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Chairperson CRC FOGSI (2004-2008)  
Vice - President FOGSI 2007

## Editorial Message

Welcome to this unique issue of FOGSI FOCUS on "Diseases Complicating Pregnancy". FOGSI FOCUS has become a ready reckoner for consultants, a brain stimulator for students, a guide to teachers and an information bulletin for researchers.

I hope you all will read and appreciate the joint efforts.

With Warm regards!

HOD, GMCH, Aurangabad,  
Chairperson CRC FOGSI (2004-2008)  
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Dr. C. N. Purandare  
MD (BOM), MA Obst.(Ireland),  
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## President's Message

"Vision is not enough; it must be combined with venture. It is not enough to stare up the steps, we must step up the stairs." Maternal Mortality in India is astronomically high at 307/ per 100,000 live births. 300 women die everyday due to pregnancy and childbirth complications and more than 90% of maternal deaths are preventable. Forty percent of pregnant women have complications and 15% need obstetric interventions for complications which are potentially life threatening to mother and baby.

During my tenure 2009-2010 the FOGSI theme was "SAVING LIVES". One of the initiatives highlighted the aspects of safe pregnancy and delivery to strengthen the knowledge of obstetricians by conducting over 60 CME's all over India in our societies.

The theme is incomplete without focusing on Medical Disorders in Pregnancy. Hence this FOGSIFOCUS.!

I am thankful to Dr. Kanan Yelikar & Dr. Madhuri Patel for editing this beautiful FOGSI FOCUS. I hope this issue will be able to give you satisfactory information on the subject.

Dr. C. N. Purandare,  
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Disclaimer:

The editors and the publishers of the volume claim no responsibility for the views expressed by different authors in their respective chapter.

## OBESITY AND PREGNANCY

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Obesity is a modern epidemic. It is remarkable to observe that younger women show the signs of obesity. RCOG also addressed the problem of obesity of young age.

Most alarming is childhood obesity which is showing significant morbidity. This is due to plentiful nutrition and less exercise.

### According to the recommendations of WHO

Overweight is defined as BMI of more than 25 kg/m<sup>2</sup> and Obesity is defined as BMI > 30 kg/m<sup>2</sup>.

The degree of obesity is classified into 3 categories.

Grade I (BMI 30-34.9 kg/m<sup>2</sup>)

Grade II (BMI – 35-39 kg/m<sup>2</sup>)

Grade III (BMI > 40/m<sup>2</sup>)

### Effect of Obesity on reproduction & pregnancy<sup>2</sup>

1. Maternal obesity is associated with basic metabolic disturbance.
2. Over weight women are more likely to suffer from problems of infertility.
3. Obese women have higher incidence of complications like pre-eclampsia, gestational diabetes and macrosomia.
4. There is (threefold) increased risk of miscarriage
5. The chances of operative delivery as well as post operative morbidity are increased.
6. The risk of pre-eclampsia increases (3.5 Vs 13.5%) in obese patient.
7. The risks of thromboembolism (0.05 Vs 12%) are higher in incidence as compared to non obese.
8. Increased perinatal mortality (1.4 Vs 5.71%)
9. Obese women are at high risk of cardiovascular disease and D. M.
10. Other problems associated with obesity include gall stones, UTI, thrombophlebitis.

### Management of options<sup>1,2,3</sup>

If an obese woman wishes to reduce her weight, she could be encouraged to lose weight before or after pregnancy.

Dietary manipulation should not be advocated during pregnancy apart from balanced diet, daily exercise program should be promoted.

During every antenatal visits, weight & B. P. recording with appropriate sized cuff. Obese women should be evaluated for gestation diabetes at 1st visit. Testing should be repeated in second & third trimester if previous findings were normal.

Women should be screened for asymptomatic bacteriuria by culture colony count of clean caught voided urine.

Screening for asymptomatic bacteriuria, with subsequent treatment, reduces the risk of pyelonephritis & its consequences.

It can be very difficult to assess fetal growth well being.

Measuring fundal height may be difficult. USG may be untrustworthy if adipose tissue limits visualization of foetus. There is no simple solution.

A detailed anomaly scan and serum screening for congenital anomalies should be recommended.

Women with severe obesity (BMI > 35 kg/m<sup>2</sup>) with one additional risk factor for hypertensive disease should be prescribed Aspirin 75mg per day from 12 weeks of gestation.

### Labour & Delivery

Fetal macrosomia is strongly associated with problems in labour including poor progress as a result of CPD, Shoulder dystocia and birth asphyxia thus resulting in a poor perinatal outcome.

#### C. section in obese patient

In view of modern anaesthesia, there should no longer be a hesitancy to perform a cesarean section in morbidly obese women.

Epidural anesthesia is technically possible and is preferred over general anesthesia, at least in experienced hands.

The use of prophylactic antibiotics during both elective and emergency cesarean section reduces the risk of maternal wound infection & febrile morbidity.

Additionally prophylactic administration of low molecular weight heparin is recommended, beginning pre-operatively & continued till the patient is fully ambulatory.

### Type of incision

Pfannestiel incision is preferred due to less post operative pain, early ambulation, more secure closure & less adipose tissue at the incision site.

Moreover this incision gives a better cosmetic result.

Potential adverse effects are

- 1) Greater chances of infection as this incision is in moist, warm area.
- 2) Potentially restricted access to the infant & more difficult exposure of upper abdomen.

Use of full thickness or one layer closure (incorporating peritoneum together with rectus sheath) with nonabsorbable suture material could avoid the problem of wound dehiscence. Placing surgical drain at the time of closure of the abdomen in obese women is a matter of debate & no conclusive evidence about how the skin should be closed after c-section.

### Postnatal

Complications after abdominal delivery in obese women include wound infection, wound dehiscence, atelectasis & pulmonary emboli.

Early mobilization with prophylactic anticoagulants appears to improve the outcome.

In newborn infants born to grossly obese women, especially those that are larger than gestational age, post natal blood sugar level should be monitored during 1<sup>st</sup> few hours of life.

### Conclusion

Obesity in pregnancy is a major predictor of obesity in latter life along with major complications like Type 2 DM & hypertension & cardiovascular complications<sup>1</sup>.

Maintaining awareness of the specific medical & obstetric problems associated with obesity will enable the clinician to maximize efforts to improve maternal health & fetal outcome<sup>1</sup>.

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## CRITICAL CARE IN OBSTETRICS

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Importance of critical care in obstetrics can not be overemphasized and it is one of the most important intervention that helps in reducing maternal mortality. The patients are young and generally healthy and respond favorably to the timely intensive care. Critical care for the obstetrical patient is required for acute conditions like amniotic fluid embolism, pulmonary thromboembolism, acute respiratory distress syndrome, hemorrhagic shock, septic shock, severe pre-eclampsia/ eclampsia with pulmonary edema, disseminated intravascular coagulation etc and also for conditions which are pre-existent but get aggravated by pregnancy like heart disease. A thorough knowledge of the physiological alterations during pregnancy is important for complete evaluation and management of the critically ill obstetric patient.

### Physiological changes in pregnancy

The cardiovascular alterations begin as early as 5 weeks of gestation. During the course of pregnancy the plasma volume increases by 30-50% as compared to 20-30% increase in red cell mass resulting in hemodilution. Cardiac output increases whereas systemic vascular resistance and pulmonary vascular resistance decrease by 30%. Uterine blood flow by term reaches around 600 ml/min. Extracellular fluid volume increases by 1-5 litres.

In respiratory system, the important physiological alterations are, a decrease in functional residual capacity by 18% which is due to the elevation of diaphragm by 4 cm and limitation of diaphragmatic excursions. Increase in respiratory rate and tidal volume leads to an increase in minute ventilation by 45%. There is a mild respiratory alkalosis and shift of oxygen dissociation curve to left which facilitates maternal-fetal oxygen transfer.

The renal changes are predominantly an increase in the glomerular filtration rate and creatinine clearance. Urinary volume increases while serum creatinine, blood urea nitrogen and uric acid levels fall. Although renin-aldosterone level increase there is a reduced sensitivity to these vasopressor resulting in decline in systolic and diastolic blood pressure<sup>1</sup>.

Pregnancy is relatively a hypercoagulable state and there is increase in fibrinogen, Factor II, VII



and X and decrease in factor XI, XIII levels and platelets though the prothrombin and partial thromboplastin time remain unaltered. There is slight increase in the white blood cell count.

### Critical Care Unit

Any serious medical or surgical condition in pregnant women may need critical care. In addition certain conditions which are specific to pregnancy may require critical care which is ideally done in a critical care unit which is equipped for providing ventilatory support and invasive monitoring. Certain hospitals in the USA have an obstetric intermediate care unit close to the labor wards which function similar to an intensive care unit<sup>2</sup>. Anaesthesia and obstetrical services are provided simultaneously by faculty and residents of each department. Medical and surgical consultancy is sought according to the specific condition being managed. The nurse patient ratio is 1:1 or 1:2. In most of the hospitals however critically ill obstetric patients are managed in the general ICU because the volume of obstetric patients needing such service is not enough to justify separate ICU<sup>3</sup>. The cost of infrastructure equipment and staff of ICU run into hundreds of crores.

The percentage of pregnant women needing ICU admission vary between 0.09% to 0.9%<sup>4,5</sup>. The mortality rate is between 12 to 21.6%<sup>6,7</sup>. The APACHE II (Acute Physiology and Chronic Health Evaluation) is used for assessment of non pregnant as well as pregnant women who are critically ill<sup>8</sup>. This article will deal with some of the important critical conditions which an obstetrician has to manage.

### Pulmonary edema

It can be of the following types:

1. Hydrostatic pulmonary edema
2. Permeability pulmonary edema

Hydrostatic pulmonary edema includes cardiogenic pulmonary edema or colloid osmotic pressure related pulmonary edema and certain rare causes like those associated with negative interstitial pressure such as acute airway obstruction or rapid re-expansion of pneumothorax. Iatrogenic causes like excessive intravenous infusion are also included in this group.

Cardiogenic pulmonary edema may be due to systolic dysfunction, diastolic dysfunction or valvular disease.

Normal colloid osmotic pressure is maintained by albumin and globulin which hold water in the intravascular compartment. It opposes the hydrostatic pressure and interstitial colloid

osmotic pressure which pulls water from circulation to the interstitium. Low albumin which may result from malnutrition, liver disease or renal loss can give rise to pulmonary edema. Hypoalbuminemia rarely precipitates pulmonary edema on its own but generally exaggerates edema due to other precipitating factors.

Permeability edema is seen in acute lung injury, ARDS, septic shock, aspiration pneumonitis etc. It results from opening of the tight junctions in endothelial cells which allows flooding of the alveolar space with water, proteins and cells from the vascular compartment.

Pulmonary artery wedge pressure of >18 mmHg in hydrostatic pulmonary edema differentiate it from permeability pulmonary edema.

Pulmonary edema presents with dyspnea, paroxysmal nocturnal dyspnea or orthopnea. Examination reveals increased respiratory rate and use of accessory muscles of respiration, positive hepatjugular reflux, neck vein distention, peripheral edema, third heart sound, and basal crepitations. Chest x-ray shows perihilar infiltration. Pulse oximetry or arterial blood gas analysis may reveal hypoxia. Twelve lead ECG and echocardiography are useful noninvasive tests for evaluation of the cardiovascular system. A Swan ganz catheter may be needed for monitoring of cardiac output, central venous pressure and pulmonary artery wedge pressure.<sup>9</sup>

Management comprises oxygen supplementation and administration of furosemide and morphine. Mechanical ventilation is needed if arterial partial pressure of oxygen is low. It should be maintained above 60 mmHg.

In pulmonary edema associated with pre-eclampsia, antihypertensives like hydralazine, labetalol, & nicardipine are beneficial. It reduces after load to the heart. NTG is useful when uncontrolled hypertension is associated with myocardial infarction and unstable angina although it is rare in pregnancy.

For systolic dysfunction as in cardiomyopathy dobutamine is effective. If hypotension is associated then dopamine, dobutamine or norepinephrine may be used.

For long term use isosorbide dinitrate is used in systolic dysfunction to reduce preload and afterload. Following delivery ACE inhibitors can be used. Aldosterone antagonist and blockers improve survival in congestive heart failure.

### Septic Shock

In obstetrics, septic shock may be encountered in puerperal sepsis, chorioamnionitis, septic abortion and pyelonephritis. Gram negative organisms are causative factor in more than 50% of cases while only 5% are as a result of gram positive organisms. Mortality rate is 40-50%<sup>10</sup>.



In the initial phase the clinical presentation is that of tachycardia, hypotension, mental confusion and flushing of skin. With further progress bradycardia sets in, skin becomes cool and clammy and cyanosis develop as a result of hypoperfusion.

Initial hemodynamic parameters reveal a decreased systemic vascular resistance and normal or elevated cardiac output. Later on maldistribution of cardiac output leads to local tissue hypoxia and lactic acidosis and end organ failure<sup>10</sup>. Acute renal failure, ARDS, thrombocytopenia and consumptive coagulopathy may develop as disease progresses.

### Management

Success of treatment depends on early diagnosis and prompt treatment. Aggressive fluid management with crystalloids or colloids is necessary to maintain a CVP of 8-12 mmHg. Pulmonary artery catheterization helps in optimal fluid management. If hypotension persists despite preload correction then vasoactive agents are added to maintain mean arterial pressure of 67-70 mmHg.<sup>11</sup> Packed cell transfusion may be required to maintain hematocrit of 30% or more. Low dose steroids may be useful for countering the inflammatory response but high dose steroids should be avoided. Source of infection should be eliminated and broad spectrum antibiotics started depending sensitivity report.

Anticoagulants like recombinant activated protein C has been used in multiorgan dysfunction but its role is controversial. Mechanical ventilation with positive end expiratory pressure may be needed if ARDS sets in.

### Acute Respiratory Distress Syndrome

According to the American European Consensus Conference ARDS is characterized by:

1. Acute onset
2. PaO<sub>2</sub>/FIO<sub>2</sub> ratio or hypoxia score of 200.
3. Bilateral pulmonary infiltrates on chest x-ray.
4. Pulmonary artery occlusion pressure of 18 mmHg or the absence of clinical evidence of left atrial hypertension<sup>12</sup>

Conditions predisposing to development of ARDS in an obstetric patient are-sepsis with prolonged hypotension as seen in chorioamnionitis, endometritis, pre-eclampsia/eclampsia, amniotic fluid embolism, trophoblastic embolism, acute fatty liver of pregnancy, chemical pneumonia, infective pneumonia, trauma, burns, transfusion related lung injury, tocolytic pulmonary edema etc.

### It has two phases:

#### Acute or exudative phase

This is characterized by increased capillary permeability leading to pulmonary edema. In alveolus the Type I alveolar cells undergo necrosis and sloughing. The alveolar walls become edematous and some alveoli get compressed, others collapse due to changes in the surface tension. Hyaline membrane deposits in the alveoli. Microthrombi form in the pulmonary circulation which exacerbates intrapulmonic shunting of blood. Sometimes macrothrombi form which cause pulmonary infarction.

#### Proliferative or fibrosis phase

This phase begins by 3<sup>rd</sup> day and is characterized by proliferation of Type II pneumocytes which later differentiate into Type I cells. Fibroblasts proliferate in the alveolar spaces which collapse and merge into large spaces giving a honey-comb appearance. The sequelae of ARDS is a compromised lung function and sometimes severe chronic debilitating lung disease.

#### Clinical course

Hypoxemia presents early on in the disease process and rapidly progresses. It is usually resistant to high concentration of oxygen supplementation because of shunting of blood from right to left through nonventilated lung segments. It responds to positive end expiratory pressure (PEEP). The lung compliance is reduced due to diffuse edema and fibrosis leading to reduced elasticity. Atelectatic lung patches further decrease the lung compliance.

The airway resistance increase due to presence of areas of consolidation which do not participate in ventilation. High airway pressure are needed to inflate the lungs but caution should be exercised to prevent the risk of barotrauma.

The dead space increases from .35 in normal to .6 in ARDS patients leading to increased partial pressure of CO<sub>2</sub>. Pulmonary hypertension and right sided heart failure may develop

#### Management

Adequate oxygenation to maintain PaO<sub>2</sub> above 60 or oxygen saturation of 90% is essential. High oxygen concentration of >21% can cause toxicity and should be avoided. Endotracheal intubation and mechanical ventilation with positive end expiratory pressure (PEEP) reduces right to left shunts across lung by restoring lung functional residual capacity.

Newer techniques like extracorporeal membrane oxygenation (ECMO) where an artificial auxiliary lung is placed in the vascular circuit allows supplementary pulmonary oxygenation. This permits the lung to repair itself and with this method hyaline formation may be less.

Complications like hemolysis, bleeding and infection may occur.

An improvisation over ECMO is the extracorporeal lung assist (ECLA) where emphasis is on removal of carbondioxide. Both these methods however have not shown any added improvement over mechanical ventilation with PEEP.<sup>12</sup>

Fluid therapy should be optimally managed by pulmonary artery catheterization. It is important to maintain low pulmonary capillary wedge pressure without reducing cardiac output to minimize interstitial edema caused by increased capillary permeability.

Artificial surfactants are not beneficial. Nitric oxide inhalation causes local vasodilatation in well ventilated areas and reduced intrapulmonic shunting but potential toxicity and limited overall improvement as seen in Phase 2 and Phase 3 trials has limited its use to special circumstances where other therapies fail.

### Amniotic Fluid Embolism (AFE)

This represents an anaphylactoid reaction to fetal antigens and presents with hypoxia, hypotension, hemodynamic collapse and coagulopathy.<sup>13</sup>

Incidence varies from 1:8000 to 1:80,000 pregnancies with mortality rate of 61-86%. The duration of time between collapse and death is short usually within 5 hours. Neurological sequelae is common among survivors.<sup>14,15</sup>

In a study by Clark et al it was seen that amniotic fluid embolism in antenatal patient presents with convulsion in 30%, fetal tachycardia in 12% and hypotension in 13%. Postpartum AFE presents with coagulopathy in 54% of cases.<sup>15</sup>

Clinical, hematological and hemodynamic parameters of AFE resemble those seen in anaphylactic and septic shock although cutaneous manifestation and fever are rare.<sup>13</sup> Like in anaphylaxis and septic shock in AFE too entry of foreign protein (fetal origin) results in release of endogenous mediators. The hemodynamic data interpretation points to a humoral etiology and not a thromboembolic event.

### Pathophysiology

Amniotic fluid enters the maternal venous circulation through veins at placental site or site of trauma. Placental abruption and rupture of membrane predispose to this condition. In the past the gold standard of diagnosis of AFE was demonstration of amniotic fluid from pulmonary artery catheter samples. Although not confirmatory such a finding in the setting of characteristic clinical findings should raise suspicion to its diagnosis.

Arachidonic acid metabolites may be responsible for the inflammatory response and point to

a humoral etiology. Humoral pathways invoking an inflammatory response is also seen in anaphylaxis and septic shock.<sup>16</sup> This inflammatory response leads on to systemic inflammatory response syndrome and development of multiorgan failure.

AFE is found to be common in patients with history of drug allergy or atopy.

### Clinical Presentation

#### *Hypoxia*

It is an early feature seen in 93% of patients and results from ventilation perfusion mismatch. Development of pulmonary edema in the later phase due to increased capillary permeability may also contribute to development of hypoxia. Neurological damage and hypoxic encephalopathy may result. Seizures may develop later on.

#### *Hypotension/Shock*

Hypotension present early in the course of AFE. Shock is due to cardiogenic left ventricular failure. Cardiac arrhythmias including bradycardia, asystole, ventricular fibrillations and pulseless electrical activity may develop. Later on both cardiogenic and obstructive factors are responsible for persistence of shock. Shock is a poor prognostic sign.

Coagulopathy/ DIC is encountered in 83% patients of AFE and may result from substances released from amniotic fluid or due to systemic inflammatory response activating the coagulation mechanism<sup>16</sup>.

#### *Diagnosis and Management*

It is a clinical diagnosis and should be suspected when sudden profound shock and cardiovascular collapse develops in a postpartum patient. Arterial Blood Gases (ABG), electrolytes, CBC, coagulation profile and echocardiography may aid in diagnosis.

Management is supportive. Proper oxygenation, fluid resuscitation and vasopressors are used to counter hypoxia and shock. DIC is treated with Fresh Frozen Plasma (FFP), cryoprecipitate or fibrinogen. Delivery is indicated to prevent fetal hypoxia as well as facilitate maternal cardiopulmonary resuscitation.

### Pulmonary Embolism

Clinically it presents with dyspnea, tachypnea, cough, hemoptysis, tachycardia, pleuritic pain and hypotension.

Chest x-ray, ECG and ABG are not diagnostic. Definite diagnosis is by pulmonary angiogram.

Ventilation perfusion scan and helical CT scan are non invasive tests which help in diagnosis. A highly probable VQ scan report mandates initiation of treatment<sup>17</sup>

Heparin remains the mainstay of management. It does not cross the placenta. Initially 5000 - 10,000 U is given as IV bolus followed by 1000 U/hour by infusion. Later on subcutaneous heparin 5000 U every 4 hourly or 7500 U every 6 hourly can be given<sup>18</sup>. Complications of heparin therapy include thrombocytopenia and osteoporosis<sup>19</sup>. Acute PE is managed by IV heparin for 5 days followed by subcutaneous heparin or low molecular weight heparin (LMWH). LMWH is less effective than unfractionated heparin. Treatment should be continued for 6 weeks. In the postpartum period warfarin can be given.

### Unstable pulmonary embolism

It may present as hypotension which is due to right heart strain. It is managed by intravenous fluids and oxygen supplementation. Vasopressors may be needed to increase systemic blood flow.

Thrombolysis and embolectomy is the gold standard of management. Drugs like tissue plasminogen activator and streptokinase is useful for thrombolysis. Inferior vena caval filter is helpful in recurrent pulmonary embolism or when anticoagulation is contraindicated. It is preferable to use retrievable filter which can be removed as soon as patient stabilizes otherwise they might perforate aorta and penetrate nearby structures if left for long time<sup>17</sup>

### Disseminated Intravascular Coagulation

It represents a process of intravascular clotting and fibrinolysis. The common triggering events in obstetrics are placental abruption, amniotic fluid embolism, retained dead fetus and sepsis.

It is important to differentiate it from dilutional coagulopathy which is seen in massive obstetric hemorrhage where replacement has been done with red cells and crystalloids leading to deficiency of platelets and clotting factors.<sup>10</sup>

### Pathophysiology

It is precipitated by endothelial disruption or by release of tissue thromboplastin into the circulation. This activates the coagulation cascade- intrinsic or extrinsic. The end result is the formation of insoluble fibrin. Simultaneously plasminogen is activated into plasmin by tissue activators which causes breakdown of the fibrin to fibrin degradation products (FDP). FDP binds with the soluble fibrin monomers to prevent further polymerization. Fibrin which had formed earlier plugs the microvascular circulation to cause tissue hypoxia and ischemia.

