Medical Disorders during Pregnancy

Updated illustrated synopsis
For Postgraduate students

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Dr: Mohamed Abd-Allah Rezk

Lecturer of Obstetrics & Gynecology

Faculty of Medicine, Menoufia University

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Cardiac Disease in Pregnancy

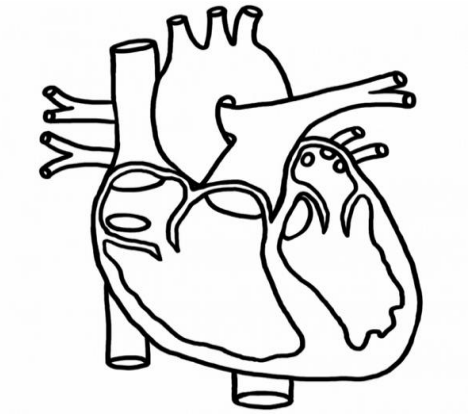
Physiological considerations:
Physiological changes that occur in the cardiovascular system during pregnancy have additional impact on cardiac disease.

(1)- Peripheral vasodilatation occurs as early as 6 weeks' gestation (induced by progesterone) leading to a decrease in systemic vascular resistance.

(2)- Increased cardiac output (COP) this is achieved predominantly via an increase in stroke volume and minimal increase in heart rate (8 beats / minute).
-During pregnancy: COP increases by 20% at 8 weeks gestation and by up to 40-50% at 20-28 weeks gestation (maximal pre-delivery COP).
-During labour further increases in COP by 15% in the first stage and 50% in the second stage due to the combination of auto-transfusion of 300-500 ml of blood back into the circulation with each uterine contraction, and sympathetic stimulation caused by pain and anxiety.
-Immediate postpartum period: COP increases again immediately after delivery due to auto-transfusion of blood via uterine contraction and relief of aortocaval compression. This may increase COP by as much as 60-80%, followed by a rapid decline to pre-labour values within 1 hour.

COP decreases by 20% when the woman is in supine position and by 16% in dorsal lithotomy position.

Peripheral vasodilatation



Increased cardiac output

↑ Cardiac Output

During pregnancy

By 20% at 8 weeks.

40-50% at 28 weeks.

During labour

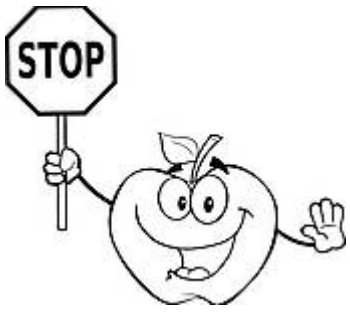
Further ↑ by 15% in the 1st stage & 50% in the 2nd stage of labour.

Immediate postpartum ↑by 60-80%.

Clinical implications

Women with the least ability to increase their cardiac output are at risk of decompensation earlier on in pregnancy and may present before the 28th week. Those who tolerate the increase during pregnancy will be at further risk at the time of delivery and immediately post-partum due to the changes described above. These changes combined with the reduction in serum colloid osmotic pressure make women with cardiovascular compromise particularly susceptible to pulmonary edema at the time of delivery and immediately post-partum.

This risk is increased if the woman is given excessive I.V. fluids (causing an increase in cardiac preload) or if she also has pre-eclampsia (resulting in an increase in pulmonary capillary permeability).



Excessive I.V. fluids in cardiac patients.

Incidence:
Cardiac disease accounts for less than 1% in pregnancy, but is the most common cause of maternal death (in developed countries).

Aetiology:
May be divided into congenital and acquired causes.
-The most common congenital heart disease are ASD, VSD and PDA.
-Acquired causes include rheumatic heart (85%, the commonest is mitral stenosis), ischemic heart, cardiomyopathies and aortic dissection.

New York Heart Association (NYHA) functional classification:

NYHA	Symptoms
I	No symptoms & no limitation in ordinary physical activity.
II	Mild symptoms & slight limitation during ordinary physical activity.
III	Marked limitation in activity, even during less than ordinary activity. Only comfortable at rest.
IV	Severe limitations, symptoms even at rest.

Maternal cardiac disease has the potential to remain undiagnosed during pregnancy, but presentation often occurs after 20 weeks gestation and frequently at the time of delivery or immediately post-partum.
Identifying deterioration of an existing cardiac condition can be a diagnostic challenge as cardiopulmonary signs and symptoms reported during normal pregnancy closely mimic heart disease.

In a healthy pregnant woman, normal findings include a mild increase in resting heart rate, a widened pulse pressure, peripheral edema, and a slight elevation of venous pressure. During the later stages of pregnancy there is a physiological fixed splitting of the second heart sound (S2).

Clinical Indications of heart disease during pregnancy

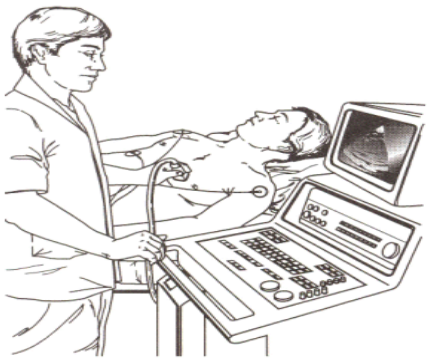
Symptoms	Clinical Findings
-Progressive dyspnea or orthopnea. -Paroxysmal nocturnal dyspnea. -Nocturnal cough. -Hemoptysis. -Syncope. -Chest pain.	-Cyanosis. -Clubbing of fingers. -Persistent neck vein distention. -Diastolic murmur. -Cardiomegaly. -Persistent arrhythmias.

Investigations:

(1)-ECG: There are several pregnancy-induced changes that need to be considered when interpretating an ECG. There is left axis deviation and in the third trimester Q waves in lead III and aVF and inverted T waves in leads III, V1, and V2 are seen.

(2)-Echocardiography: allows accurate and non-invasive diagnosis of most heart diseases during pregnancy. In a normal pregnancy a significant increase in cardiac output, cardiac index, left ventricular end-diastolic volume, and left ventricular wall thickness is observed.

(3)-Other imaging modalities: chest x-ray can be done with a lead apron shield which may be useful in complex heart disease and aortic pathology. MRI is considered to be safe from 12 weeks' gestation. Gadolinium contrast is better to be avoided.



Effect of heart disease on pregnancy:

(1)-Abortion.
(2)-Fetal growth restriction (FGR).
(3)-Intrauterine fetal demise (IUFD).
(4)-Polyhydramnios (part of systemic venous congestion).

Effect of Pregnancy on heart disease:

(1)-Heart failure: during pregnancy or labour.
(2)-Increased liability for atrial fibrillation & thrombo-embolic complications.
(3)-Infective endocarditis especially during the puerperium.
(4)-Rheumatic activation.

Maternal:
-Abortion.
-Heart failure.
-Arrythmias.
-Thromboembolism.
-Infective endocarditis.
-Rheumatic activation.

Fetal:
-FGR.
-IUFD.
-Polyhydramnios.

General Principles of management

Pre-pregnancy care:

In an ideal world, all women of reproductive age with congenital or acquired heart disease should have access to specialized multidisciplinary counseling in order to empower them to make choices about pregnancy.

Antenatal care

Once they are pregnant, all women with heart disease should be assessed clinically as soon as possible and appropriate investigations undertaken. The

core members of the team should include experienced obstetricians, cardiologists, and anaesthetists.

The main aims of management are:
(1)-Optimization of the mother's condition during the pregnancy e.g. considering β-blockers, thromboprophylaxis, or pulmonary arterial vasodilators in appropriate cases.
(2)-Monitoring for deterioration; and minimize any additional load on the cardiovascular system from delivery and the post-partum period. Women with heart failure can be safely treated with diuretics, digoxin, and hydralazine, nitrates, or both as vasodilators to offload the left ventricle.
(3)-Additional fetal assessment may be needed in order to monitor for potential problems arising from pharmacological treatment of the mother.

FDA class	**Drug**	**Remarks**
B	Aspirin Nitrates Thiazide duiretics	 Avoid maternal hypotension. Hypovolemia may lead to↓ uterine perfusion.
C	Digoxin Beta-blockers CCBs Heparins Loop diuretics	Monitor serum level. FGR, fetal hypoglycemia & bradycardia. Only nifedipine can be used. Levels may fluctuate during pregnancy. Avoid hypovolemia.
D	ACE inhibitors ARBs Amoidarone Spironolactone	Renal dysplasia, renal failure & fetal death. Fetal renal failure & death. Thyroid insufficiency. Feminization of the male fetus.
X	Statins	Skeletal anomalies & fetal death.

Indications of termination of pregnancy:

(1)-NYHA grade III & IV.
(2)-History of heart failure before pregnancy.
(3)-History of heart failure in previous pregnancy.
(4)-Major risk for the mother (see later).

Management of delivery

Delivery team

Timing and mode of delivery should be discussed in advance in a multidisciplinary team consisting of at least an obstetrician, an anesthesiologist, and a cardiologist. The patient's preference should to be taken into account and she should be thoroughly counseled about the delivery plan and potential complications.

Timing

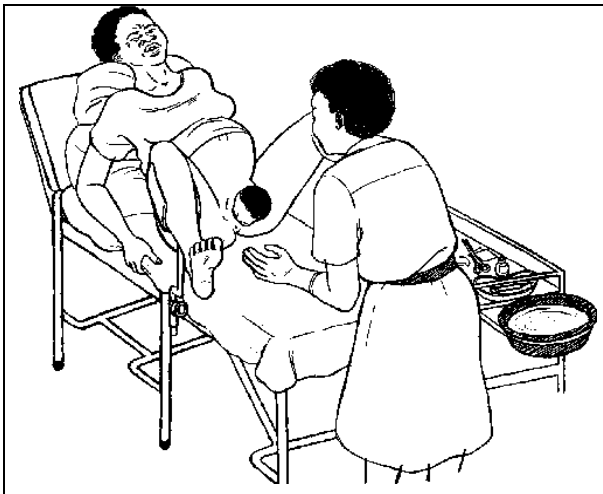
In asymptomatic women in good condition, spontaneous delivery can be awaited. In women with complex lesions, severe cardiac dysfunction, heart failure, aortic dilatation, Eisenmenger syndrome, or mechanical valve switched to heparin, a planned delivery might be more appropriate. Maternal or fetal condition might warrant a planned delivery before 37 weeks.

Induction of labour may be *appropriate* in order to optimize the timing of delivery in relation to anticoagulation and availability of specific medical staff, or because of deteriorating maternal cardiac function.
Cervical ripening using either prostaglandins or mechanical methods and induction of labor with oxytocine are relatively safe in most women with cardiac disease.

Mode of delivery

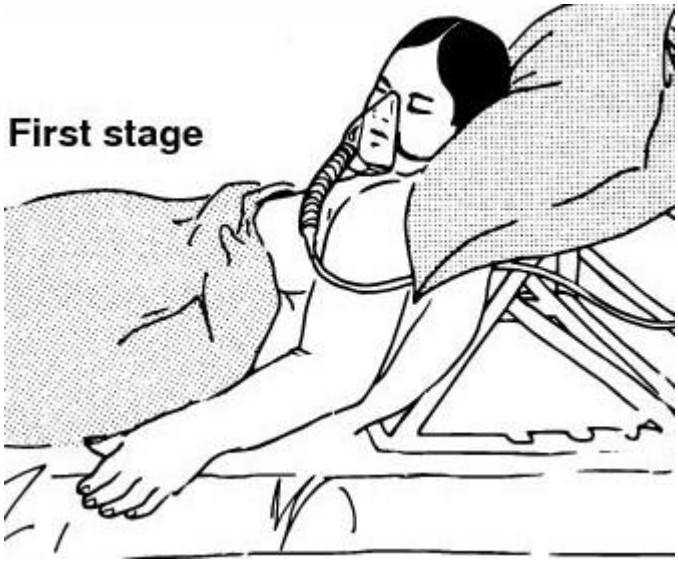
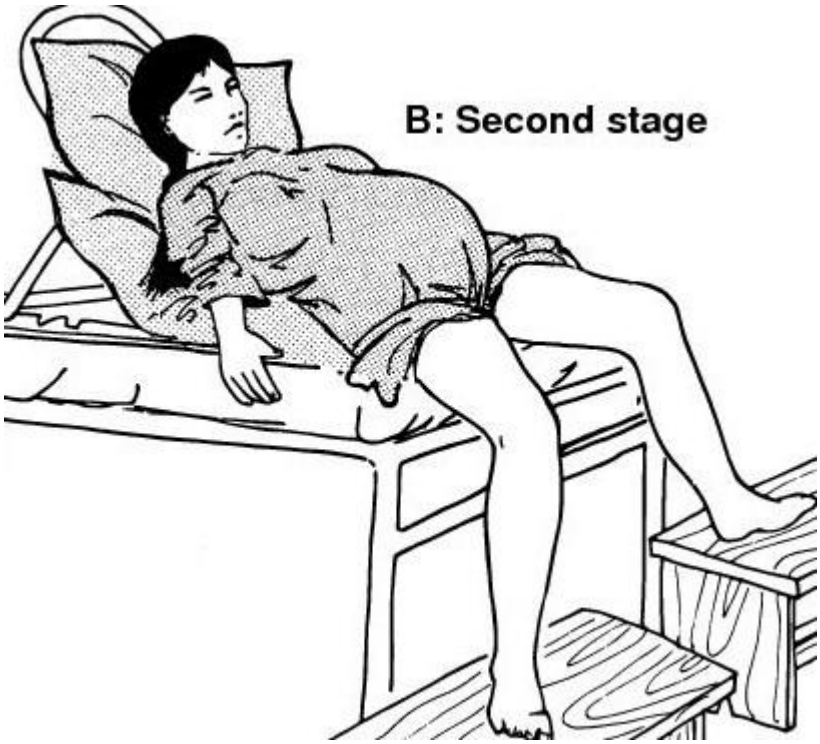
The mode of delivery mainly depends on obstetric indication and the maternal hemodynamic condition. Vaginal delivery is preferred in women with adequate cardiac output. According to the European Society of Cardiology (2011) guidelines, primary Cesarean section should be considered for the patient on oral anticoagulants (OAC) in pre-term labour, in women with severe heart failure, aortic root diameter >45 mm, and patients with acute or chronic aortic dissection.

I. Vaginal delivery:

	***Vaginal delivery*** is uncomplicated in most women with heart disease. Decreased blood loss, more rapid recovery, absence of abdominal surgery, and decreased thrombosis risks are the most important benefits over Cesarean section.

- Adequate pain relief (epidural analgesia or I.V. if contraindicated) is recommended.

- Epidural analgesia can help to attenuate the hemodynamic changes that accompany labour and delivery. It also allows controlled fetal descent to the pelvic floor by suppressing bearing down reflex. It will also facilitate instrumental delivery. Adequate measures to prevent a sudden fall in peripheral vascular resistance associated with epidural anesthesia should be taken in women with left ventricular outflow tract obstruction.

	-Rest in bed in semi-sitting position. -Oxygen inhalation if there is dyspnea or cyanosis. -Analgesia (epidural is preferred). -Observation of the mother & fetus.
	-Rest in bed in semi-recumbent position. -Oxygen inhalation if there is dyspnea or cyanosis. -Analgesia (epidural is preferred). -Straining is avoided. -Shortening of the 2nd stage by ventouse or forceps.

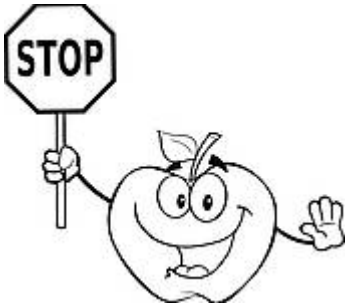
During labour:

(1)- Oxytocin should only be administered by infusion with the omission of a bolus. It has been argued that the cardiovascular effects of a post-partum hemorrhage in a patient with a fixed cardiac output, and the potential risk of large amount of fluid replacement in response, are worse than the potential cardiovascular effects of a slow infusion of oxytocin (which include peripheral vasodilation, tachycardia, and fluid retention).

(2)-Ergometrine should be avoided in severe cardiac disease as it leads to vasoconstriction and hypertension, and increases the risk of myocardial infarction and pulmonary oedema.

(3)-Carboprost is not recommended in cardiac disease as it has the potential to cause or exacerbate pulmonary oedema.

(4)- Glyceryl trinitrate infusion post-delivery may improve pulmonary oedema ; however, it may also increase the risk of PPH due to uterine relaxation.



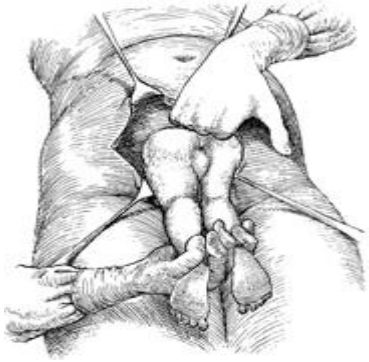
I.V. bolus oxytocin.

Ergometrine.

Carboprost.

Glyceryl trinitrate.

II. Cesarean section



Cesarean delivery permits more appropriate invasive and non-invasive hemodynamic monitoring and management.
However it increases the risk of venous thrombo-embolism, infection, and PPH.
Controlled loco-regional anesthesia is often possible and preferred. However some cases may warrant general anesthesia.

During the puerperium:

- In patients with low risk for heart failure and with normal ventricular function, a short observation period of several hours up to 48 h post-partum might be sufficient.
-Rest in bed for at least 3 weeks after delivery.
-Sedatives may be given in the 1st few days to reduce tachycardia.
-Breast feeding is allowed unless there is heart failure. While lactation is possible in most women with heart disease, it might be contraindicated due to medication use, severely decreased effort tolerance, or risk of mastitis and bacteremia in some women. The use of diuretics can complicate the initiation of milk production.
-Contraception: sterilization may be advised if there is heart failure in this pregnancy.

Follow up

Approximately 4–6 weeks after delivery, the cardiovascular changes of pregnancy will have resolved and the patient should be re-evaluated by a cardiologist.
The infant's pediatrician can decide whether or not to perform a cardiac evaluation of the neonate, depending on the results of the targeted fetal ultrasound examination and echocardiogram, and the newborn examination. Based on the outcome of the pregnancy and the results of the cardiac re-evaluation, the patient can be counseled regarding the risks of subsequent pregnancy, and appropriate contraception can be provided if indicated.

		
Bed rest	**Lactation**	**Follow up**

Special cardiac conditions

Myocardial Infarction

Myocardial infarction became a leading cause of cardiac death. All the women who died had identifiable risk factors including obesity, older age and high parity, smoking, diabetes, pre-existing hypertension, and a family history.

A low threshold for diagnosis of myocardial infarction and acute coronary syndrome in women with risk factors is recommended and appropriate intervention in the form of coronary angiography, emergency coronary intervention, and thrombolysis should not be withheld in the pregnant or puerperal woman.

Thrombolysis at the time of delivery, however, carries a significant risk of haemorrhage and management therefore needs to be on an individual basis. The first choice for treatment of acute coronary syndrome in pregnant women is ***percutaneous coronary intervention***.

There are several case reports in the literature describing the management of delivery in women with coronary artery disease, ranging from spontaneous delivery with or without epidural analgesia to elective Caesarean under combined spinal-epidural anaesthesia or elective Caesarean under general anaesthesia. The need for anti-platelet medications would at present preclude the use of regional analgesia or anaesthesia.

Aortic Dissection

Aortic dissection is a particular risk in women with **Marfan's syndrome**; however, it can also occur in previously apparently normal women. The risk is thought to be highest near full-term or the immediate post-partum period, in particular in the presence of systolic hypertension.

The management of women with known Marfan's syndrome should include pre-pregnancy counselling if possible. If the aortic root diameter is **> 4 cm**, the risk of aortic dissection and maternal death is greatly increased, so aortic root replacement should be offered before pregnancy.

β-Blockers should be continued or started in pregnant patients with Marfan's syndrome who have aortic dilatation or hypertension as they have been

found to reduce the rate of aortic dilatation.
Monitoring during pregnancy will normally include regular (e.g. every 4-8 weeks) transthoracic echocardiography to assess aortic root diameter. The timing of delivery will be dependent on the root diameter and the rate of dilatation, and also any other complicating factors.
The occurrence of severe chest pain requiring opioid analgesia should always prompt investigation, including CT scan or trans-oesophageal echocardiogram where aortic dissection is suspected.

Valvular Heart Disease

The valvular condition which carries the highest risk in pregnancy is mitral stenosis. Rheumatic heart disease is still common in developing countries and often complicates pregnancy. Therefore, a high index of suspicion should be maintained, particularly in immigrant women, and those with symptoms of heart failure should be investigated carefully.
Pregnant women with mitral stenosis should be managed in tertiary centres with expertise in this condition. The greatest risk associated with **mitral stenosis** is pulmonary oedema at the time of delivery due to the increase in cardiac output. This risk of pulmonary oedema is considerably increased if pre-eclampsia develops (increased pulmonary capillary permeability).

Women with **severe mitral stenosis** associated with a large left atrium will often be started on β-blockers and heparin in pregnancy to prevent atrial fibrillation. Early admission is advised and, if vaginal delivery is planned, invasive arterial monitoring is recommended early in labour, before slow and careful institution of epidural analgesia. IV fluid administration should be avoided; if necessary, it should be given in small (100-200 ml) boluses.
The management of other valvular conditions in pregnancy will largely be governed by the severity of the condition, using the general principles of management described above. In particular, both **mitral and aortic regurgitation** are usually well tolerated in pregnancy, provided there is no significant left ventricular dysfunction. This is because the decrease in systemic vascular resistance in pregnancy is usually associated with a reduction in regurgitant flow across the affected valve. However, the onset of pre-eclampsia may lead to decompensation.

Percutaneous catheter interventions are safe in the management of mitral and pulmonary stenosis during pregnancy. However, balloon dilatation for aortic valve disease should only be considered in high-risk cases as it carries a lower success rate and a higher risk.

Cardiac surgery during pregnancy should only be considered in cases refractory to medical treatment or when there is no catheter-based intervention alternative. Hypothermic cardiopulmonary bypass carries a risk of 30% mortality to the fetus; however, if hypothermia is avoided and perfusion pressures maintained at a relatively high level, fetal mortality can be reduced to 10%.

Mechanical heart valves

The problem for women with metal heart valve replacement is that they require life-long anti-coagulantion , and this must be continued in pregnancy because of the increased risks of thrombosis.

Warfarin provides the best protection but, is associated with warfarin embryopathy and increased risks of miscarriage , stillbirth and fetal intracerebral hemorrhage. Heparin, even in full anticoagulant doses , is associated with increased risks of valve thrombosis and embolic events (1-4% maternal mortality).

The method of thromboprophylaxis is therefore usually determined after discussion with the mother.

Management options include:

I. The safest option is to continue warfarin throughout pregnancy.

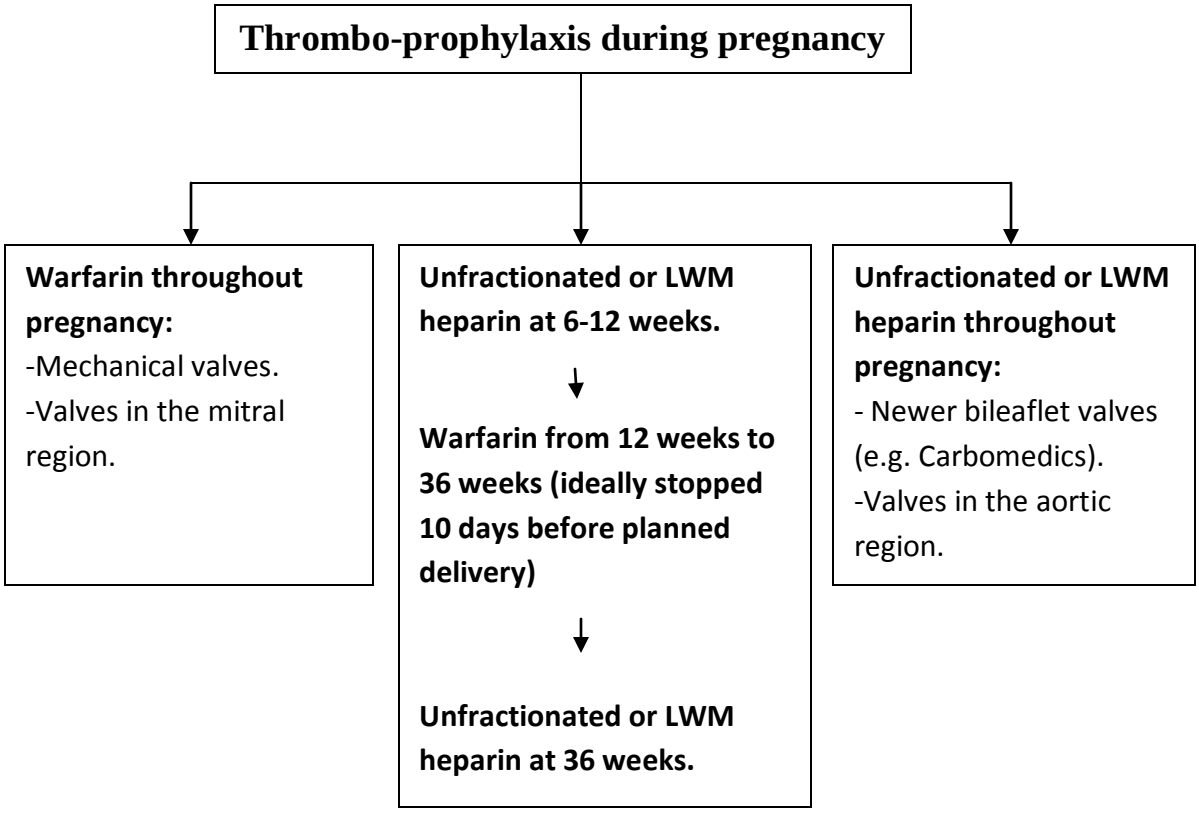
II. Other option include replacing warfarin with high dose unfractionated or LMW heparin either:

(1)-From 6-12 weeks gestation to avoid warfarin embryopathy.

(2)-Throughout pregnancy especially with the newer bileaflet valves (e.g. Carbomedics) and valves in the aortic position.

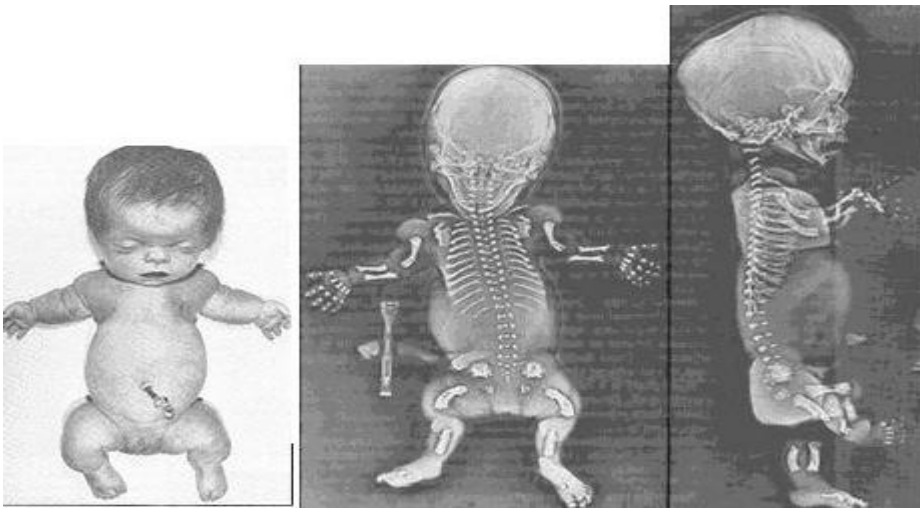
If heparin or LMWH is used, doses should be adjusted according to APTT or anti-Xa levels and low dose aspirin is usually also given.

Whichever management option is chosen, warfarin should be discontinued and substituted with heparin for **10 days** prior to delivery to allow clearance of warfarin from the fetal circulation.



For delivery itself, heparin therapy is stopped and re-started **4-6 hours** postpartum and warfarin is re-commenced **5-7 days** post-partum.
Aspirin is stopped at least 5 days before delivery.
In the event of bleeding or the need for urgent delivery in a fully anticoagulant patient , warfarin may be reversed with fresh frozen plasma (FFP) and vitamin K, and heparin with protamine sulphate (1mg for every 100 unit).

Warfarin Embryopathy:
Incidence: 1.6% (if dose > 5 mg/day).
-Major features: nasal hypoplasia & stippling of the bone epiphyses [at 6-12 weeks].
-Minor features: occurs in the 2nd & 3rd trimesters and include neurologic (NTDs, hydrocephalus, cerebellar atrophy), developmental delay, cardiac anomalies, eye anomalies and gastroschisis.



Pulmonary Hypertension
The most common cause is idiopathic pulmonary artery hypertension and Eisenmenger syndrome or secondary to pulmonary thromboembolism, connective tissue disease as scleroderma, sickle cell disease and cardiac lesions as mitral stensis.
Pulmonary arterial hypertension carries a very high risk during pregnancy (30-50% mortality). If possible, this needs to be discussed pre-conception. If this has not been possible, it is appropriate in most cases for the question of termination to be raised and discussed with the mother, ideally by the multidisciplinary team who has carried out her risk assessment and who can advise on further management. If the decision is made to continue with the pregnancy, efforts will be made to optimize her condition, usually including

the use of a pulmonary arterial vasodilator such (e.g. sildenafil) and plans made for the rest of the pregnancy and delivery as described above.
Owing to the increased risk of mortality at delivery, most units tend to opt for elective Caesarean section under a 'cardiac' general anaesthetic, as this allows control over ventilation, permits more invasive monitoring (e.g. transoesophageal echocardiography), and may lead to greater cardiovascular stability. However, successful management using regional anaesthesia for Caesarean section has also been described in pulmonary hypertension.

Peripartum Cardiomyopathy

Definition : Peripartum cardiomyopathy is defined according to (NIH , 2000) as

(1)-Development of heart failure without any other obvious cause in a pregnant woman occurring anytime from 1 month pre-delivery up to 5 months post-partum.

(2)-Absence of any obvious cause of heart failure.

(3)-Absence of recognizable heart disease prior to the last month of pregnancy.

(4)-Left ventricular systolic dysfunction by echocardiography.

Any pregnant or post-partum woman has unexpected and persistent dyspnoea or is noted to be unusually tachypnoeic or tachycardic, and pulmonary embolus has been excluded, she may have peripartum cardiomyopathy.

Risk factors: include multiple pregnancy, hypertension, multiparity and increased age.

Diagnosis: is confirmed by echocardiography which revealed left ventricular dysfunction with dilatation of the 4 chambers of the heart.

Treatment: as in HF with oxygen, diuretics, vasodilators as ACE inhibitors and inotropics if required.

Prognosis & recurrence: depend on the normalizationof the left ventricular size within 6 months of delivery.

N.B. **Endocarditis Prophylaxis:**
The current NICE recommendation, 2008 are that antibiotic prophylaxis against infective endocarditis is not required for childbirth.

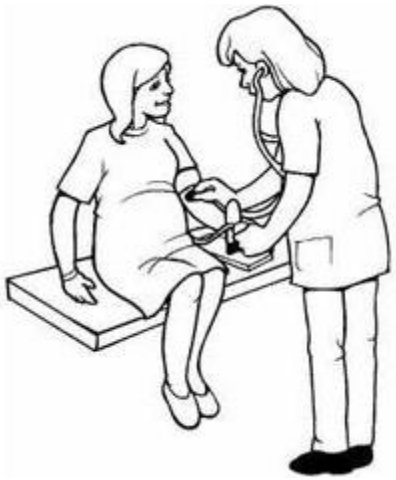
Pregnancy-associated maternal mortality in cardiac disease (ACOG):

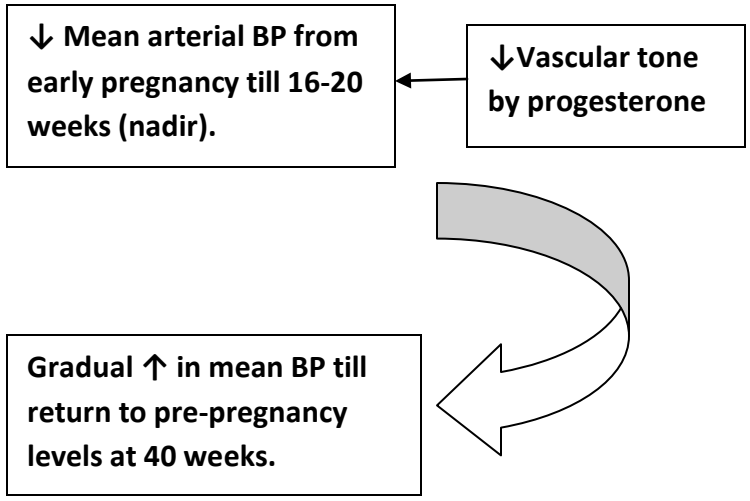
Major Risk (Mortality 25-50%):
Coarctation of aorta (with valvular involvement).
Marfan syndrome (with aortic involvement).
Pulmonary hypertension.
Moderate Risk (Mortality 5-15%):
Aortic stenosis, Mitral stenosis, NYHA classes III and IV .
Mitral stenosis with atrial fibrillation.
Coarctation of aorta (without valvular involvement).
Uncorrected tetralogy of Fallot .
Marfan syndrome with normal aorta.
Artificial valve (mechanical).
Previous myocardial infarction.
Mild or No Risk (Mortality less than 1%):
Atrial septal defect, Ventricular septal defect & Patent ductus arteriosus.
Pulmonic or tricuspid disease.
Artificial valve (bioprosthetic).
Mitral stenosis, NYHA classes I and II.
Corrected tetralogy of Fallot.

