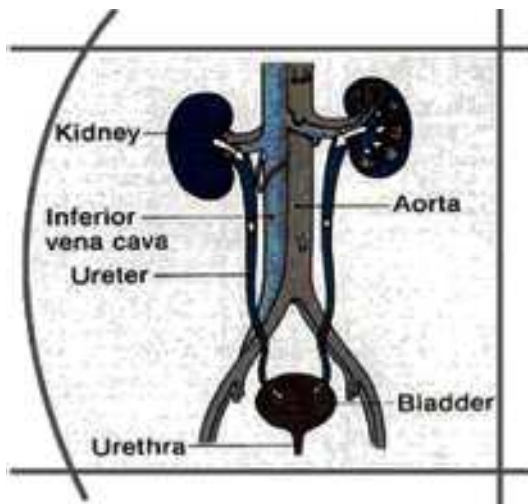
(GFR) is increased by 50% by the second month and increases steadily to term. BUN (blood urea nitrogen) is reduced to  $8.5 = 1.5$  mg, %. The normal level in the non pregnant state is  $1.3 + 3$  mg %. serum creatinine is reduced to  $0.46 = 0.6$  mg%. The normal level in the non pregnant state is  $0.767$  1:  $0.17$  mg %. clearance studies are not particularly reliable in pregnancy (i.e. inulin etc.). However, creatinine clearance parallels roughly to the glomerular filtration rate, so it is increased in pregnancy. These changes in GFR, BUN and serum creatinine may lead to a false assumption that the diseased kidney in pregnancy is functioning satisfactorily, other changes which are important to the kidney's function should be noted but are less important clinically; plasma aldosterone level is increased; and sodium reabsorption is increased.

These physiological alterations may be necessary for the maintenance of fluid homeostasis and blood pressure. Glucosuria and lactosuria may occur in the normal pregnant patient due to failure of the kidney to increase its resorptive power".

**Anatomical changes in the renal tract:**

From early pregnancy and throughout the puerperium, the renal collecting system is dilated (physiological hydronephrosis); peristalsis is decreased. These changes are clearly established as early as the second trimester. Dilatation is usually greater on the right side. The cause of the dilatation is unknown, but it is assumed to be largely hormonal, although mechanical obstruction of the

ureter at the pelvic brim may play some part in this process.



**Fig6.2: Shows course of ureters**

These changes of dilatation of the urinary tract that extend from the calyceal system of the kidney to the junction of the ureter and bladder, coupled with decreased peristalsis, may predispose to urinary tract infection which is one of the commonest complication of the pregnancy and the puerperium.

The changes noted in the urinary tract in early pregnancy persist throughout puerperium, and the full effect of these altered anatomical features may persist for as late as 12 weeks postpartum.

During pregnancy, in a small number of women, the vesicoureteric function is altered, so that reflux of urine from the bladder into the ureter is increased and, should bacteruria be present, may predispose the patient to infection of the upper urinary tract.

**The diagnosis of renal disease in pregnancy** - History and physical examination, along with urinalysis and

certain tests to be outlined, form the basis for accurate evaluation of the renal system in the pregnant patient. Familial history of renal abnormalities particularly polycystic renal disease should be looked for. Congenital disorders recognized in childhood or adolescence, which may or may not have required surgical correction is important. In the adolescent or the mature woman, one must be careful to survey the history, to suspect that the patient has suffered from glomerulo nephritis. If the woman has borne children, careful review of the details of previous pregnancies and the outcome is essential for the accurate evaluation of the present pregnancy and the potential problem arising from the renal tract.

General physical examination is important, with particular attention to the blood pressure. Although eye ground changes of renal disease are generally confined to the advanced serious problems, the opportunity to study the eye grounds in every pregnant patient should not be missed. The urine specimen to be studied should preferably be collected after a period of fluid restriction, and the specific gravity should be at least 1020 or greater. Specific gravities of less than 1020 after a period of fluid restriction suggest impairment of renal concentrating function. If possible, the specimen should be a clean voided specimen. Although the dipstick method is commonly used at present, it lacks some of the advantages of 3% salicylic acid Le. Detecting globulin in the urine. In addition, dipstick testing may be too highly sensitive. Most normal pregnant women will demonstrate at least a trace of albumin in a clean voided specimen using the dipstick technique. In view that the dipstick or salicylic acid method

indicate an abnormal amount of protein (I + or greater), a 4 hour urine.

Collection should be carried out. Ideally, this 24 hour urine specimen should be a clean voided specimen, and it should not contain in excess of 200 mg. of protein over 24-hours. Even in the event of heavy vaginal discharge, urinary protein content in excess of 500 mg. per 24-hours is abnormal. Heavy proteinuria in excess of 2 grams per 24 hours suggests glomerular damage. In addition to chemical studies of the urine, microscopic examination of the urinary sediment is an extremely important step. Normal urinary sediment may contain one red blood cell per high power field, or five white blood cells; occasionally hyaline casts may occur, approximately one in 15 high power fields in a spun drop of urine. The content of white cells, red cells and hyaline casts will be increased in the presence of fever or following exercise. It is obvious but important to mention that if granular casts are detected in the examination of the urinary sediment, a high index of suspicion for renal pathology should exist. Bacteria should not be seen in a gram stain of ordinary unsung specimen in a high power field. If bacteria are present in the specimen, in a high power field, it is a rough indication that the colony count of bacteria in the urine will be in excess of 100,000 colonies per ml. of urine. If bacteria are demonstrated on Gram stain in a high power field of the unsung specimen, a culture should be carried out and colony counts and sensitivity performed. Other laboratory studies that assist in evaluation of renal function include the BUN, creatinine, 24 hour creatinine clearance (which must be corrected for pregnancy).

Radiological studies are usually unnecessary in the pregnant patient, but sometimes become mandatory. While the principle of avoiding x-ray exposure to the fetus in utero is a good one, in certain cases (particularly of obstructive uropathy) important information will be missed if the IYP is not carried out. In our unit we prefer to do a 'short IYP'. The use of an image intensifier is desirable if available to limit x-ray exposure.

In the non pregnant state, renal biopsy is often important to the complete elucidation of complex renal problems. In pregnancy, however, it is rarely necessary, and should usually be deferred until after the pregnancy has been completed. The risk of significant hemorrhage from renal biopsy during pregnancy is 1 %, and it should be weighed against the advantages of carrying out this procedure at that time.

#### **Abnormalities of the urinary tract in pregnancy:**

(a) Orthostatic albuminuria - In this condition albuminuria (which is considered significant) occurs when standing or walking or following exercise. When the 'patient is placed at rest, and in late pregnancy at rest on her left side, the albuminuria will disappear. The relationship of orthostatic albuminuria to true disease of the urinary tract is uncertain. In cases where albuminuria is demonstrated, with no other abnormal findings, one may suspect the orthostatic nature of the disorder. Follow up examination in cases suspected of being orthostatic in nature is extremely important to rule out underlying diseases which may be missed because of the limited investigation possible in the pregnant patient.



**Fig6.3: Shows location of kidney in the body.**

(b) **Asymptomatic bacteriuria** - The incidence of asymptomatic bacteriuria is about 5% in the pregnant population. There are no symptoms. Diagnosis will be established when the colony count of bacteria in the urine exceeds 100,000 or more per mi. of urine. In cases where particular care is taken in establishing a clean midstream catch, a colony count of 10,000 per mi. may be significant. Cass was one of the workers who first drew attention to the importance of identifying patients with asymptomatic bacteriuria. His work appeared to demonstrate an increase in prematurity and perinatal loss in patients who suffered from this problem. In our unit, we have been unable to arrive at the conclusions stated by Casso. However, all would agree that early prenatal examination of the urine for the presence of bacteria is important, because of the women who develop acute pyelonephritis in pregnancy, 75% of them come from the group of patients demonstrating asymptomatic bacteria.

Screening for bacteria in the urine in early pregnancy is expensive. Our unit has not been satisfied with the chemical tests for bacteria. Undoubtedly, the most effective and least expensive screening test is microscopic examination of a Gram stain of the urine. The presence of bacteria in a high power field of UN

spun urine indicates a colony count in excess of 100,000. The urine under these circumstances should then be sent for culture and sensitivity.

(c) **Acute pyelonephritis** - Acute pyelonephritis in pregnancy is the most common cause for medical admission to hospital during pregnancy. The incidence throughout the world varies from 1 % to 5%. In our own unit it is approximately 2%. The signs and symptoms are those of acute onset of fever, pain over the flanks occasionally radiating down along the course of the ureter and into the bladder. Occasionally the pain is associated with frequency and dysuria. The presence of rigor, high fever associated with renal tenderness, nearly always indicates an involvement of the renal parenchyma.

Examination of the urine usually makes the diagnosis easy because of the presence of massive pyuria. In rare instances, however, ureteric obstruction may obscure the flow of infected urine and the urinary sediment may be relatively free of pus. Although the classic case of pyelonephritis in pregnancy is easy to diagnose, the presence of nausea, vomiting and right lower quadrant pain may raise the suspicion of acute appendicitis. This is an extremely important differential point to be established. In cases of high fever, marked ureteric tenderness and colicky pain, it may be necessary to carry out an IVP to exclude ureteric obstruction from renal calculi. The commonest organism to cause acute pyelonephritis is *E. coli*, but a spectrum of organisms may be the offending bacteria, therefore, culture and sensitivity of the urine should be obtained prior to the institution of treatment.

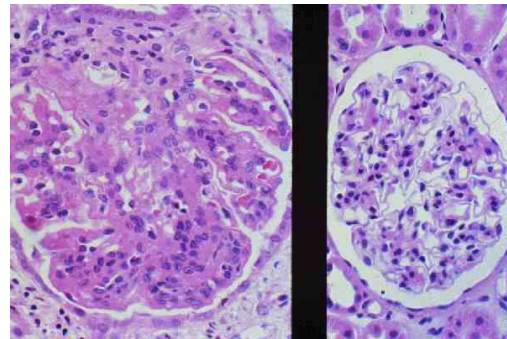
Once appropriate urine and blood cultures have been obtained, treatment may be established. Because the aetiological agent in the majority of cases is *E. coli*, ampicillin is generally effective: 2-4 grams of ampicillin per 24 hours is usually adequate, but higher doses may be required. Intravenous ampicillin in the seriously ill patient should be employed. Other antibiotic may be required to control the infection, but the employment of the antibiotic should be based on the accurate culture and sensitivities. Care must be used in selecting appropriate agents for treating the pregnant patient, to avoid secondary effects on the fetus and nephrotoxicity in the mother. Ideally a patient should be treated intensively from 7 to 10 days. After this regimen, lower doses in the range of 1 gram of ampicillin per day may be carried on for an additional two weeks. It is extremely important, upon completion of therapy, to re culture the urine to see that effectively sterilized urine has been achieved. In certain complicated cases, the original bacteria may be destroyed by the appropriate antibiotic, only to find alternate bacteria of more resistant strains to be growing out. Consultation with infectious disease personnel, as to the appropriate and ongoing treatment of patients with this difficulty is advisable.

Chronic pyelonephritis cases may require small daily doses of sulfonamide during pregnancy and the puerperium. In undertaking this form of therapy, one must be aware of the side effects of this type of treatment. Chronic pyelonephritis, particularly where there has been significant renal damage, may be one of the major causes of underlying undiagnosed hypertension in pregnancy, and certainly represents a serious cause

of morbidity arising from the renal tract in women in their late 30's and early 40's.

Renal tuberculosis, a form of chronic pyelonephritis, is rare in this country presently, the suspicion that it exists may arise in cases where pyuria exists but cultures are repeatedly negative for the common bacteria. In the event that an acid fast infection of kidney is diagnosed, appropriate treatment must be instituted immediately, using multiple drug therapy in most instances.

Rarely termination of pregnancy is wanted because of renal tuberculosis. In cases of renal tuberculosis, where azotaemia persists and increases, despite adequate treatment, continuation of the pregnancy may not be feasible.



**Fig6.4: Shows histopathology of glomerulonephritis.**

Glomerulonephritis tends to be a grab-bag of diagnosis. During pregnancy, it may be difficult, to assign the patients to the various stages of this relatively uncommon, serious form of renal disease. Acute glomerulonephritis is rarely seen in pregnancy, and is associated with an increased fetal and maternal loss, particularly if complicated by the addition of toxemia in late pregnancy. Diagnosis may be difficult.

A clear cut history of streptococcal infection of the throat, going on to the development of hematuria (tea like urine) and generalized oedema may raise suspicion. The urine demonstrates significantly elevated protein, with blood and granular casts. BUN. Is usually somewhat elevated? In some cases, hypertension will develop. It is in this context that the addition of pregnancy induced hypertension becomes an additional hazard, treatment consists of rest.

Adequate diet (which in some cases is considered to be advantageously protein-sparing), careful observation of the pregnancy, and in rare instances termination of the pregnancy if deterioration is in evidence. The broad range of possible renal involvement makes it mandatory that each case must be individually dealt with.

ii) Chronic glomerulonephritis (chronic nephritis) unfortunately, the definitive diagnosis of chronic glomerulonephritis in pregnancy is very difficult, and therefore many patients manifest in abnormal proteinuria and some elevation of BUN. With or without hypertension, will be assigned to this category of disease for lack of accurate diagnosis. In all cases presenting in this category, careful history and physical examination including examination of the eyegrounds and blood pressure must be carried out. This coupled with BUN, creatinine clearance rate, and careful examinations of the urinary sediment are most important.

In the event (as is commonly the case) that accurate designation of the disease process cannot be achieved during pregnancy, then the plan of management

should be expectant; increased rest, possibly hospitalization depending upon the severity of the situation, with careful surveillance for the onset of pregnancy induced hypertension or failure of the pregnancy to grow at an appropriate rate. The risk basically in this category of patients is the establishment of pregnancy induced hypertension (PIH) or preeclampsia and with it the development of intrauterine growth retardation, the risk of abruptio placentae, and other catastrophic complications.

The difficulty in establishing the prognosis for patients in this form of chronic renal disease is acknowledged by most workers in the field. In cases that have been diagnosed prior to the pregnancy and the disease process worked out by renal biopsy, a more reasonable prognosis may be offered although, in some of the most severe and florid cases of advanced renal disease, pregnancy may be surprisingly well tolerated. The most important step in assessing the prognosis and carrying the patient through pregnancy is a history of the details of previous pregnancies.

If the patient has normal blood pressure, modest amounts of proteinuria, normal BUN, creatinine and creatinine clearance care should be taken through her pregnancy with a satisfactory fetal and maternal outcome. In a relatively large series of patients with documented ('chronic nephritis" free of hypertension and proteinuria, essentially normal fetal and maternal outcome was demonstrated. In those cases that demonstrated proteinuria, in the absence of hypertension, a generally favorable outcome was noted, while fetal mortality was increased moderately. In those cases combining hypertension and proteinuria,

approximately 18% fetal mortality was noted; 17% of the patients developed pregnancy induced hypertension. Patients with nephrotic syndrome present a reasonably optimistic outcome in the absence of hypertension or azotaemia. However, with the advent of either or both, careful review of the case should be undertaken to determine the feasibility of continuation of pregnancy.

### **Other forms of renal disease to be considered in pregnancy**

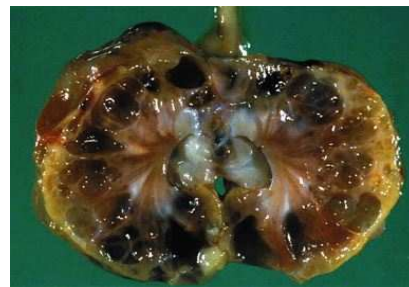


**Fig6.5: Shows rash of Lupus.**

### **Systemic Lupus Erythematosus (SLE)**

- It has been demonstrated that two-thirds of the patients who have SLE have renal involvement which may be apparent only on renal biopsy. Ideally, patients who suffer from SLE and who anticipate pregnancy should be seen, evaluated, and counselled prior to conception. Those cases; of SLE who have com-promised renal function, particularly with super added hypertension, present a very significant risk in pregnancy both to the fetus and to the mother. The superimposed pregnancy induced hyper tension, even in the normotensive patient with Lupus, can be frighteningly abrupt and lead to a serious deterioration of the maternal state. The question of carrying patient's through pregnancy with SLE remains controversial. Even within our own university,

two reputable nephrologists take diametrically opposite views: on the one sides the view that no woman known to have systemic Lupus should be allowed to consider undertaking pregnancy. On the other side, in the light of a relatively large experience, the fact that although renal impairment has been identified and moderate hypertension is present, with extremely careful prenatal care, in active pregnancy outcome may be achieved. It is my personal view that in the case where renal impairment has been demonstrated, particularly if hypertension is present, pregnancy should be discouraged. In the situation where pregnancy is desired and the patient is aware of the risks, control of hypertension by appropriate agents is desirable. Hypotensive agents that will improve renal blood flow should be chosen. Careful monitoring of the patient's state by an obstetrician and nephrologist is mandatory for the evaluation of the integrity and growth of the fetu-placental unit. The sudden advent of pregnancy induced hypertension in the vast majority of cases will warrant immediate termination of the pregnancy. In patients with SLE, delivery does not end the chapter. Determination of the Lupus may lead to a progressive downhill course, acute renal failure or the onset of a nephrotic syndrome in the mother.



**Fig6.6: Shows section of polycystic kidney.**

- (a) **Polycystic renal disease** - Fortunately, this is an uncommon condition in women in the childbearing age. In the event, however, a pregnancy is encountered with a patient suffering from this disorder, one should anticipate a satisfactory outcome if there is no evidence of azotaemia or hypertension.

In counseling patients who suffer from this disorder, it must be pointed out that this is autosomal dominant and 50% of the offspring may inherit the abnormality.

The second important factor to be aware of is that in those people who have polycystic renal disease, 20% have intracranial aneurysms which provide a serious risk in pregnancy.

(b) **Diabetic nephropathy** - All diabetic patients who have the onset of diabetes less than 10 years of age will have some renal disease when they enter their childbearing period. Kimmelstiel Wilson's disease is the classic form of advanced diabetic nephropathy.

The out look and treatment of this condition should be roughly comparable to other forms of chronic renal disease. The increased hazard to the diabetic patient who is pregnant and has renal involvement is well recognized in White's writings and classification of the pregnant diabetic.

(c) **Renal calculi** - Although dilatation and stasis predisposes to calculi formation in the renal tract, the incidence in pregnancy is less than one in a thousand pregnancies. Diagnosis is usually based

on the classic history of renal colic with or without hematuria and the findings of pain and tenderness in the region of the kidney or ureter.



**Fig6.7: Shows vascular changes in the periphery especially big toe and glomerular sclerosis.**

In some instances, this condition, as previously mentioned, may mimic appendicitis and other intraperitoneal catastrophes. Concerns for x-ray exposure should not prevent the obstetrician from taking an IVP where this may be required to make specific diagnosis. In certain instances the treatment is conservative, anticipating that the stone will pass.

Frequently, cystoscopy with catheterization of the ureter will dislodge the stone and permit drainage of the kidney. Retrograde recovery of a calculus by endoscopic manipulation may be possible. Open lithotomy should be reserved for cases where a danger of sepsis is present and the calculus cannot be removed from below. If a stone is recovered it should be analyzed. The patient's serum calcium and phosphorus levels should be ascertained.



**Hyperparathyroidism, an uncommon cause of renal calculi should be ruled out.**

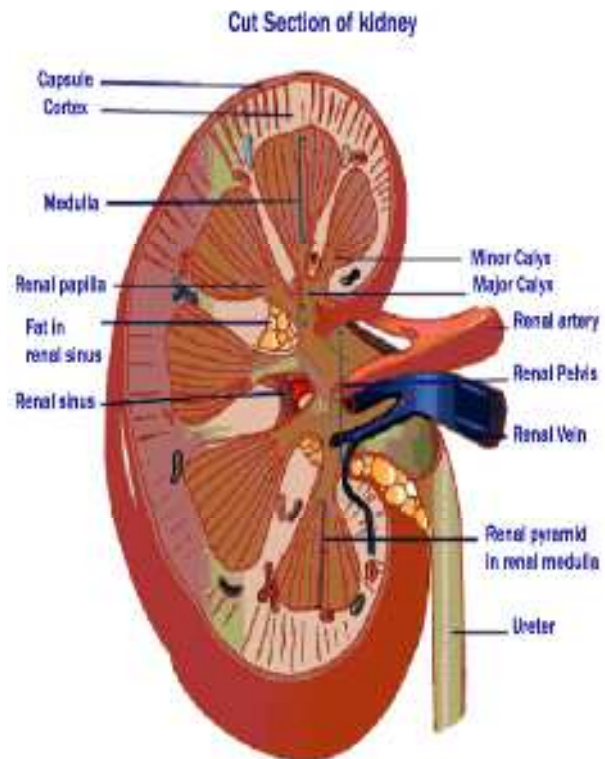
#### **Acute renal failure:**

This is an uncommon but serious complication of pregnancy. The incidence has been reported as varying between one in 1400 and one in 5,000 pregnancies, prior to the change in abortion laws in North America, in the era of frequent septic abortion, many women presented to this unit in acute renal failure as the result of sepsis or blood loss initiated by a criminal abortion. The other common groups of cases of acute renal failure we see are in late pregnancy, where the condition develops as a complication of abruptio placentae, toxanemia, sepsis, hemorrhage, amnionitis, or other rare renal conditions. In our own unit, prior to the development of adequate renal dialysis and now renal transplant, the maternal mortality associated with late pregnancy acute renal failure was approximately 25%. These figures have been reduced in latter years with more sophisticated modalities of treatment.

The management of patients with acute renal failure is a complicated, labour, intensive situation. I will attempt to refer in generalities to some of the principles that should be adhered to. In risk situations i.e., abruptio placentae, severe toxemia, sepsis, severe hemorrhage and amnionitis, vigilant observation of the urinary output is mandatory. It goes without saying that vigorous treatment of the underlying cause, particularly abruptio placentae, must be undertaken.

Regrettably, in the development of acute renal failure often the physician incharge has incorrectly assessed the am-

ount of blood and fluid lost, proper replacement of the appropriate agents - fluid, blood and electrolytes cannot be over emphasized. If oliguria presents (i.e., urinary output under 400 cc, in 24-hours) or anuria is present or anticipated, or an increasing BUN. is noted, the general principles of management should include:-



**Fig6.8: Shows cut section of kidney.**

Fluid restriction to 400 cc. for 24 hours, plus measured loss; Low protein, high-carbohydrate, high fat, diet;

**The use of ion exchange resins to protect against hyperkalemia:** Where sepsis exists, appropriate antibiotic therapy must be instituted. The nephrotoxicity of commonly used antibiotic agents must be considered in dealing

with patients in this category. In patients who have established oliguria and anuria, we feel it is important to establish a CVP line, hourly outputs of urine must be done, preferably with an indwelling catheter. Our first move in an attempt to produce diuresis is to undertake a trial of volume expanders' using intravenous glucose or Ringer's lactate. Increasingly our experience has led us away from the use of frusemide or other diuretic agents, preferring instead a flush of intravenous fluids to help correct a shutdown kidney.

In cases where diuresis is not established, consultation with a nephrologist is mandatory. Indications for hemodialysis or peritoneal dialysis are available in all of the common texts dealing with this subject. In our own unit, we prefer hemo dialysis, but the lifesaving value of peritoneal dialysis must not be forgotten.

When dialysis has been instituted, and the condition is reversible, one will hopefully see the anuria reversed and the kidneys begin to function. In those cases where intractable kidney damage has been sustained, chronic dialysis may be necessary. Those patients condemned to chronic dialysis become candidates in certain situations for renal transplant.

### **Renal transplantation in pregnancy -**

In general, a patient who has received a renal transplant and becomes pregnant may be considered to be in the same high risk group of patients as those who have significant renal disease. The expected complications correlate well with the patients who have chronic renal disease of some substance. As expected, the outcome of the patient and her kidneys' ability to withstand the stress of pregnancy, are dependent upon the quality of

the graft function. In those patients with renal transplant who are normotensive and who have stable renal function, a BUN of less than 2 mg. per 100 mL., who are on less than 10 mg. of prednisone daily, and patients with Azathioprine dosage which does not exceed 3 mg. per kilogram per day, a good outcome may be predicted. In the patient undertaking pregnancy with a transplanted kidney, careful monitoring such as in chronic renal disease is mandatory. The pre pregnancy function of the kidney transplant does not always herald a satisfactory outcome. Sudden alarming deterioration of the kidney function has been encountered in some of these cases. The major problems noted in our unit have been prematurity, unexplained premature rupture of the membranes, intrauterine growth retardation on the fetal side, and on the maternal side deterioration of renal function and pregnancy induced hypertension. Because of the increased risk to the fetus, it is almost redundant to suggest careful monitoring of the fetal maternal unit, as well as the vigilant care of the mother who undertakes this pregnancy at such great risk.

With respect to the use of immunosuppressive therapy during pregnancy in cases of renal transplant, although theoretically the incidence of fetal maldevelopment should be increased, it is not inevitable. However, appropriate antenatal counseling should take place to warn the woman with the renal transplant who anticipates pregnancy of the possible problems to both herself and her fetus.

With respect to delivery of the patient who has had a renal transplant, in our own unit cesarean section has usually

been preferred because of the site of the transplant on the pelvic side-wall, which provides relative cephalopelvic disproportion and possibly increased trauma to the transplanted kidney as the fetus proceeds through the pelvis.

Experienced obstetricians will know how many times they have encountered the patient with renal disease, identified for the first time during pregnancy. From the foregoing text, students will suspect it is extremely important that all patients who manifest evidence of renal disease for the first time during pregnancy should be carefully followed after the pregnancy, details of their renal disease worked out, and appropriate counseling offered for future pregnancies.

That many of the signs and symptoms of renal disease will present for the first time during pregnancy, and that because of the pregnancy state appropriate investigation and delineation of the true aetiology of the problem is impossible.

### **Management options:**

#### **Systemic lupus erythematosus:**

##### **Pre-pregnancy:**

Establish good control of SLE: adjust maintenance medications, If possible, discontinue azathioprine, methotrexate this should be done only under careful supervision. Laboratory assessment for anemia, Thrombocytopenia, underlying renal disease and antiphospholipid antibodies (? +anti RO/SSA and anti-La/SSB) Counsel patient regarding potential for SLE exacerbations, pregnancy induced hypertension risk, and fetal/neonatal risks

**Prenatal:** Joint obstetrician and physician surveillance, Encourage early prenatal care. Accurate dating with ultrasonography in early pregnancy. Close follow-up every 2 weeks in first and second trimesters: every week in third trimester. Watch for signs or symptoms of SLE flare, superimposed pregnancy-induced hypertension, fetal growth restriction for SLE patients with renal involvement, perform. Monthly 24h urine collections for creatine clearance and total protein. Drugs: glucocorticosteroids are safe: azathioprine as second line therapy if steroids ineffective (IUGR risk): methotrexate and cyclophosphamide as third-line therapy after the first trimester: avoid antimalarials and full dose NSAIDs. Serial ultrasonography examinations for fetal growth, umbilical artery Doppler recordings and amniotic fluid volume. Being prenatal testing at 30-32 weeks gestation (earlier in patients with worsening disease, evidence of fetal compromise, or with a history of poor pregnancy outcome). Consider low-dose aspirin therapy.

**Labor/delivery:** Deliver at term in absence of complications: avoid postdates. Continuous electronic fetal monitoring. Steroid boluses at delivery for patients on chronic steroid therapy. Pediatric and anesthesiology notification

##### **Postnatal:**

Watch for SLE exacerbation. Restart maintenance therapy. Evaluate neonate for SLE-associated manifestations.

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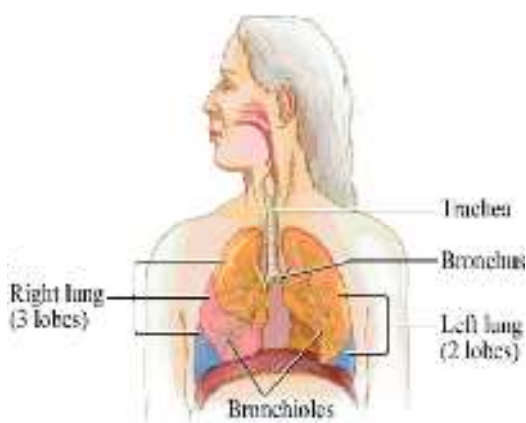
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## Chapter No: 7

**RESPIRATORY DISEASES IN PREGNANCY****Respiratory physiology:**

Pregnancy induces profound changes in the mother, resulting in significant alterations in normal physiology. The anatomical and functional changes affect the respiratory and cardiovascular systems. Management of respiratory diseases in pregnancy requires an understanding of these changes for interpretation of clinical and laboratory manifestations of disease states.



**Fig7.1: Shows anatomical section with respiratory tract**

**Anatomical changes:**

Hormonal changes in pregnancy affect the upper respiratory tract and airway mucosa, producing hyperemia, mucosal edema, hypersecretion, and increased mucosal friability. Estrogen is probably responsible for producing tissue edema, capillary congestion, and hyperplasia of mucous glands. The enlarging uterus and the hormonal effects produce anatomical changes to the thoracic cage. As the uterus expands, the diaphragm is displaced cephalad by as much as 4 cm,

the anteroposterior and transverse diameter of the thorax increases, which enlarges chest wall circumference. Diaphragm function remains normal and diaphragmatic excursion is not reduced.

**Pulmonary function:**

Anatomical changes to the thorax produce a progressive decrease in functional residual capacity, which is reduced 10-20% by term.

The residual volume can decrease slightly during pregnancy, but this finding is not consistent; decreased expiratory reserve volume definitely changes.

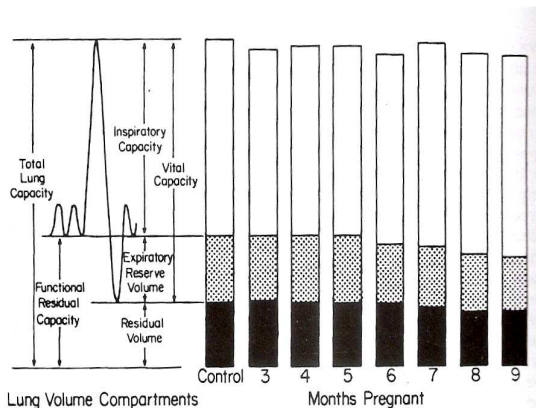
The increased circumference of the thoracic cage allows the vital capacity to remain unchanged, and the total lung capacity decreases only minimally by term. Hormonal changes do not significantly affect airway function. Pregnancy does not appear to change lung compliance, but chest wall and total respiratory compliance are reduced at term.

**Ventilation:**

The minute ventilation increases significantly, beginning in the first trimester and reaching 20-40% above baseline at term. Alveolar ventilation increases by 50-70%. The increase in ventilation occurs because of increased metabolic carbon dioxide production and because of increased respiratory drive due to the high serum progesterone level. The tidal volume increases by 30-35%. The respiratory rate remains relatively constant

increases slightly.

**Arterial blood gases:** Physiological hyperventilation results in respiratory alkalosis with compensatory renal excretion of bicarbonate.



**Fig7. 2: Serial measurements of lung volume compartments during pregnancy. (From Prowse CM, gaensler EA: Respiratory and acid base changes during pregnancy. Anesthesiology 26:381, 1965)**

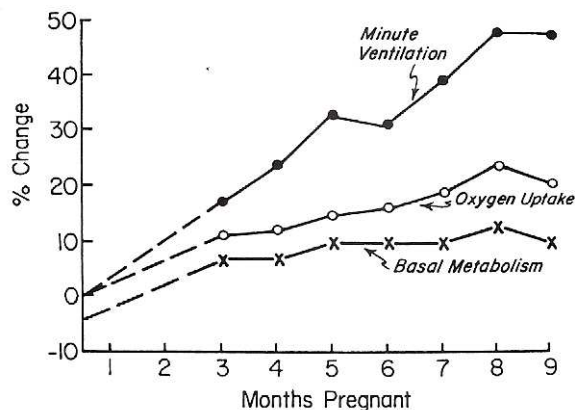
The arterial carbon dioxide pressure reaches a plasma level of 28-32 mm Hg, and bicarbonate is decreased to 18-21 mmol/L, maintaining an arterial pH in the range of 7.40-7.47. Mild hypoxemia might occur when the patient is in the supine position. Oxygen consumption increases at the beginning of the first trimester and increases by 20-33% by term because of fetal demands and increased maternal metabolic processes.

In active labour, hyperventilation increases and tachypnea caused by pain and anxiety might result in marked hypocapnia and respiratory alkalosis, adversely affecting fetal oxygenation by reducing uterine blood flow. In some patients, severe pain and anxiety can lead to rapid shallow breathing with

alveolar hypoventilation, atelectasis, and mild hypoxemia.

Dyspnea during pregnancy is quite common, occurring by most estimates in approximately 60% of women with exertion and fewer than 20% at rest. Physiologic dyspnea can occur early in pregnancy and does not interfere with daily activities.

Although mechanical impediment by the gravid uterus is often blamed, hyperventilation due to increased progesterone levels probably is the most important mechanism. The presence of other symptoms and signs of cardiopulmonary disease indicates a possible pathologic nature of dyspnea.



**Fig7.3: Time course of % changes in minute ventilation, oxygen uptake, and basal metabolism during pregnancy. (From Prowse CM, Gaensler EA: Respiratory and acid-base changes during pregnancy. Anesthesiology 26:381, 1965)**

**Safety of drugs used in pregnancy:**

**Methylxanthine:**

Both theophylline and aminophylline readily cross the placenta, but no fetal ill

effects or malformations have been reported. Theophylline pharmacokinetics are unaffected by pregnancy, and this drug also appears in breast milk.

### **Betagonists:**

These have little systemic absorption and a more potent bronchodilatory effect via inhalation. Data on the use of inhaled beta-agonists showed no difference in perinatal mortality, congenital malformations, birth weight, or Apgar scores.

### **Corticosteroids:**

The use of corticosteroids during pregnancy continues to be controversial, although numerous reports confirm their use without adverse fetal effects. In 3 reports on human pregnancies, no congenital malformations or adverse fetal effects were found from inhaled corticosteroids.

Prednisone has been used extensively during pregnancy for a variety of conditions. It is associated with an increased incidence of cleft palates in animals but not in humans.

### **Ipratropium and bromide:**

Neither of these medications has been associated with adverse fetal outcomes.

### **Antihistamines and decongestants:**

Patients frequently request these medications for nasal symptoms, mucosal edema, and hyperemia that accompany normal pregnancy. The available data does not indicate safety of antihistamines in pregnancy. Brompheniramine is associated with congenital malformations.

### **Common antibiotics used for respiratory infections:**

The major antibiotics considered safe during pregnancy are penicillin, cephalosporins, and erythromycin. Although penicillin and ampicillin readily cross the placenta, no adverse effects to the fetus are reported. Cephalosporins also traverse the placenta to a moderate degree, but no adverse fetal effects occur. Erythromycin crosses the placenta to a low degree but achieves high levels in breast milk. The estolate formulation is contraindicated due to potential hepatic toxicity in the mother. Antibiotics that have relative contraindications include sulfonamides, trimethoprim, aminoglycosides, nitrofurantoin, antituberculosis drugs, tetracyclines, and quinolones.

### **Teratogens used in pulmonary disease:**

These drugs include iodine-containing compounds. Brompheniramine, antihistamine, coumarin, and anticoagulants cause various teratogenic effects. Ciprofloxacin, sulfonamides, tetracyclines, chloramphenicol, streptomycin, and rifampin have been associated with various effects. Ionizing radiation exposure to the fetus is associated with growth retardation, CNS effects, microcephaly, and eye malformations.

Maternal radiation exposure of less than 0.05 Gy is associated with no adverse effects, a dose of 0.05-0.1 Gy is considered the gray zone, and exposure to more than 0.1 Gy is associated with significant fetal effects. Fetal ionizing radiation might cause increases in childhood leukemia. A chest radiograph results in 0.002-Gy exposure; perfusion lung scan, 0.002 Gy; ventilation lung

scan, 0.004 Gy; pulmonary angiography, 0.004 Gy; and venography, 0.004 Gy.

### **1. Asthma:**

Asthma is by far the most common chronic disease of children and young adults. Asthma deaths are rising in many countries. Asthma probably causes more preventable deaths than any other disease of young people. Population studies of asthma predict that up to 5% of pregnant women may be asthmatic. Patients may accept as normal their symptoms of cough, wheeze and breathlessness, and until recently doctors have often mislabeled such individuals as having chronic bronchitis. 'Have you woken at night with wheezing or noisy breathing in the past year?' It would identify almost all women with significant asthma and indicate the need for more detailed assessment.

### **Effect of pregnancy upon asthma:**

The sensation of breathlessness which often accompanies normal pregnancy may be mistaken for a loss of asthmatic control. Many women experience worsening symptoms to avoid their usual medication. There does seem to be a tendency towards improvement in asthma in the last trimester, and laboratory measurements of bronchial responsiveness support this. Similarly, there is a tendency to postnatal deterioration. A tendency to improvement or deterioration in one pregnancy is also likely to occur in the next. Severe uncontrolled asthma resulting in prolonged maternal hypoxemia can result in fetal loss. Studies suggested an association between asthma and low birth weight. More recent careful study found no difference.

Maternal preeclampsia and neonatal hypoglycaemia was both commoner in the asthmatic group. A recent review of over 24000 deliveries suggested an association between pregnancy-induced hypertension and asthma during pregnancy. Schatz and colleagues II made multiple measurements during pregnancy of forced expiratory volume in 1 s (FEV<sub>1</sub>) a measure of airways obstruction. They found a correlation between mean FEV<sub>1</sub>, as a percentage of predicted values, and birth weight, suggesting a relationship between poor asthma control and intrauterine growth retardation. Asthmatic mothers had an increased incidence of preterm labor and delivery with appropriate management, almost all young asthmatics pregnant or not - can be rendered virtually asymptomatic and unlimited in their daily activities.

**Treatment:** Treatment of asthma during pregnancy should essentially be the same as treatment in non pregnant individuals. Individuals with the very mildest asthma (symptoms once daily or less) may be managed with intermittent inhaled  $\beta_2$ -agonists such as salbutamol (albuterol) or terbutaline, regular inhaled anti-inflammatory medication such as inhaled corticosteroids or cromoglycate should be introduced for more frequent problems. Those with persisting symptoms should be treated with high dose inhaled corticosteroids, followed by the addition of inhaled anticholinergics, oral  $\beta_2$ -agonists, oral methylxanthine (aminophylline, theophylline) or oral steroids. Inhaled therapy is preferred to oral. There is no evidence for teratogenic effect in humans from any of the drugs commonly used to treat asthma:  $\beta_2$ -agonists, methylxanthine, cromoglycate, oral steroids and inhaled beclomethasone, zo,



Zl L-ong acting inhaled fJ-agonists such as salmeterol are now being introduced in Europe. It seems sensible practice to avoid new drugs for asthma during pregnancy. It should be remembered that both oral steroids and oral fJ-agonists influence glucose metabolism. Neither oral nor inhaled fJ-agonists have been demonstrated to delay the onset or slow the progress of labour. Inhaled fJ-agonists must not be withheld during labor. Ergometrine has been reported to cause bronchospasm and should be avoided. Breast feeding is safe with asthma medication.

Objective measurements of airways obstruction, like peak flow measurements, are essential. Asthma is usually worse during the night and early morning; a pregnant woman seen in normal working hours may appear well but still have severe asthma with profound sleep disturbance. It is these individuals with wide diurnal swings of airways calibre who are at greatest risk of sudden catastrophic deterioration; excellent daytime lung function may be present, but the risk to mother and fetus is high.

## **2. Pneumonia:**

The incidence of pneumonia in pregnancy is rising again. Berkowitz & LaSalle reported pneumonia in 1 in 367 deliveries. LaSalle suggest that in their population this rise is at least in part attributable to human immunodeficiency virus (HIV) infection and drug abuse. It has been suggested that pneumonia is commoner in pregnancy than in the non-pregnant state, and that this may be due to the depression of cell-mediated immunity that occurs during pregnancy. In varicella pneumonia during pregnancy, both maternal and fetal mortality is high.

28 The outcome may be improved by the early use of intravenous acyclovir. Non-immune pregnant women exposed to varicella should receive varicella-zoster immune globulin. Physical signs in the chest may be scanty or even absent and a cursory examination may be falsely reassuring. If there is any clinical suspicion of a respiratory disorder, chest radiography must not be omitted simply because a woman is pregnant. Even experienced Clinicians can miss cyanosis and blood gas analysis can reveal profound hypoxia in patients who superficially look well. Pneumococcal pneumonia (which can present with a sudden onset of breathlessness, pleuritic pain, hemoptyses and circulatory collapse) can all too easily be mistaken for pulmonary thromboembolism. In the latter case the central venous pressure will be raised rather than the low values likely to accompany infection. Penicillins, cephalosporins and erythromycin are safe in pregnancy, but tetracyclines and aminoglycosides should be avoided.