Thrombocytopenia results from consumption and destruction caused by the fibrin degradation products.

### Diagnosis

Elevated fibrin degradation products is sensitive and specific for DIC although values may be normal in 10-15% of patients. Prolongation of prothrombin time and partial thromboplastin time occurs only after 40-50% of the clotting factors have been consumed. Clot retraction time is increased. Platelet count is low.

### Management

Heparin is generally not used in obstetric DIC except in case of retained dead fetus where low dose heparin 5000U is given two times per day in patients with intact circulation. It blocks consumption of fibrinogen and other clotting factors.

Replacement of platelets and soluble clotting factors is effective in preventing hemorrhage. If surgery is planned then platelet transfusion is needed if counts are <30000/ cu mm. Fresh frozen plasma is transfused in bleeding patients with fibrinogen less than 100mg/dl or when prothrombin and partial thromboplastin time are prolonged. In patients who are not bleeding and not likely to require surgery, mild to moderate coagulopathy may be simply observed.<sup>10</sup>

### Hypovolemic shock

Massive hemorrhage leading to volume deficit of more than 25% can lead to hemodynamic instability since at this level of loss the compensatory mechanisms are unable to maintain cardiac output and blood pressure. Further hypoxia and acidosis sets in leading to cellular death and organ ischemia. Hematocrit falls by 3 volume% after 1 litre of blood loss.

Management includes tackling the cause of hemorrhage and starting resuscitative measures simultaneously. In recent reviews there has been a concern over type of fluid used for resuscitation. Crystalloids and blood replacement has shown a decreased mortality as compared to colloids. Acute blood loss should ideally be replaced with whole blood. For stable patients who do not have massive hemorrhage packed red cells may be used. Both increase the hematocrit by 3-4 volume % per unit. Component replacement is rarely needed. Evaluation of platelet count, clotting studies and fibrinogen concentration is essential. Platelet count in bleeding women should be maintained above 50000/cu mm. A fibrinogen level of <100mg/dl or prolonged prothrombin and partial thromboplastin time requires fresh frozen plasma transfusion at dose of 10-15 ml/kg<sup>20</sup>

## Key Points

- Critical care in obstetrics requires multidisciplinary approach. A thorough knowledge of the pathophysiological process and co-relation with the altered physiology in pregnancy is essential for proper management of the critical condition.
- Septic shock should be aggressively managed by intravascular fluid resuscitation, elimination of the septic focus and appropriate antibiotics.
- Hypovolemic shock due to obstetric hemorrhage is a common condition and requires skillful management of the cause along with active resuscitation with crystalloids and blood.
- Amniotic fluid embolism, anaphylactoid reaction to fetal antigens, presents with hypoxia, hypotension, hemodynamic collapse and coagulopathy. Supportive therapy to correct the hemodynamic collapse and mechanical ventilation to support respiration is important although prognosis is dismal.
- For pulmonary embolism a high index of suspicion and evaluation of risk factors is paramount to diagnosis. An abnormal ventilation perfusion scan may aid in diagnosis although a pulmonary angiography remains the gold standard. Heparin, thrombolytic agents, IVC filters and embolectomy can be used for treatment depending on the need of the situation.
- ARDS & DIC may be precipitated by many conditions in pregnancy and should be managed with assisted ventilation with positive end expiratory pressure and component therapy respectively.

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**VALVULAR HEART DISEASE IN PREGNANCY**

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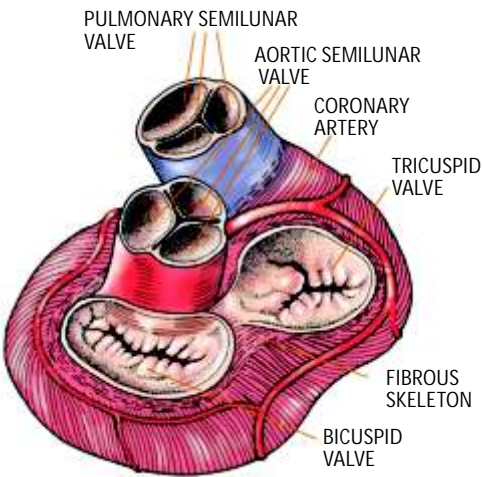
Valvular heart disease is any disease process involving one or more of the valves of the heart (the aortic and mitral valves on the left and the pulmonary and tricuspid valve on the right). Valve problems may be congenital (inborn) or acquired (due to another cause later in life)

The presence of valvular heart disease continues to pose a challenge to both, the clinicians and their pregnant patients. This condition increases the risk of pregnancy to both the mother and the fetus and requires specific care during the preconception period as well as during the pregnancy and labor.

The prevalence and incidence of all heart disease in pregnancy varies from 0.3to 3.5%. Valvular dysfunction originates from Rheumatic heart disease leading to calcification of the valves and loss of elasticity leading to dysfunction

Profound hemodynamic alterations occur during pregnancy, labor and delivery, and in the post-partum period These and other normal physiological changes pose a substantial demand on cardiac function in patients with valvular heart disease and may require the initiation or titration of cardio-vascular medication to manage volume overload, hypertension or arrhythmias.

The marked hemodynamic changes explain the characteristic signs and symptoms that occur during pregnancy, which mimic those of heart disease.



**Physiological hemodynamic changes during pregnancy**

Hemodynamic Parameters	Change During Normal Pregnancy	Change During Labor and Delivery	Change During Postpartum
Blood volume	40% - 50%		
Heart rate	10-15 beats per minute		
Cardiac output	30-50% above baseline	Additional 50%	Initially with in Preload, then - with diuresis
Blood pressure	- 10 mm Hg		Returns to baseline
Stroke volume	1 <sup>st</sup> and 2 <sup>nd</sup> trimester; slight- 3 <sup>rd</sup> trimester	(300-500 cc per contraction)	-
Systemic vascular resistance	-		Returns to baseline

**Predictors of Cardiac complications-**

- Prior heart failure, transient ischemic attack, arrhythmia or stroke
- Baseline NYHA Class III or greater or cyanosis
- Mitral valve area <2 cm<sup>2</sup>
- Peak left ventricular outflow tract gradient >30 mm Hg
- Ventricular ejection fraction < 40%

The risk index comprising of the factors shown here, accurately predicts the woman's chance of having adverse cardiac and perinatal outcome. Classification of Valvular Heart Lesions According to Maternal, Fetal, and Neonatal Risk.

Table 1. Classification of Valvular Heart Lesions According to Maternal, Fetal and Neonatal Risk.*			
Low Maternal and Fetal Risk	High Maternal and Fetal Risk	High Maternal Risk	High Neonatal Risk
Asymptomatic aortic stenosis with A low mean outflow gradient (<50 mm Hg) in the persence of normal left ventricular systolic function	Severe aortic stenosis with or without symptoms	Reduced left ventricular systolic function (Left ventricular ejection Fraction <40%)	Maternal age <20 yr or >35 yr
Aortic regurgitation of NYHA class I or II with normal left ventricular systolic function	Aortic regurgitation with NYHA class III or IV symptoms	Previous heart failure	Use of anticogulant therapy through out pregnancy
Mitral regurgitation of NYHA class I or II with normal left ventricular systolic function	Mitral stenosis with NYHA class III or IV symptoms	Previous stroke or transient ischemic attack	Smoking during pregnancy
Mitral regurgitation of NYHA class I or II with normal left ventricular systolic function	Mitral regurgitation with NYHA class III or IV symptoms		Multiple gestations
Mitral-valve prolapse with no mitral regurgitation or with mild-to-moderate mitral regurgitation and with normal left ventricular systolic function	Aortic-valve disease, mitral-valve disease, or both, resulting in severe pulmonary hyper tension (pulmonary pressures) >75% of systemic pressures)		
Mild-to-moderate mitral stenosis (mitral-valve area> 1.5 cm <sup>2</sup> , gradient<5 mm Hg) without severe pulmonary hypertension	Aortic-valve disease, mitral-valve disease, or both, with left ventricular systolic dysfunction (ejection fraction < 0.40)		
Mild-to-moderate pulmonary-valve stenosis	Maternal cyanosis		
	Reduced functional status (NYHA class III or IV)		

\* Derived from ACC/AHA Guidelines<sup>6</sup> and Siu et al. <sup>45</sup> NYHA denotes New York Heart Association.

Management

Whenever possible, symptomatic or severe valvular lesions should be addressed and rectified before conception and pregnancy.

Women with pre-existing cardiac lesions should receive pre - conception counseling on maternal and fetal risks, potential long term maternal morbidity and mortality and counseling on contraception.

Preconception workup

- Detailed history and careful cardiac examination with assessment of functional capacity
- 12 lead ECG
- Echocardiogram
- Doppler study
- In patients with impaired or questionable functional capacity an exercise tolerance test is advocated, with measurement of oxygen consumption.
- Risk of pregnancy on basis of evaluation discussed with patient and family by both cardiologist and obstetrician

Antepartum and Peripartum care

Joint Obstetric and Cardiology evaluation ensures a thorough understanding of the disease as well as the physiology of pregnancy.

Frequency of ANC visits depends on the type and severity of the disease and patient's condition but the standard first trimester visit is a must, followed by the second trimester 3D screening. The frequency of visits should increase in the third trimester when the hemodynamics undergo a major change .When drug therapy indicated, the smallest therapeutic dose known to be safe for the fetus should be used Prophylaxis against rheumatic fever is advocated.

Signs and Symptoms

The most frequent symptom of heart disease is breathlessness which should be assessed keeping in mind that it is a variable feature of normal pregnancy.

The New York Heart Association (NYHA) classification is based on limitation of physical activity.

Class 1 - No limitation of physical activity.

Class 2 - Slight limitation of physical activity .Ordinary physical activity causes fatigue, dyspnoea.

Class 3 - Marked limitation of physical activity. Less than normal physical activity causes fatigue, dyspnoea.

Class 4-Symptoms of cardiac insufficiency and anginal syndrome present at rest.

Syncope occurs particularly in the middle trimester, especially in severe AS.

Chest pain may be present in severe AS

Physical sign

Peripheral pulse is increased in volume

The heart apex beat is more forceful

Premature atrial and ventricular ectopic beats are common

Neck vein pulsations are more prominent

Oedema

Murmurs

As seen all these signs are misleading in a pregnant pt as they are present often in normal pregnancy also, but the presence of increased right atrial pressure(>10mmhg) and apex beat >2cm outside midclavicular line is considered definitely abnormal. Ejection systolic murmur can be heard in 96% of apparently normal women. Venous hum- continuous murmurs are usually audible in pregnant state. The significant murmurs are-

1. Pansystolic murmur
2. Late systolic murmur
3. Ejection systolic murmurs louder than grade 3/6

### Medical Management

- Most patients with valvular heart disease can be managed medically by the following guidelines
- Reassurance, Restricted physical activity
- Salt restricted diet
- Diuretics, Daily weight record, Tranquilisers and sedatives
- Treat anaemia, hypertension and inter current infection
- Digitalis, beta-blockers, adenosine, sotalol, lidocaine and procainamide can be safely used for arrhythmias
- ACE inhibitors, Angiotensin receptor blockers and Amiodarone avoided during pregnancy

Table 2. Fetal Effects of, Maternal Indications for, and Risks Associated with Drugs Used in the Treatment of Maternal Valvular Heart Disease

Drug	Fetal Effects	Indication in Pregnant Patients with Valve Disease
Diuretics		
Furosemide	Increased urinary sodium and potassium levels	To decrease congestion associated with valvular heart disease
Antihypertensive agents		
Beta-blockers	Possible decreased heart rate, possible lower birth weight	Hypertension, supraventricular arrhythmias, to control heart rate in woman with clinically significant mitral stenosis
Methyldopa Vasodilator agents	No major adverse effects	Hypertension
Angiotensin-converting-enzyme inhibitors	Urogenital defects, death, intrauterine growth retardation	Not indicated during pregnancy and should be discontinued
Hydralazine	No major adverse effects	For vasodilation in cases of aortic regurgitation and ventricular dysfunction
Nitrates	Possible bradycardia	Rarely used to decrease venous congestion
Anticoagulant and antithrombotic agents		
Warfarin	Hemorrhage, developmental abnormalities used between wk 6 and wk 12 of gestation	For anticoagulation of mechanical heart valves, valvular heart disease with associated atrial fibrillation during wk 12-36 of pregnancy
Unfractionated heparin	Hemorrhage, no congenital defects	For anticoagulation of mechanical heart valves, valvular heart diseases with associated atrial fibrillation during wk 6-12 and after wk 36 of pregnancy
Low-molecular-weight heparin	Hemorrhage	Not currently indicated during pregnancy
Aspirin Antiarrhythmic agents	Hemorrhage, prolongation of labor, low birth weight (when taken in high doses)	Low dose aspirin (81 mg/day) occasionally used as an adjunct in patients with previous embolic events or prosthetic-valve thrombosis
Digoxin	No major adverse effects	For suppression of supraventricular arrhythmias
Adenosine	No major adverse effects	For immediate conversion of supraventricular arrhythmias
Quinidine	High doses may be oxytocic	Occasionally used for suppression of atrial or ventricular arrhythmias
Procainamide	No major adverse effects	Occasionally used for suppression of atrial or ventricular arrhythmias
amiodarone	Hypothyroidism, intrauterine growth retardation, premature birth	Rarely used during pregnancy because of side effects; may be used to suppress atrial or ventricular arrhythmias in high-risk patients

Derived from: Uri Elkayam, Journal of the American College of Cardiology, 2005 vol 46, PA: Elsevier 2005

### Surgical management

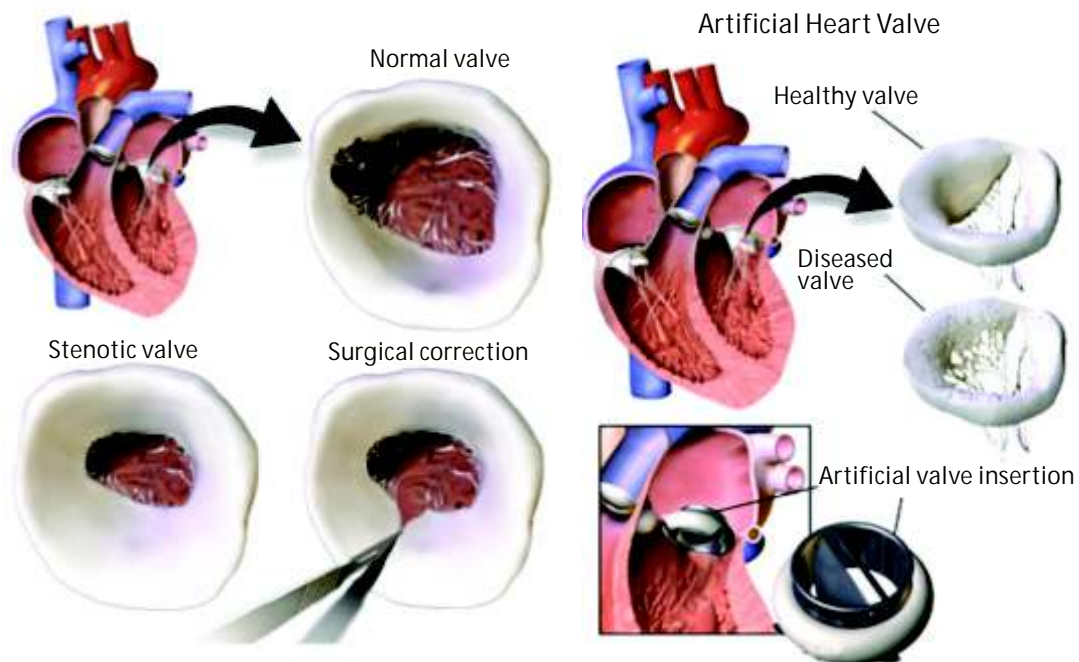
- Valvotomy
- Decalcification
- Complex mitral valve repair

Second trimester is the safe and preferred period of pregnancy for a repair. Valvular Heart Disease is the most common indication for cardiovascular surgery during pregnancy. The procedure is relatively safe with maternal mortality of 3 to 6% and fetal mortality of 20 to 30%. Maternal deaths are reported in 9% of valvular surgical procedures.

Strategies to repair a defective valve:

#### Commissurotomy

A surgical procedure performed to open a stenotic (narrowed) valve. A stenotic valve restricts the flow of blood. A scalpel incision widens the valve.



### Percutaneous balloon mitral valvuloplasty

### Prosthetic valves

- Are of two types
- Mechanical
- Biological

Many factors determine the choice of prosthetic heart valves in patients of childbearing age i.e risk of reoperation in cases of bioprosthetic valves versus the risk of bleeding, thromboembolism and valve thrombosis with mechanical valves, as well as effects on fetus. Pregnancy is tolerated well by patients with prosthetic valves.

### Biological valves

*Homografts:* Preserved human valves are used in a minority of patients.

*Xenografts:*

1. Porcine models: Carpentier-Edwards valves, Hancock II and Mosaic valves
2. Bovine Pericardial valves : Perimount series valves. Stentless porcine valves : Edwards Prima Plus, Medtronic Freestyle, and Toronto SPV valve.

### Mechanical valves

Starr Edwards

Caged ball valve



Tilting disc valve



Bileaflet valve





### Anticoagulant therapy in pregnancy

Table 2. Recommendations of the Seventh ACCP Consensus Conference on Antithrombotic therapy for Prophylaxis in Patients With Mechanical Heart Valves

1. Aggressive adjusted-dose UFH, given every 12 h subcutaneously throughout pregnancy; mid-interval activated partial thromboplastin time maintained at  $>2$  x control levels, or anti-Xa heparin level maintained at 0.35 to 0.70 IU/ml.

OR

2. LMWH throughout pregnancy, in doses adjusted according to weight or as necessary to maintain a 4-h postinjection anti-Xa heparin level of about 1.0 IU/ml

OR

UFH or LMWH, as above, until the 13th week, change to warfarin until the middle of the third trimester, then restart UFH or LMWH therapy until delivery

Reprinted, with permission, from Bates et al<sup>60</sup>.

ACCP = American College of Chest Physicians; LMWH = low molecular weight heparin; UFH = unfractionated heparin.

### Indications for Anticoagulation

1. Patients with mechanical heart valves
  2. Chronic atrial fibrillation
  3. DVT and PE
- **Warfarin:** Causes fetal skeletal stippling, craniofacial deformities, microcephaly, optic atrophy, limb defects. Exposure in first trimester causes dorsal or ventral midline dysplasia. Warfarin embryopathy consists of mid face and nasal hypoplasia, optic atrophy, hypoplasia of digits, stippled epiphysis (chondrodysplasia punctata), mental illness,
  - It also causes 1st trimester abortions, still births, neonatal deaths and fetal hemorrhages.
    - bleeding - 2 to 4% in patients on anticoagulants

### Contraception

- **Permanent methods:**
  - Vasectomy
  - Tubal ligation
- **Temporary Methods:**
  - IUD : excellent and safe method - meticulous care and prophylactic antibiotics at time of insertion
  - COCS: contraindicated
  - POP: pills, patches and vaginal rings can be used

### Labor and Delivery

- The timing and mode of delivery is to be discussed jointly by the obstetrician, cardiologist and obstetric anaesthesiologist.
- All the patients with NYHA classes III & IV and some from class II hospitalised prior to delivery to achieve optimal conditions. Before delivery, optimization of left atrial pressure is achieved by diuretics and reduction of heart rate with beta blockers. Antibiotic prophylaxis is essential.

### Mode of Delivery

Patients are preferably kept in left lateral position. Vaginal delivery with shortened second stage with regional anesthesia preferred.

Epidural analgesia : provides pain relief, minimizes intrapartum fluctuations in cardiac output and lowers left atrial and pulmonary artery pressures

- Avoid ergots and oxytocics
- CS performed for obstetric reasons. No place for trial / prolonged and difficult labor
- Hemodynamic monitoring with Swan Ganz catheter during delivery and several hours into puerperium in patients with heart failure / moderate to severe mitral stenosis / left ventricular dysfunction / PAP  $> 50$  mm Hg
- Vaginal delivery preferred by Hammed et al and Silversides et al - 90 to 95 %
- Incidence of CS 20% - Bhatla et al

Monitoring for 7-10 days in the postpartum period in high risk patients

### Mitral Stenosis

Mitral stenosis is most common rheumatic valvular lesion seen in pregnancy. 25% of patients become symptomatic for first time during pregnancy. Mortality depends on the severity of the lesion. Mortality less than 1 % with minimal symptoms and about 5% with severe mitral stenosis

### Grades of severity

- Mild: MVA  $1.5-2\text{cm}^2$
- Moderate: MVA  $1-1.5\text{cm}^2$
- Severe: MVA  $<1\text{cm}^2$
- Critical: MVA  $<0.6\text{cm}^2$
- Higher incidence of morbidity with moderate to severe MS

*Hammed et al, Barbosa et al & Silversides et al*

### Management of MS

Management of Mitral stenosis is complex because of the potential impact on the fetus, related to drug therapy and exposure to ionizing radiation associated with diagnostic and therapeutic procedures such as cardiac catheterization or PBMV, as well as the effect of anesthesia and cardiopulmonary bypass in cases of cardiac surgery.

Patients are divided into 2 groups:

- 1) Non pregnant and contemplating pregnancy
- 2) Patients already pregnant

#### Non Pregnant Group

- Severe mitral stenosis (MVA  $<1\text{cm}^2$ ) - PBMV
- Moderate mitral stenosis - patients asymptomatic or mildly symptomatic - Medical therapy  
(If patient not suitable for PBMV)
- Mild mitral stenosis have favourable pregnancy outcome

### Already Pregnant Patients

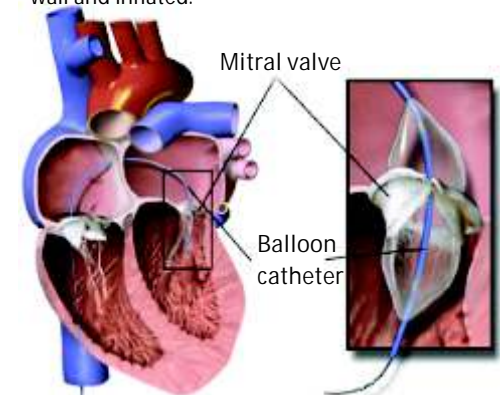
- Aims to reduce heart rate and left atrial pressure. Risk of maternal events include progression of heart failure with need for PBMV or cardiac surgery – strongly associated with severity of mitral stenosis and NYHA functional class before pregnancy
- Use of beta mimetic tocolytics contraindicated
- Mild mitral stenosis: Medical treatment
- Reassurance, limitation of physical activity, salt restricted diet, treatment or correction of anaemia, hypertension, infection, obesity, arrhythmias, and thyrotoxicosis. Digoxin, diuretics and beta blockers. Beta blockers recommended if pulmonary artery pressure  $>50\text{mm Hg}$  by echo - attenuates the heart rate and increases the diastolic filling period
- Atrial fibrillation may result in rapid deterioration with the risk of embolism and stroke. Hence prompt treatment with anti coagulants, beta blockers, cardioversion, digoxin and diuretics is a must

### Indications for surgical intervention

1. MVA  $<1\text{cm}^2$
2. Cardiac failure before / in early pregnancy
3. Uncontrollable haemoptysis
4. Patients not responding to medical treatment

#### Valvuloplasty

A procedure to improve blood flow through a narrow valve. A catheter is threaded to the valve through a hole temporarily created in the septal wall and inflated.