Chronic hypertension and Pregnancy

Vascular Physiology of Normal Pregnancy

In uncomplicated pregnancy, mean arterial pressure drops, reaching its nadir between the 16th and 20th weeks of gestation. The decline in diastolic pressure is somewhat greater than that in systolic pressure. The reduction is typically 8–10mmHg or just less than a 10% decline from pre-pregnancy levels. After the 20th week, mean arterial blood pressure slowly returns to pre-pregnancy levels at about 40-week gestation. Causes include reduced vascular smooth muscle tone by progesterone with paradoxical increase the plasma levels of the rennin-angiotensin aldosterone system as well as catecholamines, induced by reduction in plasma volume or diminished renal perfusion. Nonetheless, enhanced activity of the renin-angiotensin axis is a hallmark of the volume-expanded state of gestation.





Chronic hypertension and Pregnancy

Definition

Chronic hypertension is defined as blood pressure exceeding 140/90 mm Hg before pregnancy or before 20 weeks' gestation.

Incidence

Hypertension complicates 1-3% of pregnancies.

Pathophysiology

About 20-25% of women with chronic hypertension develop superimposed preeclampsia during pregnancy.

●**Primary chronic hypertension**: Chronic hypertension is a primary disorder (essential hypertension) in 90-95% of cases.

●**Secondary causes**:

-**Renal causes:** parenchymal disease (e.g. polycystic kidneys, glomerular or interstitial disease), renal vascular disease (e.g. renal artery stenosis).

-**Endocrine causes:**

(1)-Adrenal: adrenocorticosteroid or mineralocorticoid excess (Conn's syndrome) and pheochromocytoma.

(2)-Thyroid: hyperthyroidism or hypothyroidism.

(3)-Others: growth hormone excess and hyperparathyroidism.

-**Cardiac causes:** Coarctation of the aorta.

Effect of Hypertension on Pregnancy:

(1)-Maternal: There is increased incidence of abortion, preterm labour (28%), placental abruption and preeclampsia (developed in 20-25% of women).

(2)-Fetal: fetal growth restriction (16%), IUFD (4%) may occur secondary to placental insufficiency and admission to NICU (20%).

Maternal:
-Abortion.
-Preterm lab our.
-Placental bruption.
-Superimposed PE.

Fetal:
-FGR.
-IUFD.
-Admission to NICU.

Effect of Pregnancy on Hypertension:

The blood pressure may drop in the 2nd trimester but it is raised again in the 3rd trimester. This drop is attributed to vasodilatation and decreased peripheral resistance which may be caused by progesterone, prostacyclin and the placenta acts as an arterio-venous shunt and decreases the peripheral resistance as well.

Management of maternal hypertension

●Pre-pregnancy Care:

(1)-Review of her anti-hypertensive therapy and advice suitable alternatives for pregnancy. ACEIs, ARBs and diuretics should be changed.

(2)-Life-style modifications: advice weight loss in women with high BMI, smoking cessation, salt and alcohol restriction as they increase the blood pressure & adverse pregnancy outcome.

(3)-Review of other body systems for secondary causes of hypertension and Signs of end-organ damage.

●Antenatal Care:

History

Determining whether elevated blood pressure identified during pregnancy is due to chronic hypertension or to preeclampsia is sometimes a challenge, especially if no recorded blood pressures from the first half of the gestation are available.

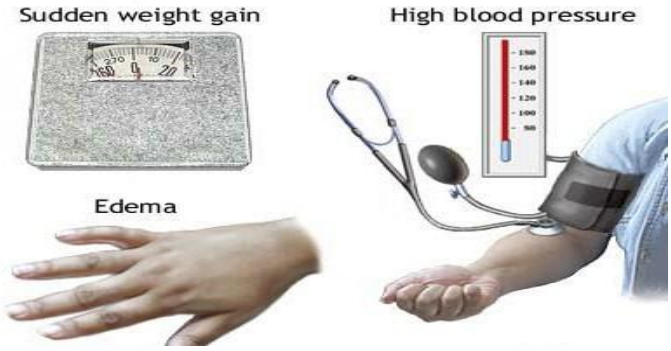
Clinical characteristics obtained via history, physical examination, and certain laboratory investigations may be used to help clarify the diagnosis.

Physical findings

(1)-Blood pressure : Maternal SBP greater than 160 mm Hg or DBP greater than 110 mm Hg denotes severe disease; depending on the gestational age and maternal status, delivery should be considered for sustained BPs in this range.

Measurement of BP during pregnancy: [A]
• Instrument: mercury/aneroid sphygmomanometer or validated automated device.
• Cuff size: it is imperative that the appropriate cuff size is used; it is better to use one that is too big than one that is too small.
• Setting: relaxed, quiet environment, preferably after rest.
• Position: lying at a 45-degree angle or sitting (cuff at heart level).
• Arm: left or right (higher value if difference is greater than 10 mmHg).
• Dependent arm, if in a lateral position.
•Korotkoff sounds: first (systolic) and fifth (diastolic); if diastolic is persistently less than 40 mmHg use muffling or fourth sound and make a note.

(2)-Fundus examination : Retinal vasospasm is a severe manifestation of maternal disease; consider delivery. Retinal edema is known as serous retinal detachment. This can manifest as severely impaired vision if the macula is involved. It generally reflects severe preeclampsia and should lead to prompt consideration of delivery. The condition typically resolves upon completion of pregnancy and resolution of the hypertension and fluid retention.
(3)-Abdominal examination: Right upper quadrant (RUQ) abdominal tenderness stems from liver swelling and capsular stretch. Consider delivery.
(4)-Lower limb examination: In most normal pregnancies, the woman has some lower extremity edema by the third trimester. In contrast, a sudden worsening in dependent edema, edema in nondependent areas (such as the face and hands), or rapid weight gain suggest a pathologic process and warrant further evaluation for preeclampsia.



(5)-Signs suggesting a secondary cause of chronic hypertension

- Centripetal obesity, "buffalo hump," and/or wide purple abdominal striae suggest glucocorticoid excess.
- A systolic bruit heard over the abdomen or in the flanks suggests renal artery stenosis.
- Radiofemoral delay or diminished pulses in lower versus upper extremities suggests coarctation of the aorta.
- Clinical signs may demonstrate hyperthyroidism, hypothyroidism, or growth hormone excess.

(6)-Signs of end-organ damage from chronic hypertension.

Investigations

Laboratory Studies

Laboratory testing to evaluate chronic hypertension (if not done previously or recently) includes testing for target organ damage, potential secondary causes of hypertension, and other risk factors.

(1)-Blood picture & electrolytes.

(2)-Renal function tests: urinalysis; urea, creatinine, and creatinine clearance, microalbuminuria, 24-hour urinary protein, serum calcium and uric acid.

(3)-Liver function tests: AST, ALT, bilirubin & LDH.

(4)-For secondary causes & end organ damage as indicated.

Imaging Studies

(1)-Echocardiography: may be performed to evaluate for left ventricle hypertrophy (LVH) in chronic hypertension and to exclude cardiomyopathy or occult valvular disease in pregnant women with pulmonary edema.

(2)-CT scan of the brain: Perform a CT scan to exclude cerebral hemorrhage in the setting of seizures, severe headache, or altered level of consciousness.

CBC & coagulation profile.

Renal function tests: Urea, creatinine, creatinine clearance, microalbuminuria, 24-hour urinary protein, serum calcium and uric acid.

Liver function tests: AST, ALT, bilirubin & LDH.

Prediction of PE by Platelet count & serum uric acid.

C.T. scan brain in:
-Seizures.
-Severe headache.
- Altered consciousness.

Echocardiology in pulmonary edema to exclude cardiomyopathy & occult valve disease.

Uterine artery Doppler waveforms to predict PE.

Fetal monitoring: fetal growth (serial US) & well-being (fetal kicks, non-stress test & BPP).

Maternal and fetal assessment

(1)-Monitoring for development of PE:

-A strict antenatal schedule and that blood pressure and urine analysis are checked at least every 2 weeks.

-Uterine artery Doppler waveforms have been used to assess the risk in these women (22-24 weeks' gestation).

-Measurement of platelets and uric acid may help to identify women who are going to develop PE, as abnormalities may predate proteinuria by some weeks.

(2)-Fetal monitoring: Close fetal monitoring is essential. In this setting, order fetal assessments twice each week in the form of alternate a biophysical profile with a fetal non-stress test to assess fetal well-being. Serial ultrasounds may be necessary to document fetal growth velocity and/or to monitor amniotic fluid volume.

Treatment of maternal hypertension

Pregnant patients should be started on antihypertensive therapy if the SBP is greater than 160 mm Hg or the DBP is greater than 100-105 mmHg. The goal of pharmacologic treatment should be a DBP of less than 100-105 mmHg and an SBP less than 160 mmHg.

Women with preexisting end- organ damage from chronic hypertension should have a lower threshold for starting antihypertensive medication and a lower target BP (<140/90 mmHg).

Antihypertensive treatment is known to reduce the risk of later coronary heart disease by approximately 16% and stroke by 38% [A].

Treatment options of mild to moderate chronic hypertension in pregnancy (140/90-160/100 mmHg).

-Antihypertensive medication may be withheld or discontinued, with subsequent close observation of blood pressure. Because blood pressure drops during normal pregnancy and no data support the use of medication in patients with pressures less than 160/100 mm Hg.

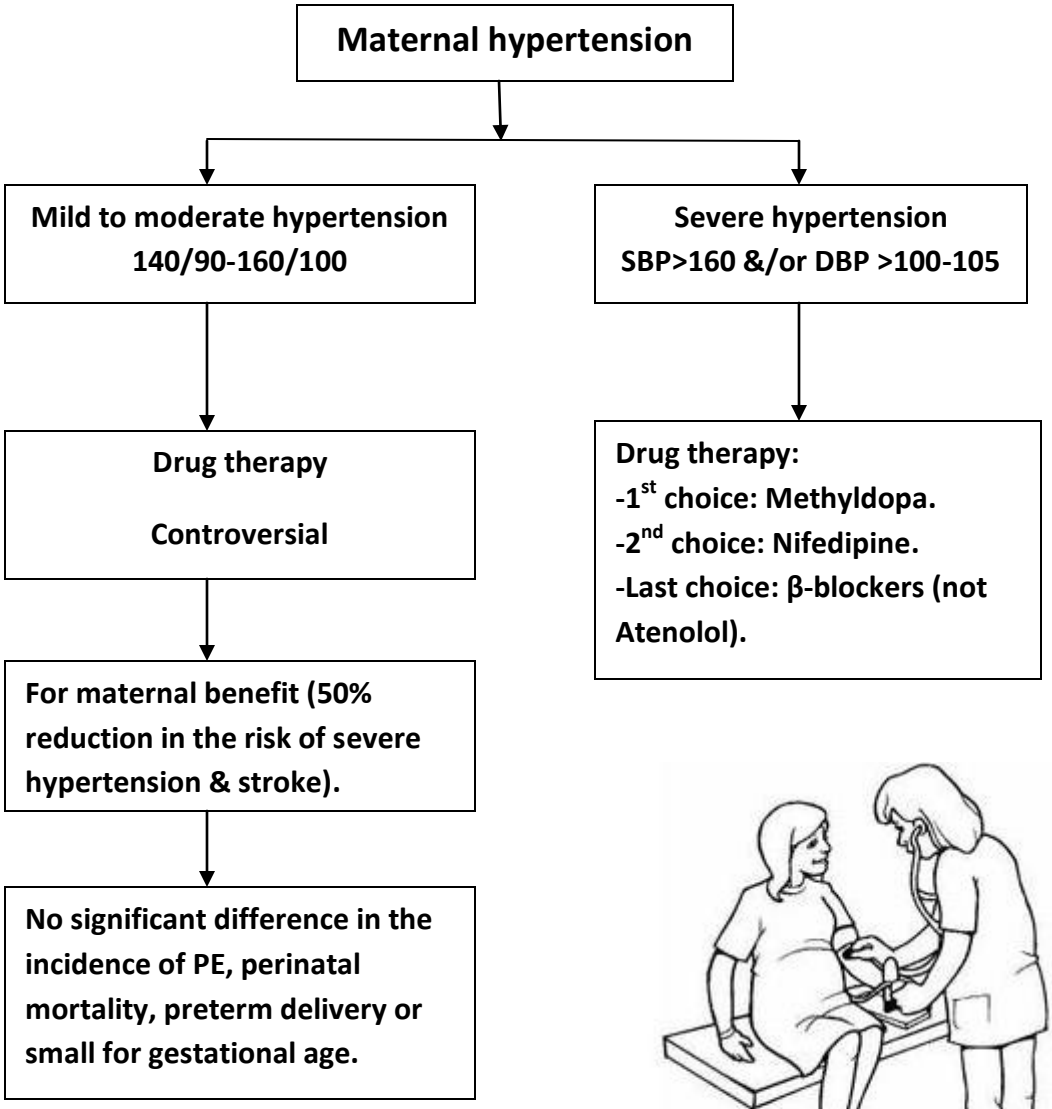
-Treatment of patients with mild to moderate hypertension is associated with a reduction in severe hypertension (by approximately 50%). However, there is no significant difference in the incidence of PE, perinatal mortality, preterm delivery or small for gestational age [A].

Evidence-based guidelines from the American Association of Clinical Endocrinologists and current NICE recommendations single out **methyldopa** or **nifedipine** as preferable antihypertensive medications in pregnancy. The drug with the longest, most established safety profile (fetal, neonatal & longer term outcome) is methyldopa [B]. There have been several reports that beta blockers especially Atenolol are associated with FGR [B].

●**Postpartum Care**:

-Women with severe hypertension should be carefully monitored for at least 48 hours after delivery as they are at risk of developing renal failure, pulmonary edema, and hypertensive encephalopathy.

-Antihypertensive therapy should be continued in the immediate postpartum period and then reviewed 2 weeks after delivery.
Methyldopa should be discontinued within 2 days of birth and the previous antihypertensive treatment the woman was receiving prior to pregnancy re-commenced.



Preeclampsia

Definition:

Preeclampsia (PE) is a pregnancy-specific multisystem disorder of unknown etiology. The disorder affects approximately 5 to 7 % of pregnancies and is a significant cause of maternal and fetal morbidity and mortality.

Preeclampsia is defined by the new onset of elevated blood pressure and proteinuria after 20 weeks of gestation.

The international Society for the Study of Hypertension in Pregnancy (ISSHP) classification (2001):

A.Gestational hypertension and/or proteinuria developing during pregnancy, labour or the puerperium in a previously normo-tensive non proteinuric woman: 1.Gestational hypertension (without proteinuria). 2.Gestational proteinuria (without hypertension). 3.Gestational proteinuric hypertension (PE).
B.Chronic hypertension (before the 20th week of pregnancy) and chronic renal disease (proteinuria before the 20th week of pregnancy): 1. Chronic hypertension (without proteinuria). 2. Chronic renal disease (proteinuria with or without hypertension). 3. Chronic hypertension with super-imposed PE (new onset proteinuria).
C.Unclassified hypertension and/or proteinuria.
D. Eclampsia.

Aetiology

Preeclampsia is a disorder of unknown etiology that is *peculiar to human pregnancy*. Many theories regarding its etiology have been suggested, including:

- Abnormal placentation.
- Immunologic phenomena.

- Coagulation abnormalities.
- Abnormal cardiovascular adaptation.
- Dietary factors.
- Genetic factors.
- Increased pressor responses.
- Vasculopathy and inflammatory changes.
- Prostaglandins, Nitric oxide, Endothelines and angiogenic factors.

●Abnormal Trophoblastic Invasion

In normal implantation, the uterine spiral arteries undergo extensive remodeling as they are invaded by endovascular trophoblasts . In preeclampsia, however, there is *incomplete trophoblastic invasion*. In this case, decidual vessels, but not myometrial vessels, become lined with endovascular trophoblasts. The magnitude of defective trophoblastic invasion of the spiral arteries correlated with the severity of the hypertensive disorder.

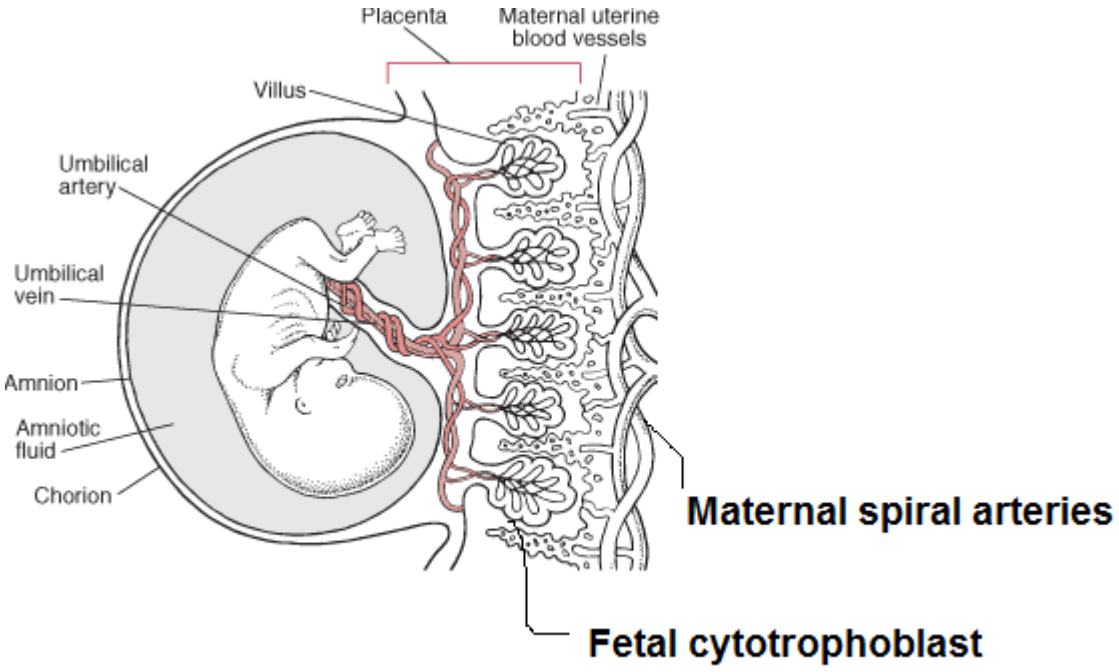
●Immunologic phenomena

There is circumstantial evidence to support the theory that preeclampsia is immune mediated. Certainly the microscopic changes at the maternal–placental interface are suggestive of acute graft rejection. For example, the risk of preeclampsia is appreciably enhanced in circumstances where formation of blocking antibodies to placental antigenic sites *might* be impaired. This may arise in situations in which effective immunization by a previous pregnancy is lacking, as in first pregnancies; or in which the number of antigenic sites provided by the placenta is unusually great compared with the amount of antibody, as with multiple fetuses.

The possible role of immune maladaptation in the pathophysiology of preeclampsia. Beginning in the early second trimester, women destined to develop preeclampsia have a significantly lower proportion of helper T cells (Th_1) compared with that of women who remain normotensive . This Th_1/Th_2 imbalance, with Th_2 dominance, may be mediated by adenosine, which is found in higher serum levels in preeclamptic compared with normotensive women. These helper T lymphocytes secrete specific

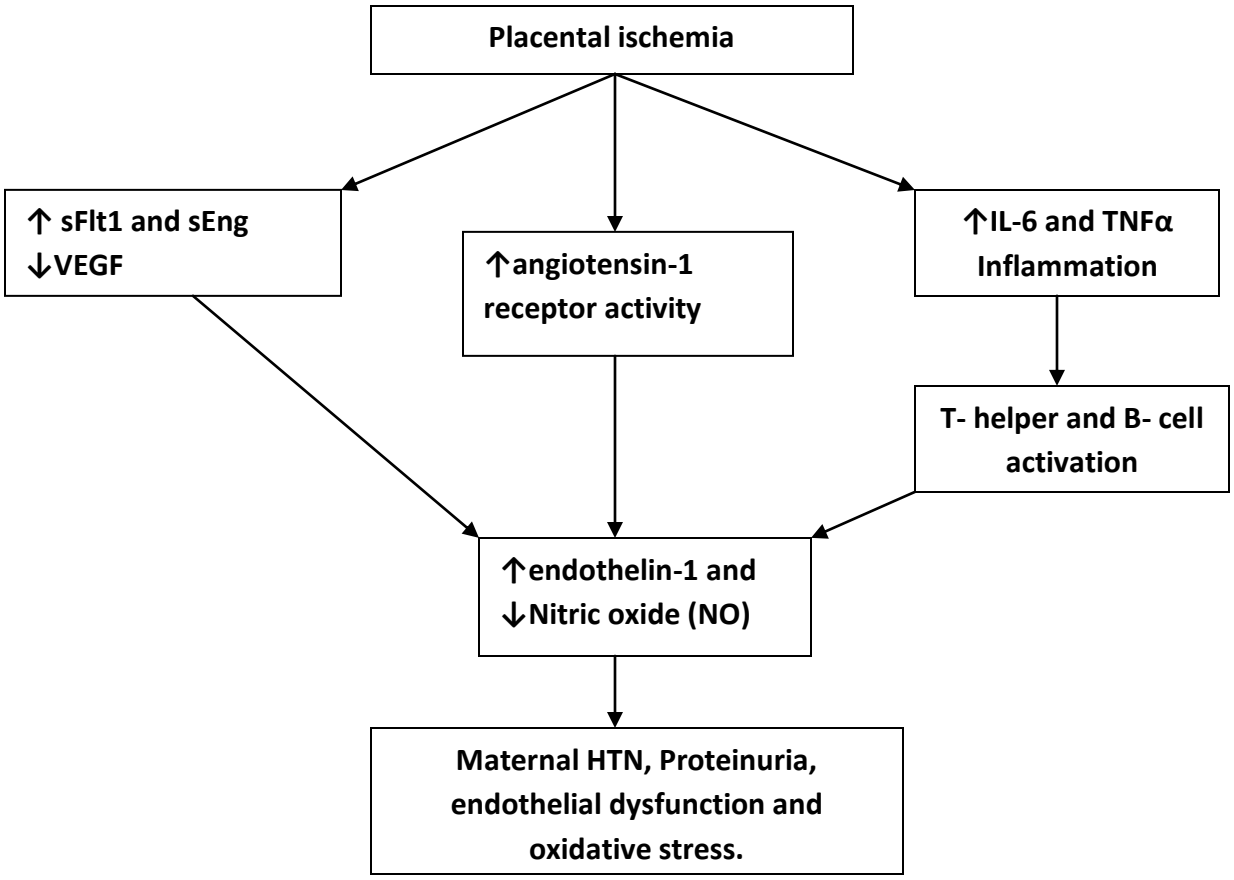
cytokines that promote implantation, and their dysfunction may favor preeclampsia.

There is an interaction between maternal natural killer (NK) cells & fetal cytotrophoblasts which penetrate the deciduas for re-modeling of spiral arteries.
NK cells are recognized by MHC (HLA) antigens on the surface of cytotrophoblasts leading to modification of the action of NK cells from cytotoxic role to secretory role with production of specific vasoactive cytokines to promote re-modeling of spiral arteries.



●A Unifying Hypothesis on Preeclampsia: Deranged Endothelin and Nitric Oxide Signaling

Placental ischemia activates the preeclampsia cascade and alters the balance between endothelin-1 and nitrous oxide (NO), resulting in the observed endothelial dysfunction, hypertension, and proteinuria.



Nitric oxide (NO), soluble endoglin (sEng), soluble Fms-like tyrosine kinase 1 (sFlt1), vascular endothelial growth factor (VEGF), tumor necrosis factor *α* (TNF*α*) and interleukin 6 (IL-6).

Risk Factors for Preeclampsia

Pregnancy-associated factors

- Chromosomal abnormalities.
- Hydatidiform mole.
- Hydrops fetalis.
- Multifetal pregnancy.
- Oocyte donation or donor insemination.

Maternal-specific factors

- Age > 35 years or < 20 years.
- Black race.
- Family history of preeclampsia.
- Nulliparity.

- Preeclampsia in a previous pregnancy. - Stress.
- Specific medical conditions: gestational diabetes, type I diabetes, obesity, chronic hypertension, renal disease, thrombophilias.

Paternal-specific factors

- First-time father.
- Previously fathered a preeclamptic pregnancy in another woman.

Pathophysiology of Preeclampsia

(1)-One of the most striking physiologic changes is *intense systemic vasospasm*.
(2)- Vascular hemoconcentration and third spacing of intravascular fluids.
(3)- An exaggerated inflammatory response and inappropriate endothelial activation.
(4)-Activation of the coagulation cascade and resultant microthrombi formation
End result→ decreased perfusion of virtually all organ systems.

●Vascular Changes

Hemoconcentration, in addition to hypertension, is a significant vascular change, because women with the preeclampsia–eclampsia syndrome may not develop the normal hypervolemia of pregnancy .
Changes in vascular reactivity may be mediated by prostaglandins.
-↑ thromboxane A2 & endothelins (potent vasoconstrictors).
-↓ prostacyclin & nitric oxide (potent vasodilators).

↓

Intense vasospasm

The vasospasm and subsequent hemoconcentration are associated with contraction of the intravascular space. Because of capillary leak and decreased colloid oncotic pressure often associated with this syndrome, *attempts to expand the intravascular space in these women with vigorous*

fluid therapy may result in elevation of the pulmonary capillary wedge pressure and even pulmonary edema.

●Hematologic Changes

Both thrombocytopenia and hemolysis may occur as part of the HELLP syndrome, although the etiology is unknown.
Interpretation of hematocrit levels in the face of severe PE should take into consideration that hemolysis or hemoconcentration.

↓

-↓ Hct in hemolysis with ↑ lactate dehydrogenase (LDH).
-↑ Hct in the absence of hemolysis.

●Hepatic Changes

Hepatic function may be significantly altered in women with severe preeclampsia.
-↑ Transaminases & hyperbilirubinemia .
-Hepatic hemorrhage, which usually manifests as a subcapsular hematoma (*Glisson capsule*).
-Hepatic rupture may also occur.

●Renal Changes

As a result of vasospasm, the normal expected increase in glomerular filtration rate and renal blood flow and the expected decrease in serum creatinine may *not* occur in women with preeclampsia, especially if the disease is severe.
Oliguria, also may occur secondary to the hemoconcentration and decreased renal blood flow. Rarely, persistent oliguria may reflect acute tubular necrosis, which may lead to acute renal failure.

●Neurologic and Cerebral Manifestations

Eclampsia remains a cause of maternal mortality, usually in association with intracranial hemorrhage.
Although uncommon, *temporary blindness* (lasting a few hours to up to a week) also may accompany severe PE and eclampsia.

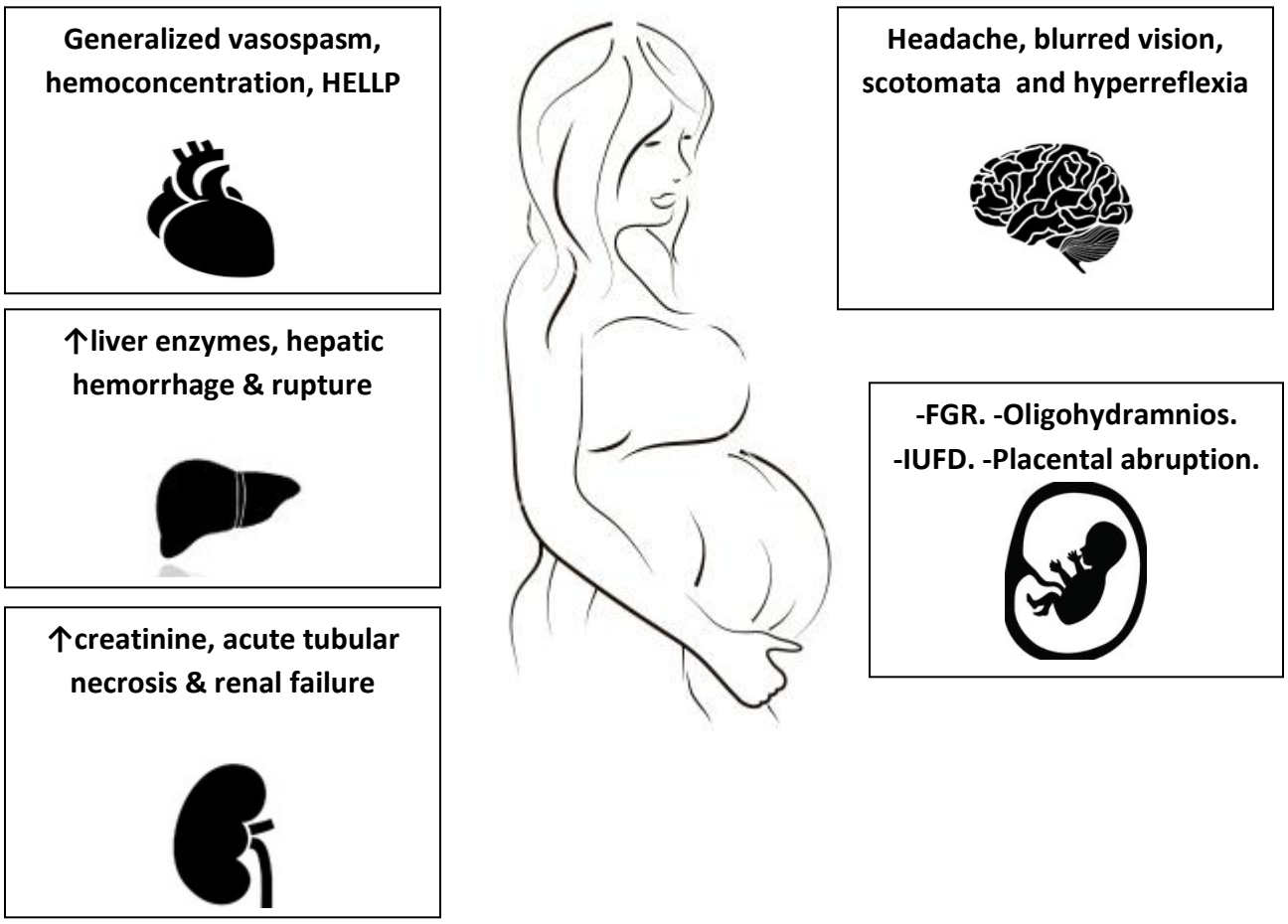
Other nervous system manifestations include headache, blurred vision, scotomata and hyperreflexia.

●Fetal Changes

As a result of impaired uteroplacental blood flow or placental infarction, manifestations of preeclampsia also may be seen in the fetal placental unit. These include intrauterine growth restriction, oligohydramnios, placental abruption, and non-reassuring fetal status demonstrated on antepartum surveillance.

●HELLP Syndrome

Women with severe preeclampsia and hepatic involvement may develop HELLP syndrome. In one study, HELLP syndrome occurred in approximately 20% of women with severe preeclampsia.



Diagnosis

Diagnostic Criteria for Preeclampsia

Blood pressure: 140 mm Hg or higher systolic or 90 mm Hg or higher diastolic after 20 weeks of gestation in a woman with previously normal blood pressure.

Proteinuria: 0.3 g or more of protein in a 24-hour urine collection (usually corresponds with 2+ or greater on a urine dipstick test).

Severe preeclampsia

Blood pressure: 160 mm Hg or higher systolic or 110 mm Hg or higher diastolic on two occasions at least six hours apart in a woman on bed rest

Proteinuria: 5 g or more of protein in a 24-hour urine collection or 3+ or greater on urine dipstick testing of two random urine samples collected at least four hours apart.

Other features:
-Oliguria (less than 500 ml of urine in 24 hours).
-Cerebral or visual disturbances: severe headache & blurred vision.
-Pulmonary edema or cyanosis.
-Epigastric or right upper quadrant pain.
-Impaired liver function.
-Thrombocytopenia.
-Intrauterine growth restriction.

Protein excretion in the urine increases in normal pregnancy from approximately 5 mg per 100 ml in the first and second trimesters to 15 mg per 100 ml in the third trimester.
Significant proteinuria should be defined as >300 mg per 24-hour urine sample.

Clinical Presentation

The clinical presentation of preeclampsia may be insidious or fulminant:

- Some women may be asymptomatic at the time they are found to have hypertension and proteinuria.
- Others may present with symptoms of severe PE, such as visual disturbances, severe headache, or upper abdominal pain.
- Increasing maternal facial edema and rapid weight gain also should be noted because fluid retention often is associated with PE. Although these symptoms (e.g., facial edema, rapid weight gain) are not unique to PE, it is wise to follow affected patients for hypertension and proteinuria.
- HELLP syndrome may be a variant of severe PE or a separate entity, but its development is ominous because mortality or serious morbidity can occur in 25% of affected women.

-Severe headache.
-Blurred vision.
-Facial edema.

-Epigastric or right upper quadrant pain.
-Oliguria.

-↓ Fetal kicks (IUGR, IUFD).
- Oligohydramnios.
-Vaginal bleeding (APH).

At the time of diagnosis, all patients with preeclampsia should be evaluated regarding maternal/fetal condition.

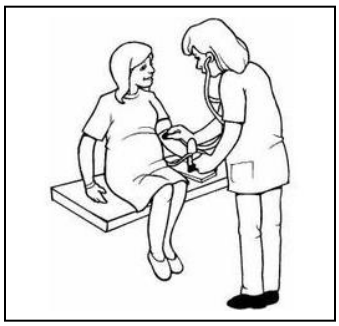
●Maternal Evaluation

History

Markers for possible severe preeclampsia:

- Persistent occipital or frontal headaches.
- Visual disturbances.
- Right upper-quadrant abdominal or epigastric pain.

Physical Evaluation



- Blood pressure assessment daily.
- Urine protein assessment by dipstick daily.
- Assessment of facial or pedal edema daily.
- Weight daily.

Laboratory Evaluation

- Hematocrit and platelet count one or two times a week.
- Liver function tests one or two times a week.
- Twenty-four hour urine collection at diagnosis for total protein excretion and creatinine clearance.