## **3. Acquired immune deficiency syndrome:**

The immunosuppression associated with the progression of HIV infection to AIDS means that such individuals are at increased risk of Pneumocystis carinii pneumonia (PCP), tuberculosis, Mycobacterium avium-intracellulare infection, cytomegalovirus and other opportunistic infections. The antiretroviral drug zidovudine prolongs survival in AIDS and advanced AIDS related complex, but there is debate about its role in slowing progression from HIV seropositivity to AIDS. It appears to be safe in pregnancy. Cotrimoxazole is safe in pregnancy. HIV infected pregnant women with a history of PCP or a low

CD4 + cell count (200/ml) should receive pro-phylactic co-trimoxazole or nebulize pe-ntamidine.

#### **4. Tuberculosis:**

TB is of relevance to obstetricians for three reasons. First, the serious consequences of untreated TB and the risk of its spread to others, particularly children. Secondly, obstetricians may be consulted by women worried about the effect of TB - and particularly of the drugs used in its treatment. Thirdly, the presence of TB may, in some populations, indicate the risk of concomitant infection with HIV.

Routine microscopy and culture of specimens will not detect tubercle bacilli. Chest x-ray is suggestive fibre optic bronchoscopy and aspirations of secretions with topical anaesthesia are safe.

The treatment regime is supervised by a physician who deals with TB. Fears about the teratogenicity of antituberculous drugs have in the past been grounds for termination of pregnancy but this can no longer be justified.

Standard antituberculous therapy is an initial three-drug regime for 2 months, continuing with two of these drugs for a further 7 months, totaling 9 months of treatment. A 2-month four-drug regime, continuing with two drugs to total just 6 months, is also highly effective. In the developed world, the two drugs used throughout the treatment period are usually rifampicin and isoniazid. Most physicians now prefer pyrazinamide, which does not have the problems of ocular toxicity seen with ethambutol, and clinical improvement is faster.

Earlier workers suggested avoiding rifampicin if possible. There is no evidence of teratogenicity in humans and from this point of view the drug is now widely regarded as safe. Isoniazid and ethambutol similarly have no adverse effects on the fetus. Streptomycin with its high risk of fetal (and indeed maternal) ototoxicity should not be used. The emergence of multi drug-resistant strains of TB (MDR-TB), mainly in HIV-positive individuals, is necessitating a major reconsideration of treatment stratagems.

A woman who is not coughing sputum or whose sputum contains no tubercle bacilli on direct microscopy by an experienced laboratory may be regarded as non infectious and isolation is not necessary. Treatment of individuals whose sputum is positive on direct microscopy for tubercle bacilli renders them non-infectious after about 2 weeks.

#### **5. Restrictive lung disease:**

The term covers a highly heterogeneous group of conditions which produce similar, but not identical, disturbances of ventilatory function. A disorder commonly results from processes affecting the lung parenchyma referred to as interstitial lung diseases. It may also occur, however, as a result of neuromuscular weakness or chest wall and other skeletal deformities.

#### **Sarcoidosis:**

Sarcoidosis is the parenchymal lung disease encountered by obstetricians. A multisystem granulomatous disorder of unknown cause, the lungs are the organ most frequently involved. The condition may be asymptomatic, and discovered incidentally on chest x-ray. Acute

presentations with systemic upset, arthralgia, fever, erythema nodosum and bilateral hilar lymphadenopathy seen radiologically are usually self limiting. Corticosteroids are given with acute presentation if systemic symptoms are severe, if there is hypercalcemia (some times seen in sarcoidosis), significant parenchymal lung disease with impairment of function, or significant involvement of other organs, particularly eye and central nervous system. Sarcoidosis rarely significantly complicates a pregnancy.

Connective tissue diseases, such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and systemic sclerosis may involve the lungs. The first two conditions may give rise to pleural involvement, with effusions, but the commonest pulmonary manifestation of connective tissue disease is interstitial pulmonary fibrosis of the type seen in cryptogenic fibrosing alveolitis.

Kyphoscoliosis and neuromuscular disorders will also cause a restrictive defect on pulmonary function testing. Unlike interstitial lung diseases, however, affected individuals are prone to develop type II (hypoxic and hypercapnic) respiratory failure, sometimes without gross breathlessness. As in cases of severe cystic fibrosis, it is essential that the confusion and oedema of progressive respiratory failure are not mistaken for pre-eclampsia. Severe scoliosis may progress during pregnancy due to the development of ligamentous laxity. Provided measurements of lung function are 50% or greater of predicted values, complications are uncommon. Like cystic fibrosis, pulmonary hypertension at the onset of pregnancy carries very high risks for both mother and fetus.

**6. Cystic Fibrosis:** Three aspects are of particular relevance: the risk of the baby being affected by CF, the consequences to mother and fetus of poor lung function during advancing pregnancy, and the outlook for the mother after delivery. CF is an inherited disorder of epithelial membranes and is characterized by abnormal glandular secretions. The most important clinical manifestations are intestinal malabsorption, with associated nutritional consequences, and recurrent chest infections leading to progressive lung damage and ultimately death from respiratory failure. All pregnant women with CF should be closely monitored by such a unit. CF is an autosomal recessive disorder, the affected individual possessing two copies of the CF gene. The frequency of heterozygous carriers (with a single copy of the gene) in a white population is approximately 1 in 20 to 1 in 25 individuals, and considerably less than this in Afro-Caribbean populations. Recent advances in molecular biology mean that most (but not all) heterozygous carriers can be identified from blood or buccal cells, and a genetic counsellor can then give advice before a planned pregnancy about the chances of an affected fetus. All offspring of a CF woman will be heterozygous CF gene carriers, even if they are not homozygous with clinical disease. These carriers and, vitally, the homozygous (and thus potentially clinically affected) fetus may be detected by chorionic villus sampling. In the past, women with CF were in general counselled to avoid pregnancy because of its adverse effects upon respiratory function. The most seriously ill may be less likely to be sexually active, and those who are active may be less likely to

embark upon a pregnancy. Severe air-flow limitation, with lung function measurements below 60% of predicted, leads many units to advise CF women against becoming pregnant although, as Canny et al demonstrate, more seriously limited women can come through pregnancy successfully.<sup>60</sup> It is vital that the development of edema, headaches and mental confusion is recognized as respiratory failure and not mistaken for pre-eclampsia.

After a pregnancy, women with CF have worse lung function than before, but this deterioration is no greater than that seen in non pregnant CF women over a 9-month period.

### **7. Influenza and the common cold:**

Influenza is generally self limited in healthy young adults. However, if pneumonia develops, it can be life-threatening and may be more severe in pregnancy.<sup>25</sup> The influenza vaccine is recommended for all women who will be in the second or third trimester of pregnancy during the influenza season. Because influenza does not usually result in a viremia, transplacental infection rarely occurs. Concern has been raised about a possible association between influenza in early pregnancy and anencephaly, but there is no firm evidence.

Influenza-specific antibody is transmitted to the fetus in utero and protects the newborn. However, susceptible newborns are at increased risk for influenza, with manifestations ranging from mild coryza to sepsis. If influenza occurs in late pregnancy, delivery should be delayed until the mother has recovered, if possible, to allow the newborn to acquire transplacental antibodies. This usually

occurs by five days after the onset of symptoms. The common cold is the most frequent acute illness affecting humans.

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## Chapter No: 8

## LIVER DISEASE IN PREGNANCY

Isolated hepatic disease rarely occurs during pregnancy. A number of associations between hepatic dysfunction and pregnancy exist. These relationships are discussed in the context of obstetric management.



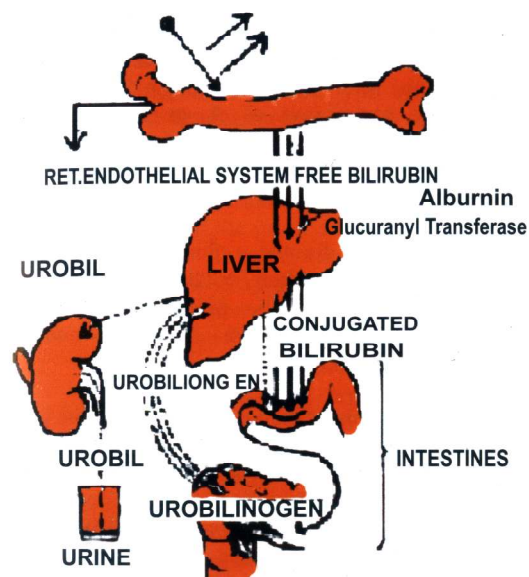
**Fig8.1: Shows surface anatomy of liver and its relations**

The liver serves multiple functions: the biotransformation of insoluble compounds (e.g., drugs, toxins, bilirubin), the metabolism and excretion of cholesterol and bilirubin, the production of plasma proteins (e.g., albumin, coagulation factors, alpha- and beta globulins, transferrin, haptoglobin), and the metabolism of amino acids, carbohydrates and lipids.

The main source of bilirubin in the body is the red cells. There is daily destruction of about 1% of the total red cell mass. Hemoglobins when broken produce globin and heme, the latter is a trivalent iron complex of haem. When iron is removed from heme, the compound left behind is protoporphyrin

which is oxidized later to biliverdin this in turn is reduced to bilirubin.

The iron released is stored in the liver, the globin enters the protein pool of the body and is available for the formation of new hemoglobin. The bilirubin however is left behind as a waste product. Haemoglobin degradation occurs in the reticuloendothelial system, particularly in the liver, spleen and bone marrow. In an average adult woman who has a blood volume of 5 liters and a hemoglobin concentration of 15 gm per 100 ml; the daily destruction of 1 per cent of the circulating red cells will produce 7.5 gm of haemoglobin and from this about 250 mg of bilirubin is produced.

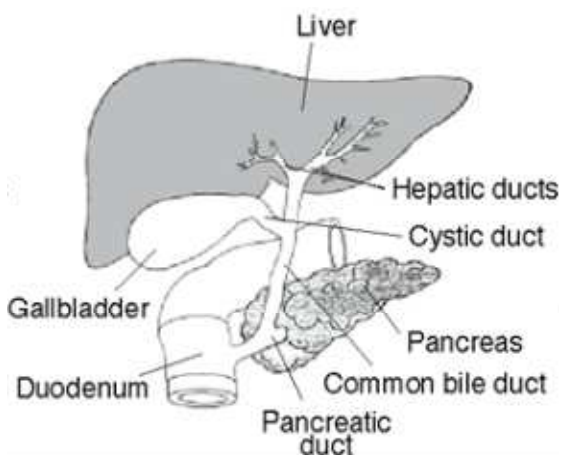


**Fig8.2: Shows bilirubin transport routes**

### Bilirubin transport:

From reticuloendothelial system the bilirubin reaches the liver by binding self with albumin; a minor fraction may be bound to an alpha globulin. Tiny amounts of bilirubin can also be absorbed onto the red cell membrane, while rest of the bilirubin is set free. When the red cell is coated with antibody this bilirubin can appear in the lymph, ascitic, pleural and cerebrospinal fluids as it happens in some jaundiced states

**Interference with protein binding** - Salicylate, sulphonamides, caffeine and sodium benzoate compete with bilirubin for binding sites on the albumin molecule and can thus reduce the binding capacity.



**Fig 8.3: Shows hepatic circulation paths**

### Intrahepatic circulation and Metabolism:

How the circulating bilirubin is transferred from plasma into the liver cell is not completely known. However, on passing through liver, bilirubin is converted from a lipid soluble pigment to a

water soluble one. The posthepatic bilirubin (soluble bilirubin) is present in bile and sera of patients with obstructive Jaundice. This gives an immediate red colour with diazotized sulph anilic acid (direct reacting bilirubin) whereas the prehepatic bilirubin which is present in sera of patients with hemolytic jaundice requires addition of alcohol before the reaction can take place, therefore it is known as indirect-reacting bilirubin. The free bilirubin is conjugated in the liver. Conjugation is dependent upon the transfer of an active glucuronide moiety which is obtained from Uridine diphosphoglucuronic acid. This transfer is helped by a microsomal enzyme, glucuronyl transferase. The glucuronide donor, UDPGA is a unique substance in man, through which glucuronic acid is made available for conjugation. The formation of UDPGA is dependent on another specific enzyme, such as Uridine diphosphoglucose dehydrogenase.

**Mechanism of bilirubin conjugation** - Unconjugated bilirubin is lipid soluble and non polar. This is converted to a polar and water-soluble compound on conjugation. Conjugated bilirubin can pass through the glomerular membrane, and thus into the urine. This explains why bilirubin is absent in urine in the hemolytic jaundice but present in jaundice due to regurgitation of post hepatic bilirubin which is conjugated. Difference between free and conjugated bilirubin lies in solubility.

**Secretion and enterohepatic circulation:** The existence of an enterohepatic circulation of bilirubin in man has been confirmed in experiments using labelled bilirubin, and it has been shown that lipid soluble unconjugated bilirubin is readily absorbed from the

bowel, but conjugated bilirubin is not. On reaching the ingestible bilirubin is acted upon by the bacterial flora and is enzymatically reduced to a series of colorless urobilin-nogen. About 50 per cent of the urobilin-nogen is reabsorbed into the portal circulation and thus returned to the liver. Most of this compound is removed from the blood and re excreted into bile. If the liver is normal and the rate of urobilino-gen return is not too rapid. The tiny amount of absorbed urobilinogen which is not re excreted amounts to less than 4 mgm per day this passes into the systemic blood stream and is then removed in the urine. The excretion of bilirubin is dependent on mechanisms which limit biliary and intestinal reabsorption. Uro-bilinogen is formed predominantly in the lower intestinal tract, while absorption of bilirubin metabolites occurs maximally in an area which is proximal to the terminal ileum. The urobilinogen in the lower intestine is excreted in the stools and amounts to about 300 mgm daily. Oxidation of urobilinogen to urobilin gives colour to the stool.

**Jaundice:** Jaundice is a clinical state where there is an increase in the level of bilirubin in the blood. This can occur in four different ways. Firstly, there might be an increased load of the pigment on the liver cell. Second, there might be a disturbance in the process by which bilirubin diffuses into the cells from the sinusoids and is actively transported to the microsome for conjugation.

Thirdly, there may be defects in the actual con-jugation process and finally, there may be difficulty in the passage of bile via the biliary tract, to the intestine. Multiple disturbances can coexist in anyone patient.

### **Liver function in pregnancy:**

In normal pregnancy there is very little significant change in the liver function. Both the blood flows as well as the parenchymal structure of the liver are not affected. However some of the biochemical tests show slight alteration. Liver biopsy does not show any pathological change.

### **Jaundice in Pregnancy:**

**Incidence** - Jaundice occurs in 1: 1500 pregnancies in Europe. The exact incidence in Pakistan is not known. There were 3 cases of Jaundice at Lahore General Hospital in 1000 pregnancies.

**Causes** - In a number of studies viral hepatitis has been reported to be responsible in 40 per cent cases, re-current intrahepatic cholestatic jaundice in about 20 per cent, bile duct obstruction in another 5 per cent and in the remaining 35 per cent cases there may be other causes.

**Different types:** Recurrent Intrahepatic Cholestatic Jaundice of Pregnancy' - This is an obstructive type of jaundice which occurs in the later half of pregnancy, usually in the last trimester. The exact cause of this complication is not known but an abnormal cholestatic reaction to steroids produced in pregnancy has been implicated. Similar changes occur in patients who have been using synthetic sex steroids for contraceptive purposes.

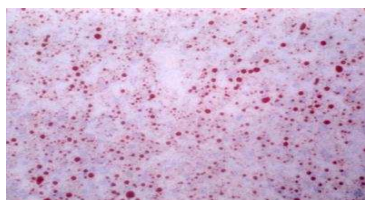
**Diagnosis** – Liver Biopsy shows dilated bile canaliculi with stasis of bile. Both conjugated bilirubin and alkaline phosphatase are increased. The



transaminases are normal or may be slightly raised. The jaundice is usually mild and may manifest itself in the later weeks of pregnancy. The main symptom is pruritus. The stools are pale and the urine is dark. Usually there is no hepatosplenomegaly.

**Treatment** - The pruritus is due to accumulation of bile salts and not the bilirubin. This disappears shortly after delivery. The jaundice also settles in few weeks. The drug cholestyramine may help to alleviate distressing cases of pruritus. It is an anion exchange resin that binds the bile acids in the intestine and interferes with their absorption. The safety of this drug in pregnancy has not been fully evaluated therefore it should be used with great caution and after organogenesis has been completed which occurs at 12 weeks of gestation. The disease often recurs in subsequent pregnancies and there may even be a family history. The fetal as well as maternal prognosis is good but there have been sporadic reports of repeated still-births in recurrent cases. Since a similar picture may develop in patients who are on oral contraceptives such patients should not be further prescribed these drugs.

**Obstetric management:** Simple reassurance, with treatment of pruritus is all that is required. Both pregnancy and labour often proceed normally. The diagnosis must be established correctly before adopting such expectant attitude.



**Fig8.4: Shows histopathology of fatty liver**

**Acute fatty liver of pregnancy** - This condition is also described in the literature as obstetric acute yellow atrophy. Most cases are associated with severe malnutrition or occur in patients who have been given large doses of tetracyclines. Liver cells during pregnancy are especially sensitive to cytotoxic effect of these drugs. This condition is not very common. It usually occurs in the last trimester. The hepatic cells become grossly infiltrated with fat. Both transaminases and alkaline phosphatase are slightly increased. The prognosis for both mother and the fetus is very poor. There is no specific treatment. Lipotropic factors, corticosteroids, B complex vitamins and early delivery have all been tried without much success. These measures on the other hand may be harmful.

**Preeclampsia and eclampsia** - Jaundice in such patients is due to hemolysis. It is a rare condition but when it occurs; it is usually fatal.

**Hyperemesis gravidarum** - In very severe cases of hyperemesis gravidarum, malnutrition leads to fatty infiltration of the liver, and then subsequently to jaundice. Dehydration produced by excessive fluid loss may also cause jaundice.

**Jaundice coincidental to pregnancy** - Usual medical and surgical causes of jaundice may be present during pregnancy and should be kept in mind for differential diagnosis.

**Pre hepatic causes** - Hemolysis due to defects in RBC shape and size, hemoglobinopathies, parasites like malarial, incompatible blood transfusion, drugs and pyogenic infections can cause jaundice.

**Hepatic causes** - Viral hepatitis both A and B, types can produce jaundice. Drugs such as chloroform, halothane, phenothiazine and tetracycline can also produce jaundice due to toxicity or hypersensitivity. Jaundice may also be produced in cases of cirrhosis of the liver.

#### **Post hepatic obstructive jaundice –**

The most common cause of the clinical pattern of obstructive jaundice is blockage of the main extra hepatic bile channels, "surgical jaundice". This is usually due to impaction of gall stones in the common bile duct or due to neoplasm which involves most commonly the head of the pancreas with extrinsic pressure. Since the obstruction occurs at a point distal to the hepatic cell, the resultant hyperbilirubinemia is composed, initially at least, of conjugated pigment. Following prolonged obstruction secondary degenerative changes in hepatic parenchymal cells are probably responsible for a subsequent rise in the unconjugated fraction.

By preventing bile pigments from reaching the intestine the stools become pale and the increased quantity of conjugated, water soluble bilirubin retained in the circulation passes through the glomerular membrane and appears in the urine. Since bacterial degradation in the gut is prevented, urobilinogen is not found in the urine.

Absence of bile salts from the intestine may cause steatorrhea with its resultant secondary effects, and their retention within the blood stream gives rise to pruritus. There will be increased alkaline phosphatase, hyperlipidemia, and lipoprotein.

**Diagnosis** - This can be made from detailed review of the history, Enquiry into the events of previous pregnancies such as jaundice or pruritus are important. Similar signs and symptoms if appeared while the patient was on the pill are very significant. Recent exposure to viral hepatitis, blood or serum transfusion or any invasive procedure should be noted. Drugs used, biliary tract surgery, history of cholecystitis or biliary colic should be carefully evaluated.

**Clinical examination** - Enlargement and consistency of liver should be noted. It may be tender. The spleen may be enlarged. Other viscera like the gall-bladder and abdominal wall veins should be palpated for any neoplastic growth.

Spider nevi should be noted; these are normally present in pregnancy and should not be confused with liver disease. Rectal examination should be done to exclude any growth. The urine and stools should be examined for bilirubin and colour.

**Investigations** - Serum bilirubin both conjugated and unconjugated should be estimated. Alkaline Phosphatase is usually raised to levels above 35 I.U. in obstructive jaundice.

Transaminases are markedly elevated in infective hepatitis. Both Pro-thrombin and Fibrinogen may be depleted. These are of great importance, especially if labour is imminent. Reticulocyte count may be elevated due to hemolysis, ultrasounds can or a cholecystography may show gall stones.

**Management: prophylaxis includes** (1) Administration of gammaglobulin to contacts at high risk like; in pregnancy.

(2) In hepatitis 'B' Australia Antigen positive cases, special precautions are taken to avoid spread to the baby as well as to the attendants. (3) The babies thus born are given hepatitis 'B' I immunoglobulin and possibly hepatitis B vaccine. (4) These babies need to be taken off the breast feed.



**Fig8.5: Shows source of infection which is usually infected needle**

**Obstetric management** - In most cases this is not influenced by the presence of jaundice. However, if investigations show deficiency of blood clotting factor, then fresh blood or prothrombin complex should be available to avoid post-partum hemorrhage.

**Drug in the jaundiced Patient** - Most drugs are detoxicated by the liver. The drugs have also toxic effect on the liver especially when it is damaged. Their action may be prolonged so a careful individual assessment and adjustment will be required.

**Mortality:** Contrary to that in European countries, fatality from viral hepatitis in pregnancy is high in underdeveloped countries, particularly in third trimester. No single liver function test is available to quantify liver disease. The designation "liver function tests" describes a panel of laboratory tests profiling discrete aspects of liver function.<sup>1</sup> Liver cell injury or

necrosis is measured by determining aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, while liver synthetic function (depressed in cirrhosis or severe acute liver disease) is quantified by determining albumin level and prothrombin time. Cholestasis and biliary obstruction are evaluated by measuring alkaline phosphatase, bilirubin, and nucleotides or gamma glutamyl trans-peptidase levels<sup>1</sup> (Figure 1). In normal pregnancies, alkaline phosphatase levels may be elevated three- to fourfold, secondary to placental alkaline phosphatase levels. Elevations of ALT occurring during pregnancy can be evaluated using a diagnostic algorithm (Figure 2). Elevated ALT is frequently the result of viral hepatitis, which can be easily diagnosed using serologic tests. Other possible etiologies of mild or moderate elevations of ALT are drug induced hepatotoxicity, hyperemesis gravidarum, cholelithiasis, HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome or acute fatty liver of pregnancy.

**Pregnancy and hepatitis acute viral hepatitis:** Viral hepatitis is the most common cause of jaundice in pregnancy.<sup>4</sup> The course of most viral hepatitis infections (e.g., hepatitis A, B, C and D) is unaltered by pregnancy.<sup>6,7</sup> However, a more severe course of viral hepatitis in pregnancy has been noted in patients with hepatitis E and disseminated herpes simplex virus (HSV) infections.<sup>2,6,8-11</sup> Hepatitis E is a waterborne virus spread through fecal-oral transmission. Infection occurs most commonly in developing countries after flooding. Pregnant women with hepatitis E infection exhibit markedly increased fatality rates (10 to 20 percent).

Immunoprophylaxis at birth followed by a hepatitis B vaccination series reduces vertical transmission of hepatitis B virus to less than 3 percent. Disseminated HSV infection is associated with prodromal systemic illness, vesicular skin rash and leukopenia. Maternal and fetal mortality rates reach 50 percent without treatment. Acyclovir (Zovirax) effectively treats early disseminated HSV infection.

**Hepatitis B virus:** In the United States, 15,000 pregnant women who are hepatitis B surface antigen (HBsAg)-positive deliver annually.<sup>6</sup> Universal screening of pregnant women for HBsAg is now performed to reduce perinatal transmission of hepatitis B virus. The risk of hepatitis B virus transmission to the fetus is proportional to maternal hepatitis B virus DNA, as reflected in hepatitis B antigen (HBeAg) and antibody (HBeAb) status. The risk of hepatitis B virus vertical transmission is 10 percent in mothers with negative HBeAg and positive HBeAb and 90 percent in those with positive HBeAg.<sup>3,6</sup> The risk of chronic hepatitis B virus infection in a neonate who does not receive immunoprophylaxis and vaccination for hepatitis B virus is 40 percent. Infants of HBsAg-positive mothers' should receive hepatitis B immune globulin immunoprophylaxis at birth and hepatitis B vaccine at one week, one month and six months after birth.

This regimen reduces the incidence of hepatitis B virus vertical transmission to zero to 3 percent. In cases of acute hepatitis B virus infection complicating pregnancy, the prevalence of neonatal infection depends on the time during gestation that maternal infection occurs.

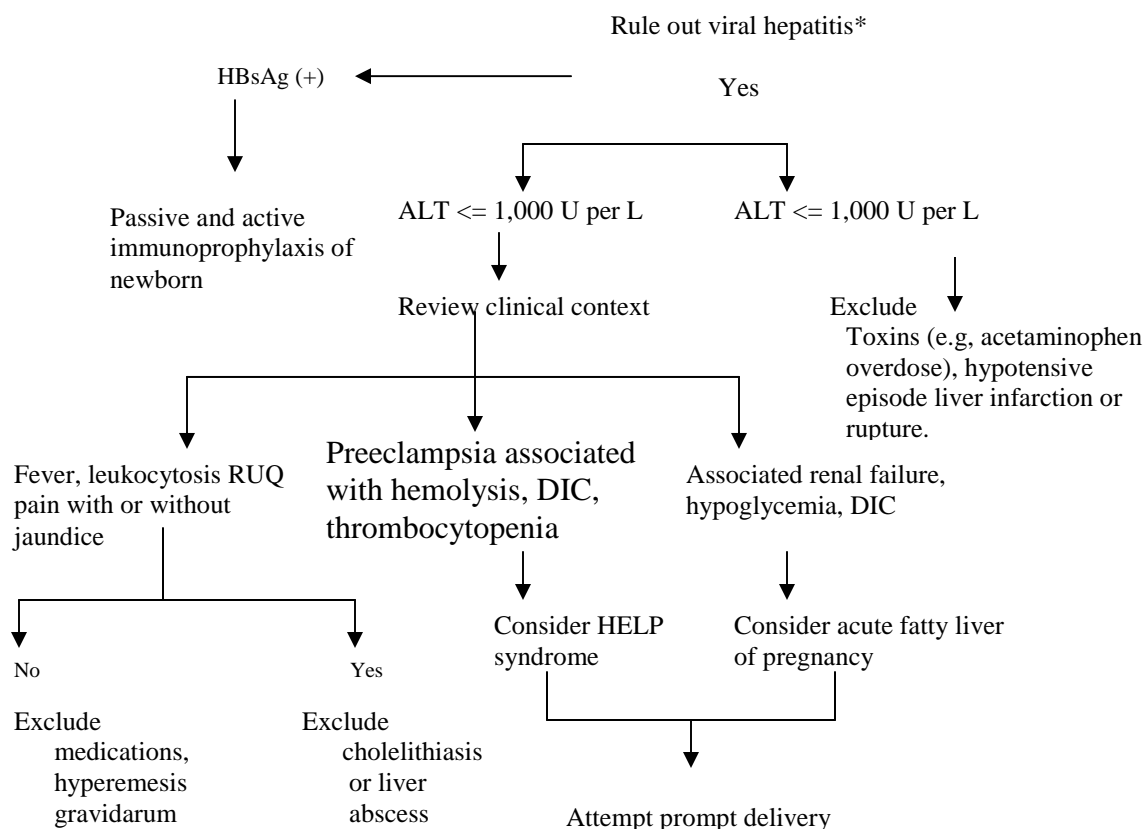
Neonatal hepatitis B virus infection is rare if maternal infection takes place in the first trimester. The infection occurs in 6 percent of neonates of women infected in the second trimester, in 67 percent of those infected in the third trimester and in virtually all of those infected in the immediate postpartum period.<sup>12</sup> Neonates of mothers experiencing acute hepatitis B virus infection should receive immunoprophylaxis and vaccination, as outlined above.

**Hepatitis C virus:** Chronic hepatitis C virus infection affects 1.4 percent of the U.S. population the incidence of hepatitis C virus infection is rising most rapidly among persons 20 to 45 years of age.

Therefore, an increasing number of patients with hepatitis C virus infection are requesting information about vertical transmission of the virus during pregnancy.

Patients with risk factors for hepatitis C virus infection, such as intravenous drug use or other parenteral exposures, should undergo screening for hepatitis C virus infection before pregnancy with second- or third generation hepatitis C virus antibody assays to confirm exposure to the virus.

Women with documented hepatitis C virus infection who are contemplating pregnancy should be encouraged to undergo human immunodeficiency virus (HIV) testing and repeated quantitative hepatitis C virus RNA measurements to determine their probable risk of hepatitis C virus vertical transmission. exposure, the risk of hepatitis C virus vertical transmission is zero to 18 percent.



*\*Recommended serologic tests: Hepatitis A IgM, hepatitis B surface antigen and hepatitis B core antibody, hepatitis C antibodies, cytomegalovirus IgM, herpes simplex virus IgM, and Epstein-Bar virus IgM.*

### Alanine aminotransferase elevation during pregnancy

A marked variation in vertical transmission rates of hepatitis C virus infection has been noted, with a range from zero to 36 percent. Vertical transmission is strongly supported by the finding of identical hepatitis C virus subtypes in mothers and infants infected with hepatitis C virus.<sup>14</sup> In hepatitis C virus positive, HIV negative mothers without a history of active intravenous drug use or transfusion prenatal transmission of hepatitis C virus is

greatest in patients with hepatitis C virus RNA titers greater than 1 million copies per mL; mothers who did not have hepatitis C virus RNA did not transmit hepatitis C virus infection to their neonates.

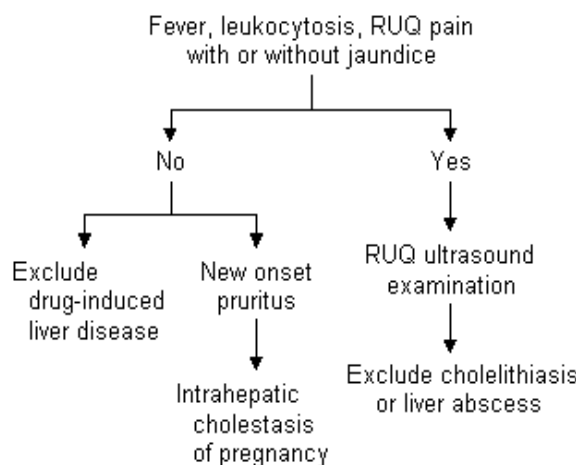
In patients who are HIV negative with ongoing intravenous drug abuse (or blood transfusions) during pregnancy, a 23 percent hepatitis C virus vertical transmission rate has been reported. The

highest reported rate of vertical transmission in this group occurs in infants born to hepatitis C virus positive, HIV positive mothers, with transmission rates of 6 to 36 percent. No therapy has been shown to influence neonatal transmission of hepatitis C virus. Vertical transmission of the virus has been reported to occur in two of three infants of mothers with acute hepatitis C virus infection, suggesting a higher risk of vertical transmission than occurs in patients with chronic infection, secondary to the high levels of hepatitis C virus RNA that occur in acute infection. Interferon therapy should not be administered during pregnancy because of its possible adverse effects on the fetus.

### Cholelithiasis in pregnancy:

Cholelithiasis is noted in as many as 6 percent of pregnant women. Pregnancy induced changes in bile composition predispose these patients to cholelithiasis.

### Cholestasis during pregnancy:



The bile salt pool decreases in the second trimester, and biliary cholesterol levels may increase, resulting in lithogenic bile. In addition, gallbladder

emptying slows in the second trimester, increasing the risk of cholelithiasis. Surgical treatment of biliary colic is safely accomplished in the first and second trimesters but should be avoided in the third trimester. Symptoms of cholelithiasis are similar in pregnant and non pregnant patients. Patients with cholecystitis typically present with laboratory abnormalities, including leukocytosis and mild to moderate elevations of transaminase and bilirubin levels. The alkaline phosphatase level progressively increases during normal pregnancy and is unhelpful in distinguishing hepatobiliary disease. A liver ultrasound examination is most helpful in determining the presence of cholelithiasis or sludge in symptomatic patients.

Surgical treatment (i.e., laparoscopic cholecystectomy) of biliary colic can be safely accomplished in the first or second trimester. As the uterus enlarges, surgery becomes more difficult and should be avoided during the third trimester.

A retrospective review<sup>17</sup> of 19,000 pregnancies revealed that 11 percent of surgical emergencies were attributable to biliary tract disease. Choledocholithiasis accounts for approximately 7 percent of patients with jaundice in pregnancy.<sup>17</sup> Of patients presenting with pancreatitis during pregnancy, 90 percent have choledocholithiasis.<sup>17</sup> Gallstone pancreatitis is associated with a 15 percent maternal mortality rate and a 60 percent fetal mortality rate. One group of investigators<sup>17</sup> reported safely performing endoscopic retrograde cholangiopancreatography and endoscopic retrograde sphincterotomy without complications in five pregnant

women (in the second and third trimesters) with choledocholithiasis using minimal fluoroscopy and lead aprons to shield the abdomen. All of the women delivered healthy babies at term.

### **Pregnancy specific liver disease:**

#### **Intrahepatic cholestasis of pregnancy:**

Intrahepatic cholestasis of pregnancy occurs in 0.01 percent of pregnancies in the United States. It typically arises in the third trimester of pregnancy, although it has been reported as early as 13 weeks' gestation. The pathophysiology of intrahepatic cholestasis of pregnancy remains poorly understood.<sup>19</sup> Pruritus alone occurs in 80 percent of patients; pruritus and jaundice develop in 20 percent of patients. Laboratory abnormalities include a bilirubin level less than 5 mg per dL (85.5  $\mu$ mol per L), minimal or no elevation in transaminase, cholesterol and triglyceride levels, and infrequent, mild to moderate steatorrhea. Liver histopathology reveals centrilobular bile stasis.<sup>20</sup> Intrahepatic cholestasis of pregnancy is associated with a 12 to 44 percent incidence of prematurity, a 16 to 25 percent incidence of fetal distress and an increased perinatal mortality rate (1.3 to 3.5 percent). A clear racial and genetic predisposition for this disorder has been described. Intrahepatic cholestasis complicates 0.01 to 0.02 percent of pregnancies in North America, 1 to 1.5 percent of pregnancies in Sweden and 5 to 21 percent of pregnancies in Chile.<sup>20</sup> The disease is rare in black patients.<sup>20</sup> A strong family history of cholestasis of pregnancy is typically described by the patient.<sup>20</sup> Kindred studies reveal alterations in bromosulphophthalein clearance following estrogen treatment in both male and

female relatives of women affected by intrahepatic cholestasis of pregnancy.<sup>19</sup>

Multiple medications have been tried as treatments for cholestasis of pregnancy.<sup>19</sup> parenteral vitamin K (phytonadione; Aqua MEPHYTON) supplementation is advocated in patients with prolonged cholestasis (secondary to malabsorption of this fat-soluble vitamin). Ursodeoxycholic acid (Actigall), given at dosages of 15 mg per kg per day, has been the most successful therapy for cholestasis of pregnancy, as it ameliorates both the pruritus and liver function abnormalities and is well-tolerated by both mother and fetus.<sup>21</sup> Ursodeoxycholic acid has been proved safe in trials of cholestatic liver disease in infants, children and adults. Studies in rats, mice and rabbits have revealed no teratogenicity or other negative effects on the developing fetus. Studies in humans examining the use of ursodeoxycholic acid in pregnancy have been uncontrolled and limited by small patient numbers. However, in pregnant patients with cholestatic liver disease, the pruritus can be severely disabling, and ursodeoxycholic acid therapy provides safe and effective relief.

Cholestyramine (Questran) binds bile acids and may improve pruritus; however, it may exacerbate steatorrhea and does not alter liver function or fetal prognosis.<sup>19</sup> Phenobarbital has not been shown to improve pruritus or alter liver tests and may cause neonatal respiratory depression. Patients exhibiting cholestasis of pregnancy should receive close fetal surveillance at delivery. Symptoms of cholestasis usually resolve within two days of delivery. Elevated serum bilirubin and alkaline phosphatase levels re-turn to normal four to six weeks after delivery.<sup>3</sup> Cholestasis of pregnancy re-

curs in 60 to 70 percent of subsequent pregnancies.

### **Preeclampsia:**

Hepatic dysfunction with preeclampsia has long been recognized.<sup>22</sup> more recently, this dysfunction has been associated with other findings in the HELLP syndrome. This syndrome may complicate the course in 3 to 10 percent of patients with preeclampsia and is noted in 0.1 percent of all pregnancies. The pathophysiology of HELLP syndrome reflects that of preeclampsia, with microvascular damage, platelet activation and vasospasm. Liver biopsy reveals periportal hemorrhage and fibrin deposition.<sup>25</sup> recent data suggest that a defect in nitric oxide metabolism may contribute to preeclampsia and HELLP syndrome. Notable hepatic abnormalities in the HELLP syndrome include hemolysis (with elevated bilirubin levels and lactate dehydrogenase levels greater than 600 IU per L), moderately elevated transaminase levels (AST and ALT levels of 200 to 700 IU per L) and a platelet count less than 100,000 per mL ( $100 \times 10^9$  per L).<sup>2,3</sup> Patients typically present with right upper quadrant pain and malaise.<sup>2,3</sup> Sixty percent of patients exhibit significant weight gain or edema; 50 percent have nausea or emesis.<sup>3</sup> No correlation has been noted between extent of hypertension, liver function test abnormalities or liver biopsy findings.<sup>25</sup> The maternal and fetal complications of HELLP syndrome are significant. The maternal mortality rate is 2 percent, and the perinatal mortality rate is 33 percent. Among the hepatic consequences are a 2 percent incidence of ruptured liver hematoma (with frequent concomitant mortality) and a 4 to 38 percent incidence of disseminated intravascular coagulation.<sup>3</sup>

The most effective treatment for HELLP syndrome is prompt delivery.<sup>2,3</sup> Postpartum corticosteroids have proved efficacious in improving maternal platelet counts, ALT levels and blood pressure.<sup>28</sup>

Therapies that have not proved efficacious include plasmapheresis,<sup>29</sup> anti-thrombotic agents and immunosuppression.<sup>3</sup> Following delivery, laboratory abnormalities peak in the first one to two days postpartum and return to normal within three to 11 days. The risk of recurrence of HELLP syndrome in subsequent pregnancies has been reported as 3.4 percent.

### **Acute fatty liver of pregnancy:**

Acute fatty liver of pregnancy most frequently complicates the third trimester and is commonly associated with preeclampsia (50 to 100 percent).<sup>2,3</sup> Although rare (with an incidence of one in 13,000), acute fatty liver of pregnancy is a life threatening condition, with an 18 percent maternal and a 23 percent fetal mortality rate.

Symptoms associated with acute fatty liver of pregnancy include anorexia, nausea, emesis, abdominal pain, jaundice, headache and central nervous system disturbances. Hepatic histopathology reveals pericentral microvesicular fat with minimal inflammation or necrosis. Liver biopsy is not indicated for diagnosis.<sup>31</sup> The laboratory abnormalities in acute fatty liver of pregnancy include moderate elevations of transaminase levels (AST and ALT less than 1,000 IU per L), prolongation of prothrombin time and partial thromboplastin time, decreased fibrinogen, renal failure, profound hypoglycemia and bilirubin levels of 1 to

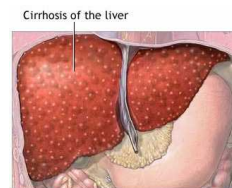


10 mg per dL (17.1 to 171.0  $\mu\text{mol}$  per L). Some children of mothers with acute fatty liver of pregnancy have been noted to express homozygous deficiency of long chain 3-hydroxyacyl-CoA dehydrogenase, resulting in severe metabolic and neurologic consequences to the infants.<sup>32,33</sup> Their mothers were found to exhibit a heterozygous deficiency of long chain 3-hydroxyacyl-CoA dehydrogenase, contributing to acute fatty liver of pregnancy. Such defects in fatty acid oxidation are initially suggested by elevations in urinary organic acid levels and in plasma carnitine and acyl carnitine levels, detected after an overnight fast.<sup>32</sup> Recurrent acute fatty liver of pregnancy has been reported in mothers expressing heterozygous long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Ursodeoxycholic acid, at dosages of 15 mg per kg per day, has been the most successful therapy for cholestasis of pregnancy. The treatment of acute fatty liver of pregnancy is expeditious delivery and intensive care. Patients usually improve promptly following delivery and, in the absence of long chain 3-hydroxyacylCoA dehydrogenase deficiency, the prognosis in pregnancies following acute fatty liver of pregnancy is good.