### Percutaneous Balloon Mitral Valvuloplasty

#### Observations

- Mean valve area increased from  $0.75-1.2\text{cm}^2$  to  $1.7-2.2\text{cm}^2$  (Uri Elkayam)
- Maternal Mortality 1.96% and perinatal mortality 1.96% - Algotar et al (52 cases)
- Maternal Morbidity 3.5 % and perinatal mortality 7.1 % - Kore et al (26 cases)
- PBMV: gives good results in young patients with non-calcific valves without sub valvular thickening or significant MR

- Performed at end of second trimester or early third trimester
- Complications few and include transient AF, blood loss, cardiac tamponade and worsening of MR. Minimal fetal risk are there because of ionizing radiation
- Because of high risk to the fetus, mitral valve repair or replacement considered only in cases of severe MS who are refractory to optimal medical therapy and are not suitable candidates for PBMV
- Open heart surgery avoided in pregnancy because of morbidity and mortality to the fetus (especially in the first trimester)

### Labor Management

Before delivery, optimization of left atrial pressure achieved by diuretics and reduction of heart rate with beta blockers. Antibiotic prophylaxis

### Mode Of Delivery

Vaginal delivery with shortened second stage with regional anesthesia preferred.

Epidural analgesia : provides pain relief, minimizes intrapartum fluctuations in cardiac output and lowers left atrial and pulmonary artery pressures

- Avoid ergots and oxytocics
- CS performed for obstetric reasons . No place for trial / prolonged and difficult labor
- Hemodynamic monitoring with Swan- Ganz catheter during delivery and several hours into puerperium in patients with heart failure / moderate to severe mitral stenosis / left ventricular dysfunction / PAP > 50 mm Hg
- Vaginal delivery preferred by [Hammed et al and Silversides et al](#) - 90 to 95%
- Incidence of CS 20 % - [Bhatla et al](#)

### Aortic Stenosis

*Etiology:* congenital, rheumatic mild to moderate stenosis with valve area > 1cm<sup>2</sup> : pregnancy is tolerated well

*Severe stenosis:* balloon valvuloplasty / valve repair before pregnancy. Maximize cardiac output by avoiding exercise, vasodilators and diuretics

### Medical management

Asymptomatic patients with mild to moderate stenosis with preserved left ventricular function

treated medically : close monitoring, bed rest, O<sub>2</sub>, beta blockers, diuretics(if volume overload present)

### Severe AS

- Results in hemodynamic and symptomatic deterioration
- Associated with significant maternal morbidity and unfavourable fetal outcome
- Increased risk of left sided failure, angina, dyspnoea in second or third trimester
- Maternal mortality high - 17 %

### Management

- If symptoms severe and refractory to medical treatment and patient cannot be delivered MTP (if patient symptomatic before end of first trimester)
- Valve repair/ balloon valvuloplasty / valve replacement carries a mortality of 11%
- High incidence of complications with moderate to severe AS [Hameed et al, Silversides et al](#)

### Labor management

- Hemodynamic monitoring , Vaginal delivery with shortened second stage under
- Regional anesthesia used with caution to prevent fall in systemic vascular resistance (poorly tolerated)
- When intervention seems indicated and fetal maturity confirmed-patient delivered and valve repair / replacement after delivery
- General anesthesia and CS allows optimal hemodynamic control .

### Mitral Regurgitation(MR)

*Etiology:* Rheumatic / MVP

*Before pregnancy:* If MR is severe: mitral valve repair

*Mitral regurgitation with MVP:* Pregnancy is uneventful. Serious complications like endocarditis, arrhythmias and cerebral ischemia may occur

*If left ventricular function good:* pregnancy tolerated well

*Complications:* New onset atrial fibrillation or severe hypertension can result in pulmonary edema or cardiac decompensation

### Management of MR

Asymptomatic patients: No treatment

- Symptomatic patients with left ventricular dysfunction with hemodynamic abnormalities and symptoms of heart failure : Medical treatment : Diuretics, digoxin, vasodilators, organic nitrates and hydralazine.
- Surgery indicated for severe symptomatic patients : valve repair-good option. Valve replacement-last resort

### Aortic regurgitation

- *Etiology*: congenital / rheumatic / endocarditis / dilated aortic annulus
- Commonly seen with mitral valve disease
- AR without left ventricular dysfunction - tolerated well
- AR with left ventricular dysfunction-medical management : close monitoring, limitation of physical activity, salt restriction, diuretics, digoxin, beta blockers, vasodilators - hydralazine and nitrates
- Surgery delayed if possible until after delivery
- Hemodynamic monitoring during labor
- Patients tolerate bradycardia poorly . Heart rate maintained around 80-100 bpm
- **No prophylactic surgery for asymptomatic patients with severe MR / AR with normal left ventricular function who are contemplating pregnancy.**

### Pulmonary Stenosis

*Etiology*: Congenital : Obstruction at valvular / subvalvular / supra valvular levels /

Treatment: In non pregnant symptomatic patients with severe PS: balloon valvuloplasty PS, even when severe is well tolerated during pregnancy in contrast to severe MS and severe AS. The severity has no impact on maternal or fetal outcome

- If patient asymptomatic/ mildly symptomatic : no surgery
- Cases with right heart failure - balloon valvuloplasty indicated
- Vaginal Delivery tolerated well and recommended in majority of patients

### Tricuspid Regurgitation

Isolated tricuspid regurgitation : managed conservatively, protect against diuretic induced hypoperfusion

In presence of impaired right ventricular function, the increased stroke volume is poorly tolerated, resulting in worsening of symptoms

Pregnancy is tolerated well.

- Management of valvular heart disease during pregnancy is challenging. A thorough knowledge of the expected natural history of the disease during pregnancy and of the possible treatment options is required for clinical decision making

### Looking Back into the Future

#### Recent advances

Researchers are continuously exploring possible causes and treatments for heart valve diseases as well as the long term effects of those treatments. Recent findings include.

- Stem cell research for congenital heart disease .
- Robotically – assisted surgery for mitral valve repair
- Cells from patients blood vessels grown over pig/human cadaver valves
- Percutaneous trans catheter heart valve implantation
- Medical therapy with Statins and ACE inhibitors

ACKNOWLEDGEMENT: All pictures courtesy google.

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## PREGNANCY WITH SURGICALLY CORRECTED CARDIAC LESION

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With wider availability and improved techniques of cardiac surgery obstetricians are increasingly required to supervise the pregnancies of women with corrective cardiac surgery. The cardiac defects requiring surgery can be congenital or acquired. Most of the clinically significant congenital cardiac lesions are repaired early in life and these women usually behave as non cardiac patients during pregnancy. The acquired cardiac lesions are consequent to rheumatic heart disease involving the valves. These defects are treated with either valvotomy or valve replacement. The women with valve replacement present specific management difficulties during pregnancy. For optimum management of these women, combined effort of a team comprising of an obstetrician, cardiologist, anesthesiologist and pediatrician is required.

It is essential that a woman with surgically corrected heart lesion undergoes a thorough preconception evaluation, receives appropriate preconception counseling and is closely supervised during her pregnancy and labour.

### Prepregnancy evaluation

This plays an important part in ensuring a successful pregnancy outcome and involves reviewing the old records of the woman and assessing her functional cardiac status. It is important to know the type of cardiac lesion, type of corrective procedure done, type of valve used if any, level of cardiac functional status and the drugs the woman is taking.

For the assessment of functional cardiac status the woman is subjected to various investigations like ECG, X-ray chest, 2D echocardiography and stress echocardiography. Certain hematological tests like hemoglobin, hematocrit, and total and differential leucocyte count are carried out to rule out anemia or any infection which if present should be corrected prior to her planning a pregnancy. In women on anticoagulant drugs, coagulation profile and platelet count is done.

A general medical examination including a dental check up is indicated. All the drugs which the woman is taking need to be reviewed for the risk of teratogenesis associated with some and the need of switching over the woman to safer drugs once she conceives.

### Preconception counseling

This includes counseling the couple regarding the maternal and fetal risks associated with pregnancy so that the couple can take an informed decision.

### Maternal risk counseling

It is important for the couple to realize that long term survival of patients with significant acquired cardiac lesion is never the same as that of general population. However, the long term survival is unaffected by pregnancy. The pregnancy related risk depends upon factors like nature of cardiac lesion, type of surgery done, type of valve used, cardiac functional status of the woman, whether she's on anticoagulants or not.

Women with congenital cardiac lesions completely corrected by surgery early in life, usually have no problems during pregnancy. Likewise women with acquired cardiac lesions such as rheumatic heart disease in class I or II after successful correction are unlikely to deteriorate to class III or IV unless some new cardiac insult like arrhythmia or failure of valve develops. Women with pulmonary hypertension, Marfan's syndrome, pulmonary arteriovenous fistulae or uncorrectable cardiac lesion in class III or IV in spite of medical treatment should be advised against pregnancy due to increased maternal mortality associated with these. Women in class III or IV should be advised to undergo corrective surgery prior to conception.

Women with prosthetic valves on anticoagulants are at increased risk of thromboembolism due to suboptimal anticoagulation consequent to pregnancy associated hypercoagulability and switch over from warfarin to heparin in first trimester of pregnancy. These women are also at increased risk of side effects like osteoporosis, alopecia, painful nodules etc. associated with long term use of heparin. There is an increased risk of bleeding complications like PPH, episiotomy hematoma, abdominal wound hematoma etc. and subacute bacterial endocarditis.

### Fetal risk counseling

The increased fetal risk in pregnant women with surgically corrected cardiac lesions is due to following factors:

- Genetic transmission of certain congenital cardiac defects.
- Adverse effects of drugs like anticoagulants in women with valve replacement.
- Limited cardiac output due to mitral valvular disease

In women with congenital heart defects like pulmonary stenosis, patent ductus arteriosus, coarctation of aorta and cyanotic heart disease, the risk of transmission to the foetus is 6-9% whereas with defects like aortic stenosis, ventricular septal defect and atrial septal defect the risk of transmission is 12-17%.<sup>1,2,3</sup>

Women with prosthetic valves are on life long anti coagulation and warfarin is the preferred anticoagulant. Warfarin is contraindicated in pregnancy due to 5 - 10% risk of embryopathy and congenital birth defects like nasal and limb hypoplasia associated with it. It also causes early pregnancy loss and bleeding complications in fetus manifesting as microcephaly mental retardation, optic atrophy, cerebellar atrophy etc. It can result in intracranial hemorrhage and still birth during pregnancy.

These risks are minimized by replacing warfarin by heparin in the first trimester while organogenesis is taking place. However it has been recently reported that the risk of embryopathy with warfarin is very small if the dose is less than 5mg daily.<sup>4</sup> Warfarin is replaced by heparin near term close to delivery as heparin has a shorter half life and has an antidote protamine sulphate available.

Women with mitral valvular disease have limited cardiac output with resultant decrease in uterine blood flow. This results in low birth weight babies and increased incidence of intrauterine growth retardation.

#### Management of a pregnant woman with surgically corrected cardiac lesion

As soon as the woman with surgically corrected cardiac lesion conceives she should get booked and undergo cardiac evaluation in case she has not had it in the prepregnant state. All those with features of valvular failure or cardiac decompensation or any other high risk factors associated with increased maternal mortality should be offered medical termination of pregnancy. It is best done in first trimester. Those who wish to continue pregnancy, appropriate counseling regarding the maternal and foetal prognosis, need for frequent and regular follow ups and need for hospitalization is done.

The basic principles of management of these women are the same as any other women with cardiac disease. These include limitation of physical activity, dietary counseling and restriction of sodium intake, avoidance of exposure to infections and prompt treatment of the same and prevention of anemia by encouraging regular intake of iron and folic acid supplements. However there are certain ante partum, intra partum and post partum considerations specific to women with surgically corrected cardiac lesions.

#### Ante partum considerations:

Anticoagulation during pregnancy:<sup>5,6</sup>

This involves fine balancing between maternal and fetal risks. All women with mechanical valves and some with biologic valves with coexistent atrial fibrillation, left atrial

enlargement and history of prior embolisation need long term anticoagulation.

One of the following three regimens can be used for anticoagulation during pregnancy;

- Aggressively adjusted dose of low molecular weight heparin throughout pregnancy with monitoring of Anti-Xa levels. It should be administered subcutaneously twice a day. The dose should be adjusted to maintain the Anti Xa levels between 0.7 to 1.2 U/ml 4 hrs after administration of drug. If it is not possible to assess these levels then aPTT should be maintained at or above 2.0.
- Adjusted dose subcutaneous heparin throughout pregnancy with monitoring of aPTT. Usually subcutaneous dose of 17,500 to 20,000 IU of UFH is required twice a day. Although it is safer for the fetus but is associated with a higher risk of thromboembolism, osteoporosis, alopecia, painful subcutaneous nodules and heparin induced thrombocytopenia in the mother.
- Use of either subcutaneous LMWH or subcutaneous or continuous intravenous UFH between 6 to 12 weeks and close to term i.e. at 36 weeks onwards and use of warfarin at, all other times. Warfarin is monitored by INR and the lowest possible dose to maintain the INR between 2.5 to 3.5 should be administered.

Warfarin should be avoided in first trimester due to the risk of spontaneous abortion, embryopathy and prematurity associated with it. In Europe some physicians do continue warfarin in the first trimester if the dose is less than 5 mg per day as they believe that warfarin related embryopathy is dose dependent. However, there is still lack of sufficient ground for recommendations about optimal antithrombotic therapy in pregnant women with mechanical valves. Some physicians add low dose aspirin to the anti thrombotic regime.<sup>6</sup>

Fetal monitoring:

In women on anticoagulants an early first trimester scan (9-13 weeks) for fetal viability and another level 2 scan at 16-20 weeks to rule out any congenital anomaly is indicated. In women with congenital cardiac defect a fetal echocardiography is done at 22 weeks to rule out any inherited cardiac defect in the fetus. In late pregnancy close monitoring of the fetal growth by clinical and ultrasonic evaluation is done for early detection of intrauterine growth restriction.

#### Intrapartum considerations

Antibiotic prophylaxis should be given as indicated and complete asepsis is maintained. Spontaneous onset of labour is awaited. Vaginal route of delivery is preferred except if the

patients who go into labour while still on warfarin. In these women warfarin should be stopped immediately, Vitamin K is given intravenously, INR is corrected by administering fresh frozen plasma in a dose of 1 unit per every 15 kg body weight and LSCS is done under general anesthesia once INR is less than two. This is indicated to prevent intracranial hemorrhage in the fetus. Regional block is contraindicated in these women. A liberal uterine incision should be given to avoid difficult extraction of baby. Meticulous hemostasis is achieved specially in the area under the bladder flap.

In women switched over to heparin, the drug is stopped at onset of true labour. The effect of heparin wanes off in 6-8 hours. In case an emergency caesarean section is indicated the effect of heparin can be neutralized by administering protamine sulphate intravenously in the dose of 1 mg for every 100 units of heparin. It is important to titrate the dose of protamine sulphate according to the time elapsed since the last dose of heparin. It is better to undercorrect as excess protamine sulphate has anticoagulant effect. During vaginal delivery pudendal block is avoided for the risk of hematoma formation. Complete haemostasis should be achieved while repairing episiotomy or any tear. Post delivery 20 units of oxytocin in 1 litre of normal saline is infused over 24 hours.

### Postpartum considerations

Patient is carefully observed for any PPH or episiotomy hematoma following delivery. She may be advised to rest for 24-48 hours for sealing of small bleeders. Heparin is restarted 4-6 hours after normal delivery and 24 hours after caesarean section. Oral anticoagulants can be started concomitantly. Breast feeding is not contraindicated. Patient should be encouraged to ambulate early and is discharged after a week if stable. Appropriate contraceptive advice should be given before the woman is discharged. According to the WHO eligibility criteria for contraceptive use (2004) in uncomplicated valvular heart disease in addition to barrier contraception Cu IUCD, LNG IUCD, POP, DMPA /NET-EN and LNG implants all can be safely prescribed (category 1). However combined oral contraceptives (COCs) are category 2 i.e benefits outweigh risks. Antibiotic prophylaxis is advised for insertion of IUCD and female sterilization. In case of complicated valvular disease i.e associated with pulmonary hypertension, risk of atrial fibrillation, h/o SABE, COCs are contraindicated (category 4) and IUCDs are category 2. Condoms, progestin only pill (POP), DMPA / NET-EN and LNG implants are safe.

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## ANAEMIA IN PREGNANCY

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Anaemia is the most common medical disorder of pregnancy. It is one of the important causes of direct maternal death. In 47% of the maternal deaths in developing countries it is an indirect cause of death (ICMR Report, 2000). It leads to serious morbidities in the mother (CCF, haemorrhage, infection) and in fetus (Preterm delivery, IUGR, low iron stores.<sup>1</sup> The best part of anemia is that it is preventable.

### Magnitude of Problem:

The overall prevalence of anemia is estimated to be 40% of the world's population. Prevalence of anemia is 35% for non-pregnant women and 51% for pregnant women globally.<sup>2</sup> The prevalence of anemia in Indian pregnant population is about 88%.<sup>3</sup> In India, anemia antedates pregnancy, "Too early, Too frequently, Too many" is the rule. Therefore anaemia is the most common medical disorder in pregnancy in the developing country.

### Definition of Anaemia:

The WHO definition for diagnosis of anaemia in pregnancy is haemoglobin concentration of less than 11 gm% and the haematocrit less than 33%. The Center for Disease Control (CDC) USA, defines anemia as 10.5 gm% in second trimester of pregnancy.<sup>4</sup>

### Severity of Anemia:

According to ICMR anemia is categorized into 4 groups depending upon the haemoglobin level. This is the most acceptable categorization.<sup>5</sup>

Category	Anaemia severity	Hb level (gm%)
1	Mild	10.0-10.9
2	Moderate	07.0-10.0
3	Severe	< 7
4	Very severe (Decompensated)	< 4



### The Story of Anaemia

The story of anemia starts in Indian women right from birth. The fetus born to an anemic mother has no iron stores and hence it manifests with anemia in early infancy. During adolescence the menstrual blood loss results in fall in the haemoglobin of the girl child. Excessive menstrual loss, worm infestation (Hook worm and schistosomiasis), bleeding from the GIT, haemorrhoids, diarrhoea all contribute to the pathological causes of iron loss.<sup>6</sup> This leads to iron depletion.

Early age marriage and an early conception further compounds the problem of anemia. The woman starts her pregnancy with depleted iron stores. During pregnancy her iron demands increase i.e. 4 gm% in early pregnancy, 5.5 gm% from 20-32 wks and 6-8 gm% from 32 wks onwards.<sup>7,8</sup> An average Indian diet contains 19-20 mg of iron/day. As absorption rate of iron is around 10%, an average of 40-60 mg of iron should be available in the diet during pregnancy. Diet alone cannot supply such high amounts of iron. Hence iron supplementation during pregnancy is a must. Lack of ANC also adds to the problem as iron and FA supplements are not taken by the patient. This leads to further lowering of the haemoglobin.

Physiological hemodilution occurs during pregnancy where plasma volume increases by 40% and RBC volume increased by 20%, this leads to a apparent fall in haemoglobin leading to dilutional anemia of pregnancy.<sup>9</sup>

Faulty diet rich in phytates and phosphates make the iron salts insoluble.<sup>10</sup> Defective absorption due to presence of tea, coffee, milk, calcium make the iron unavailable to the mother.

The bioavailability of haem iron is good accounting for a absorption rate of 15-30% in anemic patient.<sup>11</sup> The non-haem iron pool is made up of all other sources such as cereals, seeds, vegetable, milk.<sup>11</sup> Its absorption rate is only 5-10%. The predominance of nonhaem iron in Indian diet makes the iron bioavailability less.<sup>12</sup>

The pregnant women starts a pregnancy with depleted iron stores, compounded by physiological haemodilution, inadequate and faulty diet, increase demands by fetus, low bioavailable iron, diet low in ascorbic acid and high with phytates.

Most deliveries in rural and tribal areas are home confinements conducted by traditional birth attendants who do not practice active management of third stage making them more prone to postpartum haemorrhage.<sup>8</sup> Repeated and closely spaced pregnancies with prolonged period of lactation make most women enter pregnancy with little or no iron reserve.<sup>2,8</sup>

The fetus born to this anemic mothers do not have any iron stores although they are not anemic at birth.

### Effects of Anaemia on Pregnancy

Maternal-mild anaemia does not have any effect on pregnancy labour except that the iron stores are low and mother becomes moderate to severely anaemic in subsequent pregnancies. Moderate anaemia may cause increase weakness, lack of energy, fatigue and poor work performance. Severe anaemia, is however associated with poor outcome. The women may have palpitation, tachycardia, breathlessness leading to CCF which may be fatal.<sup>3,8,13,14</sup> There is increase incidence of preterm labour (28.2%), PIH (31.2%) and sepsis.<sup>3,15,16</sup>

Fetal-irrespective of the maternal iron status, the fetus derives iron from the mother. Hence the fetus is not anaemic at birth. However no iron stores are present in this baby. Adverse perinatal outcome in the form of preterm labour, IUGR and increase perinatal mortality rates are observed in neonates of anemic mother.<sup>15,17</sup>

### Clinical Features

Symptoms : There are no symptoms in mild and moderate anemia. Patient may complain of feeling of complaints, exhaustion, indigestion, loss of appetite and lassitude. Palpitation, dyspnoea, edema, giddiness and rarely anasarca and even CCF can occur in severe cases. There may be however symptoms of the original condition causing anemia e.g. bleeding piles.

Signs : There may be no signs in mild anemia. There may be pallor, glossitis and stomatitis. Patient may have edema due to hypoproteinemia. Soft systolic murmur may be heard due to hyperdynamic circulation. There could be fine crepitations at lung base in severe cases.

### Diagnosis

Haemoglobin estimation is most practical, simple and easy method of diagnosis of anemia. It can be done by Talquist's scale, CuSO<sub>4</sub> method, Sahli's method and cyanomethhaemoglobin method. According to WHO haemoglobin less than 11 gm% is diagnostic of anemia.