●Fetal Evaluation

- Daily fetal movement assessment (kick counts).
- Non stress test (NST) twice weekly.
- Biophysical profile if nonreactive NST.
- Amniotic fluid volume assessment weekly.
- Ultrasound evaluation of fetal growth every 3 weeks.

Treatment

- *Delivery remains the ultimate treatment for pre-eclampsia*. Although maternal and fetal risks must be weighed in determining the timing of delivery, clear indications for delivery exist.
  When possible, vaginal delivery is preferable to avoid the added physiologic stressors of cesarean delivery. If cesarean delivery must be used, regional anesthesia is preferred because it carries less maternal risk. In the presence of coagulopathy, use of regional anesthesia generally is contraindicated.
  Because the only cure for severe preeclampsia is delivery, there is unanimous agreement that all patients should be delivered if severe disease develops beyond 34 weeks' gestation or if there is evidence of fetal lung maturity or fetal jeopardy before that time.
  In this situation, appropriate management should include
    - Magnesium sulphate to prevent convulsions.
    - Control of maternal blood pressure within a safe range.
    - Induction of labour to initiate delivery.
- Management of patients with severe disease remote from term (<34 weeks) is highly controversial.
    - Some institutions consider delivery as the definitive therapy for all cases, regardless of gestational age.
    - Others recommend prolonging pregnancy in all patients remote from term until one or more of the following is achieved:
        - Fetal lung maturity.
        - Fetal jeopardy.
        - Maternal jeopardy.

Conservative management of severe pre-eclampsia

In a tertiary care center:

• Initial intravenous magnesium sulfate for 24hours.

• Antihypertensives: intravenous boluses, then shift to oral administration, nifedipine, labetalol.

Hydralazine: 5–10mg boluses every 20–30min (maximum dose 20mg)

Labetalol: 20–40mg boluses (maximum dose 220mg). Then 200mg orally every 8h (maximum 600mg every 6h).
Nifedipine: 10–20mg orally every 30min (maximum 50mg). Then 10–20mg every 4–6h (maximum 120mg/day) The aim is for diastolic BP 90–100mmHg and systolic BP 140–150mmHg. Avoid normal BP because of the risk of decreased uteroplacental perfusion. Adequate therapeutic response is expected in 12hours.

• Give steroids for fetal lung maturation and attempt to delay delivery at least for steroid benefit (48hours).

• Daily fetal–maternal testing. The majority of patients with severe pre-eclampsia managed conservatively will require delivery within 2 weeks of admission. Indications for delivery of these patients include the following:

• *Maternal indications:* thrombocytopenia or HELLP (hemolysis, elevated liver enzymes, low platelets), disseminated intravascular coagulation (DIC), pulmonary edema, renal failure, eclampsia, uncontrolled severe hypertension, suspected abruptio placentae, labour or rupture of membranes, ascites; warning signs: persistent and severe headache, blurring of vision, epigastric pain.

• *Fetal indications:* fetal distress irrespective of gestational age or lung maturity, persistent severe oligohydramnios, severe intrauterine growth restriction (IUGR; less than 5th percentile), or gestational age greater than 34 weeks achieved.

There are insufficient data for any reliable recommendations about which policy of care should be used for women with severe early onset PE. Further large trials are needed ***(Cochrane Database of Systematic Reviews, 2002).***

Conservative Treatment

Severe PE diagnosed on the basis of blood pressure measurement &/or degree of proteinuria.

In tertiary health care hospital with on-site blood banking, ICU & NICU services.

Medications:
-Magnesium sulphate for 48 hours.
-Antihypertensive drugs (initial I.V. then oral).
-Steroids.

Observation:
-Maternal: Bp, urine protein, symptoms & weight.
-Fetal: kicks, NST, BPP & serial U/S for growth & amniotic fluid.

Urgent Delivery

Maternal indications:
-Symptoms.
–Eclampsia (2%).
-HELLP (20%).
-Uncontrolled BP.
-End organ damage (2-5%).
-APH (abruption).
-PROM or labour pains.

Fetal indications:
-Non-reassuring FHR tracing.
-Persistent oligohydramnios.
–FGR (40%).
-Reaching 34 weeks.

During labour, the management goals are to prevent seizures and control hypertension. Magnesium sulfate is the medication of choice for the prevention of eclamptic seizures in women with severe preeclampsia and for the treatment of women with eclamptic seizures.
One commonly used regimen is a 4-6 g loading dose of magnesium sulfate followed by a continuous infusion at a rate of 1-2 g per hour.
Magnesium sulfate has been shown to be superior to phenytoin (Dilantin) and diazepam (Valium) for the treatment of eclamptic seizures. Although magnesium sulfate commonly is used in women with preeclampsia, studies to date have been inadequate to show that it prevents progression of the disorder.

The Collaborative Eclampsia Trial regimen for administration of magnesium sulphate:
-Loading dose of 4 g should be given intravenously over 5 minutes, followed by an infusion of 1 g/hour maintained for 24 hours.
- Recurrent seizures should be treated with a further dose of 2–4 g given over5 minutes.
-Do not use diazepam, phenytoin or lytic cocktail as an alternative to magnesium sulphate in women with eclampsia. **(NICE, 2011).**

Antihypertensive drug therapy is recommended for pregnant women with systolic blood pressures of 160 to 180 mm Hg or higher and diastolic blood pressures of 105 to 110 mm Hg or higher. The treatment goal is to lower systolic pressure to 140 to 155 mm Hg and diastolic pressure to 90 to 105 mm Hg. To avoid hypotension, blood pressure should be lowered gradually.

Hydralazine (Apresoline) and labetalol are the antihypertensive drugs most commonly used in women with severe preeclampsia .
Nifedipine and sodium nitroprusside are potential alternatives, but significant risks are associated with their use.
Labetalol therapy should not be used in women with asthma or congestive heart failure.
Use of ACE inhibitors is contraindicated in pregnant women.

Initiation of the Process for Delivery

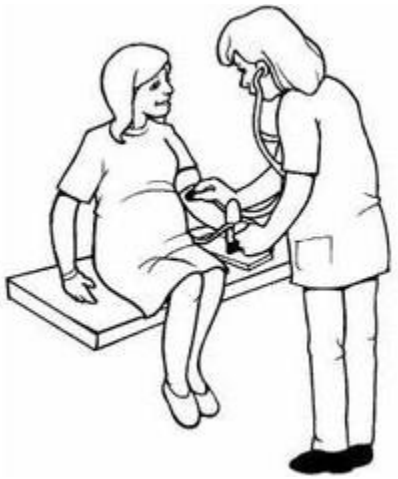
- Vaginal delivery, *unless obstetrically contraindicated,* is the preferred method of delivery.
    - An oxytocin infusion for induction or augmentation of labour may be administered simultaneously with the magnesium sulfate infusion.
    - Total fluid intake is limited to 80-100 ml per hour (1 ml/kg/hour).
    - The protocol for oxytocin infusion for preeclampsia or eclampsia is the same as for routine patients; yet, because of fluid restrictions, oxytocin may need to be more concentrated and dosages per minute adjusted accordingly.
    - Continuous fetal monitoring should be performed.
- At delivery, neonatal side effects of maternal administration of magnesium sulfate include:
    - Hypotension.
    - Hypotonia.
    - Respiratory depression.
    - Lethargy.
    - Decreased suckling reflex.
- The pediatrician and newborn nursery should be informed of patients receiving magnesium sulfate. Calcium gluconate may also be administered to the newborn if magnesium toxicity is suspected.
- Following delivery, the patient should be monitored in the recovery room or on the labour and delivery unit under close observation for a minimum of 24 hours. During this time, magnesium sulfate should be continued, maternal vital signs and intake-output should be monitored hourly.
- Some of these patients may require intensive and invasive hemodynamic monitoring because they are at increased risk of developing pulmonary edema from fluid overload, fluid mobilization, and compromised renal function.
  Oliguria without rising serum urea & creatinine is a manifestation of

severe PE and not of renal failure, foley catheter with CVP placement is advised to monitor fluid balance. If the CVP is high (above 8 mmH2O) with persistent oliguria, a dopamine infusion should be considered. If creatinine or potassium rises, hemodialysis is considered. The use of diuretics is contraindicated except if there are signs of pulmonary edema.

- Magnesium sulfate administration should continue until improvements in blood pressure, urine output, and sensorium are noted.

Follow-up and remote complications

- In women with preeclampsia, blood pressure usually normalizes within a few hours after delivery but may remain elevated for two to four weeks. As previously noted, a diagnosis of chronic hypertension is made if blood pressure remains elevated at 12 weeks postpartum.
- Women with PE should be counseled about future pregnancies. In nulliparous, the recurrence rate for the disorder may be as high as 40 % in future pregnancies. Multiparous women have even higher rates of recurrence.
- Women with PE have 4-fold increased risk of developing hypertension and 2-fold increased risk of ischemic heart disease, stroke & venous thrombo-embolism, even up to 14 years after the index pregnancy.



Prevention of PE

- Salt restriction .
- Low-dose aspirin.
- Calcium supplementation.
- Administration of fish oil or evening primrose oil.
- Antioxidant therapy.

There are currently no well-established measures for preventing preeclampsia.
(1)- Low-dose aspirin therapy: the use of antiplatelets agents particularly low dose aspirin resulted in a significant 10% reduction in the relative risk of both PE and serious adverse outcome.

Advise women at high risk of pre-eclampsia to take 75 mg of aspirin daily from 12 weeks until the birth of the baby.
- Women at high risk are those with any of the following: hypertensive disease during a previous pregnancy, chronic kidney disease, autoimmune disease such as SLE & APS, diabetes mellitus and chronic hypertension.
-Women with two or more of the following risk factors: first pregnancy, age 40 years or older, pregnancy interval of more than 10 years, body mass index (BMI) of 35 kg/m² or more at first visit, family history of pre-eclampsia and multiple pregnancy. **(NICE, 2010).**

(2)- Calcium supplementation: resulted in a significant reduction (52%) in the relative risk of PE with a higher effect in those at high risk (78%) but calcium supplementation warrants further research.
(3)-Fish-oil containing n-3 fatty acids are thought to inhibit platelet thromboxane-A2, however their use have not shown any reduction in PE.
(4)- The use of antioxidants as vitamin C & E supplementation has not shown any benefit.

Prediction of PE

Measurement in early pregnancy of a variety of biological, biochemical, and biophysical markers implicated in the pathophysiology of preeclampsia has been proposed to predict its development.

●Uterine Artery Doppler Velocimetry

Measurement of uteroplacental vascular resistance during Doppler ultrasound evaluation of uterine artery impedance in the second trimester has been used as an early screening test for preeclampsia . The rationale for this is based on the presumption that the pathophysiology of preeclampsia includes impaired trophoblastic invasion of the spiral arteries leading to reduction in uteroplacental blood flow. Bower and colleagues (1993) used a two-step screening test beginning at 18 to 22 weeks and its sensitivity for prediction of preeclampsia was 78 percent, but the positive predictive value was only 28 percent.

●Roll-Over Test

A hypertensive response induced by having women at 28 to 32 weeks assume the supine position after lying laterally recumbent predicted gestational hypertension Women who demonstrated a positive "roll-over" test were also found to be abnormally sensitive to infused angiotensin II. With preeclampsia, rather than gestational hypertension, as the end point, the positive predictive value (true positive) was only 33 percent .

●Uric Acid

Elevated serum uric acid levels due to decreased renal urate excretion are frequently found in women with preeclampsia. Plasma uric acid values exceeding 5.9 mg/dL at 24 weeks had a positive predictive value for preeclampsia of 33 %. Because uric acid levels have not even proven useful in differentiating gestational hypertension from preeclampsia, they are not widely used .

●Fibronectin

Endothelial cell activation likely is the cause of elevated serum cellular

fibronectin levels in some women with preeclampsia by four-week sampling beginning at 16 weeks in low-risk nulliparas. The women who subsequently developed preeclampsia had significantly higher levels by 12 weeks but the positive predictive value was only 29 %, however, the negative predictive value was 98 %.

●Coagulation Activation

Thrombocytopenia and platelet dysfunction are integral features of preeclampsia, Increased destruction causes platelet volumes to increase because of relatively younger, and therefore larger, platelets. high platelet volumes to be a marker of impending preeclampsia. However, there was substantive overlap with normotensive women. Fibrinolytic activity is normally decreased in pregnancy due to increased plasminogen activator inhibitors (PAI) 1 and 2. In preeclampsia, PAI-1 is increased relative to PAI-2 because of endothelial cell dysfunction .

●Oxidative Stress

Increased levels of lipid peroxides, coupled with decreased activity of antioxidants in women with preeclampsia, have raised the possibility that markers of oxidative stress might predict preeclampsia .
Hyperhomocysteinemia is an independent risk factor for atherosclerosis in women who are not pregnant. Women with elevated serum homocysteine levels around midpregnancy had a three- to fourfold risk of preeclampsia. Although clinical studies substantiate this association, they have not shown elevated serum homocysteine levels to be a useful predictor. Homocysteine levels are influenced by folic acid supplementation.

●Cytokines

These protein messengers are released by vascular endothelium and leukocytes as well as by macrophages and lymphocytes at the trophoblast–decidua interface. There are over 50 cytokines, and a number of these are elevated in preeclampsia. These include some interleukins and TNF-. A cascade of markers (e.g., C-reactive protein) arise from these reactions, and

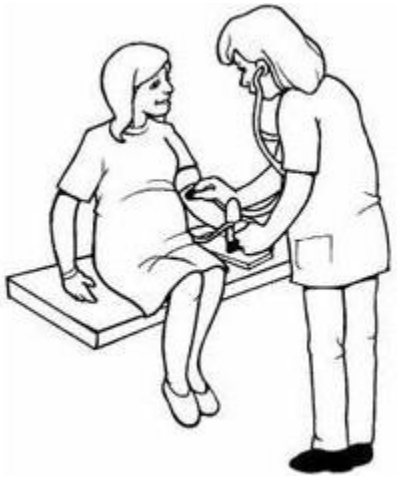
elevations of their levels have been suggested as possibly predictive of preeclampsia.

●Placental Peptides

As a result of the inflammatory cascade, a number of peptides are produced by the placenta, and some may prove to be markers for prediction of preeclampsia. Those studied include corticotropin-releasing hormone, chorionic gonadotropin, activin A, and inhibin A . The problems with these are similar to those with other markers, they are variably elevated depending on the duration and severity of preeclampsia.

●Fetal DNA

Identification of fetal DNA in maternal serum may be predictive of preeclampsia. At the same time that endothelial activation and inflammation occur, fetal cells and cellular material are released into the maternal circulation .maternal serum levels of cell-free fetal DNA were elevated at two stages. They suggested that screening for fetal DNA in earlier pregnancy may be predictive of subsequent preeclampsia, but that elevations after 28 weeks indicate impending disease.



HELLP Syndrome

Background

- Hemolysis, abnormal liver function tests, and thrombocytopenia have long been recognized as complications of preeclampsia and eclampsia.

- In 1982, Weinstein described 29 cases of severe preeclampsia and eclampsia complicated by these abnormalities. He suggested that this collection of signs and symptoms constituted an entity separate from severe preeclampsia and coined the term HELLP syndrome:
  - **H** for hemolysis
  - **EL** for elevated liver enzymes
  - **LP** for low platelet count.
- In an attempt to standardize the diagnosis of HELLP syndrome, investigators at the University of Tennessee at Memphis published criteria using cutoff values of more than two standard deviations above the mean to indicate abnormality. Their criteria for the diagnosis of HELLP syndrome are summarized below.
- The incidence of severe preeclampsia or eclampsia complicated by HELLP syndrome has been reported to range from 2% to 12%.

Criteria for The Diagnosis of HELLP Syndrome

Hemolysis

Abnormal peripheral smear
Total bilirubin >1.2 mg/dl
Lactic dehydrogenase >600 U/l

Elevated liver functions

Serum aspirate amniotransferase >70 U/l
Lactic dehydrogenase >600 U/l

Low platelets

Platelet count <100,000/mm^3

Management of HELLP Syndrome

- Patients with HELLP syndrome who are remote from term should be referred to a tertiary care center, and initial management should be as for any patient with severe preeclampsia.
- Following is an outline of the management of antepartum HELLP syndrome:
    - Maternal condition is assessed and stabilized.
        - If disseminated intravascular coagulopathy (DIC) present, coagulopathy is corrected.
        - Anti-seizure prophylaxis is given with magnesium sulfate.
        - Treatment of severe hypertension is begun.
        - Computed tomography or ultrasound of the abdomen is done if a subcapsular hematoma of the liver is suspected.
    - Fetal well-being is evaluated.
        - NST
        - Biophysical profile
        - Ultrasonographic biometry.
- If the patient is <34 weeks' gestation, fetal lung immaturity is assumed. Without laboratory evidence of DIC in a stable patient, steroids can be given to accelerate fetal lung maturity, and delivery should then be done 48 hours later. Maternal and fetal conditions should, however, be assessed continuously during this time.
  If the syndrome develops at or beyond 34 weeks' gestation, or if there is evidence of fetal lung maturity or fetal or maternal jeopardy before that time, then delivery is the definitive therapy.

Do not use dexamethasone or betamethasone for the treatment of HELLP syndrome. (NICE, 2010).

Eclampsia

Definition

Eclampsia is the development of convulsions or coma unrelated to other cerebral conditions during pregnancy or in the postpartum period in patients with signs and symptoms of preeclampsia.

Clinical features

It is that of severe PE plus fits (convulsions). The fit may follow stimuli of various kinds as visual, auditory or touch. Each fit occurs in 4 stages without intervals inbetween:

(1)-Premonitory stage: The pupils are dilated & the eyes move from side to side. Muscular twitches occur in the tongue, face & hands.

(2)-Tonic stage: All the voluntary muscles of the body undergo tonic contraction. The respiratory muscles are affected causing cyanosis, the swallowing muscles are affected causing accumulation of saliva in the mouth. The patient may acquire certain positions due to spasm of the muscles of the back.

(3)-Clonic stage: The voluntary muscles of the body undergo irregular intermittent contractions & relaxation. The tongue may be bitten. The patient may pass urine or stools involuntarily.

(4)-Coma stage: This stage may last for minutes, hours or even days. A new fit may start while the patient is still in coma or after recovery from coma. The body temperature rises during a fit because of increased muscular activity.

Causes of convulsions in eclampsia:
Unknown, it may be due to cerebral edema, cerebral vasoconstriction leading to ischemia & cerebral hypoxia, microthrombi or retention of sodium ions causing cerebral irritability. It is not due to hypertensive encephalopathy because it may occur in women with normal blood pressure in 10% of cases.

Differential diagnosis of convulsions:

- Idiopathic: epilepsy.
- Brain lesions: head trauma, encephalitis, abscess, tumour or aneurysm.
- Metabolic: renal or hepatic failure, hypoglycemia, hyponatremia and hypoparathyroidism.
- Toxic: arsenic poisoning, barbiturate withdrawal and alcohol withdrawal syndrome

Types of eclampsia:
(1)-Antepartum eclampsia: The fits start during pregnancy before the onset of labour (35%).
(2)-Intrapartum eclampsia: The fits start for the first time during labour (15%).
(3)-Postpartum eclampsia: The fits start after delivery, usually within the first 48 hours (50%).

Signs of bad prognosis: Eden criteria
Eclampsia is considered severe with bad prognosis if two or more of the following signs are present:
(1)-Number of fits: more than 10.
(2)-Duration of coma more than 6 hours.
(3)-Pulse rate above 120 beats/minute.
(4)-Temperature above 39°C.
(5)-Systolic BP above 200mmHg.
(6)-Respiratory rate over 40/minute.
(7)-Absence of edema (dry eclampsia) indicating severe vascular spasm.
(8)-Heavy proteinuria.

(9)-Anuria.
(10)-Presence of jaundice.

Complications of Eclampsia

-Abruptio placentae.
-Acute renal failure.
-Intracerebral hemorrhage.
-Pulmonary edema.
-Aspiration pneumonia.
-Retinal detachment.

Treatment

The basic principles in the management of eclampsia involve the following measures:

Support of cardiorespiratory functions

- Airway patency should be assessed and established to ensure adequate maternal oxygenation.
- Suction should be used as needed and the patient protected from injury by making sure the bed side-rails are elevated and padded.
- Oxygen should be administered to improve maternal oxygen concentration and to increase oxygen delivery to the fetus.

Control of convulsions and prevention of recurrent convulsions

- The natural tendency for those caring for an eclamptic patient is to provide therapy to immediately abolish the seizure activity; however, this may increase maternal risk of aspiration and acute change in blood pressure.

Magnesium Sulfate Therapy

- Parenteral magnesium sulfate is the drug of choice for convulsions resulting from eclampsia.
- Its major advantages include relative maternal and fetal safety when properly used. The mother is awake and alert most of the time, and laryngeal reflexes are intact, which helps protect against aspiration problems.

An intravenous loading dose of 6 g of magnesium sulfate ($MgSO_4$) prepared as 6 g diluted in 150 ml D5W or lactated Ringer's solution is administered via infusion pump over 20 to 30 minutes.

    - If the patient develops recurrent convulsions after the initial infusion of magnesium sulfate, a further dose of 2 g can be infused over 5 to 10 minutes.
    - On completion of the magnesium sulfate loading infusion, a maintenance infusion of 2 to 3 g per hour is used.
    - The infusion rate of magnesium sulfate should be adjusted on the basis of physical examination and serial serum magnesium levels.
- Patients receiving magnesium sulfate therapy must be monitored for evidence of drug toxicity.
- Magnesium is excreted by the kidneys, and renal dysfunction may cause toxic accumulation. Magnesium toxicity can be avoided by [**3R**]
    - **R**enal function with hourly urinary output assessment: 30-60 ml/hour (1-2 ml/kg/hour) or more than 100 ml in the past 4 hours.
    - **R**eflexes: serial evaluation for presence of patellar reflex.
    - **R**espiratory rate over 12-16/ minute.
    - Monitoring serial serum magnesium levels.
- If magnesium toxicity is suspected, the following steps should be taken:
    - The magnesium sulfate infusion should be discontinued.
    - Supplemental oxygen should be administered.
    - A serum magnesium level should be assessed.
- If magnesium toxicity is recognized, 10 ml of 10% calcium gluconate is administered (1 g total) intravenously.
    - This medication must be given slowly (i.e., 2 to 5 ml per minute) to avoid hypotension, bradycardia, and vomiting.
    - Calcium competitively inhibits magnesium at the neuromuscular junction, but its effect is only transient because the serum concentration is unchanged. Symptoms of

magnesium toxicity can recur following calcium gluconate administration if the magnesium level remains elevated.

- If respiratory arrest occurs, prompt resuscitative measures including intubation and assisted ventilation are indicated.

Serum magnesium level (mg/dl)	Clinical findings
1.5-2.5	Normal pregnancy level.
4-8	Therapeutic range
9-12	Loss of patellar reflex.
15-17	Respiratory arrest.
30-35	Cardiac arrest.

Correction of Maternal Hypoxemia and Acidemia

- Maternal hypoxemia and acidemia may result from
  -Repeated convulsions.
  -Respiratory depression from the use of multiple anticonvulsant agents.
  -Aspiration.
  -A combination of these factors.
  -Supplemental oxygen may be administered by face mask or face mask with an oxygen reservoir at 8 to 10 l per minute.
  -At 10 l O_2 per minute, the oxygen concentration delivered approaches 100% using a face mask with an oxygen reservoir.
- Maternal oxygenation can be monitored noninvasively by transcutaneous pulse oximetry, whereas acid-base status may be assessed by arterial blood gas analysis.

Control of Severe Hypertension

- The objective of treating severe hypertension is to prevent maternal cerebrovascular accidents and congestive heart failure without

compromising cerebral perfusion or jeopardizing uteroplacental blood flow, which is already reduced in eclampsia.

- Although the underlying causative factors are not completely delineated, hypertension in preeclampsia is clearly a consequence of a generalized arterial vasoconstriction.

-Desirable antihypertensive agent properties for the use in hypertensive emergencies in pregnancy include a rapid onset of action following administration and short duration of action in the event of overtitration.
Labetalol is administered in intermittent intravenous boluses of 20 to 80 mg.
Hydralazine is administered in intermittent bolus injections with an initial dose of 5 mg. Blood pressure should be recorded every 5 minutes.
If an adequate reduction in blood pressure is achieved 20 to 30 minutes after the initial dose, then a repeat dose of 5 mg or one increased to 10 mg in increments of every 20 to 30 minutes should be given for a maximum of 25 mg per hour.

Nifedipine

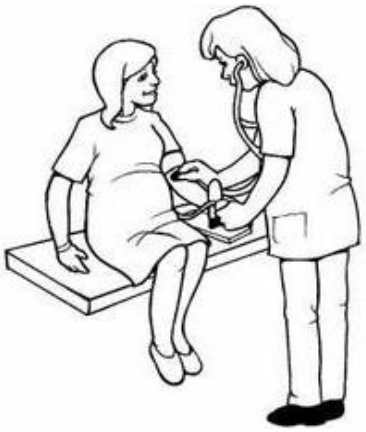
- A calcium-channel antagonist.
-It improves renal function with a beneficial effect on urine output when treating preeclampsia in the postpartum period.
-Nifedipine is administered 10 to 20 mg orally every 4 hours.
-Profound reductions in blood pressure with nifedipine can be partially reversed by the slow intravenous administration of calcium gluconate.

Sodium nitroprusside

-Sodium nitroprusside relaxes arteriolar and venous smooth muscle by interfering with both influx and the intercellular activation of calcium.
-Onset of action is immediate, and duration of action is very short (1 to 10 minutes).
-Because preeclamptic patients have a propensity for depleted intravascular volume, they are especially sensitive to its effects. The initial infusion dose should therefore be 0.2 µg/kg/min, rather than 0.5 µg/kg/min as is standard in non-pregnant patients.
-Cyanide and thiocyanate are products of metabolism of this drug.

Postpartum Eclampsia

- Approximately 30% of eclampsia cases will occur during the postpartum period, with one half within the first 48 hours from delivery.
- Late-onset postpartum eclampsia is defined as convulsions occurring more than 48 hours after delivery in patients with signs and symptoms of preeclampsia.
- If postpartum eclampsia is confirmed, the management is as previously noted for antepartum convulsions.
- More vigorous control of blood pressure is possible, however, because there is no longer a concern about compromising the uteroplacental circulation in the postpartum patient.
- Magnesium sulfate therapy should be continued for 24 to 48 hours from seizure onset.
- Intracerebral hemorrhage is the most serious.
- Fortunately, most of the complications resolve after delivery with proper management.



Diabetes Mellitus and Pregnancy

Definition

Diabetes mellitus (DM) is a disorder of carbohydrate metabolism that requires immediate changes in lifestyle. In its chronic forms, diabetes is associated with long-term vascular complications, including retinopathy, nephropathy, neuropathy and vascular disease.

Incidence:

DM is the most common medical complication of pregnancy. Approximately 3% to 5% of pregnancies are associated with gestational diabetes mellitus (GDM), whereas 0.5% to 1% of pregnant women are complicated by pre-gestational DM.

Classification Systems

I. Pre-gestational DM : Type 1 and Type 2

	Type 1 DM	**Type 2 DM**
Synonomous	-Juvenile-onset . -Insulin-dependent DM.	-Adult-onset . -Non insulin-dependent DM , Includes maturity-onset DM of the young.
Pathophysiology	Insulinopenia	Tissue resistance to insulin.
Complications	Patients are prone to severe hypoglycemia and diabetic ketoacidosis (DKA).	Patients are not at risk for DKA but, in rare cases, may develop hyperosmolar coma, Lower incidence of microvascular disease.

II. Gestational DM:

Definition: carbohydrate intolerance of variable severity first diagnosed during pregnancy.

Two categories:

(1)-The classic GDM diagnosed at 24 to 28 weeks' gestation carbohydrate intolerance unmasked by diabetogenic hormones of pregnancy.

(2)-GDM diagnosed before 24 weeks probably undiagnosed type 2 DM and

is managed as pre-gestational DM. Of the women who develop GDM, 20% to 50% will develop overt diabetes in the next 5 to 10 years, and 33% to 50% will have recurrent GDM in any future pregnancy. If GDM develops in subsequent pregnancies, the risk increases of developing overt diabetes.

III. The Priscilla White classification system *(historical)* provides an estimate of the level of microvascular damage present in a patient to assist in effective management during the pregnancy .

Gestational diabetes(GDM)	
Class A	**Class A1:** Diet-controlled GDM. **Class A2**: GDM requiring insulin or oral hypoglycemic agents.
Pre-gestational diabetes mellitus	
Class B	Onset at older than age 20, or of less than 10-yr duration.
Class C	Onset between ages 10 and 19, or of 10- to 19-yr duration.
Class D	Onset at younger than age 10, or of 20-yr duration or longer.
Class F	Diabetes with ne**ph**ropathy.
Class R	Diabetes with proliferative **R**etinopathy.
Class H	Diabetes with **H**eart disease.
Class T	Diabetes requiring Renal **T**ransplant.

IV. Clinical classification *(historical)***:**
(1)-Clinical or overt diabetes: abnormal oral glucose tolerance test(OGTT) associated with manifestations of diabetes.
(2)-Subclinical or chemical diabetes: abnormal OGTT with no manifestations of diabetes e.g. use of combined oral contraceptives (COCs).
(3)-Potential diabetes: normal OGTT but with risk factor for diabetes as obesity & bad obstetric history.
(4)-Gestational diabetes.

Physiological changes in carbohydrate metabolism in pregnancy:

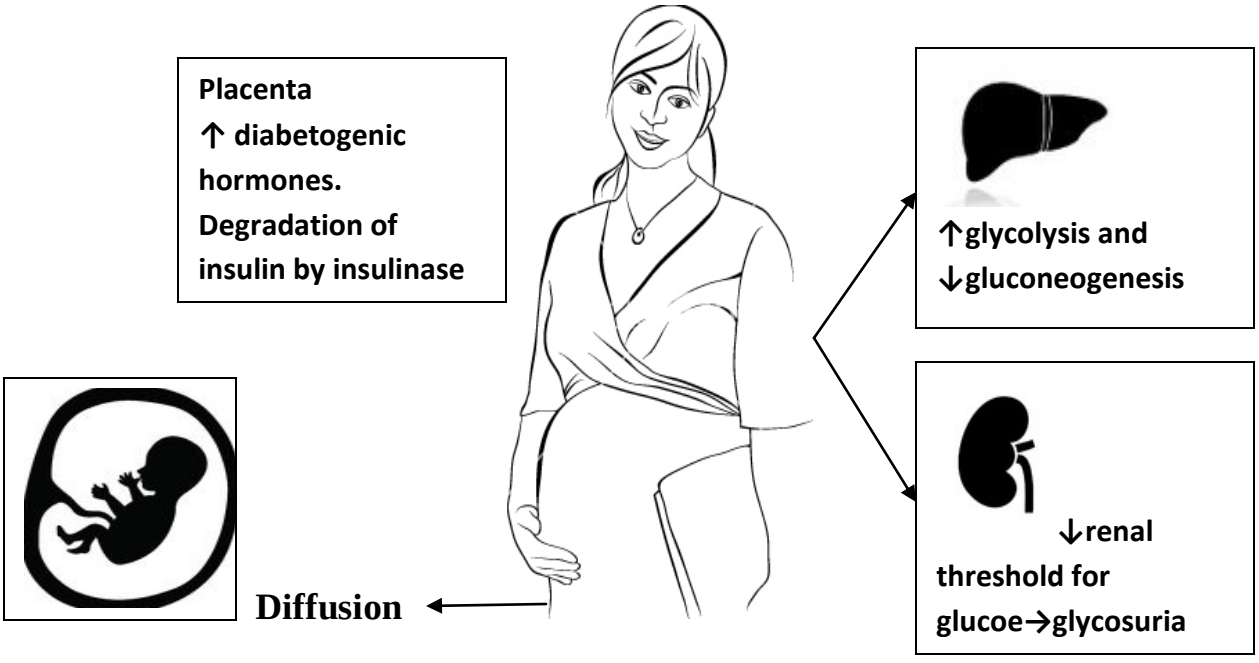
Maternal metabolism changes during pregnancy to provide adequate nutrition for both the mother and the fetus. Glucose is transported to the fetus by means of *facilitated diffusion*.

Active transport is needed for amino acids to gain access to the fetus. In the fasting state, maternal glucose levels are lower in pregnancy than in the non-pregnant state (55 to 65 mg/dl), whereas the concentrations of free fatty acids, triglycerides, and plasma ketones increase.

A state of relative maternal starvation exists in pregnancy, during which glucose is spared for fetal consumption while alternative fuels are used by the mother.

In addition to the increased glucose uptake of the fetus, there is increased peripheral uptake, increased glycolysis and reduced hepatic gluconeogenesis.

The renal tubular threshold for glucose (180 mg/dl) falls, such that glycosuria is common. During the second half of the pregnancy, glucose levels increase, in part, as a result of diabetogenic hormones, predominantly human placental lactogen, while estrogen, progesterone, cortisol, and prolactin are involved as well. Degradation of insulin is also increased during pregnancy by placental insulinase.



Effect of Pregnancy on diabetes mellitus:

(1)-The disease may appear for the first time during pregnancy.
(2)-The insulin requirements gradually increase after the 3rd month until term and ketoacidosis can occur with lower levels of blood glucose.
(3)-Aggrevation of diabetic microangiopathy (nephropathy, retinopathy & neuropathy).
(4)-During delivery, there is liability to hypoglycemia because of uterine activity.
(5)-After delivery, insulin requirement decreases due to drop in the placental hormones.