#### **Hepatic rupture and infarction:**

Hepatic rupture and infarction, extremely rare complications of Preeclamptic liver disease, usually occur in the third trimester. The incidence of hepatic rupture varies from one in 40,000 to one in 250,000 pregnancies<sup>35</sup>; hepatic infarction is even rarer. Older multi-gravida mothers with preeclampsia (75 to 85 percent) are at higher risk. Less commonly, hepatic rupture complicates growth of hepatic adenomata or other

masses during pregnancy.<sup>3</sup> Hepatic rupture most commonly involves the right lobe. It is believed to be a continuum of preeclampsia, in which areas of coalescing hemorrhage result in thinning of the capsule and intra-peritoneal hemorrhage. Case reports have documented numerous pseudo aneurysms in the area of hemorrhage, raising the possibility of a vasculopathy contributing to this rare disorder. Patients with hepatic rupture typically present in shock, with preceding right upper quadrant pain, hypertension, elevated transaminase levels (greater than 1,000 IU per L) and coagulopathy.<sup>4</sup> Therapy for hepatic rupture has included transfusion of blood products and intravenous fluids, surgical evacuation and arterial embolization.<sup>4</sup> These therapies have met with only moderate success; a 59 to 70 percent maternal mortality rate and a 75 percent perinatal mortality rate have been noted in hepatic rupture.<sup>4</sup> Late complications arising after treatment of hepatic rupture include hepatic abscess formation and pleural effusions. Hepatic infarction is best detected by using computed tomographic scans or magnetic resonance imaging. Patients typically present with fever and marked elevations in transaminase levels. In surviving patients, liver function and histopathology are normal within six months of delivery. Intrahepatic hemorrhage has been reported to recur in a minority of subsequent pregnancies.



**Fig8.6: Shows cirrhosis of liver in the specimen.**

**Chronic liver disease:**

An increased risk of fetal loss has been noted in pregnant patients with chronic liver disease.<sup>37</sup> Therapy with penicillamine (Cuprimine), trientine (Syprine), prednisone or azathioprine (Imuran) can be safely continued during pregnancy in patients with Wilson's disease or autoimmune hepatitis.<sup>37</sup> In patients with primary biliary cirrhosis, ursodeoxycholic acid therapy can be safely continued.<sup>37</sup> In patients with chronic hepatitis B or C infection, interferon therapy should be discontinued during pregnancy, as its effects on the fetus are unknown.<sup>37</sup>

A marked reduction in fertility has been noted in cirrhotic patients.<sup>37</sup> Cholestasis may worsen during pregnancy in patients with primary biliary cirrhosis. Infants of patients with marked hyperbilirubinemia during pregnancy may require exchange transfusion at birth.

**Quick review:****Management options:****Acute fatty liver of pregnancy:****Pre pregnancy:**

None, except discussion of recurrence risks (see 'Postnatal').

**Prenatal:** Establish diagnosis, resuscitate, Intensive care, Supportive therapy (see labor/delivery) and Plan delivery.

**Labor/delivery:**

Maternal resuscitation by correction of hypoglycemia, fluid imbalance, coagulopathy and treatment of liver failure and intensive fetal monitoring. Urgent delivery when maternal condition

is stabilized, vaginal delivery preferable for mother. Meticulous homeostasis, including adequate wound drainage.

**Postnatal:**

Continue intensive care management watch for postpartum wound hematoma formation, sepsis, postpartum hemorrhage, recurrence risk is difficult to estimate, perhaps as high as 10-20% Support contraceptive measures.

**Management options:****Intrahepatic cholestasis of pregnancy:****Pre pregnancy:**

Not applicable, unless diagnosed in previous pregnancy, counsel for 60-80% chance of recurrence, biliary ultrasonography to detect stones, or other disease.

**Prenatal:**

Local antipruritic measures, consider cholestyramine, ursodeoxycholic acid, Steroids, Vitamin K supplement, for mother, Monitor fetal wellbeing, consider elective delivery and Biliary tract ultrasonography

**Labor/delivery:**

Anticipate preterm labour, Increased risk of postpartum hemorrhage.

**Postnatal:**

Monitor biochemical resolution, Vitamin K supplement for baby, Use oral contraceptives only with close clinical and biochemical monitoring, Consider liver biopsy if diagnosis is suspect, for condition progressive

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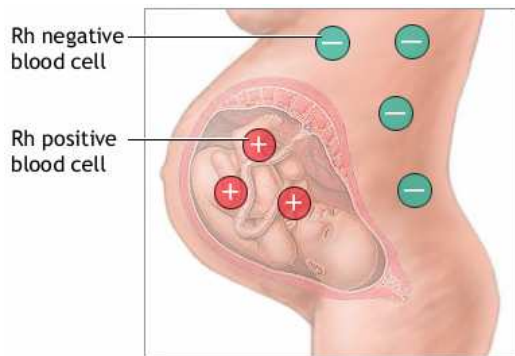
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## Chapter No: 9

## RHESUS DISEASE IN PREGNANCY

This disease is produced by isoimmunization to D antigen of the Rh. System and is the commonest form of sensitization; however other antigens of the Rh. system (Cc Ee) also cause sensitization in a significant number of cases.



**Fig 9.1: Showing process of immunization in women's body by the Rh positive foetus.**

**Incidence** - It has been estimated that 15 percent women are Rh negative of which 3 per cent will marry Rh negative men and hence have no sensitization, will occur 5 percent will marry homozygous Rhesus positive men and have 50 per cent chance of having Rh sensitization, 7 per cent will marry heterozygous Rhesus positive men and have 1: 15 chances of Rh. sensitization, as some babies will be Rh. negative and some Rhesus positive. The incidence of erythroblastosis foetalis is 1: 200 pregnancies i.e. 0.5 per cent and accounts for 15 per cent of still births.

First child has 90% chance of spontaneous survival. Second child has 70% chance of spontaneous survival. ABO incompatibility is almost 100% protective. However, in mothers where ABO

compatibility is present between her and her baby, at least 10% of such mothers will develop antibodies in their blood.

Nearly 90% cases of isoimmunization are due to antigen D while others are due to capital C, E, Duffy, Kell and Lewis.

**Mechanism** - When Rh. Negative woman is exposed to an antigen she does not possess because she is pregnant with Rh. positive baby who possesses antigen D. Antibodies which are gammaglobulin in nature are produced in her serum.

**Antibodies** - There are two types of antibodies which are formed in response to Rh. antigen; 19S which are IgM are formed first these are of large size and hence do not cross the placenta, later on 7S which are IgG are produced. Usually they appear after 4 months, they are of smaller size and cross the placenta and are responsible for immune reactions. They can be detected in the maternal serum by the Coombs' antiglobulin technique.

These antibodies attack the fetal red blood cells containing antigen on their walls. The cells are rapidly destroyed in the spleen and liver and result in fetal anemia. When the anemia is severe, congestive heart failure develops leading to hydrops fetalis. This can happen as early as twenty weeks of Pregnancy. When the hemolysis is not so severe this results in hemolytic disease of the newborn.

### Anaemia:

Which is the greatest danger in utero, can be corrected by transfusion soon after delivery. During pregnancy fetal

bilirubin is transported across the placenta and eliminated by the mother, but after delivery it begins to accumulate in the baby's body and endanger his health and even existence, if not controlled by appropriate treatment.

### **Production and conjugation of bilirubin:**

The exact mechanism of red cell destruction by antibody is not known. Haemoglobin liberated from the ruptured cells, breaks down and produces bilirubin, which on entering the circulation binds to serum albumin and is carried to the liver where it is converted to Bilirubin glucuronide by a liver enzyme called glucuronyl transferase. Bilirubin glucuronide is readily excreted in the urine and bile. The liver of the fetus and newborn infant produces little or no glucuronyl transferase. Therefore very little or no bilirubin glucuronide is produced, soon after birth.

When the bilirubin binds to the infant's serum albumin it circulates and does not deposit in the tissues, while free bilirubin which is not bound to albumin is very toxic.

It is lipid soluble and combines with the lipid rich nerve cell membrane of the brain and causes kernicterus. Albumin has special affinity for ions such as sulfonamides, salicylates, heparin and caffeine; if these are present in fetal-circulation there will be competition for the albumin and less bilirubin will be bound. Increased hydrogen ion concentration (acidosis) also produces a reduction in bilirubin binding.

The red cell antigen that stimulates the prenatal patient to produce an antibody

may have been received by anyone of the following methods i.e. during a prior pregnancy, during delivery of an incompatible fetus, by transfused red cells that possessed a foreign antigen or incompatible red cells that were injected intramuscularly. Once the immune mechanism is triggered (primary response), antibody production may continue for years without additional stimulation.

### **Factors limiting primary immunization during pregnancy:**

It has been reported that the intermittent loss of fetal erythrocytes to the mother is a physiological occurrence throughout pregnancy. Placental transfer of red cells from fetus to mother, occurs regularly in almost all cases, but the amount of leak is small to trigger antibody production in most cases.

Kleihauer -ET-al developed a means to estimate the number of fetal cells in the maternal circulation. Using this technique,

### **Kleihauer and betke:**

Could demonstrate fetal red cells in 71 % of all women after delivery; however, in most cases only an occasional fetal cell was found in large population of maternal cells. The number of fetal cells may be the essential factor in determining the risk of primary immunization during pregnancy. More than 1 ml. of blood is necessary to initiate a primary response, in most cases. However, as little as 0.25 ml cells have been reported to produce sensitization in some women.

**ABO incompatibility:** Fetal red cell with the mother's ABO blood group determines their survival time in the

maternal circulation. If the child's red cells are of group A or group B and the maternal serum contains anti A or anti B, the antibodies will destroy the invading red cells quite rapidly so that they have a limited survival time. This natural protection is not 100% effective and may break down once the Rh negative woman carried an ABO compatible Rh positive fetus.

**Follow-up of mother in antenatal period** - Screening test for antibodies should be performed early in pregnancy on sera of all pregnant women since woman may produce an antibody to any antigen she lacks. A woman whose serum does not contain irregular antibody is on initial testing should be retested in the second and third trimesters of her pregnancy. Since optimum conditions for antigen/antibody interactions vary quite considerably, screening test must be done at different temperatures and in more than one medium i.e. saline and albumin.

For detection of patients at risk, all patients at the initial prenatal visit should have atypical antibody screening, blood group and Rh. type determination. The screening test is done even in primigravida patients to detect previous sensitization due to conditions not known by the patient or known but not revealed to the physician, e.g. abortions, transfusion, etc. The assessment of patients for determination of risk is shown in Flow Sheet 1.

The high risk patients can be screened by using indirect antiglobulin technique (indirect Coombs' test). The titration should be carried out serially and frequently during the whole pregnancy. The critical level of antibody titre

reported by most authors is 1:16. No intrauterine death or severely affected baby has been reported when the titer was below 1:16. However we suggest that titer of 1:18 should be adopted.

The policy of determining; antibody titer at monthly intervals during the first and second trimester and then fortnightly in the third trimester is generally accepted. If the titre is 1:32 or greater, the patient should be followed by amniotic fluid analysis, obtained by amniocentesis.

When the serum antibodies are less than or equal to 1:8 in albumin at 34 weeks of gestation then there is no chance of a still-birth before term. If the titre rises to 1:16 at 36 weeks of pregnancy then deliver the baby. On the other hand when the titre is less than 1:16 before 36 weeks of pregnancy and there is a history of previous stillbirth or exchange transfusion then amniocentesis should be done to establish severity of the disease.

Prediction of severity of the Rhesus disease is only 60% accurate when it is based on history and antibody titres alone, but with amniocentesis. it is 95% accurate.

Effective method of predicting and evaluating the severity of hemolytic disease of the newborn is therefore by amniocentesis. TED to spectrophotometric scanning. Complications include maternal infection, placental injury, fetal injury and even, premature induction of labour.

Once started, amniocentesis should be repeated at 1 to 3 weeks intervals. With antibodies titre greater than 1:16 and pregnancy less than 32 weeks there is 10% chance of still-birth before term and

when the titre is greater than 1: 32 the chance of still birth is 25%, with amniocentesis can be performed as early as 22 weeks of pregnancy. It is a simple procedure but should be done with complete asepsis. The skin over the suprapubic area should be prepared. The presenting part should be identified and elevated. Placenta should have been localized by ultrasound scanning or preferably the amniocentesis should be done directly under the scanner monitoring.

A 20 gauge lumber needle is passed into the amniotic cavity under local anesthetic cover and guided by the ultrasound scanner, 5 to 10 ml of amniotic fluid is obtained. This fluid sample should be put in a dark tube and protected from light and centrifuged at 4000 RPM. The supernatant is subject 1:64 it becomes 50% and with 1:256 it rises to greater than 900A>.

For a child to possess a red cell antigen which the mother lacks, the antigen must be inherited from the father, thus test of the father's blood allows one to predict the degree of probability that the child has inherited the antigen from his father. If the father is homozygous for a gene that controls a particular antigen all of his children will inherit the gene. When the father is heterozygous, statistically only half of his children will receive the gene from him.

In the first pregnancy in which the fetus is affected, a rising titre/and the height of the titre can generally be related to the severity of disease. Titre in subsequent pregnancies does not always reflect the condition of the child or even its antigenic status. A drop in titre may mean either that the fetus lacks the

antigen and is healthy or that the cells of a positive fetus are absorbing antibody faster than the mother can produce it. Titres are of particular value in indicating whether or not amniocentesis should be performed.

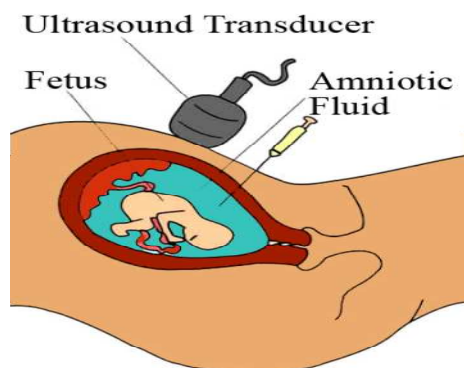
The limiting level of titre should be below where there has been no intrauterine death and this must vary from laboratory to laboratory. Since there is no centralization of Rhesus disease cases in our country, no 'definite titre can be adopted for this purpose.

Until such time a proper screening and follow up system is established, it is suggested that titre of 1:8 or over should be an indication for amniocentesis.

Liley has shown that amniotic fluid has a relatively linear absorption curve when plotted on semi logarithmic paper. The 450 m ~ peak produced by bilirubin and its height in fresh amniotic fluid correlates well with the severity of hemolytic disease. His zoned graphic method attempts to predict the severity of the hemolytic disease, if delivery should occur within one week of the measurement. When amniotic fluid analysis is carried out by measurement of absorption at various wave lengths in a recording spectrophotometer, the absorption curve shows a hump when bilirubin is present.

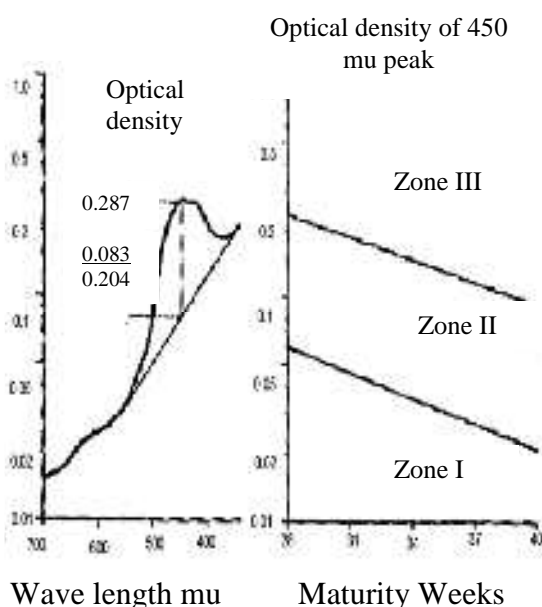
The height of the hump at 450 m is also called the pigment peak or Optical density which tends to become lower as pregnancy advances in unaffected babies. Liley plotted weeks of gestation against optical density of the amniotic fluid and described three zones, as follows:





**Fig 9.2: Shows amniocentesis under**

Acceleration of fetal growth for non hydropic fetuses that often are growth retarded.



### Zone I:

When the optical density of the amniotic fluid analyzed at 28 to 31 weeks was noted in this zone, the fetus was unaffected or may have mild hemolytic disease, Liley advised repeat taps in two to three weeks. The baby may be Rhesus positive.

**Zone II:** This is intermediate zone and the prognostic value of this zone is not so clear cut. Repeat taps should be

performed to determine the trend. This is zone.

**Intrauterine transfusion** - When the amniotic fluid analysis shows the disease in upper zone II or zone III this suggest that death of the fetus is likely to occur in the near future. This is particularly so if the trend in the repeat tests is rising. The ideal time for carrying out intrauterine transfusion is around 23 to 24 weeks of pregnancy. To carry out this procedure about 20 ml of renograffin is injected in the amniotic sac and the fetal position and location are determined by biplane fluoroscope. If the fetus is face up or lateral the procedure is carried but when the face is down, the procedure is post-poned due to difficulty in approaching the peritoneal cavity of the fetus.

A 15 gauge Tuohy's needle is inserted through the mother's abdominal wall into the peritoneal cavity of the fetus and its position is determined by injecting a small amount of Renograffin, a plastic catheter is passed through this needle and the needle is then removed. Group "0" rhesus negative blood is used for transfusion, packed cells are preferred and about 110 ml. of cells are given at 30 weeks and 10 ml are added for every additional week. The same amount is reduced for every week less than 30. The total amount is transfused slowly over a period of one hour. Nearly 70% of the cells transfused are absorbed into the circulation over a period of six days. The absorption takes place via the diaphragmatic lymphatics.

**Prenatal management of Rhesus disease:** Early induction combined with exchange transfusion postnatal is treatment of choice in mild to moderately affected babies and can save many lives.

**Induction of labour:**

When screening tests for antibody titre show rising trend and the amniotic fluid analysis places the baby in the Zone where it is affected, premature delivery by elective induction can save the baby.

Prematurity carries an additional risk in these babies because their ability to conjugate bilirubin is poorer than in the mature infants. The risk of death from prematurity must be carefully weighed against still-birth due to Rhesus disease.

Elective delivery at 37 weeks when the fetal lungs are mature and the risk of respiratory distress syndrome is minimum has many advantages. Care of such patient requires special team work.

Coordination of blood bank, laboratory and nursing personnel will help in improving the results of elective induction much more than leaving the time of delivery to chance. The services of these personnel may not be available if delivery took place at odd hours of the night.

**Symptoms of hyperbilirubinemia:** The following are the most common symptoms of hyperbilirubinemia. However, each baby may experience symptoms differently. Symptoms may include:

- yellow coloring of the baby's skin (usually beginning on the face and moving down the body)
- poor feeding or lethargy

The symptoms of hyperbilirubinemia may resemble other conditions or medical problems. Always consult your baby's physician for a diagnosis.

**Differential diagnosis:** The timing of the appearance of jaundice helps with the diagnosis. Jaundice appearing in the first 24 hours is quite serious and usually requires immediate treatment. When jaundice appears on the second or third day, it is usually "physiologic." However, it can be a more serious type of jaundice. When jaundice appears on the third day to the first week, it may be due to an infection. Later appearance of jaundice, in the second week, is often related to breast milk feedings, but may have other causes.

**Diagnostic procedures** - Diagnostic procedures for hyperbilirubinemia may include:

- **Direct and indirect bilirubin levels**  
These reflect whether the bilirubin is bound with other substances by the liver so that it can be excreted (direct), or is circulating in the blood circulation (indirect).
- Red blood cell counts
- Blood type and testing for Rh incompatibility (Comb's test)

**Laboratory evidence of hemolytic disease:** A direct anti globulin test (direct comb's test) on blood of the infant provides valuable information for making diagnosis of hemolytic disease, especially where mother has received no prenatal care. Routine collection and refrigerated storage of 10 ml. of cord blood should be practiced in all modern hospitals. If there are signs of trouble, cord blood is available for investigation.

**Maternal antibody (Anti RhD)** - Not uncommonly one sees a baby suffering from hemolytic disease of the newborn whose mother's serum contains potent

anti Rh-O; the direct antiglobulin test on the baby appears to be negative, in such a situation it should be established that the maternal serum contains only anti Rh-O and, if this is found to be the case, one must assume that the child is Rh positive. The maternal antibody acts as a physical barrier or block between the antigen sites and the anti Rh O reagent used in testing.

Rh typing of an infant who has received intrauterine transfusion for Rh (0) hemolytic disease may also be misleading. The baby may appear to be Rh negative at birth since transfused Rh negative blood survives and the production of the baby's Rh positive cells, is often suppressed.

A positive direct antiglobulin test does not indicate the severity of the disease process. Hemoglobin and indirect bilirubin levels are better reflectors of the extent of red cell destruction and elimination.

#### **Cord hemoglobin:**

Cord hemoglobin value below 14 gm/100 ml, is considered abnormal and suggestive of a hemolytic process. Severely affected infants may have cord hemoglobin levels as low as 3 or 4 gm/100 ml.

Serum bilirubin level in normal full-term infants seldom exceeds 13 mg/100 ml, at 48 hours of age but premature babies with physiological jaundice may have serum bilirubin as high as 30 mg/100 ml. By the third or fourth day the liver of the full term infant produces sufficient glucuronyl transferase to convert bilirubin to its excretable form; bilirubin glucuronide.

#### **Tests for assessment of disease process:**

##### **Serial hemoglobin determinations -**

There is hardly any great change in hemoglobin concentration in severe hemolytic disease in the critical first two days of life. Actually, the hemoglobin level may not only fall during the first two days of life, but also remain high these infants are in special danger of developing kernicterus. To wait for falling hemoglobin as an indication for exchange transfusion in hemolytic disease may be dangerous. Comb's Test is only a diagnostic test. Many infants with a positive Coombs test do not require exchange transfusion. On the other hand, some with a negative Comb's Test (as, for example, cases of erythroblastosis due to ABO incompatibility) do require transfusion to prevent kernicterus. Therefore this test should never be the sole criteria for exchange transfusion.

#### **After birth:**

An antibody causes destruction of the red cells and cause. Anaemia which can in turn cause heart failure. When build up of bilirubin is controlled or treated by either photo therapy or ex-change transfusion. Kernicterus can occur and result is severe retardation.

Bilirubin has been postulated to cause neurotoxicity via 4 distinct mechanisms: Clinical signs of bilirubin encephalopathy typically evolve in 3 phases. Phase 1 is marked by poor suck, hypotonic and depressed sensorium. Fever and Hypertonia are observed in phase. Phase 3 is characterized by high-pitched cry hearing and visual abnormalities, poor feeding.

**Blood brain barrier and bilirubin encephalopathy:** This barrier prevents free union gusted bilirubin from crossing from blood to brain. The barrier is less effective in premature infants and in unwell infants, in bilirubin encephalopathy there will be Hypotonia, High pitched cry and Seizures, Long term sequelae of encephalopathy will result in Athetoid CP or Endoneural deafness.

### **Prolonged jaundice:**

Common in breast fed infants; around 20% it is very common in premature breast fed infants where it is >30%

### **Investigations of persistent Jaundice for more than 2 week:**

Blood for split bilirubin check urine for WBC 'S, urobilinogen screen for TSH.

### **Phototherapy:**

The efficacy of phototherapy depends on the spectrum of light deviled, the blue – green region of visible light being the most effective; irradiance (mW/cm<sup>2</sup>nm); and surface area of the infant exposed. Nonpolar bilirubin is converted into 2 type of water soluble photo isomers as a result of phototherapy. The initial and most rapidly formed configurational isomer 4z, 15e bilirubin accounts for 20% of total serum bilirubin level in newborn undergoing phototherapy and is produced maximally at conventional levels of irradiance (6-9 mW/cm<sup>2</sup>/nm). The structural isomer lum rubin is formed slowly and its formation is irreversible and is directly proportional to the irradiance of phototherapy on skin. Lum rubin is the predominant isomer formed during high intensity phototherapy. Decrease in bilirubin is

mainly the result of excretion of these photo products in bills and removal via stool. In the absence of conjugation, these ph-oto isomers can be reabsorbed by way of the enterohepatic circulation and dimin-ish the effectiveness of phototherapy.

**Indications of phototherapy:** It should be used only when significant unconjugated (indirect) hyperbilirubinemia is present. Its use with elevated conjugated (direct) bilirubin levels is contraindica-ted. Skin jaundice is not a reliable indi-cator of serum bilirubin level, therefore determination of serum bilirubin level of infants receiving photo therapy is necessary.

The eyes of the babies receiving photo therapy should be protected from intense light. Conjunctivitis and corneal abrasion may occur if eyes are not protected. Water intake should be increased during photo therapy.

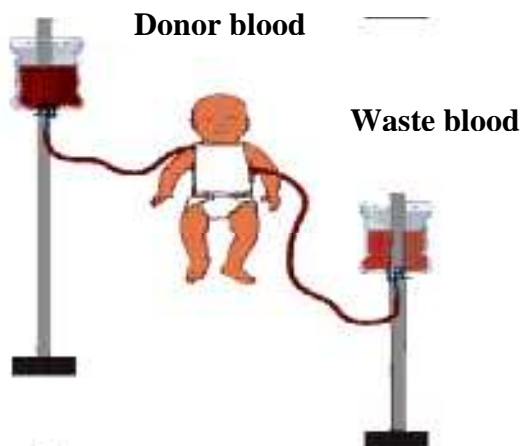
**Exchange transfusion** - Neonatal mortality can be reduced to less than 5 per cent and kernicterus, almost eliminated by this method. Anemia as well as excess fluid containing anti-bodies and bilirubin can be removed along with the bulk of the infant's vulnerable red cells and substituted with red cells that are compatible with the maternal antibodies. Nearly a third of the total bilirubin in the body can be removed with the infant's blood. In case of congestive heart failure more blood is removed than given. The aim should be to reduce the venous pressure to normal. Venous pressure can be measured by the same plastic tubing inserted into the umbilical vein for exchange transfusion. Normal venous pressure is usually less than 7 em of water. About 10 ml. of blood is

transfused at a time to prevent overloading and cardiac embarrassment. Fresh albumin can also bind bilirubin that is liberated as a result of subsequent hemolysis. The volume of blood required for a seven pound baby is about 500 mL. Three, and sometimes more, exchange transfusions are usually needed.

### Pre requisites for exchange transfusions:

Severe anemia (Hb < 10 g/dl), rate of bilirubin rises more than .5 mg/dl despite optimal phototherapy, hyper-bilirubinemia and DAT.

**Objectives:** Decrease serum bilirubin and prevent kernicterus, provide compatible red cells to provide oxygen carrying capacity, decrease amount of incompatible antibody and remove fetal antibody coated red cell.



**Fig 9.3: Showing exchange transfusion under process**

**Potential complications of exchange transfusion:** Cardiac arrhythmia, volume overload, congestive failure and arrest. Hematologic over heparinization, neutropenia, thrombocytopenia and graft versus host disease. Infectious bacterial,

viral (CMV, HIV, hepatitis) and malarial. Metabolic acidosis, hypocalcemia, hypoglycemia, hyperkalemia hypernatremia. Vascular Embolization, thrombosis, necrotizing enterocolitis, and perforation of umbilical vessel and systemic hypothermia.

**Reserve albumin binding capacity** - It has been reported that when the reserve albumin binding capacity is 50 per cent of normal, jaundiced infants can escape brain damage even when the serum indirect bilirubin concentration is as high as 30 mg. per 100 ml. Unfortunately there is no way of being sure that in which neonate and at what critical value of bilirubin in the serum the brain damage will occur. Kernicterus is preventable by exchange transfusion. The higher bilirubin levels still have some statistical validity in causing brain damage therefore the levels should be followed closely, and repeated exchange transfusions should be done to control high and increasing bilirubin concentrations.

**Follow up:** TSB that needs photo therapy should mandate an investigation for cause. History, physical examination, lab tests, etc. etc.

**Recommendation:** Adequate follow up should be ensured for all infants who are jaundiced. Infants under phototherapy should be investigated for determination of the cause of jaundice. Prior to the discharge of every newborn, there should be a process and protocol in place for assessing the risk for development of significant hyperbilirubinemia in all newborns nurseries. There should be a systematic approach to the assessment of all infants before discharge for this risk and program and follow up should be in

place if the infant develops jaundice. All newborn infants who are visibly jaundiced, near (between 35 – 37 weeks) and full (>38 weeks) term should have a bilirubin level determined. Infants, although not visibly jaundiced but with two or more risk factors should have at least one bilirubin level preformed prior to discharge. Serum bilirubin may be done on either capillary or venous blood sample. Infants with severe or prolonged jaundice should have further investigations including an analysis of the conjugated component of the bilirubin. A Transcutaneous bilirubin measurement may be used if available as a screening device.

#### **Inhibition of conjugation:**

Certain physiologically produced steroids i.e. pregnanediol, progesterone, and others inhibit conjugation of bilirubin. Successive infants of certain apparently normal mothers have been found to develop high levels of unconjugated bilirubin which lead to kernicterus. The mechanism of jaundice production is probably an exaggeration of physiological inhibition of conjugation. (Lucey-Driscoll Syndrome). In survivors the resulting jaundice disappears within a month as normal conjugation mechanisms appear. Novobiocin has also been shown to inhibit conjugation in vitro, and there is an increased incidence of unconjugated hyperbilirubinemia in infants receiving this drug, which is now seldom used and is not available in Pakistan.

**Treatment of hyperbilirubinemia** - Early milk feedings and glycerin suppository have been shown to decrease the serum bilirubin level, presumably by enhancing early evacuation of gut con-

tents, including bilirubin. In infants with hemolytic processes, regular check up of hematocrit and reticulocyte count is necessary. Treatment depends on many factors, including the cause of the hyperbilirubinemia and the level of bilirubin. The goal is to keep the level of bilirubin from increasing to dangerous levels. Treatment may include:

#### **Prevention of Rh sensitization** -

Usually large fetomaternal bleeds which are enough to produce Rh sensitization occur during delivery, after abortion and separation of placenta. With Kleihauer acid elution and staining technique an actual count of the number of fetal cells in the maternal circulation, can be made. It has been observed that dose of more than 0.25 ml. of fetal Rh-positive cells is needed to produce immunization.

When ABE incompatibility between mother and child, is present the frequency of Rh sensitization is diminished, because the maternal anti A and Anti-B destroys the fetal Group A or B. Rh positive cells before a maternal response can occur. Avoidance of unnecessary intrauterine manipulation can also help to lower the incidence of sensitization.

#### **Anti D gamma globulin:**

Rh-immune globulin is produced from plasma of highly sensitized men and women. This plasma is pooled and clear fraction is separated which contains highly concentrated IgG, Anti Rh-D and is free of the hepatitis virus. The antibodies are concentrated and distributed in 1 ml dose containing approximately 300 mcg of Anti D, and is given intramuscularly, within 72 hours after delivery. This 72 hour period is specified because the clinical trials which tested

the efficiency of this immune globulin included limited follow up period of 72 hours only.

### **Prognosis:**

Toxic levels of bilirubin can cause damage when it passes from the serum into the basal ganglion cells of the brain. Neurosensory hearing loss is the most common sequela of excessive serum bilirubin. Kernicterus is a clinical syndrome where deposition of unconjugated bilirubin in certain nuclei of the brain, affects central nervous system. The albumin binding capacity is decreased in conditions where there is acidosis or history of Sulpho amide administration and or where free fatty acid levels are elevated.

These conditions predispose the neonate to Kernicterus even with lower levels of bilirubin.

The baby, who develops kernicterus, suddenly becomes lethargic and stops feeding.

His cry becomes high pitched. The respiratory rate becomes slow. Apnea, respiratory, arrest, and even convulsions may occur in severe cases. Infants who survive, have severe motor impairment, including hypotonia, spasticity, and athetosis.

Mental retardation may occur but it is generally less severe. In terminal stages, the babies have irregular gasping respirations, bloody discharge from the nose and mouth. Most babies die within 48 to 72 hours.

**Mortality or morbidity:** Unlike unconjugated bilirubin, conjugated

bilirubin does not bind significantly to neural tissue and does not lead to kernicterus or other forms of toxicity.

- The morbidity and mortality associated with conjugated hyperbilirubinemia result from the underlying disease process.

In certain disease states, such as alcoholic hepatitis or primary biliary cirrhosis, bilirubin levels correlate strongly with, but do not contribute to, short term mortality.

**The Group "0"** rhesus negative packed cells should be cross matched and found compatible with mother's blood. The hemoglobin in these cells should be around 26 to 28 gram per 100 ml and hematocrit of 85 to 95 per cent.

The second transfusion could be given after 10 days and the 3rd and 4th within 3 to 4 weeks interval from the second. Delivery should be conducted around 34 to 35 weeks.

If on x-ray hydropic fetus with ascites is found then ascitic fluid is withdrawn first and mother is given digitalis and diuretic.

### **Risks of intrauterine transfusion:**

Only 45% of intrauterine transfused babies are born alive and one third actually survive.

The risk of immediate death after first intrauterine transfusion is around 10 to 12 per cent and another extra 5 per cent with each successive transfusion. The overall risk is around 7 per cent. Neonatal death rate in these babies is around 8 per cent.

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## Chapter No: 10

# THROMBO EMBOLISM IN PREGNANCY

**Incidence** - This complication occurs; once in 5,000 pregnancies. The incidence increases during puerperium where it occurs once in about 300 cases. The condition seems to have racial influence and occurs less commonly in oriental and Negroid races.

### Coagulation phase:

Two major pathways: Intrinsic pathway and extrinsic pathway both converge at a common point 13 soluble factors are involved in clotting. Biosynthesis of these factors is dependent on Vitamin K1 and K2 Normally inactive and sequentially activated hereditary lack of clotting factors lead to hemophilia A.

### Intrinsic pathway:

All clotting factors are within the blood vessels, Clotting slower and Activated partial thromboplastin test (aPTT).

### Extrinsic pathway:

Initiating factor is outside the blood vessels tissue factor, clotting faster in seconds and prothrombin test (PT).

### Patho physiology:

During pregnancy certain physiological changes occur in the maternal blood clotting factors. The Fibrinogen level rises from 300 to 500 mgs per 100 ml of blood.

There is considerable increase in prothrombin level. Factors VII, VIII and X are increased. The platelets rise from

150,000 to 500,000j comm. These changes make pregnancy a hypercoagulable state. Normally a fine balance is maintained between the clotting and fibrinolytic mechanisms.

This balance if upset in favour of clotting by an event, the blood starts clotting in the uterine veins and then extends to the ovarian or iliac veins. The clot may originate in the veins of the soleus muscle and extend to the tibial, popliteal, femoral and iliac veins.

### Mechanism of clot formation:

The platelets adhere to each other as well as to the endothelial lining and form a pale thrombus.

If the clot is small it is endothelialis Ed and causes no problems. However, if through surface persists it encourages the trapping of other blood elements such as red blood cells and produces a thrombus of blood clot, which is red and therefore called the red thrombus.

This thrombus may be so large that it occludes the whole lumen of the blood vessel.

Usually a large column of blood beyond the primary site of thrombus formation is involved in the pathological process and leads to a long tail of clot.

This tail can readily break and produce pulmonary embolism. In thrombophlebitis the clot is usually well anchored by the in filamentary reaction, and therefore does not separate so easily. The danger

of embolus formation is far less in thrombo phlebitis. In 'White Leg' of pregnancy there is iliofemoral vein thrombosis which is often associated with arterial spasm.

**Predisposing causes:** Factors which may predispose thrombus formation are many but important one are increasing age of the patient, immobilization, operative manipulation, and obesity. In deep vein thrombosis a single or multiple factors may be at work. The Virchow's Triad which comprises of endothelium, blood flow, and blood constituents, when affected by any factor can start thrombus formation.

**Endothelial damage** - This may occur at the time of Cesarean Section or forceps delivery and/or as a result of pelvic manipulation.

Pressure can produce ischaemic damage to the endothelium; therefore lying on operating table for a long time may be dangerous. Bacterial infection, heat, cold, and chemicals can damage the endothelium, and thus predispose to clot formation. Blood flow may be slowed when aneurysms or varicosities are present. Pressure from outside such as operating table can also affect the flow pressure. Gravid uterus can be equally effective in slow-ing the blood flow.

Blood flow is also decreased in cardiac patients and in those who are comatose or lying in bed under the effect of massive sedation. Obesity too increases pressure effect.

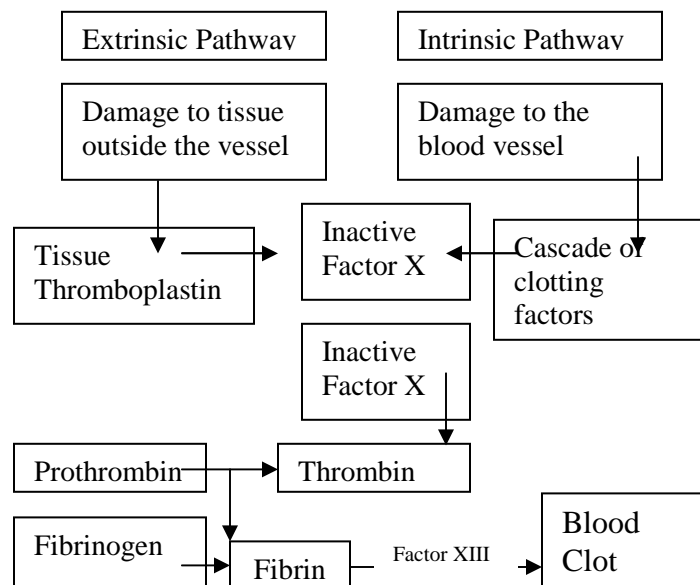
**Blood constituents:** A number of changes such as stickiness of platelets, increase of fibrinogen and dehydration which occur after ordinary trauma, or

trauma of surgery, and postpartum period, encourage thrombus formation.

**Stages of coagulation** - There are four main stages involved in the clotting of blood in vivo.

Drugs Class	Prototype	Action	Effect
Anticoagulant Parenteral	Heparin	Inactivation of clotting Factors	Prevent Venous Thrombosis
Anticoagulant Oral	Warfarin	Decrease synthesis of Clotting factors	Prevent Venous Thrombosis
Anticoagulant Drugs	Aspirin	Decrease Platelet aggregation	Prevent arterial Thrombosis
Thrombolytic Drugs	Streptokinase	Fibrinolysis	Breakdown of thrombi

**Fig10.1: Shows blood constituents and sites for anticoagulant**



**Fig10.2: Shows both intrinsic and extrinsic factors activating clotting mechanisms**

### First stage:

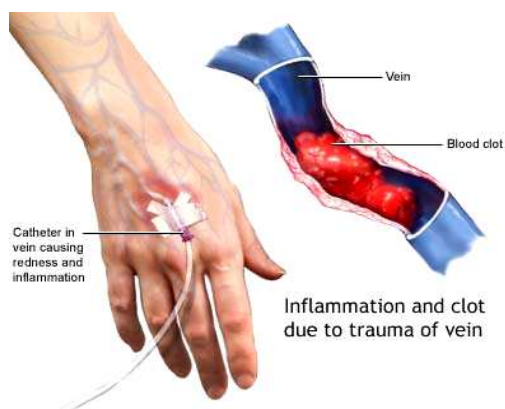
In this stage thromboplastin is formed and activated. Thromboplastin which is derived from blood platelets or endothelial wall is activated by anti hemophilic globulin Factor (VIII), Christmas factor (Factor IX), and Factor V. When thromboplastin is derived from damaged tissues (Extrinsic system) it is activated by Factor V, Factor VII and Factor X.

**Second stage** - In this stage thrombin formation occurs and prothrombin (Factor II) is converted into thrombin. Both calcium ions (Factor IV) and the activated thromboplastin (Factor III) are needed for this reaction to take place.

**Third stage** - In this stage thrombin reacts with fibrinogen (Factor I) and forms fibrin monomer.

**Fourth stage** - In this stage polymerization of fibrin monomer occurs. Thus strands of fibrin are formed which trap platelets and clot is formed.

**Clinical features** - Majority of patients with thrombosis remain silent. The symptoms manifest by its complications.



**Fig10.3: Shows thrombo phlebitis and clot in the vein due to trauma**

### Thrombophlebitis:

This complication when present usually presents with edema, Pain and tenderness over the involved area. Homan's sign may or may not be positive. Lisker's sign i.e. tenderness on tibial percussion is usually present if leg veins are involved. Pratt's sign i.e. failure of superficial veins to collapse when the leg is raised to 45 degree may be present. Sometime one may be able to palpate the thrombosed vein. The patient may be pyrexial. In Phlegmasia Alba dolens or white leg one may see a pale, puffy, pulseless, limb which is quite painful. O edema, pain and deep tenderness when present provide sufficient evidence to support the diagnosis of deep vein thrombosis. Thrombophlebitis of the pelvic or leg veins usually starts between the fourth and tenth days of the puerperium. It is often associated with anaemia and anaerobic streptococcal infection in the pelvis. Increase of skin temperature may be noticed when a hand is placed on the affected calf. With the deep veins blocked, more blood must pass through the superficial venous plexus. Arterial spasm is responsible for the pain and is a marked feature in this condition. In the puerperium pelvic thrombophlebitis is relatively more common. Thrombosis starts in the veins of the uterus and later extends to the ovarian and thence to the iliac veins or even into the inferior vena cava.