Peripheral smear is a bed side method. Presence of microcytic hypochromic RBCs is diagnostic of iron deficiency of anemia. Anisocytosis, poikilocytosis and target cells are also seen in iron deficiency anemia. Presence of malarial parasite in the peripheral smear can help to find the cause.<sup>18</sup>

MCV (<80 fl), MCH (<27 pg) and MCHC are all low in iron deficiency anemia. There is evidence of increase TIBC, and decrease serum iron levels in iron deficiency anemia. Serum ferritin gives a good idea about the iron stores. If serum ferritin is less than 12 g/l then it is indicative of depleted iron stores. Bone marrow biopsy is indicated only if there is no response to oral or parenteral therapy after 4 weeks. Stool for ova cyst is done to diagnose worm infestation which

is very common cause of anemia. X - ray chest rules out tuberculosis. Significant bacteriuria should also be ruled out as a cause of anemia. Serum proteins and KFTs can be done to find out the cause of anemia.

### Management

It is very common experience for the obstetricians to see the patients of moderate to severe anemia late in pregnancy. They have nil or inadequate ANC and have suboptimal or no iron therapy during pregnancy. If the women present with mild to moderate anemia in second trimester or early third trimester, oral iron therapy can be started. WHO recommends 30 - 60 mg of iron per day in women with iron stores (serum ferritin 80 pmol/L) and 120-180 mg/day of iron in women without stores.<sup>19</sup>

The current situation demands that a cheap and easily available iron preparation (preferably free of cost in Government Hospital) should be prescribed and the importance of taking iron daily in pregnancy should be emphasized.

Government of India, Ministry of Health recommends 100 mg elemental iron with 0.5 mg FA for prophylaxis, for treatment 180 mg of elemental iron per day. This large dose of iron can lead to serious side effects like nausea, vomiting, loose motions, abdominal cramping and constipation. One needs to change the brand or iron salt if the patient cannot tolerate a particular brand of iron. Unfortunately many patient do not take iron and compliance is hence poor.<sup>2,3,5</sup> Various methods have been used to increase compliance, giving drugs less frequently initially, followed by daily later will increase the compliance.<sup>20</sup>

The patients response to therapeutic iron therapy is fast with rise in reticulocyte count at 5 - 10 days of start of therapy and increase haemoglobin by 0.7- 0.8 gm/week. Addition of FA helps in improving results in supervised supplementation.<sup>21</sup> Unsupervised supplementation however did not give good results.<sup>22</sup> Treatment with large doses is recommended till haemoglobin becomes normal, then maintenance dose of 60 - 100 mg of iron per day is started till 3 months post delivery.

The disadvantage of oral iron therapy is intolerance to medication, unpredictable absorption and noncompliance. If there is no significant clinical or haematological improvement within 3 weeks, diagnostic re-evaluation is needed.<sup>8,23</sup> Reasons of failure to oral therapy are inaccurate diagnosis (non iron deficiency microcytic anaemia e.g. thalasemia, pyridoxine deficiency), noncompliance, continuous blood loss through hook worm infestation or piles, faulty iron absorption and concomitant folate deficiency.<sup>8,23,24</sup>

Parenteral iron therapy : The rise in haemoglobin after giving parenteral iron therapy is same as oral iron therapy (0.7-1.0 gm/week). The main advantage is certainty of administration and to

correct iron stores. It is indicated with patients intolerance to oral iron therapy, serious side effects leading to noncompliance. Parenteral iron is available as iron dextran (imferon) which can be given IM or IV and iron sorbital citrate (Jectofer) which can be given IM. Iron sucrose can be given IV with no risk of anaphylactic reactions.

The elemental iron needed to correct iron deficiency is calculated as (Normal haemoglobin - Patients haemoglobin) x Weight (Kg) x 2.21 + 1000. Another simple method is to give 250 mg of elemental iron for each gram of haemoglobin below normal.

The IM route is most popular and is associated with less side effects. It is given by deep IM injection with a thick needle on outer quadrant of buttock using a 'Z' technique to prevent dark staining of the skin. The disadvantage of IM iron include pain, skin discoloration, abscess formation, nausea, vomiting, headache, fever and lymphadenopathy.

*Blood Transfusion* : Blood transfusion is very rarely required. It is indicated in severe anemia after 36 weeks of gestation, APH cases where active blood loss is present, PPH and cases not responding to oral or parenteral iron therapy. PCV is preferred for transfusion.<sup>8,23</sup>

*Management of Labour* : In first stage, patient should be in comfortable position. Oxygen should be kept ready and should be given in dyspnoea. Digitalization may be required in CCF. The aim is to delivery the patient vaginally. The second stage is curtailed by forceps delivery. Third stage is managed with prostaglandins as ergometrin is contraindicated.

*Puerperium* : The mother should have adequate rest, iron and FA therapy for 3 months. Any infection is energetically treated. Puerperial sepsis, failing lactation, subinvolution of uterus and thrombolism are common problem of the puerperium.<sup>8,23</sup> The anemic patient should be given contraceptive advice and asked not to conceive for atleast 2 years.

*Antenatal Care in next pregnancy* : The WHO recommends estimation of haemoglobin at first visit, 16 weeks and 36 weeks of gestation in all patients. Prognosis is good if anemia is detected and treated in time.

### Prevention Strategies:<sup>19</sup>

- Supplementation iron to nonpregnant women
- Supplementation iron to pregnant women
- Diet advice
- Food fortification
- Treatment of hookworm / malaria
- Improvement of sanitation, personal hygiene, better education and alleviation of poverty

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## THROMBOEMBOLIC DISEASE DURING PREGNANCY

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VTE venous thromboembolism is the most common cause of Maternal death in the U.K. The maternal mortality is 1.45 deaths per 1 lac pregnancies. Pulmonary embolism remains the leading direct cause of maternal mortality. VTE is a major cause of concern particularly during pregnancy, patients on O. C. Pills or HRT (Hormonal Replacement Therapy) It is also important to remember the considerable morbidity from the miserable and disabling postphlebitic syndrome, which develops in > 20% of survivors.

### Maternal Risks

Pregnancy introduces a significant risk of VTE events. Many important changes in the coagulation and vascular systems occur during pregnancy and these changes support the accepted orthodoxy that pregnancy is a state of hypercoagulation, due to presence of venous stasis, hypercoagulability and vascular damage (Virchow's triad)

Pregnancy introduces a significant risk of VTE events. Many important changes in the coagulation and vascular systems occur during pregnancy, and these changes support the accepted paradox that pregnancy is a state of hypercoagulation. Each element of Virchow's triad is present: venous stasis, hypercoagulability, and vascular damage. Table 43-1 summarizes additional features in pregnancy that add to the risk of VTE, based on individual case analysis reporting.

Risk Factors Identified from Individual Case Analysis of 31 Maternal Deaths  
as A Result of Venous Thromboembolism (1997-19990)

Risk Factor	Number of Cases	Comment
Age	31	The rate of death is double in women older than 30 years.
Obesity	13	Body mass index > 30. All patients diagnosed in the third trimester were overweight. Increased dosage of low molecular-weight heparin is recommended for the treatment of venous thromboembolism (VTE)
Immobility	5	All patients had prolonged bed rest.
Family History of VTE	4	Strong history of VTE. All deaths occurred in the antenatal period
Cesarean delivery	4	The number of events decreased dramatically from the previous report after the 1995 Royal College of Obstetricians and Gynaecologists guideline.
History of VTE	3	Two patients were obese.
Air Travel	2	Both cases occurred antenatally.

### Other Risk Factors :

1. Age > 30 yrs risk is doubled.
2. Obesity BMI > 30
3. Immobility.
4. Family history of VTE
5. Cesarean Delivery.
6. History of VTE
7. AIR travel during pregnancy

### Thrombophilias

This term has been coined to describe, the tendency of some individuals to develop thrombosis more easily than others is often inherited thrombophilia.

"Thrombophilia" (Thrombos = coagulation; philia = love) refers to cluster of disorders that are associated with a tendency towards thrombosis and a persistent hypercoagulable state. This phenomenon may be due to factors that are inherited (genetic), acquired or complex, wherein genetic factors interact with environmental influences



### Normal changes in coagulation during pregnancy

Normal pregnancy is associated with major changes in all aspects of haemostasis-increasing concentrations of most clotting factors, decreasing concentrations of some of the natural anticoagulants, and reducing fibrinolytic activity-so that as pregnancy progresses and during the puerperium the overall balance is shifted towards apparent

### Hypercoagulability:

We know that the plasma fibrinogen level increases during pregnancy by 50% from 200 - 300 mg% to 400 - 600 mg% as compared to the non-pregnant females.

Other clotting factor activities that are increased appreciably during pregnancy are factors VII, VIII, IX & X. Factor II is increased only slightly, whereas activities of factors XI & XIII are decreased somewhat.

There is a modest decrease in platelet concentration as pregnancy advances.

### Antiphospholipids

The most common and important acquired thrombophilic defects are those broadly grouped together as "antiphospholipids", which comprise Lupus Anticoagulants and raised anticardiolipin antibody concentrations. Antiphospholipids occur in a variety of conditions, including connective tissue disorders (such as systemic lupus erythematosus, systemic sclerosis, and Bechet's syndrome), some infections, exposure to certain drugs (such as phenothiazines, hydralazine, and procainamide), and sometimes with no evident underlying pathology or drug exposure. The persistent presence of antiphospholipids (persisting in at least two samples collected at least six weeks apart) is associated with an increased risk of both venous and arterial thrombosis, and has for many years been known to increase the risk of recurrent fetal loss.

### Thrombophilia and adverse pregnancy outcome

Recent data suggest that endothelial dysfunction, vasoconstriction, placental ischemia and enhanced coagulation are associated with abnormal placental development, which may lead to inadequate fetomaternal circulation and decreased placental perfusion.

The subsequent vasculopathy and secondary thrombosis from hyper coagulability may result in inadequate perfusion of the intervillous space, preeclampsia, placental infarcts, IUGR, placental abruption and IUFD. The term placental vasculopathy has been coined to describe pathological placental changes characterized by superficial endovascular cytotrophoblast invasion in the spiral arteries, acute atherosclerosis and thrombotic processes in the spiral arteries

and / or the intervillous space. Clinically, placental vasculopathy is associated with preeclampsia, IUGR, placental abruption and some cases of fetal loss and preterm labour.

Not all women with thrombophilia will develop VTE during pregnancy, suggesting the existence of additional, yet unidentified, environmental factors. The risk of VTE depends on the type of thrombophilia and the existence of additional risk factors. As previously described, Anti-Thrombin III deficiency is the most thrombogenic of the hereditary thrombophilias, with a 50 percent lifetime risk of thrombosis.

### Risk assessment and scoring : who should be offered thrombophilia screening ?

It is now obvious that heritable thrombophilic defects are much more prevalent than what we used to think and most carriers remain asymptomatic. Routine screening of all women for thrombophilic defects, however, is not justifiable and may cause more harm than good because finding a defect might lead to unnecessary intervention with antithrombotics.

In Europe, most clinicians recommend screening of women who have : A past history of VTE and

- Asymptomatic women who have a family history of confirmed VTE.

### Thrombophilia screening

The workup on thrombophilia screen runs as follows :

- Antithrombin III
- Protein C & S
- APTT
- ACA & LA
- Fibrinogen level
- Homocysteine
- CBC

### Diagnosis

The typical clinical features of deep vein thrombosis in pregnancy differ somewhat from those in the nonpregnant patient in relation to lateralization and extent. In up to 90% of cases, thrombosis affects the left leg, and in most patients, the proximal veins are affected. Deep venous thrombosis restricted to the calf veins is uncommon during pregnancy, although it may complicate the postpartum period.

The differential diagnosis of a painful, swollen leg in this situation is narrow. Alternative causes, such as ruptured Baker's cyst and hematoma, are rare in this age group, and cellulitis is uncommon. Symptoms may be subtle and may be confused with common benign changes in pregnancy, such as lower extremity edema or muscle cramping. The unilateral nature of VTE is a useful distinguishing characteristic. Generalized and point tenderness are common features. Dorsiflexion of the calf causes pain (Homan's sign) if the clot is: in that region,

Tender, indurated veins may be palpable on careful inspection of the popliteal fossa. Asymmetry of the legs is usually seen below the level of the venous obstruction. Localized erythema suggests concomitant superficial thrombosis.

The clinical features of pulmonary embolism are no different from those in the nonpregnant patient, but may be masked by the physiologic dyspnea seen in pregnancy. In most cases, the features are those of pulmonary infarction, with pleuritic chest pain of acute or subacute onset with or without dyspnea.

Diagnosis of dvt during pregnancy (TABLE 1)

Clinical diagnosis is notoriously inaccurate for diagnosing DVT. Doppler ultrasonography has a sensitivity and specificity of 95% for proximal DVTs (table 1) Doppler ultrasonography is more accurate for detecting symptomatic, proximal, and first-time DVTs than for detecting those that are asymptomatic, distal, or recurrent. Radiological studies are contraindicated in pregnancy.

Table 1  
Operating Characteristics of diagnostic tests for proximal DVT

Diagnostic test	Sensitivity%	Specificity%	Positive LR	Negative LR
Venography	100	100	infinity	0
Doppler ultrasonography	95	95	19	0.05
Duplex ultrasonography	95	95	19	0.05
Impedence plethysmography	80	95	16	0.21
Loadine 125 fibrinogen scan	79	62	2.1	0.34
D-Dimer level	88-100	50-80	1.9-5.0	0-0.02

Although heparin does not cross the placenta, its use to treat VTE can precipitate adverse pregnancy outcomes by causing maternal hemorrhage. Warfarin crosses the placenta and is associated with specific teratogenic effects.

Thromboembolism in pregnancy

General

The key elements of the management of VTE in pregnancy are a high index of clinical suspicion, objective confirmation by imaging, and administration of heparin for the rest of the pregnancy followed by heparin or warfarin for at least 6 weeks postpartum and 6 months in total

Interventions to prevent and treat VTE are pharmacologic antithrombotics, thrombolytic and mechanical measures (Table 2). Amongst the pharmacologic agents, heparins and warfarin are the principal drugs. The efficacy of aspirin in preventing VTE is debated. A meta-analysis and a randomized study of thrombo-prophylaxis in lower limb orthopedic surgery showed evidence of an antithrombotic effect, but the use of aspirin for this purpose in pregnancy cannot be supported. Novel oral anticoagulants are under investigation, including an oral direct thrombin inhibitor, ximelagatran. The role of these agents has not been established, and there are no data on their use in pregnancy. In VTE thrombolytic therapy is restricted to emergency management of massive pulmonary embolism and limb salvage in rare cases of massive lower limb deep venous thrombosis with venous gangrene. Thrombolytic agents are associated with miscarriage or fetal death and maternal bleeding. Their use is relatively contraindicated in pregnancy. Similarly, these agents would likely induce hemorrhage soon after delivery and therefore empirically should not be used. Under these circumstances, massive pulmonary embolism has been treated with heparin anticoagulation and emergency pulmonary embolectomy. A recent review of anecdotal report of thrombolytic therapy in pregnancy implied that the risk to the mother and fetus may be lower than previously suggested.

Pharmacologic and Non pharmacologic Intervention	
Antithrombotic and thrombolytic agents	Mechanical measures
Heparins	Graduated compression
Unfractionated heparin	Stokings
Low-molecular-weight heparin	Mechanical calf compression
Synthetic pentasaccharide	
Oral anticoagulants	Filters
Warfarins	
Direct thrombin inhibitors	
Aspirin	
Thrombolytics	
Streptokinase	
Urokinase	
Recombinant tissue	
Plasminogen activator	

Management Options: Thromboprophylaxis in Pregnancy

Thromboprophylaxis should not be offered to all pregnant women. Routine population screening for hereditary thrombophilias is not justified. In assessing thrombotic risk, acquired factors are at least as important as genetic predisposition. A history of VTE is an important consideration for thromboprophylaxis in pregnancy. In addition, patient age, parity, and weight are associated with venous thrombotic risk during pregnancy and in the puerperium. Immobilization and serious medical disorders are other important risk factors. In the postpartum period, the risk of venous thrombosis is increased in women who have had cesarean delivery, especially as an emergency procedure.

Recommendations for Thromboprophylaxis in Pregnancy	
Risk Category	Management
Women who have no personal history of venous thrombosis, but a positive family history and who are heterozygous for protein S deficiency, heterozygous for factor V leiden, or heterozygous for prothrombin G20210A	In general, pharmacologic thromboprophylaxis is not required antenatally, but anticoagulant prophylaxis may be considered after delivery in those with previous venous thromboembolism and others who have an additional risk factor.
Women with a history of venous thrombosis in association with a temporary risk factor that is no longer present.	Postpartum thromboprophylaxis with heparin or warfarin should be given. Antenatal thromboprophylaxis should be considered, such as fixed prophylactic doses of unfractionated or low-molecular-weight heparin (e.g. 4000-5000 units dalteparin once daily SC or unfractionated heparin 7500 IU every 8-12 hours SC)
Intermediate Women who have a personal history of apparently spontaneous venous thromboembolism who are no longer receiving anticoagulant prophylaxis. Women who have no personal history of venous thrombosis, but a positive family history of venous thrombosis and who are heterozygous for protein C deficiency, are homozygous for factor V Leiden or the prothrombin G20210A mutation, or have combination of defects.	Adjusted doses of low-molecular weight or unfractionated heparin, higher than those usually used to prevent venous thrombosis should be administered (e.g. low-molecular weight heparin introduced at approximately dalteparin 75 units/kg early pregnancy weight every 12 hours SC; the dose may be adjusted to give a peak antixa level of 0.35 to 0.5 units 3-4 hours after injection).
High Women who are receiving long-term anticoagulant therapy for venous thromboembolism. Women who have type I antithrombin deficiency or a type II reactive site antithrombin defect (regardless of whether they have had a thrombotic episode)	The use of fixed prophylactic doses of unfractionated or low-molecular weight heparin (e.g. heparin 7500 IU every 12 hours SC or dalteparin 4000-5000 units once daily SC respectively) is an alternative strategy.

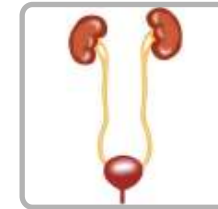
Conclusion : take home message

1. VTE is a major cause of maternal mortality, especially in developed countries.
2. Better understanding of genetic pattern of inheritance of important disorders like Antithrombin III deficiency, Factor C and S, Factor V Leiden, MTHFR, and Hyperhomocysteinaemia has led to screening and selection of high - risk patients, and therefore, more efficient thromboprophylaxis and management. Deficiency of Antithrombin deserves special attention as it is much more thrombotic than the rest.
3. The implication of thrombophilia- induced "placental vasculopathy" (endothelial dysfunction, vasoconstriction, placental ischemia and enhanced coagulation at the

uteroplacental bed) has been emerging as the causative factor for PIH, IUGR and Fetal death.

4. Association of APLS with recurrent early pregnancy loss has been clearly demonstrated and with successful treatment with LMWH and Aspirin, fetal outcome has improved appreciably.
5. Routine thrombophilia screening is not recommended during pregnancy.
6. Low Molecular Wt. Heparin is gradually replacing Fractionated Heparin in the management of all thromboembolic disorders.
7. Unlike venous thromboembolism, the role of thrombophilia in arterial thrombosis is much more unclear, and no association could be demonstrated till date.

## UTI IN PREGNANCY



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### Urinary tract infection in pregnancy

The incidence of asymptomatic (significant growth of a uropathogen in absence of symptoms) is 2 to 10% which is same during pregnancy as it is in sexually active non pregnant women. And during pregnancy, 12.5 to 30% of women with untreated bacteriuria will develop acute pyelonephritis.

Physiologic changes of pregnancy can both mask and mimic renal disease in pregnancy

### Pregnancy Mimic Renal Disease<sup>1</sup>

- Increased Proteinuria
- Decreased S. Albumin
- Increased cholesterol by 50% in III trimester
- SAH and water retention
- Dilatation of the renal tracts.
- Glycosuria
- Hyper Calciuria
- Physiologic reduction in HB %
- Symptoms Mimicking Cystitis
- Metabolic acidosis

### Pregnancy Mask Renal Disease<sup>1</sup>

- Physiologic vasodilatation reducing systemic BP.
- Increased GFR reducing serum creatinine and blood urea.



Pregnancy predisposes women with bacteriuria which in non pregnant state is usually self limiting. Normal pregnancy related physiologic changes contribute to UTI'S and include dilatation of upper collecting systems, increasing urinary tract dead space, increase vesicoureteral reflux, hypotonic renal pelvises, decrease in natural antimicrobial activity in urine and a decrease in phagocytic activity of leucocyte at mucosal surface.

UTI in pregnant women usually do not present with typical symptoms and may be asymptomatic. Pyelonephritis is a serious complication.

### Diagnosis of UTI<sup>1,2</sup>

Symptoms : Urinary frequency, nocturia, urge incontinence, strangury, dysuria, offensive smell of urine.

Microscopic examination : of a freshly voided midstream urine reveals more than 10 leucocytes/ml in bacterial UTI.

Urine culture is conventionally recognized as significant if there is growth of more than 10<sup>5</sup> CFU/ml. of a single recognized uropathogen in association with pyuria.

During pregnancy, most common uropathogens are bowel commensals, E-Coli (70-80%) , Klebsiella, proteus, enterobacter, and staphylococcus saparophyticus.

A dipstick leucocyte esterase test can be used to detect WBC and a nitrate reductase test can be used to detect nitrites. These urine sticks are not sensitive, so microscopy examination and cultural is must.

Haematuria and proteinuria are unreliable indicators of UTI but important signs of renal disease.

Asymptomatic bacteriuria<sup>1</sup>: In this condition, true bacteriuria exists but there are no symptoms or signs of acute UTI.

Untreated asymptomatic bacteriuria will develop into acute pyelonephritis in 12.5 to 30% of women, but if treated less than 1% of pregnant women develop pyelonephritis.

After successful treatment of asymptomatic bacteriuria, monthly screening of midstream urine is necessary as approx 30% of women will have a relapse of bacteriuria making them vulnerable to acute pyelonephritis again.

This is also associated with an increased risk of preterm delivery and low birth weight.

Screening for asymptomatic bacteriuria (every 4-6 weeks) is recommended for following groups of pregnant women.

- 1) H/O asymptomatic bacteriuria.
- 2) H/O recurrent UTI.
- 3) Preexisting renal disease.
- 4) Renal calculi.
- 5) structural and neuropathic abnormalities of renal tracts.
- 6) Pre existing Diabetes mellitus.
- 7) Lower socioeconomic group.

### Treatment of UTI<sup>2</sup>

For Cystitis

Amoxicillin 500 mg by mouth three times per day for 3 days.

or

Trimethoprim / Sulfamethaxazole one tablet (160/800 mg) by mouth 2 times per day for three days.

If this treatment fails, treat patient according to C/s of organism with appropriate antibiotic.

If infection recurs 2 to 3 times check C/s of organism and treat accordingly.