Effect of diabetes mellitus on pregnancy

I. Maternal complications:

-Metabolic: increased risk of diabetic ketoacidosis and severe hypoglycemia.
-Worsening of microvascular disease (coronary artery disease, hypertension, nephropathy, retinopathy & neuropathy).
-Increased risk and severity of infection e.g.vulvovaginitis & UTI.
-Increased risk for pre-eclampsia, polyhydramnios , cesarean section, birth trauma & postpartum infection.

II. Fetal complications:

(1)-Congenital anomalies can involve any organ system; however, the cardiovascular system is the one most commonly affected. Embryogenesis occurs during days 34-71 from LMP (the 5th through 10th) gestational weeks. During this critical period, the fetus is extremely sensitive to the maternal environment (i.e., glycemic control). Also during this early period of fetal development, the woman is often unaware of her pregnancy. Poorly controlled diabetes greatly increases the risk of congenital anomalies with the greater the elevation of glycosylated hemoglobin HbA1C, the higher the likelihood of a structural fetal abnormality.
(2)-Spontaneous abortion risk is increased in poorly controlled diabetic patients. This risk increases with elevated HbA1C levels.
(3)- Intrauterine growth restriction (IUGR) may complicate the pregnancies of the diabetic patient with underlying microvascular disease.

(4)- Intrauterine Fetal Demise (IUFD) poorly controlled diabetic patients are also at increased risk for fetal demise in the third trimester (after 35 weeks). It may be due to maternal ketosis, hypoglycemia, congenital malformations, associated PE or placental insufficiency.
(5)-Fetal macrosomia, and shoulder dystocia.

III. Neonatal Sequelae:
-Iatrogenic prematurity.
-Respiratory distress syndrome (RDS), hyperbilirubinemia, hypoglycemia, hypocalcemia and hypothermia.
-Consequences of small for gestational age (SGA) and large for gestational age (LGA) infants.

-Development of DM in later life as follows:
(1)-Type 1: the child of an affected mother has a 2% risk of developing diabetes, while the child of affected father has a 8% risk. If both parents have type 1 diabetes, there is a 30% risk to their offspring.
(2)-Type 2: *higher than in type 1*.Offspring of an affected mother or father have a 15% risk, and if both parents are affected the risk is 75%.

-Pruritus vulvae.
-Pyelonephritis.
-Polyhydramnios.
-PROM & PTL.
-PPH (atonic & traumatic).
-Puerperal sepsis.
-↑ surgical interference.

-DKA & hypoglycemia.
-Worsening of micro-vascular diseases.

-Abortion.
-Congenital anomalies.
-Abnormal growth (macrosomia or IUGR).
-IUFD.

Neonatal complications:
-RDS.
-Cardiomyopathy.
-Neonatal jaundice.
-Neonatal death.
-Inheritance of DM.

Diagnosis of diabetes mellitus

●Independent risk factors for GDM:

Body mass index above 30 kg/m².
Previous macrosomic baby weighing 4.5 kg or above.
Previous gestational diabetes.
Family history of diabetes (first-degree relative with diabetes).
Family origin with a high prevalence of diabetes: South Asian, black Caribbean and Middle Eastern.

●Screening for GDM according to NICE guidelines, 2014

Screening for gestational diabetes using fasting plasma glucose, random blood glucose, glucose challenge test and urinalysis for glucose should *not* be undertaken .The 2-hour 75 g oral glucose tolerance test (OGTT) should be used to test for gestational diabetes and diagnosis made using the criteria defined by the WHO.OGTT should be offered to women with risk factor at 24–28 weeks. Women who have had GDM in a previous pregnancy should be offered early self-monitoring of blood glucose or an OGTT at 16–18 weeks, and a further OGTT at 28 weeks if the results are normal.

Women with elevated fasting and 2-hour levels are diagnosed with GDM.

	Whole blood venous	**Whole blood capillary**
Fasting	Above 6.1mmol/L (105mg/dL)	Above 6.1mmol/L (105mg/dL)
2-hours	Above 6.7mmol/L (120mg/dL)	Above 7.8mmol/L (140mg/dL)

●Screening for GDM according to ACOG, 2005 and ADA, 2008

One-hour glucose screening test:

A 50-g, one-hour glucose challenge test at 24 to 28 weeks of gestation. Patients do not have to fast for this test. To be considered normal, serum or plasma glucose values should be less than 140 mg per dL (7.8 mmol per L). Positive screening test require confirmation with oral glucose tolerance test.

3-hour oral Glucose Tolerance Test (GTT):

If the patient's glucose level is equal to or greater than the threshold value chosen, then the 3-hour diagnostic GTT should be administered by administering 100 g of glucose orally in at least 400 mL of water after an overnight fast for 8-14 hours (for a patient who has been consuming a normal carbohydrate diet).

In the past, the modified O'Sullivan scale was used to make a diagnosis of GDM. Since 1998, however, the American Diabetes Association has recommended the use of Carpenter and Coustan values.

Blood sample	***National Diabetes Data Group***	***Carpenter and Coustan****
Fasting	105 mg/dl (5.8 mmol/l)	95 mg/dl (5.3 mmol/l)
1-hour	190 mg/dl (10.5 mmol/l)	180 mg/dl (10.0 mmol/l)
2-hour	165 mg/dl (9.2 mmol/l)	155 mg/dl (8.6 mmol/l)
3-hour	145 mg/dl (8.0 mmol/l)	140 mg/dl (7.8 mmol/l)

If any two or more of the diagnostic values are met or exceeded, then the diagnosis of GDM is made. In patients with significant risk factors and a normal GTT, a follow-up GTT may be performed at 32 to 34 weeks to diagnose late-onset GDM.

Diagnosis of Pre-gestational DM:

Patients with type 1 diabetes are typically diagnosed during an episode of hyperglycemia, ketosis, and dehydration; this occurs most commonly in childhood or adolescence, before pregnancy.

Diagnosing type 2 insulin-resistant diabetes is difficult during pregnancy because severe forms of gestational diabetes mellitus have similar clinical characteristics. On the other hand, it is not unusual for women diagnosed with gestational diabetes mellitus in early pregnancy to be found to have overt diabetes after delivery. Although a first-trimester HbA1C value of 8% is highly suggestive of preexisting type 2 diabetes, definitive diagnosis of type 2 diabetes must be made after pregnancy using the 75-gram, 2-hour glucose tolerance test.

According to the American Diabetes Association (ADA, 2008) diagnostic criteria for diabetes mellitus are as follows, and one of the following must be met:

- **Symptoms of diabetes** and a casual plasma glucose greater than 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
- **Fasting plasma glucose** greater than 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 hours.
- **Two-hour plasma glucose** greater than 200 mg/dl (11.1 mmol/l) during a 75 g, 2-hour oral glucose tolerance test (OGTT).

- **Impaired fasting glucose** is a condition in which the fasting blood sugar level is elevated (100-125 mg/dl) after an overnight fast but is not high enough to be classified as diabetes.
- **Impaired glucose tolerance** is a condition in which the blood sugar level is elevated (140-199 mg/dl after a 2-h oral glucose tolerance test) but is not high enough to be classified as diabetes.

Management of Diabetes Mellitus during pregnancy

I. Pre-pregnancy Care:

-Optimize glycemic control aiming for HbA1c of 6.1% or less, women with levels greater than 10% should be advised to postpone pregnancy until better control is achieved.
-Review diet and advice weight loss in obese patients.
-Review diabetic complications: assess renal function, blood pressure & retinal examination.
-Review other medications: stop teratogenic drugs as ACEIs, ARBs (for hypertension) and statins (for hyperlipidemia).
-Smoking cessation & reduce alcohol intake.
-Prescribe folic acid 5 mg starting before conception to reduce the incidence of NTDs.

II. Antenatal Care:

Ideally, diabetic women desiring pregnancy should seek preconception consultation and achieve euglycemia before conception.

The patient should have a detailed history and physical examination, and

(1)-Ophthalmologic fundus examination.

(2)-An electrocardiogram (ECG) for women older than age 35 and smokers.

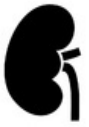
(3)-Renal evaluation with a 24-hour urine collection for measurement of protein and creatinine clearance.

(4)-Echocardiography and a cardiology consultation should also be obtained upon presence of, or concern for, cardiac disease.

(5)-Measurement of HbA1C is helpful in evaluating degree of glycemic control and assessing risk of fetal malformations in the 1st trimester. HbA1C levels of 10% or higher are associated with significant risk (about 20%) of fetal malformations. Normal levels of HbA1C provide a similar risk to that of non-diabetic women.

Fundus examination

Blood pressure, ECG if age > 35 years, echocardiography & cardiac consultation.



Renal function tests, 24-hour urine for protein & creatinine clearance


Review medications. Prescribe Folic acid 5mg/d. Measure HbA1c.

Specific antenatal care for women with diabetes (NICE, 2014)

Appointment	Care should be given
First appointment (joint diabetes & ANC)	- Offer information, advice and support in relation to optimizing glycaemic control. -Take a clinical history to establish the extent of diabetes-related complications. - Review medications for diabetes and its complications. - Offer retinal and/or renal assessment if these had not been undertaken in the previous 12 months.
7–9 weeks	Confirm viability of pregnancy and gestational age.
Booking appointment (ideally by 10 weeks)	Discuss information, education and advice about how diabetes will affect the pregnancy, birth and early parenting.
16 weeks	Offer retinal assessment at 16–20 weeks to women with pre-existing diabetes who showed signs of diabetic retinopathy at the first antenatal appointment.
20 weeks	Offer four-chamber view of the fetal heart and outflow tracts plus scans that would be offered at 18–20 weeks as part of routine antenatal care.
28 weeks	Offer ultrasound monitoring of fetal growth and amniotic fluid volume. Offer retinal assessment to women with pre-existing diabetes who showed no diabetic retinopathy at their first antenatal clinic visit.
32 weeks	Offer ultrasound monitoring of fetal growth and amniotic fluid volume. Offer to nulliparous women all investigations as part of routine antenatal care.
36 weeks	Offer ultrasound monitoring of fetal growth and amniotic fluid volume. Offer information and advice about delivery and postpartum care.
38 weeks	Offer induction of labour, or caesarean section if indicated, and start regular tests of fetal well-being for women with diabetes who are awaiting spontaneous labour.
≥ 39 weeks	Offer tests of fetal well-being.

Glycemic Control:

●Management of GDM

GDM is divided into two categories:

I. GDM-A1 (euglycemia achieved by diet alone).

(1)-Diet:

Women with newly diagnosed GDM should be started on an American Diabetic Association diet with a daily intake of 1,800 to 2,400 kilocalories (30 kcal/kg/day) made up of 15% to 20% protein, 50% to 60% carbohydrates, and 20% fat. CHO counting, with 180 to 210 g of CHO allowed daily, is rapidly replacing the kilocalorie-based diet. A nutritional consultation should also be provided as part of early pregnancy counseling.

(2)-Exercise:

Moderate exercise has been shown to lower maternal glucose concentrations in women with GDM. Patients should be encouraged to maintain a healthy, consistent level of activity throughout pregnancy, provided that no complicating factors (i.e., preterm labor, pre-eclampsia, etc.) exist. Exercise alone may achieve euglycemia and therefore avoid the need for medical therapy. Appropriate exercises are those that use the upper body muscles and place a little mechanical stress on the trunk region.

II. GDM-A2 (glycemic status inadequately controlled by diet alone). If glucose levels cannot be controlled with diet alone, then further therapy is needed.

Glucose monitoring is carried out using a glucometer. The patient should record fasting glucose values and 1-hour (or 2-hour) postprandial glucose values with each meal to determine the adequacy of diabetic control for goal values.

HbA1C reflects glycemic control over the past 8 to 12 weeks, and is used to assess risk of fetal anomalies in the first trimester of pregnancy.

Goal values for adequacy of control	
Fasting	60-90 mg/dl
Pre-meal	<100 mg/dl
1 hour postprandial	<140 mg/dl
2 hours postprandial	<120 mg/dl
Bedtime	<120 mg/dl
2:00-6:00 A.M.	60-90 mg/dl

Oral Hypoglycemic Agents:

Indications: Glyburide (Glicenclamide) is an acceptable alternative to insulin when dietary management of GDM fails.

Mechanism of action: Glyburide works by increasing tissue sensitivity to insulin.

Dosage: The starting dose is usually 2.5 mg at bedtime or 2.5 mg twice daily. The frequency and dosing may vary, depending on the degree of glycemic control. The maximum dose is 10 mg BID, and the lowest available dose is 1.25 mg.

Side-effects associated with glyburide include hypoglycemia, cholestatic jaundice, nausea, heartburn, and allergic skin reactions.

● **Management of pre-gestational DM**

-Patients with pregestational DM are usually continued on their normal pre-pregnancy insulin regimen while initial assessment of diabetic control and paneling (recording of blood glucose levels) is performed.

Goal glucose values should be discussed with the patient and adjustments in the insulin dosing made accordingly.

-In patients with type 1 DM, insulin requirements are usually increased 50% to 100% in the second half of pregnancy, whereas in patients with type 2 DM, insulin needs usually more than double.

-The American Diabetic Association recommends the use of human insulin for pregnant women with DM and for women with DM considering pregnancy. Patients taking oral hypoglycemic agents (except glyburide) or a regimen of 70/30 mixed (NPH/regular) insulin are switched to human NPH and a rapid-acting regular insulin analog. The use of metformin and Lantus in pregnant patients is still under investigation.

-NICE recommendations : for women who conceive on oral hypoglycemic agents to be switched to insulin therapy as soon as they are pregnant. However, there is growing interest in the use of metformin and glibenclamide in the management of women with type 2 DM, GDM and those with PCOD. These drugs are cheaper, easier to administer & more convenient, have fewer risks of hypoglycemia and may have beneficial effects on long term prognosis.
Metformin is used in the first trimester in women with PCOD as it reduces the risk of miscarriage and the risk of developing gestational diabetes. It crosses the placenta, but systematic reviews of its use in early pregnancy have not shown any increase in the risk of congenital malformations.

Hospitalization may be necessary during pregnancy in events of severe hypoglycemia, concurrent infection, or for obstetric indications.

Insulin Management (classic method)
-Depending on the maternal weight and recorded glucose levels, the insulin dosage should be initiated as follows:
0.7 units/kg for gestational age of 6 to 18 weeks;
0.8 units/kg for gestational age of 18 to 26 weeks;
0.9 to 1.1 units/kg for gestational age of 26 to 40 weeks.
-Usually do not start at more than 60 U insulin per day.
-Total daily dose should be divided in half, given every morning and evening.
-Morning dose (before breakfast): two-thirds of dose given as neutral protamine Hagedorn (NPH) insulin, one-third of dose given as a rapid acting insulin.
-Evening dose (before dinner): one-half of dose given as NPH, one-half of dose given as rapid acting insulin.
-Evening NPH insulin may need to be moved to bedtime to achieve optimal fasting blood sugars.
-Occasionally, patients may require only one dose of NPH insulin at bedtime to obtain euglycemia.

0.7 units/kg for gestational age of 6 to 18 weeks;
0.8 units/kg for gestational age of 18 to 26 weeks;
0.9 to 1.1 units/kg for gestational age of 26 to 40 weeks.

½ of the total dose in the morning

½ of the total dose in the evening

2/3 as NPH and 1/3 as regular insulin

1/2 as NPH and 1/2 as regular insulin

4 injection Insulin dosage regimen for diabetic pregnancy

Pregnancy NPH plus rapid-acting insulin schedule
"Big I" = total daily units of insulin :

Gestational weeks =	0–12	13–28	29–34	35–40
	k = 0.7	0.8	0.9	1.0

Calculate desired units of insulin from above line. "Big I" = _____ (*k* units × weight kg)/24 hours "Big I" = Basal insulin requirement + Bolus (meal-related) insulin requirement
Basal =1⁄2 "Big I," …….Bolus =1/2 "Big I,".
***Basal*:** Divide so that 1⁄6 of "Big I" is NPH given before breakfast, 1⁄6 of "Big I" is NPH given before dinner, and 1/6 of "Big I" is NPH given before bedtime.
***Bolus*:** Divide so that 1⁄6 of "Big I" is rapid-acting insulin given before breakfast, 1⁄6 of "Big I" is rapid-acting insulin given before lunch, and 1⁄6 of "Big I" is rapid-acting insulin given before dinner. The rapid-acting insulin is then titrated based on the blood glucose.

0800 Pre-breakfast:
NPH =1⁄6"Big I" = _____.
Check yesterday's pre-dinner BS:
If yesterday's pre-dinner BS <60, then decrease today's AM NPH by 2 units.
If yesterday's pre-dinner BS 61–90, no change in today's AM NPH.
If yesterday's pre-dinner BS >91, then increase today's AM NPH by 2 units.

Rapid-acting insulin =1⁄6 "Big I" = _____ to be adjusted according to the following scale:
Pre-breakfast BS <60 = _____ = (1⁄6 "Big I" dose) – 3% of the "Big I."
Pre-breakfast BS 61–90 = _____ =1⁄6 "Big I" dose.
Pre-breakfast BS 91–120 = _____ = (1⁄6 "Big I" dose) + 3% of the "Big I." Pre-breakfast BS >121 = _____ = (1⁄6 "Big I" dose) + 6% of the "Big I."
If today's BS 1 hour after breakfast is <110, then decrease tomorrow's pre-breakfast rapid insulin by 2 units.
If today's BS 1 hour after breakfast is 111–120, no change in tomorrow's pre-breakfast rapid insulin.
If today's BS 1 hour after breakfast is >121, then increase tomorrow's pre-breakfast rapid insulin by 2 units.
Do not feed the patient until the blood sugar is below 120 mg/dL.

1200 Pre-lunch:
Rapid-acting insulin is 1⁄6 "Big I" = _____ to be adjusted according to the following scale:
Pre-lunch BS <60 = _____ = (1⁄6 "Big I" dose) – 3% of "Big I."
Pre-lunch BS 61–90 = _____ =1⁄6 "Big I" dose.
Pre-lunch BS 91–120 = _____ = (1⁄6 "Big I" dose) + 3% of "Big I."
Pre-lunch BS >121 = _____ = (1⁄6 "Big I" dose) + 6% of "Big I."
If today's BS 1 hour after lunch is <110, then decrease tomorrow's pre-breakfast rapid insulin by 2 units.
If today's BS 1 hour after lunch is 111–120, no change in tomorrow's pre-breakfast rapid insulin.
If today's BS 1 hour after lunch is >121, then increase tomorrow's pre-breakfast rapid insulin by 2 units.
Do not feed the patient until the blood sugar is below120 mg/dL.

1700 Pre-dinner:
NPH =1⁄6"Big I" = _____.
Rapid-acting insulin is 1⁄6 "Big I" = _____ to be adjusted according to the following scale:
If yesterday's pre-bedtime BS <60, then decrease today's dinner NPH by2U.

If yesterday's pre-bedtime BS 61–90, no change in today's dinner NPH.
If yesterday's pre-bedtime BS >91, then increase today's dinner NPH by 2 units. Pre-dinner BS <60 = _____ = (1⁄6 "Big I" dose) – 3% of "Big I."
Pre-dinner BS 61–90 = _____ =1⁄6 "Big I" dose
Pre-dinner BS 91–120 = _____ = (1⁄6 "Big I" dose) + 3% of "Big I."
Pre-dinner BS >121 = _____ = (1⁄6 "Big I" dose) + 6% of "Big I."
If today's BS 1 hour after dinner is <110, then decrease tomorrow's dinner rapid insulin by 2 units.
If today's BS 1 hour after dinner is 111–120, no change in tomorrow's dinner rapid insulin.
If today's BS 1 hour after dinner is >121, then increase tomorrow's dinner rapid insulin by 2 units.
Do not feed the patient until the blood sugar is Below120 mg/dl.

2400 Bedtime

NPH: Give 1⁄6 "Big I" = _____.
If today's pre-breakfast BS is <60, then decrease today's bedtime NPH by 2 units. *If today's pre-breakfast* BS is 61–90, no change in today's bedtime NPH.
If today's pre-breakfast BS is >91, then check the 3 AM BS and, if it is <70 (regardless of today's pre-breakfast BS), decrease today's bedtime NPH by 2 units. *If today's pre-breakfast* BS is >91, and the 3 AM BS >70, increase today's bedtime NPH by 2 units. Also, if the 3 AM BS is >91, then call the doctor for 3 AM rapid insulin scale equal to the pre-lunch rapid scale.

Gestational weeks = 0–12	13–28	29–34	35–40
k **= 0.7**	**0.8**	**0.9**	**1.0**

½ Basal NPH divided into 3 parts→ 3/6

½ Bolus Regular insulin divided into 3 parts→ 3/6

8 am: Pre-breakfast: NPH (1/6) + Regular (1/6).
12 pm: Pre-lunch: Regular (1/6).
5 pm: Pre-dinner: NPH (1/6) + Regular (1/6).
12 am: Bedtime: NPH (1/6).

Glycemic goals according to ACOG, 2005 and ADA, 2008

-Fasting glucose level < 5.3 mmol/l (<95mg/dl).
-Pre-meal values <5.5mmol/l (100mg/dl).
-One-h postprandial levels <7.8mmol/l (140mg/dl) & 2-h postprandial levels <6.7mmol/l (12omg/dl).
-During the night, glucose levels should not decrease to<3.3mmol/l (<60mg/dl).
-Mean capillary glucose levels should be maintained at an average of 5.5mmol/l (100mg/dl) & HbA1c ≤ 6%.

Glucose monitoring according to ACOG, 2005 and ADA, 2008

-Daily self-monitoring in the fasting state, before and 1 or 2 h after each meal and before bed. In selected patients, especially those on insulin pumps, glucose determinations at 2:00 AM–3:00 AM may help detect nocturnal hypoglycemia.
-HbA1c measurement provides an indication of glycemic control over the past 2–3 months and should be performed during each trimester.

Progress in the management of type-1 DM in pregnant women

●The use of insulin analogs

-The goal of rapid-acting insulin administration is to achieve postprandial glucose control. Compared with regular human insulin, bolus insulin analogs have a more rapid onset and a shorter duration of action resulting in a more effective reduction of postprandial hyperglycemia and avoidance of hypoglycemic events between meals. Two rapid-acting insulin analogs, lispro and aspart, are currently classified as pregnancy risk category B, based on reports demonstrating fetal, perinatal and maternal outcomes similar to regular human insulin. Lispro and aspart are at least as effective as regular human insulin in achieving glucose control, as evident from HbA1c levels. The main benefit of insulin analogs is the reduction of severe hypoglycemic events in pregnant type-1DM patients.

- Basal insulin is required for the maintenance of glycemic control between meals. Until recently, neutral protamine Hagedorn (NPH), an intermediate-

acting insulin, was the only insulin approved for use as basal therapy in pregnant type-1DM patients and was considered as the standard of care for diabetes in pregnancy. However, NPH use can be associated with a peak in concentration 4–8 h post-injection and high intra-subject variability that may lead to an increased risk of hypoglycemic events between meals and at night. In recent years, glargine and detemir have become the basal insulin analogs of choice in the general type-1DM population. Glargine shows a relatively flat action profile with a near 24-h duration. Glargine also shows lower intra-subject variability compared to NPH. While there are numerous reports on the off-label use of glargine in pregnant women, there are no randomized clinical trials assessing its safety during pregnancy. Therefore, insulin glargine is currently classified as pregnancy risk category C and is not approved for use in pregnant women.

Insulin or insulin analog	Onset of action (minutes)	Time to peak concentration (minutes)	Maximum duration of action (hours)
Insulin			
Regular insulin	30-60	90-120	5-12
NPH insulin	60-120	240-480	10-20
Bolus Insulin analogs			
Insulin lispro	10-15	30-60	3-4
Insulin aspart	10-15	40-50	3-5
Basal Insulin analogs			
Insulin glargine	60-120	None	24
Insulin detemir	60-120	None	20-24

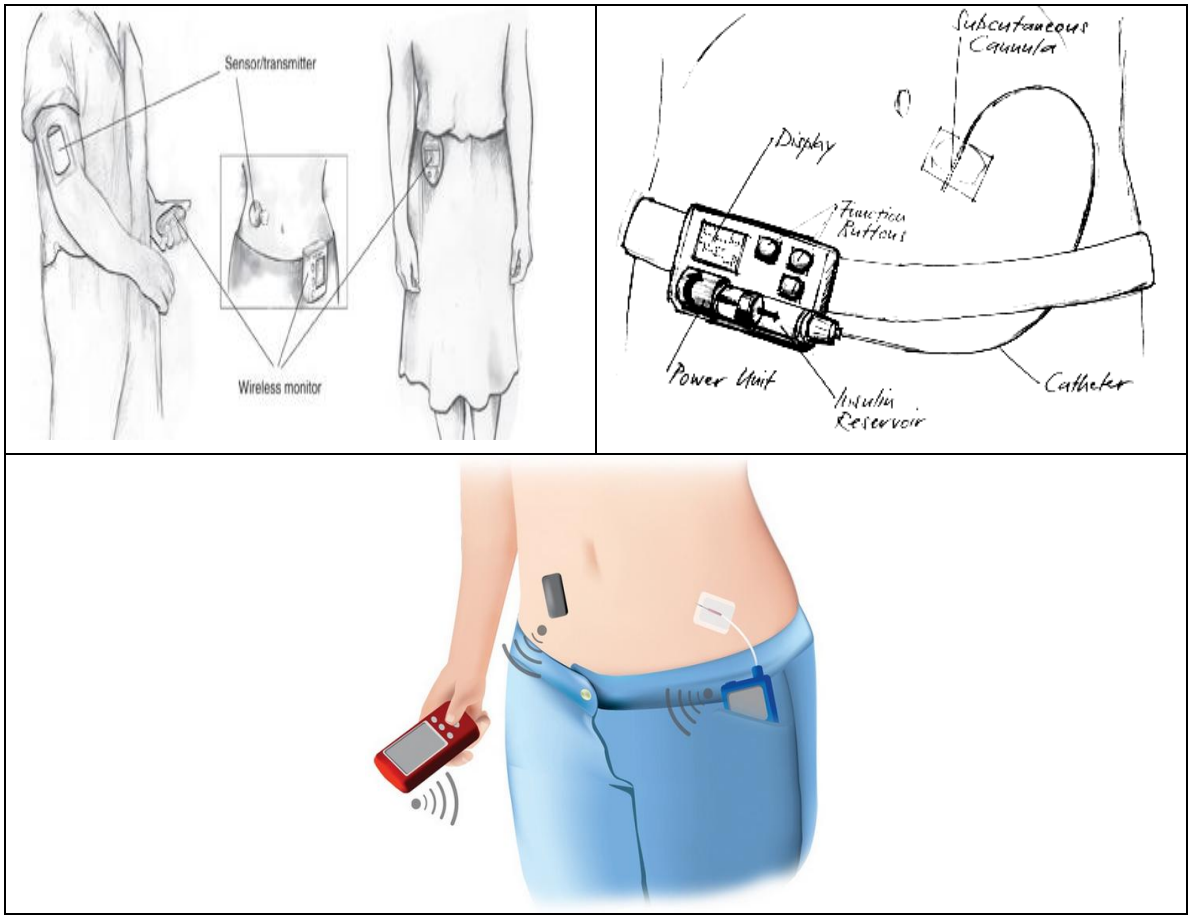
●Methods for glucose monitoring and insulin administration

-The development of continuous glucose monitoring (CGM) devices represents an advance that can provide real-time measurements and warnings when patients face hypoglycemia. Based on results of RCT, the

American Association of Clinical Endocrinologists (2010) recommended the use of CGM for all pregnant patients with type-1DM.

- Patients requiring insulin therapy need to consider the method of administration. Patients can choose between multiple daily injections using a syringe or insulin pen and continuous subcutaneous insulin infusion (CSII) via an insulin pump. CSII insulin delivery has drawbacks, such as higher cost of the pump and pump supplies, difficulty of use requiring the patient to be motivated and compliant and willingness to test glucose multiple times daily, that might limit its usefulness in pregnant patients. In addition, there is a risk of hypoglycemia or even diabetic ketoacidosis in case of a pump malfunction or infection at the infusion site.

- Sensor-augmented pump (SAP) therapy (combinations of CGM and CSII) might further improve the treatment of type-1 DM patients in the future.



Fetal monitoring

GDM-A1 diabetic patients are not at increased risk for fetal demise before 40 weeks' gestation. Therefore, no antepartum testing is required beyond that recommended for a normal pregnancy. Women with GDM-A2 require antenatal testing similar to that recommended for pre-gestational DM (twice weekly NSTs/BPP from 32 to 34 weeks until delivery). **For all women with GDM** (A1 and A2), delivery by 40 weeks' gestation is recommended.

Fetal Assessment and Pre-gestational DM

-First Trimester: A dating ultrasound is recommended for confirmation of gestational age. Documentation of fetal heart tones and first trimester screening for fetal aneuploidy should be offered in the form of nuchal translucency, beta hCG, and PAPP-A serum markers.

-Second Trimester: Screening for fetal aneuploidy may also be offered in the second trimester in the form of the triple screen [maternal serum alpha-fetoprotein (AFP) levels, unconjugated estriol and hCG] quadruple screen [maternal serum alpha-fetoprotein (AFP) levels, unconjugated estriol, hCG, and inhibin A].This screening is typically performed between 16 and 18 weeks' gestation but can be measured up to 21 weeks. If the patient had a normal first-trimester screening, the physician should still offer a maternal AFP to screen for neural tube defects.
Ultrasonography at 18 to 20 weeks is recommended for evaluation of fetal anatomy. Because fetal cardiac anomalies are the most common congenital malformations with pre-gestational DM, a fetal echocardiogram is recommended at 19 to 22 weeks' gestation.

-Third Trimester: In the third trimester, regular fetal surveillance should be initiated for all pregnancies in diabetic women. Fetal surveillance should be performed frequently in the presence of maternal vascular disease, hypertension, ketoacidosis, pre-eclampsia, and poor patient compliance. Obstetric ultrasonographic examinations for fetal growth should be considered at 28 to 30 weeks and then at 34 to 36 weeks. If the patient has evidence of microvascular disease, monthly (2-4 weeks) ultrasonographic

examinations starting at 24 to 26 weeks may be necessary to closely follow fetal growth and assess for IUGR.

-Doppler Umbilical Artery Velocimetry: In pregnant women at risk for vascular disease, Doppler ultrasonographic studies of the umbilical artery can help in assessing fetal outcome. An elevated umbilical S/D ratio may be associated with fetal growth restriction and pre-eclampsia. With increased resistance of the placenta, the systolic pressure of the umbilical artery increases, which causes an elevated ratio.

Preterm labour in women with diabetes

Diabetes should not be considered a contraindication to antenatal steroids for fetal lung maturation or to tocolysis.
Women with insulin-treated diabetes who are receiving steroids for fetal lung maturation should have additional insulin according to an agreed protocol and should be closely monitored.
Beta-mimetic drugs should not be used for tocolysis in women with diabetes.

Management of labour in diabetic patient

Timing and mode of birth

-Pregnant women with diabetes who have a normally grown fetus should be offered elective birth through induction of labour, or by elective cesarean section if indicated (cesarean section is safer with estimated fetal weights greater than 4.25 kg, thus some advocate this fetal weight as a cut-off) , after 38 completed weeks to reduce the risk of shoulder dystocia in macrosomic infants of women with diabetes. Diabetes should not in itself be considered a contraindication to attempting vaginal birth after a previous caesarean section (NICE, 2014).
-Amniocentesis to test for fetal lung maturity is recommended before elective delivery for patients without accurate gestational dating or for gestations of <39 weeks. Tests for fetal lung maturity include lecithin/sphingomyelin (L/S) ratio: an elevated L/S ratio (ratio at lung maturity is above 2.0) is associated with a low incidence of RDS, even if

phosphatidylglycerol (PG) is absent. PG levels: presence indicates advanced fetal lung development.

-If antenatal testing is non-reassuring, the decision to deliver the fetus requires determination of the risks to the fetus of remaining in utero compared to the risks of delivery of a premature infant.

-Glucose Control and Monitoring. The patient must be euglycemic during the intrapartum period . Maternal hyperglycemia results in fetal hyperglycemia, which then causes fetal hyperinsulinemia. Elevated insulin levels increase the neonatal risk of severe hypoglycemia. This, in turn, may lead to neonatal seizures and death.

During labor and delivery, continuous intravenous (IV) infusion of insulin and dextrose is the optimal mean of glycemic control. With elective induction of labor, the patient should receive her normal insulin dose during the previous evening. On the morning of her induction, the patient's usual insulin dose should be withheld.

On admission to labor and delivery, the patient should be started on IV fluids and continued with serial glucose monitoring. Normal saline should be continued until the patient reaches active labor, or when glucose levels fall below 70 mg/dL. During active labor or with glucose levels <70 mg/dL, IV administration of 5% dextrose solution (with lactated Ringer's or normal saline) should be started.

The infusion fluid is adjusted based on blood glucose levels. Short-acting insulin boluses may be added to bring glucose levels to **the target range of 80 to 100 mg/dl**. Blood glucose values should be checked **every 1 to 2 hours** and the insulin and fluids adjusted accordingly.

In type 1 DM, exogenous insulin is essential for tissue use of glucose; a low-dose insulin drip should be maintained and hypoglycemia managed with glucose infusion.

The route of delivery remains controversial. If fetal macrosomia is not suspected, a trial of labor could ensue. If the estimated fetal weight exceeds 4,000 g, the risk of shoulder dystocia and traumatic birth injuries increases. With a suspected birth weight of 4,500 g or greater, a cesarean section is indicated.

Management of elective cesarean section. The patient should withhold her morning insulin dose. Glucose levels should be monitored frequently during and immediately after surgery.

Current NICE guidelines

(1)-Maternal blood glucose should be tested hourly.
(2)-Oxytocin infusions should be administered in saline.
(3)-Diabetes alone is not a contraindication to allowing a VBAC.
(4)-Analegsia during delivery in the usual way. Women with co-morbidities as obesity or neuropathy should be offered anesthetic review during the third trimester.