**Diagnosis** - Physical signs in the vast majority of cases are absent, therefore other methods of diagnosis have to be employed.

**Phlebography** - This is quite an accurate method and can provide useful information in doubtful cases.

Unfortunately this faculty is not available to clinicians in most hospitals of this country.

**Fibrinogen uptake:** In this test labelled iodine is given intravenously. This becomes incorporated into the new thrombus in due course of time. A scintillation counter is employed to scan set points in the legs and thus areas of increased uptake are detected. This test is not recommended during pregnancy because of radiation hazards to the fetus.

**Ultrasound:** The frequency of an ultrasound beam passed through a moving column of blood is altered according to the rate of flow because of Doppler Effect. When thrombosis is present the rate of flow may be severely compromised. This change in flow can be detected by the help of doppler, used in obstetrical wards for recording fetal heart rate.

## Management

### Prophylaxis:

This can be achieved by early post operative and post partum ambulation. The physiotherapist can play an important role in this connection. Tight bed clothes that restrict leg movements should be avoided. The patient must be adequately hydrated by generous supply of appropriate fluids. Oversedation must be avoided.

Anaemia should be corrected before surgery. All high risk patients, e.g. cardiac, obese, and those with a previous history of deep vein thrombosis should be covered with prophylactic anti coagulants. The patient should be instructed to keep her legs moving in

bed both before and after delivery. The foot of the patient can be raised, this will lessen venous stasis. Elastic stockings help to increase the blood flow through leg veins. Breathing exercises and early ambulation after delivery prevents venous stasis and thus improves blood flow. Operative procedure should be carried out gently. The incidence of venous thrombosis and pulmonary embolism after section is at least six times than after normal delivery.

**Anti coagulants** - The pain of deep thrombophlebitis, is quickly relieved by anticoagulant drugs especially heparin. Anti coagulant therapy should be used for all cases of deep vein thrombosis. They do not dissolve thrombus but prevent further deposition of red thrombus and embolization. They can be safely used within twenty four hours of delivery. Once anti coagulants have been started they should be continued until the patient has been up and about for at least two weeks.

**Ante partum thrombophlebitis** - In this condition anticoagulant therapy should be used. The prothrombin content of the blood should not be allowed to fall below 30 per cent for fear of causing retroplacental hemorrhage. Vitamin K, 20 mg intravenously should be given to the mother at the onset of labour in order to avoid the risk of postpartum hemorrhage. Heparin does not cross the placenta and may be use.

**Heparin** - Initial dose of heparin varies between 5000 to 10,000 I U. This can be repeated after every 4 to 6 hours. The clinical target should be to give sufficient heparin capable of lowering clotting time 2 to 3 times that of the normal control. This criterion should

also be used for arranging the next dose of heparin. Over dosage of heparin can be easily reversed by giving protamine sup late 1 mg per 1000 units of heparin.

### Heparin:

Sulph ated carbohydrate: Different size bovine lungs, Administration parenteral do not inject IM - only IV or deep S.C. Half-life 1 - 5 hrs - monitor aPTT. Adverse effect: hemorrhage Anti-dote: protamine sulphate.

### Oral anticoagulants:

Examples: Coumarins - warfarin, dicumarol, structurally related to vitamin K, Inhibits production of active clotting factors, Clearance is slow - 36 hrs, Delayed onset 8 - 12 hrs overdose - reversed by vitamin K infusion and can cross placenta - do not use during late pregnancies.

### Mechanism of action:

Normally, vitamin K is converted to vitamin K epoxide in the liver. This epoxide is then reduced by the enzyme epoxide reductase. The reduced form of vitamin K epoxide is necessary for the synthesis of many coagulation factors (II, VII, IX and X, as well as protein C and protein S). Warfarin inhibits the enzyme epoxide reductase the liver, thereby inhibiting coagulation.

### Warfarin side effect:

Severe Side effects: Severe bleeding from the rectum or black stool Skin conditions such as hives, a rash or itching. Swelling of the face, throat, mouth, legs, feet or hands, bruising that comes about without an injury you

remember, Chest pain or pressure Nausea or vomiting, fever or flulike symptoms. Joint or muscle aches diarrhea, difficulty moving Numbness of tingling in any part of your body and Painful erection lasting four hours or longer.

### Other less serious warfarin side effects:

Gas, feeling cold, fatigue, pale skin changes in the way foods taste and Hair loss.

### Drug interaction with warfarin:

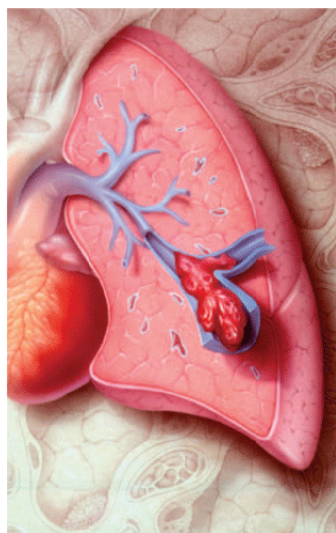
Category	Mechanism	Representative Drugs
Drugs that Increase Warfarin Activity ↑	Decrease binding to Albumin inhibit degradation decrease synthesis of clotting Factors	Aspirin, Sulfonamides, Cimetidine, Disulfiram, Antibiotics (oral)
Drugs that promote bleeding ↑	Inhibition of platelets Factors Inhibition of clotting	Aspirin, heparin, antimetabolites
Warfarin activity Drugs that decrease ↓	Promote clotting factor Reduced absorption Synthesis	Vitamin K, Colestipol, Cholestyramine

**Naphthoquinone** - This group of drugs include dicoumarol, and phenindione. These drugs are chemically similar to Vitamin K. They act by replacing Vitamin K at the site of prothrombin formation. They also prevent the hepatic synthesis of factor VII, IX and X. The anticoagulant effect of heparin is immediate and maximal after intravenous injection, but decreases rapidly over the course of few hours. The effect of oral anticoagulants on the other hand, is negligible for the first 24

hours. The maximal effect takes 36 to 72 hours to develop, after initial administration of the drug.

The clinical target in achieving desired anticoagulant effect is to reduce the prothrombin time or activity to about 20 per cent of normal control. The effect of these drugs can be reversed by intravenous injection of 50 to 150 mg of Vitamin K" given very slowly and no more than 10 mg per minute. The activity of Vitamin K dependent clotting factors reaches to safe level within 4 to 8 hours. Oral anticoagulants cross the placenta and may cause serious bleeding.

Warfarin is preferred over other agents since it produce less side effects. The initial dose is around 35 to 40 mg followed by 10 mg, depending upon the prothrombin time.



**Fig 10.4: Shows embolism in place in one of the lungs**

Pulmonary embolism is the second most common cause of maternal death in pregnancy. This occurs when a thrombus breaks free from the vein. It enters into the pulmonary artery at the

time of right ventricular systole, becomes impacted in its branch whose lumen is narrow and the thrombus cannot pass through it. The effect of the embolism on the patient depends upon the size of the embolus. The clinical symptoms may be delayed until the fourth or fifth week after delivery, when the patient has returned home.

**Etiology:** The causes of pulmonary embolism are the same as for deep venous phlebothrombosis. Pulmonary embolism is a recurrent disease. The woman who has cine attack is liable to have another within a few hours or day.

**Pathology:** Embolism can occur before there is any sign of venous thrombosis. Pulmonary infarction occurs when a large clot is lodged in one of the main branches of the pulmonary artery. This clot comes from the femoral or iliac vein in majority of cases, but in few cases it may come from the pelvic veins.

The embolus can be lethal if half of the lung capacity is affected, An immense spasm of the unblocked pulmonary arteries play an important role in producing this fatal effect. Small emboli do not produce infarction of healthy lungs, therefore they go unnoticed and the student may confuse the clinical features with pleurisy or pneumonia. However, multiple and recurrent small emboli can result in pulmonary hypertension

#### **Pathophysiology of infraction:**

The emboli can stop venous flow from the pulmonary segment supplied by these vessels. The alveoli continue to be no rushed by the bronchial arteries which carry oxygenated blood.

The alveolar capillaries rupture and the alveoli become tightly packed with blood cells and finally infarct is formed. The infarct can extend to the surface of the lung.

### **Clinical features:**

Pulmonary embolism, like deep venous thrombosis, manifests itself on the 8th post operative day, but can occur earlier if the patient had been kept in hospital for longer periods before operation. The longer the patient is kept resting and immobilized in hospital for medical investigations, the greater the risk of embolization. The patient complains of pleural pain over the affected area of the lung. Hemoptysis may occur either before or after the development of pain, tachycardia and/or slight dyspnea may be present. The temperature may rise to about 37.80C (100°F). A pleural rub may be audible. The diaphragm may be raised on the affected side due to reflex paralysis.

**X-ray** - Lungs may reveal the infarct in the lower lobe. The complication occurs more frequently on the right side.

**Small embolus with infarction** - This condition is much more common than is generally realized. There may be no signs, or symptoms. Sometimes these small emboli cause transient syncopal attacks. The patient may feel faint and sweaty and have tachycardia, but the attack passes off in a few minutes. This occurs between the fourth and eighth. Day of the puerperium. Unfortunately these symptoms are often dismissed by the physician as being due to postural hypotension following long and continuous stay in bed. If these emboli could be recognized and anticoagulant

therapy is started the risk of further and larger emboli can be very much reduced.

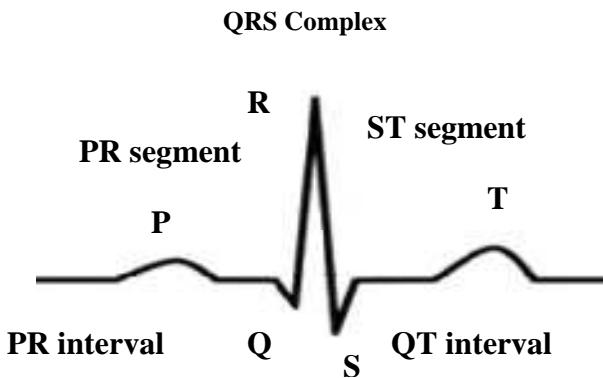
**Minor degrees of embolism** - These may result in peripheral infarction of the lung and present by way of pain over one or other lung. This quickly leads to pleurisy and the pain becomes worse by deep breathing and by any movement of the chest wall. Cough and blood stained sputum may develop. There may also develop clinical signs of consolidation of the lung at this stage. Pyrexia is generally a prominent feature and persists for a considerable time especially if a pleural effusion develops.

The sequence of clinical features makes it easy for the student to confuse it with a painful muscular condition, and for pleurisy and pneumonia.

**Massive embolism** - The patient complains of sudden violent pain in the chest; which is followed by shock or even death from ventricular fibrillation or cardiac arrest. Severe dyspnea is usually a leading symptom but generally this is followed by initial non-fatal chest pain and collapse. Tachycardia, cyanosis and congestion of the neck veins, may be noticeable and the patient becomes mentally confused or comatose.

**Large pulmonary embolus** - A large thrombus may break free and reaches pulmonary artery through the heart and occlude it. The pressure in the artery rises and the right ventricle dilates. Similarly the neck veins are dilated. Liver is enlarged, and a gallop rhythm may be heard at the lower end of the sternum. Occasionally a pericardial friction rub may be heard over the pulmonary artery. The systemic blood pressure falls, the patient looks pale and

may complain of constricting type of pain due to fall in coronary blood flow. The patient may suddenly collapse, turn cyanosed, sweat and gasp. There may be no cough or hemoptysis.



**Fig10.5: Shows normal ECG**

The E.C.G. shows right ventricular strain with T wave inversion in leads V1, V2 and V3. Q wave is deep, T wave is inverted in standard lead III, S wave is inverted in standard lead I. These changes remain for several days and are most helpful in confirming the diagnosis.

Nearly 25 per cent of the patients die within an hour or two. A recurrent embolus will occur in at least 25 per cent of those who survive the first attack. This may be prevented, if anti-coagulant therapy is instituted in time.

A very large embolus can completely block the outflow of blood from the right ventricle and lead to sudden death within a few seconds. Multiple small pulmonary emboli may develop during puerperium. They can obliterate pulmonary arteries and in succeeding months result in pulmonary hypertension. As the months go by, the patient becomes increasingly breathless and on exertion may faint or develop anginal

pain. Increasing pulmonary hypertension causes right ventricular hypertrophy. Left parasternal heave, gallop rhythm, a systolic ejection click and pulmonary element of the second heart sound is accentuated. Central cyanosis may develop at a later stage. The dyspnea gradually increases and results in death from right heart failure. If diagnosis is made early and patient is given long term anti-coagulant therapy a marked reduction in pulmonary artery pressure may occur with considerable improvement.

**Diagnostic aids** - The diagnosis is usually made on clinical evidence particularly in the early stages of the disease, because ancillary aids such as; direct radiography which usually gives negative findings until consolidation of the lung or a pleural effusion had developed a few days later is not very helpful. Electrocardiography in general reveals no abnormality unless at least one half of a lung is out of action. Serum albumin tagged with radioactive isotopes can be injected intravenously and the lung fields scanned. This method unfortunately is unreliable and non specific. Arteriography is useful but a complicated test and should not be done unless embolectomy is contemplated.

Since the first embolic incident is often not fatal. Proper diagnosis in time can be life saving. Whenever an embolism is discovered there will be deep venous thrombosis present some where in the body. The possibility of a second embolus which may be fatal in most cases should be kept in mind. Women who had one embolism will have a second, in nearly one third of the cases if left untreated, and one fifth of these will die as a result. However, if treatment is



started promptly and efficiently with proper anticoagulants. It can help to prevent the recurrence in majority of cases.

### **Diagnostic tests:**

#### **Reference chart of diagnostic tests panels available:**

For a more detailed description of tests, please see page 22. Please refer to page 4 for instructions on the collection, processing and storage of samples.

#### **Test or panel sample reference frequency comment range of testing:**

Activated Partial 1 mL frozen plasma 22-35 sec Daily Thromboplastin Time (APTT) Anti-beta 2 1 mL frozen serum < 10 units T, F Part of antiphospholipid glycoprotein I panel. Anticardiolipin IgA 1 mL frozen serum < 12 APL T, F Part of antiphospholipid panel. Anti-cardiolipin IgG 1 mL frozen serum < 12 GPL T, F Part of antiphospholipid panel. Anticardiolipin IgM 1 mL frozen serum < 15 MPL T, F Part of antiphospholipid panel. Anti phospholipid 1 mL frozen serum see individual tests Includes anticardiolipin Panel IgG, IgM & IgA plus or anti beta 2 glycoprotein I. APTT (1:1 mix) 1 mL frozen plasma call (206) 598-6066 daily Activated Protein 1 mL frozen plasma negative M, Th Modified Factor V method. C Resistance (APCR) Test plasma not affected by oral anticoagulant therapy, heparin or lupus anticoagulant. Part of venous thrombosis panel. Anticardiolipin 0.5 mL serum Test performed in IgG/IgM Immunology Di- vision, call (206) 598-6066. Antithrombin 1 mL frozen plasma 75 - 125 % M. The Chromogenic method. Part of Activity 1-29 day's 41 - 125% venous thrombosis panel. 1 month 48 -

125% Patient should be off heparin for at least 3 days prior to testing. Arterial Thrombosis 3 mL frozen plasma see individuals tests Weekly Panel includes PAI-1, TPA Panel 0.5 mL frozen serum antigen, lupus inhibitor, and C-reactive protein. Collect blood between 0700 and 1000. The patient should not have an ongoing thrombosis and 2 months should have elapsed since the thrombotic event. C - reactive protein 0.5 mL frozen serum Test performed in (high sensitivity) Immunology Division, call (206) - 598-6066.

**Treatment:** When a massive embolism is suspected, resuscitation by administration of intratracheal tube) administration of oxygen and external cardiac massage where necessary should be carried out immediately. Morphine, atropine, Antispasmodics and digitalis should be at hand and given intravenously when needed. The patient should is moved to intensive care unit where the pulse rate, blood pressure and E C G. of the patient are regularly monitored. Intravenous hep-arin is drug of choice and must be started at once. This relieves the bronchospasm which probably occurs due to the release of serotonin from the platelets. Morphine injection should be given to relieve severe pain. If systolic blood pressure remains under 88 mm Hg. It is sign of bad prognosis. The patient with pulmonary embolism should be kept in bed until anti coagulant has been given for at least a week and desired increase in the prothrombin time has been achieved. The anticoagulants are continued after she becomes ambulant for a further period of three or four weeks. Blood gases and electrolytes should be checked and any imbalance discovered should be corrected.

When the embolus is small and non fatal, oxygen and a potent analgesic for relief of pain should be given. When pyrexia develops, as it often does, then indiscriminate use of antibiotics is not indicated: as the pyrexia will settle on its own accord, when the extravasated blood is absorbed. If a pleural effusion has developed, it will resolve spontaneously in the course of a few weeks. Once the acute phase is under control, and pain permits active physiotherapy, ambulation should be started. These measures should be started without further delay and continued till the patient is completely recovered.

#### **Deep venous thrombosis:**

Some prefer to change heparin with one of the oral anticoagulants after 24 to 48 hours especially if treatment is to be continued for several weeks.

#### **Embolectomy:**

When the patient shows no response to resuscitative measures death occurs within 2 hours in two third of the fatal cases, and leaves no time for any form of surgery to be performed. The results of surgery even in the specialized centre are not good. Even successful embolectomy is accompanied with a recurrence of embolism in great majority of cases. The merit of this operation therefore must be weighed against its benefits and success rate. However where facilities and expertise for such measures are present/patient should be given the benefit of this heroic therapy. Inferior Vena Cava may be tied just beyond its origin. This is performed by an extraperitoneal approach to the vessels through a right paramedian muscle-

splitting incision. Some prefer partial occlusion of the inferior vena cava and ovarian veins with serrated teflon clips in order to lessen the risk of severe oedema. Anti-coagulant therapy is necessary even when ligation is performed. Indications for surgery are, repeated emboli occurring in a woman for whom anti-coagulant therapy is contra indicated i.e. infective hepatitis, peptic ulcer or hamate. Mesi in the past.

#### **Thrombolytic therapy:**

This form of treatment is as yet in the experimental stage. Powerful fibrinolytic enzyme can cause dissolution of recently formed thrombo plasmin or activators of plasminogen. Streptokinase and urokinase may be used for this purpose. Specially trained physician should only undertake the type of therapy.

#### **Amniotic fluid embolism:**

It is very difficult to assess the exact incidence of this complication, since the diagnosis of this complication is often made by postmortem examination of the lungs or right ventricular blood. It is also possible that some patients recover from minor episodes, and are never diagnosed.

#### **Commonly used drugs for thromboembolic disease: and their mechanism of action: antiplatelet drugs:**

Example: Aspirin, Prevents platelet aggregation /adhesion, Clinical use prevents arterial thrombus: Myocardial infraction (MI), stroke, heart valve replacement and shunts and other anti-platelet drugs are dipyridamole, sulfinpyrazone and Ticlopidine.

**Mechanism of action:**

Aspirin inhibits cyclooxygenase (COX) COX is a key enzyme involved in the synthesis of thromboxanes 2 (prostaglandins) and inhibits platelet aggregation.

**Prophylactic use of aspirin:**

Low dose daily. Prevents ischemic attack (minestrone) and MI 335 mg/day reduced the risk of heart attack in patients over 50. More than 1000 mg/day NO EFFECT: Contraindication - DO NOT give to patients with glucose 6-PO4 dehydrogenase deficiency.

**Fibrinolysis:**

Enhance degradation of clots, Activation of endogenous protease, Plasminogen (inactive form) is converted to Plasmin (active form), Plasmin breaks down fibrin clots. Exogenously administered drugs; Streptokinase bacterial product: Continuous use immune reaction, Urokinase human tissue derived no immune response and tissue plasminogen activator (tPA) genetically cloned: no immune reaction and EXPENSIVE.

**Drug preparations: To reduce clotting:**

Heparin (generic, Liquaemin sodium), parenteral - 1000 - 40,000 U/ml, Warfarin (generic, Coumadin), oral: 2 - 20 mg tablets and Dipyridamole (Persantine) Oral: 25, 50, 75 mg tablets.

**Drug preparations: to lyse clots:**

Alteplase recombinant (TPA, Activase)

20, 50 mg Lyophilized powder reconstitute for IV, streptokinase (Kabikinase, Streptase). Parenteral: 250000 - 1.5 million units per vial.

Lyophilized powder. Reconstitute for IV Urokinase (Abbokinase). Parenteral: 250000 units per vial. Powder to reconstitute to 5000 u/ml for injection.

**Drug preparations: clotting deficiencies:**

Vitamin K (Phytonadione (K1), Mephyton Oral: 5 mg tablets, Plasma fractions for hemophilia Antihemophilic factor (VIII, AHF) Parenteral. Factor IX complex (konyne HT, Proplex T) parenteral: in vials.

**Drug Preparations: to stop bleeding:**

Systemic use: aminocaproic acid (Amicar); Tranexamic acid (Cyklokapron), Vitamin K. Local adsorbable drugs, Gelatin sponge (Gelfoam), Gelatin film, Oxidized cellulose (Oxycel) and Microfibrillar collagen (Avitene) Thrombin.

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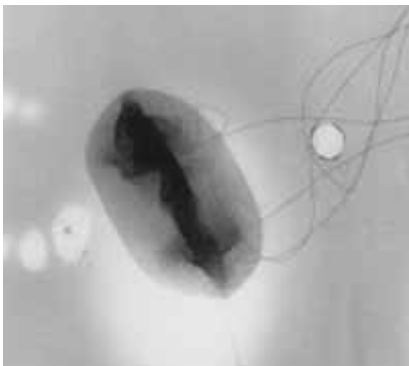
## Chapter No: 11

# INFECTIONS IN PREGNANCY

### Introduction:

All infections occurring in pregnancy can not be discussed in this chapter. Specific bacterial infections will be discussed in the chapters on different organs or tissues affected but the viral and worm infestations will be discussed separately in the preceding chapters. General Principles of bacterial infections are discussed here in this chapter with brief account of viral and worms affecting human beings. Bacteria, viruses and other infectious organisms “germs” live everywhere. You can find them in the air, on food, plants and animals, in the soil, in the water, and on just about every other surface “including your own body. These microbes range in size from microscopic single-celled organisms to parasitic worms that can grow to several feet in length.

Most of these organisms won't harm you. Your immune system protects you against a multitude of infectious agents. However, some bacteria and viruses are formidable adversaries because they're constantly mutating to breach your immune system's defenses.



**Fig11.1: Shows bacteria under the microscope.**

*E. coli* O157:H7 is a bacterium responsible for food borne infections often linked to eating undercooked ground beef or improperly washed vegetables.

### Bacteria:

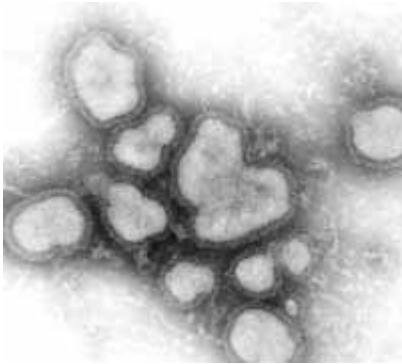
Bacteria are one-celled organisms visible only with a microscope. They're so small that if you lined up a thousand of them end to end, they could fit across the end of a pencil eraser. They're shaped like short rods, spheres or spirals. Bacteria are self sufficient they don't need a host to reproduce and they multiply by subdivision.

Among the earliest forms of life on earth, bacteria have evolved to thrive in a variety of environments. Some can withstand searing heat or frigid cold, and others can survive radiation levels that would be lethal to humans. Many bacteria, however, prefer the mild environment of a healthy body.

Not all bacteria are harmful. In fact, less than 1 percent cause disease, and some bacteria that live in your body are actually good for you. For instance, *Lactobacillus acidophilus* “a harmless bacterium that resides in your intestines” helps you digest food, destroys some disease causing organisms and provides nutrients to your body.

But when infectious bacteria enter your body, they can cause illness. They rapidly reproduce, and many produce toxins “powerful chemicals that

damage specific cells in the tissue they've invaded. That's what makes you ill. The organism that causes gonorrhea (gonococcus) is an example of a bacterial invader. Others include some strains of the bacterium *Escherichia coli* — better known as *E. coli* — which cause severe gastrointestinal illness and are most often contracted via contaminated food. If you've ever had strep throat, bacteria caused it.



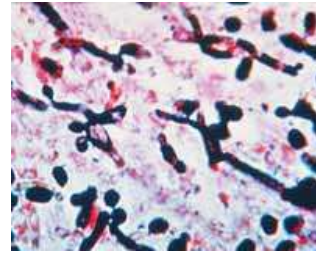
**Fig11.2:-Shows virus infected structure under microscope.**

The influenza virus takes over healthy cells, spreads through your body and causes illness. Signs and symptoms include fever, chills, muscle aches and fatigue.

**Viruses:** In its simplest form, a virus is a capsule that contains genetic material — DNA or RNA. Viruses are even tinier than bacteria. To put their size into perspective, consider that, according to the American Society for Microbiology, if you were to enlarge an average virus to the size of a baseball, the average bacterium would be about the size of the pitcher's mound. Just one of your body's millions of cells would be the size of the entire ballpark.

The main mission of a virus is to reproduce. However, unlike bacteria,

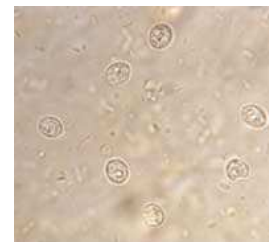
viruses aren't self-sufficient — they need a suitable host to reproduce. When a virus invades your body, it enters some of your cells and takes over, instructing these host cells to make what it needs for reproduction. Host cells are eventually destroyed during this process. Polio, AIDS and the common cold are all viral illnesses.



**Fig11.3: Shows hyphae and spores of candida under microscope.**

Infection with candida fungus can lead to problems such as diaper rash, vaginal yeast infections and oral thrush.

**Fungi:** Molds, yeasts and mushrooms are types of fungi. For the most part, these single-celled organisms are slightly larger than bacteria, although some mushrooms are multicelled and plainly visible to the eye. Mushrooms can't infect you, but certain yeasts and molds can. Fungi live in the air, water, soil and on plants.



**11.4: Shows protozoa under the microscope.**

They can live in your body, usually without causing illness. Some fungi have

beneficial uses. For example, penicillin — an antibiotic that kills harmful bacteria in your body — is derived from fungi. Fungi are also essential in making certain foods, such as bread, cheese and yogurt. Other fungi aren't as beneficial and can cause illness. One example is candida — a yeast that can cause infection. Candida can cause thrush — an infection of the mouth and throat — in infants and in people taking antibiotics or who have an impaired immune system. It's also responsible for most types of infection-related diaper rash.

Cryptosporidium is a protozoan that can survive outside the body for long periods of time.

### **Protozoa:**

Protozoa are single-celled organisms that behave like tiny animals — hunting and gathering other microbes for food. Protozoa can live within your body as a parasite.

Many protozoa call your intestinal tract home and are harmless. Others cause disease, such as the 1993 *Cryptosporidium parvum* invasion of the Milwaukee water supply, sickening more than 400,000 people. Often, these organisms spend part of their life cycle outside of humans or other hosts, living in food, soil, water or insects. Most protozoa are microscopic, but there are some exceptions. One type of ocean-dwelling protozoa (foraminifer) can grow to more than 2 inches in diameter.

Some protozoa invade your body through the food you eat or the water you drink. Others can be transmitted through sexual contact.

Still others are vector-borne, meaning they rely on another organism to transmit them from person to person.

Malaria is an example of a disease caused by a vector-borne protozoan parasite. Mosquitoes are the vector transmitting the deadly parasite plasmodium, which causes the disease.



**Fig11.5: Shows worm's gross appearance.**

Infection by one type of roundworm, known as a hookworm, can cause problems in your small intestine or lungs. The average hookworm is about half an inch long.

### **Helminths:**

Helminths are among the larger parasites. The word "helminth" comes from the Greek for "worm." If this parasite — or its eggs — enters your body, it takes up residence in your intestinal tract, lungs, liver, skin or brain, where it lives off the nutrients in your body. The most common helminths are tapeworms and roundworms.

The largest of the roundworms can be more than 12 inches long. And the largest of the tapeworms can grow to be 25 feet or longer. Tapeworms are made up of hundreds of segments, each of which

is capable of breaking off and developing into a new tapeworm.

### **Understanding infection vs. disease:**

There's a distinct difference between infection and disease. Infection, often the first step, occurs when bacteria, viruses or other microbes enter your body and begin to multiply. Disease occurs when the cells in your body are damaged " as a result of the infection " and signs and symptoms of an illness appear.

In response to infection, your immune system springs into action. An army of white blood cells, antibodies and other mechanisms goes to work to rid your body of whatever is causing the infection. For instance, in fighting off the common cold, your body might react with fever, coughing and sneezing.

### **Warding off germs and infection**

What's the best way to stay disease-free? Prevent infections from happening in the first place. You can prevent infection through simple tactics such as regular hand washing, vaccinations and appropriate medications.

#### **Hand washing:**

Often overlooked, hand washing is one of the easiest and most effective ways to protect yourself from germs and most infections. Wash your hands thoroughly before preparing or eating food, after coughing or sneezing, after changing a diaper and after using the toilet. When soap and water aren't readily available, alcohol-based hand sanitizing gels can offer protection.

**Vaccines:** Vaccination is your best line of defense for certain diseases. As researchers understand more about what causes disease, the list of vaccine-preventable diseases continues to grow. Many vaccines are given in childhood, but adults still need to be routinely vaccinated to prevent some illnesses, such as tetanus and influenza.

**Medicines:** Some medicines can help you from becoming susceptible to germs. For example, taking an anti-parasitic medication might protect you from contracting malaria if you travel to or live in an area where your risk is high. Or when you are at high risk of exposure to certain organisms " such as those that cause bacterial meningitis " your doctor may prescribe antibiotics to lower your risk of infection. Using over-the-counter antibiotic creams can decrease the chance of infection of minor cuts and scrapes. But long term, indiscriminate use of antibiotics isn't recommended in most cases. It won't prevent bacterial infections and instead may result in a more resistant, harder to treat strain of bacteria when infections do occur.

#### **When to seek medical care:**

Although some infectious diseases, such as the common cold, might not require a visit to the doctor, others might. Seek medical care if you suspect that you have an infection and you have experienced any of the following:

- An animal or human bite
- Difficulty breathing
- A cough lasting longer than a week
- A fever of 100.4 F (38.0 C) or more
- Periods of rapid heartbeat



- A rash, especially if it's accompanied by a fever
- Swelling
- Blurred vision or other difficulty seeing
- Persistent vomiting
- An unusual or severe headache

Your doctor can perform diagnostic tests to find out if you're infected, the seriousness of the infection, and how best to treat that infection.

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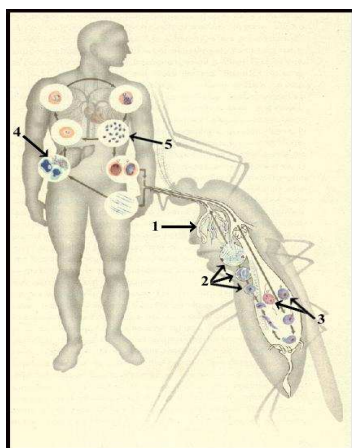
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## Chapter No: 12

## PARASITIC INFECTIONS IN PREGNANCY

### General considerations:

Parasitic diseases are a major health problem. Poverty, mal nutrition and inadequate medical facilities, make their control difficult, therefore, they constantly remain a major cause of both maternal and fetal morbidity and mortality in Pakistan and other countries of this region.

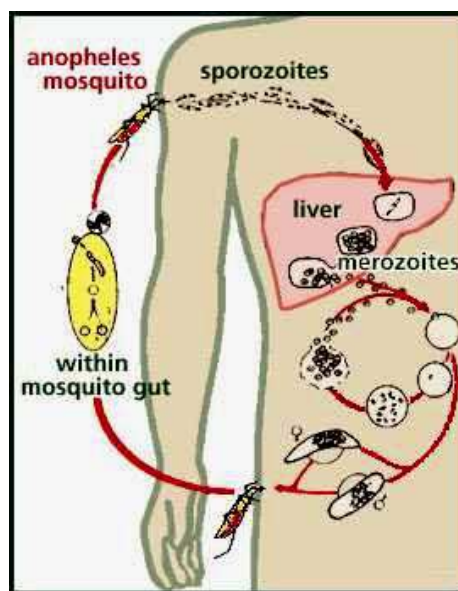


**Fig12.1: Shows malarial cycle from mosquito bit to schizont.**

A number of Parasitic diseases can interfere with pregnancy either directly or indirectly. The maternal health can be affected adversely, or the parasite can predispose her to complications such as abortion, premature labour and still-birth. The pregnancy wastage can also occur because of damage to the maternal reproductive system. Features common to a number of parasitic infections are diarrhoea, fever, and anaemia, loss of weight, hepatomegaly, and splenomegaly. Many individuals tolerate parasitic infection well and have no signs or complaints.

As a rule parasitic infections during pregnancy should only be treated, if they pose serious threat to the welfare of the mother and her child. Drugs available for treatment of most helminthic infections are toxic and can damage the fetus, therefore their treatment should be postponed until after delivery.

In this chapter only those parasitic infections will be discussed which are relatively common in this country and the Physician can face the problem of diagnosing and treating them in his practice. Diseases more rarely encountered in this part of the world will not be discussed.



**Fig12.2: -Shows merozoite cycle after mosquito bite.**

**MALARIA:** Malaria still remains one of the most widespread, communicable diseases of mankind. According to a 1978 report of the world health

organization, 1,612 million people live in 107 countries where malaria is endemic. More than 1.25 million people died of malaria in 1977. The disease is usually acquired by the bite of an infected female anopheles mosquito, but it can be transmitted by infected blood trans-fusion. Sporozoite released in the blood stream enters the liver cells (exoerythrocytic stage) and divide. The sporozoite matures into merozoite inside the liver cells. The liver cell ruptures and the merozoite are released they invade red blood cells (erythrocytic stage). The intra erythrocytic parasite divides again and the infected red blood cell ruptures. The cycle is repeated again by invasion of other red blood cells. This process takes 72 hours for *P. malariae* and 48 hours for the other species. Some merozoite develops into male and female gametocytes and initiates the sexual cycle of reproduction.

Gametocytes usually appear in the blood of the infected host in about two weeks after the onset of symptoms. If they are ingested by a female anopheles mosquito during the bite~ the male and female gametocytes unite in the stomach of the mosquito. The sporozoite takes 1 to 5 weeks to develop, depending on their species. Sporozoites become concentrated in the salivary glands of the mosquito and are injected into man during the bite.

When sporozoite of *P. vivax* or *P. ovale* which have persisted in the liver mature into merozoite and are released into the bloodstream> relapse of symptoms occurs. *P. falciparum* and *P. malariae* do not persist in the liver, but can remain dormant within the erythrocyte and the infection may reoccur after many months or years.

**Pathology** - The disease is caused by four different species of plasmodium. The plasmodium vivax, and plasmodium malariae, is transmitted to man by anopheles mosquitoes. It is occasionally seen in patients who have received a blood transfusion from an infected donor and in heroin addicts. Infrequently, it can be transmitted by mother to the fetus in utero. The pathological lesions which occur can be due to changes caused by the parasite i.e. the reaction which the host produces in response to the presence of parasite and the effect of the infection on the individual organs.

The pathophysiology of malaria is basically the result of local disturbances of the microcirculation, particularly in the brain, liver, lungs and kidneys.

A major factor in malaria pathogenesis is the disturbance this infection causes to tissue oxygenation. Local tissue anoxia occurs due to stasis and is aggravated by anemia produced by hemolysis. Sometimes anoxia is so severe that complete circulation is blocked. Disseminated intravascular coagulopathy can be initiated and tissues may be severely damaged. When the host is non immune, death from malaria is often seen in *P. falciparum* infection. Shock secondary to hypovolemia, adrenal insufficiency, renal failure, hepatic insufficiency, pulmonary edema, or cerebral ischemia is usually the cause of death. In *P. vivax* infection, death is occasionally caused by splenic rupture. Nephrotic syndrome can occur as a result of longstanding *P. malariae* infection, but this is not very common.

**Clinical features** - An infected mosquito bites a susceptible woman and infests her with plasmodia in the

sporozoite stage. The main characteristics of malaria are periodic fever, splenomegaly and pancytopenia. Incubation period is 10 to 40 days. Chemoprophylaxis can lengthen this period. Onset of fever is sudden; this starts with a shaking chill and is then followed by a marked rise in temperature. Spike of temperature lasts for several hours and is accompanied by profuse sweating. The temperature pattern can be irregular or continuously high during the first few days. The febrile paroxysms later on become periodic with intervals of 48 hours in *P. vivax* and *P. ovale*. This interval is 72 Hours in *P. malariae*. The fever spike in malaria coincides with schizont rupture and the release of merozoite, at the completion of the erythrocytic cycle. In *P. falciparum* malaria, parasite development is usually asynchronous and the fever may be continuous or several spikes may occur in a single day. Other common symptoms include headache, malaise, myalgia, anorexia and vomiting. Between febrile paroxysms, patients usually feel quite well.

**Effect of pregnancy on malaria** - Pregnancy aggravates acute attack and increases the frequency of "cerebral" malaria. Labor activates "latent" malaria and intensifies the effect of an existing attack. The patient may even collapse following delivery and die. Rupture of an enlarged malarious spleen can occur during labor. Patients with high degree of immunity show no increase in the incidence of abortion.

**Effect of malaria on pregnancy** - In first trimester, hyperpyrexia may cause abortion while later on it may result in intra-uterine death, premature labour, or neonatal death. Rapid red cell hemolysis

can produce folic acid deficiency and megaloblastic anaemia. Parasites along with macrophages can accumulate in the placenta and the intervillous spaces and block them. The growth of the foetus can be severely affected resulting in intrauterine growth retardation or death. Most frequent cause of stillbirth among infants of mothers with malaria is intrauterine asphyxia due to placental edema, necrosis and hemorrhage.

Albuminuria is commonly found in pregnancies complicated with malaria; Convulsions and coma may also occur and thus confuse this disease with eclampsia. Detection of numerous parasites in the blood with a normal or low blood pressure in cerebral malaria can help to differentiate this condition from eclampsia.

**Diagnosis** - Apart from history and clinical features, this can be done by examination of the red blood cells in a thick blood smear which will reveal parasites in over 90 per cent of the active cases.

After delivery" the placenta and cord blood should be examined for plasmodia in all patients. (Notwithstanding repeated claims of complete malarial eradication in the country, one finds positive blood films for malarial parasites in pyrexial pregnant women.

**Treatment** - The drug of choice in acute attack is Chloroquine phosphate. This is administered orally in a single dose of 1 g and then followed by 0.5 gm. daily for 3 days. In critically ill patients and in newborn infants, intramuscular route is preferred. Symptoms often subside in 24 hours and Parasitemia in 72 hours. Chloroquine may cause headache,

nausea, vomiting, purities and exfoliative dermatitis. When administered for prolonged periods, it may produce lenticular opacities and retinopathy. The former disappears when the drug is stopped.

An acute attack of malaria during pregnancy should be treated promptly. To patients with severe nausea and vomiting, chloroquine hydrochloride should be given parenterally until these symptoms subside. Severe anemia should be corrected by blood transfusion. There is no indication for therapeutic abortion in these cases. No data is available with regard to possible teratogenic effects of chloroquine. Pyrimethamine is another antimalarial. This is a folic acid antagonist and may cause abortion or fetal malformation if given during early pregnancy.

During pregnancy regular suppressive therapy should be continued in non immune patients. It should be started by the end of the first trimester to prevent febrile paroxysms. A paroxysm consists of a chill which lasts for 20 to 60 minutes and high fever which can last for 1 to 4 hours and profuse sweating. High fever can cause intrauterine death.

Chronic or latent malaria occurs as a result of repeated re infections in endemic areas. It is remarkably well tolerated by adult populations that have survived the disease since infancy and have acquired a high degree of immunity. Latent malaria may become active following surgery, during pregnancy, or after delivery.

To give reliable protection to the fetus, an increased dose of chloroquine phosphate i.e. 0.5 gm. every third day is

recommended during the month before term. Suppressing drugs should be given to exposed infants as soon after birth as possible. Most antimalarials are secreted in human milk. It has been suggested that a 50 per cent increase in the dosage of suppressive drug given to a nursing mother can protect the breast feed infant during the first months of life. Chemotherapy will usually pre-vent anaemia when given at the onset of the disease but will not cure it once it has developed. Folic Acid 5 milligram daily should be given by mouth to pre-vent megaloblastic anemia) but trans-fusion will be required for severe anemia near term.