For prophylaxis against further infections give antibiotics by mouth once daily at bed time for remainder of pregnancy and 2 weeks postpartum.

Give

Trimethoprim / Sulfamethoxazole one tablet (160/800 mg)

OR

amoxicillin 250 mg.

Prophylaxis is indicated after recurrent infection not after a single episode.

### Acute Pyelonephritis<sup>1</sup>

Acute pyelonephritis is an infection of the upper urinary tract mainly of the renal pelvis which may involve the renal parenchyma. The same uropathogens that cause asymptomatic bacteriuria and cystitis are responsible for acute pyelonephritis.

Unless acute pyelonephritis is treated promptly there is considerable maternal and fetal morbidity.

### Maternal S/S

Most women present in second and third trimester.

Over 80% of women present with backache, fever, rigors and costo vertebral angle tenderness and half have lower urinary tract symptoms, nausea and vomiting.

Bacteremia is present in 15-20% of pregnant women with acute pyelonephritis and a small proportion of these women will develop septic shock and increased capillary leak leading to pulmonary oedema.

Women with pyelonephritis at risk of serious complications are those who present with highest fever ( $> 39.4^{\circ}\text{C}$ ), tachycardia ( $> 110/\text{min}$ ) at more than 20 weeks gestation and who received tocolytics and injudicious fluid replacement.

### Fetal Risk:- Preterm labour

Treatment<sup>2</sup>:- If shock is present or suspected.

- ? Start IV infusion and infuse IV fluids at 150 ml/hr.
- ? Check urine C/s. if possible, and treat with an antibiotic appropriate for the organism.
- ? If urine culture is unavailable treat with antibiotics until the woman is fever free for 48 hours.
- ? Ampicillin 2 gm IV every 6 hrs. + gentamycin 5 mg/kg body weight IV every 24 hrs.

Once the woman is fever free for 4 hrs, give amoxicillin 1 gm by mouth 3 times per day to complete 14 days of treatment

**Note:- Clinical response is expected within 48 hours.**

If no clinical response in 72 hours re-evaluate results and antibiotic coverage.

For prophylaxis against further infection, give antibiotics by mouth once daily at bed time for the remainder of pregnancy and for 2 weeks postpartum.

Give

Trimethoprim/Sulfamethoxazole one tablet (160/800 mg)

OR

Amoxicillin 250 mg.

Along with adequate hydration by mouth or IV along with paracetamol 500 mg by mouth as needed for pain and to lower temperature.

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## THYROID DISORDERS AND PREGNANCY

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### Introduction

The thyroid gland in itself is an enigma!! Dysfunction either way leads to a host of problems for women. Thyroid disease is present in 2 - 5% of all women and 1- 2% of women in the reproductive age group. Not unexpectedly, thyroid problems are common in women who are pregnant. Thyroid disorders are the second most common endocrinologic disorders found in pregnancy. Overt hypothyroidism is estimated to occur in 0.3 - 0.5% of pregnancies. Subclinical hypothyroidism appears to occur in 2 - 3%, and hyperthyroidism is present in 0.1-0.4%.

Autoimmune thyroid dysfunctions remain a common cause of both hyperthyroidism and hypothyroidism in pregnant women. Graves' disease accounts for more than 85% of all cases of hyperthyroid, whereas Hashimoto thyroiditis, is the most common cause of hypothyroidism.

Postpartum thyroiditis (PPT) reportedly affects 4 -10% of women. PPT is an autoimmune thyroid disease that occurs during the first year after delivery. Women with PPT present with transient thyrotoxicosis followed by hypothyroidism, or transient thyrotoxicosis followed by hypothyroidism. This presentation may be unrecognized, but is important because it predisposes the woman to develop permanent hypothyroidism.

Of interest, symptoms of autoimmune thyroid diseases tend to improve during pregnancy. A postpartum exacerbation is not uncommon and perhaps occurs because of an alteration in the maternal immune system during pregnancy. The improvement in thyroid autoimmune diseases is thought to be due to the altered immune status in pregnancy.

### Spectrum of thyroid disease in pregnancy

Several of the thyroid disorders which tend to occur during pregnancy are autoimmune in nature. By this we mean that the body develops antibodies directed against thyroid cells,

which then affect the way the thyroid gland functions. Antibodies which damage the thyroid cells may result in lymphocytic thyroiditis (inflammation of the thyroid), also known as Hashimoto's disease. These damaging antibodies can reduce the function of the thyroid and lead to hypothyroidism. On the other hand, your body can make antibodies against thyroid tissue which can stimulate thyroid cell function. In this case, hyperthyroidism due to over-function of the thyroid (Graves' disease) may be the result.

Postpartum thyroiditis (PPT) is a recently discovered problem that spans the spectrum of both hyper - and hypothyroidism. This condition, which tends to occur immediately after pregnancy, may produce antibodies which damage thyroid tissue, thereby releasing thyroid hormone passively into the bloodstream and producing hyperthyroidism. During the recovery phase, thyroid levels may fall, producing either temporary or permanent thyroid failure. Since this condition is common, occurring in 8 - 10% of all women after pregnancy, postpartum thyroid testing is advisable for all women.

Thyroid nodules, goiters, and other thyroid problems are also sometimes first detected in pregnancy but are less common.

### Thyroid disease and fertility

Hypothyroidism may be associated with an increased frequency of menstrual periods in patients with mild to moderate thyroid failure, and a lack of menstruation (amenorrhea) when hypothyroidism is severe. There may be problems with ovulation and conception due to the hypothyroidism itself or to associated hormonal changes. For example, in some patients with severe hypothyroidism, the pituitary gland produces increased amounts of a hormone known as prolactin. Increased prolactin secretions can "turn off" normal menstrual cycles. Very rarely, autoimmune ovarian problems coexist with hypothyroidism, with destructive antibodies directed against ovarian tissue. Hyperthyroidism may also be associated with irregular or absent menses, and infertility is common. Thyroid disease should be considered in patients undergoing investigation for menstrual problems or infertility. Fortunately, once treated adequately, neither hypo - nor hyperthyroidism have a major impact on fertility.

### Planning pregnancy for women with thyroid disease

#### Hypothyroidism

The diagnosis and treatment of hypothyroidism is straightforward. It is strongly advised that the adequacy of thyroid hormone replacement therapy be assessed by thyroid function

tests, including the thyroid - stimulating hormone (TSH) level, before proceeding with the pregnancy, so as to minimize any possible risk to the mother or her baby that might occur due to hypothyroidism during pregnancy.

### Hyperthyroidism

The investigation and management of hyperthyroidism in young women is a bit more complex. First, radioactive iodine thyroid scanning, used for the diagnosis of hyperthyroidism, as well as radioiodine treatment of hyperthyroidism, should never be used until the physician conducting these tests is certain that the patients is not pregnant. With regard to treatment, physicians may recommend either antithyroid medications or radioactive iodine in women of reproductive age. In either case it is essential to control the women's hyperthyroid state before proceeding with pregnancy; this usually takes three to six months. A one-to-two-year course of antithyroid medications, hoping for a remission of thyrotoxicosis, is recommended by some physicians. In the interim, effective birth control measures should be used to prevent pregnancy. There are concerns raised by the prospect of continuing to take antithyroid drugs in pregnancy. Other physicians prefer to use radioiodine to treat women who are contemplating pregnancy, since a complete cure of the of the hyperthyroid condition is assured. Of course, if and when hypothyroidism develops after radioiodine therapy, treatment with thyroid hormone is necessary.

### Thyroid function in pregnancy

Thyroid gland function is normal in pregnancy, although normal pregnant women often develop symptoms and signs suggesting hyperthyroidism, such as rapid heart beat or palpitations, sweating, and heat intolerance. The metabolic rate is also increased in pregnancy, so it is easy to see why hyperthyroidism is often suspected even though it is actually present in only one out of 1,000 pregnancies. The normal thyroid gland may be slightly larger in pregnancy, but the presence of even a modestly enlarged gland usually means that there is an underlying thyroid problem which requires investigation. The total serum thyroxine (T4) and triiodothyronine (T3) levels are increased in pregnancy due to high levels of estrogen which, in turn, increase the thyroid hormone-binding protein concentrations. Although this makes thyroid functions more difficult to interpret, thyroid hormone production is normal in pregnant women.

The baby's thyroid begins to function after ten to twelve weeks of pregnancy. Thyroid hormones are important for development of the fetal nervous system and these are probably derived from both the baby's thyroid gland secretion as well as small amounts of the mother's thyroid hormone that cross the placenta. Iodine in the mother's diet readily crosses the placenta and is used by the fetal thyroid gland to make thyroid hormone. Iodine

deficiency can cause newborn hypothyroidism or mental retardation (cretinism) and is a major world health problem in underdeveloped countries.

### Thyroid disease in the mother during pregnancy

#### Subclinical hypothyroidism

- Subclinical hypothyroidism affects 2 - 3% of women in pregnancy.
- The symptoms of subclinical hypothyroidism are vague and nonspecific.
- The diagnosis is based on a normal level of free thyroxine (FT4) and an elevated TSH level.

#### Hypothyroidism

If hypothyroidism is suspected in a pregnant patient, the physician can perform a TSH blood test. Just as in non - pregnant women, the TSH will be increased if hypothyroidism is present. If a woman is already being treated with thyroxine when she becomes pregnant, she should continue to take this medication during pregnancy. Thyroxine is safe to take and is well absorbed during pregnancy. Although there is usually no need for a dose change, most women require readjustment and higher doses during pregnancy. Physicians generally monitor the TSH level to detect even mild hypothyroidism and increase the thyroxine dose, if necessary.

#### Hyperthyroidism

Thyrotoxicosis (hyperthyroidism) during pregnancy, most often due to Graves' disease, presents a challenge for diagnosis and treatment because of unique fetal and maternal considerations.

The risk of miscarriage and stillbirth is increased if thyrotoxicosis goes untreated, and the overall risks to mother and baby further increase if the disease persists or is first recognized late in pregnancy. The diagnosis is suggested by specific physical signs such as prominent eyes, enlarged thyroid gland, and exaggerated reflexes, and is confirmed by markedly elevated serum thyroid hormone levels. As noted above, radioactive iodine scans are never performed in pregnancy. However, if a thyroid scan is inadvertently done in pregnancy, this should cause little concern, since the amount of radioactivity delivered to the fetus is barely above the background level in the environment.

On the other hand, if radioactive iodine treatment is inadvertently administered in pregnancy, this raises concerns about the radiation effects on the developing fetus in early



pregnancy. The amount of radiation may approach levels which can be harmful and, after appropriate counseling, some patients may opt for a therapeutic abortion. Still a number of completely normal infants have been born in this situation. Later in pregnancy radioactive iodine can destroy the fetal thyroid, but this is probably not a sufficient reason to end the pregnancy, since recognition and treatment of hypothyroidism shortly after delivery usually assures normal growth and development in the child.

The treatment of choice for thyrotoxicosis during pregnancy is antithyroid medication, either propylthiouracil or methimazole, since radioactive iodine cannot be used. Propylthiouracil (PTU) remains the drug of choice, since it does not cross the placenta as well as methimazole. The initial goal is to control the hyperthyroidism and then use the lowest medication dose possible to maintain the serum thyroid hormone levels in the high normal range. In this way the smaller doses of medications are used, and there seems to be little risk to the baby. If a mild allergy to one of these medications develops, the other medication may be substituted. If there is a problem with taking pills or more severe drug allergy, then an operation may be performed to remove most of the thyroid gland. This is usually done in the middle part of the pregnancy. Fortunately, it is rarely necessary.

The natural course of hyperthyroidism in pregnancy is for the disease to become milder or remit totally near term. In many patients antithyroid medications can be tapered to low levels or even discontinued. For those patients who are not so fortunate, it is important to maintain control of the hyperthyroidism throughout pregnancy to avoid severe thyrotoxicosis (thyroid storm) developing during labour and delivery. If this does develop, additional acute treatment with beta-adrenergic blocking drugs such as propranolol (Inderal) and high doses of nonradioactive iodine are used. Long-term treatment with these agents is not advised in pregnancy, although some physicians use propranolol when the disease is first diagnosed to control symptoms until the antithyroid medications have had a chance to work.

#### Fetal thyroid disease

Antithyroid medications, nonradioactive iodine and, very rarely, maternal thyroid antibodies can all cross the placenta and cause hypothyroidism in the baby. Nonradioactive iodine, which is present in some medications, including some cough medications, can cause a goiter in the fetus, making delivery difficult or causing respiratory obstruction. For this reason, iodine containing drugs should never be used in pregnancy except in the case of thyroid storm. Unfortunately, there is no simple blood test to assess the baby's thyroid function in the womb, although measurements of thyroid hormone or TSH levels in the amniotic fluid sac have been used in research studies. Plain X-rays sometimes show delayed

bone development in fetal hypothyroidism, but this test is usually not recommended. Screening for hypothyroidism at birth, now done routinely in North America on all babies, identifies the need for early short- or long-term thyroxine treatment, with excellent long-term follow-up results.

Fetal thyrotoxicosis (hyperthyroidism) occurs occasionally due to transfer of maternal thyroid-stimulating antibodies across the placenta. Most often, the mother herself has hyperthyroidism which is being treated with antithyroid drugs that also passively treat the baby by crossing the placenta. Sometimes, however, the mother's thyrotoxicosis occurred in the past and was controlled by either radioactive iodine treatment or an operation in which the mother's thyroid gland was removed. In such a situation the mother has less thyroid tissue and cannot be hyperthyroid, even though she continues to have thyroid stimulating antibodies in her blood. Since the mother is well, fetal thyrotoxicosis may not be suspected. Clues to the presence of fetal hyperthyroidism are fetal heart rate consistently above the normal limit of 160 beats per minute and the presence of high levels of thyroid stimulating antibodies in the mother's blood.

All women with Graves' disease or a history of Graves' disease should be tested for thyroid stimulating antibodies late in pregnancy. The consequences of untreated fetal thyrotoxicosis include low birth weight and head size, fetal distress in labour, and neonatal heart failure and respiratory distress. Administration of antithyroid drugs to the mother during pregnancy can treat the baby in this situation. Close follow-up and continued treatment is required after delivery.

#### Postpartum thyroid disease

##### Pre-existing thyroid disease

For pre-existing hypothyroidism, thyroid hormone treatment is continued after delivery and breast feeding is encouraged. Thyroid hormones do not get into breast milk in significant amounts.

Graves' disease (hyperthyroidism due to a diffusely overactive thyroid) is prone to relapse or worsen in the postpartum period. If that happens, antithyroid drugs can be started or their dose increased, or radioactive iodine can be given if the mother is not breast feeding. Women taking PTU (propylthiouracil) may breast feed, since little of this drug crosses into the milk. Nursing is also possible for women who take methimazole, although more of the drug gets into breast milk. In both cases the baby's thyroid function should be monitored. Definitive therapy with radioactive iodine should be considered, although many breast-

feeding women will wish to postpone this, since some of the mother's radioiodine crosses into her baby through the breast milk.

#### Postpartum thyroiditis

Postpartum thyroiditis (PPT) may occur in 8 to 10 percent of women. This disease also occurs in the nonpostpartum period, as well as in men, and is probably an autoimmune thyroid disease related to Hashimoto's thyroiditis. Typically, it consists of a temporary period of hyperthyroidism lasting from six weeks to three months postpartum, followed by hypothyroidism between three and nine months after delivery. Women at risk include those with a previous history of postpartum thyroiditis or those who can be shown to have thyroid antibodies in their blood but are not taking thyroxine. Usually, no treatment or only symptomatic treatment is required for the hyperthyroid phase, and a short course of thyroxine treatment for six to twelve months is sufficient for the hypothyroid phase. Some women do not recover from the hypothyroid phase and, therefore, require long - term thyroid replacement therapy.

During the first three months after delivery, symptoms of fatigue, depression, and impairment of memory and concentration are common and often unrelated to a woman's thyroid hormone level. However, after this time, hypothyroid women have more of these symptoms and may feel better if their hypothyroidism is corrected by thyroid hormone treatment.

Not every woman who has an emotional disorder after pregnancy will be found to have thyroid dysfunction as the cause of her problem. Nevertheless, it is still reasonable to perform thyroid tests (including a TSH blood level) in those women who do experience emotional disorders following pregnancy.

#### Solitary thyroid nodule in pregnancy

A thyroid nodule (lump) is an isolated area of thyroid enlargement usually noticed by the patient or detected on a routine examination by her physician. Most nodules are benign (harmless), but there is invariably some concern because of the remote possibility of thyroid cancer. Thyroid scans are contraindicated in pregnancy, and while an ultrasound examination of the thyroid is safe, this test does not usually help in excluding the possibility of cancer. The best test to perform is a fine-needle aspiration biopsy to determine whether the nodule is benign or malignant. If examination of the biopsy specimen suggests that a cancer is present, necessary surgery can be performed in the middle part of pregnancy. If a nodule is discovered later in pregnancy, investigation and treatment can probably be deferred until the postpartum period.

#### Summary

In dealing with thyroid disease in pregnancy, the physician and patient should be aware of problems that occur before and after, as well as during the actual pregnancy. There should be equal concern for the welfare of both the mother and baby. Fortunately, most thyroid conditions can be recognized, problems can be anticipated, and effective treatment is available. The outcome is almost always a healthy one, for both the mother and her baby. Nevertheless, further research is needed to answer crucial issues concerning whether systematic screening should be performed before and during pregnancy.

## VIRAL INFECTIONS IN PREGNANCY

Dr. Sadhna Tayade



### Introduction

Viral infections in pregnancy are major causes of morbidity and mortality for both mother and fetus. Infections can occur in the neonate transplacentally, perinatally, postnatally. Amniocentesis and Chorionic villous sampling assist in confirming viral infections in pregnancy.

Viral infections of concern during pregnancy are CMV, HIV, VZV, B19, and HSV.

### Human Immunodeficiency Virus

Maternal HIV is primarily acquired by sexual contact or by parenteral exposure to blood components. 25–35% of HIV positive pregnant mothers will pass HIV to their newborns.

Diagnosis of HIV infection is done by serology, virus culture, viral DNA detection or by RNA using PCR.

Perinatal transmission of HIV can occur in utero (30%), during labour and delivery, or postnatally through breastfeeding (14%). Most transmission occurs during the intrapartum period (70%). Risk factors for mother to child transmission are STDs and coinfections, PROM, malaria in pregnancy, intrapartum invasive procedures and seroconversion (29%) during pregnancy.

Transmission can be reduced by early detection, antiretroviral prophylaxis and avoidance of invasive fetal monitoring and PROM.

National guidelines for prophylaxis: Single dose nevirapine to mother and baby to mother at the start of labor (200mg) and to baby 2mg/kg body wt. within 2hrs of delivery.

Detailed management of HIV in pregnancy is itself a separate topic for discussion.

### Cytomegalovirus

CMV is the most common virus to be transmitted in utero with high mortality (15%). CMV may be present in breast milk, saliva, feces, and urine.

Petechiae, hepatosplenomegaly, jaundice, microcephaly, intracerebral calcifications, IUGR, sensorineural hearing loss, hydrocephalus and prematurity are most common in CMV infection. CMV transmission can occur transplacentally, intrapartum, and during breastfeeding. Acute infection is asymptomatic but may present with a infectious mononucleosis like picture, with fever, fatigue, and lymphadenopathy in mother.

CMV infection is determined with antigen, PCR, or culture of amniotic fluid. Quantitative PCR is also be used. Neonates are diagnosed by viral culture of urine or PCR of urine or blood. Detection of CMV-specific IgM is useful in the diagnosis of active infection.

Treatment of CMV consist of CMV hyperimmune serum to prevent congenital CMV infection in infants of women with primary infection during pregnancy, Ganciclovir (5mg/kg bid for 14-21 days) for postnatal treatment of congenital CMV infection.

### Herpes Simplex Virus

Neonatal infection is usually acquired perinatally from contact with infected genital secretions at delivery and is associated with skin lesions, encephalitis, and neurological disability IUGR, preterm labor, and miscarriage. The risk of neonatal herpes and death is highest in infants born to mothers who have not seroconverted at the time of birth.

HSV-1 and HSV-2 antibodies are used to confirm past exposure and current infection of the mother. HSV culture or PCR is used to diagnose lesions. In a neonate, HSV lesions are diagnosed by viral cultures of the throat, eyes, nasopharynx, and rectum which are generally performed at 5-10 day intervals to screen for development of infection.

### Treatment

Surgical treatment of recurrent HSV genital infection ocuring in late pregnancy is elective LSCS to prevent neonatal infection..

Acyclovir prevents recurrences of HSV lesions during pregnancy. Antiviral therapy with valacyclovir (500 mg once daily) has been shown to reduce the transmission of HSV-2. In neonatal HSV infections oral acyclovir (60 mg/kg per day, divided into 3 doses) is given for 21 days

### Rubella

Rubella is an acute viral infection of adults and adolescent girls that characteristically includes rash, fever, suboccipital lymphadenopathy, arthralgias, fever and cough. Maternal infections usually transmitted transplacentally.

Maternal infection during the first trimester leads to fetal infection and malformations in ~50% of cases.

Congenital rubella syndrome in the first 16 weeks of pregnancy causes IUGR, intracranial calcifications, microcephaly, cataracts, sensorineural defects, cardiac defects, hepatosplenomegaly, osteitis, or miscarriage. If rubella virus infection occurs in the first 12 weeks of pregnancy, up to 90% of patients have manifestations of the congenital rubella syndrome.

Laboratory studies of Rubella virus include an ELISA for IgG and IgM antibodies, PCR or viral culture of amniotic fluid. Infections in infants can be confirmed by serology or viral cultures of the throat or urine.

Immunisation of all infants at 12 - 15 months of age with MMR vaccine has reduced the rate of rubella. Vaccine is contraindicated in pregnant women, and pregnancy be avoided for 3 months.

### Parvovirus B19

B19 causes 20% of all cases of Non immune hydrops; also is a causative agent of erythema infectiosum. Transmission occurs via the respiratory route and is followed by the onset of rash and arthralgia, hydrops fetalis and/or fetal loss, congenital anemia, myocarditis and IUFD.

B19V has a tropism for the fetal bone marrow and liver, causing apoptosis of erythroid precursors and thus inhibiting erythropoiesis. Fetal liver erythroblasts exhibit viral DNA and pathognomonic changes of B19V infection.

Investigation includes IgM serology, PCR is more sensitive and can be used with amniotic fluid, cord blood, maternal serum, or placental tissue.

Treatment includes administration of high-titer intravenous immunoglobulin (IVIG).

### Varicella

VZV is a common virus that carries risk for both mother and fetus during pregnancy. If the mother develops primary varicella during pregnancy, especially in the third trimester, she is at risk for varicella pneumonia. Subclinical infection or CVS (Congenital Varicella Syndrome)

causes neonatal morbidity from spontaneous abortion, chorioretinitis, vesicular rash, cataracts, limb atrophy, cerebral cortical atrophy, and neurological disability.