Postpartum care

After delivery, glucose levels should be checked every 4 to 6 hours, while administering 5% dextrose with lactated Ringer's or normal saline (at approximately 125 mL/hr).
During the initial postpartum period, short-acting insulin is used only when glucose levels are higher than 150 mg/dL. Once the patient is taking a full diabetic diet, insulin can be started at one-third to one-half of the antepartum dosage or a dosage comparable to her pregestational dosage.

Table 13.6 Low-dose Continuous Insulin Infusion for Labor and Delivery

Blood glucose (mg/dL)	Insulin dosage (U/hr)[a]	Fluids (125 mL/hr)
<100	0	D5 LR
100-140	1.0[b]	D5 LR
141-180	1.5[b],[c]	D5 LR
181-220	2.0[b],[c]	D5 LR
>220	2.5[b],[c]	Normal saline

[a]Type 1 diabetic patients need a baseline insulin dose when blood glucose is > 60 mg/dL.
[b] Increase as needed.
[c]Boluses of insulin may be required in addition to an increase in the insulin drip. D5 LR, 5% dextrose with lactated Ringer's solution.

Common practice is to reduce the insulin dose to 50% of the pre-pregnancy dose for the first 12-36 hours after delivery and then to increase the dose gradually to the pre-pregnancy dose. Women delivered by cesarean section will require continuation of the sliding scale until normal eating is resumed. Women with type 2 diabetes can change from insulin back to their oral hypoglycemic agents.

Breastfeeding

Breastfeeding increases the frequency of hypoglycemia in insulin dependant- diabetics, thus women should have a snack before or during breastfeeding. Women with pre-existing type 2 diabetes can safely take metformin and glibenclamide (but not other oral agents) while breastfeeding.

Contraception

Low dose estrogen containing pills have little impact on diabetic control , and progestin only pills can be used in women with type 1 diabetes providing there is good control of blood glucose and plasma lipids.FDA package for copper T 380 A IUD lists overt DM as one of the contraindications. Many women may elect puerperal sterilization.

Postpartum Evaluation in GDM:

In the postpartum period, a woman with GDM (A1 and A2) should have a follow-up fasting blood glucose and 2-hour 75-g glucose tolerance test (6 to 12 weeks postpartum) to assess for persistent diabetes.

If the threshold values are met or exceeded in postpartum testing, the patient is given a diagnosis of type 2 diabetes.

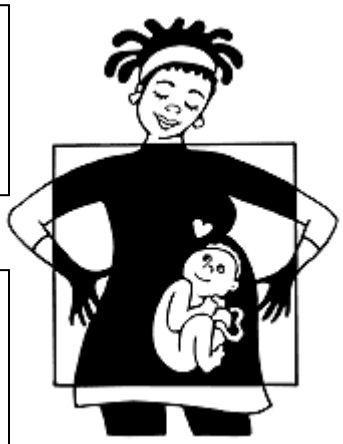
Threshold Values in Postpartum Evaluation for Carbohydrate Intolerance:

Time since 75-g glucose load	No DM	Impaired glucose tolerance	Overt DM
Fasting	<100	100-125	above126
2 hr	<140	140-199	above200

Values are plasma glucose levels in mg/dL. DM, diabetes mellitus.

Timing of Delivery

Well controlled DM: at 39-40 weeks. (NICE → 38 weeks).



Mode of delivery

-Vaginal route.
-Elective CS: if EFW >4500 gm (NICE if > 4250 gm)

Glycemic control during labour

Target glucose 80-100 mg/dl . Continuous IV infusion of glucose & insulin.

Postpartum Care

-↓insulin dose to 50% of the pre-pregnancy dose.
-Breastfeeding is allowed.
-Contraception: low dose COCs, progestin only methods & sterilization.

Diabetes-Associated Maternal Complications

(1)-Diabetic Ketoacidosis (DKA) : is a metabolic emergency that can be life threatening to both mother and fetus. In pregnant patients, DKA can occur at lower blood glucose levels (i.e., less than 200-250 mg/dL) and more rapidly than in nonpregnant diabetic patients.

Although maternal death is rare with proper treatment, fetal mortality rates that range from 30% to 90% after a single episode of DKA have been reported.

Causes: Medical illness, usually an infection, is responsible for 50% of cases of DKA, 20% result from neglect of dietary or insulin therapy, or both. In 30% of cases, no precipitating cause is identified. Antenatal administration of steroids to promote fetal lung maturity can precipitate or exacerbate DKA in pregnant pregestational diabetic women.

Pathophysiology: DKA results from either a relative or an absolute deficiency of insulin and an excess of anti-insulin hormones. The resulting hyperglycemia and glucosuria lead to an osmotic diuresis, which results in the loss of urinary potassium and sodium, as well as fluid loss. Insulin deficiency increases lipolysis and therefore hepatic oxidation of fatty acids, which leads to the formation of ketones and the development of metabolic acidosis.

Diagnosis: Signs and symptoms include abdominal pain, nausea and vomiting, polydipsia, polyuria, hypotension, rapid and deep respirations, and impaired mental status, which can vary from mild drowsiness to profound lethargy. The diagnosis is made by objective documentation of maternal hyperglycemia, acidemia, ketonuria, and serum ketones. Ketoacidosis is usually defined as a plasma bicarbonate level less than 15 mEq/L and arterial pH <7.3, in the presence of hyperglycemia.

Management: Initial treatment consists of vigorous IV fluid hydration and administration of IV insulin.

One liter of normal saline should be administered in the first hour, followed by 500 to 1,000 cc per hour for 2 to 4 hours, followed by 250 ml/hr thereafter. Initial insulin therapy consists of administration of a rapid-acting insulin at 0.1 U/kg IV push (up to 0.2 to 0.4 U/kg), then an IV infusion of 2 to 10 U/hr.

If glucose levels do not decrease by 25% in the first 2 hours of treatment, the amount of insulin infused should be doubled. 5% dextrose in water (or in normal saline) should be started when glucose levels decrease to 250 mg/dl. The insulin infusion rate should be decreased to 1 to 2 U/hr when the serum glucose level decreases to 150 mg/dl or lower.
IV insulin and glucose administration should be continued until urine ketones are cleared. Potassium replacement (20 to 40 mEq/L) should be started with initial insulin therapy, unless potassium levels are above 5.5 mEq/L, or if urine output is inadequate. IV sodium bicarbonate (1 ampule, 44 meq) should be given to patients with an arterial pH <7.1.
Levels of plasma glucose should be monitored hourly, and electrolytes and arterial blood gases need to be monitored approximately every 4 hours until DKA is resolved. When the patient is able to tolerate food, her usual insulin regimen may be restarted.

(2)-Hypoglycemia: The strict glycemic control that is recommended during pregnancies, and complicated by diabetes, places patients at increased risk for hypoglycemic episodes. The presence of hyperemesis in early pregnancy also predisposes these patients to severe hypoglycemia. Up to 45% of pregnant patients with type 1 DM experience episodes of hypoglycemia serious enough to require emergency care or hospitalization. Severe hypoglycemia may have a teratogenic effect in early gestation, but the potential adverse effects on the developing fetus are not fully understood.

Symptoms of hypoglycemia include nausea, headache, diaphoresis, tremors, palpitations, sweating, blurred vision, weakness, hunger, confusion, paresthesia, and stupor.

Diagnosis: The diagnosis is made through a careful history and review of symptoms, and confirmed with a blood glucose reading of <60 mg/dl.

Treatment: If the patient is symptomatic, but otherwise alert and oriented, the level of hypoglycemia should be confirmed. Once confirmed, 4 ounces of juice, or glucose tablet, may be used. A glucose reading should be obtained 15 to 20 minutes later. This should be repeated until the glucose value increases to>70 mg/dl. Then, oral complex carbohydrates should be

given or the patient should have the scheduled meal or snack. If the patient is unable to have oral intake, an ampule of dextrose 10% should be given immediately by IV push, and IV fluids (5% dextrose with Ringer's solution or normal saline) should be started.

The Somogyi phenomenon is a rebound hyperglycemic response to an episode of hypoglycemia and is secondary to a counter-regulatory hormone release. It manifests as widely varied blood glucose levels over a short period of time (i.e., 2:00 to 6:00 A.M.), with or without symptoms.
Treatment of this phenomenon involves decreasing insulin for the critical time period (i.e., 2:00 to 6:00 A.M.).
The dawn phenomenon is an early morning increase in plasma glucose, possibly as a response to growth hormone. The treatment is an increase in bedtime insulin dosing to maintain euglycemia.
Differentiating between these two phenomena requires evaluation of a **3:00 A.M**. blood glucose level. If the patient is hypoglycemic, the Somogyi phenomenon may be in effect, and the bedtime insulin dose should be decreased. If she is euglycemic, she is appropriately treated. If she is hyperglycemic, however, she may have a dawn phenomenon, and the bedtime dose of insulin should be increased.

Early morning hyperglycemia		
	Somogyi phenomenon	**Dawn phenomenon**
Cause	↑ counter-regulatory hormones in response to hypoglycemia.	↑ in growth hormone in the early morning.
3 am blood glucose	↓↓	↑↑
TTT: NPH at bedtime	↓↓	↑↑

(3)-Retinopathy. Proliferative retinopathy is the most common manifestation of vascular disease in diabetic patients and is one of the principal causes of adult-onset blindness . Diabetic retinopathy is believed to be a direct consequence of persistent hyperglycemia and is related to the duration of the disease process. The prevalence of any form of retinopathy has been found to be approximately 2% within 2 years of onset of type 1

DM and 98% among patients who have had diabetes (types 1 or 2) for at least 15 years.

(4)-Nephropathy is a progressive renal disease characterized by increased glomerular permeability to protein, glomerular scarring, and, eventually, renal failure. Diabetic nephropathy develops slowly, appearing an average of 17 years after the onset of DM, and has an estimated prevalence of 6% among pregestational diabetic pregnant women.
Diabetic nephropathy is of particular concern in the pregnant patient because of its association with chronic hypertension, pre-eclampsia, fetal growth restriction, nonreassuring fetal well-being, preterm delivery, and perinatal death (fetal and neonatal).
The criteria for diagnosis is persistent proteinuria of more than 3 g per 24 hours (in the absence of pre-eclampsia), serum creatinine level higher than 1.5 mg/dL, hematocrit less than 25%, and hypertension with mean arterial pressure higher than 107 mm Hg. Creatinine clearance level is an important prognostic indicator because a clearance of less than 50 mL/min has been associated with a high incidence of severe pre-eclampsia and fetal loss. Patients with diabetic nephropathy require intensive maternal and fetal surveillance throughout gestation. With intensive management, a fetal survival rate of over 90% has been reported.

(5)-Atherosclerosis is present in some diabetic patients. A complete history and physical examination should be performed to elicit any evidence of ischemic heart disease, heart failure, peripheral vascular disease, or cerebral ischemia. Evaluation of a pregnant patient (over age 30) with pregestational DM should always include an ECG. A maternal echocardiogram and cardiology consultation should be obtained if clinically indicated.
Maternal mortality is increased among diabetic patients with ischemic heart disease or diabetic cardiomyopathy. Therefore, preconceptual counseling is important. If conception occurs, termination of the pregnancy may be considered to preserve the health of the patient.

(6)-Spontaneous Abortion. Spontaneous abortion among patients with pregestational DM ranges between 6% and 29% and is associated with poor

glucose control and an elevated HbA1C during the periconceptual period. No increase in incidence of abortion is found in diabetic women with good periconceptual glucose control (normal HbA1C).

(7)-Polyhydramnios is a common complication of diabetic pregnancies, with a reported incidence of 3% to 32%. The incidence of polyhydramnios in diabetic patients is 30 times than that in nondiabetic controls.
Diabetes alone is the leading known cause of polyhydramnios, followed by fetal abnormalities of the central nervous system (CNS) and gastrointestinal (GI) system. The pathogenesis of polyhydramnios is **not** clear.
Proposed mechanisms include increased fetal glycemic loads, decreased fetal swallowing, fetal GI obstructions, and fetal polyuria secondary to hyperglycemia. Higher perinatal morbidity and mortality rates have been associated with polyhydramnios.
These higher rates can be attributed, in part, to the increased incidence of congenital anomalies and preterm delivery associated with this condition.

(8)-Chronic Hypertension and Pre-eclampsia. The incidence of chronic hypertension is increased in pregnant patients with pregestational DM, particularly in those with diabetic nephropathy. Limited activity, sodium restriction, and antihypertensive therapy are the principal management strategies. Affected patients must be monitored carefully after 24 weeks' gestation for the potential development of pre-eclampsia, fetal growth restriction, and fetal death.
ECG and a 24-hour urine collection for total protein and creatinine clearance should be obtained on any pregnancy complicated by chronic hypertension.
Many antihypertensive medications are safe to use during pregnancy. Therefore, only those medications that are contraindicated during pregnancy (i.e., ACE inhibitors) should be discontinued. The fetus must be evaluated carefully during the third trimester (and second trimester, if indicated), with fetal growth sonograms and fluid status, S/D ratio, and fetal heart reactivity assessed.

Fetal & neonatal complications

Complications during the neonatal period are increased in infants of mothers with both gestational and pregestational DM. The incidence of complications, however, is much higher among infants of patients with pregestational DM, especially those with poor glycemic control, than among those of mothers with GDM.

(1)-Congenital Malformations: Congenital malformations are the most common contributor to perinatal mortality in pregnancies of women with pregestational DM. The incidence is linked to periconceptional diabetic control and correlates with the level of HbA1C. About 30% to 50% of perinatal mortality in diabetic pregnancies can be attributed to congenital malformations.

Skeletal: Sacral Agenesis/Caudal Regression. The single defect that is closest to being pathognomonic for diabetic fetopathy is sacral agenesis or caudal regression. This rare malformation is diagnosed up to 400 times more frequently in pregnancies complicated by diabetes.

Cardiovascular anomalies: the most common congenital malformations in diabetic pregnancies, are increased fivefold in fetuses of diabetic patients. Defects include transposition of the great vessels, ventricular and atrial septal defects, hypoplastic left ventricle, situs inversus, aortic anomalies, and complex anomalies. Fetal septal hypertrophy is associated with poorly controlled diabetes and is diagnosed in the second half of pregnancy.

CNS: A 10-fold increase is seen in the incidence of CNS malformations, including anencephaly, holoprosencephaly, open spina bifida, microcephaly, encephalocele, and meningomyelocele.

GIT: Malformations of the GI system are also found, including tracheoesophageal fistula, bowel atresia, and imperforate anus.

Genitourinary (GU) System: GU anomalies include absent kidneys (Potter's syndrome), polycystic kidneys, and double ureters.

(2)-Macrosomia is defined as an estimated fetal weight >90th percentile, or 4,000 g, and occurs much more frequently in pregnancies of diabetic women than in nondiabetic women (25% to 42% versus 8% to 14%).

Maternal diabetes is the most significant single risk factor for the development of macrosomia. Diabetic macrosomia is characterized specifically by a large fetal abdominal circumference and a decrease in the ratio of head circumference to abdominal circumference.
These changes are due to the increased subcutaneous fat deposits caused by fetal hyperinsulinemia. Insulin is anabolic hormone which causes more formation of glycogen, fat and protein resulting in increase in body fat, muscle mass and organomegaly (except the brain and kidneys).
Macrosomic fetuses are at risk of intrauterine death, hypertrophic cardiomyopathy, vascular thrombosis, neonatal hypoglycemia, and birth trauma. Macrosomic infants are at increased risk for shoulder dystocia with fractured clavicles, facial paralysis, Erb's palsy, Klumpke's palsy, phrenic nerve injury, and intracranial hemorrhage.

(3)-Neonatal Hypoglycemia. Twenty-five percent to 40% of infants of diabetic mothers develop hypoglycemia during the first few hours of life. The nadir for neonatal hypoglycemia occurs at 24 hours of life. Poor maternal glycemic control during pregnancy and elevated maternal glucose levels at the time of delivery increase the risk of neonatal hypoglycemia. This involves the stimulation in utero of the fetal pancreas by significant maternal hyperglycemia. This leads to fetal islet cell hypertrophy and beta-cell hyperplasia. When the transplacental source of glucose is eliminated, the newborn exhibits overproduction of insulin. The clinical signs of neonatal hypoglycemia include cyanosis, convulsions, tremor, apathy, sweating, and a weak or high-pitched cry. Severe or prolonged hypoglycemia is associated with neurologic sequelae and death. Treatment should be instituted when the infant's glucose level drops below 40 mg/dL.
(4)-Neonatal Hypocalcemia and Hypomagnesemia: Alterations in mineral metabolism are common in infants of diabetic mothers. These alterations are related to the degree of maternal glycemic control.
(5)-Neonatal Polycythemia: Thirty-three percent of infants born to diabetic mothers are polycythemic (hematocrit higher than 65%). Chronic intrauterine hypoxia leads to an increase in erythropoietin production, with a resultant increase in red blood cell production. Alternatively, elevated glucose may lead to early and increased red blood cell destruction, followed

by increased erythrocyte production.

(6)-Neonatal hyperbilirubinemia and neonatal jaundice occur more commonly in the infants of diabetic mothers than in infants of nondiabetic patients of comparable gestational age. The reason is a delay in in-utero liver maturation among infants of diabetic mothers with poor glycemic control.

(7)-RDS in infants of diabetic mothers is associated with delayed fetal lung maturation. Fetal hyperinsulinemia is thought to suppress production and secretion of the major component of surfactant required for inflation of the lungs.

(8)-Fetal and Neonatal Cardiomyopathy

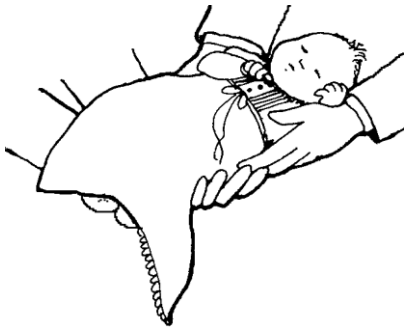
Infants of diabetic mothers are at increased risk of developing cardiac septal hypertrophy and congestive heart failure (CHF). One study reported that up to 10% of these infants have evidence of hypertrophic changes. A strong correlation between the increased risk of cardiomyopathy and poor maternal glycemic control has been documented. As an isolated finding, cardiac septal hypertrophy is a benign neonatal condition. However, it increases the risk of neonatal morbidity and mortality in infants with sepsis or congenital structural heart disease.

●Infant of Diabetic mother

(1)-Weight: *large* for GA (macrosomic) or *small* for GA (if there is maternal microvascular disease).

(2)- Colour: *plethoric* (due to polycythemia from intrauterine hypoxia), *cyanosed* (due to RDS) or *jaundiced* (due to prematurity, enzyme deficiency, birth trauma with hematoma formation).

(3)-Laboratory investigations: hypoglycemia, hypocalcemia , hypomagnesemia and hyperbilirubinemia.



Thyroid disease in Pregnancy

Physiological Background

The circulating thyroid hormones are thyroxine (T4) and triiodothyronine (T3), of which only the free portions (f), fT4 and fT3, are active.
The biologically more important fT3 is formed mainly peripherally in the liver, kidneys and muscle, where it is converted from fT4 by de-iodinase enzymes.
Most tissues, including heart, brain and muscle, have specific nuclear receptors for fT3 by which metabolic and cellular activities can be influenced.
In normal circumstances, the anterior pituitary gland produces thyroid stimulating hormone (TSH) as part of a negative feedback loop controlled by fT3 concentration.
Dietary iodine is essential for thyroid hormone synthesis.

In the fetus, the pituitary–thyroid axis is controlled in a very similar way, with iodine supplied transplacentally.
-Prior to 12 weeks' gestation, maternal thyroxine (but not fT3) crosses the placenta. Following binding to receptors in fetal brain cells, thyroxine is converted intra-cellularly to fT3, a process thought to be important for normal fetal brain development.
-From 12 weeks onwards, placental changes prevent significant passage of maternal thyroxine and fetal thyroid function is controlled independently of the mother, provided that her iodine intake is adequate.

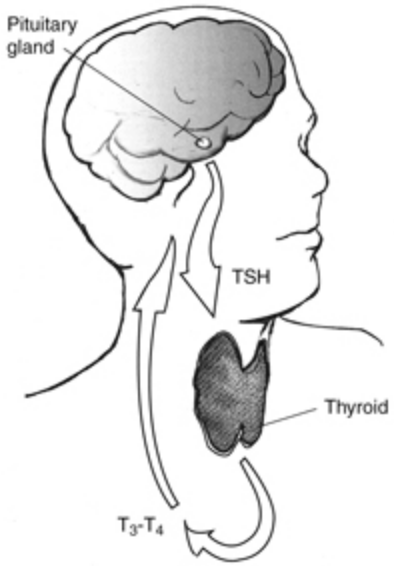
Four important pregnancy-specific changes occur:
1.The half-life of thyroxine binding globulin extends from 15 minutes to 3 days and its concentration triples by 20 weeks of gestation, as the result of estrogen-driven glycosylation.
Total thyroid hormone levels increase and, therefore, measurements of total T4 and total T3 are not reliable in pregnancy, fT4 and fT3 remain relatively constant and are the tests of choice in pregnancy: they should be interpreted in relation to pregnancy-specific reference ranges.
2. Human chorionic gonadotrophin (hCG) and thyroid stimulating hormone

(TSH) have similar alpha subunits and receptors.
In the first trimester a hormone spillover syndrome can occur in which hCG stimulates the TSH receptor and gives a biochemical picture of hyperthyroidism. This is particularly common in multiple pregnancy, gestational trophoblastic disease and hyperemesis gravidarum , where concentrations of both total hCG and thyrotropic subtypes can be greater. Thyroid function tests should be interpreted with great caution in these circumstances.
3. Increased glomerular filtration and greater uptake of iodine into the thyroid gland driven by increased total thyroxine concentration can deplete iodine and cause or worsen iodine deficiency.
Transplacental transfer can also exacerbate this but when there is severe maternal iodine deficiency, maternal iodine trapping overrides fetal needs, resulting in cretinism.
4. Three de-iodinase hormones control metabolism of T4to the more active T3 and their breakdown to inactive compounds.The concentration of deiodinase III increases in the placenta with gestation, releasing iodine where it is required for transport to the fetus and, possibly, contributing to reduced thyroxine transfer.

In conclusion:

(1)-Thyroid-Binding Globulin(TBG): increased due to increase its synthesis by the liver secondary to estrogen rise.
(2)-TSH: not affected by pregnancy as it is not bound to protein and does not cross the placenta.
(3)-Thyroxine (T4) and Triiodothyronine (T3) levels:
-Total T3&T4 levels are increased secondary to rise in TBG.
-Free T3 & T4 are unchanged.
(4)-Manifestations that mimic thyrotoxicosis: tachycardia, palpitation, warm extremities and mild thyromegaly (due to relative iodine deficiency secondary to active transport of iodine to the fetus as well as increased ioine excretion in urine).

-Total T3 & T4 levels and TBG are increased.
-Free T3 & T4 are unchanged.



TSH: NOT changed
-Can't cross the placenta.
-Not protein bound.

Before 12 weeks

fT3 is needed for normal brain development in the 1st trimester.

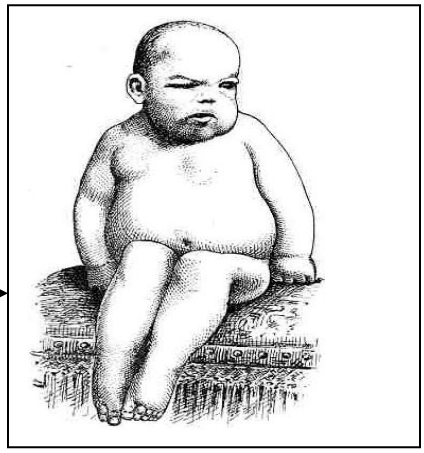
-fT4 crosses the placenta before 12 weeks' gestation.
-After 12 weeks' gestation, only iodine passes to the fetus.

At 12 weeks onwards

Iodine is needed for normal development in the 2nd trimester for:
-Cerebral neocortex (most sensitive).
-Basal ganglia.
-Cochlea (inner ear).

The fetal thyroid gland starts to secrete T3 & T4 at 12 weeks.

Iodine deficiency:
-Cerebral neocortex→ mental handicap.
-Basal ganglia→ spastic motor disorder.
-Cochlea→ deaf-mutism.



Hypothyroidism

Incidence:

Occurs in around 1% of pregnant women. Most cases have been already diagnosed before pregnancy and will be on thyroxine therapy as severe untreated hypothyroidism is associated with anovulation and infertility.

Aetiology:

-Primary hypothyroidism:

(1)-Hashimoto's autoimmune thyroiditis: the commonest cause.

(2)- Treatment of hyperthyroidism: antithyroid drugs, radioactive iodine or surgery.

(3)-Others: iodine deficiency or ingestion of goitrogens as thiocyanates & lithium.

-Secondary hypothyroidism:

Secondary to hypothalamic or pituitary disease as in case of Sheehan syndrome & chromophobe adenoma

Symptoms:

Constipation, tiredness, weight gain and hair thinning resembling common features of normal pregnancy. The most discriminatory features in pregnancy are cold intolerance, slow pulse rate and delayed relaxation of tendon reflexes.

Diagnosis:

There can be confusion between women with:

• **Untreated hypothyroidism** (low fT4, highTSH, often symptomatic) : who require urgent initiation of treatment with thyroxine

• **Previously diagnosed hypothyroidism :** who may be on optimal therapy (normal fT4 and TSH) at conception or who may not (low fT4, high TSH): in the latter, rapid achievement of euthyroidism is important, particularly in the first trimester.

• **Subclinical hypothyroidism** (normal fT4, raised TSH, asymptomatic) in whom the place of thyroxine therapy is debatable

Effect of hypothyroidism on pregnancy:

I. Maternal complications: There is increased risk of abortion & PTL.
II. Fetal complications: Affection of the fetal brain development leading to mental retardation and reduced intelligence quotient (IQ) and diminished school performance.

Treatment:

- It is important to decide the targets of treatment in pregnancy. From a fetal perspective, maternal thyroxine concentrations do not have a major impact on fetal thyroid function beyond the first trimester.
- Factors that could influence thyroxine dosage during pregnancy must be considered which include:
• Reduced absorption in the first trimester related to nausea and vomiting.
• Malabsorption resulting from binding of thyroxine to newly-commenced iron and calcium supplements
• Suboptimal control prior to conception or altered compliance, with either an improvement, resulting in an apparent need to reduce the dosage, or a deterioration (perhaps from false concerns of safety), resulting in apparent need to increase the dosage.
- Finally, the therapeutic window of thyroxine is broad, with dose adjustments usually of 25 or 50 micrograms daily.

Remarks:

Overall, for women with under- or untreated hypothyroidism, optimal replacement doses should be reached prior to conception or early in the first trimester.
Some women with established hypothyroidism need to increase their dose of thyroxine during pregnancy to maintain euthyroidism according to trimester-specific ranges but only first trimester control influences fetal wellbeing.
For women with hypothyroidism who intend to become pregnant and who are on the correct dose of thyroxine, thyroid testing is needed only pre-pregnancy, early in the first trimester and again later in the second or third trimester.

Hyperthyroidism

Incidence:
Autoimmune thyrotoxicosis or Graves'disease affects around 2 per 1000 (0.2 %) pregnancies.

Aetiology:
(1)-Grave's disease (85%).
(2)- Toxic nodular goitre , toxic adenoma, thyroiditis or a carcinoma.
(3)-Prenancy causes: pregnant women present with hyperthyroidism , hyperemesis or molar pregnancy must be considered. About 40% of women with hyperemesis gravidarum have elevated T4 and suppressed , they don not require antithyroid treatment as this usually resolve by 20 weeks gestation.
(4)-Struma ovarii which is ovarian teratoma composed mainly of thyroid tissue.

Complications of hyperthyroidism:

Maternal	**Fetal**
Thyroid storm	Fetal growth restriction
Congestive cardiac failure	Prematurity
Pre-eclampsia	Stillbirth

Symptoms:

Heat intolerance, increased appetite, sweating, palpitations and tachycardia resembling common features of normal pregnancy. Failure to gain weight, despite a good appetite, and tachycardia greater than 100 beats per minute that fails to slow with the Valsalva manoeuvre, are good indicators of thyrotoxicosis, as is the rare finding of onycholysis (elevation of the distal nail bed).
Eye signs and pretibial myxoedema do not reflect disease activity.

Diagnosis:
Thyroid function should be measured monthly when control is good and more frequently when the diagnosis is new or there is a relapse.

Treatment:

The main goal is to ensure euthyroidism is achieved as early as possible in pregnancy, preferably prior to conception, as this minimises the likelihood of maternal or fetal complications.

Beta blockade, usually with propranolol hydrochloride and the antithyroid agents carbimazole or propylthiouracil are usually used during pregnancy.

The antithyroid agents These block thyroid hormone synthesis and have an immunosuppressive effect, reducing the titre of TSH receptor stimulating antibodies and, thereby, directly influencing the course of the disease.

As both of these drugs cross the placenta in similar amounts, it is important that the lowest effective dose is used to minimise the risk of fetal hypothyroidism. Clinical disease activity follows the titre of TSH receptor stimulating antibodies, which rises in the first trimester and puerperium and falls in the second and third trimesters. Most women can, therefore, reduce their dose and almost one-third of women can stop treatment during pregnancy, which helps prevent fetal hypothyroidism. Most women will need to restart or increase their dose in the puerperium to avoid a relapse.

Propylthiouracil or carbimazole?

Propylthiouracil is more heavily protein-bound than carbimazole , it was less likely to be transferred across the placenta and should, therefore, be the agent of choice.

carbimazole causes aplasia cutis congenita of the scalp in the infant, a rare congenital defect affecting 0.03% of the general population. This association is either spurious or, at most, extremely rare and should not influence the choice of drug in pregnancy. No other teratogenesis has been linked with antithyroid drugs. Both drugs cause agranulocytosis and pregnant women should be reminded to report a sore throat immediately. This reaction is unpredictable and is a reason not to change agent routinely during pregnancy. No differences in fetal thyroid function were found in babies whose mothers were taking one or other of the agents.

Lactation is the period when there is some difference between the drugs. There are concerns that high doses, especially of carbimazole, could cause neonatal hypothyroidism. Doses should, therefore, be split through the day,

with feeding to occur before a dose when possible, monitoring of neonatal thyroid function and regular consideration given to switching to propylthiouracil.

Recent guidelines, both drugs probably cross the placenta in the same proportion and there is no need to change from carbimazole to PTU, both drugs are expressed in the breast milk , but have little effect on thyroid function.

Beta Blockade with propranolol to early control of symptoms or during relapse to improve symptoms of tachycardia, sweating and tremors keeping the resting pulse rate below 100/min.
It decreases the peripheral response to thyroid hormones and decreases the conversion of T4 to T3.
Its hazards include IUGR & neonatal hyperbilirubinemia.

Thyroid surgery or Radioactive iodine?
Thyroid surgery can be carried out in pregnancy if required, most usually in the second trimester.
Indications include: compression from a large goitre, suspicion of malignancy and failed antithyroid therapy. Surgery may be more challenging than usual because of the pregnancy- associated increase in the vascularity of the thyroid and so should only be undertaken by an experienced thyroid surgeon and when truly indicated.
Radioactive iodine crosses the placenta and binds to and destroys the fetal thyroid. It is totally contraindicated in pregnancy.
Lactation should be stopped (preferably 4 weeks prior to treatment) if it is given in the puerperium.
Also, pregnancy must be postponed for at least 4 months after TTT with radioactive iodine for fear of teraratogenicity. If pregnancy occurs earlier, therapeutic abortion should be considered.

Fetal and neonatal consequences of thyrotoxicosis
Fetal or neonatal problems relating to well- controlled Graves'disease are rare. However, TSH receptor stimulating antibodies cross the placenta and

the risk of fetal Graves'disease after 20 weeks (the gestational age at which the fetal thyroid can respond to these antibodies) is directly proportional to their titre (although even at the highest titres,the risk is very low).
It is very important that women who have had Graves'disease in the past treated by surgery or radioactive iodine, as well as those actively being treated for the condition during pregnancy, have this antibody measured. Women with positive results should be monitored for signs of fetal thyrotoxicosis, including tachycardia, excessive movements, fetal growth restriction, oligohydramnios and goiter.
Fetal Graves' disease can cause premature delivery in untreated women and, in addition to the features above, can be accompanied by any of the following:
-Craniosynostosis and associated intellectual impairment.
-Hydrops fetalis.
-Intrauterine death.
-Polyhydramnios related to oesophageal pressure
-Obstructed labour from neck extension related to goitre.

Management is usually based on delivery if the gestational age is sufficiently advanced. If this is not appropriate, high doses of propylthiouracil or carbimazole should be given to the mother and the response titrated against the fetal heart rate; the pregnant woman can take thyroxine if she becomes clinically hypothyroid and this will not cross the placenta. Although fetal reference ranges for thyroid function are known, fetal blood sampling is not routinely needed unless the diagnosis is in doubt. At delivery, thyroid function should be measured using cord blood. Rarely, hypothyroidism is reported secondary to transplacental passage of antithyroid drugs but this is usually self-limiting. Hyperthyroidism is also occasionally detected, although this more typically presents 7–10 days postnatally , since the half-life of maternally-derived antithyroid drugs is shorter than that of TSH receptor antibodies.
In practice, parents should be warned to look for changes in their baby, such as weight loss or deteriorating, poor feeding, and local procedures should be followed for paediatric involvement. Neonatal treatment, when required, rarely lasts for more than a few months.