Progressive hemolytic anemia can often be arrested by giving prednisone, 20 milligram daily by mouth.

**Congenital malaria:** The parasite can cross the placenta and cause "congenital" malaria. Its incidence varies from 0.03 to 1 per cent. The parasites have special affinity for the decidual blood vessels. Infection occurs when the placenta is damaged. This breaks the maternal fetal barrier. The placental barrier is often quite effective in immune patients.

**Symptoms:** These are fever, vomiting, convulsions" pallor, jaundice, and hepatosplenomegaly, which usually appears in the newborn 48 to 72 hours after birth. Death may result from acute pulmonary edema. Passive immunity is transmitted from mother to child, in countries where malaria is endemic.

### **Prophylaxis of congenital malaria**

In malarial areas all newborn infants should be protected by mosquito netting,

insect repellents and insecticide sprays. The antibodies to malaria are contained in the gammaglobulin fraction of the serum protein, which can cross the placenta readily. Newborns of indigenous population, which have acquired immunity, rarely develop congenital malaria. The passive immunity transmitted from the mother lasts in the infant for about a month but the antibody is highly specific for the variety of parasite endemic in the area.

### **Treatment:**

The newborn should receive chloroquine hydrochloride intramuscularly with a starting dose of 5.0 mg per Kg body weight and then followed by 2.5 mg per Kg of body weight at 8 hour intervals. After control of the acute infection the drug should be continued orally in single doses of 60 mg daily for 4 days.



**Fig12.3: -Shows structure of ameba.**

### **AMEBIASIS:**

**Incidence** - The incidence of amebiasis bears a direct relationship to the level of sanitation in a community. Human beings acquire infection by ingestion of amebic cysts which are present in water and food. In developing countries such

as Pakistan the incidence of this disease is much greater than in the developed countries where the standard of sanitation is relatively better.

**Clinical features:** Most women who have amebiasis have few or no symptoms. The symptoms include bloody diarrhoea, lower abdominal cramps and anorexia. There is often history of weight loss or no weight gain. The infection may be acute or chronic.

**Acute infection:** There is prostration. Dehydration, intestinal hemorrhage, and anaemia. If perforation of the bowel occurs diffuse peritonitis will result with its serious consequences for the mother as well as the baby.

**Chronic infection:** This is far more common than it is realized and many pregnant patients with low or no weight gain may be suffering from this complication.

**Genital infection:** The vulva, vagina and uterus can get involved when there is contamination with ameba laden anal discharge or from a rectovaginal fistula. The genital lesions resemble carcinomatous ulcers. Amebic skin ulcer may be formed and is usually seen around the anus and vagina.

Amebiasis of the genital tract can be an important cause of infertility. Peritonitis and result in pelvic adhesions and tubal occlusion. If blood vessels are invaded by the parasite, the liver, lungs and brain may get involved with abscess formation.

When liver abscess is present the patient presents with fever, weight loss, upper abdominal pain and an enlarged tender

liver. The abscess may rupture into the peritoneal, pleural, or pericardial cavity, with serious consequences.

### **Effect on pregnancy:**

During pregnancy the infection is generally increased. Corticosteroids and progesterone have been reported to aggravate the severity of amebic infection.

### **Management**

#### **Diagnosis:**

This can be confirmed by finding cysts or trophozoites of *E. histolytica* in stool or in the exudate from the abscess. Trophozoites may be detected from the biopsy of the rectal mucosa or vagina.

It is important to isolate *E. histolytica* before subjecting the pregnant patient to a therapeutic agent which may have teratogenic effect.

There is no justification of delaying treatment after first trimester has been completed. In acute and severe form of the disease the treatment should be instituted without waiting for completion of first trimester.

Unnecessary delay may place the life of the mother in jeopardy. Treatment during pregnancy will help to prevent a possible infection of the newborn from the mother during the neonatal period.

#### **Amebic liver abscess:**

This requires combined medical and surgical treatment. Large abscesses can be drained by needle aspiration after chemotherapy has been started.

**Local amebic lesions:** genital lesions respond to local applications of Vioform cream.

**Drugs:** The specific therapeutic drug and its dosage recommended is as follows; Patients who have mild symptoms can be treated by Diodoquin (Di-Iodo-hydroxyquinoline). This drug does not have significant toxicity and cure rate is 75 per cent with one course. Second course can be given if results are poor. So far there is no reported teratogenic effect on fetus.

For moderate to severe cases emetine oride is given subcutaneously in a dose of 1 mg/Kgm body weight daily for three to five days or until clinical improvement. It is contra indicated in pregnancy.



**Fig12.5: -Shows tablets of metronidazole.**

**Metronidazole** - This is the drug of choice for the treatment of intestinal amebiasis. For invasive intestinal disease where the subject is susceptible 5 tablets (2000 mgs) once daily for three days will suffice. Where the subject is less susceptible 2 tablets Le. (400 mgs) thrice daily for five to ten days is usually required. The later regimen is more tolerable and acceptable because of less severe side effects. The dosage of metronidazole in hepatic disease including amebic liver abscess and hepatitis and other forms of extra intestinal amebiasis

is 2 tablets i.e. (400 mgs) thrice daily for 5 days. When there is history of passing symptomless cysts only; the dosage is 2 to 4 tablets (400 - 800 mgs) thrice daily for five days.

Metronidazole crosses the placental barrier. Although it has been given to pregnant patients without apparent complication and there is no evidence to suggest that metronidazole is embryopathic, it is a sound medical principle to avoid prescribing any drug during the first three months of pregnancy unless considered absolutely necessary.

Adverse side effects of Metronidazole are minor and infrequent. These include metallic taste, furry tongue, dry mouth, diarrhoea, anorexia, nausea, vomiting, epigastric distress and constipation. Flushing and headache can also occur especially when alcohol beverages are ingested while the patient is receiving this drug. Other infrequent side effects are dizziness, transient ataxia, confusion, insomnia, rash, vaginal dryness and dysuria. The urine may be darkened but this is of no clinical significance. It is probably due to metabolites of metronidazole. The drug may produce leukopenia in some cases. Various trade names of metronidazole used in different countries include Novimidazole, Flagyl and Neotric.

### TRICHURIASIS:

*Trichuris trichiura* is a common parasite of the human intestine and is common in warm and moist regions. Man is infected by ingesting mature embryonated ova that have developed in soil contaminated by faeces. The adult nematode lives in the Caecum, but in heavily infested

subjects colon and rectum are also involved.

**Clinical features:** Light infections are asymptomatic. Patients with very heavy infections may have severe anemia, bloody diarrhea, diffuse lower abdominal pain, tenderness, and weight loss. Rectal prolapse with visible worms may be seen. The exact role of *Trichuris* in the production of anemia is difficult to determine, since multiple infections with hookworm, ascaris, and other helminths are often found.

**Relation to pregnancy:** Infection may cause a severe iron deficiency anemia.

**Diagnosis:** Ova can be detected readily by microscopic examination of a faecal smear.

**Treatment:** Dithiazanine Iodide, 200 mg. orally three times daily for 2 weeks. This drug causes severe nausea and vomiting. The only valid indication for the specific treatment of this infection during pregnancy is a heavy worm load causing intractable diarrhea and severe anemia.



**Fig12.6: Shows Trichuris Trichiura**

### OXYURIASIS:

*Oxyuris vermicularis* is a common parasite of man in the temperate regions. Incidence is highest among urban populations. Transmission is by close personal contact i.e. in families, schools



and institutions. The adult worms live in the rectum and anus.

### **Clinical features:**

Pruritus ani and vulvi are the most frequent symptoms. In females, the worms enter the vagina to cause vaginitis, and may migrate through the genital tract to the peritoneal cavity. Invasion of the fallopian tubes may result in pyosalpinx. Dense adhesions and granulomas in reaction to the adult worms and ova may form in the pelvis.

**Relation to pregnancy:** The infection can rarely cause tubal obstruction and therefore infertility. Pregnancy is known to intensify anal pruritus and may aggravate this symptom when caused by these parasites.

**Diagnosis:** Adult worms may be seen on the surface of formed stool. The characteristic ova are easily demonstrated when transparent adhesive cellophane tape is examined microscopically after application to the anal skin.

**Treatment:** The drug of choice is piperazine citrate in tablets or syrup form. The adult dose is 1.0 gm. twice daily for 7 days. The treatment can be safely carried out during pregnancy. A high level of personal hygiene should be maintained. All infected members of the family should be treated simultaneously.



**Fig12.7: Shows Tapeworm.**



**Fig12.8: Shows hookworm.**

### **HOOKWORM:**

Hookworm infection is very common in the tropical countries. It is an important cause of iron deficiency anaemia. The adult worms (*Necator americanus* and *Ankylostoma duodenale*) attach to the mucosa of the small intestine and cause a steady loss of blood the incidence of infection is related to the quality of sewage disposal. Infecting larvae develop in soil contaminated by faeces. Warm and moist climate facilitates their development. Human infection is contracted by walk-ing barefooted. Both species occur in Asia.

**Clinical manifestations** - Skin is penetrated by hookworm larvae and causes "ground itch", on the feet, legs and buttocks. Adult worms in the intestine cause no symptoms. The degree of iron deficiency anemia depends on the worm load, the dietary intake of iron, the state of the body's iron stores and pregnancy. In the severe cases, chronic aere-mia, tachycardia, facial and ankle edema and hypoproteinemia are found.

**Relation to pregnancy** - Hookworm infection can cause abortion, and remains an important factor in producing high maternal and infant mortality rates.

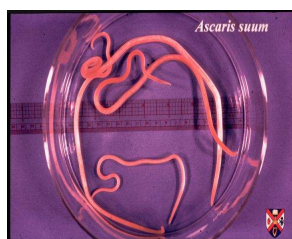
Cardiac failure resulting from severe anemia induced by hookworms is probably the commonest cause of maternal death during labor.

**Diagnosis:** This can be reliably made by stool examination. The ova of both species have the same appearance. Stools are usually positive for occult blood.

**Treatment:**

The specific chemotherapeutic agent of choice is tetrachloroethylene, administered orally in gelatin capsules. The dose is 0.12 ml. per kg of body weight but the total should not exceed 5.0 ml. Headache and dizziness may follow therapy. A single treatment cures 80 per cent of infections with *N. Americanus* and 25 per cent with *A. Duodenale*. During Pregnancy, if anemia is absent the infection should be disregarded. In severely anemic patients, the hemoglobin level should be raised promptly by the administration of iron and vitamins. There is no evidence that tetrachloroethylene produces fetal malformations.

**ASCARIASIS:**



**Fig 12.9: Shows ascaris worm**

*Ascaris lumbricoides* or round worm infection results from the ingestion of mature embryonated ova present in the soil or on raw vegetables.

**Clinical manifestations:** The Larvae migrate from the small intestine to the blood stream and becomes adult. The mechanical effect of the adult worms in the small intestine, and the nutritional defects induced by a heavy worm load are manifested in the form of abdominal pain and anaemia.

**Pulmonary symptoms:**

The migration of larvae through lungs can produce pneumonitis with fever, cough, chest pain, and sometimes signs of pulmonary congestion.

**Hepatomegaly:**

This may result from the presence of larvae in the hepatic parenchyma.

**Intestinal obstruction:**

The mass movements of the adult worms may cause partial or complete small bowel obstruction, which is generally marked by vomiting and abdominal pain. This can lead to malabsorption which can result in growth retardation and malnutrition in the young infants. Adult worms may invade the vagina and uterus and cause menorrhagia. They have also been occasionally found in tubo-ovarian abscesses.

**Diagnosis:**

Diagnosis is made by finding the characteristic ova in the stool specimens. Adult worms may be found in the vomitus or in the feces.

**Treatment:**

The drug of choice remains piperazine citrate which is most effective. The total

dose should not exceed 3.0 gm. in 48 hours. It is usually given on two successive days. Treatment is repeated if ova are still present on reexamination, 6 weeks after the first therapy. There are no contraindications to treatment during pregnancy as there is no evidence that piperazine has teratogenic effects.



**Fig12.10: Shows echinococcus**

#### **Echinococcus (Hydatid disease):**

The parasite *Echinococcus granulosis* has two species. These species differ in their geographic distribution and in their definitive mammalian hosts. *E. Granulosis* is found in areas where sheep are raised such as Asia. The disease is transmitted by close contact between men, sheep, and dogs. *E. multilocularis* is limited in distribution to Russia, central Europe and Northern Canada. The sources of spread in these areas are Wolves, and Foxes.

#### **Mode of infection:**

The larvae of this parasite penetrate the intestinal wall and are carried by the portal blood stream to the liver where majority of them are destroyed. Those who survive give rise to hepatic cysts. This variety comprises 75 per cent of the primary cases. Some pass through the hepatic capillaries to the lungs which are the second most common site for cyst.

A few larvae pass through the pulmonary filter and produce primary cysts in the brain, bone, kidney, and spleen. The cysts can be clinically evident even 10 to 20 years after the infection.

#### **Clinical features:**

The pressure of the slowly enlarging cysts on the surrounding structures can produce symptoms." Anaphylactic" reactions can occur when there is escape of cyst fluid after spontaneous or traumatic rupture of the cyst. Bacterial infection of the cyst can produce abscess, even the "secondary" cysts can be formed. Hepatic cyst which is the commonest type, causes marked enlargement of the liver. When the cyst ruptures into the bile duct it produces obstructive jaundice. In the peritoneal cavity it may produce peritonitis and secondary cysts.

#### **Pulmonary cysts:**

Nearly 10 per cent of the pulmonary cysts rupture into the bronchus but on rare occasions it may rupture into the pleura and cause pleural effusion, or hydatid pneumothorax.

**Pelvic cysts:** The cysts of the Pelvis are almost always multiple and secondary. There is usually a history of a previous operation or an abdominal complication indicative of primary cyst rupture. The cysts are commonly found in the pouch of Douglas or between the leaves of the broad ligaments, and in the uterovesical pouch. These cysts may involve the ovaries, Fallopian tubes and even the uterus. They may become very large and extend to the anterior abdominal wall, causing progressive abdominal enlargement. They may cause

dysmenorrhea, dysuria, and even obstruction of urine. The hydatid disease of the pelvic organs can be a cause of infertility.

### **Differential diagnosis:**

In gynecological patient the cystic mass must be differentiated from primary ovarian cyst, uterine fibromyoma and chronic inflammatory disease of the adnexa. The pelvic cysts can rupture during labor and result in expulsion of cyst fluid. This produces daughter cysts into the peritoneal cavity or into the vagina. They may even obstruct the course of labour.

**Diagnosis:** An echinococcus cyst should be suspected in the differential diagnosis of hepatic, abdominal, and pelvic masses associated with eosinophilia.

When ring like calcified shadows are seen in the liver or in the lung fields on x-rays, this disease should be suspected. The specific diagnosis may be made by the demonstration of positive skin test sensitivity to echinococcus antigen. This test is called the Casein reaction or test. Similarly complement fixation test can be done. Microscopic examination of aspiration of a liver cyst shows hydatid scolices and hook lets.

### **Treatment:**

### **Surgery:**

An entire cyst can be excised if it can be mobilized. However, if the cyst is inoperable, it should be drained with extreme care to prevent spillage, and the cavity should be filled with dilute formalin to kill the germinal layer.

If a cyst interferes with pregnancy, no attempt should be made to push it up out of the pelvis since it is usually fixed and such manipulation might lead to rupture. The treatment of choice is Cesarean Section. Puncture of the cyst and its evacuation and formularization through the vagina is not recommended.

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## Chapter No: 13

# VIRAL DISEASES IN PREGNANCY

Viral infections during pregnancy are of great concern to the obstetrician and the neonatologist because some viruses are capable of crossing the placenta and causing serious damage to the fetus.

Acute infections with small pox, influenza, measles and varicella virus, may produce profound systemic toxemia. This may affect both pulmonary and/or cardiac function and lead to reduced arterial O<sub>2</sub> saturation, which can result in fetal injury without actually infecting the fetus. The gestational age at the time of fetal infection is a critical factor in producing malformations. In general, the earlier the interference with normal patterns of growth occurs, the more numerous and more severe are the resultant defects.

The characteristic abnormality produced in the embryonic host occurs as a result of pathologic effects of the virus and is dependent on the quantity and virulence of the virus. It is also dependent on the genetic type and conditioning of the host.

There are a number of routes by which the virus can pass from the mother to her fetus. This can be better understood by considering the anatomical relationships that exist between the mother and the conceptus. Infectious agents can ascend from the perineum or introitus through the vagina or the cervix and enter into the uterine cavity. These agents either cross by pyknocytosis or by penetrating the uterine wall and result in infection and destruction of the fetal membranes. Once in the amniotic cavity, these microorganisms might be ingested or

inhaled by the embryo or the fetus or penetrate his skin. A mother's placental route is the most likely way by which microorganisms pass from the mother to the fetus.



**Fig13.1: Shows rubella virus rash on the body**

### **Rubella infection:**

The infection with rubella virus is generally mild. The patient is often an adult female.

**Clinical features:** This includes arthritis, especially of the distal joints, which are usually symmetrical. Other features are malaise, lymphadenopathy and the spotty skin. Rash. Coryza, conjunctivitis. encephalitis and thrombocytopenia may also occur. Its incubation period ranges between 11 to 14 days. The women who are infected shed virus from the cervix during the first week of the disease. In nearly 50 per cent of the infected cases there is no rash.

**Mode of infection** - The fetus can be infected by direct invasion of the virus. The infection occurs at the time of maternal viremia. The virus persists and multiplies in the fetal tissues. In areas

where epidemics of Rubella occur (unlike measles), a large number of females may escape infection and hence remain susceptible to future infection. Many may reach to the child bearing age. It has been reported that about 10 per cent of women in this age group are susceptible to rubella infection during pregnancy. The need for screening & these women with Hal (hemagglutination inhibition) test for rubella viruses during antenatal period is therefore highly desirable.

**Effects on the fetus** - The effects on the fetus are maximal during the first 8 weeks. The most frequent combination of fetal anomalies seen at birth include cardiac lesions, cataract and low birth weight. Classically, one or more organs or systems are involved. Cardiovascular, ophthalmological, hematological, neurological, auditory and osteological systems can all be involved.

Deafness, psychomotor retardation and microcephaly have been reported following infections between 14 and 21 weeks of pregnancy. The auditory changes may not be detected until school age. The live rubella viruses have been isolated from the throats, urine and stools of affected infants for up to one year of age. Live virus has been obtained from an eye lens of a baby at 3 years of age.

The mechanism by which the viruses persist is not clear. Immune tolerance does not seem to be involved, since specific antibody production by the fetus has been demonstrated as early as 16th week of fetal life. The infected infants at birth have elevated Rubella IgM antibody titers, in addition to the presence of maternally derived IgM

antibody. Abnormalities in cellular immunity have been postulated as contributing to the problem of virus persistence, and recent observations has confirmed that infants with Rubella syndrome do have impaired cell mediated immunity. Another possible explanation related to the small size of babies with the rubella syndrome which has been shown to be due to a reduction in the number of cells in various organs and tissues, is consistent with the hypothesis that the widely distributed infected clones of cells have a reduced life span and therefore gradually drops out. Only when such clones have disappeared there is clearance of the virus from the tissues.

**Management** - This depends on whether the mother to be is immune or susceptible to rubella, and at what stage of pregnancy she contacted infection. When there is history of exposure to Rubella, then the student should inquire about the nature of the contact, whether intimate and prolonged or casual and brief. Rubella is not highly communicable except under conditions of close contact as exists in the family setting. If the exposure of a susceptible woman has been to a child in the home, the chance of infection is great, while if the contact was outside the home and transient, the likelihood of transmission is much reduced. Another serologic method that may be used to establish the current nature of the infection is the complement fixation test. CF antibodies appear later in the course of the infection i.e. 7 to 10 days after the onset of rash in the course of clinical disease. It is often possible to show a rise in CF titer when the serum has been obtained too late in the course of disease than to detect a significant increase in HAL titer level. Absence of CF antibody 3 to 4 weeks

after exposure favors but does not prove the interpretation that the HAI antibodies represent an infection that occurred sometime earlier. Unlike HAI antibodies the CF levels tend to drop off and disappear after a few days.



**Fig13.2: Shows hydrocephalic head of the baby**

**Cytomegalovirus infection:** This virus is a member of the herpes group, but is antigenically distinct from Herpes virus Homini (HVH), varicella zoster and EB virus. Like other herpes viruses, it may persist in a latent form following a primary infection, and produce large chromatin positive (viral particles) intranuclear inclusion bodies. The affected cells markedly increase in size. CMV is a DNA virus which takes 5 to 21 days to produce cytopathic changes in tissue culture.

#### **Route of infection:**

Children become frequently infected early in life, presumably by contact. Although exact mechanisms are unknown, the virus is shed for long periods (often several years) in saliva and urine and spread probably involves these sources. In adults CMV has also been recovered from cervical secretions, semen and mother's milk. Acquisition of infection is related to age and to socioeconomic factors.

**Clinical features:** Although acquired infections are usually not accompanied by clinical signs, a heterophil antibody negative, infectious mononucleosis like syndrome has been described in young adults and in recipients of transfusion of fresh blood (postperfusion syndrome). Like other herpes viruses, CMV has a strong tendency to become latent. Reactivation of such infections in immunosuppressed patients, particularly trans-plant recipients, constitutes a major problem. The rare individual with a primary infection who develops CMV mononucleosis presents with an acute onset of fever and non specific symptoms. The peripheral WBC count reveals a relative and absolute lymphocytosis, with many atypical lymphocytes. Liver function tests are frequently abnormal. The fever is apt to persist for several weeks, and in convalescence there is little lymphadenitis. Pharyngitis is unusual and the heterophil antibody test is negative.

**Diagnosis:** Specific laboratory diagnosis can be made by recovering the virus from saliva, cervical swab or liver biopsy specimen, but urine is the best source and may contain as many as million virus particles per ml. The virus grows slowly and cultures may not become positive for a month or more. The presence of owl eyed cells containing intranuclear inclusions in fresh urine or cervical smear helps in establishing a presumptive diagnosis, but this is a much less sensitive method than viral culture. Serologic tests include CFT, which is the most widely used test, but the recently introduced fluorescent antibody test appears to be very promising and has the potential of



identifying a primary infection accurately.

**Immunity:** Infection with CMV confers immunity in the host because persistence of the agent in a latent phase and reactivation in response to various stimuli occurs. Although unusual, a woman may bear a second child with congenital infection of the same serotype. Since cytomegalovirus exists in multiple serotypes, reinfection of a woman in the childbearing age with a different type can result, in the birth of another infected infant to the same mother. These occurrences nevertheless are very rare. In general after the birth of a congenitally infected infant the fetus in the subsequent pregnancy is not at significantly greater risk.

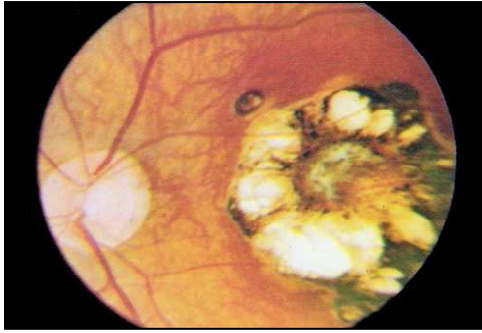
**Fetal infection:** Intrauterine infection with CMV is probably the most common viral infection of the human fetus. It has been estimated that the prevalence of CMV infection at birth shows a frequency of 4 to 10 infected infants per 1,000 births. Many points of similarity can be found between congenital CMV and Rubella, but in general there is a lower frequency of congenital disease in CMV with a preponderance of damage to the CNS in contrast to the combination of malformation and congenital disease which is to be found in infants with congenital Rubella. Another common feature is that the infant may be excreting virus at birth yet show no symptoms. The majority remain unaffected as they grow older. Approximately one in 10 of congenitally infected infant develops symptoms. The fulminating illness may present with hepatosplenomegaly, jaundice, petechial rash and low birthweight. The infant may also be premature. The mortality

rate is high, particularly if CNS involvement is prominent or respiratory distress is present. The prognosis for infants with jaundice and thrombocytopenic purpura alone is better than for those who have CNS involvement. In many infants with the former symptoms recovery is complete in 6 to 8 weeks, but there is always the possibility that other symptoms may develop later. The neurological symptoms are of the greatest consequence both in the short terms and long terms. Microcephaly may be obvious at birth or become apparent later in infancy. Cerebral diplegia, spasticity and fits presenting early in life usually have a bad prognosis. Henshaw et al (1973) found a higher incidence of CMV infection determined by the presence of CF antibody in children with undiagnosed seizures and microcephaly than in patients with genetically determined CNS disease and in a control group of normal children.



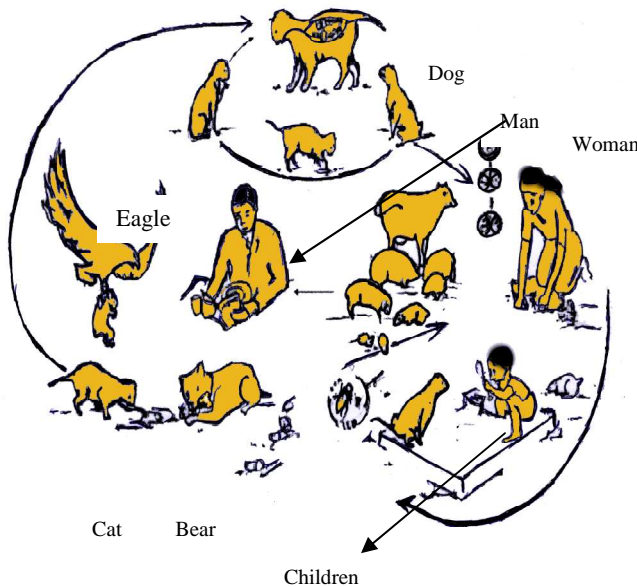
**Fig13.3: shows CMV infection rash on the body**

**Toxoplasmosis:** *Toxoplasma gondii* is a parasite which has a proliferative (invasive) phase and a cystic (resistant) phase. The resistant phase is formed in response to the immune reaction of the host. The mode of infection is unknown. The infection occurs in most parts of the world but is particularly prevalent in warm and humid climates.



**Fig13.4: shows CMV infection rash on the Retina of the eye**

**Clinical features:** There may be no symptoms but several clinical syndromes reported includes, acute generalized lymphadenopathy with or without fever. Sometimes the condition mimics infectious mononucleosis, or acute typhus pneumoniae and myocarditis.



**Fig13.5: Shows roots of transmission for toxoplasmosis infection**

**Congenital toxoplasmosis:** When a nonimmune pregnant woman is infected, the parasite can pass through the placenta and infect the foetus. The

earlier the infection occurs in the course of pregnancy, the more severe is the fetal disease. Maternal infection during the first trimester usually does not involve the foetus; since the placenta is not sufficiently mature to develop foci of infection. However abortion may still occur.

Maternal infection during the second trimester has been associated with severe congenital toxoplasmosis at birth, stillbirth, and prematurity. When the maternal disease is acquired during the third trimester, pregnancy approaches term but the newborn is invariably damaged. The infection of the infant may not be apparent at birth, and remain latent for many years. Mild cases of congenital toxoplasmosis show a few retinal lesions at birth, and additional evidence of the disease may develop during the first year of life.

In severe cases there are signs of generalized infection, i.e. fever, diffuse lymphadenopathy, hepatosplenomegaly, jaundice, and a maculopapular rash. The condition may be compared with erythroblastosis foetalis and hemorrhagic disease of the newborn. Appropriate serological tests must be carried out to differentiate this complication.

In very severe cases involvement of the central nervous system and the eyes can occur. Chorioretinitis, cerebral calcifications, psychomotor retardation, convulsions, microphthalmos, hydrocephalus and microcephaly, have all been reported. The central nervous system and ocular lesions usually occur together. Epilepsy and mental retardation have been regarded by some authorities as the most common evid-

ence of congenital brain damage. The exact incidence of congenital toxoplasmosis is not known in Pakistan, but there is every possibility that some neurologic abnormalities of undetermined origin are due to toxoplasmic infection. It is, therefore, strongly recommended that pregnant women should be screened for this disease during antenatal period. National Health Institute Islamabad has a good virology department where blood can be sent for testing. The physician will note that the infected mothers are usually healthy, and give no history of illness during or prior to pregnancy. A pregnant woman, who has fever and lymphadenopathy or complains of excessive fatigue, should be thoroughly investigated. When serologic evidence of acute acquired maternal toxoplasmosis is confirmed, therapeutic termination of pregnancy is indicated.

**Diagnosis:** Toxoplasmosis is usually diagnosed by serological methods. The test is based on the observation of the parasites, after incubation with normal human serum. The organism stains deeply with alkaline methylene blue. Toxoplasmas incubated with serum containing antibodies remain unstained. The presence of antibodies can be detected by this method as early as 10 days after infection. The titre rises sharply to high levels such as me: 260,000 and remains high for months. The titre falls slowly to low levels 1:4 over a period of many years. Positive serologic diagnosis in acute cases requires either a change in antibody titre from negative to positive; a rapidly rising titre; or a very high stable titre (1:64,000) or greater. The toxoplasma complement fixation test becomes positive a few weeks after the dye test. A

high dye test titre in the presence of a negative complement fixation test indicates a recent active infection. This excludes the possibility of passive transfer of antibodies to the child from the mother. The test should be repeated after 4 months to detect the persistence of a high antibody titre in the child. Like rubella screening, a strong case can be made for routine screening of toxoplasmosis in all pregnant women. It is only the awareness of hazards and serious complications which make this test mandatory. Toxoplasma may be recovered from the blood, spinal fluid, and biopsied tissues.

**Treatment:** Triple sulphonamides mixture, (sulfadiazine, sulfamethazine, and sulfamerazine) combined with pyrimethamine, a folic acid antagonist, has been reported to be of value in acute cases. The safety of treatment during pregnancy has been questioned, because the folic acid antagonist may cause abortion and also be teratogenic.



**Fig13.6: Shows herpetic rash over the body**

#### **Herpesvirus hominis infection:**

Incubation period varies between 4 to 7 days. HYH affects the female genital tract and causes infection of the new born and may result in abortion. About

three quarters of HYH strains isolated from the newborn are of HYH type 2, but no significant difference in clinical manifestations can be seen in HYH-1 and HYH-2~ strains. HYH type 2 is of particular importance, since it is the only virus so far suspected of an oncogenic role in carcinoma of cervix. Many women are asymptomatic. More than 90% of the genital infections are caused by the type 2 virus, while the majority of infection of the oral mucosa, cornea and brain are caused by type 1. After the initial infection the condition can be reactivated by temperature change, emotional trauma, premenstrual tension, menstruation, and the use of oral contraceptives.

**Clinical features:** Superficial ulcers of the vulva with burning, pain, malaise, inguinal adenopathy and fever may be found. Diffuse cervicitis with superficial or deep ulcers may be present. An association between maternal herpes infection and spontaneous abortion has been reported and type 2 virus isolated from aborted fetuses. The virus has been implicated as a cause of congenital abnormalities. There is thus some evidence that the virus may be transmitted transplacental.

**Diagnosis in mother:** HYH can be cultured within 2 to 4 days and wherever possible a smear for cervical cytology should be tested. Cytological changes, including multinucleate cells and prominent eosinophilic intranuclear inclusions can be detected even though attempts to cultivate the virus fail. Recent surveys have indicated, that the incidence of genital herpes may be higher in pregnant and puerperal women than in the over all population. Most neonatal infections are caused by type 2

viruses which are probably transmitted during the second stage of labour. The incidence of disseminated Herpes is greater among premature infants. The liver and adrenals are involved, with focal coagulative necrosis as the characteristic lesion. The virus may be recovered from many organs. Infection of the CNS may be the dominant feature.

**Diagnosis in the foetus** – The diagnosis can be made clinically, if typical vesicular eruption of the skin occurs during first week of life, but about 50% of infants who go on to develop disseminated infection do not have vesicles in the early stages of disease. Diagnosis is confirmed by examination of cells scraped from the base of local lesions. None of the methods of HYH antibody measurement is valuable in early diagnosis.

**Method of delivery:** If virus is known to be present in genital tract at or near term caesarean section should be considered and the case for this procedure is strengthened if there is active lesion present. There is as yet no real evidence, that caesareans section reduces the probability of neonatal disease. Similarly, the effectiveness of serum containing immuno globin has not been unequivocally demonstrated. Antiviral agent such as. Idoxuridine (I.D.U.); a thymidine antagonist, is currently under trial but its usefulness has not been fully established.



**Fig13.7: Shows rash of chicken pox over the body.**

**Varicella, (Chickenpox)** - This is quite uncommonly seen in pregnancy. Incubation period is 14 to 16 days. The period of contagiousness is from one day before to two days after appearance of the rash. Viremia is a regular feature but transmission to the fetus is unpredictable. Prospective studies do not indicate significant increase in abortions or congenital anomalies following maternal infection; although a number of published case reports suggest that at times there may be an association. When varicella occurs near term, there is greater risk of congenital infection. The closer to the time of delivery the maternal infection occurs, the greater there is the risk of severe course including death. In general, neonatal infections are mild with few skin lesions and no significant systemic symptoms usually occur.



**Fig13.8: Shows smallpox rash over the face.**

**Variola (Smallpox)** - This disease is now very rare even in the general population. Older reports indicate that the mortality rate was significantly higher in pregnant than non pregnant women. Abortion, still birth and premature labor were frequently encountered. Immunization with vaccinia virus is not without hazard, since the vaccine contains live virus. Viremia occurs in the course of primary infection and like smallpox virus; vaccinia can cause lesions in the placenta and be transmitted to the foetus.

Intrauterine infection and congenital disease are seen chiefly in infants whose mothers received their first immunization during pregnancy, although it has been reported after revaccination. Vaccination whether primary or revaccination, thus continues to be contraindicated in pregnancy.

**Influenza:** The available evidence at present suggests that usually there are adverse effects of influenza infection during the first trimester of pregnancy. Both abortion and congenital defects have been reported. There is no conclusive evidence that influenza causes congenital defects. Anencephaly and other CNS malformations have been reported, but their significance has been difficult to confirm. Other anomalies reported are cleft palate and oesophageal atresia. It has been reported that when infection occurs late in pregnancy the infant mortality rate is increased as a result of the high incidence of premature delivery. The infants born at term may have low birth weight.

#### **Echo viruses:**

This group of virus does not appear to be teratogenic to the foetus.

**Coxsackie virus** - Woman infected with this virus may have no symptoms or may complain of upper respiratory tract infection. The virus may cross the placenta to cause a fierce infection in the neonate with fever, diarrhoea tachycardia, circulatory collapse and death. There is no evidence that the disease is teratogenic.

**Screening against viral infections in pregnancy:** The student will realize at this stage that screening for (TORCH)

where 'T' stands for toxoplasmosis 'R' stands for rubella 'C' stands for cytomegalo virus and 'H' stands for Herpes, should become a part of routine antenatal screening in all pregnant women in this country.

### **Immunization:**

A practicing obstetrician is often confronted with a pregnant woman who is susceptible to a disease against which a particular vaccine is protective, and has to make a decision whether to vaccinate her or not. As a rule the use of immunizing agents during pregnancy should be reserved for high risk cases only. Live virus vaccines, in particular, should be avoided.

**Prophylactic therapy:** During pregnancy, it is preferable to reduce exposure rather than vaccinate, especially here. Live virus vaccines are involved. A pregnant woman can avoid certain diseases by not entering areas endemic for those diseases. She should be advised against travel in areas endemic for plague, yellow fever, or smallpox unless, it is absolutely necessary for her to make such journey. Sanitary precautions will decrease the chance of exposure to typhoid, cholera, and hepatitis.

**Types of Vaccines:** Generally three different types of vaccines are used for immunization purposes. These are toxoids, killed bacterial and viral vaccines, and live virus vaccines. The toxoids are preparations of chemically altered bacterial exotoxin. The killed vaccines contain heated, chemically inactivated microorganisms. The live virus vaccines contain strains of virus selected for their reduced virulence. The

other type of immunizing agent is gamma globulin, which is a protein fraction of human plasma. This can produce a transient, passive antibody protection in the recipient. The pooled gamma globulin is also useful but only for protection against hepatitis or against measles.

### **Criteria for vaccination:**

Pregnancy should be confirmed in the first trimester, since ten fetuses is most vulnerable to the teratogenic effect of maternal infections during this period. If live virus vaccine is to be given, then pregnancy must be prevented in the following 2 months. As a rule live vaccines such as rubella should not be given during pregnancy.

### **Susceptibility should be determined:**

Once it is established that the patient is pregnant, her susceptibility to the particular vaccine preventable disease, should be determined. Serologic testing should be used to confirm susceptibility. If the test is positive, only then vaccine should be given to the patient.

When it is determined that exposure is likely or unavoidable and the patient has been tested for susceptibility then the Obstetrician must balance the hazards of the disease against the potential deleterious effects of vaccination.

**Risk from disease to the pregnant woman** - In the case of tetanus, the high morbidity and mortality does not change during pregnancy. Smallpox (variola major), produces a significantly higher mortality. According to one estimate it is around 90% among pregnant females but far less in non-pregnant women.

Poliomyelitis has also been reported to produce paralysis more frequently during pregnancy. Vaccination against smallpox and polio is therefore mandatory, when the risk of exposure is high, while tetanus toxoid can be given to pregnant women, in whom immunity has been found to have lapsed.

Cholera, typhoid, and influenza vaccines are known to offer poor or transient immunity. Globulins provide protection for only a defined period of time and are used primarily for the prophylaxis of measles and hepatitis.

Rubella vaccine viruses, potentially share the same teratogenic properties as the wild rubella virus, but they have not been shown to produce birth defects. However, pregnancy is a contraindication to rubella as well as to measles and mumps vaccination, because a viral infection of the foetus can occur and may damage the foetus. Exaggerated.

Febrile responses to any vaccination may also jeopardize the pregnancy. Gamma globulin usually protects the susceptible individual from measles if given within 48 hours of exposure. Since measles have been reported to cause abortion in up to 50% of infected pregnant women. The use of gamma globulin is justified on this account.

**Immunization against tetanus:** Active immunization against tetanus can be carried out during pregnancy without injury to the foetus. The infant can be protected against neonatal tetanus by vaccinating the mother. This is a matter of great importance in rural areas, where the incidence of neonatal tetanus may be high as a result of infection of the

umbilical stump. A subcutaneous injection of tetanus toxoid adsorbed on to aluminium hydroxide should be given as early in pregnancy as possible. The second dose should follow six weeks later and the final dose six months after that, or earlier if labour is due before that time. When a woman has already been immunized in the past a booster dose of toxoid may be given in the last trimester.

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## Chapter No: 14

**DRUGS IN PREGNANCY****Introduction:**

The drug used without regard to risks and without medical advice is regarded as drug abuse. It is excessive self administration of chemicals that change the user's perception, mood and consciousness.

**ANAESTHETICS**

**General information:** If a procedure requires anaesthesia, help the mother to express her breast milk in advance and store it in a refrigerator so that her baby can be fed her expressed breast milk by cup while she is undergoing the operation and recovering from the anaesthesia.

**General anaesthetics and oxygen:**  
 Ether: Compatible with breastfeeding,  
 halothane: Compatible with breastfeeding,  
 ketamine: Compatible with breastfeeding,  
 nitrous oxide: Compatible with breastfeeding,  
 oxygen: Compatible with breastfeeding and  
 thiopental: Com-pati-ble with breastfeeding.

**Local anaesthetics**

**Bupivacaine:** Compatible with breastfeeding, lidocaine.

**Complementary drug:** Ephedrine (C): Compatible with breast-feeding, Monitor infant for side effects (irritability and disturbed sleep).

**Preoperative medication and sedation for short term procedures:**

Atropine: Compatible with breast-feeding. Monitor infant for side effects (drying of secretions, Temperature elevation and CNS disturbance), chloral hydrate: Compatible with breastfeeding in single dose. Monitor infant for drowsiness, diazepam: Compatible with breast-feed-ing in single dose. Avoid giving repeated doses, if possible. Monitor infant for drowsiness. Short acting benzodiaze-pines preferred. Morphine: Compatible with breast-feeding in single dose. Avoid giving repeated doses, if possible. Monitor infant for side effects (apnoea and bradycardia) Promethazine: Com-patible with breast feeding in single dose. Avoid giving repeated doses, if possible. Monitor infant for drowsiness

**Analgesics, antipyretics, nonsteroidal anti inflammatory drugs, drugs used to treat gout and disease modifying agents used in rheumatic disorders:****Non opioids analgesics and antipyretics and nonsteroidal anti-inflammatory drugs:**

**General information:** ibuprofen and paracetamol have the best documentation on safety during breast-feeding. Acetyl salicylic acid. Compatible with breastfeeding in occasional doses. Avoid long-term therapy, if possible. Monitor infant for side effects (hemolysis, prolonged bleeding time and metabolic acidosis) ibuprofen: Compatible with breast-feeding and paracetamol compatible with breastfeeding.