If the mother develops varicella within 5 days before delivery to 2 days after, her neonate is at high risk for neonatal varicella.

For diagnosis of VZV; serologic testing, viral culture from skin lesions, PCR of skin tissue have been used. Chest X-ray is performed in any pregnant patient with a recent VZV infection and respiratory symptoms

Acyclovir is indicated for the treatment of varicella pneumonia during pregnancy (5mg/kg tds for 5 days) and in neonates born with CVS (10mg/kg tds for 7 days) in order to stop the progression of eye disease. VZV immunization of unexposed adolescent girls helps prevent CVS. If an unimmunized woman who has never had varicella is exposed to VZV during pregnancy, VZV immune globulin should be given within 72 hours of exposure to prevent varicella.

Other viruses postulated to cause congenital infections include enteroviruses, echovirus, hepatitis B virus, hepatitis C virus, and adenovirus. Up to 20% of pregnant women who acquire HEV develop hepatic failure.

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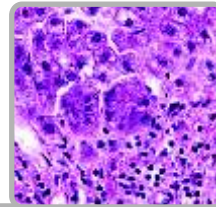


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## HEPATITIS IN PREGNANCY

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Viral hepatitis in pregnancy has been a subject of continuing interest and controversy.<sup>1</sup>

It is caused by six distinct types of viruses A, B, C, D, E and G. Acute viral hepatitis is the most common cause of jaundice in pregnancy.<sup>2</sup>

Reports from Europe and US have shown the course of viral hepatitis during pregnancy to be in no way different from non pregnant women.<sup>3</sup> However studies carried out in India, Iran & Africa have found the incidence of fulminant hepatitis to be higher in pregnancy. Malnutrition superimposed on the normal demands of pregnancy and inversion of T and B lymphocytes in early pregnancy have been postulated to be the contributing factors.<sup>4</sup> Diagnosis of viral hepatitis in pregnancy is not different from the diagnosis in the non pregnant state.

### Hepatitis A virus infection

Acute hepatitis A in pregnancy is self limited and maternal fetal transmission is very rare. Transmission may occur if delivery takes place during the incubation period because of viral shedding and contamination during vaginal delivery.<sup>5</sup> The risk of premature labor may be increased in women who are seriously ill during the third trimester however it is not associated with fetal loss or developmental abnormalities.<sup>6</sup> Treatment is supportive. Mothers with HAV infection have no restrictions about breast feeding. Infant of acutely infected mother should take Ig as passive immunization to prevent horizontal infection.

### Hepatitis B virus infection (HBV)

Asia, China, Philippine are highly endemic area with a prevalence rate > 8%. If acute hepatitis B occurs during pregnancy, the outcome of the pregnancy is no different from the non pregnant state.<sup>7</sup> A major concern however is the transmission of hepatitis B to the fetus. The prevalence of neonatal infection depends on the time during gestation that maternal infection occurs.<sup>8</sup>

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>9</sup> 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 0-3%.<sup>10</sup>

Unlike HIV, caesarean section is not recommended to prevent vertical transmission as the vaccine is efficient. Prevention of vertical transmission entails the diagnosis of acute or chronic HBV infection in pregnant women. This justifies mandatory serum HBsAg testing for all pregnant women (*ACOG Technical Bulletin 1992*).<sup>11</sup> Universal vaccination of children before age 2 months is recommended by IAP. Women with chronic HBV infection should be referred for appropriate evaluation and care after pregnancy.

Hepatitis B infection is a preventable disease, and all at-risk individuals, particularly health care workers, should be vaccinated. Pregnancy is not a contraindication for active, passive immunization or both. Breastfeeding is not contraindicated in women with hepatitis A virus (HAV) infection with appropriate hygienic precautions, in those chronically infected with hepatitis B if the infant receives HBIG passive prophylaxis and vaccine-active prophylaxis, or in women with hepatitis C virus (HCV) infection.

### Hepatitis C infection

Chronic hepatitis C virus infection affects 1.4 percent of the U.S. population.<sup>12</sup> 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.

HCV infection does not affect the course of pregnancy and also pregnancy does not affect the natural history of HCV unless the patient has cirrhosis with associated complications. Vertical transmission of HCV is a possibility with a calculated risk of 5% to 15%. Risk factors for vertical transmission include HIV co infection and high maternal HCV RNA levels of more than 1 million copies/ml.

In the absence of maternal treatment during pregnancy and no effective vaccination for neonates, efforts have been focused on dealing with the obstetric variables that may increase the likelihood of viral transmission. Avoidance of invasive procedures either during pregnancy (e.g. CVS – cordocentesis) or during delivery (e.g. scalp electrode-scalp blood

sample) may help to prevent fetal to maternal blood exposure. It is well documented now that CS before ROM is an effective measure in HIV-1 transmission to the fetus. But in HCV little evidence is present to support this. Risk of transmission by breast feeding is significant only when HIV co infection is present.

### Hepatitis D

HDV may be acute or chronic. It does not occur in the absence of acute or chronic HBV infection because HDV requires the HBV for coating and cell to cell spread. Thus, HDV is the result of either acute HDV and HBV co infection or HDV infection in a chronic HBV carrier. The course during pregnancy is similar to that of HBV. No documented cases of vertical transmission of HDV are reported. Hepatitis D is able to infect individuals who already carry hepatitis B, so taking precautions to protect a baby against hepatitis B will also protect against hepatitis D.

### Hepatitis E virus infection (HEV)

Hepatitis E is a waterborne virus spread through fecal-oral transmission. Infection occurs most commonly in developing countries after flooding. The incidence of acute viral hepatitis E is identical in pregnant and non-pregnant persons. However, pregnant women are at high risk for acute and fulminant hepatitis.<sup>13</sup> Mortality rate in pregnancy can reach 25% whereas it is 0.65% in non-pregnant women.<sup>14,15</sup>

Majority of the cases die undelivered.<sup>16</sup> Vertical transmission to the newborn occurs in 50% if mothers are positive for HEV PCR at the time of delivery. Infection in the 3<sup>rd</sup> trimester carries increased risk for fetal complications. Death of the neonate is much more common than it is from other types of viral hepatitis. Premature deliveries, miscarriages and stillbirths have been reported.<sup>17</sup>

Immunoprophylaxis is not available. There is no vaccine either. Treatment of infection remains supportive. Fulminant hepatitis by HEV may resemble liver failure in acute fatty liver of pregnancy and in HELLP syndrome so it should be considered in pregnant women in endemic areas who develop fulminant hepatitis.<sup>18</sup>

### Other Hepatitis viruses

Between 5% - 20% of cases of acute and chronic hepatitis do not appear to be caused by known hepatitis viruses, or toxic metabolic or immune-mediated mechanisms. Untyped hepatitis may infect women during pregnancy and be a source of diagnostic confusion,

particularly during the 3<sup>rd</sup> trimester, when jaundice may be a complication of PIH or a sign of acute fatty liver of pregnancy.

### Conclusion

Viral hepatitis often affects women of child bearing age and their infants. So all obstetricians and gynecologists are likely to encounter patients with viral hepatitis specially those working in areas where this is an endemic disease. Viral hepatitis with pregnancy continues to be a major health issue that must be understood and well known to all Obstetricians. Understanding the epidemiology of the virus, the course of the disease and its effect on pregnancy or vice versa as well as the rate of vertical transmission and the neonatal outcome will help in protecting both the mother and her child either by vaccination or prevention.

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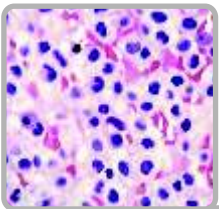
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**LEUKEMIA IN PREGNANCY**

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Leukemias are a group of malignant disorders of the haemopoietic tissues characteristically associated with increased number of white cells in the bone marrow and / or peripheral blood.

Incidence of leukemia is 10/1,00,000, in general population, males being affected more than females.<sup>1</sup> Leukemia may be acute or chronic. The categorization of acute leukemia into biologically distinct groups is based on morphology, cytochemistry, and immunophenotype as well as cytogenetic and molecular technique. The two sub-types of acute leukemia are acute myeloblastic leukemia [AML] and acute lymphoblastic leukemia [ALL]. AML is further classified based on morphology and cytochemistry, according to French American and British [FAB] scheme, which includes eight major subtypes, M0 to M7 [table 1]. The WHO classification was based on modification of the FAB classification in the year 2001 [table 1].<sup>2</sup>

French-American-British (FAB) Classification of AML:

- M0 Minimally differentiated leukemia
- M1 Myeloblastic leukemia without maturation
- M2 Myeloblastic leukemia with maturation
- M3 Hypergranular pro-myelocytic leukemia
- M4 Myelo-monocytic leukemia
- M5 Monocytic leukemia
- M6 Erythrocytic leukemia
- M7 Megakaryoblastic leukemia



WHO Classification – main categories are as follows:

1. AML with recurrent genetic abnormalities
2. AML with multilineage dysplasia
3. AML and myelodysplastic syndrome
4. AML not otherwise categorized

Chronic leukemia is classified into chronic lymphocytic leukemia [CLL] and chronic myelocytic leukemia [CML]. Adult leukemias are more prevalent after 40 years of age. The incidence complicating pregnancy is only about 1 case per 1,00,000<sup>3</sup>. As it is extremely rare, the gynaecologists are not fully aware of the proper diagnosis and management. It is imperative that patient has to be managed with a team of an oncologist, haematologist, physician, obstetrician and neonatologist and others, like social workers etc.

Acute leukemias represent about 90% of leukemias co-existing with pregnancy. AML accounts for about 60% and ALL for about 30% of cases. More than 3/4<sup>th</sup> of cases are diagnosed after the first trimester-. The coincidence of CML and pregnancy is an uncommon event, in part because CML occurs mostly in the older age group<sup>4,5</sup>.

#### Pathophysiology:

Acute leukemia is characterised by failure of cell maturation and proliferation of cells which do not mature, leading to an increasing accumulation of useless cells which take up more and more marrow space at the expense of normal haematopoietic elements. Eventually, the proliferation spills into the blood.

However in chronic leukemia, maturation proceeds fairly normally. It is a disorder of proliferation which is unrestrained and excessive. It is characterised by biphasic or triphasic clinical course [chronic phase, accelerated phase, and blast crisis] in which a terminal blastic phase follows a chronic phase of variable distribution. CML arises from a cytogenetic abnormality that results in production of Philadelphia chromosome [chromosomal translocation involving BCR gene on chromosome 9 and ABL gene on chromosome 22] in about 90% patients. As a result BCR/ABL fusion gene is produced and encodes for a protein with tyrosine kinase activity.<sup>1</sup>

#### Diagnosis

The diagnosis of acute leukemia is rarely difficult. The signs and symptoms are due to consequences of anemia, granulocytopenia, and thrombocytopenia causing fatigue, weakness, fever, infection and easy bleeding as petechiae, bleeding from nose, gums or

other organs. These symptoms prompt an examination of complete blood count. Blood examination usually shows anemia with a normal or raised MCV. The leucocyte count may vary from as low as  $1 \times 10^9/L$  to as high as  $500 \times 10^9/L$  or more. In the majority of patient the count is below  $100 \times 10^9/L$ . The blood film appearance of blast cells and other primitive cells is usually diagnostic.

The diagnosis of leukemia should be confirmed by bone marrow biopsy and aspirate. The biopsy material is usually hypercellular with leukemic cells. The smear of aspirate reveals decreased erythrocyte and megakaryocytic precursors. According to W.H.O  $\geq 20\%$  blast cells in blood or bone marrow is diagnostic of acute leukemia. A positive myeloperoxidase reaction in  $> 3\%$  of the blasts may be the only feature distinguishing AML from ALL.

The morphology of the marrow and the peripheral leukemic cells help to distinguish between lymphocytic and non-lymphocytic leukaemia. The latter group includes acute myelocytic leukemia, promyelocytic leukemia, myelomonocytic leukaemia and erythroleukemia.

Chronic leukemia has an insidious onset and is characterised by weight loss / excessive fatigue and dragging sensation due to splenomegaly. Marked leukocytosis often  $\geq 100,000$  per microlitre is seen. Circulating cells are pre-dominantly neutrophils, metamyelocytes, myelocytes with less than 10% myeloblasts.

#### Treatment

Once the diagnosis of leukemia is suspected, a rapid evaluation and initiation of appropriate therapy should follow. In addition to clarifying the subtype of leukemia, initial studies should evaluate the overall functional integrity of the major organ systems, including the cardiovascular, pulmonary, hepatic and renal systems. Factors that have prognostic significance, either for achieving complete remission [CR] or for predicting the duration of CR, should also be assessed before initiating treatment for eg. age at diagnosis, chromosomal finding at the diagnosis, anemia, leukopenia, thrombocytopenia for more than one month before diagnosis.

In general, aggressive multiagent chemotherapy is given as soon as leukemia is diagnosed, even in the first trimester, if the patient's general condition is fit and stable. There is no evidence that pregnancy has a deleterious effect on leukemia, thus termination will not improve the prognosis. Abortion is a consideration in early pregnancy in acute stage to avoid potential risk of teratogenesis from chemotherapy and to simplify management of acutely ill women; however patient's desire to continue pregnancy with concomitant chemotherapy has to be considered particularly in 2<sup>nd</sup> or 3<sup>rd</sup> trimester.

The strategy for acute leukemia is remission induction and remission consolidation by maintenance therapy in a fit patient. However specific treatment is generally aggressive and has number of side effects. Specific therapy for induction of remission is combination of vincristine, prednisolone, L-asparaginase, and daunorubicin in ALL and combination of daunorubicin, cytarabine, etoposide, and thioguanine in AML. Acute leukemia and its therapy are associated with increase in still births, prematurity, and fetal growth restriction<sup>6,7</sup>. In a report by Aviles and Colleagues, no serious long term effect of in utero exposure to chemotherapy was recorded<sup>8,9</sup>. Treatment given for acute promyelocytic leukemia in pregnancy has included All-trans retinoic acid[tretinoin]. This is a potent teratogen. Although outcome have been generally good, Siu and Colleague in 2002, described transient dilated cardiomyopathy in a newborn exposed to tretinoin in second trimester<sup>10</sup>. The oral medication, like other retinoids, is likely to be highly teratogenic, although no affected fetus have been reported to date by Briggs and Colleagues<sup>11</sup>.

The management of CML during pregnancy is a difficult problem because of the potential effects of the therapy on the mother and fetus. While CML may not need to be treated immediately and pregnancy does not appear to affect the course of CML, there is still a risk of leukostasis as well as the risk of placental insufficiency with consequent low birth weight, increased prematurity and increased mortality in mother if CML is left untreated for the duration of the pregnancy<sup>12</sup>.

Conventional therapeutic options of chronic phase CML include hydroxyurea, interferon based regimen and stem cell transplant, bone marrow transplantation being the only curative therapy<sup>13,14</sup>.

The management of CML was revolutionised by the introduction of the specific tyrosine kinase inhibitor, imatinib mesylate (GLEEVEC). Standard dose of Imatinib is 400mg/day in chronic phase, 600 mg in advanced CML and it can be increased upto 800 mg/day. Imatinib entered clinical trials in 1998 and has since been shown to induce dramatic hematologic and cytogenetic responses<sup>14,15</sup>. However, despite its remarkable efficacy and toxicity profile, little is known about the potential for long term toxicity. Patient treated with imatinib should be counselled against becoming pregnant because there are no good data on its use in pregnancy.

Newer BCR-ABL tyrosine kinase inhibitors like nilotinib can induce response in patient with all phases of imatinib-resistant CML.

Leukapheresis has been successfully used in both acute and chronic leukemia for the rapid reduction of high WBC count in patients with impending vascular occlusion. Since chronic mechanical cytoreduction does not prolong survival in these patients and because it is

inconvenient, costly and time consuming, leukapheresis is not currently recommended as maintenance therapy for this disease. However, this form of treatment does offer an attractive short term alternative to the chemotherapy for the pregnant patient, since exposure to the potentially hazardous effect of alternative chemical agent can be avoided<sup>16,17</sup>.

Supportive therapy in the form of red cell transfusion, platelet transfusion, or fresh frozen plasma transfusion, infection control by parenteral antibiotic therapy is administered and sometimes antifungal therapy and antiviral therapy may have to be considered too. Patient may need isolation, monitoring of renal, hepatic and haemostatic function and psychological support.

### Summary

- Leukemia in pregnancy is extremely rare, the incidence being 1 in 100,000 pregnancies.
- Clinical features are due to anemia, thrombocytopenia, granulocytopenia resulting in fatigue, weakness, bleeding disorder, increased leukocyte count, infection
- Investigations include complete blood count, peripheral smear, bone marrow aspirate and biopsy for diagnosis.
- Multiagent chemotherapy is advisable and is started as soon as leukemia is diagnosed particularly in 2<sup>nd</sup> and 3<sup>rd</sup> trimester, if the patient is in a stable condition, otherwise supportive treatment is started.
- There is no deleterious effect of pregnancy on leukemia, hence termination of pregnancy does not improve prognosis.
- Abortion is considered in early trimester to avoid teratogenic effect of chemotherapy.

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## ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN PREGNANCY

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In 1956 Egeberg coined the term "Thrombophilia" which is a range of conditions with an increased tendency for recurrent thrombus formation. It is an important cause of venous thromboembolism in pregnancy. It can be inherited and acquired. Most important cause of acquired thrombophilia is "Antiphospholipid antibody syndrome (APS)", also known as "Hughes syndrome."

Antiphospholipid antibodies (APLA) are a family of autoantibodies that bind to negatively charged phospholipids and/or phospholipids binding proteins. The first APLA to be detected was the false positive Wasserman test and the key antigen found was 'cardiolipin'. APLA includes lupus anticoagulant (LAC), anticardiolipin antibody (aCL) and anti beta2 glycoprotein I (GPI). APLA are found in about 5-7% of healthy subjects and upto 35% of patients with SLE.

APS can either be primary (without underlying disorder) or secondary to connective tissue disorders or SLE. APS mainly results in thrombosis and adverse pregnancy outcome.

The main mechanisms by which these antibodies cause these adverse effects are

- 1) These antibodies are directed against anionic phospholipids and phospholipids binding proteins like GPI, prostacyclin, protein C, annexin V and tissue factor expressed on the cell membrane and thus interfere with prothrombotic and antithrombotic mechanisms
- 2) They mainly cause endothelial cell activation and oxidant mediated endothelial injury
- 3) They also lead to platelet and complement activation
- 4) APS related adverse pregnancy outcome is related to abnormal placentation, defective spiral artery formation, defective trophoblastic invasion, and defective trophoblastic hormone production.

The adverse manifestations of APS in pregnancy are

- a) Maternal : venous thromboembolism, arterial thrombosis, early onset severe preeclampsia.
- b) Fetal : recurrent fetal and embryonic losses, severe IUGR, oligohydroamnios, preterm birth and intrauterine death.
- c) Placental : Abruption, thrombosis and infarcts.  
5-20% of patients with recurrent pregnancy loss have APS. 33-50% with APS have preeclampsia/gestational hypertension. 20–30% with APS have IUGR.

#### Thrombotic complications of APS are

- 1) APLA are present in 2% individuals with unexplained thrombosis.
- 2) Predisposing factor for 4 - 28% of cases of strokes in young patients.
- 3) APS in pregnancy has a 5% risk for thrombosis and 12% risk for stroke. APS is diagnosed based on Revised Sapporo criteria, 2006. It is diagnosed if at least one clinical and one lab criteria is fulfilled.

#### The criteria are

##### Clinical criteria

- 1) Vascular thrombosis: One or more clinical episodes of arterial, venous or small vessel thrombosis confirmed by imaging or Doppler study or histopathology.
- 2) Pregnancy morbidity
  - a) One or more unexplained death of morphologically normal fetus at or beyond 10wks
  - b) One or more premature births of morphologically normal neonate before 34wks because of eclampsia or severe preeclampsia or placental insufficiency.
  - c) Three or more unexplainable consecutive spontaneous abortions before 10wks.

##### Laboratory criteria

The following should be present on two or more occasions at least 12 weeks apart -

- 1) Anticardiolipin antibodies of IgG or IgM type in blood in medium or high titers
- 2) Lupus anticoagulant
- 3) Anti beta2 glycoprotein I

Around 70% patients with APS have both LAC & aCL positive. Anticardiolipin antibody is more sensitive while LAC is more specific for APS. IgG isotype of aCL in medium to high titers is more specific than IgM isotype.

#### Management of APS in pregnancy without prior thrombosis

Aspirin (75-150mg OD) should be started as soon as the pregnancy is diagnosed and should be given upto 34 weeks of gestation & Heparin (unfractionated or low molecular weight) in prophylactic dose should be started after documentation of fetal heart activity and stopped at 34 weeks. In the postpartum period prophylactic warfarin should be given till 6 weeks. No monitoring is required for prophylactic dose of heparin.

#### Dose of heparin used for prophylaxis is as follows

- a) Unfractionated heparin given subcutaneous 12hrly - 5000 IU, 7500 IU, and 10000 IU in first, second and third trimester respectively.
- b) Low molecular wt. heparin (LMWH) : Enoxaparin 40mg s.c od or Dalteparin 5000 IU s.c od. The role of heparin in APS is more of an immunomodulatory one rather than its antithrombotic action. Various studies have shown that aspirin plus prophylactic heparin increases the live-birth rates in APS to around 80% and also reduces the incidence of other adverse pregnancy outcomes dramatically.

#### Management of APS in pregnancy with prior thrombosis

Therapeutic anticoagulation is to be started as soon as fetal heart is documented and given throughout pregnancy. Dose of heparin used for therapeutic anticoagulation is as follows

- a) Unfractionated heparin either subcutaneously 3 times daily or continuous infusion to maintain the midinterval APTT 1.5-2.5 times.
- b) LMWH - Enoxaparin 1mg/kg 12 hrly or dalteparin 200 IU/kg 12 hrly to maintain antifactor Xa levels between 0.6-1.1%.

If unfractionated heparin is used in therapeutic doses then monitoring of platelet count and APTT is required. Platelet count is to be done every 3-4 days from day 4-14 of heparin therapy to rule out heparin induced thrombocytopenia (HIT). APTT is to be monitored every 6 hours of change of dose and once therapeutic target APTT is achieved, then it should be repeated monthly. No monitoring of platelet count is required with use of LMWH except in morbidly obese, renal failure or patients with concomitant use of unfractionated heparin. During



heparin treatment proper calcium supplementation and daily weight bearing exercise is important to combat the adverse effects of heparin that is osteoporosis. Overall LMWH is preferred over unfractionated heparin except near labour, and during acute thrombosis.

LMWH heparin is stopped 24 hours before induction or as soon as patient feels labor pain. If patient is at a very high risk for thromboembolism then LMWH can be switched over to unfractionated heparin at 36 weeks. Unfractionated heparin is to be stopped when patient is in active labour.