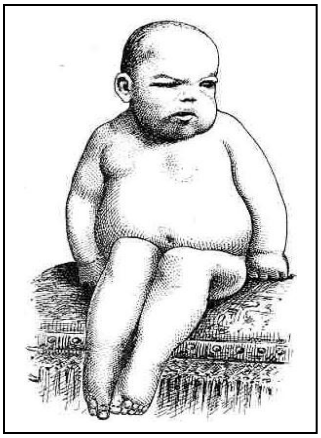
Iodine deficiency

Worldwide, neurological cretinism is the leading preventable cause of mental handicap. It affects 2–10% of people in iodine deficient areas and causes mild mental handicap in a further 10–50%, such that the IQ distribution curve is moved 10 points to the left with a significant negative impact on the economy of afflicted regions.

The developing cochlea, cerebral neocortex and basal ganglia are most sensitive to iodine deficiency, especially in the second trimester, resulting in deaf-mutism, intellectual deficiency and spastic motor disorder. Less severe maternal iodine deprivation spares hearing, speech and motor function but causes mental handicap (myxoedematous cretinism), presumably because the mother is able to transfer enough T4 and iodine and the fetus is subsequently able to make enough T3 to protect these functions.

Iodine administration prior to conception or up to the second trimester can protect the fetal brain and, when given early enough,reduce miscarriage and later pregnancy losses.

Programs to deliver annual boluses of iodine to susceptible women to iodinate flour, salt or water continue to increase.



Postpartum Thyroiditis

Definition:

Postpartum thyroiditis can occur up to one year following delivery and can manifest as high or low T4.

Incidence:

variable being as low as 1-2% in USA and as high as 17% in Wales.

Aetiology:

The condition is thought to be autoimmune and presents postpartum following a return to normal immunity after delivery.

Clinical manifestations:

The disease may present initially between 1 and 3 months postpartum with

thyrotoxicosis and later with hypothyroidism. Usually a symptomatic. If symptomatic with hyperthyroidism, beta blockers but NOT antithyroid drugs can be used. If symptomatic with hypothyroidism which is more common presentation, the patient complains of tiredness, cold intolerance and even goiter, a course of thyroxin may be given.

Investigations:

(1)-Thyroid function tests.

(2)-Serology: 90% of women will have positive thyroid antiperoxidase antibodies.

(3)-Radioactive iodine or technetium uptake tests: shows low uptake in thyroiditis but high uptake in Grave's disease.But lactation should be stopped during testing.

(4)-Thyroid biopsy: suggests chronic thyroiditis with lymphocytic infilteration but no fibrosis (which is a typical feature of Hashimoto's thyroiditis).

Prognosis:

The condition will recur in 70% of future pregnancies and women should be followed up by annual thyroid functions to ensure that permanent hypothyroidism does not occur.

Thyroid cancer in Pregnancy

Thyroid cancer is more common in women, and 50% of cases occur within the reproductive age group.

If a pregnant woman presents with thyroid nodule, thyroid functions tests, an ultrasound and fine needle aspiration cytology should be performed.

Thyroidectomy can be performed safely in the second trimester of pregnancy. Radioactive iodine is contraindicated during pregnancy.

Thyroid globulin concentration can NOT be used to detect a relapse of thyroid cancer in pregnancy as it is already elevated.

Thyroid disease in Pregnancy

Hypothyroidism	Hyperthyroidism
-Psychosis, cold intolerance, ↓ intellectual performance. -Hair loss, puffiness of eyes, expressionless features, hoarse voice & large tongue.	-Emotional lability, heat intolerance, anxiety, headache, tremors. -Hair is soft & silky, ophthalmopathy (eye signs) and fatigue.
CVS: cardiomegaly, pericardial effusion & cardiomyopathy	CVS: tachycardia, palpitations, arrhythmias & heart failure.
GIT: constipation & moderate weight gain.	GIT: diarrhea & weight loss.
Skin: pale, cold, thin & dry.	Skin: warm & sweaty (diaphoresis).
Muscle cramps, myopathy & delayed relaxation of tendon reflexes.	Pretibial myxedema & fine tremors.

Indications of screening

-Personal history of a thyroid disorder
-Family history of a thyroid disorder
-Goitre
-History of positive thyroid antibodies
-Symptoms/signs of thyroid hypo/hyperfunction
-History of type 1 diabetes mellitus
-History of other autoimmune disorders
-Infertility
-History of head/neck irradiation
-History of miscarriage or preterm delivery

Renal Disease and Pregnancy

Anatomic changes during pregnancy

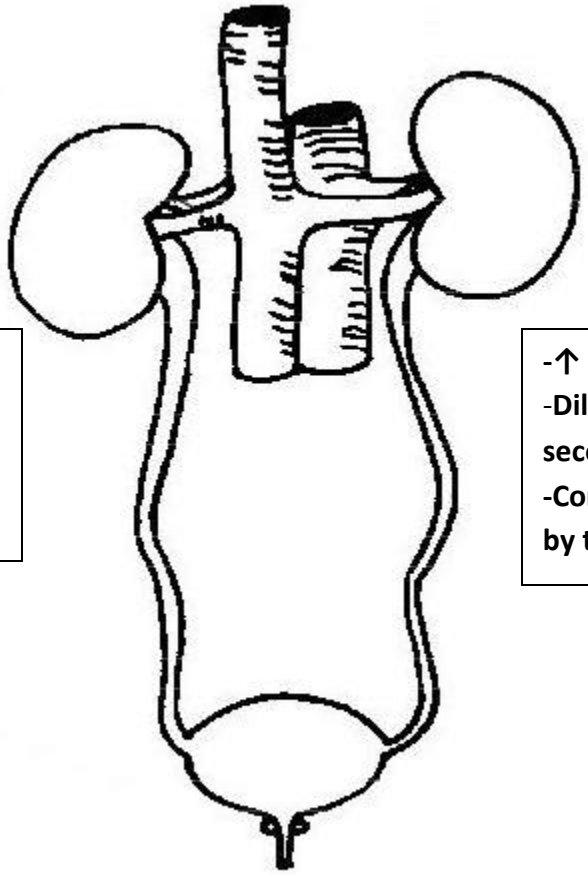
The anatomic changes are primarily in the collecting system. A dilatation of the ureters and pelvis occurs and is presumed to be secondary to the smooth muscle–relaxing effect of progesterone. This dilatation is often more pronounced on the right secondary to dextrorotation of the uterus and dilatation of the right ovarian venous plexus. This can lead to urinary stasis and an increased risk of developing urinary tract infections (UTIs).
There is also an increase in overall kidney size by about 1-1.5 cm.
As a rule, all the physiologic changes maximize by the end of the second trimester and then start to return to the prepregnancy level, whereas changes in the anatomy take up to 3 months postpartum to subside.

Physiologic and hemodynamic changes in pregnancy

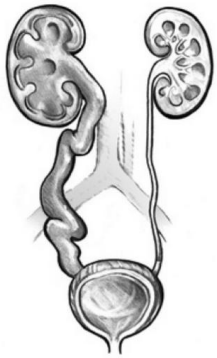
(1)-The kidneys increase by about 1-1.5 cm during pregnancy.
(2)-Renal plasma flow increases by 50-70% in pregnancy (in the first two trimesters) → increased glomerular filtration rate (GFR), reaching up to 150% of its normal level.
(3)-The plasma creatinine falls (not greater than 0.8 mg/dl during pregnancy).
(4)-Blood pressure falls shortly after conception due to peripheral vasodilation, mediated by nitric oxide synthesis and relaxin, and is resistance to the action of angiotensin II. There is a compensatory increase in heart rate and activation of the renin-angiotensin-aldosterone axis. Blood volume increases by 20%, and sodium retention of up to 900 mEq occurs. While edema may therefore be benign in pregnancy, blood pressure greater than 120/80 mm Hg is usually not normal.
(5)-The increased GFR increases urate clearance, lowering serum uric acid values, and there is an increased filter load of glucose, which may result in renal glycosuria.
(6)-Increased ventilation in pregnancy also causes a chronic respiratory alkalosis and an appropriate fall in the serum bicarbonate value.

Effects of progesterone also result in a state of mild respiratory alkalosis and a blood gas of 7.44/30 pCO_2/HCO3 of 22 is representative.

-↑ Renal blood flow (50-70%).
-↑ GFR.
-↓ Urea, creatinine & uric acid.



-↑ Kidney size.
-Dilatation (hydroureter) secondary to progesterone.
-Compression on the ureters by the uterus esp on Rt side.



Acute renal failure in pregnancy

I. Renal failure in early pregnancy

Pre-renal azotemia

-Hyperemesis gravidarum secondary to dehydration.

-Bleeding in early pregnancy: spontaneous abortion & ectopic pregnancy.

Acute tubular necrosis

Septic abortion, most commonly due to *Escherichia coli*; in some cases, however, *Clostridium*, which can cause myonecrosis of the uterus and myoglobinuria, is responsible.

Renal Cortical Necrosis

The disorder is most likely initiated by primary disseminated intravascular coagulation in the setting of severe renal ischemia.

II. Renal failure in late pregnancy

Acute tubular necrosis

It can arise in late pregnancy, it most commonly results from preeclampsia, HELLP syndrome or with abruptio placentae.

Acute fatty liver of pregnancy

This rare disorder is characterized by the onset of abdominal pain and jaundice, typically occurring after week 34 of gestation.

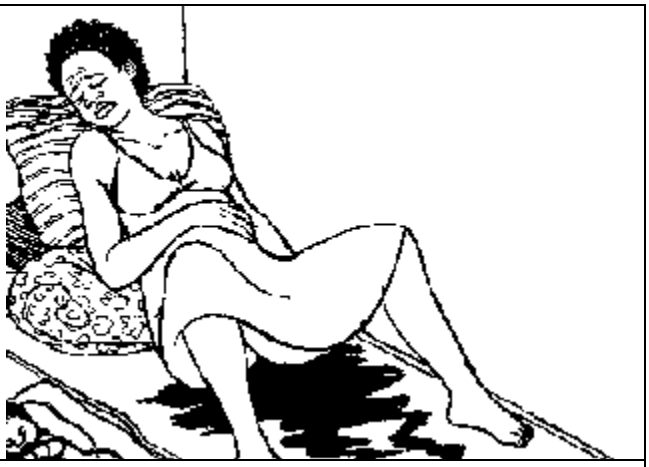
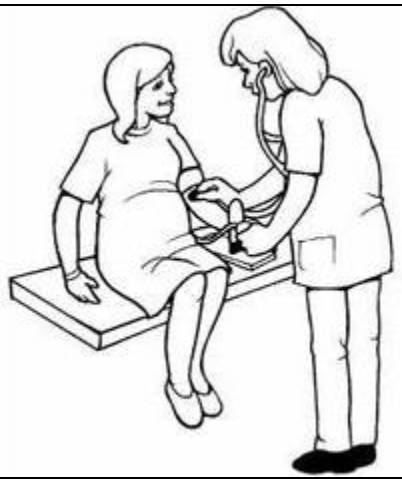
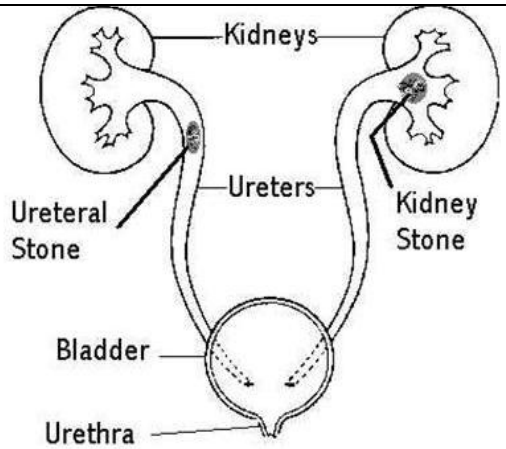
III. Postpartum renal failure

This condition represents overlapping syndromes that have in common severe hypertension, microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure.

IV. Other causes:

Obstructive Uropathy

Aetiologies of obstructive uropathy include gravid uterus, polyhydramnios, kidney stones, and enlarged uterine fibroids.

	
Hyperemesis gravidarum	**Major obstetric hemorrhage**
	
Hypertensive disorders	**Kidney stones**

Common causes of acute renal failure during pregnancy

Pregnancy in women with underlying chronic kidney disease

Causes:

Glomerular diseases: Membranoproliferative glomerulonephritis, focal glomerulosclerosis, and reflux nephropathy.

Polycystic kidney disease: Women with this disorder who are hypertensive have a high risk for poor outcome, but women who are normo-tensive with mild kidney disease usually have uncomplicated pregnancies.

Systemic lupus erythematosus: The best outcomes occur in women who have had stable, inactive lupus for 6 months or longer prior to conception.

Diabetes mellitus: Pregnant women with diabetic nephropathy may also develop worsening proteinuria and hypertension.

Effect of pregnancy on renal function

- Renal function is most likely preserved, especially with mild renal insufficiency.
- Patients with moderate or severe renal insufficiency were much more likely to have accelerated renal impairment. About 20% of pregnant patients with moderate renal insufficiency (serum creatinine level 1.5-2.4 mg/dl) progressed to end-stage renal disease (ESRD).
  Severe renal insufficiency (serum creatinine level >2.5 mg/dl) progressed to ESRD within a year after delivery in 45% of patients.

Worsening of the Renal functions occurs secondary to:

(1)-↑ in renal blood flow → ↑ arteriolar dilatation → ↓ GFR (diseased glomeruli).

(2)-Pressure on the ureters → hydroureter & hydronephrosis.

(3)-↑ liability to infections secondary to stasis & ↓ immunity.

Prognosis:

Depends on the degree of functional impairement and the presence or absence of hypertension &/or proteinuria prior to pregnancy NOT on the nature of underlying renal disease.

Poor prognostic factors:

(1)-Worsening of hypertension &/or proteinuria.

(2)-Occurance of lupus flares or poor glycemic control.

(3)-Recurrent UTIs.

(4)-Use of immunosuppressive drugs.

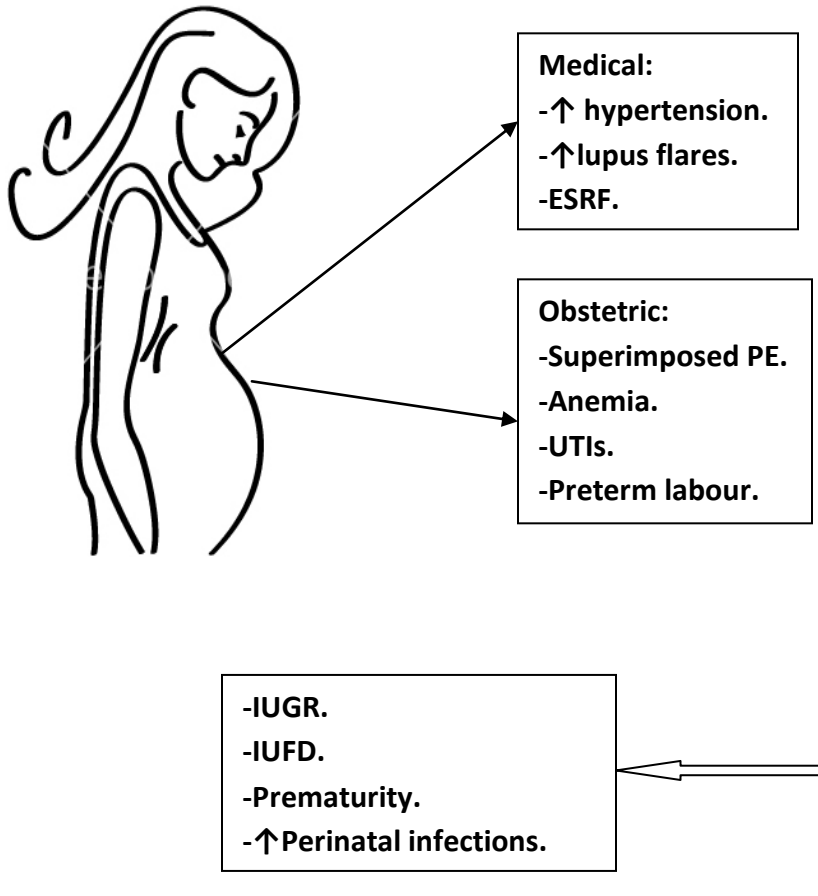
Effect of renal impairement on pregnancy

I. Maternal complications:

-Medical:↑ hypertension, lupus flares & ESRF.

-Obstetric: superimposed PE, anemia, UTIs, PTL (spontaneous & iatrogenic).

II. Fetal complications: in general, fetal survival rates are good, approaching 95% in most studies. The success rate of pregnancy is no better than 52% in dialysis patients. Complications including SGA infants, preterm labour, stillbirth and ↑ perinatal fetal infections.



Management of women with kidney failure in pregnancy

I. Pre-pregnancy Care:

-Optimization of the maternal condition.
-Review of medications and stoppage of teratogenic drugs e.g. ACEIs, ARBs & cyclophosphamide.
-Correction of anemia by erythropoietin.
-Nutritional consultation.
-Prerequisites before pregnancy in women with renal transplantation.

II. Antenatal Care:

-Frequency of visits: bi-weekly till 24-28 weeks then weekly thereafter.
-Conducted by obstetrician & nephrologist.
-Maternal surveillance: repeated renal functions.
-Fetal surveillance: tests for growth & well-being.

Patients are classically considered in three categories:

(1)- *Preserved or only mildly impaired renal function:* serum creatinine 1.4 mg/dl (124mmol/L) and no hypertension.
(2)- *Moderate renal insufficiency:* serum creatinine 1.5–3.0 mg/dl or 133–275mmol/L (some use 2.5mg/dl or 221 mmol/L as the cut-off).
(3)- *Severe renal insufficiency :* serum creatinine ≥3mg/dl or 275mmol/L.

Management is best undertaken at a tertiary care center under the coordinated care of a maternal–fetal medicine specialist and a nephrologist. The initial laboratory tests should include specialized tests, which help in the early detection of renal functional loss as well as superimposed pre-eclampsia.

1. Serum creatinine, its timed clearance and 24-hour protein excretion: monitors for change in function.
2. Blood urea nitrogen, albumin, and cholesterol concentrations: important in regard to nephrotic complications.
3. Electrolytes, to control for osmolar, potassium, and acid–base homeostasis; urine analysis; and more frequent screening for bacterial

culture .
4. Uric acid levels, aspartate and alanine aminotransferases, lactic dehydrogenase, prothrombin time, activated partial thromboplastin time, and platelet count (superimposed pre-eclampsia screening tests) should also be determined.

Dialysis - Early dialysis is necessary in pregnant women and should be considered when the serum creatinine reaches 3.5 mg/dl or the GFR is less than 20 ml/min.

- Longer, more frequent dialysis (20 hrs/week) is associated with the best fetal outcome. Hemodialysis may therefore be necessary at least 5 days per week
- Careful avoidance of hypotension is important.
- Peritoneal dialysis with smaller volumes and frequent exchanges is another option.
- Premature labour and fetal size that is small for the fetus' gestational age are typical in women who deliver on dialysis.
- Anemia should be treated with erythropoietin and careful attention to iron therapy.
- Nutritional support that allows weight gains of 0.3 to 0.5 kg/wk should be maintained in the second and third trimesters
- While the spontaneous abortion rate is approximately 50% for pregnant women who require dialysis, the fetal survival rate for pregnancies that continue is as high as 71%.

Transplantation - This procedure restores fertility, and while most women with kidney transplants can deliver successfully, there is a higher risk of miscarriage, therapeutic abortion, stillbirth, ectopic pregnancy, preterm birth, low birthweight babies, and neonatal death.

Guidelines for pregnancy in kidney transplant recipient:

-Two years post-transplant, with good general health and serum creatinine less than 2.0 mg/dl (preferably <1.5 mg/dl).
-No recent or ongoing graft rejection.

-Normotension, or minimal antihypertensives.
-Absent or minimal proteinuria .
-No evidence of pelvi-calyceal dilation on renal ultrasonogram.

Immunosuppression

-Prednisone - Less than 15 mg per day
-Azathioprine - Less than or equal to 2 mg/kg/d.
-Calcineurin inhibitor–based therapy - Therapeutic levels.
-Mycophenolate mofetil and sirolimus - Discontinue 6 weeks prior to conception.
-Methylprednisolone - The preferred agent for treatment of rejection during pregnancy.

Complication Risks

- Immunosuppressive agents increase the risk of hypertension during pregnancy.
- Preeclampsia occurs in approximately one-third of transplant recipients.
- Almost 50% of pregnancies in these women end in preterm delivery due to hypertension.
- Blood levels of calcineurin inhibitors need to be frequently monitored due to changes in volumes of distribution of extracellular volume.
- There is an increased risk of cytomegalovirus, toxoplasmosis, and herpes infections, which arouse concern for the fetus.

Obstetric management

Timing of delivery:
The literature reflects a debate about elective early delivery (34-36 wk) in patients with chronic renal insufficiency or those receiving dialysis, especially when fetal lung maturity is present. In patients who have had a transplant, however, delaying delivery until the onset of labour is generally

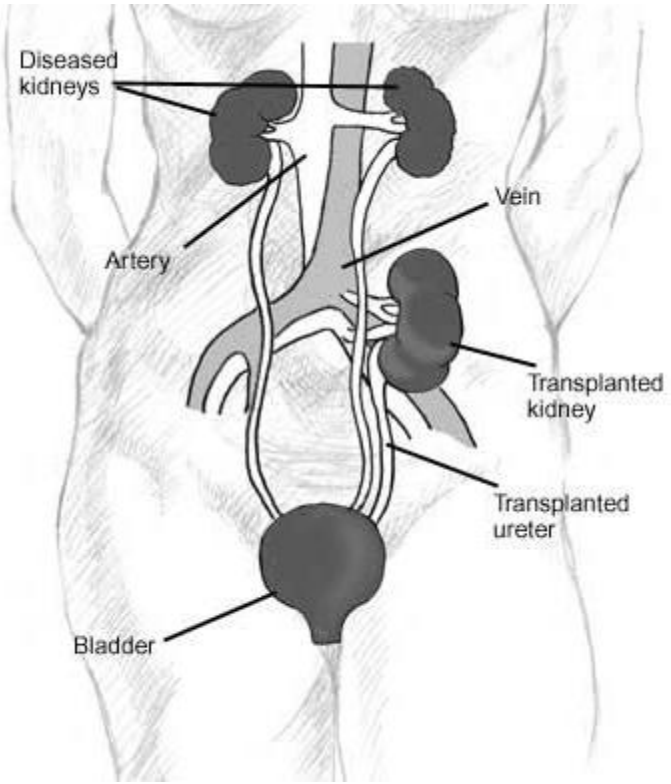
thought to be the most prudent step, provided, of course, that the mother and fetus show no signs of distress.

Mode of delivery:

By elective CS in most cases.

Prerequisites:

-Two years after transplant.
-Good general health.
-Serum creatinine < 2mg/dl (better < 1.5 mg/dl).
-No graft rejection.
-Absent or minimal proteinuria.
-Absent or mild hypertension.
-Prednisone or prednisolone as immunosuppressive.

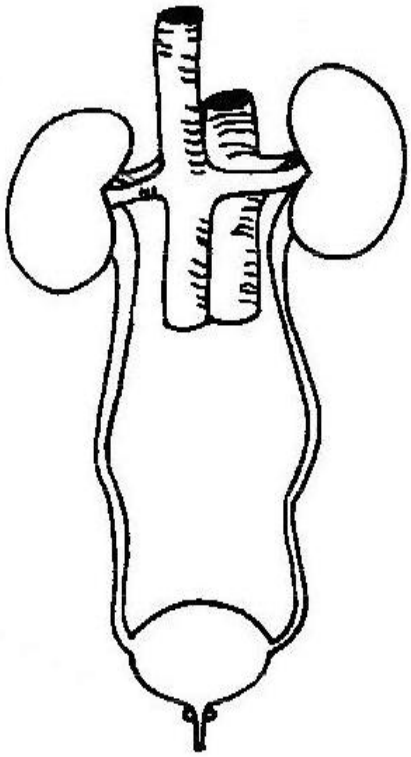


Risks & complications:

-↑ risk of hypertension & PE.
-↑ risk of maternal infection e.g. toxoplasmosis, CMV & herpes simplex virus.

Urinary Tract Infections (UTIs)

Urinary tract infections are common in pregnancy.

Predisposing factors: -Congenital anomalies of the urinary tract: polycystic kidney, duplex ureter. -Pressure on the ureter (stasis). -Atony & dilatation of the ureter (progesterone). -Ureteric stricture or stone. - Stasis associated with hydroureter and hydronephrosis. - Traumatized bladder with compressed and edematous cystic tissue. - Vesicoureteral reflux in some women. -Increased urinary glucose excretion. -Medical illness: DM, sickle cell anemia & immunosuppressive drugs. -Neuropathic bladder : as in spina bifida and multiple sclerosis. -Increased presence of pathogens.	

Routes of infection:

(1)-Blood spread: from septic focus e.g. tonsils & teeth.

(2)-Ascending infection (the commonest): from the bladder along the peri-ureteric lymphatics or along the lumen of the ureters as a result of vesicoureteric reflux. Organisms present in the urethra may enter the bladder by pressure on the urethra during coitus and by catheterization.

(3)-Spread from nearby organs e.g. from the colon.

Pathology:

(1)-Kidney: The renal pelvis is dilated. Its wall is congested, edematous, with leucocytic infiltration and may be ulcerated. The renal tissue shows a variable degree of inflammatory reaction.

(2)-Ureter: It is dilated, elongated & tortuous.
(3)-Bladder: shows cystitis.

Asymptomatic bacteriuria (ASB)

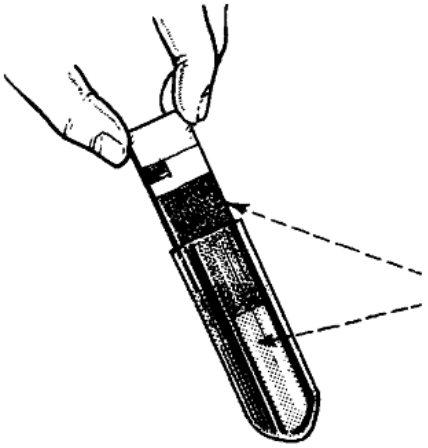
Definition:
ASB is defined as the presence of actively multiplying bacteria within the urinary tract, excluding the distal urethra, without symptoms of infection. The presence of more than 100,000 organisms per milliliter in 2 consecutive urine samples in the absence of declared symptoms.

Incidence:
The incidence of ASB during pregnancy ranges from 2% to 7%.

Complications:
Untreated ASB is a risk factor for acute cystitis (40%) and pyelonephritis (25-30%) in pregnancy. These cases account for 70% of all cases of symptomatic UTI among unscreened pregnant women.
Treatment of ASB reduces this rate to 3%. All women should undergo screening for bacteriuria at their first prenatal visit.

Diagnosis:
A clean-catch urine culture with more than 100,000 organisms per mL should prompt treatment of ASB.
Urine cultures that grow 20,000 to 50,000 colonies of a single uropathogen should also be treated, because pyelonephritis may also occur with lower counts. Escherichia coli accounts for 75% to 90% of infections, whereas Klebsiella species, Proteus species, Pseudomonas species, coagulate-negative Staphylococcus organism, and Enterobacter species account for the remainder.

A variety of proprietary culture systems are available and allow bacterial count to be obtained on the basis of the number of colonies counted on a slide.



Techniques of counting
Various methods are used to provide a simple screening test. The 'Uricult' system uses a slide coated with agar which is dipped into the fresh urine, cultured overnight and read the next day.

Treatment:

Initial therapy is usually empiric, and various regimens have been shown to be safe and effective.

Test-of-cure urine cultures should be obtained 1 to 2 weeks after treatment and again each trimester for the remainder of the pregnancy.

Failure of treatment should be treated with appropriate antimicrobial based on antibiotic sensitivities. After the second course of treatment, suppression therapy is indicated for the remainder of their pregnancy.

Acute cystitis

Occurs in approximately 1% of pregnant women.

Symptoms include urinary frequency, urgency, dysuria, hematuria, and suprapubic discomfort.

Treatment similar to that for ASB is recommended .

Urethritis is usually caused by Chlamydia trachomatis. It should be suspected in the clinical settings of urinary frequency, urgency, dysuria, and pyuria, with a negative urine culture. Mucopurulent cervicitis may coexist. The treatment of choice is azithromycin 1g PO as a single dose.

Acute pyelonephritis

Incidence:
Occurs in approximately 1-2% of all pregnancies. Acute pyelonephritis is the leading cause of septic shock in pregnancy.

Symptoms:
-General symptoms of infection: high fever, chills, nausea, and vomiting.
-Acute onset of loin pain which usually radiates along the course of the ureter to the suprapubic region.
-Frequency, urgency, and dysuria are variably present (cystitis).

Signs:
-General: Fever & tachycardia.
- Abdominal: Tenderness & rigidity in one or both renal angles.

To elicit loin tenderness, first palpate the spine gently to accustom the patient to the touch, then tap gently with the thenar eminence over the loin. If positive, the patient gives an unmistakeable wince.

Complications, including preterm labor, preterm premature rupture of membranes, bacteremia, sepsis, adult respiratory distress syndrome, and

hemolytic anemia, are seen more frequently in the gravid patient.
Prompt diagnosis and treatment of pyelonephritis in pregnancy is crucial.

Investigations:
(1)-Urine analysis, urine culture & sensitivity testing.
(2)-CBC shows leucocytosis and blood culture in severe cases.
(3)-Kidney function tests in chronic & recurrent cases.
(4)-Chest x-ray should be obtained if there is dyspnea or tachypnea.

Treatment:
- Hospitalization
- intravenous (IV) hydration to obtain adequate urinary output and the use of antipyretics.
-Administration of broad-spectrum IV antibiotics. Cefazolin sodium, extended-spectrum penicillin, and ampicillin plus gentamicin (or clindamycin plus gentamicin for penicillin-allergic patient) are most commonly used and should be continued until the patient has been a febrile for at least 48 hours.
Dosing of gentamicin every 8 hours is currently preferred over daily dosing the pregnant patient, given pregnancy-related changes in renal function. Gentamicin levels should then be followed. Antibiotic therapy should be tailored as necessary, based on urine culture sensitivity results.

Follow up:
After resolution of acute pyelonephritis, the patient should continue antibiotic therapy for 2 weeks followed by suppressive therapy for the remainder of the pregnancy.
Recurrence rate is approximately 20%.

Antimicrobial Agents for Treatment of UTI (Cochrane guidelines, 2007):

Oral antibiotics

Amoxicillin, 500 mg tds.
Cefadroxil, 500 mg bd.
Cephalexin, 250 tds.
Nitrofurantoin, 100 mg tds (not in third trimester).
Trimethoprim, 200 mg bd (not in first trimester).

Intravenous antibiotics for pyelonephritis

Amoxicillin, 1 g tds.
Cefuroxime , 750 mg-1.5 g tds.
Gentamicin 5-7 mg/kg daily as one dose and then further doses as determined by serum gentamicin concentrations (for organisms resistant to, or women allergic to penicillins and cephalosporins).

Duration of treatment

Asymptomatic bacteria: 3 days
Acute cystitis: 7 days.
Pyelonephritis: 10-14 days

Suppression therapy

Cephalexin, 250 mg od
Amoxicillin 250 mg od
For patients with a history of multiple urinary tract infections or pyelonephritis, suppressive therapy may be initiated as soon as pregnancy is confirmed.

Treatment Failures If symptoms do not respond to appropriate antibiotic treatment after 72 hours, antibiotic sensitivity results and dosing regimens should be reviewed.
Renal ultrasonography should be performed to evaluate for the presence of anatomic anomalies, nephrolithiasis, and intrarenal or perinephric abscess.

Special instructions for women with recurrent UTIs:

Re-infection is thought to arise from fecal bacteria (mainly E-coli) coming from the anus & contaminating the urethra. Pressure on the urethra during coitus may force the organisms to enter the bladder.

-The woman is asked to pass urine immediately after coitus.

-Cranberry juice provides some prophylaxis by preventing colonization of the lower genital tract by bacteria.

Liver and GIT Diseases in Pregnancy

Background

Certain liver diseases are uniquely associated with pregnancy, whereas others are unrelated. The liver diseases unique to pregnancy include hyperemesis gravidarum , acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hemolysis and elevated liver enzymes and low platelets (HELLP) syndrome. Liver disease such as acute viral hepatitis can occur in pregnancy, and pregnancy may occur in a patient with underlying chronic liver disease, including patients with cirrhosis and portal hypertension, and patients who have undergone liver transplantation.

The liver during normal pregnancy

I. Cholestasis: There are no histologic changes in the liver during normal pregnancy. However, a mild cholestatic state can be appreciated in the later stages of pregnancy, the hormonal changes that accompany pregnancy may account for the mildly cholestatic state.
(1)- Change the permeability of the biliary canalicular membrane, reducing bile flow as well as diminish hepatic transporter expression.
(2)- Smooth muscle relaxation in the biliary tree, leading to increased gall bladder volume and decreased contractility.
(3)-Bile lithogenicity also may be increased because of the relative increase in cholesterol synthesis and excretion into bile.
Despite these physiologic abnormalities, symptomatic cholestasis is not a typical feature of normal pregnancy.

II. Hepatic blood flow: Cardiac output increases until the second trimester and then may decrease or plateau during the third trimester. Despite these systemic hemodynamic changes in pregnancy, absolute hepatic blood flow is unchanged.
This relative decrease in hepatic blood flow is a result of the generalized hyperdynamic state of pregnancy. This relative reduction may impair the clearance of substances requiring adequate hepatic perfusion.
III. Physical examination of the liver: Physical examination of the liver

does not show major changes. The enlarging uterus often causes the liver to shift upward under the rib cage, relatively hidden from examination. The liver is impalpable during a normal pregnancy, and its detection should raise the possibility of underlying disease. Spider angiomas and palmar erythema, classic cutaneous signs of liver disease, may be normal features of an uncomplicated pregnancy (if low in number) and usually disappear after delivery.