**Opioid analgesics: General Information:** Single doses of most



opioids are excreted in breast milk only in small amounts. Repeated doses may result in accumulation in the infant. Avoid repeated doses, especially if the infant is premature or less than 4 weeks old. Avoid drugs from this category if the infant has had an episode of apnoea, bradycardia or cyanosis. If given during delivery, the infant may be drowsy at birth, which may interfere with the initiation of breastfeeding. Codeine morphine complementary drug.

### **Pethidine:**

Compatible with breastfeeding in occasional doses. Avoid repeated doses, if possible. Monitor infant for side effects (apnoea, bradycardia and cyanosis), Compatible with breastfeeding in occasional doses. Avoid, repeated doses, if possible. Monitor infant for side effects (apnoea, bradycardia and cyanosis), Compatible with breastfeeding in occasional doses. Avoid repeated doses, if possible. Monitor infant for side effects (apnoea, bradycardia and cyanosis). Side effects occur more comm-only than with morphine.

### **Drugs used to treat gout:**

Allopurinol and colchicine compatible with breast feeding.

### **Disease modifying agents used in rheumatic disorders: Antiallergic and drugs used in anaphylaxis:**

Chlorphenesin: Avoid if possible. Monitor infant for side effects (drowsiness, irritability). May inhibit lactation, dexamethasone Compatible with breast feeding in single dose. About prolonged usage epinephrine (adrenaline).

Hydrocortisone: Compatible with breastfeeding in single dose. About prolonged usage prednisolone: Compatible with breast-feeding.

### **Antidotes and other substances used in poisonings:**

#### **Non specific:**

Charcoal, activated and ipecacuanha compatible with breastfeeding.

#### **Specific:**

Acetylcysteine: Atropine: Compatible with breastfeeding. Monitor infant for side effects (drying of secretions, temperature elevation and CNS disturbance) calcium gluconate, deferoxamine available dimercaprol. Avoid if possible, especially if the infant is pre-mature or less than 1 month old. Monitor infant for side effects (hemolysis and jaundice). Avoid in G-6-PD deficient infants azathioprine, chloroquine, cyclo phosphatide, Methotrexate, penicillamine and sulfasalazine: Avoid breastfeeding, compatible with breastfeeding. Monitor infant for side- effects (hemolysis and jaundice), especially if the infant is premature or less than 1 month old. Avoid in G-6-PD deficient infants. Use alternative medicine, avoid breast feeding, and avoid if possible, especially if the Infant is premature or less than 1month old. Monitor the infant for side-effects (bloody diarrhea, hemolysis and jaundice). Avoid in G-6-PD deficient infants, DL methionine, methylthionine chloride, (methylene blue), Avoid if possible, especially if the infant is premature or less than 1 month old. Monitor infant for side effects, (hemolysis and jaundice) naloxone: Penicillamine, potassium ferric,

hexacyanoferrate (II) 2H<sub>2</sub>O (Prussian blue), Sodium calcium edetate: Sodium nitrite and sodium thiosulfate.

#### **Anticonvulsants or antiepileptic:**

**General information:** Breastfed infants of mothers who are taking anticonvulsants sometimes develop drowsiness. For mothers who need anticonvulsants there is often little alternative. It is essential that they take their medication and it can be dangerous to change antiepileptic medicines suddenly. Breastfeeding is usually possible, but the infant must be monitored. It helps if the dose is kept as low as possible within the effective therapeutic range. Carbamazepine: Compatible with breastfeeding. Monitor infant for side effects (jaundice, drowsiness, poor suckling, and vomiting and poor weight gain) diazepam: Compatible with breastfeeding in single dose. Avoid repeated doses, if possible. Monitor infant for drowsiness ethosuximide: Avoid if possible. Monitor infant for side-effects (drowsiness, poor suckling and poor weight gain) magnesium sulfate compatible with breastfeeding, phenobarbital: Compatible with breastfeeding. Monitor infant for side effects (drowsiness, poor suckling and poor weight gain), Phenytoin compatible with breastfeeding. Monitor infant for side effects (cyanosis and methemoglobinemia) valproic acid: Compatible with breastfeeding. Monitor infant for side effects (jaundice).

**Complementary drug:** Clonazepam: Compatible with breastfeeding. The mother should receive only normal dose.

#### **Anti infective drugs, Anthelmintics: Intestinal anthelmintics:**

**General information:** There are limited data available on the use of drugs in this category. However, they act mainly in the intestinal system of the mother and little is absorbed into the general system. They can be considered compatible with breastfeeding.

Albendazole: compatible with breastfeeding levamisole: Compatible with breastfeeding mebendazole: Compatible with breastfeeding niclosamide: Compatible with breastfeeding praziquantel. Compatible with breastfeeding pyrantel: Compatible with breastfeeding.

#### **Antifilarial:**

Diethylcarbamazine and ivermectin.

#### **Complementary drug:**

#### **Suramin Sodium:**

#### **Antischistosomal and other anti trematode drugs:**

Praziquantel: Compatible with breastfeeding, triclabendazole.

#### **Complementary drug:**

#### **Oxamniquine:**

Compatible with breastfeeding

#### **Antibacterial:**

**General information:** If the drug is excreted in breast milk, there is a possibility of altering the infant's intestinal flora. Monitor the infant for gastrointestinal disturbances, such as thrush and diarrhoea. If they occur, stop the drug and choose an alternative if necessary. Continue breastfeeding.

**Lactam drugs: General information:** Breastfeeding is generally safe.

Theoretically, penicillins can cause an allergic reaction in the infant. If the infant develops a rash, it could be a sign of allergy. Stop the drug and choose an alternative if necessary. Continue breastfeeding. Warn the mother that the infant should not be given the drug in the future. Amoxicillin: Compatible with breastfeeding ampicillin: Compatible with breastfeeding benzathine benzylpenicillin: Compatible with breastfeeding benzylpenicillin, cloxacillin: Compatible with breastfeeding, phenoxymethylpenicillin, procaine benzylpenicillin compatible with breastfeeding.

#### **Restricted indications:**

Amoxicillin clavulanic acid, ceftazidime, ceftriaxone, imipenem cilastatin: Compatible with breast-feeding.

#### **Other antibacterial:**

Chloramphenicol: Avoid if possible, especially if the infant is less than 1 month old. Monitor the infant for side effects (hemolysis, and jaundice). Theoretically, there is a risk of bone marrow depression, but this has never been reported, ciprofloxacin: Avoid if possible, until more data are available, doxycycline: Avoid if possible. Possibility of staining the infant's teeth. Single dose is probably safe erythromycin: Compatible with breastfeeding. Gentamicin: Compatible with breast feeding. Monitor infant for thrush and diarrhoea. Metronidazole: Avoid if possible.

Animal data suggest it may be carcinogenic. If given in single dose of 2 grams, discontinue breastfeeding for 12 hours. Help the mother to express her

breast milk in advance and store it in a refrigerator so that her baby can be fed by cup during that time nalidixic acid. Avoid if possible, especially if the infant is premature or less than 1 month old. Monitor the infant for side effects (hemolysis and jaundice).

Avoid in G-6-PD deficient infants nitrofurantoin: Compatible with breastfeeding for healthy full-term infants. Avoid if possible if the infant is premature or less than 1 month old.

Monitor the infant for side-effects (hemolysis and jaundice). Avoid in infants with G-6-PD deficiency spectinomycin: sulfadiazine. Avoid if possible, especially if the infant is premature or less than 1 month old. Monitor the infant for side effects (bloody diarrhea, hemolysis and jaundice). Avoid in G-6-PD deficient infants sulfamethoxazole trimethoprim (Cotrimoxazole): Compatible with breastfeeding for older, healthy full term infants. Avoid if possible if the infant is premature or less than 1 month old. Monitor the infant for side effects (Hemolysis and jaundice).

**Deficiency:** Trimethoprim: Compatible with breast-feeding.

**Chloramphenicol:** Avoid if possible, especially if the infant is less than 1 month old. Monitor the infant for side effects (hemolysis and jaundice). Theoretically, there is a risk of bone-marrow depression, but this has never been reported.

#### **Clindamycin:**

Avoid if possible. Monitor infant for diarrhoea or bloody stools.

**Restricted indications:****Anti leprosy drugs:**

Clofazimine may cause skin discoloration, which is reversible dapsone. Compatible with breast feeding. Monitor for side-effects (hemolysis and jaundice), especially if the infant is premature or less than 1 month old. Avoid in infants with G-6-PD deficiency rifampicin. Compatible with breastfeeding.

**Antituberculosis drugs:****General information:**

If the baby develops significant jaundice, stop or change the drug if possible. If this is not possible, it may be necessary to consider feeding the baby artificially. Ethambutol compatible with breastfeeding. Monitor the infant for jaundice isoniazid compatible with breastfeeding. Monitor the infant for jaundice isoniazid + ethambutol compatible with breastfeeding. Monitor infant for possible tox-icity pyrazinamide compatible with breast feeding. Monitor the infant for jaundice rifampicin compatible with breastfeeding. Monitor the infant for jaundice rifampicin + isoniazid Compatible with breastfeeding. Monitor the infant for jaundice rifampicin + isoniazid + pyrazinamide, Compatible with breast-feeding rifampicin + isoniazid + pyrazinamide+ ethambutol. Compatible with breastfeeding streptomycin Monitor the infant for thrush and diarrhoea.

**Complementary drug:** Thioacetazone + isoniazid (A) Compati-ble with breastfeeding.

**Restricted indications:** For drugs used in treatment of multidrug resistant tuberculosis, see section 9 of the main

text of the Ninth report of the WHO Expert Committee. A woman who is breastfeeding and has TB should receive a full course of anti TB chemo therapy. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby. All the anti-TB drugs are compatible with breastfeeding and a woman taking them can safely continue to breastfeed her baby. The mother and baby should stay together and the baby should continue to breastfeed in the normal way. The baby should receive isoniazid prophylaxis and BCG immunization. ( Quote from : Maher D, Chaulet P, Spinaci S, Harries A. Treatment of tuberculosis: Guidelines for national programmers. 2nd edition 1997 Global tuberculosis Programme, World Health Organization. Geneva, Switzerland.).

**How drugs affect pregnancy:**

Most of the "drugs of abuse" produce addiction that is, tolerance, and dependence. The risk of withdrawal syndromes is very real. The fetus is a non consenting addict.

Use of potent agents such as alcohol, cocaine, and heroin is associated with accidental trauma, respiratory failure and myocardial infarction.

Cocaine-induces vasospasm and pulmonary edema. Uteroplacental blood flow is affected during repetitive use of cocaine. It contributes to the high incidence of placental insufficiency or distress. Placental abruption and even fetal death can occur. Prostitution as a profession encourages sexually transmitted diseases. The passivity of some patients in the face of serial or

multiple sexual users, often results in drug abuse. Evaluation of drug using mother must include search for sexually transmitted pathogens in unexpected and multiple orifices.

Drug abuse and syphilis are important associates of human immunodeficiency virus (HIV) infection.

Immunodeficiency syndrome and the opportunistic infections are associated with immuno incompetence.

Hepatitis B is also common among drug users. A variety of microbes not usually regarded as sexually transmitted can be spread by oro genital, oro anal, and a genital sexual practice, including Haemophilus influenzae type B, Giardia lamblia, Entamoeba histolytica, Campylobacter jejuni, Shigella and Salmonella.

Indigenous flora such as staphylococci, streptococci, aerobic gram-negative rods (especially pseudomonades) and various anaerobes including Bacteroides clostridial species, and fungi, such as Candida. Septic thrombophlebitis, superficial Cellulitis, and abscess formation are common associates' conditions. Clinical tetanus may follow subcutaneous injection ("skin popping"). Bacteremia following UN sterile intravenous injection may cause pyrogen reactions, septicemia, metastatic abscess of bone and cartel-age, and even endocarditis.

**Management:**

**History and physical examination:**

The specific questions about substance must be asked and urine testing for drugs must be carried. The physician must be alert to the psychosocial clues of drug

abuse and to the complications. The appearance of needle tracks or tattoos which are used to cover needle tracks cause unusual infections in unusual locations, signs of physical torture. Unexplained indifference to the need for careful prenatal nutrition and care are often good clues to potential drug abuse. Questions about drug-using behavior and urine testing must be repeated, some times with every visit, because the presence of drugs and drug metabolites in the urine is transient and because drug use may occur in binges, not continuously. False positive results on urine tests can be caused by urinary tract infections and the use of anesthetic lubricants for urinary catheters or for sexual purposes. A coordinated team approach including drug abuse treatment social and legal services along with obstetric and medical care yield good results. Drug abuse is a lifetime problem. Pregnancy can be unique opportunity to help the drug using woman learn a different way of life.

**Alcohol in pregnancy:** Some adverse fetal effects can be attenuated by abstinence in the second half of pregnancies. The capacity of heavy drinkers to disguise their drinking is strong. Questions about drug use enquiry should include: "Have you ever had a drinking problem?" and "When was your last drink?" History of motor vehicle accidents or tickets for risky driving, are important clues for further investigation.

**Management:** 2 to 6 days of treatment with a short acting barbiturate, such as pentobarbital, is preferable in pregnancy. Concern about the possible teratogenicity and neonatal effects of the benzodiazepines has restricted their use in pregnancy. Disulfiram (Antabuse) is a

potential Teratogen and inhibits many enzyme systems. Its use in pregnancy should also be avoided. The opiate antagonist, naltrexone, unlike disulfiram, does not cause severe reactions. The recommended dose of naltrexone is 50 mg day. The drug should be discontinued at least 72 hours in advance of delivery. Liberal thiamin and vitamin replacement should be instituted. Pregnant problem drinkers should be counseled about HIV and tested if they consent. They should be continually screened for other sexually transmitted infections and alcohol-related hepatitis, pancreatitis, and neuropathy. Alcohol abusers are twice as likely as nondrinkers to have a history of habitual abortion. The use of alcohol has been abandoned as a treatment for prevention of premature labor. Support for alcohol may be obtained through self help groups like Alcoholics Anonymous.

**Withdrawal syndrome:** The most common withdrawal is, "the shakes," It is tremulousness and irritability, which begins within 48 hours after termination of drinking and usually subsides within a few days. Sedation with hydroxyzine or a benzodiazepine may retard the development of full blown delirium tremens (DTs). The DTs remain a life threatening metabolic disease characterized by marked sympathetic over activity, fever, and encephalopathy, with terrifying visual hallucinations and confabulation. As many as 15% of patients with DT's die. Alcohol withdrawal seizures, (rum fits," begin within 12 to 48 hours after cessation of drinking). Any of these withdrawal phenomena may occur, during labor and delivery. Abnormalities of almost every organ system have been noted to occur with increased frequency in off spring of

alcoholic mothers. Effects on ocular, oral, auditory, skeletal, hepatic, and cardiac development have been observed. Among the cardiac defects, ventricular septal defect is the most common. Of special note is radioulnar synostosis, which is almost unknown in the general population.

**Fetal alcohol syndrome:** Both alcohol and its metabolite, acetaldehyde, directly affect cell growth. Microcephaly is a characteristic feature of FAS. Mental retardation, behavior problems, learning and language disabilities, hyperactivity, and sleep disturbances have all been reported with greater frequency in off spring of alcoholic mothers. A FA is now believed to be the leading cause of mental retardation, in excess of Down syndrome, cerebral palsy, and spine bifida. The full blown FAS are found in 30% to 40% of the neonates of mothers consuming more than 2 oz of absolute alcohol per day during the first trimester. Nutritional deficits, particularly folic acid and zinc deficiency, seem to potentiate the teratogenicity of alcohol.

### **Cocaine:**

It is a potent stimulant of the central and periphery sympathetic nervous systems. Cocaine acts indirectly as a potent vasoconstrictor by interfering with norepinephrine and dopamine uptake by adrenergic nerve terminals. These actions account for the usual physiologic effects of tachycardia, hypertension, dilated pupils, and muscle twitching. Cocaine decreases uptake of tryptophan and thus diminishes serotonin biosynthesis. Decreased serotonin levels decrease the need for sleep and contribute to the post stimulant depression.

**Effect of cocaine on pregnancy:**

1. It decreases umbilical artery prostacyclin production and can deplete antithrombin III and protein C, thus enhancing the risk for thrombogenesis.
2. It interferes with the low-pressure, high flow physiology of gestation, with predictable ill effect on both the mother and the fetus.
2. The mature placenta can convert cocaine into less active metabolites, presumably by placental cholinesterases. Despite this potential protection for the fetus, low birthweight, neonatal withdrawal, intrauterine fetal death, fetal vascular complications, and accelerated fetal lung maturity are regular complications.
3. After Cocaine intake, there is a rapid onset of intense "high" euphoria. As tolerance develops, the euphoric effects are quickly replaced by depression, exhaustion, and anxiety,
4. Maternal cocaine use produces decreased uterine blood flow and there is dose dependent increase in fetal heart rate. Chronic Cocaine use appears to be a cause of maternal cardiomyopathy, which may be confused with peripartum cardiomyopathy.
5. Cocaine exaggerates uterine contractions. Half of cocaine-using women not receiving prenatal care deliver prematurely.

**Effect of cocaine on fetus:**

Teratogenicity exclusively to cocaine use has not been established. Limb reduction defects, genitourinary malformations, cardiac anomalies, and gastrointestinal atresia are commonly reported.

**Other complications:**

Maternal hyperthermia during cocaine intoxication may contribute to the increased incidence of congenital malformations. Seizures and Pulmonary complications have been associated with smoking crack cocaine. Pulmonary edema and bronchiolitis bitemporalis have been less commonly reported. "Crack lung" is the name given to the constellation of hemoptysis, chest pain, and diffuse alveolar infiltrates. The association among crack cocaine use, syphilis and HIV infection is compelling.

**Management:**

Good prenatal care and sheltered withdrawal from drugs and the drug scene are the principal management objectives. There are no known effective pharmacologic agents available to block cocaine craving and to sustain abstinence.

**Amphetamines:**

These drugs continue to be popular among drug users and experimenters because of their euphoric, sympathomimetic properties. Amphetamine use increases the risk of serious arrhythmias, including ventricular tachycardia and asystole, during obstetric anesthesia. Inhaled amphetamine ("ice") has repetitive drug induced vasospasm. It is thought to be the cause of prematurity,

placental abruption, and intrauterine growth retardation. The major fetal problem has been retarded intrauterine growth confirmed by finding amphetamines in the urine.

**Antidepressant:** Most antidepressants are inhibitors of serotonin uptake. Fluoxetine, sertraline, paroxetine are common antidepressants. No teratogenic or addicting effect has been reported by their use.

Their popularity as a ("feel-good" pill) has generated a street market. Fluoxetine (Prozac) crosses the placenta and is excreted in breast milk. No association has been found between first trimester exposure to fluoxetine and congenital anomalies.

**Tranquilizers:** (Benzodiazepines) and (barbiturates i.e. Glutethimide, have not been proven, to have direct toxic or teratogenic effect on the fetus. These drugs are often used to blunt the symptoms of over stimulation and abstinence by users of alcohol, cocaine, and amphetamines. All of the tranquilizers and sedatives produce tolerance and an abstinence syndrome in both the mother and the child.

#### **Barbiturates:**

Rapid withdrawal of barbiturates before delivery may be accompanied by intrauterine fetal withdrawal and distress similar to that seen in children of narcotics addicts. Neonatal withdrawal can occur in the children of mothers treated with phenobarbital in doses appropriate for seizure control. Barbiturate withdrawal may be exceptionally difficult during labor and delivery. Blood and urine levels of bar-

biturates must be measured to help confirm the diagnosis.

During the third trimester, benzodiazepines readily cross the placenta and accumulate in fetal tissue. As a result, severe neonatal depression, the floppy baby syndromes and neonatal withdrawal can occur. It is desirable to attempt withdrawal from benzodiazepines before delivery and to stop their use late in Pregnancy.

#### **Narcotics:**

The heroin users have around them dirty needles and often a criminal behavior. Premature labor and low birthweight infants in heroin-addicted mothers are common.

There is a trend toward higher perinatal morbidity and mortality among the infants of these mothers. The overdosed patient is comatose, with pinpoint pupils, and should be given naloxone.

Naloxone is a narcotic antagonist without respiratory depressant effect. The dose of naloxone is 0.01mg/kg and is given intravenously. Pulmonary edema may occur with heroin overdose.

#### **Effect of heroin on Foetus:**

In the first trimester the fetus may be expelled. Later in pregnancy, maternal withdrawal is accompanied by fetal withdrawal. It produces hyperactivity, hypoxia, and the passage of meconium by the foetus.

Intrauterine fetal death may occur. Narcotic withdrawal is not encouraged during pregnancy, and narcotic antagonists, such as pentazocine (Talwin) and naloxone (Narcan), should



be used with great caution. Heroin detoxification using clonidine usually takes 5 to 7 days. Doses for moderate withdrawal symptoms are 0.1 to 0.2 mg every 4 to 6 hours for 3 days, then tapering the dose by 0.2mg/day.

### **Management:**

Heroin addicts should be enrolled in narcotic maintenance programs. Methadone is a drug of choice and a long acting, synthetic opiate that can be taken by mouth; it reduces the risk of needle complications.

Methadone blocks the euphoria produced by heroin and blunts the appetite for "shooting up."

Daily methadone doses suppress withdrawal symptoms. It has the same properties as heroin but it is not a narcotic antagonist.

LAAM does not have psychoactive effects and is not addictive. Its advantage over methadone is its prolonged duration of action, with suppression of withdrawal symptoms for up to 72 hours.

Usual doses range from 30 to 100 mg by mouth every 2 to 3 days. There is, as yet, not a lot of experience with maintenance during pregnancy.

Detection and treatment of infections, improved nutrition, and improved prenatal and psychosocial care contribute to the improved pregnancy outcome. One third of neonates of methadone maintained mothers are under-sized.

Pentazocine abusing mothers should be

with-drawn during the second trimester and should be cautiously placed on methadone maintenance.

### **Hallucinogens:**

Phencyclidine (PCP), or "angel dust" and lysergic acid diethylamide (LSD), or ("acid," are two commonly used agents. There is suggestive but not conclusive evidence that illicit or "street" LSD can produce chromosomal anomalies in fetal tissue if taken during the first trimester of pregnancy.

### **Tobacco and marijuana:**

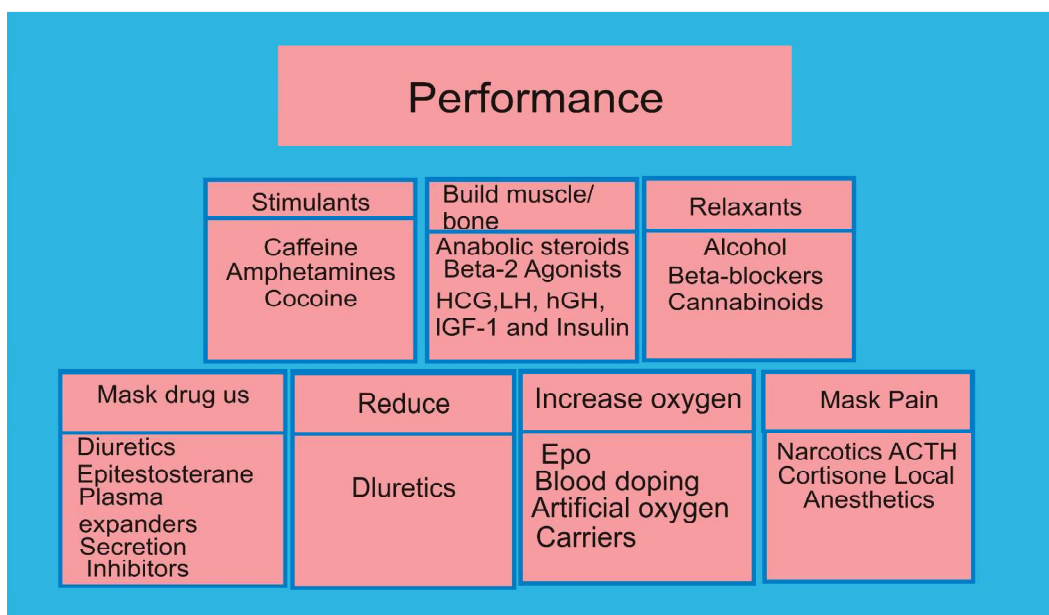
Cigarette smoking is one of the major health hazards of pregnancy. Spontaneous abortion rate, perinatal mortality, fetal growth and childhood development are all affected adversely.

Marijuana is frequently used by the cigarette smokers, alcohol users; low socioeconomic status is associated with drug abuse.

Prolonged heavy marijuana smoking is causes diminished libido and psychological symptoms including depression and lethargy. Increase in precipitous delivery, meconium passage, and need for neo-natal resuscitation in marijuana users is more. Marijuana may be teratogenic in animals. Fried reported dose related nervous system abnormalities and diminished visual responses in neonates exposed to these substances in utero.

### **Other inhaled substances:**

Pregnant women may engage in "sniffing" glue, paint thinner or other substances containing organic solvents.



**Fig14.1: Shows schematic presentation of various drugs in pregnancy.**

Inhalation of volatile organic compounds is a particular practice of children and teenagers. A variety of other materials are also used i.e. glue, toluene, gasoline, solvents, thinners, and aerosols. Maternal and neonatal renal tubular acidosis, pulmonary injury, and cardiac arrhythmias are exacerbated. Preterm delivery, intrauterine growth retardation, and fetal death have been reported when these agents are abused during pregnancy.

#### **Caffeine:**

Caffeine, like theophylline is rapidly absorbed from the gastrointestinal tract. Its half-life is increased two to three fold in pregnancy.

It is known to cross the placenta. The average daily intake is 99 mg, and approximately 28% of pregnant women consume more than 150 mg of caffeine per day throughout pregnancy.

There is no evidence that caffeine intake has any adverse effect on late pregnancy outcome or fetal growth.

Caffeine intake of greater than 150 mg/day increases the risk of late first trimester and second trimester spontaneous abortion. Coffee per se may be more embryo toxic than other caffeine sources.

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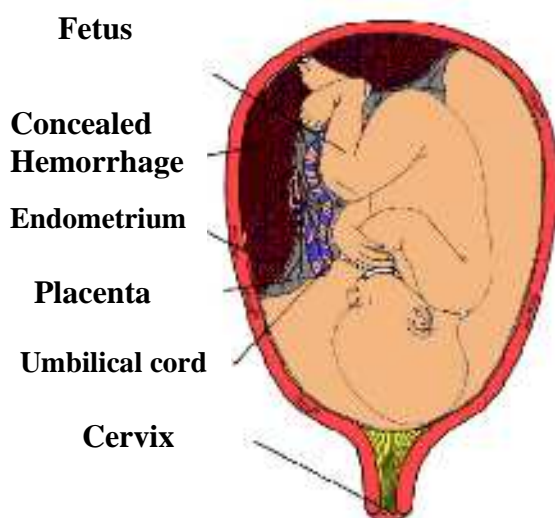
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## Chapter No: 15

### HIGH RISK PREGNANCY

Pregnancy is a normal physiological phenomenon which successfully occurs in a normal healthy woman. The health according to WHO definition is the absence of definable disease and a low risk of future disease. The risk is a measure of statistical chance and probability of a future occurrence which can result in adverse consequences due to the presence of one or more factors.

#### Concealed Bleeding:



**Fig15.1: Shows concealed hemorrhage behind the placenta**

**High Risk Pregnancy** - Obstetrical complications can occur in any pregnancy and at any time. However, it is recognized that certain categories of patients are particularly high risk. In these categories, both maternal and perinatal mortality are considerably increased. The accompanying list is presented to remind the student of these dangers. It is recommended that patients

falling into these groups should be assessed carefully and that, if more than minor complications exist, consideration should be given to referral of the case to an appropriate hospital where properly trained obstetrical neonatal and supporting diagnostic staff is available.

The concept of classifying pregnancy as low and high risk is not a new one. In fact it provides an objective quantification of numerous environmental, socioeconomic, racial, genetic, physiological, nutritional, diagnostic and therapeutic factors, which affect the growth and development of an individual and our society. Maternal and child health play the most vital, pivotal role in maintaining health and growth of a society.

The risk of certain factors, such as medical disorders like anemia, diabetes mellitus, hypertension, toxanemia, tuberculosis etc; have been known to exert adverse effect on the health of individuals.

The special attention, screening and treatment of risk factors other than medical, need further explanation.

Factors such as, low socioeconomic class, smoking, teenage pregnancy and elderly primigravida, have been proven to affect the outcome of pregnancy adversely. These factors are generally not recognized it is only in the last few decades, that the improvement in diagnostic screening and followup studies have shown association of these

factors, with poor maternal, fetal and neonatal outcome.

The very gist of obstetrical practice centers on the well being of mother and her baby. In practice categorization of obstetrical patients as low, moderate and high risk is necessary to distribute and decide about the level of care required. The ultimate aim of such a care is to guarantee good maternal and fetal health. Advantages of risk approach in health care - The characteristics used to identify the risk can be measured directly or by proxy. The strength of association of a risk factor with the adverse outcome is known as the relative risk.

It is well recognized fact that high risk mother usually gives birth to a high risk newborn. If the problem of high risk newborn is to be lessened, a meaningful assessment scoring system can be very helpful. The highest score of 10 may be adopted as universal figure. Any mother, who scores 10 or more, carries a good chance to deliver a sick newborn. Such an assessment has to be universally acceptable, it should be simple, practical and easily communicable among paramedics, nurses, physicians, obstetricians and neonatologist. A list of risk factors along with their score values.

**Management:** - The boundaries between the normal pregnancy, the low risk and the so called high risk, which is associated with a recognizable complication rate, are temporary. For this reason, it is very difficult to clearly define this condition and provide a set treatment for management of such cases. In my opinion the confusion can be lessened, if we adopt a comprehensive and well organized risk approach at the primary health care level, for the care of

all gravida and their children, rather than limit our focus on the physical, medical and socioeconomic characteristics of a few high risk categories of obstetrical patients. The need for identifying women with greater risk can not be fulfilled by providing intensive screening to a small number of populations. This can only become possible if done at the expense of low risk and normal patients, where the physician may be caught off guard in a situation, where false sense of security may lead him to an ugly and disastrous situation just because the resources and personal had not been alerted to deal with the unexpected.

Management of most high risk obstetrical situation has been adequately dealt within appropriate sections of this book. In general, intensive care and tertiary care hospitals and specialists are required for treatment of all high risk pregnancies. Prenatal diagnosis: Prenatal diagnosis employs a variety of techniques to determine the health and condition of an unborn fetus. Without knowledge gained by prenatal diagnosis, there could be an untoward outcome for the fetus or the mother or both. Congenital anomalies account for 20 to 25% of perinatal deaths. Specifically, prenatal diagnosis is helpful for: Managing the remaining weeks of the pregnancy, determining the outcome of the pregnancy, planning for possible complications with the birth process, planning for problems that may occur in the newborn infant, deciding whether to continue the pregnancy and finding conditions that may affect future pregnancies. There are a variety of non-invasive and invasive techniques available for prenatal diagnosis. Each of them can be applied only during specific

time periods during the pregnancy for greatest utility. The techniques employed for prenatal diagnosis includes:

Ultrasonography, amniocentesis, Chorionic villus sampling, fetal blood cells in maternal blood, maternal serum alpha fetoprotein, maternal serum beta HCG and Maternal serum estriol.

### **Assessment of maternal and fetal well being:**

**Maternal assessment** - There is no alternative to a detailed history which includes present, past reproductive, medical and surgical history.

History of past obstetrical performance is especially important because it highlights and forewarns about the recurrence of certain risks and their potential to the maternal and fetal health. Similarly previous history of reproductive failure such as abortion, and stillbirth points towards some genetic and structural defects. History of smoking drug addiction and alcoholism needs special consideration, because of withdrawal symptoms and teratogenic effects of these agents.

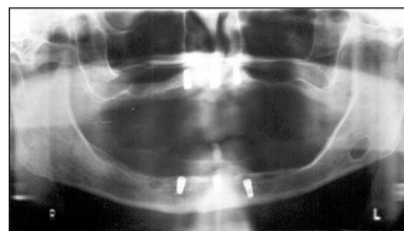
**Physical examination** - Conventional recording of weight, height, and general body built and review of the different systems such as gastrointestinal, cardiovascular, musculoskeletal and neurological also help in exposing potential risks to the mother and her baby.

### **Fetal assessment:**

#### **Methods:**

**Clinical assessment:** The time honored clinical methods for assessment of fetal well being, which include indirect

assessment of fetal growth from maternal weight gain, enlargement of the uterus, fundal height, abdominal girth, quickening, fetal movements and heart rate still remain the most important and practical measures even today.



**Fig15.3: Radiological appearance of maternal pelvis with baby.**

**Radiological assessment** - This old method of assessment of fetal growth (has been generally discarded) because of the radiation hazards to the mother and the fetus. In any case it is useless in early pregnancy, because the fetal skeleton is not visible before 16 weeks of gestation and no soft tissue deformity can be detected by this technique.

### **Hormonal assessment:**

A number of hormones where fetus plays a direct or indirect role in their production and excretion have been used for assessment of fetal well being. These hormones include HCG, HPL, and estriol.

### **HCG:**

Human chronic gonadotrophin (a placental polypeptide hormone) is produced by the trophoblastic tissue and has been used for diagnosis of normal and abnormal pregnancy. i.e. hydatidiform mole. In certain medical disorders such as diabetes, Rh isoimmunization and pre-eclampsia, the level of this hormone is

reported to be higher, especially when fetal death is impending. Similarly the level of HCG relates quite well in cases of threatened abortion, where it shows continuous fall. In general, the use of this hormone for assessing the fetoplacental well being is limited.

### **Maternal serum beta HCG:**

This test is most commonly used as a test for pregnancy. Beginning at about a week following conception and implantation of the developing embryo into the uterus, the trophoblast will produce enough detectable beta HCG (the beta subunit of human chorionic gonadotropin) to diagnose pregnancy. Thus, by the time the first menstrual period is missed, the beta HCG will virtually always be elevated enough to provide a positive pregnancy test. The beta HCG can also be quantified in serum from maternal blood, and this can be useful early in pregnancy when threatened abortion or ectopic pregnancy is suspected, because the amount of beta HCG will be lower than expected. Later in pregnancy, in the middle to late second trimester, the beta HCG can be used in conjunction with the MSAFP to screen for chromosomal abnormalities, and Down syndrome in particular.

An elevated beta HCG coupled with a decreased MSAFP suggests down syndrome. Very high levels of HCG suggest trophoblastic disease (molar pregnancy). The absence of a fetus on ultrasonography along with an elevated HCG suggests a hydatidiform mole. The HCG level can be used to follow up treatment for molar pregnancy to make sure that no trophoblastic disease, such as a choriocarcinoma, persists.

**HPL** - This human placental lactogen hormone is also produced by the placenta. Its level has been reported to correlate with placental weight. Change in rate of production and its level in the maternal serum, as well as in the amniotic fluid, can be used as a sensitive indicator of placental function.

Serial monitoring of HPL can help to anticipate the hazards of placental failure, especially in situations where intrauterine growth retardation is suspected, i.e. in cases of toxemia, hypertension and diabetes mellitus.

**Estriol** - This hormone is very important for monitoring the fetal well being. Biosynthesis of estriol occurs, from precursor such as dehydroisoandrosterone which is produced in the fetal adrenal gland.

This precursor is converted in fetal liver by 16-hydroxylation and aromatized to estriol in the placenta. The level of estriol increases progressively in three trimesters. The increase is exceptionally sharp during the last four weeks.

Nearly 90 per cent of the total estrogen excreted in urine during late pregnancy is found in the form of Sodium estriol glucuronide. The amount of estriol in maternal serum is dependent upon a viable fetus, a properly functioning placenta, and maternal well being. The substrate for estriol begins as dehydroepiandrosterone (DHEA) made by the fetal adrenal glands.

This is further metabolized in the placenta to estriol. The estriol crosses to the maternal circulation and is excreted

by the maternal kidney in urine or by the maternal liver in the bile.

The measurement of serial estriol levels in the third trimester will give an indication of general well-being of the fetus. If the estriol level drops, then the fetus is threatened and delivery may be necessary emergently. Estriol tends to be lower when Down syndrome is present and when there is adrenal hypoplasia with anencephaly.

In general estriol excretion is increased progressively from a level of 0.1 mg/ml at the 6th week of gestation to value of 12 to 15 mg/ml at term. Estriol levels are useful only after the 20th week of gestation, as regards monitoring of fetal well being.

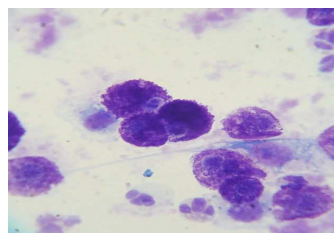
When there is a progressive and dramatic fall in estriol level, fetal death becomes very likely. Low values are found in cases of anencephaly. Serum estriol is much easier to determine in the laboratory. The test is available in most advanced obstetrical units. The problem of 24 hours urine collection is also avoidable, where serum estriol is used for fetal monitoring.

A number of drugs interfere in determination of the estriol level in the urine by chemical competition. When acid hydrolysis is employed, methenamine, mandelate, ampicillin and sugar in the urine all interfere with estimation of estriol. Low levels of maternal urinary estriol may in some cases, be due to renal problems where inadequate clearance of estriol occurs from maternal plasma.

False low urinary estriol level may also be noted in patients who are on cortisol

therapy. High levels are often present in urine of patients with severe erythroblastosis:

**Progesterone** - Although it is produced in increasing amount by the placenta, measurement of its metabolites, such as pregnanediol has very poor correlation with the fetal well being, therefore, it is useless test for clinical purposes.



**Fig15.4: Shows stained vaginal cells used to determine KP index.**

**Cytology** - Maternal cells which have desquamated from vagina during pregnancy have been employed to assess the hormonal status of the pregnancy. An inverse relationship between number of cells with pyknotic nuclei and estriol level has been reported. Risk of abortion increases with rising level of K P index. The value of hormone cytology has not been fully established.

**Enzymes:**

**Alkaline phosphatase:**

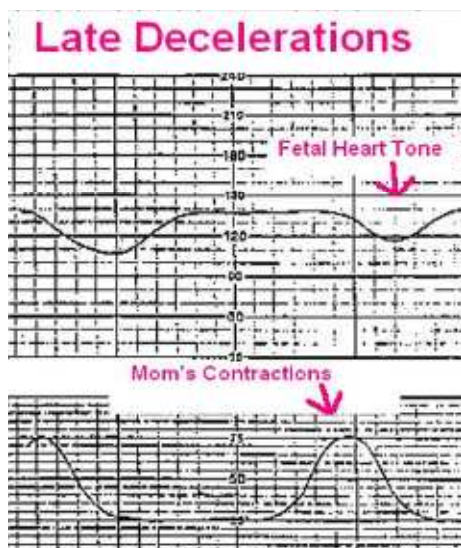
Heat stable alkaline phosphatase is produced by the placenta and has been used for assessment of placental function. There is considerable increase in alkaline phosphatase production in pregnancy the non gestational enzyme is destroyed by heat, while the placental alkaline phosphatase when heated at 60°C for 30 minutes remains stable. If there is a progressive increase in the heat stable enzyme level the fetal prognosis is



generally good. Diamine Oxidase - This enzyme is produced in large amounts during pregnancy and its level increases with advancing gestation. If the level is persistently low, missed abortion is strongly suspected. This test is useful in diagnosing the pregnancy in the first and second trimester.

**Oxytocinase** - It is produced by the placenta. The enzyme levels are low in missed abortion and intrauterine death. While the levels are high in cases of prolonged pregnancy, and multiple pregnancy.

**Cardiotachometry** - Fetal heart auscultation is widely used as a clinical method for assessing the fetal well being. When persistent bradycardia is present at the end of the uterine contraction, this is generally indicative of fetal distress.



**Electronic heart rate monitoring** - Hon and his colleagues have clearly demonstrated variations in the fetal heart beats by electronic instrumentations. The interval between fetal heart beats and even, measurement of distance between one fetal R waves to the other has been mastered.

The fetal electrocardiography can help to time the interval between two R waves. Intravaginal use of scalp electrode is required for such recording, which is an invasive technique, and therefore not very practical. The precision afforded by electronic technique is far exceeded from human ear. The student will realize that there is fluctuation in the heart rate baseline, which is not detectable clinically. It is a normal phenomenon, and reflects the balance between vagal and sympathetic tone, and occurs at a frequency of about 3 to 5 cycles per minute. The variation in the rate can range up to 10 per cent of the baseline rate. When this variability in rate, which is normal, is absent, certain pathological conditions can be expected. Some of these conditions include prolonged hypoxia, vagal blockage by effect of atropine, and immaturity of the autonomic nervous system.

**Patterns of heart rate deceleration** - Hon has described three different patterns of fetal heart rate according to its relationship with the peak of the uterine contraction. These patterns are early deceleration, late deceleration and variable deceleration, also described by others as Type-I, Type-II and Type-III dips respectively.