Postpartum therapeutic anticoagulation with heparin is to be restarted 6 hours after a vaginal delivery or 12 hours of cesarean delivery & simultaneously warfarin should be started orally. Once a prothrombin time (PT INR) of 2-3 is achieved with warfarin, heparin should be discontinued. Postpartum anticoagulation is given at least for 6 weeks.

Pregnant patients with APS should be followed up in high-risk antenatal clinic. As patients with APS are at high risk for IUGR they should undergo serial ultrasonography with growth parameters and amniotic fluid index every 4 weeks after 18-20 weeks of gestation onwards. Antenatal surveillance with daily fetal movement count and modified biophysical profile should be done after 30-32 weeks of gestation.

Thus the ideal treatment for APS in pregnancy should

- 1) Improve maternal and fetal-neonatal outcome by reducing risk of pregnancy loss, preeclampsia, IUGR and preterm birth.
- 2) Eliminate the risk of thromboembolism.

Obstetric aspects of APS continue to generate considerable controversy and redefining of its diagnostic criteria is an ongoing process.

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## GESTATIONAL DIABETES MELLITUS

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Pregnancy is characterised as diabetogenic state although 95% to 97% of all women retain normal glucose tolerance, approximately 3-5% develop gestational diabetes mellitus (GDM)<sup>1</sup> which occurs when the woman's pancreatic function is not sufficient to overcome the diabetogenic environment of pregnancy. The development of insulin resistance during pregnancy usually is compensated for by a considerable increase in insulin secretion.

GDM is defined as any degree of glucose intolerance with the onset or first recognition during pregnancy, regardless of whether insulin or any diet modification is used for treatment or whether the condition persists after pregnancy<sup>2</sup>.

In the United States prevalence rates for GDM are higher for African Americans Hispanic, American Indians and Asian Women than white women. Prevalence of GDM varies in direct proportion to the prevalence of Type-2 diabetes. GDM is associated with various adverse outcomes including neonatal hypoglycaemia, hyperbilirubinaemia, macrosomia which can lead to birth trauma or caesarian delivery, increased risk of obesity or diabetes in the offspring late in life and increased risk for other maternal morbidities<sup>3</sup>. GDM recurs at the rate of 35% to 50% and 70% of affected women will progress to Type-2 diabetes in their lifetimes.

### Pathophysiology of GDM

In women with GDM, insulin resistance combined with decreased pancreatic  $\beta$ -cell reserve triggers impaired glucose tolerance. Insulin resistance during pregnancy is due to variety of factors including alterations in growth hormone, increased cortisol secretion and human placental Lactogen which is responsible for decreasing insulin sensitivity with advancing gestation

### Risk factors for GDM

- Several risk factors are associated with the development of GDM
- Strong family H/o diabetes (In 1<sup>st</sup> degree relative)
- Member of the ethnic group with higher rate of Type -2 diabetes

- Obesity – weight - >110% of ideal body weight
- Body mass index (BMI) > 30
- Age > 25 years
- Persistent Glycosuria
- H/o Macrosomia (Birth weight > 4000 gm)
- H/o Polycystic ovarian syndrome
- H/o Spontaneous abortions and unexplained still births
- H/o GDM in previous pregnancy No risk factors are identified in 50% of patients in GDM.

### Screening for GDM

There is no uniformity regarding the guidelines developed by different professional organizations for screening GDM. American college of obstetricians and Gynaecologists (ACOG-2001) recommended universal screening at 24-28 weeks of gestation, because not all women who develop GDM have risk factors. National Institute for Health and clinical Excellence, London (2003) reported that “there is an absence of evidence to support routine screening for GDM and therefore it is not recommended”. The U.S preventive services Task Force (2003) reported that there is no enough evidence to recommend or not to recommend universal screening for GDM. Recently American Diabetes Association (ADA. 2007) recommended assessing the risk factors for GDM for all women in first antenatal visit. Low risk women need not be tested for GDM. Low risk women are Caucasian, have a normal prepregnancy BMI (<20), are <25 year old and have no prior adverse pregnancy outcome. Woman with high risk factors should be tested at first antenatal visit and if initial screen test is normal, then the test is repeated at 24 to 28 weeks. Women with moderate risk be screened at 24-28 weeks. Initially for the glucose challenge test, the patient receives 50 gm of glucose and blood is drawn for the plasma glucose determination after 1 hour. A glucose value above 130 to 140 mg/dL is considered abnormal and second 3-hour test is necessary using a cut-off value of 130 mg/dL provides 90% sensitivity and 140 mg/dL cut-off value provides 80% sensitivity. Abnormal results for 1-hour screening test will occur in 15% of patients. Of those women who will have the 3-hour screening test 15% will be diagnosed with GDM. The 3-hour oral glucose tolerance test (GTT) with 100 gm glucose load after taking fasting blood sample, blood for glucose values is drawn after 1 hour, 2 hours and 3 hours. If two or more blood glucose limits exceeds, diagnosis of GDM is confirmed.

Diagnosis:- Using 100 gm, 3-hour GTT, two abnormal serum glucose values from the following criteria

- Fasting 95 mg/dL
- 1 hour 180 mg/dL
- 2 hours 155 mg/dL
- 3 hours 140 mg/dL

National Diabetes Data Group's (NDDG) criterias are slightly more liberal. The abnormal values are as follows

- Fasting serum Glucose 105 mg/dL
- 1 hour 190 mg/dL
- 2 hours 165 mg/dL
- 3 hours 145 mg/dL

If two threshold values met or exceeded, GDM is diagnosed

### Complications in GDM

#### A] Maternal

- 1) Increased incidence of asymptomatic Bacteriurea and urinary tract infection. Pyelonephritis thought to be due to the increased amount of Glucose in the urine beyond normal Glycosuria that is present in pregnancy
- 2) Increased incidence of pre-eclampsia
- 3) 10% risk of polyhydramnios which may increase the risk of preterm labour, abruption of placenta and post partum haemorrhage.
- 4) Risk of developing Type-2 diabetes

#### B] Fetal

- 1) Macrosomia which will increase operative delivery and shoulder dystocia
- 2) Increased incidence of hypoglycemia, hyperbilirubinemia and Respiratory distress syndrome

- 3) Longterm complications are obesity, diabetes during childhood, impaired motor functions and higher rates of inattention and hyperactivity.

### Management And Treatment Of GDM

Basic principle in the management of GDM is Glycemic control. Blood glucose levels should be monitored and the fasting glucose level goal is to maintain 70 to 90 mg/dL the postprandial goal is ideally below 120 mg/dL upper limit is 135 to 140 mg/dL

#### Diet

Quality nutritional intake is essential. The overall dietary requirement recommended is 33% to 40% carbohydrate, 35% to 40% fat and 20% protein. Caloric requirement based on body weight is 30 Kcal/kg for women with BMI of 22 to 25, 24 Kcal/kg for women with BMI of 26 to 29 and 12 to 15 Kcal/kg for women with BMI above 30. Decreased caloric consumption and reduction of the carbohydrate intake will result in 75% to 80% of GDM women become normoglycemic and fewer patient will require insulin.

#### Exercise

Has been shown to improve Glycemic control as a result of enhanced insulin sensitivity<sup>6,7</sup>. Though it is not clear exactly how much exercise is enough to control glucose levels, exercise 3 or more times a week at least 15 to 30 minutes duration is the recommendation<sup>6</sup>.

#### Insulin Therapy

Is recommended after failure to respond to the diet and exercise regime<sup>3</sup>. To minimize macrosomia and its associated risk to infants, insulin may be started when the fasting blood glucose is greater than 90 mg/dL on 2 or more occasions during 2 weeks period or when the postprandial blood glucose is greater than 120 mg/dL. The insulin commonly used are regular insulin and neutral protamine Hagedorn (NPH) which is intermediate acting insulin

#### Oral Hypoglycemic Agents

Glyburide (sulphonylureas) is an alternative to insulin. Glyburide is classified as category-B drug and not approved by US, FDA due to increased risk of neonatal hypoglycaemia. Usual dose of Glyburide is 2.5 mg once or twice a day but some patients are well controlled with 1.25 mg twice a day.

Another oral hypoglycemic drug is metformin. Recently Rowan and colleague<sup>8</sup> (2008) compared the use of metformin and insulin in GDM and concluded that neonatal

complications did not vary between two groups. Preterm Labour were more with metformin. There was less severe hypoglycemia in neonates. 46.3% of women on metformin had to be supplemented by insulin. Metformin has got advantage over Sulphonyl ureas for obese and insulin resistant women. This study concluded that metformin was a safe option and more acceptable to the patient in GDM.

Antepartum fetal monitoring by non-stress test is recommended in patient who do not have well controlled GDM. Frequent antenatal visits are recommended for maternal and fetal monitoring depending on severity. Daily blood sugar monitoring, urine ketone, blood pressure and urine protein monitoring is necessary.

#### Timing Of Delivery

Women with controlled glucose levels and with no other complications may be allowed to deliver spontaneously at term. Caesarian section may be considered if estimated fetal weight is 4500 gm. Active management is recommended in high risk women at 38 weeks to prevent perinatal mortality.

Blood Glucose should be monitored 24 hour after delivery to find out hyperglycemia. In postpartum period, 95% of women become normoglycemic. Glucose tolerance screening should be performed at 2 to 4 month after delivery, as 3% to 5% of women remain diabetic and require further treatment.

Counseling to prevent conversion of GDM to Type-2 diabetes and for family planning is essential. Women with GDM should have preconception counseling if contemplating a further pregnancy to minimize the risk of future pregnancy complication.

More research is necessary to determine which guidelines will produce better pregnancy outcome and long term effect and how to prevent conversion of GDM to Type-2 diabetes.

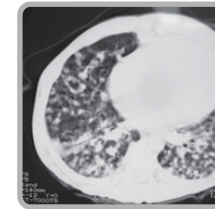
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## TUBERCULOSIS IN PREGNANCY



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### Introduction

Tuberculosis has been one of the most dreaded infections of mankind since time immemorial noted for its subtle onset and lethality. It also remains the most common cause of death among infections in women of child bearing age<sup>1</sup>. Overpopulation, human immunodeficiency virus (HIV) infection, poverty, ignorance, inadequate treatment and the increasing incidence of antibiotic-resistant has made tuberculosis a complex problem.

### Microbiology

*M. tuberculosis* belongs to the *Mycobacteriaceae* species of the order *Actinomycetales*. Humans are the major reservoir for this species. *Mycobacterium bovis* (cattle) occasionally infects select populations (3% of tuberculosis in San Diego)<sup>2</sup>.

*M. tuberculosis* is an aerobic, non-spore-forming, non-motile bacillus with a high cell wall content of high-molecular-weight lipids. Its generation time is 15 to 20 hours, compared with less than 1 hour for most common bacterial pathogens. Visible colonies require 3 to 4 weeks and appear as serpentine cording. The long culture time often delays diagnosis or leads to treatment without absolute proof of tuberculosis infection resulting in, at times, unwarranted treatment with costly and toxic drugs.

An acid-fast stain is used to screen specimens. In the classic Ziehl-Neelsen stain, a fixed smear covered with carbol fuchsin is heated, rinsed, decolorized with acid-alcohol, and counterstained with methylene blue. The Kinyoun stain is similar but modified to make the heating unnecessary. Many laboratories use a fluorochrome stain with auramine or rhodamine in the initial staining, a slightly modified acid-alcohol decolonization step, and potassium permanganate counterstaining<sup>3</sup>. The mycobacteria appear fluorescent bright orange-yellow against a dark background with a strong blue light source. Under the 100× oil-immersion objective, the mycobacteria are beaded, slightly bent rods 2 to 4 μm long and 0.2 to 0.5 μm wide. In sputum, they lie in parallel or adhere end to end to form a V shape. This



smear has a sensitivity of 78%, with 11% false-positive results. An estimated 10,000 organisms per milliliter of sputum are required for acid-fast stain positivity, and the identification of a single organism on the entire slide is highly suspicious. At least three early morning (before rising) sputum samples or gastric aspirates should be evaluated.

Before culture, sputum and other contaminated specimens require liquidization and decontamination with N-acetyl-L-cysteine in 1% sodium hydroxide solution. The sample is then neutralized and centrifuged, and the sediment is inoculated into the media. Uncontaminated specimens (i.e. surgical tissue or cerebrospinal fluid) should not be decontaminated, because doing so reduces the growth of Mycobacteria.

Solid media is of two types, agar-based or egg-based, with suppressive additives for bacteria other than mycobacteria. The BACTEC radiometric system for identification of Mycobacteria uses radioactive palmitate as the sole carbon source in this liquid culture system. Within 9 to 16 days, metabolism is detected if M. tuberculosis is present.

M. tuberculosis can be differentiated from other mycobacteria by its slow growth, lack of pigment, production of niacin and small quantities of heat-sensitive catalase, reduction of nitrates, and isoniazid sensitivity. Antibiotic resistant is determined when growth on the antibiotic-containing media exceeds 1% of the growth on antibiotic-free media.

The use of polymerase chain reaction (PCR) in the can identify as few as 10 organisms in clinical specimens. Traditional culture and sensitivity is still necessary, because PCR cannot detect antibiotic sensitivity<sup>4</sup>.

Epidemiology

Worldwide, almost 1.75 billion people have been infected with tuberculosis, and 3 million die each year as a consequence. In the past century, the epidemic has spread to those countries whose industrialization and urbanization is in process fueled by crowded living and a large pool of naive humans. The worldwide, new case rates per 100,000 persons are depicted in Table 15. In the United States, two thirds of all new cases are minority individuals.

TABLE 1. Estimated Worldwide Active Tuberculosis Rates Per 100,000 Population

Population	Rate per 100,000 Population
Africa	220
Southeast Asia	194
China	191
Western Pacific	191
Eastern Mediterranean	155
South and Central America	120
Europe	31
U.S.: correctional institutions	106
Asian/Pacific Islanders	42
African Americans	33
Hispanic Americans	21
Population	Per rate 100,000 population
Native Americans	19
White Americans	4

Tuberculosis in Pregnancy- Myths and Facts

Tuberculosis or the pulmonary scourge has been known from time immortal. Excavated remains of Egyptian mummies have shown evidence of tuberculosis. Hippocrates and Galen have described and written about it. Even the bones of the Neanderthal man have shown that these bacilli have been in existence for a long long time. It was famously called 'the consumption disease' or 'the captain of the men of death' by Bunyan<sup>6</sup>.

In our present day scenario tuberculosis has re-emerged as one of the fore runners of disease due to the following<sup>7</sup>:

- a) HIV epidemic.
- b) Multi drug resistant strains of tubercle bacilli.
- c) Poverty and malnutrition.

- d) Population explosion and inadequate sanitation.
- e) Lack of access to good health care.
- f) False sense of security due to chemotherapy.
- g) Influx of younger people from foreign countries.

Tuberculosis seems to infect a disproportionately larger number of childbearing women and their infants. When the reported cases of tuberculosis (1985 through 1990) in the United States is plotted by age, there are peaks in the first year of life (about 900), age 35 (2700), and a broader increase between the ages of 50 and 80 years (1500 to 1700 cases per year)<sup>8</sup>. This graph is remarkable for its peaks in infancy and childbearing age women. These peaks have been increasing over the past 10 years, in part because of the increasing incidence of HIV positivity and the increasing numbers of women at high risk for tuberculosis. Although the male to female ratio of new tuberculosis notifications is about 2:1 in developed countries and 1.2:1.7 in developing countries, tuberculosis in women is often underreported compared with the statistics for men<sup>1</sup>.

Between 5% and 10% of reproductive-age women in the United States have a reactive tuberculin skin test<sup>8</sup>. There have been outbreaks of multidrug resistant tuberculosis (MDR-TB) among health care workers<sup>9,10</sup>. Approximately one of three exposed health care workers become new tuberculin converters. The therapy of MDR-TB is associated with major morbidity and mortality in more than 50% of immunocompetent health care workers. Among HIV-infected patients with active MDR-TB, the mortality is 80% to 90%.

Hippocrates and Galen thought that pregnancy was beneficial to patients as elevation of the diaphragm due to the growing size of the uterus helped in the closure of the cavities in the lungs<sup>11</sup>. In the 19th century, Grisolle, Drolet and Rich said that pregnancy worsened the clinical course of tuberculosis and caused an increase in death rates. 'For the virgin no marriage, for the married no pregnancy, for the pregnant no confinement' was the dictum<sup>12</sup>. Cohen of Boston City Hospital studied 401 pregnant women with tuberculosis and came to the conclusion that 13% of these women worsened with pregnancy<sup>13</sup>.

Over the course of the 20th century, this concept changed partly because of improved healthcare and availability of anti-tuberculous therapy which later on proved to be safe during pregnancy. Stewart and Simmonds in their study found no difference in the 5 year survival in pregnant versus non-pregnant patients with tuberculosis hence showing that pregnancy did not alter the course of the disease<sup>14</sup>.

Pregnancy and puerperium may however increase the risk of re-activation of the disease. It is recommended that patients avoid pregnancy for 2 - 3 years after completion of treatment. There is no evidence to suggest that there could be development of active disease during pregnancy<sup>15</sup>.

The effect of tuberculosis is two fold i.e. on pregnancy itself and the puerperium.

#### *Effect on Pregnancy*

- a) If untreated, there is a 30 - 40% incidence of maternal or neonatal mortality<sup>16</sup>.
- b) There is an increased risk of toxemia, post partum haemorrhage or difficult labor.
- c) A marginal increase in fetal malformations after treatment (9.8% vs 3.6 - 4.1%) but this does not warrant an abortion<sup>17</sup>.
- d) Statistics shows no increase in malformations in children born to mothers with tuberculosis however prematurity, intra-uterine growth retardation, low birth weight and increase in perinatal mortality have been reported

#### *Effect on Puerperium*

- a) Crombie studied 101 patients and found that there is activation of latent infection in the first post partum year<sup>18</sup>.
- b) A study by Pugh and Gierc showed worsening of the disease and increase in mortality due to descent of the diaphragm, nutritional stress, poor sleep and hygiene, post partum hormonal changes and altered cellular immunity<sup>19</sup>. However with effective treatment this problem is insignificant.

#### *Natural History of Tuberculosis*

Tuberculosis is almost always caused by inhalation of infectious particles aerosolized by coughing, sneezing, or talking. When the index case is AFB smear negative but culture positive, the risk of infection in household contacts is 5% to 10% with women and children at greatest risk<sup>20</sup>. When exposure occurs on a hospital acquired immunodeficiency syndrome (AIDS) ward, the risk of infection is 40% to 80%<sup>5</sup>. Occasionally, tuberculosis can be transmitted by infected raw cow's milk (*M. bovis*) or skin inoculation from contamination of an abrasion or laceration.

Three to four percent of infected persons develop active tuberculosis during the first year after tuberculin conversion, and 5% to 15% will do so during the remainder of their life<sup>5</sup>. They

are at greatest risk when their host immunity is decreased: ageing, concurrent disease, pregnancy, and primary compromise of their immune system (i.e. HIV infection, immunosuppressive drug therapy, steroids, and cancer chemotherapy).

High-airflow areas, mid-lung regions (i.e. lower upper lobes or upper lower lobes), favor the initiation of infection in the subpleural spaces. In 75% of cases, there is just one area of infection, and in 25%, there are multiple areas. Alveolar macrophages ingest the bacilli which multiply intracellularly. Blood-borne lymphocytes and macrophages also ingest the bacilli. The infected macrophages migrate to the regional lymph nodes (usually hilar or mediastinal) and form granulomatous lesions. During this phase, the bacilli disseminate in the body. Certain areas with greater vascularity favor the continued multiplication of the bacilli (lymph nodes, posterior-apical lungs, meningeal areas, vertebral bodies, kidneys, and epiphysis of the long bones).

Until the development of tuberculin hypersensitivity (cell mediated immunity), bacterial growth and tissue destruction continue. The incubation period for active tuberculosis has been reported to be as short as 20 days, and in most cases, it is 1 to 3 months. The most common form is cavitory destruction of lung tissue in the apices. The most extreme form is described as miliary and is associated with high mortality and morbidity.

The tuberculin reaction occurs in 3 to 8 weeks after infection. In a minority of cases, in which the primary infection created more destruction, calcification of the primary focus (Ghon focus) and regional lymph nodes produces what is called the Ranke complex. Although most of these calcifications are sterile, some retain viable latent bacilli which may be reactivated later under favorable conditions such as old age, medical disease and immunosuppression.

Early tuberculosis is usually asymptomatic. Table 2 describes the presenting signs in

TABLE 2. Symptoms of Active Tuberculosis in Women			
Symptom	Nonpregnant	Pregnant	HIV Seropositive*
Cough	50%	70%	80%
Fever	30%	30%	90%
Hemoptysis	25%	20%	30%
Weight loss	40%	30%	55%
Symptom	Nonpergnant	Pregnant	HIV Seropositive*
Fatigue	30%	30%	60%
Night sweats	10%	10%	50%

\*There is no differences in symptoms relative to pregnancy status in HIV-positive women<sup>21</sup>.

The early symptoms are usually nonspecific-anorexia, fatigue, weight loss, chilly sensations, and night sweats. Local symptoms indicate advancing disease. A productive cough with mucopurulent sputum is usually present with bronchial involvement. Bronchial artery or vein involvement results in hemoptysis. During the primary phase of the disease, radiographic abnormalities include pulmonary consolidation (50%), cavitation (29%), hilar or mediastinal lymphadenopathy (35%), disseminated miliary disease (6%), and a normal chest radiograph (15%). During the postprimary phase of the disease, common radiographic abnormalities include exudative or fibroproductive parenchymal densities (100%), predominantly in the apical and posterior segments of the upper lobe (91%), cavitation (45%) with bronchogenic spread of the disease(21%), marked fibrotic response in the lungs (29%), pleural effusion(18%), and emphysema (4%)<sup>21</sup>.

Fiberoptic bronchoscopy can play a critical role in the diagnosis of active tuberculosis. Patients who have signs and symptom or radiographic evidence of active tuberculosis without a positive AFB smear should have a fiberoptic bronchoscopy<sup>5</sup>.

The mortality rate for untreated active tuberculosis is 50% to 60% within 5 years. This phase is characterized by caseating granulomas in various organs, severe weight loss and fatigue, increasing respiratory symptoms, and superimposed infectious disease (e.g. pneumonia). About 15% develop miliary tuberculosis. This complication, if untreated, is rapidly fatal.

Prenatal Screening for Tuberculosis

The concept of prenatal screening for tuberculosis is to diagnose tuberculosis infection at the latent stage before appearance of symptoms of the disease to reduce morbidity and infectivity<sup>22</sup>.

In countries like India with a high incidence of tuberculosis exposure and infection and universal BCG vaccination there is virtually no role of screening since the incidence of immunoconversion (positive tuberculin test) is high.