Hepatic function tests	Comment
Bilirubin	Normal; urine bilirubin may be positive in the absence of jaundice.
Albumin	Decreased (by 20-40%) because of hemodilution.
Serum bile acids	May rise, but not above upper limits of normal.
Transaminases	Unchanged or lower limit of normal.
Alkaline phosphatase	Elevated (2 times) in third trimester; placental origin.

The enlarging uterus often causes the liver to shift upward under the rib cage.

Relative decrease in hepatic blood flow

Cholestasis

Hyperemesis gravidarum (HG)

Incidence

occurs in 1-20 patients per 1,000 pregnancies. It generally occurs in the first trimester, usually between 4-10 weeks of gestation, but may occur as late as 20 weeks gestation.

The differential diagnosis of hyperemesis gravidarum includes uncomplicated nausea and vomiting of pregnancy, gastric ulcers, gastroenteritis, viral hepatitis, pyelonephritis, nephrolithiasis, ovarian torsion, hyperthyroidism, diabetic ketoacidosis, and migraines.

Risk factors:

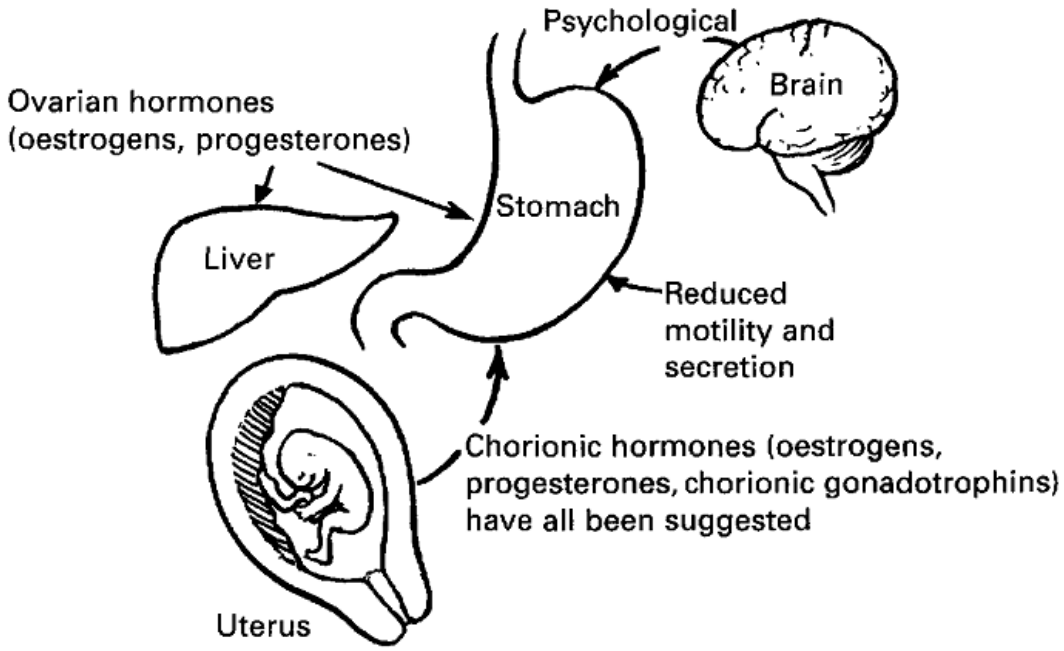
(1)-History of vomiting in previous pregnancy.
(2)-Medical illness: hyperthyroidism, psychiatric illness & preexisting diabetes.
(3)-Obstetric causes: molar pregnancy & multiple gestations.
(4)-Others: high intake of saturated fat and female gender of the fetus .

Aetiology

The cause of hyperemesis gravidarum remains unknown.
Multiple theories exist:
(1)-Psychologic theory: including conversion disorders to evolutionary adaptation to protect a mother and her fetus from certain potentially harmful foods.
(2)-Allergic theory: the patient is allergic to corpus luteum of pregnancy, so some patients improve on antihistaminics and after the 1st trimester when the corpus luteum degenerates.
(3)-Hormonal theory:
-High hCG: proved by increased vomiting in molar pregnancy & multiple gestations as well as early in pregnancy.
-High progesterone: vomiting in early pregnancy.
-High estradiol: vomiting is higher in primigravidas & in early pregnancy. Furthermore, cigarette smokers with lower estradiol levels also have a lower incidence of hyperemesis.

-Deficiency of suprarenal hormones: some patients improve with corticosteroid drugs.

(4)-Infection: about 90% of cases are infected with helicobacter pylori in the stomach.



Pathology:

-Brain: congestion, petechial hemorrhages, picture similar to Wernicke's encephalopathy (due to thiamin B1 deficiency).

-Peripheral nerves: degeneration & polyneuritis.

-Fundus examination may show: optic neuritis, retinal hemorrhage, retinal detachment.

-The Liver: Fatty infiltration & necrosis starting at the center of the hepatic lobules.

-The Kidneys: Degeneration of the renal tubules.

Biochemical Changes:

(1)-Blood changes:

-↓ blood volume & ↑ viscosity.

-Hemoconcentration (↑ Hct) & ↑ risk of VTE.

-↓ all electrolytes: sodium, potassium & chloride.

-↑ blood urea & BUN.

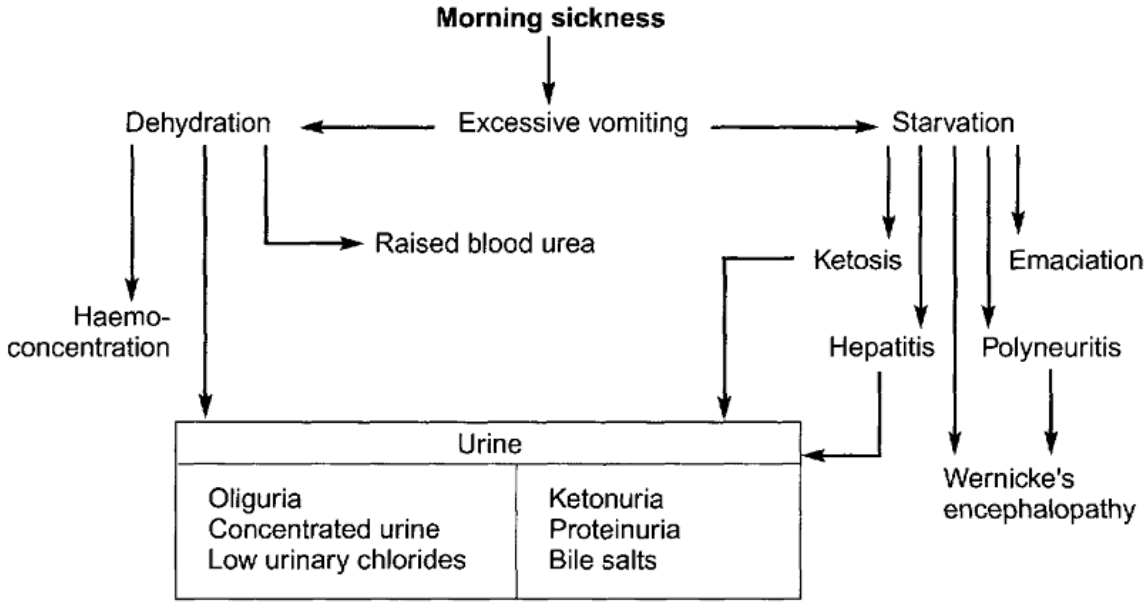
-Metabolic acidosis which aggrevates vomiting & so on.

(2)-Urine changes:

-↓ volume & ↑ specific gravity.

-Chloride is decreased or absent.

-In severe cases: proteinuria, bile salts & ketonuria.



Diagnosis

Symptoms include severe nausea and vomiting, at times requiring hospitalization. Patients often present with dehydration and may show evidence of malnutrition with poor weight gain.

Markers of severity include:

I. Weight loss > 10%.

II. Abnormal liver function tests.

III. Abnormal thyroid function tests with elevated free T4 and suppressed TSH.

IV. Abnormal liver function tests:

-Aminotransferase levels may rise up to 200 IU/L but are generally less than 300IU/L.

- Alkaline phosphatase may rise to twice the normal value.

-Both direct and indirect bilirubin values may rise to 4mg/dl.

-Serum amylase and lipase may rise up to 5 times normal values.

Treatment

Treatment of hyperemesis gravidarum consists of non-pharmacologic and pharmacologic interventions.

Non-pharmacologic interventions

- Avoiding nausea inducing triggers such as odors from perfume, smoke, cooking foods, and chemicals. Other triggers that may stimulate nausea include eating certain foods, especially spicy, salty, or fatty ones.

Therefore, low fat, frequent, small meals may help to improve symptoms.

-Crystallized ginger or ginger capsules (250 mg by mouth 4 times per day) have also been used with some success.

-Acupuncture and wristbands that apply pressure to the volar aspect of the wrist is another common intervention. No risk of adverse effects was associated with the treatment.

- Multivitamin use prior to conception.

Pharmacologic treatment

According to the ACOG practice bulletin algorithm for pharmacologic treatment of nausea and vomiting in pregnancy,

(1)- Vitamin B6 10-25 mg , in conjunction with doxylamine, an H1 receptor blocker, given as 12.5 mg given orally 3-4 times per day is the initial treatment of choice.

(2)- Promethazine 12.5 mg orally or rectally every 4 hours, or another H1 blocker, Dimenhydramine, 50-100 mg orally or rectally every 4-6 hours.

(3)- If dehydration is not evident, Metaclopramide 5-10 mg intramuscularly

or orally every 8 hours;
(4)-If dehydration is present, intravenous fluids should be started, as well as intravenous metoclopramide 5-10 mg, or promethazine 12.5-25 mg every 4-6 hours.
(5)-Finally, if all of the above are insufficient, Methylprednisolone 16 mg every 8 hours orally or intravenously for 3 days followed by a 2 week taper or Ondansetron 8 mg intravenously every 12 hours can be added. Methylprednisolone has demonstrated an association with oral clefts when used in the first 10 weeks of gestation, and therefore should be used with great caution.

Admission to the hospital should be considered in:
-Persistent vomiting and the patient cannot tolerate any liquids.
-Change in vital signs or mental status, or continued weight loss .
Intravenous fluids along with necessary electrolytes and vitamins, especially thiamine, should be given for patients who cannot tolerate liquids for a prolonged period of time or evidence of dehydration. If anti-emetics allow, diets should be advanced as tolerated, but in severe cases tube feeds and parenteral nutrition may be necessary.

Prognosis

Maternal outcomes

-Generally similar to those in the general population.
-Rare & more serious complications can include esophageal rupture, retinal hemorrhage, pneumothorax, renal damage and Wernicke encephalopathy.

Wernicke encephalopathy, is due to thiamine deficiency and is characterized by ataxia, ophthalmoplegia, and confusion. It is associated with a 10-20% mortality rate and many patients have long-term neurologic deficits.
Treatment includes prompt thiamine replacement, initially 100 mg intravenously prior to the administration of any glucose-containing fluids and may be continued until a normal diet is tolerated.

Some recommend that thiamine supplementation should be the standard of care for any patient with greater than 3-4 weeks of vomiting. In addition to physical complications, some patients can experience significant psychological morbidity, including depression.

Fetal outcome unchanged from those in the general population, except in cases of severe disease in which there is increased incidence of low birth weight and fetal death have been reported. No evidence of increased risk of fetal malformations exists.

Monotherapy: Vitamin B6, 10–25 mg, 3 or 4 times per day
Add: Doxylamine, 12.5 mg, 3 or 4 times per day

↓If No improvement

Promethazine 12.5 mg orally or rectally every 4 hours,
Dimenhydramine, 50-100 mg orally or rectally every 4-6 hours.
Metaclopramide 5-10 mg intramuscularly or orally every 8 hours.

If There is Dehydration↓

Intravenous fluid replacement
Metoclopramide, 5–10 mg every 8 hours, intravenously

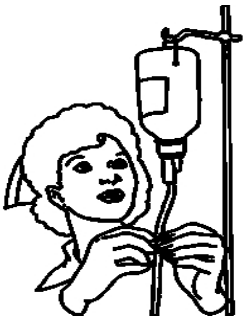
↓If NO improvement

Add: Methylprednisolone, 16 mg every 8 hours, orally or intravenously, for 3 days. Taper over 2 weeks to lowest effective dose. If beneficial, limit total duration of use to 6 weeks.

Or

Ondansetron, 8 mg, over 15 minutes, every 12 hours, intravenously

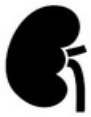
-Avoid nausea inducing triggers.
-Low fat, frequent, small meals.
-Oral or rectal antiemetics.



Hospitalization
-I.V. fluids.
-I.V.antiemetics.
-Vitamin B complex injection.
-May add steroids or ondansterone.

Indications of termination of pregnancy:
A: Appearance of jaundice.
P: Proteinuria & progressive oliguria.
C: Creatinine rise.
D: Deterioration of the general condition despite treatment.
E: Encephalopathy.
F: Fundal changes.

-Jaundice.
-Marked rise in liver enzymes.



-↑ creatinine.
-Proteinuria & oliguria.

-Encephalopathy.
-Bad general condition.

Fudal changes

Acute fatty liver of pregnancy

Incidence

The incidence of acute fatty liver of pregnancy (AFLP) is 1 per 10,000-15,000 pregnancies. The condition often develops in the second half of pregnancy (ranges from 27-40 weeks gestation), usually close to term, with a mean gestational age reported at 36 weeks, but it may not be diagnosed until the postpartum period.

The differential diagnosis includes fulminant viral hepatitis, drug-induced hepatic toxicity, idiopathic cholestasis of pregnancy, adult-onset Reye syndrome and HELLP syndrome.

Risk factors:

(1)-Maternal characteristics: older maternal age, primiparity, being underweight, and a past history of AFLP.

(2)-Obstetric causes: multiple gestations, preeclampsia & male fetus.

(3)-Studies have revealed a higher incidence of AFLP in women who:

- Have a genetic mutation that affects their mitochondrial fatty acid oxidation pathway.
- Carry a fetus with a long-chain 3-hydroxyacyl-coenzyme, a dehydrogenase (LCHAD) deficiency.

-Old maternal age.
-Primiparity.
-Multiple gestations.
-Preeclampsia.

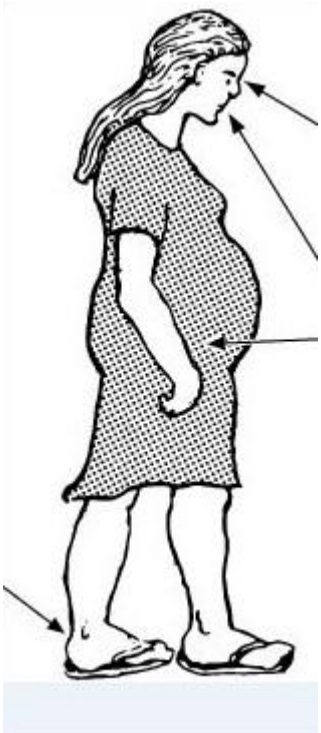
Carry a fetus with (LCHAD) deficiency.

Aetiology

AFLP is in the family of microvesicular fat diseases, along with Reye syndrome and valproate toxicity. In many cases, the condition is linked to mutations in LCHAD, which is 1 of 4 enzymes that break down long-chain fatty acids in the liver. A deficiency leads to accumulation of these fatty acids in the liver. These fatty acids eventually accumulate within the liver, causing impaired function and eventual liver failure.

Symptoms

Symptoms usually develop over several days to weeks and include nausea, vomiting, anorexia, lethargy, abdominal pain, ascites, and progressive jaundice. Transient polyuria and polydipsia may also occur due to the development of transient diabetes insipidus. Acute renal failure occurs in 50% of patients, and hepatic encephalopathy occurs in 60% of patients. Approximately 50% of patient also had hypertension, proteinuria, and edema suggestive of preeclampsia.



-Nausea, vomiting, anorexia, lethargy, and progressive jaundice.
-Abdominal pain & ascites.
- Hepatic encephalopathy (60% of cases).

-Transient polyuria and polydipsia.
- Acute renal failure occurs (50% of cases).

Approximately 50% of patient may have hypertension, proteinuria, and edema suggestive of PE.

Diagnosis

The diagnosis is usually made based on patient presentation and laboratory findings. In AFLP,

(1)-Liver function tests: serum aminotransferase levels are moderately elevated (typically 300-500 U/L). Bilirubin is usually less than 5 mg/dl but can be higher in severe cases of AFLP.
(2)-Other typical abnormalities include *hypoglycemia*, elevated ammonia levels, thrombocytopenia, neutrophilia, *coagulopathy*, and renal dysfunction.
(3)-Imaging studies: such as CT scanning may demonstrate diffuse low-density signals in the liver and ascites. However, ultrasonography of the liver usually normal because the fat deposits are microvesicular.
(4)-A definitive diagnosis can be obtained with *a liver biopsy*, but a biopsy is rarely performed because of the need for prompt therapy as well as the presence of coagulopathy. The liver biopsy reveals microvesicular steatosis, fat droplets surrounding a centrally placed nucleus.

Treatment

Any patient with a possible diagnosis of AFLP should be immediately admitted, as the disease is characterized by progressive and sudden deterioration. Continuous fetal monitoring should be initiated and labs should be drawn immediately. Supportive measures should be instituted to stabilize the mother; these often include glucose infusion and blood products as needed, with careful attention paid to the patient's fluid status. The primary treatment is **prompt delivery** of the fetus, which stops the overload of fatty acids on the mother's liver, as well as supportive measures to stabilize the mother.

Recovery before delivery has not been reported

Although induction of labor is a viable option if a rapid vaginal delivery is probable (less than 24 hours), studies have demonstrated a cesarean delivery rate of up to 75%,as it can hasten resolution of the disease secondary to earlier delivery. However, cesarean delivery may increase the risk of maternal morbidity and the need for blood products.
The route of anesthesia must be discussed between the obstetric and anesthesia team. Some patients may require general anesthesia due to coagulopathy and concern for hematoma formation with regional anesthesia.

Most patients start to improve **within 48-72 hours after delivery** and demonstrate improvement in their aminotransferases, but those with evidence of coagulopathy, encephalopathy, or hypoglycemia on admission often require continued intensive care level monitoring and possible transfer to centers capable of *liver transplants*.

Prognosis

Maternal outcome: Liver function usually normalizes within a week but may be delayed for months. Complete recovery is generally anticipated. The maternal mortality rate has been as high as 70%, but more recent estimates range from 7-18%, secondary to advances in supportive management of these patients. Maternal complications include postpartum hemorrhage, renal failure, hypoglycemia, DIC, pancreatitis, and pulmonary edema.

Perinatal mortality rates have been as high as 85%, and more recent rates range from 9-23%. Because of the urgent need for immediate delivery, approximately 75% of deliveries are preterm, with an average gestational age at delivery of 34 weeks. All infants of mothers with AFLP are tested for defects in fatty acid oxidation because prompt recognition and treatment can decrease mortality and morbidity. Recurrence of AFLP in subsequent pregnancies is rare.

Immediate delivery is indicated

Intrahepatic cholestasis of pregnancy

Incidence

Intrahepatic cholestasis of pregnancy (ICP) occurs in approximately 1-2 per 1,000 pregnancies. It generally manifests in the third trimester, with a mean onset at 30 weeks gestation, and symptoms resolve after delivery.
The differential diagnosis includes viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, and cholelithiasis.

Risk factors:

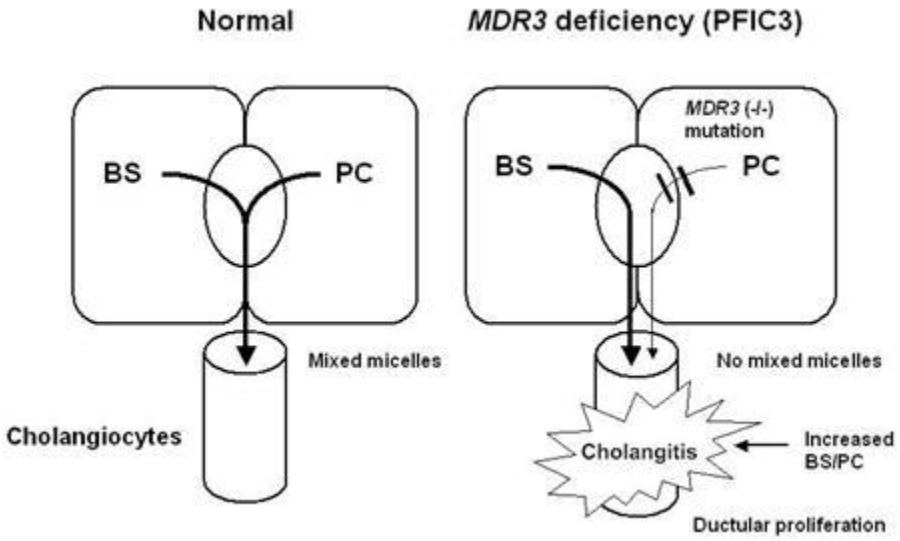
(1)-A geographic variability exists, highest incidence in South America as Chile.
(2)-Advanced maternal age, multiparity, personal or family history of the disease and a history of cholestasis while taking oral contraceptives.

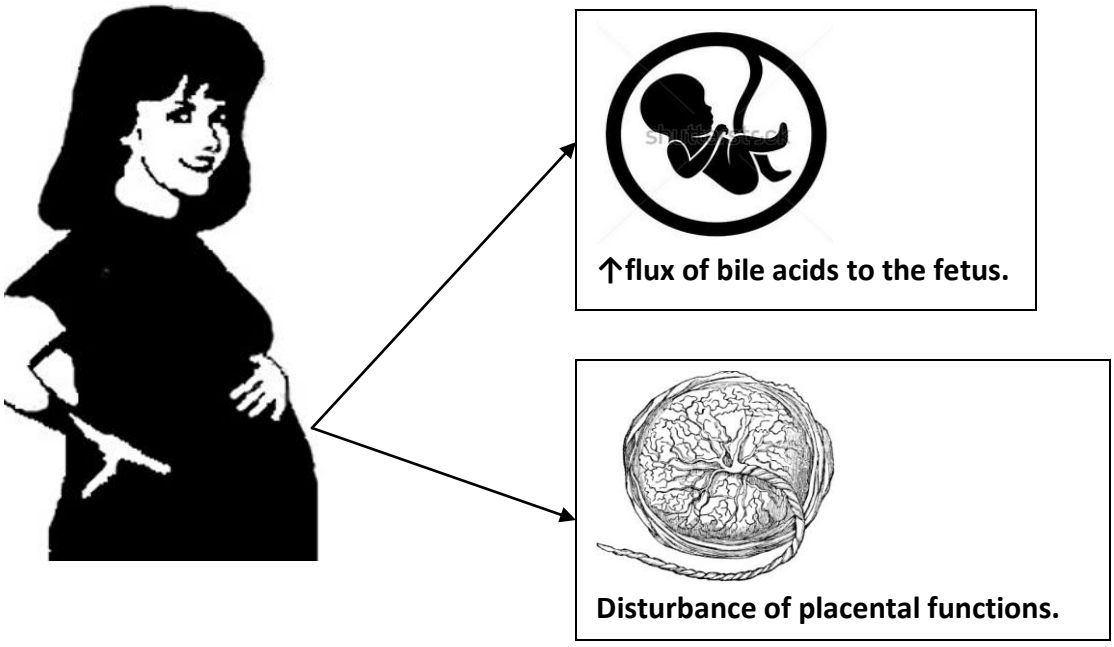
Aetiology

-The etiology of ICP is multifactorial, including genetic, hormonal, and exogenous factors. ICP is due to abnormal biliary transport resulting in saturation of the hepatic transport system. Recurrent familial ICP of pregnancy has been described as a heritable defect in the multidrug resistance 3 (MDR3) gene, which predisposes women to developing ICP, but the expression of the disease is influenced by female sex hormone levels and metabolites. Mutations in the MDR3 gene may account for up to 15% of cases of ICP.

Fetal pathophysiology

The mechanism underlying poor perinatal outcome is still poorly understood. During ICP there is an increased flux of bile acids from the mother to the fetus
The placenta plays a crucial role in protecting the fetus from the adverse effects of potentially toxic endogenous substances including total bile acid (TBA). High levels of maternal TBA affect placental transport, placental hormone production, and chorionic vessel constriction.


Normal
MDR3 deficiency (PFIC3)
BS
PC
Mixed micelles
Cholangiocytes
MDR3 (-/-)
mutation
BS
PC
No mixed micelles
Cholangitis
Increased
BS/PC
Ductular proliferation


↑flux of bile acids to the fetus.
Disturbance of placental functions.

Symptoms

Patients with ICP generally experience generalized pruritus that begins in the periphery, often worse on the palms and soles, and moves centrally to the trunk and face. The pruritus persists and worsens as pregnancy continues and resolves within 48 hours of delivery. Pruritus is often worse at night and may be so severe that it causes sleep disturbance, irritability, and psychiatric disturbances. Approximately 10-25% of patients develop jaundice, usually 1-4 weeks after the onset of pruritus. No rash is associated with ICP.

Generalized pruritus that begins in the periphery, often worse on the palms and soles, and moves centrally to the trunk and face.

Pruritus is often worse at night.

10-25% of patients develop jaundice.

No rash is associated with ICP.

ICP can be diagnosed based on clinical symptoms, but common laboratory values include elevated bilirubin levels, usually less than 6mg/dL, and elevated transaminases from a minimal rise to 20 times normal values.
The most sensitive laboratory value is serum bile acids, which may be the first or only lab abnormality and is used as confirmation of the diagnosis. Patients with ICP generally have bile acids greater than 10μmol/L and may be as high as 100 fold of normal. Laboratory abnormalities often resolve within 2-8 weeks of delivery.
Liver biopsy is rarely needed, usually only in cases in which a more serious liver disease needs to be excluded. If biopsy is performed, it reveals cholestasis with minimal or no inflammatory changes.

Treatment

Management includes symptomatic treatment of the patient as well as close monitoring and possibly early delivery of the fetus.

The medical treatment of choice is ursodeoxycholic acid (UDCA), with doses of 1 gram per day, UDCA improved pruritus and liver enzymes and enabled delivery to occur closer to term. Cholestyramine may be used to reduce pruritus in total divided doses of 10-12 g/day, but it is less effective than UDCA and has more side effects especially decreased absorption of fat-soluble vitamins.

Fetal surveillance:

Fetal mortality in patients with ICP has been recorded to be as high as 11%, and the cause of mortality is still unknown. Fetal mortality does not seem to be due to chronic uteroplacental insufficiency, but rather to an acute anoxic injury. Some believe that meconium, which complicates up to 45% of these pregnancies, causes umbilical vein constriction leading to fetal death and hypoxia.

The cause of increased meconium passage remains unknown. Animal studies have demonstrated that high maternal bile acid levels increase colonic motility in sheep.

(1)-Maternal record of fetal movement .

(2)-Once-weekly non-stress tests are a common method of fetal surveillance, often begun at 34 weeks gestation or as soon as the diagnosis of ICP is made, but these are not necessarily a good predictor for fetal outcome.

(3)- Contraction stress test if the non-stress test is nonreactive.

Although no consensus exists regarding when to begin testing for fetal lung maturity, one study demonstrated good fetal and neonatal outcome with amniocentesis for fetal lung maturity at 36 weeks .Delivery is recommended when fetal lung maturity is confirmed. Earlier delivery should be considered for severe cases with jaundice and progressive elevation in serum TBA.

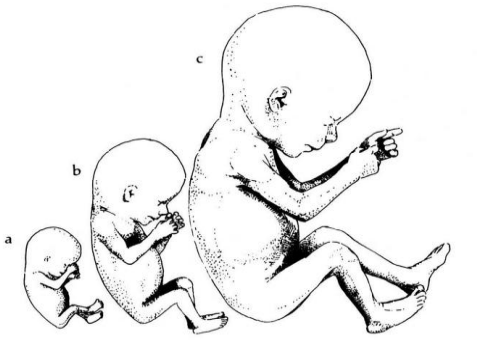
Prognosis

Maternal outcome is good, with symptom resolution after delivery.

(1)- Pruritus usually disappears in the first few days following delivery, The patients with ICP generally have no hepatic sequelae.

-If the pruritus and liver test abnormalities persist after delivery, chronic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis or chronic hepatitis must be considered.
(2)-ICP recurs during subsequent pregnancies in 45% to 70% of cases.
(3)-ICP is associated with increased incidence of intra- and postpartum hemorrhage.
(4)-The administration of oral contraceptives to women with a history of ICP rarely results in cholestatic hepatitis. These women should be advised of the risk of cholestasis to use contraceptives with low dose estrogen or progesterone-only products.

Fetal outcome:
(1)-ICP is associated with spontaneous preterm labor (19-60%), meconium-stained fluid, and perinatal mortality. perinatal mortality between 10-15%, *One study demonstrated that with every 1µmol/L increase in serum bile acids, fetal complications increased by 1-2%.*
(2)- Elevated rates of respiratory distress syndrome (RDS) exist in preterm infants, but RDS rates are also elevated in ICP patients delivered at term, suggesting that a mechanism exists through which ICP itself contributes to RDS.
(3)-Rates of stillbirth increase after 37 weeks gestation, thus supporting active management of delivery at 37 weeks, but case reports of fetal death from 31 weeks still exist



-↑Prematurity (spontaneous & induced).
-↑Meconium stained A.F.
-↑IUFD.
-↑Neonatal death.

Poor fetal outcome

HELLP Syndrome

Incidence

Hemolysis, elevated liver enzymes, and low platelets (HELLP) usually presents as a complication of preeclampsia, but it can also occur independently.

HELLP syndrome affects 1-6 per 1,000 pregnancies and 4-12% of patients with severe preeclampsia. Preeclampsia is characterized by hypertension, proteinuria, and edema with onset in the second or third trimester and affects 5-7% of pregnancies. 70% of patients with HELLP syndrome present before delivery, with the other 30% developing in the postpartum period.

The differential diagnosis includes hepatitis, pancreatitis, peptic ulcer, appendicitis, cholelithiasis, liver hematoma, acute fatty liver of pregnancy, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and systemic lupus erythematosus.

Risk factors

Risk factors for HELLP syndrome include white, multiparous, and older patients. As most patients who develop HELLP syndrome have preeclampsia, it too is a risk factor.

Aetiology

HELLP syndrome is caused by several mechanisms that, when combined, result in hemolysis, liver necrosis with elevated transaminases, and thrombocytopenia. The initial source of the insult is *unknown*, but all patients have evidence of endothelial injury with fibrin deposit that causes a microangiopathic hemolytic anemia and platelet activation and consumption, leading to thrombocytopenia. The fibrin deposits cause obstruction in the hepatic sinusoids, which leads to areas of hemorrhage and eventual necrosis in the liver, The hemorrhage can eventually develop into large hematomas and cause liver capsule tears.

Symptoms

Patients with HELLP syndrome often present with right upper quadrant or epigastric pain, nausea and vomiting, malaise, and nonspecific viral-like symptoms. Some patients also experience headache (30-60%), and fewer experience visual symptoms (17%).

Diagnosis

Physical examination findings include right upper quadrant or epigastrium tenderness and generalized edema. Hypertension and proteinuria are common, as most of the patients have preeclampsia, but are not always present. Hypertension is absent in up to 20% of patients, and proteinuria is absent in up to 13% of cases.

Laboratory abnormalities assist in confirming the diagnosis of HELLP syndrome, but currently no standardized diagnostic laboratory criteria exist. Commonly used lab values include platelet count of less than 100,000, serum aspartate aminotransferase (AST) greater than70 U/L, and serum lactic dehydrogenase greater than 600 U/L. A peripheral blood smear may also assist in the diagnosis and often demonstrates schistocytes, burr cells, and echinocytes.

Criteria for The Diagnosis of HELLP Syndrome

Hemolysis

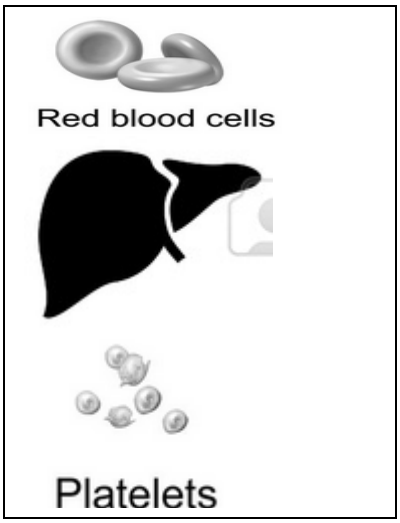
- Abnormal peripheral smear
- Total bilirubin >1.2 mg/dl
- Lactic dehydrogenase >600 U/l

Elevated liver functions

- Serum aspirate amniotransferase >70 U/l
- Lactic dehydrogenase >600 U/l

Low platelets

- Platelet count <100,000/mm^3



Studies have demonstrated that about 50% of patients diagnosed with HELLP syndrome do not have all diagnostic criteria, but those that do have more severe disease with increased rates of blood transfusions and disseminated intravascular coagulation than those with only partially

abnormal laboratory criteria.
Some studies have found that maternal morbidity varies depending upon the degree of thrombocytopenia; thus, subtype classifications of HELLP syndrome have been developed, such as:
Tennessee System classification is based on the assessment of the following parameters: AST>70 UI/L, LDH >600 UI/L, thrombocytes <100,000/ mm3.
Two forms: *complete* (all elements present) and *partial* HELLP syndrome (one or two elements present).
The Mississippi classification relies on the thrombocyte counts: class I (<50,000/mm3), class II (50,000-100,000/mm3) and class III (100,000-150,000/mm3).