**Early deceleration** - This pattern of fetal heart bradycardia coincides with onset of the uterine contraction. As soon as the uterine contraction subsides, the fetal heart rate returns to its normal baseline. The wave produced by early deceleration is uniform in shape. Such decelerations are innocent and result due to head compression.

**Late deceleration** - They start after the uterine contraction. The bradycardia

continues after the end of the uterine contraction. These decelerations are always pathological and occur as a result of fetal hypoxia.

**Variable deceleration** - They do not have any set pattern of onset. Their relationship contraction is not fixed. Even the wave is variable in shape. If variable exists for longer period, they indicate fetal distress.

**Oxytocin stress test** - This test is based on electronic monitoring of the fetal heart rate and its response to a series of uterine contractions induced by weak oxytocin infusion. The change in fetal heart rate in response to induced uterine activity adequately demonstrates the placental and fetal reserves. When there is lack of placental reserve to maintain adequate oxygenation during this test, it indicates that the fetus is unable to tolerate the stress of normal labor.

**Biochemical assessment** - Biochemical assessment of the fetus in utero can not be carried out without adopting invasive techniques. The fetal blood can be obtained by scalp puncture and reveal PH, P02, pe02 and base excess. The fall in pH and base excess shows pyruvate and lactate production from glycogen stores by anaerobic metabolism. PH values below 7.2 reflect severe fetal hypoxia. Single pH value is less useful than serial, as it may reflect maternal acidosis. PH measurements can be applied for management in high risk pregnancies.

#### **Biophysical method:**

(Ultrasonography) - proper timing of delivery in pregnancy complicated by high risk factor is required, if better

outcome of the mother and neonate is to be expected.

The rate of fetal growth and maturity can be measured from the fetal biparietal diameter (details of this technique have been provided under separate heading on Ultrasonography)

**Ultrasonography:** This is a noninvasive procedure that is harmless to both the fetus and the mother. High frequency sound waves are utilized to produce visible images from the pattern of the echoes made by different tissues and organs, including the baby in the amniotic cavity. The developing embryo can first be visualized at about 6 week's gestation. Recognition of the major internal organs and extremities to determine if any are abnormal can best be accomplished between 16 to 20 weeks gestation. Although an ultrasound examination can be quite useful to determine the size and position of the fetus, the size and position of the placenta, the amount of amniotic fluid, and the appearance of fetal anatomy, there are limitations to this procedure. Subtle abnormalities may not be detected until later in pregnancy, or may not be detected at all. A good example of this is Down syndrome (trisomy 21) where the morphologic abnormalities are often not marked, but only subtle, such as nuchal thickening.

The biparietal diameter increases by about 1.6 to 1.8 mm per week. This technique provides reproducible physical assessment of intrauterine growth and can be correlated with biochemical and endocrinological technique for assessing fetal health. Other indications for use of ultrasound scan will be discussed in chapter on imaging in pregnancy.

### **Amniocentesis:**

Transabdominal amniocentesis has greatly facilitated our access to several fetal conditions. Various fetal components such as amniotic fluid phospholipid, creatinine, sugar, amino acid, pH and osmolality can be used in determination of fetal maturity. Similarly assessment and management of the Rh isoimmunization can be carried out by measuring amniotic fluid bilirubin. This is an invasive procedure in which a needle is passed through the mother's lower abdomen into the amniotic cavity inside the uterus. Enough amniotic fluid is present for this to be accomplished starting about 14 week's gestation. For prenatal diagnosis, most amniocenteses are performed between 14 and 20 weeks gestation. However, an ultrasound examination always precedes amniocentesis in order to determine gestational age, the position of the fetus and placenta, and determine if enough amniotic fluid is present. Within the amniotic fluid are fetal cells (mostly derived from fetal skin) which can be grown in culture for chromosome analysis, biochemical analysis, and molecular biologic analysis. In the third trimester of pregnancy, the amniotic fluid can be analyzed for determination of fetal lung maturity. This is important when the fetus is below 35 to 36 weeks gestation, because the lungs may not be mature enough to sustain life. This is because the lungs are not producing enough surfactant. After birth, the infant will develop respiratory distress syndrome from hyaline membrane disease. The amniotic fluid can be analyzed by fluorescence polarization (fpol), for lecithin: sphingomyelin (LS) ratio, and/or for phosphatidyl glycerol (PG). Risks with

amniocentesis are uncommon, but include fetal loss and maternal Rh sensitization. The increased risk for fetal mortality following amniocentesis is about 0.5% above what would normally be expected. Rh negative mothers can be treated with Rho GAM. Contamination of fluid from amniocentesis by maternal cells is highly unlikely. If oligohydramnios is present, then amniotic fluid cannot be obtained. It is sometimes possible to instill saline into the amniotic cavity and then remove fluid for analysis.

Fetal cells can be examined for sex chromatin and used in managing pregnancy, where sex linked recessive disorders, such as haemophilia, muscular dystrophy, and Hunter's disease is suspected. Similarly chromosomal abnormality, such as Down's Syndrome can be diagnosed by karyotyping after culturing the fetal cells. Certain metabolic disorders, such as adrenogenital syndrome and Tay Sachs' disease can be diagnosed by detecting increase in 17-Ketosteroids, pregnanetriol and deficiency of hexosaminidase

A number of other congenital disorders can be detected by this technique. In my opinion such studies should be undertaken in certain conditions i.e. a woman who has previously delivered an abnormal infant, particularly trisomy 21, and where one parent is carrier of known chromosomal disorder. In Pakistan there is no laboratory support as yet to carry out such studies. Hopefully in the near future such screening techniques will be introduced. An informed consent must be obtained from the patient before carrying out this invasive procedure. (The sample of consent form is shown in Annexure I).

**Amniography** - In this technique radio-paque water soluble material is injected into the amniotic fluid. Abnormalities of gastrointestinal tract of the baby can be diagnosed. Similarly defects in the uterine cavity and position of the placenta can be localised. This method of assessment is not recommended for clinical use, because of in-vasive nature and side effects.

**Amnioscopy** - Specially designed endoscope can be inserted into cervical canal to the level of the internal os. The colour of the fluid can be examined along with its contents with intact amniotic sac. When the amniotic fluid is greenish due to the presence of meconium it suggests fetal distress.

**Tests for fetal maturity** - In most high risk pregnancies, decision about prolonging or interruption requires reliable means for assessing fetal maturity direct objective methods for assessment of fetal maturity are full of fraud, therefore indirect objective measurements for gestational age are of great importance. The level of correct diagnosis depends upon cumulative results of tests performed simultaneously, rather than a single ultrasonographic, Radiological or biochemical test. The student must realize that all physiological functions of the fetus may not mature according to a predictable time table.

**Brosens and Gordon orange stained cell test –**

This test is based on the principle that lipid substances appear in the fetal cells at a certain period of maturity. These cells stain orange colour when treated with 0.1 per cent Nile blue sulphate. The percentage of these orange colour cells

increases sharply after 38 weeks of pregnancy, and is related to the functional maturity of sebaceous glands and fetal skin.

**Creatinine concentration:**

Concentration of creatinine in the amniotic fluid remains constant up to 34 weeks of pregnancy and then progressively rises. A level of 2 mg/100 ml of amniotic fluid is found after 37th week. This is dependent upon fetal kidney maturity and is fairly reliable test for assessment of fetal age in utero.

**Bilirubin** - It is possible to measure very small quantity of bilirubin pigment in the amniotic fluid with the help of a spectrophotometer, where the bilirubin concentration can be measured by measuring the optical density peak at 450 milli micron. The importance of measuring bilirubin in amniotic fluid for Rh. disease has been discussed separately.

In normal pregnancy the bilirubin level decreases progressively, in later weeks of pregnancy and at 36th week most patients show no bilirubin. This indicates ability and maturity of fetal liver to conjugate bilirubin.

**Lecithin sphingomyelin ratio** - Lecithin is a phospholipid which lowers the surface tension, present at the alveolar surface, and thus helps in reducing force required for expansion of the lungs at birth. This substance has been referred in literature as surfactant. Fetal lung tissue produces both sphingomyelin and lecithin. The concentration of these two phospholipids in the amniotic fluid is equal before the lungs mature. However, the level of Sphingomyelin falls after

35 weeks of pregnancy and therefore the ratio of lecithin and sphingomyelin goes in favor of lecithin. For clinical purposes a ratio of 1:1 indicates prematurity, while ratio of 1.5:1 indicates intermediate maturity, and a ratio of 2:1 or more in favor of lecithin indicates fetal lung maturity. Conditions in which the dilution is affected in the amniotic fluid such as in hydramnios or oligohydramnios. The concentration of bilirubin and creatinine should be interpreted carefully. Fortunately as may be the case with bilirubin and creatinine.

### **Chorionic villus sampling (CVS):**

In this procedure, a catheter is passed via the vagina through the cervix and into the uterus to the developing placenta under ultrasound guidance. Alternative approaches are transvaginal and transabdominal. The introduction of the catheter allows sampling of cells from the placental chorionic villi. These cells can then be analyzed by a variety of techniques. The most common test employed on cells obtained by CVS is chromosome analysis to determine the karyotype of the fetus. The cells can also be grown in culture for biochemical or molecular biologic analysis. CVS can be safely performed between 9.5 and 12.5 weeks gestation. CVS has the disadvantage of being an invasive procedure, and it has a small but significant rate of morbidity for the fetus; this loss rate is about 0.5 to 1% higher than for women undergoing amniocentesis. Rarely, CVS can be associated with limb defects in the fetus. The possibility of maternal Rh sensitization is present. There is also the possibility that maternal blood cells in the developing placenta will be sampled instead of fetal cells and confound chro-

mosome analysis. Maternal blood sampling for fetal blood cells. This is a new technique that makes use of the phenomenon of fetal blood cells gaining access to maternal circulation through the placental villi. Ordinarily, only a very small number of fetal cells enter the maternal circulation in this fashion (not enough to produce a positive Kleihauer-Betke test for fetal maternal hemorrhage). The fetal cells can be sorted out and analyzed by a variety of techniques to look for particular DNA sequences, but without the risks that these latter two invasive procedures inherently have. Fluorescence in-situ hybridization (FISH) is one technique that can be applied to identify particular chromosomes of the fetal cells recovered from maternal blood and diagnose aneuploid conditions such as the trisomies and monosomy X. The problem with this technique is that it is difficult to get many fetal blood cells. There may not be enough to reliably determine anomalies of the fetal karyotype or assay for other abnormalities.

### **Maternal serum alpha fetoprotein (MSAFP):**

The developing fetus has two major blood proteins albumin and alpha-fetoprotein (AFP). Since adults typically have only albumin in their blood, the MSAFP test can be utilized to determine the levels of AFP from the fetus. Ordinarily, only a small amount of AFP gains access to the amniotic fluid and crosses the placenta to mother's blood. However, when there is a neural tube defect in the fetus, from failure of part of the embryologic neural tube to close, then there is a means for escape of more AFP into the amniotic fluid. Neural tube defects include anencephaly (failure of closure

at the cranial end of the neural tube) and spina bifida (failure of closure at the caudal end of the neural tube). The incidence of such defects is about 1 to 2 births per 1000 in the United States. Also, if there is an omphalocele or gastroschisis (both are defects in the fetal abdominal wall), the AFP from the fetus will end up in maternal blood in higher amounts. In order for the MSAFP test to have the great utility, the gestational age must be known with certainty. This is because the amount of MSAFP increases with gestational age (as the fetus and the amount of AFP produced increase in size). Also, the race of the mother and presence of gestational diabetes are important to know, because the MSAFP can be affected by these factors. The MSAFP is typically reported as multiples of the mean (MoM). The greater the MoM, the more likely a defect is present. The MSAFP has the greatest sensitivity between 16 and 18 weeks gestation, but can still be useful between 15 and 22 weeks gestation. However, the MSAFP can be elevated for a variety of reasons which are not related to fetal neural tube or abdominal wall defects, so this test is not 100% specific. The most common cause for an elevated MSAFP is a wrong estimation of the gestational age of the fetus. Using a combination of MSAFP screening and ultrasonography, almost all cases of anencephaly can be found and most cases of spina bifida. Neural tube defects can be distinguished from other fetal defects (such as abdominal wall defects) by use of the acetylcholinesterase test performed on amniotic fluid obtained by amniocentesis the acetylcholinesterase is elevated along with MSAFP then a neural tube defect is likely. If the acetylcholinesterase is not detectable, then some other fetal defect is suggested.

This student is advised to note that the genetic polymorphisms due to mutations in the methylene tetrahydrofolate reductase gene may increase the risk for NTDs. Folate is a cofactor for this enzyme, which is part of the pathway of homocysteine metabolism in cells. The C677T and the A1298C mutations are associated with elevated maternal homocysteine concentrations and an increased risk for NTDs in fetuses. Prevention of many neural tube defects can be accomplished by supplementation of the maternal diet with only 4 mg of folic acid per day, but this vitamin supplement must be taken a month before conception and through the first trimester.

The MSAFP can also be useful in screening for Down syndrome and other trisomies. The MSAFP tends to be lower when Down syndrome or other chromosomal abnormalities is present.

### **Inhibin A:**

Inhibin is secreted by the placenta and the corpus luteum. Inhibin A can be measured in maternal serum. An increased level of inhibin A is associated with an increased risk for trisomy 21. A high inhibin-A may be associated with a risk for preterm delivery. Pregnancy associated plasma protein A (PAPP-A). Low levels of PAPP A as measured in maternal serum during the first trimester may be associated with fetal chromosomal anomalies including trisomies 13, 18, and 21. In addition, low PAPP-A levels in the first trimester may predict an adverse pregnancy outcome, including a small for gestational age (SGA) baby or stillbirth. A high PAPP A level may predict a large for gestational age (LGA) baby. "Triple" or "Quadruple"

screen combining the maternal serum assays may aid in increasing the sensitivity and specificity of detection for fetal abnormalities. The classic test is the triple screen for alpha fetoprotein (MSAFP), beta-HCG, and estriol (uE3). The "quadruple screen" adds inhibin A.

Condition	MSAFP	uE3	HCG
Neural tube defect	Increased	Normal	Normal
Trisomy 21	Low	Low	Increased
Trisomy 18	Low	Low	Low
Molar pregnancy	Low	Low	Very High
Multiple gestation	Increased	Normal	Increased
Fetal death (stillbirth)	Increased	Low	Low

### Gross examination:

The most important procedure to perform is simply to look at the fetus or fetal parts. Obviously, examination of an intact fetus is most useful, though information can still be gained from examination of fetal parts. The pattern of gross abnormalities can often suggest a possible chromosomal abnormality or a syndrome. Abnormalities can often be quite subtle, particularly the earlier the gestational age. Consultations are obtained with clinical geneticists to review the findings. A description of the findings is put into a report (surgical pathology or autopsy). Examination of the placenta is very important, because the reason for the fetal loss may be a placental problem.

**Microscopic examination:** Microscopic findings are generally less useful than

gross examination for the fetus, but microscopic examination of the placenta is important. Microscopy can aid in determination of gestational age (lung, kidney maturity), presence of infection, presence of neoplasia, or pre-sence of "dysplasia" (abnormal organo-genesis).

**Radiography:** Standard anterior-posterior and lateral radiographic views are essential for analysis of the fetal skeleton. Radiographs are useful for comparison with prenatal ultrasound, and help define anomalies when autopsy consent is limited, or can help to determine sites to be examined microscopically.

**Microbiologic culture:** Culture can aid in diagnosis or confirmation of congenital infections. Examples of congenital infection include: T - toxoplasmosis, O - other, such as *Listeria monocytogenes*, group B streptococcus, syphilis, R - rubella C - cytomegalovirus, H - herpes simplex or human immunodeficiency virus (HIV) cultures have to be appropriately obtained with the proper media and sent with the proper requisitions ("routine" includes aerobic and anaerobic bacteria; fungal and viral cultures must be separately ordered). Viral cultures are difficult and expensive. Separate media and collection procedures may be necessary depending upon what virus is being sought. Bacterial contamination can be a problem.

**Karyotyping:** Tissues must be obtained as fresh as possible for culture and without contamination. A useful procedure is to wash the tissue samples in sterile saline prior to placing them into cell culture media. Tissues with the best chance for growth are those with the

least maceration: placenta, lung, and diaphragm. Obtaining tissue from more than one site can increase the yield by avoiding contamination or by detection of mosaicism.

**FISH (performed on fresh tissue or paraffin blocks):**

In addition to karyotyping, fluorescence in situ hybridization (FISH) can be useful. A wide variety of probes are available. It is useful for detecting aneuploid conditions (trisomies, monosomies). Fresh cells are desirable, but the method can be applied even to fixed tissues stored in paraffin blocks, though working with paraffin blocks is much more time consuming and interpretation can be difficult. The ability to use FISH on paraffin blocks means that archival tissues can be examined in cases where karyotyping was not performed, or cells didn't grow in culture. FISH technique diagram and FISH abnormalities, diagram.

**DNA Probes:**

Fetal cells obtained via amniocentesis or CVS can be analyzed by probes specific for DNA sequences. One method employs restriction fragment length polymorphism (RFLP) analysis. This method is useful for detection of mutations involving genes that are closely linked to the DNA restriction fragments generated by the action of an Endonuclease. The DNA of family members is analyzed to determine differences by RFLP analysis. In some cases, if the DNA sequence of a gene is known, a probe to a DNA sequence specific for a genetic marker is available, and the polymerase chain reaction (PCR) technique can be applied for diagnosis.

There are many genetic diseases, but only in a minority have particular genes been identified, and tests to detect them have been developed in some of these. Thus, it is not possible to detect all genetic diseases. Moreover, testing is confounded by the presence of different mutations in the same gene, making testing more complex.

**Biochemical analysis:**

Tissues can be obtained for cell culture or for extraction of compounds that can aid in identification of inborn errors of metabolism. Examples include: Long-chain fatty acids (adrenoleukodystrophy) amino acids (aminoacidurias).

**Flow cytometry:**

Flow cytometry is useful only for determination of the amount of DNA and can yield no information about individual chromosomes with aneuploidy. Thus, the condition that flow cytometry can routinely detect is triploidy.

Very little sample (0.1 gm) is required. The technique can also be applied to fixed tissues in paraffin blocks.

**Electron microscopy:** Rarely used and requires prompt fixation with no maceration. Examples of conditions to be diagnosed with EM include: mitochondrial myopathies and viral infections.

**Overview of fetal placental abnormalities:**

**Chromosomal abnormalities:**

The risk for chromosomal abnormalities increases with increasing maternal age, mainly because non dysfunctional events



in meiosis are more likely, and result in trisomies. The table below indicates the relative risk of having a baby with various trisomies based upon maternal age: Listed below are some of the more common chromosomal abnormalities that can occur. The descriptions are for the completely abnormal condition in which all fetal cells contain the abnormal karyotype. Bear in mind that "mosaicism" can occur. A "mosaic" is a person with a combination of two cell lines with different karyotype (normal and abnormal). When karyotyping is performed, multiple cells are analyzed to rule out this possibility.

<b>Maternal Age</b>	<b>Trisomy 21</b>	<b>Trisomy 18</b>	<b>Trisomy 13</b>
<b>15 – 19</b>	<b>1:1600</b>	<b>1:17000</b>	<b>1:33000</b>
<b>20 – 24</b>	<b>1:1400</b>	<b>1:14000</b>	<b>1:25000</b>
<b>25 – 29</b>	<b>1:1100</b>	<b>1:11000</b>	<b>1:20000</b>
<b>30 – 34</b>	<b>1:700</b>	<b>1:7100</b>	<b>1:14000</b>
<b>35 – 39</b>	<b>1:240</b>	<b>1:2400</b>	<b>1:4800</b>
<b>40 – 44</b>	<b>1:70</b>	<b>1:700</b>	<b>1:1600</b>
<b>45 – 49</b>	<b>1:20</b>	<b>1:650</b>	<b>1:1500</b>

An example would be a Turner's mosaic, with a 45, X/46, XX karyotype, with some cells having the abnormal karyotype and some cells having a normal karyotype. The mosaic condition is not as severe as the completely abnormal karyotype, and the features may not be as marked, and live births may be possible. Sometimes the mosaicism is confined to the placenta ("confined placental mosaicism"). A placenta with an abnormal karyotype (confined placental mosaicism) may lead to

stillbirth, even though the fetus has a normal karyotype; conversely, a placenta with a normal karyotype may allow longer survival for a fetus with a chromosomal abnormality. Rarely, a translocation of part of one chromosome to another in the parent will be passed on to the child as a partial trisomy (such as 6p+ or 16p+) which may not be as severe as a complete trisomy. Trisomy 21: Down syndrome; incidence based upon maternal age, though translocation type is familial; features can include: epicanthal folds, simian crease, brachycephaly, cardiac defects. Trisomy 21 (47, XY, +21) karyotype, diagram Trisomy 21, facial features, gross, Trisomy 21, abnormal creases, hands, gross, Trisomy syndrome, cystic Hassall's corpuscles in thymus, medium power microscopic and trisomy 18: Features include micrognathia, overlapping fingers, horseshoe kidney, rocker bottom feet, cardiac defects, diaphragmatic hernia, omphalocele. Trisomy 18 (47, XY, +18) karyotype, diagram, Clenched hand with trisomy 18, gross and diaphragmatic hernia, gross. Trisomy 13: Features include microcephaly, cleft lip and/or palate, polydactyly, cardiac defects, holoprosencephaly. Trisomy 18 (47, XY, +18) karyotype, diagram, Trisomy 18, facial features, gross, Clenched hand with trisomy 18, gross and diaphragmatic hernia, gross. Trisomy 16: Seen in abort uses from first trimester. Never liveborn. Trisomy 16 karyotype, diagram. Monosomy X: Turner's syndrome; can survive to adulthood; features include short stature, cystic hygroma of neck (leading to webbing), infertility, coarctation. Monosomy X, or Turner's syndrome (45, X) karyotype, diagram, Monosomy X, or Turner's syndrome, streak ovaries in adult, gross, Massive

fetal hydrops with monosomy X, or Turner's syndrome, gross and Cystic hygroma with monosomy X, or Turner's syndrome, gross. XXY: Klinefelter's syndrome; features include elongated lower body, gynecomastia, testicular atrophy (incidence: 1/500 males). Klinefelter's syndrome karyotype, diagram. Triploidy: There is often a partial hydatidiform mole of placenta. Fetal features include 3-4 syndactyly, indented nasal bridge, small size.

Triploidy karyotype, diagram, Partial hydatidiform mole gross and 3-4 syndactyly with triploidy, gross. A host of other chromosomal abnormalities are possible. In general, fetal loss earlier in gestation, and multiple fetal losses, more strongly suggests a possible chromosomal abnormality.

### **Neural tube defects:**

The maternal serum alpha-fetoprotein (MSAFP) is useful for screening for neural tube defects, but the gestational age must be known for proper interpretation. The frequency of neural tube defects has been shown to be reduced if women supplement their diet with folic acid (before and during pregnancy). Anencephaly: There is absence of the fetal cranial vault, so no cerebral hemispheres develop. Anencephaly is the most common congenital malformation about 0.5 to 2/ 1000 live births. Other neural tube defects are as frequent, but the incidence varies with geography. Anencephaly, gross and Anencephaly, gross. Iniencephaly: Imperfect formation of the base of the skull, with rachischisis and exaggerated lordosis of the spine. Iniencephaly gross. Iniencephaly, gross Exencephaly: Incomplete cranial vault, but the brain is present.

Exencephaly, gross. Meningomyelocele: Defect in the vertebral column allowing herniation of meninges and spinal cord; location and size determine severity.

Meningomyelocele gross and Meningomyelocele gross. Encephalocele: Herniation of brain through a skull defect. Occipital encephalocele, radio-graph and occipital encephalocele with iniencephaly, gross Spina bifida: A defective closure of the posterior vertebral column. It may not be open (spina bifida occulta).

### **Hydrops fetalis:**

There are many causes for fetal hydrops, and in about 25 to 30% of cases, no specific cause for hydrops can be identified. Multiple congenital anomalies can also be associated with hydrops, though the mechanism is obscure for everything except cardiac anomalies that produce heart failure.

Hydrops can be classified as immune and non immune. Immune causes such as Rh incompatibility between mother and fetus are now uncommon.

Non-immune causes can include: Congenital infections, Cardiac anomalies, Chromosomal abnormalities, fetal neoplasms, Twin pregnancy, fetal anemia and other anomalies (pulmonary, renal, and gastrointestinal).

**Congenital infections:** The hallmark of congenital infections is fetal hydrops along with organomegaly. Diagnosis can depend upon: TORCH titers, Tissue culture and Histologic examination.

**Disruptions:** It is becoming increasingly recognized that many fetal abnormalities

result from problems with embryogenesis early on. Some of these abnormalities may involve problems with vascular supply. The result is abnormal formation of a body region or regions. Such disruptions are generally asymmetric. Examples may include: Limb Body Wall Complex (amniotic band syndrome): Omphalocele, gross, Gastroschisis, gross. Amniotic bands, gross, Limb body wall (LBW) complex, gross, Limb body wall (LBW) complex, gross.

### **Sirenomelia:**

Sirenomelia, gross and Sirenomelia, gross. Hydranencephaly: Hydranencephaly, gross.

### **Renal cystic disease:**

For examples of these diseases, go to the tutorial on renal cystic disease. Recessive Polycystic Kidney Disease (RPKD). This condition is inherited in an autosomal recessive pattern, giving a 25% recurrence risk for parents having subsequent children. The kidneys are affected bilaterally, so that in utero, there is typically oligohydramnios because of poor renal function and failure to form significant amounts of fetal urine.

The most significant result from oligohydramnios is pulmonary hypoplasia, so that newborns do not have sufficient lung capacity to survive, irrespective of any attempt to treat renal failure. RPKD may be termed "Type I" cystic disease in the Potter's classification. A helpful finding at autopsy is the presence of congenital hepatic fibrosis, which accompanies RPKD.

### **Multicystic renal dysplasia:**

This condition has a sporadic inheritance pattern. It is perhaps the most common form of inherited cystic renal disease. It results from abnormal differentiation of the metanephric parenchyma during embryologic development of the kidney. However, in many cases it can be unilateral, so the affected person survives, because one kidney is more than sufficient to sustain life. In fact, with absence of one functional kidney from birth, the other kidney undergoes compensatory hyperplasia. Multicystic renal dysplasia is often the only finding, but it may occur in combination with other anomalies and be part of a syndrome (e.g., Meckel-Gruber syndrome), in which case the recurrence risk will be defined by the syndrome. If this disease is bilateral, the problems associated with oligohydramnios are present. Multicystic renal dysplasia was termed "Type II" in the Potter classification. There are two main subgroups. If the affected kidney is large, then it is termed "Type IIa". If the affected kidney is quite small, it can be termed "hypo dysplasia" or "Type IIb". Different combinations are possible, so that only one kidney or part of one kidney can be affected and be either larger or small; both affected kidneys can be large or both can be small, or one can be larger and the other small. It is quite common for asymmetry to be present.

**Dominant polycystic kidney disease (DPKD):** This condition is inherited in an autosomal dominant pattern, so the recurrence risk in affected families is 50%. However, this disease rarely manifests itself before middle age. It may begin in middle aged to older adults to

cause progressive renal failure as the cysts become larger and the functioning renal parenchyma smaller in volume. This is the "Type III" cystic disease in the Potter classification, but it is rarely manifested prenatally or in children.

**Cystic change with obstruction:**

In the fetus and newborn with urinary tract obstruction, it is possible for cystic change to occur in the kidneys, in addition to hydronephrosis, hydronephrosis, and bladder dilation. Depending upon the point of obstruction, either or both kidneys may be involved. For example, posterior urethral valves in a male fetus, or urethral atresia in a male or female fetus, will cause bladder outlet obstruction so that both kidneys are involved. With bladder outlet obstruction, there will be oligohydramnios and the appearance of pulmonary hypoplasia. N Grossly, this form of cystic disease may not be apparent. The cysts may be no more than 1 mm in size. Microscopically, the cysts form in association with the more sensitive developing glomeruli in the nephrogenic zone so that the cysts tend to be in a cortical location. Thus, "cortical microcysts" are the hallmark of this form of cystic disease, which is "Type IV" in the Potter's classification. There are no accompanying cystic changes in other organs in association with this disease.

**Congenital neoplasms:** Such tumors are uncommon, but those that are seen most frequently include: Teratoma. These tumors occur in midline regions (sacroccygeal, cerebral, and nasopharyngeal). Nasopharyngeal teratoma, gross: Tera-toma, low power microscopic and immature teratoma, medium power microscopic. Hemangioma. About 1/3 of all soft tissue neoplasms in the first year

of life are hemangiomas or lymphangiomas. Fibromatoses are also common. Hemangioma, gross and Hemangioma, microscopic. Neuroblastoma.

The incidence of congenital neuroblastoma is 1:8000. Neuroblastoma, gross. Neuroblastoma, microscopic. Size and location are important, for even histologically benign neoplasms can obliterate normal tissues, be difficult to resect, or recur with incomplete resection. Malignant neoplasms have the capacity for invasion and metastases.

**Skeletal abnormalities:**

Ultrasound may reveal long bones that are short-ened. There are several possibilities, including short limbed dwarfism, osteogenesis imperfecta, and short rib polydactyly syndrome. The various forms of short limbed dwarfism, which can be lethal, are more difficult to diagnose specifically. The features of these various conditions may not be well developed at 20 weeks gestation or less, making diagnosis more difficult. Limitation of survival is often due to pulmonary hypoplasia because the chest cavity is too small. Achondroplasia is a form of short-limbed dwarfism that is inherited in an autosomal dominant fashion, though in most cases there is no affected parent and the disease is due to a new mutation. The homozygous form of the disease is lethal. The heterozygous form is not lethal, and affected persons can live a normal life. They have short extremities, but a relatively normal sized thorax and normal sized head. Thanatophoric dysplasia (TD) is a lethal condition. The long bones are short and curved, with femora that have a "telephone receiver" appearance on radiograph because of the curvature. The vertebrae

have marked platyspondyly with widened disc spaces. There are two forms, TD 1 and TD 2, with the latter distinguished by the appearance of a "cloverleaf" pattern to the skull. Osteogenesis imperfecta occurs in several forms. There is a lethal perinatal form in which fractures appear in long bones even in utero. This condition is due to an abnormal synthesis of type 1 collagen that forms connective tissues, including bone matrix. Thanatophoric dysplasia, radiograph and osteogenesis imperfecta, radiograph.

### **Placental abnormalities:**

Abruptio placenta: Premature separation of the placenta near term, with retroplacental blood clot. Abruptio placenta, gross: Placenta previa: Low lying implantation site can lead to hemorrhage during delivery. Velamentous insertion: Cord vessels splay out in the membranes before reaching the placental disk and predispose to traumatic rupture. Velamentous insertion, gross, long short cord: Umbilical cord length is determined by the amount of fetal movement. More movement increases cord length.

A long cord can become entangled with the baby or more easily prolapse. Nuchal cord, gross, true knot of umbilical cord, gross and twin placenta: Monozygous twinning is associated with increased risk for both abnormalities and accidents.

A twin transfusion syndrome can occur when a vascular anastomosis is present: Vascular anastomosis in placenta, gross, vascular anastomosis in placenta, gross and hypertension: Vascular changes can be associated with pregnancy induced hypertension (PIH) and the more severe

complications of eclampsia and preeclampsia. Decidual arteriopathy, microscopic.

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## Chapter No: 16

**IMMAGING IN PREGNANCY**

**X-Ray Pelvimetry** - X-Ray Pelvimetry is a valuable aid in predicting the course of labour by providing assessment of tube pelvic capacity. This can be possible if the procedure is performed by an experienced person who is fully aware of the danger of radiation to the fetus and, the films are interpreted jointly by the obstetrician and the radiologist.



**Fig16.1: Shows X-ray of pelvis AP views.**

There is considerable danger of exposing the fetus and the maternal gonads to the hazards of radiation therefore this examination should be done with great reservation and only when absolute indications are present. Certain clinical circumstances can point to the probability of pelvic contraction or potential dystocia. It is only in such cases that the X-Ray pelvimetry should be done. The type of pelvis and measurements of its diameters, the size of the fetal head, its presentation and position can all be determined with this method. This information is very vital for the obstetrician in making decision for a safe vaginal delivery. With this information at hand the physician is forewarned and therefore forearmed to deal with problems arising due to faults in pelvic capacity. He can avoid unnecessary use

of oxytocin to correct faults of forces and thus stop trial of labour at proper time.

There is no place for routine pelvimetry in modern obstetrical practice. The student must appreciate that; for a full radiological pelvimetry four films are taken i.e. one lateral film in standing position, the supero-inferior view of the brim (Thom's view), the anteroposterior view and the subpubic arch or outlet view. Generally Thom's superoinferior view is not taken in routine pelvimetry, this helps to reduce the amount of radiation.

Since the information provided by good radiographs of the pelvis can be of great help in the conduct of a trial of labour or of a trial of forceps, pelvimetry has a definite place in cases where genuine indication is present.

It provides opportunity for measurement of various pelvic diameters which can not be determined by other means. Measurement of transverse diameter of the inlet and the antero-posterior Nd interspinous diameters of the mid pelvis and the outlet is very important since it is at these points where the arrest in progress of labour usually occurs and their precise measurement can be very helpful in guiding the physician, who is contemplating difficult forceps operation.

In any given case the progress of labour can be predicted on the basis of the size and shape of the bony pelvis, the size of the fetal head; the force of the uterine contraction and the presentation and

position of the head. The student should realize that only one of these factors is amenable to precise radio-logical measurement, therefore X-Ray Pelvimetry should be regarded as an adjunct in patients who are suspected of having difficult labour due to contracted pelvis.

### **Limitations of pelvimetry:**

The student should note that this diagnostic procedure is not simple like chest X-Ray. There are often technical difficulties and errors in measurements of pelvic diameters. Measurements are not sufficiently accurate to be used as a routine in diagnosis of disproportion, especially if the radiographer reads his films alone. In my opinion the I Pelvimetry must be interpreted jointly by the obstetrician and an experienced radiologist, who is familiar with the image magnification factor and risk of ionizing radiation.

### **Indications:**

Some of the accepted indications for radiological pelvimetry are primigravidas with clinical evidence of disproportion and free head near term. Women who have disease of the hip, pelvis or lower spine. Breech presentation in Primigravida where engagement has failed to occur during labour.

### **Other relative indications for Pelvimetry are:**

Multipara with a history of difficult labour or stillbirth or Neonatal death due to intracranial hemorrhage. Previous history of severe maternal injury following difficult forceps, previous

caesarean Section for suspected disproportion.

### **Clinical suspicion of disproportion -**

When the examiner can touch sacral promontory easily on vaginal examination (this means the diagonal conjugate is less than 11.5 cm) when the ischial spines are prominent and pelvic side-walls are converging, the sacrum is flat, the subpubic angle is narrow and the intertuberous diameter is short or the progress of labour is slow, even with good uterine contractions, or when malpresentation such as breech, face and brow are discovered pelvimetry is definitely indicated.

### **Standing lateral (Isometric Film) -**

The measurements which can be easily obtained from this view; are the anteroposterior diameters of the inlet, midplane and the outlet. The posterior sagittal diameters of these planes can also be measured. A metal ruler when placed in one of these planes is subjected to the same magnification and distortion as the pelvic diameters, therefore its image is used to measure these diameters by directly applying the principle of isometric scale. During difficult labour elongation of the head occurs as a result of moulding. The caput succedaneum makes digital findings misleading, therefore lateral view of the pelvis can prove very useful. The X-Ray film is obtained while the patient is standing during the course of labour.

This will provide important and accurate information about the descent or lack of descent of the biparietal diameter of the head, in the presence of good strong and regular uterine contractions.



### **The Procedure:**

The patient stands in a symmetric profile position with her side against the vertical Bucky diaphragm of the X-Ray machine. The X-Ray tube is centered just above the femoral trochanters. The tube-film distance is kept at 36 inches. A metallic perforated ruler is placed close to the sacrum or symphysis pubis in the midsagittal plane of the patient. It is kept parallel to the film. An experienced radiographer keeps the thickness of the patient in mind while exposing his patient to the amount of radiation necessary for a good quality X-Ray film.

The lateral isometric film provides quite accurate measurement of the obstetric conjugate and helps to rule out the inlet contraction. Such a film can be obtained by a standard X-Ray machine, the only special equipment needed is a metal ruler with centimeter notches or perforations. A review of the contours and bony anatomy of the lateral view of the pelvis will facilitate location of the symphysis, sacrum, and ischial spines. This can be easily accomplished with a little practice.

### **Technique of measurement**

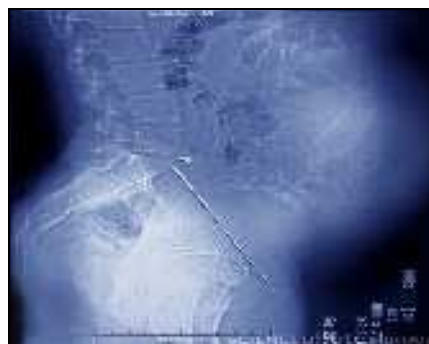
#### **The Lateral Film:**

Any diameter can be measured by measuring the area between two end points which are visible on the X-Ray film. The image of the centimeter scale on the film provides useful guide to correct magnification factor. Diameters that can be reliably measured are the obstetric conjugate; posterior sagittal of the inlet, mid pelvis and the outlet. General observations can also be made about the curvature and inclination of the

sacrum as well as the appearance of the sacrosciatic notches.

#### **The anteroposterior film:**

This view is taken to measure the transverse diameter. The divergent distortion in this view is very complicated and hinders the measurement of the transverse diameter of the inlet, the interspinous and intertuberal diameters. These diameters are at somewhat different levels. The locations of these levels are also not clearly marked anatomically. Therefore the use of isometric scales is very difficult in this situation. The magnification factors can not be eliminated, therefore correct measurements can not be made.



**Fig16.2: Shows X-ray pelvimetry**

#### **Thom's Method:**

This is quite cumbersome and involves placing the patient on the X-ray table in a semirecumbent position. Her back rests on an especially designed support so that the patient could be placed at an angle where the inlet of the pelvis is parallel to the X-ray plate. The tube-film distance is kept at 36 inches. The intensity of the exposure is varied according to the girth of the patient. The patient is removed from the table, while the tube and exposed film is left in place. The

centimeter ruler is placed alongside the film and a second (Flash) exposure is made on the edge of the previously exposed film. The top rows of centimeter perforations are used for magnification correction. The measurements made by this method are that of the transverse diameter of the inlet, the interspinous and transverse outlet diameters.

**Hazards of X radiation** - In women damage can occur to the mother's genetic contribution to future generations, damage to the fetus can be both immediate and subsequent such as childhood leukemia, damage to the gonads of the fetus. This can produce an increase in the incidence of congenital malformations in future generations.

Most geneticists believe that entirely safe dose of irradiation is zero. Chances of cancer including leukemia are increased 40 per cent in the children of mothers who receive abdominal or pelvic radiation during pregnancy. The genetics committee of the national Academy of sciences has set 10 roentgens as a permissible accumulated dose of medical radiation in the first 30 years of life. If X-ray I pelvimetry is to be used at all, it is most important to know how much radiation the fetus and mother will receive. The current evidence obtained from review of the literature indicates that the mother's gonadal dose from Pelvimetry varies from 2 to 4 roentgens, and that to the fetus varies from 0.5 to 7 roentgens. This dose can be reduced by using ultrafast films, lightening screens, shielding, and high milliamperes.

The student must realize that X-ray I pelvimetry' can not be justified as a routine procedure, because of the serious

hazards mentioned above. However, this does not mean that its importance where it is indicated should be undermined by this fear. Unfortunately the bulk of our undergraduates or post graduate students are never exposed to this method of investigation, since it is hardly ever done in any radiology department of the country. I hope this will soon become available in all Institutions parting with medical education in the country. The number of caesarean Sections performed on clinical evidence of Cephalopelvic disproportion alone will be reduced.

In expert hands, this method can provide useful information with almost negligible hazards to the fetus and the mother. The obstetrician and the radiologist must therefore carefully weigh the dangers of radiation against its potential value to the patient.

### **Ultrasound scanning in pregnancy**

#### **History:**

Ultrasonic equipment was developed during the 1914-18 war to detect submarines. Later on it was used to survey the ocean bed and locate fish shoals. In the industry it is frequently used for detection of flaws in metal structures. It has been applied as an aid to medical diagnosis in the last two decades, with considerable success and safety.

**Definition** - Ultrasound is a sound of higher frequency which is not audible to the human ear. Sound frequencies above 20,000 cycles per second (cps) are in the Ultrasound range.

**Frequency Range** - In clinical practice, it is limited to frequencies in the range from 1 to 10 million cycles per second,

that is, 1 to 10 MHz. Usually around 2 MHz frequency is considered safe. Sonography has made examination of Obstetrical patients easy, quick and safe. The interpretation of ultrasound images (sonograms) still requires considerable knowledge about clinical obstetrics.