In the developed world, in countries like the United States, screening for tuberculosis may be considered prior to or during pregnancy in the following situations:

- 1) *Patients at risk for exposure to tuberculosis:*
  - a) Immigrants from high prevalence countries
  - b) Homeless people
  - c) Medically indigent residents
  - d) Intravenous drug users
  - e) Health care workers

- f) Nursing home residents
- 2) *Patients at risk for disease once infected:*
  - a) Immunosuppression state (HIV)
  - b) Malnutrition
  - c) Medical illness (Diabetes Mellitus)
  - d) Infants
- 3) Universal screening of all women prior to or during pregnancy would be ideal but virtually impossible to implement in practice.

Screening for tuberculosis is done with the tuberculin test using protein purified derivative (PPD). 0.1 ml (5 Tuberculin Units) of PPD is administered subcutaneously on the dorsal forearm and, after 48-72 hours, the induration (not the hyperemia or erythema) at the site of injection is measured in millimeters.

The positive tuberculin reaction is because of prior sensitization of the immune system due to prior exposure to tuberculosis (infection) and is characterized by a classic mononuclear cellular infiltration and inflammation. To ensure an adequately active immune system, subcutaneous administration of mumps or candida antigen may be used simultaneously. There is no evidence that pregnancy with its associated depression of cell mediated immunity is associated with an increase evidence of false negative tuberculin test. Tuberculin testing does not activate latent infection nor does it delay diagnosis of unsuspected disease.

The immune sensitization to tuberculin wanes over time. If a PPD test is negative, it can be repeated after 2-4 weeks. A positive test implies a booster effect due to stimulation of the waning sensitivity by the previous tuberculin test (old positive reactor) and does not warrant any further investigation or treatment. A negative test implies a total absence of exposure to tuberculosis (true negative). In this case, any tuberculin positivity developing subsequently is interpreted as a new exposure (recent converter) and this patient needs further investigation and appropriate treatment<sup>23</sup>.

The interpretation of the tuberculin reaction (size in millimeters) is done according to CDC guidelines:

- 1) More than or equal to 5 mm considered positive in:
  - a) HIV patients
  - b) Recent contacts with a case of active tuberculosis
  - c) Clinical or radiological evidence of tuberculosis

- 2) More than or equal to 10 mm considered positive in:
  - a) Intravenous drug users
  - b) Health care institution residents
  - c) Immigrants from high prevalence areas
  - d) Minorities (Asians, Hispanics, Blacks and American Indians)
  - e) Diabetes Mellitus
  - f) Renal failure
  - g) Post gastrectomy or intestinal bypass
  - h) Silicosis
  - i) Malnutrition (more than 10% below ideal body weight)
  - j) Chronic alcoholics
- 3) More than or equal to 15 mm considered positive in all patients.
- 4) Less than 5 mm is considered negative for tuberculosis infection.

#### INH Prophylaxis following Tuberculin testing

In developing countries like India the tuberculin positivity may be as high as 50% in some highly endemic areas<sup>24</sup>. A positive tuberculin reaction in the absence of clinical or radiological features of active tuberculosis often implies prior exposure to tuberculosis or old infection. INH prophylaxis is medically, economically and logistically not feasible and may worsen the problem of drug resistance.

In the developed world with a strong focus on preventive care and low incidence of infection (In USA, the incidence of tuberculosis infection is estimated to be 0.3-1.9%), INH prophylaxis may be considered in the following situations with the goal of eradicating any latent infection<sup>22</sup>:

- 1) Recent converters: documented tuberculin positivity developing within the past 2 years since studies have shown an increased incidence of tuberculosis disease within 2 years of conversion.
- 2) Close contacts of a person with active tuberculosis.
- 3) Immunocompromised patients. The logical course of management in the presence of a positive tuberculin test would be to perform a chest radiograph with an abdominal shield to reduce the fetal exposure to radiation to less than 0.3 millirads. If the X-ray is normal and there is no clinical evidence of pulmonary or extra-pulmonary disease, the value of INH



prophylaxis is controversial. It would be advisable to delay treatment after delivery and the puerperium since INH therapy is associated with a significant risk of hepatotoxicity especially in the postpartum period<sup>25</sup>. Following puerperium, INH may be administered in the dose of 5mg/kg up to a maximum of 300mg for 6 months with monitoring of liver function tests.

If the chest radiograph reveals evidence of old tuberculosis, clinical evaluation is mandatory. If the woman is older than 35 years and has no clinical evidence of tuberculosis, no therapy is necessary. The age factor is considered since with advanced age the incidence of prior tuberculosis exposure rises with increase incidence of tuberculin positivity. Otherwise, in a younger woman without clinical evidence of disease, INH is administered after delivery and puerperium in the dose of 5mg/kg (maximum 300mg) for a period of 12 months.

In the presence of clinical or radiological features of recent or active tuberculosis, immediate INH therapy is considered. Rifampicin, pyrazinamide and ethambutol are added to INH and the treatment is for eradication of active tuberculosis.

Breast feeding is not contraindicated during INH prophylaxis.

### Diagnosis of Tuberculosis in Pregnancy

#### A) History

- i) Past or present contact with a patient
- ii) Prior history of pleurisy or pneumonia
- iii) Known case of diabetes mellitus, malnutrition or any other chronic illness
- iv) Alcohol addiction

#### B) Symptoms

- i) Generalized- fatigue, anorexia, slow weight loss, decrease stamina
- ii) Constitutional- low grade evening rise of temperature, dry cough, night sweats
- iii) Respiratory- haemoptysis, chest pain (may be due to pneumonia, pleuritis, pericarditis, pneumothorax)
- iv) Organ specific- hoarseness (larynx), wheezing (endobronchial), joint pains (articular), pleuritic pain (pleura)

#### C) Physical examination

- i) Lymphadenopathy

- ii) Pulmonary signs: rhonchi, rales, bronchial breathing
- iii) Examination of bony joints
- iv) Neurological signs
- v) Genitals are rarely involved

#### D) Chest X-Ray

One can detect two kinds of pattern on x-ray, namely<sup>26</sup>:

- i) Primary disease
- ii) Re-activation of the disease

During primary disease, one may note the following features on X-ray:

- i) Infection of middle or lower lobe or the anterior aspect of upper lobe
- ii) Hilar or mediastinal lymphadenopathy
- iii) Pleural effusion
- iv) Cavitation
- v) Pneumatocele
- vi) Segmental or lobar atelectasis

During reactivation, there may be the following:

- i) Exudative or parenchymal densities in anterior or posterior aspect of upper lobe
- ii) Cavitation
- iii) Empyema
- iv) Pleural effusion

#### E) Specimen evaluation

- i) Sputum: This can be obtained by various methods namely,
  - a) Morning sample by pooling the overnight specimen
  - b) Inhalation of hypertonic saline and coughing
  - c) Aspiration of 25-50cc of gastric contents in the morning
  - d) Fibre-optic bronchoscopy with lavage, brush or biopsy

- iii) Pleural fluid obtained by thoracentesis

Smear of this fluid shows lymphocyte predominance and cellular exudates. Culture of this fluid can also be done. 50% of both smears and culture show positivity.

- iii) Pleural biopsy
- iv) Tapping of the pericardial effusion
- v) Urine sample may show sterile pyuria or haematuria
- vi) Arthrocentesis may reveal inflammatory exudates in the synovial fluid
- v) Paracentesis may show evidence of peritoneal spread
- viii) Lymph node biopsy or a bone marrow biopsy or a liver biopsy may reveal disseminated disease

Specimens collected can be subjected to staining, culture or other modern techniques such as BACTEC or ELISA<sup>27</sup>.

Pregnant women are very often asymptomatic and more likely to have a negative smear. They present with non-cavitatory, small, peripheral or lower lung infiltrates. 10-20% of women may have negative chest radiograph with active disease<sup>27</sup>.

20% of cases show evidence of extra-pulmonary tuberculosis. Of these, lymphadenitis is the commonest presentation. Others like intestinal, spinal, endometrial and meningeal forms are associated with increased maternal disability, fetal growth retardation and low APGAR scores at birth<sup>28</sup>.

Patients who are HIV+ve show evidence of multi drug resistant tuberculosis and have extensive radiographic changes, longer sputum conversion time and higher neonatal complications.

Treatment Of Tuberculosis In Pregnancy

WHO has declared TB as a global emergency since 1993. Multiple drug therapy in adequate doses and for sufficient duration is the main stay in the treatment of TB<sup>29</sup>. RNTCP incorporated DOTS strategy in treating all forms of TB and helped in curing 87% of population in 2004 with a 72% case detection rate and 86% treatment success rate<sup>30</sup>.

Five components of DOTS strategy are:

1. Continued political commitment from governments
2. Case detection through quality assured bacteriology (sputum microscopy for pulmonary TB and other standard diagnostic modalities for extrapulmonary TB including genital TB)

3. Standardized short course chemotherapy (6 - 8 months) for all cases of TB under proper case management conditions and directly observing the treatment.
4. An effective drug supply and management system ensuring uninterrupted supply of quality assured drugs.
5. Monitoring and evaluation system and measurement of impact by recording and reporting assessment of all patients and overall program performance.

Table 3 provides an outline of the drugs used as a first line of treatment for tuberculosis<sup>29</sup>.

Table 3. First Line Treatment for Tuberculosis			
DRUGS	ADVERSE EFFECTS	PREGNANCY DATA	NOTES
INH (5mg/kg/d max 300mg)	Hepatitis, Peripheral Neuropathy, Cutaneous Hypersensitivity.	Category C easily passes in fetal circulation	with pyridoxine 10mg daily to decrease peripheral neuropathy.
Rifampicin (10mg/kg/d max 600 mg)	fever, neuropathy, hepatitis, flue orange colored urine	Category C	Vit K (10 mg ) po
Ethambutol (15 - 25mg/kg/d)	Retrobulbar neuritis neuropathy	Category B	mtly vision testing
Pyrazinamide (15 – 30 mg/kg/d))	Thrombocytopenia nephrotoxicity hepatotoxicity interstitial nephritis	Category C	
Streptomycin (15-25 mg/kg/d)	ototoxicity	Category D	contraindicated in pregnancy

Drugs for multidrug resistant TB include ofloxacin, ethionamide, pyrazinamide, ethambutol, cycloserine and kanamycin.

First Line chemotherapy<sup>31,32,33,34</sup>

1. INH
  - Derived from nicotinamide in 1945.
  - INH is both bacteriostatic and bacteriocidal.
  - Oral and parenteral are well absorbed.
  - Inexpensive.
  - Inhibits mycolate synthetase.
  - *Side effects*: hepatitis (age related) especially with prior hepatitis or alcohol ingestion, peripheral neuropathy due to interference with pyridoxine metabolism
  - Aad pyridoxine 50 mg/ day
2. Rifampicin
  - Bactericidal oral agent
  - Penetrates cells/tissue but poor meningeal penetration
  - Inhibits DNA dependent RNA polymerase
  - *Side effects*: hepatitis, nausea, hypersensitivity, skin rash, purpura, thrombocytopenia and febrile rash, orange discolouration of tears, contact lenses and urine.
3. Ethambutol
  - Bacteriostatic at 25mg/kg/d and bacteriocidal at 25mg/kg/d
  - Mechanism is unknown
  - *Side effects*: occasional skin rash and retrobulbar neuritis including blurred vision, central scotomata and red green color blindness.
  - Teratogenic to animal but safe in human pregnancy.
4. Pyrazinamide
  - Discovered in the 1950's
  - Bacteriostatic at low doses and bacteriocidal at higher doses.
  - Most effective in acid environment freely enter cells and excreted in urine
  - Increase serum uric acid by decreasing renal tubular excretion
  - Use in pregnancy should be avoided.

5. Streptomycin
  - First antituberculous agent
  - Extracellular bactericidal
  - Ineffective against intracellular bacteria
  - Interferes with protein synthesis
  - Teratogen at all stages of pregnancy
  - Ototoxicity and nephrotoxic
  - Avoided in pregnancy

Other Drugs<sup>35</sup>

1. PAS
  - Discovered in 1946
  - Bacteriostatic
  - Rapidly absorbed from the GI tract
  - Distributed in body fluid/ caseous tissue but poor CSF penetration
  - Inhibits mycobacterial folate metabolism
  - low risk of teratogenicity
  - Side effects: GI upset, hypersensitivity rash (5-10%)
  - Requires 20 tabs/ day for therapeutic effect.
2. Ethionamide
  - Bacteriostatic
  - Orally well absorbed
  - Poorly tolerated due to GI irritation
  - Side effects: hepatitis, optic and peripheral neuropathy
  - Nonspecific teratogenic effect when used in pregnancy.
3. Cycloserine
  - Discovered in 1955
  - Well absorbed and distributed through body tissue and fluids and CNS
  - Side effects: headache drowsiness and occasional CNS psychosis

There are various treatment regimens for tuberculosis including the daily and twice or thrice weekly regimens. The standard therapy in India remains the continuous four drug therapy for 2 months followed by two or three drug treatment for 6-9 months<sup>32</sup>.

Table 4. Treatment Regimens For Tuberculosis*			
CATEGORY	PATIENTS	REGIMEN INITIAL PHASE	REGIMEN CONTINUATION PHASE
I	<ul style="list-style-type: none"><li>• New smear positive pulmonary TB</li><li>• New smear negative PTB with extensive parenchymal involvement</li><li>• Severe concomitant HIV disease</li><li>• Severe forms of EPTB</li></ul>	2HRZE	4HR
II	<ul style="list-style-type: none"><li>• Previously treated sputum positive PTB relapse</li><li>• Treatment after default</li><li>• Treatment failure</li></ul>	2HRZES/1HRZE	5HRE
III	<ul style="list-style-type: none"><li>• New smear neactive pulmonary TB less severe form of EPTB</li></ul>	2HRZ	4HR
IV	<ul style="list-style-type: none"><li>• Chronic &amp; MDRTB cases</li></ul>	<ul style="list-style-type: none"><li>• Kanamycin</li><li>• Ofloxacin</li><li>• Ethionamide</li><li>• Pyrazinamide</li><li>• Ethambutol</li><li>• Cycloserine</li></ul> 6-9 mths intensive phase	<ul style="list-style-type: none"><li>• Ofloxacin</li><li>• Ethionamide</li><li>• Ethambutol</li><li>• Cycloserine</li></ul> 18 mths of continuation phase

\* H-INH, R-Rifampicin, Z-Pyrazinamide, E-Ethambutol, PTB-pulmonary TB, EPTB-extrapulmonary TB, MDRTB-multidrug resistant TB

A woman with PTB and EPTB must be treated with a full course of short course of short term chemotherapy irrespective of gestation (even in first trimester) as per DOTS strategy using category wise treatment. All four drugs i.e. isoniazid, rifampicin, pyrazinamide and ethambutol, are non teratogenic and safe in pregnancy and should be given. Streptomycin is avoided in pregnancy as it can cause ototoxicity in the fetus. Some authors avoid pyrazinamide in pregnancy as there are less data available on its safety in pregnancy.

**Congenital Malformation Risk with Anti-tuberculous Therapy<sup>36,37</sup>**

INH: malformation 1% less than 1.2 -6% for general population  
Rifampicin: malformation 3.35% including limb reduction, CNS lesions, hemorrhagic complications due to inhibition of DNA dependent RNA polymerase  
Ethambutol: eye development is not affected at 15 – 25mg/d  
During treatment of multi-drug resistant tuberculosis amikacin, streptomycin, kanamycin and capreomycin are contraindicated during pregnancy. No malformations have been reported with PAS. The safety of ciprofloxacin, ofloxacin ethionamide and cycloserine has not been proven hence<sup>36</sup>.

**Lactation and Anti-tuberculous Treatment<sup>37</sup>**

INH: concentration peaks after 3 hrs in blood up to 16.6mg/l with 300mg dose  
Rifampicin: peak conc. 10-30mg/l with 600mg dose  
Streptomycin: 1.3mg/l 30 min after 1 gm dose  
None of the drugs have any therapeutic value at this concentration. However, if both mother and child are receiving INH, supratherapeutic concentrations may be achieved. Hence, bottle feeding is recommended if the infant is on INH therapy. In general, however, breastfeeding is not contraindicated during treatment of maternal tuberculosis.

**Treatment of TB in HIV positive pregnant women**

The management of pregnant TB women in HIV positive cases is the similar to routine antituberculous therapy (DOTS strategy) but may need appropriate adjustments to avoid drug interactions<sup>35,38</sup>.

Possible options for antiretroviral therapy in TB patients include:

1. Defer antiretroviral therapy until TB treatment is completed.



2. Defer antiretroviral therapy until the end of the initial phase of treatment and use ethambutol and isoniazid in the continuation phase.
3. Treat TB with a rifampicin containing regimen and use efavirenz + 2NRTIs (non-reverse transcriptase inhibitors).
4. Treat TB with a rifampicin containing regimen and use 2 NRTIs; then change to a maximally suppressive HAART regimen on completion of TB treatment.

Efavirenz is contraindicated in pregnancy. Treatment of pregnant patient should be individualized depending on the severity of TB and CD4 count of the patient<sup>38</sup>.

In India, RNTCP and NACO work jointly to manage this dual epidemic of TB and HIV.

#### INH Prophylaxis of the Neonate

INH prophylaxis of the neonate is indicated in the following situations<sup>39</sup>:

- 1) Mother with active tuberculosis and sputum positivity.
- 2) Mother with active tuberculosis with no documentation of sputum evaluation.

INH prophylaxis is not warranted if the mother is tuberculin positive without evidence of active disease or if a mother on treatment for active tuberculosis for at least three months or more of pregnancy. INH prophylaxis has no role in case of multi-drug resistant tuberculosis in the mother<sup>40</sup>. If the infant is HIV negative, BCG should be administered.

In the above situations where neonatal INH prophylaxis is considered, the infant should be evaluated for active disease with sputum or gastric aspirate examination and a chest radiogram. INH prophylaxis (5mg/kg) is administered till 3 months after the mother is sputum negative.

#### BCG Administration to the Neonate

BCG administration is considered in the following situations (CDC Guidelines):

- 1) Infants and children in areas of high tuberculin positivity (greater than 1%) and where surveillance is not feasible (India and other developing countries).
- 2) PPD negative infants and children at high risk of exposure to patients with persistently untreated or partially treated tuberculosis.
- 3) PPD negative infants or children exposed to INH or Rifampicin resistant tuberculosis.

There is no role of BCG vaccination in children who are tuberculin positive since their cell

mediated immunity has been sensitized to tuberculosis infection already due to prior exposure to the bacterium. These children should be evaluated for active disease and, in the absence of active tuberculosis, be administered INH 5mg/kg for six months<sup>39,40</sup>.

#### Congenital Tuberculosis

Congenital tuberculosis is a rare occurrence. The tubercle bacilli are transmitted through<sup>41</sup>:

- a) Hematogenous transplacental infection
- b) Ingestion of amniotic fluid either prior to or intrapartum
- c) Aspiration of amniotic fluid either prior to or intrapartum.

The symptoms are variable. They usually appear within 2 weeks of birth with transplacental infection but could be delayed if infection occurs during delivery. The following may be evident in the neonate in case of congenital tuberculosis<sup>42</sup>:

- a) Prematurity or low birth weight
- b) Failure to thrive
- c) Hepatosplenomegaly with lymphadenopathy
- d) Episodic cyanosis
- e) A fulminant course because of widespread dissemination, poor mechanism of delivery, immature physiological respiration or a delay in diagnosis.

Congenital tuberculosis is often fatal and the infant often dies in 2 to 8 months<sup>43</sup>.

#### Investigations

- a) A very careful history from the mother
- b) Culture and smear of gastric contents showing positivity. This is standard modality of investigation in case of pulmonary infection<sup>44</sup>.
- c) Chest X-ray is often normal. Miliary or interstitial pattern may be seen in hematogenous dissemination with infiltration becoming more coarse and confluent with progression. Patchy bronchopneumonia to diffuse air space disease with alveolar filling could be evident. Sometimes pleural thickening or peritubular densities can be visualized<sup>45</sup>.
- d) Ultrasonography may show hepatosplenomegaly or ascites<sup>46</sup>.
- e) Occasional periostitis of humerus<sup>47</sup>.

Skeletal X-ray, bone marrow aspiration or biopsy are of poor value.

In 1935, Betzke laid down certain diagnostic criteria after reviewing 101 cases<sup>48</sup>. These criteria are:

- Tuberculous nature of lesion is proved
- Primary complex seen in the liver and glands of the porta hepatic proves congenital tuberculosis since the organisms have gone via the umbilical vein.
- Tuberculous lesion found in the fetus in-utero at birth or shortly after and all extrauterine sources have been eliminated with certainty.

However, with aspiration or ingestion of amniotic fluid, the primary complex may not be found in the liver but seen as scattered lesions in the lungs and alimentary tract.

Tuberculin test is usually negative initially and becomes positive after 4 to 6 weeks<sup>49</sup>. It is difficult to obtain sputum from neonates and hence the bacilli are cultured from gastric aspirates. Occasionally direct smears from the middle ear, trachea or even the bone marrow may show tubercle bacilli.

#### Treatment of Congenital Tuberculosis

A variable number of treatment regimes have been established<sup>50,37</sup>.

- Six months of INH, Rifampicin, and Pyrazinamide; Streptomycin for 2 months and bi-weekly INH and Rifampicin for the next 4 months have given good results with a relapse rate of 1% and no evidence of any deaths.
- Case reports of treatment with INH, Pyrazinamide and Streptomycin or INH and Streptomycin or INH, Rifampicin and Pyrazinamide have also been seen to yield good results. Streptomycin is very safe in infants in the dose of 20-30 mg/kg/day.
- The most accepted line of treatment is INH (20-30 mg/kg/day) + Rifampicin (10-20 mg/kg/day) + Pyrazinamide (15-30 mg/kg/day) + Streptomycin / ETB (15-25 mg/kg/day) for 2 months followed by INH and Rifampicin for 4-10 months.

In areas of low resistance (4%) a 3 drug regimen is effective. In spite of treatment, there is 22% mortality (38% mortality without chemotherapy).

The separation of the infant from the mother is not indicated.

#### Conclusion

Tuberculosis is one of the commonest infections encountered during pregnancy especially in India. The obstetrician should have a low threshold for performing a tuberculosis skin test (Mantoux Test) on pregnant women, especially those with household tuberculosis contacts, respiratory symptoms, or members of high-risk populations although its value in high incidence areas is uncertain. Any patient with symptoms even remotely suggestive of tuberculosis should be investigated aggressively. If tuberculosis is diagnosed, appropriate anti-tuberculous therapy should be initiated along with supportive care such as isolation, screening of household contacts, treatment of malnutrition, screening and treatment of HIV and other associated medical conditions, pediatric care and counseling with regards to breast feeding. Involvement of multiple specialties including the physician, physiotherapist and pediatrician also go a long way in providing optimal maternal and neonatal outcome.

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## Notes

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