**Principle** - Ultrasound can be propagated and directed as a beam. When this beam passes through tissues at a constant velocity" it is attenuated according to the density of the tissue and on passing through the boundary (interface) between tissues of different physical properties some of the energy is reflected. If the beam passes through the interface at right angle then this reflected energy is passed back to the source and can be recorded. The returning echoes can be converted into electrical signals and passed on to a cathode ray oscillograph where an Ultra sonogram can be pro-duced.

**Modes and displays** - There are several methods of detecting and displaying the, reflected ultrasonic information. They include A mode, B mode, M mode, and real time display.

**A-Mode** - (amplitude modulation). In this method echoes are displayed as vertical spikes along the baseline of the cathode ray tube, where the height of the spike is related to the amplitude of the detected echo.

This is one dimensional scan and can be used to measure a diameter whose position is known. The sound is passed through the fetal skull but echoes return only if it strikes the interface (the skull bones) at right angles. These echoes can be displayed as a vertical deflection or blips. Two blips can only be shown

simultaneously if the beam traverses the true biparietal diameter. The distance between the two blips can be accurately measured to within 0.5 to 1 millimeter.

This procedure requires skill in palpation and manipulation of the probe over the parietal eminence. The measurement may be erroneous if the head is deeply engaged in the pelvis where it will be impossible to manipulate the parietal eminence.

This mode is quite useful in clinical ultrasound and is used in conjunction with the B. scan. The anatomical information provided by a single beam of sound is little difficult to interpret. It is susceptible to changes produced by slight angulation of the transducer.



**Fig16.3: Shows ultrasound scan of fetus in utero.**

When the two methods are used simultaneously B scan provides anatomical information while the A mode is used for the measurement of amplitude and distance.

**B-Mode (brightness modulation):** In this method the amplitude of echo is represented by a spot of light on the cathode ray tube. Commonly used variety of B.scan in obstetrical practice is the compound contact B scan. It is obtained by moving the transducer over the surface of the body and displaying the

echoes in B mode. The operator applies a coupling medium such as mineral oil or jelly to the patient's skin and moves the transducer on the body. These produce an image on the cathode ray tube.

This mode is more complex and gives a two dimensional ultrasonogram. The probe is passed across the abdomen at various levels. The position of the echoes on the cathode ray tube represents the outline of interfaces in the body and their brightness represents the density of the tissue in terms of acoustic impedance. With experience these pictures can be interpreted in clinical terms.

**M mode** - When B scanning is used for time-motion studies it is called M mode is primarily applied in the field of cardiology.

**Grey scale** - In earlier ultrasound displays an echo either produced an image or was completely lost. This produced black and white pictures called bistable pictures. In the mid seventies a selective amplification was electronically applied to the low level echoes which originated from within the soft tissues. These echoes were then displayed at the expense of larger echoes which mainly originated from the boundaries. Thus by applying selective compression amplification, a large range of echoes returning from biological tissues was compressed into the limited dynamic range of the display system. The display then appeared as shades of grey. The strong echoes appear as white and low echoes as grey against a black background. No echoes arise from the cystic organs therefore cystic areas appear as a black area surrounded by strong white boundary. Grey scale has been

most useful in differentiating cystic from solid lesions.

**Doppler ultrasound** - This refers to the change in frequency of the ultrasound resulting from transmission to reception of the returning echo. When the wave strikes a moving target, the change in frequency becomes an audible signal and can be heard and recorded. It is used in the study of moving structures, e.g. blood vessels. At present there are three methods for detecting the fetal heart. The real-time equipment which records the heart movement as early as 10 weeks of gestation, while the Doppler Ultrasound detects the heart as early as 8 weeks and in experienced hands, is quite reliable at 12 weeks. A mode echocardiography has been reported by Robinson to be reliable as early as 6 weeks, but is a tedious procedure and not suitable for general use. The fetal movements become visible from the eighth week on and can be observed with real time scanning.

**Real time scanning** - The term real time refers to the dynamic presentation of sequential images at a present frame rate. This results in a movie of structures as they change position with time. High quality automated scans are acquired independent of the operator's skill or body motion by mechanical or electronic movement of a single or an array of piezoelectric crystals. The 'B' mode tomogram can be made either as a linear scan or sector scan. Linear scan operates electronically while the sector scan may be mechanical or electronic. The only limitation imposed is because of the velocity of sound. In ultrasound it is a rule that  $PNE = 77 \times 10^3$  (content) where P = Penetration, N = lines of sight per frame F = Frame rate. The resolution

depends on the lines of sight and frame rate.

The higher the line density per frame the better the resolution. The time machines a very well balanced and changeable line density and frame rate is electronically achieved therefore these give a very good resolution. The type of contact 'B' scanning described above has several disadvantages, it is slow and the instrument is cumbersome and expensive and needs a skilled operator. It is particularly difficult when applied to moving organs. Its only advantage is a very good resolution of the anatomical detail in the hands of an expert operator. To overcome the difficulties experienced with static 'B' machines real time machines were produced, where the transducer consists of a group of piezo electric crystals as opposed to single crystal used in static 'B' scanners. Initially due to technical difficulties the resolution of these machines was not as good as the static 'B' scanners, but in the newer machines this problem is no longer there, therefore the real time machines are gradually replacing static 'B' machines especially in obstetrics.

**Time gain control** - Time gain control is the electronic compensation of tissue attenuation, when an echo that comes from twice the distance is given four times the amplification and similar echo amplitude emanates from similar reflectors independent of the distance from the transducer and the effects of attenuation, it is called time gain control.

**Preparation of the patient** - A full urinary bladder is essential to visualize the pelvic organs in a non pregnant state or in early pregnancy. This does not only provide a sonic window but also a

landmark. The visualization is made easier as the bowel is pushed away and the uterus changes its position from a relatively caudal to a more favorable cranial.

**Measurements** - Since ultrasonographic measurements are used for important clinical decisions in management of the patient < 11 measurements should be made as accurately as possible. The student must be aware of the Mutations imposed by the equipment and the fundamental physical principles involved in these modern techniques. All measurements made with presently available instruments depend upon the assumption that the velocity of sound in tissue is constant. This is because the measuring instrument. The cathode ray tube has a sweep speed which is related to the velocity of sound in tissue. The amount of time required for a signal to return to the transducer is thus interpreted by the instrument as a distance. Instruments which are used in

North America takes as their standard, a velocity of 1540 meters per sec. This velocity is not correct for certain tissues, in particular the fetal skull. It also does not help to make an arbitrary change in the velocity calibration since the exact change one should make is not precisely known. The thickness and degree of calcification of the fetal skull does not remain constant throughout pregnancy therefore very little can be done in improving the accuracy. The accuracy of measurement also depends upon the depth resolution and lateral resolution of the instrument.

In all cases lateral resolution is superior to depth resolution. The wave from which it is produced by the transducer

also affects depth resolution and this may depend upon the energy with which the transducer is struck and the physical characteristics of the transducer backing. Finally the resolution of the cathode ray tube, the film which is used to photograph, and the electronic or mechanical calipers. Which are used to make the measurement will all affect the accuracy of the measurement. A realistic attitude toward the inherent limitations of measurements is extremely necessary and should be adopted by the practicing obstetrician.

**Applications in obstetrics** - The results of ultra sonograms must be carefully correlated with clinical considerations in the individual patient. Like most diagnostic aids it is not fool proof.

**Estimation of gestational Age** - Assessment of gestational age is the most common indication for ultrasound examination of pregnant women.

An accurate estimation of gestational age is useful in very pregnancy. Some patients do not remember their last menstrual period correctly. They may conceive during post pill or lactational amenorrhoea or have irregular menstrual cycles. In cases where pregnancy is complicated with diseases such as nephritis, diabetes or hypertension, it is desirable to deliver the fetus at the earliest possible moment consistent with fetal maturity. When intrauterine fetal growth retardation occurs, an earlier assessment of gestational age avoids confusion and on serial measurements assistant with dates i.e. those with hydramnios, oligohydramnios, multiple pregnancy or obese. Gestational age can be adequately determined by ultrasonography.

It has been suggested that all patients have a routine ultrasonic examination in the second trimester. So that an accurate assessment of gestational age is made and fetal and placental status can be studied. In my opinion this is not justified.

Historically the gestational age was assessed by measurement of fetal sac volume in very early pregnancy. This has been largely abandoned in favour of measurement of crown rump length between 7 to 11 weeks which provides accuracy of plus minus four days. Unusual sources of error are over flexed fetal attitude when the gestational age may be under assessed and inclusion of yolk sac in the measurement when it may be over estimated.

**Early pregnancy** - Diagnosis of pregnancy may be made from as early as 6 weeks. A round fluid containing sac is seen in the uterus which is often referred in books as the gestational sac. At about 8 weeks after the last menstrual period this is visible as disc like structure, one should be able to see the embryo in the amniotic cavity at this stage. The placenta can frequently be identified as early as the eighth week but is relatively easy to see by the 11<sup>th</sup> to 12<sup>th</sup> week.

By the 10<sup>th</sup> week it is possible to identify the fetal heart beat using high speed realtime equipment.

**Abortion** - This may be threatened, missed, complete, or incomplete. All of these can be differentiated with the help of ultrasound. The absence of an embryo in the gestational sac after 8 weeks is a reliable finding. Similarly real time scanning which fails to show heart beat can help to rule out viable pregnancy.

Even when an embryo is present it cannot be concluded that the gestation is viable unless the embryo is observed to move. If the uterus is empty the diagnosis of complete abortion can be made.

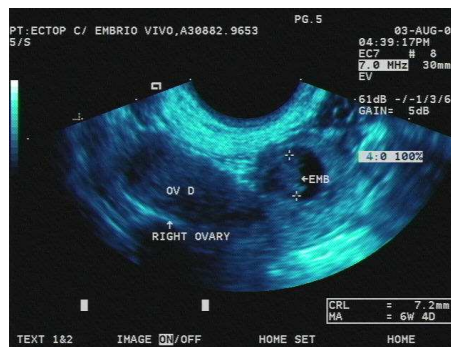
**Ectopic pregnancy** - Sonar may help in detecting a chorionic plate at an ectopic site and the presence or absence of an intrauterine pregnancy. The accuracy with which the diagnosis of ectopic pregnancy can be made by ultrasound is controversial. The most common condition confused with ectopic pregnancy is an intrauterine pregnancy with a corpus luteum cyst of the ovary. In both conditions the patient presents with lower abdominal pain, positive pregnancy test and a tender adnexal mass. Even blood may be aspirated from the culdesac in some cases. If an intrauterine gestation can be demonstrated the diagnosis of ectopic pregnancy can be excluded with confidence.

The diagnosis of an ectopic pregnancy cannot be excluded simply because an extrauterine gestation has not been identified. In about one third of ectopic pregnancies the urine pregnancy test is negative.

However, analysis of serum beta sub unit of chorionic gonadotropin is always positive. Ectopic or intrauterine, gonadotropin activity can persist for weeks after abortion therefore this test is not very helpful in diagnosing ectopic pregnancy.

### **Multiple pregnancy:**

This may be diagnosed from 8 weeks onwards. Two or more gestational sacs are seen on sonography.



**Fig16.4: Shows fetus in utero in ultrasound scan.**

**Hydatidiform mole** - The ultrasonic appearance of a mole reflects the gross pathological appearance. The individual solid elements are separated by fluid space. The mole resembles an edematous placenta on ultrasonography. The fetal sac may be absent. An atypical mole can be differentiated from an incomplete abortion, with considerable difficulty. The history physical findings and chorionic gonadotropin levels should be reviewed before diagnosis of hydatidiform mole is made.

Typical hydatidiform mole is sometimes easy to recognize. The hydropic villi in utero can be observed without difficulty. The enlarged uterine cavity is completely filled with echoes resembling an extremely thick edematous placenta. Enlarged cystic ovaries (lutein cysts) may also be observed on either side of the uterus in these cases and thus make the diagnosis easy. Late Pregnancy - Ultrasonography can be very helpful in differentiating multiple pregnancy Poly-hydramnios and pelvic tumors. In these conditions the uterus is clinically larger than dates.

### **Fetal biparietal diameter measurement:**

From twelve week onwards the biparietal diameter can be easily measured. On recent review of the literature and personal experience it has been found that biparietal diameter can also provide accuracy of plus minus four days in assessment of gestational age when performed in second trimester. This is much easier to measure and does not require a full bladder. There is no source of error such as observed with measurement of crown rump length therefore it is being used more and more for assessment of gestational age. A single measurement of biparietal diameter between 14 to 24 weeks gives consistently good results to accuracy of plus minus 4 to 5 days. After 20 weeks due to biological variations the accuracy is decreased. In the third trimester it can be as much as three to four weeks. It is best to measure a biparietal diameter on real time machine so that several scan angles can be used. The measurement once obtained should be reproducible. At least 20 sections should be studied. It is now a standard practice to obtain a horizontal section of the fetal skull at the level of cerebral peduncles. This appears as an oval section. It has sharply defined outline and shows a midline echo representing the falx which is intercepted by cavum septum pellucidum anteriorly and cerebral peduncles posteriorly.

With experience one can also measure the biparietal diameter in coronal sections. In literature quite a large number of series correlating the B P D measurements to gestational age is available. These authors used a sound velocity of 1600 or 1540 meter per second and studied different population groups. It is important to use appropriate tables and more so it is even better to

make your own tables from your own population groups. Biological variations often produce errors in the estimation of gestational age.

Use of 2 measurements of BPD, one before 26 weeks and the other at 33 weeks is recommended so that gestational age can be adjusted in accordance with growth pattern. Among the other measurements e.g. cross sectional area of the fetal skull or trunk, femur length measurement is gaining popularity. It is useful to measure femur length as a cross check with BPD Fetal weight can also be assessed by using different measurements and formula produced. Best perhaps is to use biparietal diameter and fetal trunk circumference.

**Intrauterine death** - This may be confirmed by the absence of detectable fetal heart and lack of serial growth.

**Placental localization** - Localization of placenta with ultrasonography is safe and reliable. Placenta on scanning appears as a crescentic area attached to the uterine wall displaying a speckled appearance of low medium level echoes at low gain settings. The nature of internal placental echoes varies depending on age and amount of calcification within it. This has been used to classify placental and fetal maturity.

The chorionic membrane along with amniotic membrane appears as a sharp well defined echo (a sharp white line). Within the placenta echo free areas are seen and referred to as placental lakes. Between the placenta and the uterine wall placental venous sinuses can be identified.

**Indications for Placental Localization**



1. When bleeding occurs during the second or third trimester of Pregnancy.
2. When Amniocentesis for genetic or fetal maturity studies is planned.

High risk pregnancy where fetal maturity is under question and the status of fetus in utero is to be determined. It has been reported that large number of placentas can be found in the lower uterine segment during the second trimester. Most of these are consistent with different degrees of placenta previa. It is important to note that 80 to 85% of these low lying placentas will migrate into the upper uterine segment by the end of gestation. This phenomenon is thought to be related to the formation and lengthening of the lower uterine segment as well as to changes in the fetoplacental ratio during the third trimester. Repeat examinations are therefore necessary to identify true cases of placenta previa.

In patients presenting with ante-partum hemorrhage it is important to identify the placenta. This can sometimes be difficult if placenta is posterior and is being overshadowed by the anteriorly lying foetus. To overcome this problem the patient can be put in a Trendelenburg position and distance between presenting part and sacral promontory; noted. When this distance is more than 2 cms it indicates that the placenta is intervening. When placenta is anteriorly located it can wrongly be diagnosed as placenta previa if bladder is overdistended.

To avoid this error a postvoid scan should also be obtained. In placental abruption the placenta separates partially from the uterine wall. With newer equipment it is possible to demonstrate

this area of placental separation and collection of blood which appears as an echo free zone. This allows us to assess the degree of placental abruption.

#### **Visualization of fetal anatomy and detection of congenital anomalies -**

With special equipment, details of the fetal heart (septum, valves and chambers) can be studied from the second trimester onwards. The fetal spine, spinal canal, kidney, bladder and respiratory movement usually become visible from 16 to 18 weeks. The significance of respiratory movement is yet to be understood. If only two vessels are present then it raises the possibility of fetal abnormalities.

#### **Fetal head and spine:**

For reliable diagnosis of hydrocephaly or microcephaly, repeated scanning is required. Anencephaly or meningomyelocele can be suspected but confirmed only if supported by elevated AFP levels. The sonographic finding should be considered diagnostic although Radiographic confirmation may be necessary. In advanced cases of intrauterine fetal death marked deformity of the fetal head is the leading sign. With real-time scanning the absence of FHM is readily recognized and diagnosis of intrauterine death confirmed.

#### **Chest, abdomen and genitourinary tract:**

With high resolution real-time equio"l": supplemented with M-mode scan visualization of the fetal heart can be an impo source of information. Occasionally cystic structures may also be seen in the toe chest. Fetal ascites can be detected with ultrasound and is usually associated with obst cation or other anomalies of the genitourinary

tract. Normal kidneys can easily be seen bilaterally next to the spine. Observation of the fetal bladder speaks for functioning kidneys. However, an extremely distended bladder with or without hydronephrosis may suggest obstruction in the urinary tract. Polycystic kidneys and solitary cysts have been reported IV diagnosed by ultrasound. Although much attention has been directed toward determining fetal sex in utero the results are grossly exaggerated and unconvincing. Some physicians and clinics use this for cheap publicity. This unethical and should be discouraged. Chromosomal analysis of the fetal cells is the only best method available for determining sex of the baby and can be carried out where sound indication for genetic disorder is present.

**Deep vein thrombosis** - Ultrasound has been used to detect the patency of veins utilizing the Doppler Effect. This can be used to screen high risk post operative cases and chronically ill patients who are bed ridden. This method is a good screening tool. For definite diagnosis other methods should be applied.

**Secondary post partum hemorrhage** - Ultrasound may help to show the presence or absence of placental tissue in the uterus in these cases.

#### **Hazards of ultrasound:**

The two major biological effects caused by ultrasound are thermal change and cavitation. Ultrasound used for physical therapy can cause significant heat change in tissues but conventional diagnostic equipment works with much less energy. Cavitation will be caused only if levels of frequency are above the normal range.

Based on experimental and human data it seems that diagnostic ultrasound is harmless to mammalian tissues when used in the conventional way with a justified clinical indication. Recent studies reported in the literature have not shown any danger of chromosomal damage in leucocytes of rat cells bombarded with considerably higher frequency of ultrasound.

In the past radiography was the main diagnostic intervention employed in obstetric patients particularly in pelvimetry and chest X-ray similarly in emergency situations X-ray abdomen and IVP were carried out keeping in view the hazards of radiation to the fetal gonads and teratogenic effects on the embryo and fetus. At present both CT scan and MRI has become available and is being used in pelvimetry and other emergency conditions Unlike Ultrasound scanning there is definite risk of ionized radiations when these diagnostic procedures are employed therefore all precautions must be taken into consideration to safe guard both the fetus and mother.

The increasing use of imaging in the population will inevitably result in an increase in requests for imaging in women who are pregnant or lactating. The objectives of these guidelines are to review:

**Teratogenesis after exposure to ionizing radiation:** Organogenesis occurs predominantly between 2 and 15 weeks gestation. This is the period when the fetus is most susceptible to the teratogenic effects of ionizing radiation, which include micro-cephaly, microphthalmia, mental retardation, growth retardation, behavioral defects, and cataracts.

Teratogenic effects are extremely unlikely in fetuses before 2 weeks of gestation and after 15 weeks of gestation.

Teratogenesis is considered a non-stochastic effect of radiation (i.e., a threshold dose exists below which there is no risk). The threshold radiation dose below which no

teratogenic effects occur is not known, but is estimated to range from 5 to 15 rad.

The radiation dose to the fetus from a spiral CT study of the maternal pelvis using typical technical parameters is variable and depends on gestational age and scanning parameters such as slice thickness and mAs.

That said, estimated doses range from 2.4 rad in the first trimester to 4.6 rad in the third trimester. An older study that is probably not representative of current technology suggested fetal doses of up to 5-10 rad.

Therefore, the radiation dose of pelvic CT is likely at or below the estimated threshold level for induction of congenital malformations. In practice, studies have shown the incidence of malformations is not measurably increased after in utero irradiation in humans.

Teratogenesis is not a major concern after diagnostic CT studies of the pelvis in pregnancy, because the radiation dose is generally too low to cause such effects.

Carcinogenesis after Exposure to Ionizing Radiation: Carcinogenesis is believed to be a stochastic effect of radiation (i.e., no threshold dose).

The risk of childhood malignancy after in utero irradiation was first reported in 1956, though the association was not widely accepted until the early 1960s. The existing data, derived from different sources, are relatively consistent. These data (which utilize several different end-points) are shown below:

End-point	Risk
Baseline risk of childhood cancer	19/10,000
Baseline risk of fatal childhood (0-15 yrs) cancer [2]	5/10,000
Excess risk of fatal childhood cancer per rad of fetal whole body dose [3]	4.6/10,000
Excess risk of childhood cancer per rad of fetal whole body dose [4]	6.4/10,000
Excess risk of childhood cancer per rad of fetal whole body dose [5]:	6/10,000
Relative risk of childhood cancer after fetal radiation exposure of 5 rad [6]:	2

**Table 16.1 shows incidence of cancer**

Using a fetal dose estimate from pelvic CT of 2-5 rad, this implies an increased risk of childhood cancer of up to 2 times baseline for a standard pelvic CT. The relationship between the risk of carcinogenesis and gestational age at the time of radiation exposure is more controversial. The OSCC study suggests the risk is higher with exposure in the first trimester than with exposure in the second or third trimesters, with relative risks of

3.19, 1.29 and 1.30, respectively [10]. However, this may be an artifactual result, since radiographic studies in the first trimester may have included a disproportionately high fraction of high dose non-obstetric studies such as IVPs and barium enemas. Also, experimental work in dogs suggests exposure later in gestation is more carcinogenic.

None-theless, the possibility of pre-malignant change in the first trimester remains, leading the NRPB to assume that some risk exists after irradiation in the first weeks of pregnancy. Assuming a relatively high fetal dose estimate of 5 rads for a pelvic CT during pregnancy, the relative risk of fatal childhood cancer may be doubled. This relative risk may appear substantial, but it should be remembered that the baseline risk is very low, so that the odds of dying of childhood cancer go from 1 in 2000 (baseline) to 2 in 2000 (after 5 rads). To assist with patient counseling, some practical risk comparisons may be helpful. The excess risk (of 1 in 2000) is equivalent to driving 20,000 miles in a car or living in New York City for 3 years. It should also be noted that the guidelines of the American College of Obstetricians and Gynecologists are superficial in their discussion of the carcinogenic risk of radiation during pregnancy, describing it as "very small" and concluding "abortion should not be recommended". The ACOG guidelines do not indicate what information or risk estimates should be provided during parental counseling, if any. CT of the fetus should be avoided in all trimesters of pregnancy, because it may cause up to a doubling of the risk of fatal childhood cancer.

**Avoiding exposure in pregnancy:** No law or professional standard requires that radiologists determine in advance whether a patient of childbearing age is pregnant. However, it is clearly good practice to implement the following guidelines:

Signs should be prominently displayed in all radiology departments asking each patient to notify a technologist or physician if she is, or thinks she could be, pregnant. All technologists should ask women of childbearing age if they might be pregnant prior to performing a radiologic procedure. Radiology requisition forms filled out by referring physicians should include a section dealing with the possibility of pregnancy. No radiological procedure involving exposure to the pelvis should be undertaken in a patient who declares she may be pregnant without consultation with a radiologist. The radiologist should discuss risks and benefits with the patient, and determine if it is appropriate to proceed, perform an alternative procedure, or delay the study to allow performance of a pregnancy test. It should be noted that current recommendations do not recognize a safe period during the menstrual cycle, and so the concept of the "ten day rule" is obsolete.

A patient who thinks she may be pregnant should be discussed with the referring physician, in order to determine the appropriate course of action (e.g., rescheduling after pregnancy testing, proceeding with the test after counseling, or changing to another modality). It is the responsibility of the patient to disclose any possibility of pregnancy, although appropriate sign-age and questioning of all women of

reproductive age is also critical. The supervising radiologist should discuss any cases of possible pregnancy with the referring physician.

### **Managing pregnant patients who are irradiated:**

Relative agreement exists on when to recommend termination of pregnancy after radiation exposure.

The so called "Danish rule" was offered in 1959 by Hammer Jacobsen, who suggested termination was advisable for a fetal dose of over 10 rads.

This guideline has been widely followed. Wagner et al suggest termination should only be considered if a radiation dose of over 5 rad occurs between 2 and 15 weeks of gestation, and is probably indicated only for doses over 15 rad.

Hall suggests termination may be considered for a radiation of over 10 rad received between a gestational age of 10 days and 26 weeks.

In practice, it is exceptionally unlikely that any single radiological study would deliver a radiation dose sufficient to justify termination.

Nonetheless, it is helpful to be aware of the expected radiation dose from common procedures, and the magnitude of risk to the fetus per unit dose.

This information, which is listed below, can be used to counsel pregnant patients who require a study involving ionizing radiation to the pelvis, or who inadvertently undergo such a study at a time when pregnancy is unsuspected.

<b>Procedure</b>	<b>Conceptus radiation dose (rads*)</b>
Abdominal radiograph	0.25
Intravenous pyelogram	0.8
Barium enema	0.8
Lumbar spine radiographs	0.6
CT pelvis	1-10

Note: 1 rad = 1 cGy = 10 mGy = 10,000  $\mu$ Gy

### **Table 16.2 Shows dosage of radiation with different procedures**

In practice, it is exceptionally unlikely that any single diagnostic radiological study would deliver a radiation dose sufficient to justify termination.

**Iodinated contrast media in pregnancy:** In general, intravascular contrast media should be avoided in pregnancy, in order to avoid any possible hazard to the fetus. In vitro experiments have shown iodinated contrast to be mutagenic to human cells. Reassuringly, animal studies have failed to show an in vivo teratogenic effect. The iodine content of contrast media has the potential to produce neonatal hypothyroidism, and this has been observed after the direct instillation of ionic contrast into the amniotic cavity during amniocentesis. The intravascular use of nonionic contrast media has been reported to have no effect on neonatal thyroid function. It is standard pediatric practice to screen all neonates for hypothyroidism, but it is particularly important to perform this test in the infants of mothers who received

iodinated contrast during pregnancy. Despite in vitro concerns, iodinated contrast seems safe to use in pregnancy.

## **MRI DURING PREGNANCY:**

### **Risks from MRI during pregnancy:**

The current guidelines of the FDA require labeling of the MRI devices to indicate that the safety of MRI with respect to the fetus "has not been established". Safety concerns arise with respect to both mother and fetus. Maternal safety concerns are the same as for non-pregnant patient, and are addressed by pre-scan screening. Fetal concerns are twofold; first, the possibility of teratogenic effects, and second, and the possibility of acoustic damage. In general, it should be noted that most studies evaluating MRI safety during pregnancy show no ill effects.

Most studies evaluating MRI safety during pregnancy show no ill effects.

### **Risk of teratogenesis from MRI during pregnancy:**

A small number of studies have raised the possibility of teratogenic effects of MRI exposure in early pregnancy. A reduction in crown-rump length was seen in mice exposed to MRI in mid-gestation. Exposure to the electromagnetic fields simulating a clinical study caused eye malformations in a genetically predisposed mouse strain. Several hours of exposure of chick embryos in the first 48 hours of life to a strong static magnetic field and rapid electromagnetic gradient fluctuations resulted in an excess number of dead or abnormal chick embryos, when examined at day 5. Possible mechanisms for apparent deleterious effects include the heating

effect of MR gradient changes, and direct non thermal interaction of the electromagnetic field with biological structures. Tissue heating is greatest at the maternal body surface, and approaches negligible levels near the body center, making it unlikely that thermal damage to the fetus is a serious risk. A possible criticism of many of these studies is that they are not applicable to humans. However, they provide sufficient cause for concern such that a cautionary approach should be taken regarding fetal MRI in the first trimester. Accordingly, the guideline of the National Radiological Protection Board in the United Kingdom is that "it might be prudent to exclude pregnant women during the first three months of pregnancy". An additional concern in the first trimester is the underlying relatively high rate of spontaneous abortion in this period. An MRI study could be coincidentally followed by a spontaneous abortion, but might give rise to parental concerns regarding causal effect. From a practical view point, first trimester MRI will usually be performed for maternal rather than fetal indications, and in this context MRI is still preferable to any imaging study involving ionizing radiation. It is good practice to avoid MRI during pregnancy, particularly for elective studies or during the first trimester, but MRI remains preferable to any studies using ionizing radiation.

**Risk of acoustic damage from MRI during Pregnancy:** A less obvious concern is the potential risk of acoustic damage to the fetus, due to the loud tapping noises generated by the coils of the MR scanner as they are subjected to rapidly oscillating electromagnetic currents, especially with EPI, which is the noisiest sequence in current clinical

use. In a follow up study of 18 patients who had undergone EPI as fetuses, 16 passed their 8 month hearing test, compared to 16.7 expected. In a second study, a microphone was passed through the esophagus into the fluid filled stomach of a volunteer. The aim was to simulate the acoustic environment of the gravid uterus. The sound intensity in the stomach was measured during MRI scanning across a range of radiofrequencies. The attenuation of the transmitted sound was greater than 30 dB, sufficient to reduce sound intensity from near the dangerous level of 120 dB to an acceptable level of under 90 dB. The results of these studies provide reassuring clinical and experimental evidence that there is no significant risk of acoustic injury to the fetus during prenatal MRI.

Acoustic damage from MRI during pregnancy appears to be a theoretical rather than a real concern.

### **RISK OF TERATOGENESIS FROM GADOLINIUM:**

Intravenous gadolinium is teratogenic in animal studies, albeit at high and repeated doses. While teratogenic effects have not been observed in a small number of human studies where gadolinium has been given in pregnancy, it is clear that gadolinium should not be administered in pregnancy unless there is an absolutely essential clinical indication, particularly during the period of organogenesis. Administration of gadolinium later in pregnancy may be reasonable, although such indication would likely be for a maternal or obstetric indication rather than for evaluation of a fetal abnormality. Examples might include gadolinium enhanced

imaging for a maternal brain tumor or suspected placenta accreta. Gadolinium crosses the placenta where it is presumably excreted by the fetal kidneys into the amniotic fluid. In the era of gadolinium-induced nephrogenic systemic fibrosis, this raises theoretical concerns of toxicity related to disassociation and persistence of free gadolinium.

Such concerns reinforce the regulatory advice on gadolinium use in pregnancy. The 2007 ACR guidance document for safe MRI practices recommends that intravenous gadolinium should be avoided during pregnancy and should only be used if absolutely essential; furthermore, the risks and benefits of gadolinium use must be discussed with the pregnant patient and referring clinician. Gadolinium is classified as a category C drug by the Food and Drug Administration and can be used if considered critical (only to be administered “if the potential benefit justifies the potential risk to the fetus”).

Intravenous gadolinium is contraindicated in pregnancy, and should only be used if absolutely essential and only after discussion of risks and benefits with the patient and referring clinician.

### **USE OF CONTRAST MEDIA DURING LACTATION:**

The traditional and standard recommendation is that lactating women who receive intravascular iodinated contrast or gadolinium should discontinue breastfeeding for 24 hours, and the expressed milk during this period should be discarded. The rationale for this recommendation appears weak, for several reasons:

Only tiny amounts of iodinated or gadolinium-based contrast medium given to a lactating mother reach the milk. For example, a recent study of 20 lactating women found that less than 0.04% of the maternal dose of intravenous gadolinium passes into the breast milk. Only a tiny fraction of iodinated contrast or gadolinium entering the infant gut is absorbed. For example, only 1-2% of oral iodinated contrast is absorbed into the blood stream.

Given these considerations, and in accordance with the results of a comprehensive review by the European Society of Urogenital Radiology, the very small potential risk associated with absorption of contrast medium may be insufficient to warrant stopping breastfeeding for 24 hours following either iodinated or gadolinium contrast agents. A recent review in the *New England Journal of Medicine* also concluded that iodinated contrast administered to breast-feeding women posed no risk to the infant.

Lactating women who receive iodinated contrast or gadolinium can continue breast feeding without interruption.

### **Imaging of suspected pulmonary embolism in pregnancy:**

Three large studies showed that the rate of pregnancy associated pulmonary embolism was approximately 1 to 2 per 7000 pregnancies (less than previously supposed), and that the majority occurred post-partum, particularly with pre-eclampsia, Caesarean section, and multiple births. Several considerations suggest that CT pulmonary angiography, rather than ventilation perfusion scintigraphy is the preferred technique for

imaging suspected pulmonary embolism in pregnancy:

Available data can be interpreted to support the general superiority of CT pulmonary angiography over ventilation perfusion scintigraphy.

Ventilation perfusion scintigraphy is indeterminate in up to 25% of patients imaged during pregnancy.

The fetal radiation dose from CT pulmonary angiography is substantially less than that from ventilation perfusion scintigraphy in all trimesters and even if half-dose perfusion only scintigraphy is used.

CT is the preferred modality for imaging of suspected pulmonary embolism in pregnancy.

### **Imaging of Suspected Acute Appendicitis in Pregnancy:**

Acute appendicitis complicates approximately 1 in 1500 pregnancies, and is one of the leading indications for surgery in pregnancy. The diagnosis of appendicitis in pregnancy can be clinically difficult, particularly in later pregnancy, as evidenced by a perforation rate of 31% for appendicitis occurring in the first and second trimester but rising to 69% in the third trimester. With respect to imaging, graded compression should be considered the initial modality of choice in the first and second trimesters. In a series of 42 women with suspected appendicitis during pregnancy, ultrasound was found to be 100% sensitive, 96% specific, and 98% accurate in diagnosing appendicitis. Three patients were unable to be adequately evaluated due to the technical difficulties



associated with advanced gestation (over 35 weeks), and the choice of imaging in later pregnancy is more problematic. The only published study on the use of CT for appendicitis in pregnancy showed 100% accuracy in a small series of 7 patients, 2 of whom were found to have appendicitis. More recently, there has been some interest in the use of MRI to diagnose appendicitis in pregnancy. In a Dutch study of 12 suspected cases between 7 and 35 weeks gestation (3 with subsequently proven appendicitis at surgery), MRI correctly identified all 3 cases of acute appendicitis and correctly identified 7 normal cases. The appendix was not seen in two patients (at 17 and 35 weeks gestation). Our institutional experience suggests all modalities (US, CT, and MRI) become problematic in later pregnancy (past 35 weeks gestation) and consultation with on call faculty may be appropriate in such patients.

Ultrasound is the preferred modality for imaging of suspected acute appendicitis in pregnancy, except in later pregnancy (> 35 weeks) when CT or MRI may be required (consult with radiology faculty).

#### **Imaging of suspected renal colic in pregnancy:**

Obstructive urinary calculi complicate approximately 1 in 3300 pregnancies. Imaging is complicated by the normal physiological hydronephrosis that occurs in pregnancy. Despite this confounding factor, ultrasound correctly visualized 21 of 35 (60%) stones in a retrospective study. This suggests ultrasound remains the initial study of choice, but that additional imaging by non contrast spiral CT or IVP may be required if ultrasound

is negative. Non contrast CT is probably the more accurate modality, although the radiation dose to the fetus is probably higher. However, radiation dose comparisons between CT and IVP are not straightforward because both can be performed with a wide range of techniques that may or may not incorporate dose-reducing approaches. Ultrasound is the preferred modality for imaging of suspected renal colic in pregnancy; if negative, CT or MRI may be required (consult with radiology faculty).

#### **Imaging of trauma in pregnancy:**

Trauma and accidental injuries complicate 6-7% of all pregnancies, and are usually due to motor vehicle accidents, domestic abuse or assaults, and falls. Common adverse consequences include uterine contractions, preterm labour or delivery, and placental abruption. Fetal or maternal demise is rare. In many cases, external fetal monitoring and ultrasound may be adequate for assessment, including detection of placental abruption or uterine rupture (the most serious complication) and documentation of fetal well being. That said, trauma to the pregnant patient must be considered with the utmost seriousness because even minor trauma can cause fetal demise. The cardinal principle in the management of trauma in pregnancy is that there can be no fetal survival without maternal survival, with the rare exception of the gravely injured mother late in pregnancy where urgent Cesarean section may allow for fetal survival. From an imaging perspective, ultrasound is an excellent tool for initial evaluation of the traumatized pregnant patient, but CT is the preferred modality when clinical or ultrasound findings suggest visceral injuries unaccompanied by

intraperitoneal hemorrhage, or injuries of the chest, mediastinum, aorta, spine, retroperitoneum, bowel, bladder, and bones.

MRI is not a practical option for rapid evaluation of all these body parts in an unstable patient after trauma. Placental infarction or abruption typically appears at CT as a single avascular area of varying size that extends from the placental base to the placental surface. High attenuation in the non placental portion of the uterus indicates contusion, tear, or partial uterine.

**Disruption** Loss of amniotic fluid into the maternal peritoneum or free fetal parts in the maternal abdomen indicate an obstetric catastrophe, but it may be difficult to determine if free intraperitoneal fluid is amniotic fluid or hemorrhage from a maternal visceral injury.

Ultrasound may be sufficient for the initial imaging evaluation of a pregnant patient who has sustained trauma, but CT should be performed if serious injury is suspected.

### **CT Pelvimetry:**

Pelvimetry is occasionally requested when vaginal delivery is being considered for breech presentation (especially in a primigravida) or for patients with suspected cephalopelvic disproportion, although reports on the utility of pelvimetry are conflicting and the reproducibility of pelvimetry measurements has also been questioned [1-3].

Pelvimetry can be performed by conventional radiography, CT, or MRI

[4]. While MRI has the theoretical advantage of not using ionizing radiation, the fetal dose from a limited CT pelvimetry study (low doses lateral and frontal digital radiographs with a single axial slice through the femoral heads to measure interspinous diameter) is under 0.1 rad. Even assuming the worse case scenario that the dose is 0.1 rad and that such a dose is as dangerous as radiation earlier in pregnancy, the risk of fatal childhood cancer would only be increased by 2%, a minimal risk. For such reasons, if pelvimetry is considered appropriate, it is reasonable to perform pelvimetry by CT rather than MRI. Pelvimetry can be performed either by low dose CT or by MRI, and written informed consent is not required.

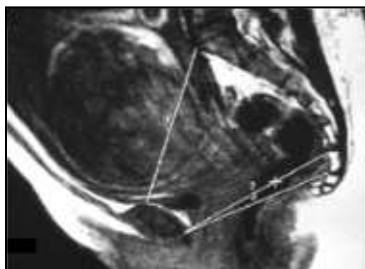
### **Risks and precautions**

CT of the fetus should be avoided in all trimesters of pregnancy, because it may cause up to a doubling of the risk of fatal childhood cancer.

No radiological procedure involving ionizing radiation to the pelvis should be undertaken in a patient who declares she may be pregnant without consultation with radiology faculty.

MRI poses no known risk to the fetus in the second and third trimester. MRI in the first trimester should only be performed after consultation with radiology faculty. Breast feeding can be continued without interruption after administration of iodinated contrast or gadolinium to a lactating patient. It is advisable to obtain written informed consent for CT of the abdomen or pelvis in a pregnant patient. For studies that pose minimal risk (including CT pelvimetry, CT of other body parts, and

MRI) it is advisable to explain the negligible nature of the risk to the patient and document this discussion in either the chart or the radiology report.



**Fig16.5: Shows pelvimetry with baby done for pelvic disproportion**

### Specific points:

The most common indications for urgent CT during pregnancy are:

Appendicitis - For first and second trimester pregnancies US and/or MR should be performed prior to obtaining a CT

Pulmonary embolism - In this case a CT pulmonary angiogram exposes the fetus to less radiation than a VQ scan. Therefore, CT should be the initial modality.

Renal colic - US is the initial study of choice. Trauma. US may be sufficient for the initial imaging evaluation of a pregnant patient who has sustained trauma, but CT should be performed if serious injury is suspected.

All patients undergoing CT of the abdomen or pelvis during pregnancy should sign the written informed consent form the consent form can be completed by either the referring physician or the involved radiologist (including the radiology resident on call). Patients referred from the Department of Obstetrics, Gynecology and Reproductive

Sciences will be consented by the referring physician.

For studies that pose minimal risk (including CT pelvimetry, CT of other body parts, and MRI) it is advisable to explain the negligible nature of the risk to the patient and document this discussion in either the chart or the radiology report.

This discussion can be undertaken by either the referring physician or the involved radiologist.

CT contrast seems safe to use in pregnancy and should be administered in the usual fashion in this is far preferable to repeating a study because the initial examination was non-diagnostic due to lack of intravenous contrast.

Intravenous gadolinium is contraindicated in pregnancy, and should only be used if absolutely essential and only after discussion of risks and benefits with the patient and referring clinician and radiology faculty.

Pelvimetry can be performed either by low dose CT or by MRI, and written informed consent is not required.



**Fig16.6: Shows pelvic CT scan without fetus**

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