Treatment
After initial diagnosis of HELLP syndrome, the disease often continues to progress and can sometimes have sudden and severe advancement, eventually compromising maternal and fetal outcome.
If the diagnosis of HELLP syndrome is still in question, women should be stabilized initially with good blood pressure control. Intravenous hydralazine or labetalol may be used to maintain systolic blood pressure less than 160 mm Hg and diastolic blood pressure less than 105 mm Hg.
After diagnosis is confirmed or highly suspected, stable patients should be transferred to tertiary care facilities for both maternal and possible neonatal treatment.
Delivery is the definitive treatment for HELLP syndrome.
Controversy exists regarding treatment of patients with HELLP syndrome at less than 34 weeks gestation. Generally, if a reassuring fetal and maternal status exists, delivery may be delayed for a steroid course of betamethasone 12 mg intramuscularly every 24 hours for 2 doses, with delivery 24 hours after the last dose. During the steroid course, the patient and fetus are continually monitored, and any sign of distress or deterioration of condition should prompt immediate delivery.
Delivery is indicated for women with HELLP syndrome at greater than 34 weeks' gestation. During labour and for 24 hours postpartum, patients should receive intravenous magnesium sulfate for seizure prophylaxis,

usually with a 4-gram loading dose, followed by 2 g/h. If the patient is already in labour, a vaginal delivery may proceed, as long as no evidence exists of fetal distress or disseminated intravascular coagulopathy. Any evidence of the above, multiorgan dysfunction, renal failure, or abruption should prompt immediate delivery, usually by cesarean section. Induction of labour is *not* indicated in these patients, as the induction process can take several hours to days and places the patient and neonate in danger.
Platelets are generally transfused when the platelet count is less than $20,000/mm^3$, if less than $50,000/mm^3$ and cesarean delivery necessary, or with any significant bleeding. Multiple platelet transfusions are generally unnecessary without significant bleeding, as delivery eventually leads to improvement in thrombocytopenia.
There is to date insufficient evidence of benefits of corticosteroids on substantive clinical outcomes. Those receiving steroids showed significantly greater improvement in platelet counts which was greater for those receiving dexamethasone than those receiving betamethasone. There is to date insufficient evidence to support the routine use of steroids for the management of HELLP (NICE, 2010).
The use of corticosteroids may be justified in clinical situations in which increased rate of recovery in platelet count is considered clinically worthwhile. (Cochrane Database Syst Rev, 2010).

Patients should be monitored very carefully for at least 48 hours in the post-partum period for evidence of pulmonary edema due to fluid shifts or renal or hepatic dysfunction. Laboratory abnormalities usually tend to nadir 24 hours postpartum and begin to recover 48 hours after delivery.

Prognosis
HELLP syndrome is associated with increased maternal and fetal morbidity and mortality. The risk of maternal death is approximately 1%. Multiple maternal complications are associated with HELLP syndrome, including pulmonary edema, acute renal failure, DIC, abruptio placenta, liver hemorrhage or failure, acute respiratory distress syndrome, and stroke. Patients with HELLP syndrome also have higher rates of blood transfusion. HELLP syndrome not only increases maternal morbidity and mortality but

also that of the fetus. The rate of perinatal death has been demonstrated to range from 7.4-20.4% and is largely dependent upon gestational age and any additional complicating factors to the pregnancy or delivery.
The highest morbidity and mortality rates are associated with the earlier gestations (less than 28 weeks), and studies have demonstrated that the rates are not any higher than those found at the same gestational age in women diagnosed only with preeclampsia.

Maternal complications:
- Pulmonary edema.
-Acute renal failure.
-DIC.
-Abruptio placentae.
-Liver hemorrhage or failure.
-Acute respiratory distress syndrome (ARDS).
- Stroke.
-↑rate of CS & blood transfusion.

Stabilization of the general condition:
-Antihypertensive drugs.
-Magnesium sulphate.
-Steroids ??.
-Lab investigations.
-Preparation of blood products.

Delivery:
-Vaginal delivery is allowed if in labour.
-Induction of labour not recommended.
-Cesarean section in most cases usually under general anesthesia.
-Follow up for at least 48 hrs after delivery.

Viral Hepatitis

Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis E
Incidence : 9 per 100,000 .	acute hepatitis B is 1-2 per 1000 and chronic hepatitis B is 1 per 100 .	0.5-1.4%. as in the general population	higher incidence and mortality rate in pregnancy.
Transmission: oral-fecal exposure,vertical during first trimester.	multiple routes, including mucosal, parenteral, sexual, and vertical exposure.	transfusion of unscreened blood products and intravenous drug use. Less commonly sexual contact, from infected mother,and needle-stick injuries.	through oral-fecal exposure, vertical transmission does occur.(as HAV)
Symptoms: malaise, fatigue, nausea, vomiting, right upper quadrant pain, and pruritus, which may be more severe in pregnancy.	Patients with acute hepatitis present with nausea, vomiting, fever, and fatigue, with jaundice and pruritus.	20-30% of new infections develop symptoms of acute hepatitis, The remainder of patients have asymptomatic infections.	range from asymptomatic infection to fulminant hepatitis with hepatic encephalopathy.
Diagnosis: -detection of hepatitis A IgM antibodies. -elevated levels of hepatitis A IgG in	**Acute infection** with detection of hepatitis B surface antigen (HBsAg) and IgM antibodies	detection of the antibody to hepatitis C. The antibody may not be detected until 6-10 weeks	by the presence of anti-hepatitis E antibody, and active infection is indicated with HEV-RNA.

the infant at 6 months of life.	to hepatitis B core antigen (HbcAg). **The chronic carrier** by the presence of HBsAg.	after clinical illness, but hepatitis C RNA can be detected soon after infection.	
Prophylaxis: hepatitis A vaccine and immuno-globulins. The immunoglobulin provides protection for up to 3 months if given within 2 weeks after exposure.	all infants born to mothers who are HbsAg positive should receive single agent hepatitis B vaccine and HBIg within 12 hours of birth and the vaccine series completed in the first 6 months of life.	No vaccine for hepatitis C exists, and primary prevention is necessary in order to avoid infection.	Postexposure or pre-exposure anti-HEV immunoglobulins have demonstrated **no** benefit,
Sequale: Hepatitis A does not lead to chronic infection and rarely leads to serious complications. The overall case fatality rate is less than 1%.	chronic hepatitis B may lead to liver cirrhosis and hepatocellular carcinoma.	75-85% of people develop chronic infection, Of the patients who develop chronic disease, 60-70% develop chronic liver disease, 5-20% develop cirrhosis, and 1-5% die from cirrhosis or liver cancer.	

Cirrhosis and Portal Hypertension

Cirrhosis is not a contraindication to pregnancy, but patients with decompensated cirrhosis are unlikely to conceive secondary to hypothalamic pituitary dysfunction. Patients with cirrhosis are often anovulatory, but after treatment may start to have regular menstrual cycles.
Controversy still remains regarding the effect of pregnancy on cirrhotic patients. increased maternal mortality, with increased rates of preterm deliveries, spontaneous abortions, stillbirths, and neonatal mortality are demonstrated.

Aetiology

Cirrhosis is an irreversible disease characterized by damage to the liver and subsequent fibrosis that compromises its ability to metabolize toxins. Due to fibrosis, blood is shunted away from the liver, which eventually leads to elevated pressures in the portal system.

Diagnosis

A diagnosis can often be made with history, physical examination, and laboratory findings. Physical examination findings may include spider angiomas, ascites, caput medusae, palmar erythema, and splenomegaly. Lab abnormalities include hypoalbuminemia, prolonged prothrombin time, and thrombocytopenia.

Symptoms

Patients can have a range of symptoms depending upon the extent of their disease. Some patients may have essentially asymptomatic cirrhosis with mild portal hypertension, while others with more advanced disease can have complications including acute gastrointestinal hemorrhage, liver failure, and encephalopathy.
Esophageal variceal bleeding occurs in up to 25% of pregnant patients with cirrhosis and portal hypertension. It is more common during the second and third trimesters due to increased pressure of the expanding uterus on the inferior vena cava. Maternal mortality with acute variceal bleeds ranges from 25-50%.

Liver failure occurs in up to 25% of patients with cirrhosis during pregnancy. Patients may present with hypoglycemia, coagulopathy, confusion, severe mental deterioration, and even encephalopathic coma.

-Spider angiomas.
-Ascites.
-Caput medusa.
-Palmar erythema.
-Splenomegaly.

-Hypoalbuminemia.
-Prolonged PT.
-Thrombocytopenia.

Presentations:
-Hypoglycemia.
-Coagulopathy.
-Confusion.
-Encephalopathy & coma.

Treatment

All patients should be monitored in the antenatal period with close surveillance of liver function with laboratory tests every 2-4 weeks, including serum albumin and prothrombin time. Nonstress tests should be started at approximately 28 weeks. Additionally, any patients with recurrent hematemesis or on immunosuppressants should have ultrasounds in the third trimester to evaluate fetal growth, as they have been associated with intrauterine growth restriction.

Unless maternal deterioration or evidence of fetal distress is found, labor should be conducted as in pregnancies not complicated with cirrhosis. Once the patient is admitted to the labor and delivery unit, additional laboratory tests should be obtained, including liver, renal, and coagulation studies. Any laboratory abnormalities, especially coagulation, platelet, and hematocrit abnormalities, should be addressed and treated with blood products prior to delivery, if possible.

Variceal bleeding

Known esophageal varices can be sclerosed endoscopically prior to pregnancy to prevent hemorrhage.

During Pregnancy:

Acute treatment of variceal bleeding in pregnancy is similar to treatment in nonpregnant patients and includes continuous hemodynamic monitoring (in an intensive care unit as needed), transfusions, balloon tamponading, endoscopy, or pharmacological treatment. Endoscopy with variceal ligation or sclerotherapy injection is considered safe in pregnancy.

One medication commonly used in nonpregnant patients, vasopressin, is contraindicated in pregnant patients because it can cause arteriolar spasm that can lead to placental ischemia and abruption. Vasopressin has also been associated with fetal digit and limb reductions due to fetal ischemia.

Portasystemic shunts have been placed in pregnant patients and may decrease the risk of recurrent hemorrhage, but these procedures should be reserved for patients with bleeding refractory to other treatment methods.

During Delivery:

If the patient has known esophageal varices, a gastroenterologist should be consulted and alerted to the patient's presence on labor and delivery, in the case that an emergent endoscopy or Sengstaken-Blakemore tube needs to be placed. Unless contraindicated, an early epidural is also helpful in order to decrease pain and intra-abdominal pressure, which increases the pressure on any varices.

Hepatic failure

Patients with hepatic failure should be carefully monitored in an intensive care setting. Treatment is similar to nonpregnant patients with hepatic failure, including blood products as needed to correct coagulopathies and mannitol diuresis with intubation and hyperventilation for cerebral edema.

Prognosis

Maternal and fetal prognosis depend upon the severity of liver disease and incidence of complications, especially variceal bleeding. Maternal mortality ranges from 10-18% and is often due to acute gastrointestinal hemorrhage or hepatic failure.

Biliary Disease

Gallstones or cholelithiasis are common in pregnancy, with up to 10% of patients developing stones or bile duct sludge during pregnancy or in the 6-week postpartum period.

Risk Factors

Risk factors for gallstone formation and biliary sludge include elevated BMI (>25 kg/m^2), with one study demonstrating that 2.7% of women with normal pre-pregnancy BMI developed gallbladder disease, versus 11% in obese women.

Aetiology

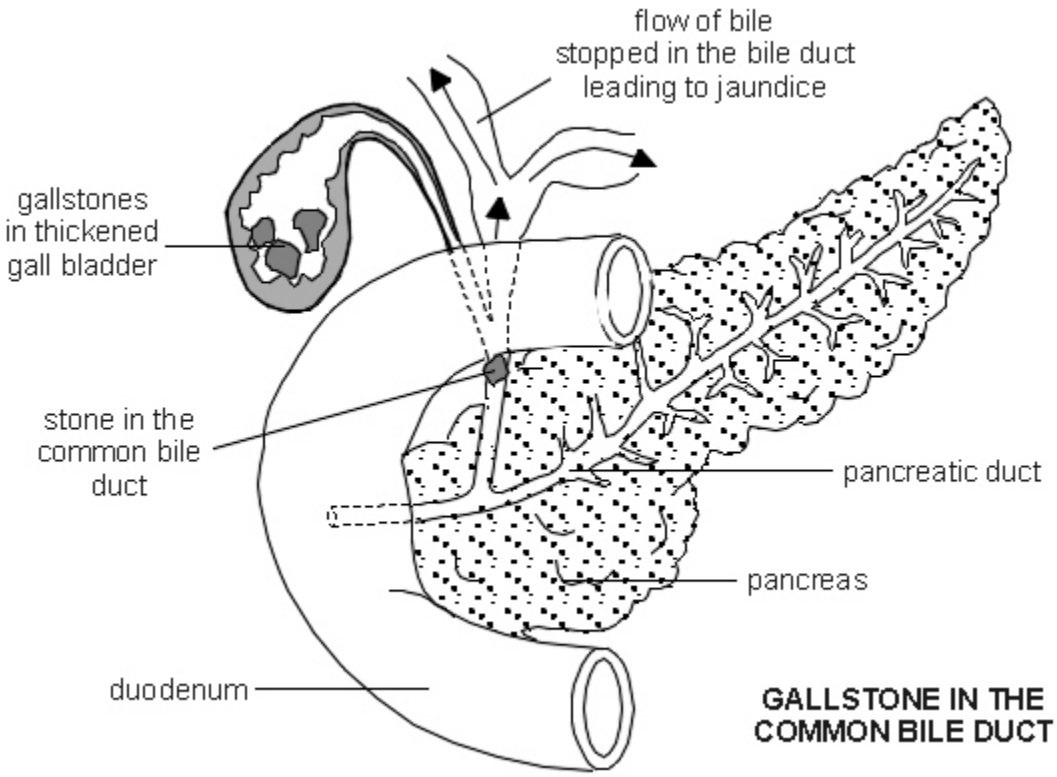
Gallstones are more common during pregnancy because cholesterol secretion increases relative to bile acid and phospholipids, thereby causing supersaturated bile. Furthermore, gallbladder volume is larger with decreased emptying, thus leaving supersaturated bile in the gallbladder with eventual gallstone formation.

Symptoms

Despite the high prevalence of the disease, only approximately 0.1-0.3% of gallstones are symptomatic. Gallstones can manifest with right upper quadrant pain, nausea, and vomiting. In addition to these symptoms, acute cholecystitis can manifest with low grade fever and mild leukocytosis.

Diagnosis

Biliary sludge and gallstones are diagnosed by ultrasound. In addition to pain and evidence of gallstones on ultrasound, patients with acute cholecystitis also have fever or elevated white blood cell counts.
Patients with gallstone pancreatitis have gallstones and elevated levels of serum amylase and lipase. Choledocholithiasis is diagnosed with evidence of gallstones in the common bile duct on ultrasound or endoscopic retrograde cholangiopancreatography (ERCP).



Treatment

Uncomplicated biliary colic and acute cholecystitis can often be treated with conservative therapy, including bowel rest, intravenous fluid, pain control, and antibiotics as needed. This is the primary treatment method in the first and third trimester and is successful 80% of the time. Because biliary colic recurs 50% of the time in pregnancy, readmission rates for those initially treated conservatively range from 38-70%, with each subsequent admission being more severe than prior.

If performed, a cholecystectomy is recommended during the second trimester, due to the risk of abortion in the first trimester and the risk of preterm labor in the third trimester.

Surgical intervention is the primary treatment for acute cholecystitis that fails medical management, or if obstructive jaundice or gallstone pancreatitis exists, or if peritonitis is suspected. Most of the procedures can be performed laparoscopically, especially if performed in the second trimester.

Special considerations for laparoscopic surgery include the use of open cannulation by the Hasson technique for the umbilical port site,

pneumoperitoneal pressure between 10 and 12 mm Hg, placing the patient in left lateral position and using electrocautery carefully and away from the uterus.

With an impacted common bile duct stone, an endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stone extraction is safe to perform during pregnancy. Case reports thus far have not demonstrated serious harm to the mother or fetus. The major maternal risk is pancreatitis, with an incidence of approximately 5%.

-Surgey, if failed medical treatment.
-Laparoscopy or ERCP can be performed safely in the 2nd trimester .

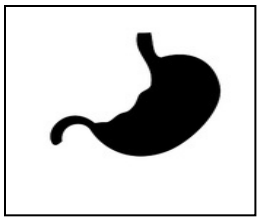
Presentations:
-Acute cholecystitis.
-Biliary colic.
-Gall bladder stones or mud on ultrasouns scan.
Primary treatment is conservative

Peptic ulcer & Gastro-esophageal Reflux

About two-thirds of women experience heartburn in pregnancy, commonly in the third trimester.
This partly because of increased reflux dut to decreased lower esophageal pressure, decreased gastric peristalsis and delayed gastric emptying and partly due to enlarging uterus.
Reflux is manifested by pain and dyspepsia (food-related discomfort).

Treatment:

(1)-Postural changes such as sleeping in semi-recumbent position.
(2)-Avoiding food or fluid intake immediately before sleep.
(3)-Drugs as antacids better to use liquid preparations, metoclopramide, sucralfate and ranitidine can be safely used.

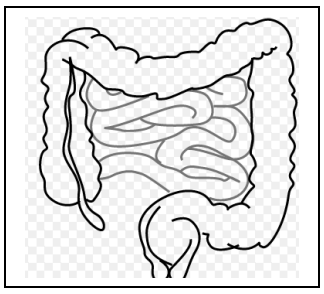


Inflammatory Bowel Disease (IBD)

Both Crohn's disease and ulcerative colitis tend to present in young adulthood. Ulcerative colitis is more commonly encountered during pregnancy. The course of IBD is not affected by pregnancy. Most exacerbations occur early in pregnancy or the early postpartum period. Flares cause abdominal pain, diarrhea and passage of blood and mucous. Active disease may be associated with PTL.

Treatment:

Sulfasalazine and related drugs are safe in pregnancy, but folic acid 5 mg/day should be given concomitantly.
Corticosteroids and azathioprine may be safely used for acute or maintenance management of IBD.



Bronchial Asthma& chest diseases during Pregnancy

Physiological Background:

Pregnancy has a significant effect on the respiratory physiology of a woman.

During pregnancy: oxygen consumption increases by about 40% and the maternal metabolic rate by about 15%,this extra-demand is met by 40-50% increase in the resting minute ventilation (mainly in tidal volume and *not* respiratory rate) with resultant decrease in functional residual capacity and residual volume of air as a consequence of the elevated diaphragm.

In addition, airway conductance is increased and total pulmonary resistance is reduced, possibly as a result of progesterone.

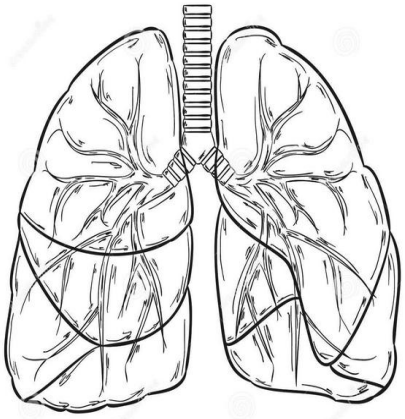
The result of all of these physiologic changes is a hyperventilatory picture as a normal state of affairs in the latter half of pregnancy. This results in the picture of a *chronic respiratory alkalosis* during pregnancy with a decreased pCO_2, decreased bicarbonate (to 18-22 mmol/L), and increased pH (about 7.44).

	Non-pregnant state	**Pregnant state**
pH	7.35	↑ 7.4-7.44
Bicarbonate	28 mmol/L	↓ 18-22 mmol/L
pO_2	93%	↑ 102%
pCO_2	40%	↓ 30%

A normal pCO_2 in a pregnant patient may signal impending respiratory failure. The increased minute ventilation and improved pulmonary function in pregnancy promote more efficient gas exchange from the maternal lungs to the blood. Therefore, changes in respiratory status occur more rapidly in pregnancy than in the non pregnant patient.

Up to 75% of women experience a subjective feeling of breathlessness during the second half of pregnancy possibly due to increased awareness of the physiological hyperventilation.

40-50% ↑ in Tidal volume.
↑ Airway conductance. ↓ Total pulmonary resistance.



Hyperventilatory state

↓

Chronic respiratory alkalosis: ↓ pco2 & bicarbonate and ↑ po2 & pH.

Bronchial asthma

Definition & types

Asthma is a chronic inflammatory disease of the airways that is characterized by increased responsiveness of the trachea-bronchial tree to various stimuli.

Asthma is an episodic disease of acute exacerbations intermingled with symptom-free periods. Asthma is classically divided into 2 distinct types: allergic (extrinsic) and idiosyncratic (intrinsic).

Incidence

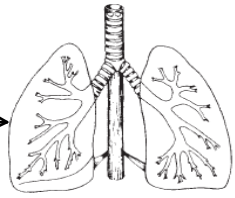
The commonest chronic respiratory disease during pregnancy affecting about 1-4% of pregnant women.

Pathophysiology

Asthma is characterized by inflammation of the airways, with an abnormal accumulation of eosinophils, lymphocytes, mast cells, macrophages, dendritic cells, and myofibroblasts.

This leads to a reduction in airway diameter caused by smooth muscle contraction, vascular congestion, bronchial wall edema, and thick secretions.

Bronchoconstriction with wall edema & thick secretions



Physiological factors affecting asthma in pregnancy

• Increase in free cortisol levels may protect against inflammatory triggers.
• Increase in bronchodilating substances (such as progesterone) may improve airway responsiveness.
• Increase in broncho-constricting substances (such as prostaglandin F2 α) may promote airway constriction.
• Placental 11 β hydroxysteroid dehydrogenase type 2 decreased activity is associated with an increase in placental cortisol concentration and low birth weight.
• Placental gene expression of inflammatory cytokines may promote low birth weight.
• Modification of cell mediated immunity may influence maternal response to infection and inflammation.

Effect of pregnancy on asthma

The effect is influenced by the severity of asthma, those with mild disease will pass without complications while those with severe disease will experience deterioration of their condition.
The potential benefits of pregnancy-induced immune system alterations and progesterone-mediated broncho-dilatation may be opposed by the reluctance of patients and physicians to treat asthma for fear of harming the fetus through drug exposure.

Effect of asthma on pregnancy

It is still accepted that severe and poorly controlled asthma have a detrimental effect on pregnancy, so closer surveillance for hypertensive disorders, IUGR and preterm labour can be justified.

Clinical picture

Precipitating factors include the following:
• Allergens, as pollens, house-dust mites, animal dander & molds.
• Irritants, including cigarette smoke, wood smoke, air pollution, strong odors, occupational dust, and chemicals.
• Medical conditions, including upper respiratory infections, esophageal

reflux.
• Drugs and chemicals, including aspirin, nonsteroidal anti-inflammatory drugs, beta-blockers, radiocontrast media, and sulfites.

Symptoms

- Cough and wheezes.
- Shortness of breath.
- Chest tightness.
- Nocturnal awakenings.

Physical

- Physical examination may be completely normal during remission.
- Retraction (sternomastoid, abdominal, pectoralis muscles), Tachypnea.
- Agitation, usually a sign of hypoxia or respiratory distress.
- Pulmonary findings:
  - Diffuse wheezes.
  - Bronchovesicular sounds.
- Signs of fatigue and near respiratory arrest
  - Alteration in the level of consciousness, such as lethargy, which is a sign of respiratory acidosis and fatigue.
  - Abdominal breathing.

Cough and wheezes.
Shortness of breath.
Chest tightness.
Nocturnal awakenings.

Retraction.
Tachypnea.
Agitation.
Bronchovesicular sounds.
Diffuse wheezes.
Lethargy & drowsiness.

Investigations

(1)-Complete blood cell count (CBC) with differential count.
(2)-Arterial blood gas level (ABG) analysis indicates the level of oxygenation and respiratory compensation. Physiologic changes that accompany pregnancy in the pulmonary system slightly alter normal ABG values: pH 7.4-7.45, pO_2 95-105 mm Hg, pCO_2 28-32, and bicarbonate 18-31 mEq/L.
(3)-Blood cultures must be obtained in patients in whom pneumonia is found or reasonably suggested.
(4)-Chest radiography:
-Chest radiography is indicated when the other coexistent conditions such as pneumonia, CHF, or chronic obstructive pulmonary disease are likely.
-Chest radiographs (2 views) are done with a shielded maternal abdomen.
(5)-Pulmonary function tests:
-Reversible airflow obstruction is central to the diagnosis and assessment of asthma.
-Changes in pulmonary function during acute asthma include the following:

- Decreased peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV1)
- Mild reduction in the forced vital capacity (FVC)
- An increased residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC)

- Patients with asthma usually demonstrate a greater than 15% increase in FEV1, FVC, and PEFR when treated with steroids.

Treatment

6 groups of drugs can be used:
(1)-Beta2-receptor agonists: They are effective after an inhaled or oral dose and have a long duration of action. Terbutaline, metaproterenol, and bitolterol are available as metered-dose inhalers. Salmeterol, has a long duration of action (at least 12 hours). Therefore, it is an effective agent for the treatment of nocturnal asthma.

(2)-Theophylline: Importance of theophylline as an antiasthmatic agent is decreasing because adrenoreceptor agonists and anti-inflammatory drugs are successful. Theophylline has a very narrow therapeutic window. The dose should be increased in the 2^{nd} & 3^{rd} trimesters.

(3)-Anticholinergic drugs: These agents are particularly beneficial for patients with coexistent heart disease in whom beta-adrenergic stimulation may be dangerous. e.g. Ipratropium bromide.

(4)-Mast cell stabilizers: Cromolyn (Intal) Inhibits degranulation of sensitized mast cells following exposure to specific antigens.

(5)-Corticosteroids: This category includes the oral corticosteroids (eg, prednisone), inhaled corticosteroids (eg, beclomethasone, triamcinolone). Aerosol use is the most effective way to decrease the systemic effects of corticosteroid therapy. Their chronic use reduces symptoms and improves pulmonary function in patients with mild asthma. If bronchodilator therapy is not sufficient, inhaled corticosteroids should be started.
Systemic corticosteroids are reserved for patients who require more urgent treatment.

(6)- leukotriene-receptor antagonists: under trials during pregnancy.

Severity of asthma	Preferred medication	Alternatives
Mild	inhaled corticosteroid	leukotriene-receptor antagonist or cromolyn or theophylline
Moderate	inhaled corticosteroid +long-acting beta-agonist	inhaled corticosteroid + leukotriene-receptor antagonist or theophylline
Severe	inhaled corticosteroid + long-acting beta-agonist + oral corticosteroid	-

Main differential diagnoses in pregnant women with dyspnea

• **Asthma**: Acute or progressive dyspnea with wheezing and cough, more often with a history of asthma and precipitating factors; diagnosis confirmed by pulmonary function tests
• **Physiological dyspnea of pregnancy**: Hyperventilation due mainly to increased progesterone; may occur early in pregnancy and does not interfere with daily activities
• **Pulmonary embolism**: Acute respiratory distress or gradually progressive dyspnea with or without tachycardia, cough, chest pain, hemoptysis, or signs of deep venous thrombosis; diagnosis established by scintigraphic ventilation perfusion scan, computed tomographic angiography, or pulmonary angiography
• **Pulmonary edema**: Acute or progressive respiratory distress in the presence of heart disease, hypertension, embolic disease, tocolytic therapy, aggressive fluid replacement, or sepsis; diagnosis confirmed by chest radiography
• **Peripartum cardiomyopathy**: Dyspnea caused by dilated cardiomyopathy occurring during the final month of pregnancy to six months after delivery; signs and symptoms of heart failure confirmed by echocardiographic evaluation
• **Amniotic fluid embolism**: Acute respiratory distress occurring more often during the evacuation of the uterus and which may be complicated by hypotension, seizure, disseminated intravascular coagulation, and cardiac arrest

Special considerations in pregnant women with asthma

• Manage asthma exacerbations aggressively.
• Treat rhinitis, gastric reflux, and other comorbidities adequately.
• Assess pulmonary function (expiratory flow) with spirometry at least monthly.
• Do not give flu vaccination until after 12 weeks of pregnancy.
• Be aware of the risk of pre-eclampsia and intrauterine growth retardation.

Management of labour & delivery

• Continue medications and give short acting β2 agonists or corticosteroids, or both, if asthma is not well controlled.
• Provide ample hydration with intravenous fluid.
• Evaluate pulmonary status and oxygen saturation on admission, and later as needed.
• Asthmatic women may safely use all forms of pain relief in labour, including epidural analgesia and Entonox. In the unlikely event of an acute asthmatic attack, opiates should be avoided. If anesthesia is required, women should be encouraged to have epidural rather than general anesthesia because of the increased risk of chest infection and associated atelectasis.

• Give stress dose of corticosteroids (hydrocortisone 100 mg 6–8 hourly) for women on oral steroids (> 7.5 mg prednisolone daily for more than 2 weeks) at the onset of labour or delivery.

• Prostaglandins E1 & E2 used to induce labour are safe (PG E2 is a bronchodilator) on the other hand, PG F2α , ergometrine and carboprost may cause bronchospasm and should be avoided.

• NSAIDs used for pain relief after delivery should be avoided as they may precipitate an attack in susceptible patients.

-General anesthesia.
-Opiates & NSAIDs.
-Bronchoconstrictor uterotonic agents: PGF2α, ergometrine & carboprost.

Do not forget:
-Bronchodilators.
-Good I.V. hydration & oxygen.
-Stress corticosteroids.

Breast feeding and risk of asthma in the newborn

Women with asthma should be encouraged to breast feed. All medications are safe with lactation (inhaled and oral), although high dose oral steroid (more than 40 mg/day) carries the risk of neonatal adrenal suppression.

The risk of atopic disease developing in the child of an asthmatic woman is about one in 10, or one in three if both parents are atopic. This risk may be reduced by breast feeding.

Contraception: Like any patient.

Pneumonia

-Risk factors for pneumonia:
(1)-History of upper respiratory infections.
(2)-Chronic respiratory disease e.g. asthma, cystic fibrosis.
(3)-Smoking.Anemias.
(4)-Immunosuppression: HIV , substance abuse ,alcoholism and steroids.
(5)-General anesthesia (aspiration pneumonitis).
-Common organisms: sterpt. pneumoniae and hemophilus influenza. a typical organisms include mycoplasma and legionella. In HIV-positive individuals,unusual organisms include mycobacteria, cryptococci and pseudomonas.
-Treatment according to culture and sensitivity, mostly third generation cephalosporins,erythromycin and clarithromycin.

Pulmonary Tuberculosis

-There is *no evidence* to suggest that pregnancy is an independent risk factor for infection with mycobacterium tuberculosis or that the course and outcome of TB are altered by pregnancy.
-Diagnosis by chest x-ray, sputum examination with Ziehl-Nelsen stain and culture with sensitivity tests.
-Active infection is treated with combination of antibiotics mainly Isoniazide, Rifampicin, Pyrazinamide and sometimes Ethambutol.
-Risks of multidrug therapy include peripheral neuropathy, liver toxicity with vitamin K deficiency, thus supplementation with vitamin B complex and oral vitamin K supplements in the third trimester to prevent hemorrhagic disease of the newborn.
-Patients will be non-infectious after 2 weeks of starting antibiotics.

- If infectious during labour, the newborn should be immunized with BCG and also given prophylactic antibiotics usually isoniazide, and the placenta is sent for histopathology & microbiological investigations, evidence of acid-fast bacilli should increase surveillance of the newborn.

-Combination of antibiotics mainly Isoniazide, Rifampicin & Pyrazinamide.

-Vitamin B complex & vit K supplements.

-Newborn vaccination ± prophylactic antibiotics as isoniazide.

Cystic Fibrosis

Predictors of pregnancy outcome:

(1)-Absolute pre-pregnancy pulmonary functions.
(2)-Presence of pulmonary hypertension.
(3)-Degree of pancreatic insufficiency: glucose intolerance or diabetes predating pregnancy.
(4)-BMI and maternal weight gain during pregnancy.
(5)-Presence of liver disease and portal hypertension.

-Pregnancy *accelerates* the loss of respiratory functions in severe cases of cystic fibrosis.
-Mild and moderate cases pass without complications while severe cases may experience miscarriage, IUGR and PTL.
-Preconception counseling is mandatory, patients with poor pulmonary functions or pulmonary hypertension may be advised against pregnancy.
-Regular ANC with serial lung functions (spirometry, ABG, chest radiography) and careful surveillance for chest infections, pneumothorax, atelectasis, respiratory failure and cor pulmonale.
-Observation of cardiovascular status and pancreatic enzymes.
-CS is reserved for obstetric indications preferably under regional anesthesia.

-Abortion.
-IUGR.
-PTL

-Chest infections.
-Pneumothorax.
-Atelectasis.
-Respiratory failure.
-Cor pulmonale.

Epilepsy with pregnancy

Incidence:
Approximately 6 in every 1000 pregnancies are complicated by a past or current history of epilepsy being the most common chronic neurologic disorder complicating pregnancy.

D.D. of seizures during pregnancy and the postpartum period

Primary: Idiopathic epilepsy.
Secondary to specific causes: **Trauma** **Intracranial infections** (meningitis, encephalitis, brain abscess)**,** **Vascular disease** (cerebral hemorrhage or infarction, hypertensive encephalopathy, eclampsia , cerebral vein thrombosis ,thrombotic thrombocytopenic purpura)**,** **Metabolic** (liver and kidney failure) **and drug toxicity .**

Effect of pregnancy on epilepsy
In general, pregnancy does not affect the frequency of seizures. About 25% of women report improvement and 10-30% of women experience increased seizure frequency particularly poorly controlled patients.
Women with epilepsy who are seizure free for at least 9 months prior to pregnancy probably have a high likelihood (84–92%) of remaining seizure free during pregnancy.

Reasons for deterioration of seizure control during pregnancy:
(1)-Decreased drug levels: decreased intake (fear of teratogenecity), decreased GIT absorption (decreased gastric emptying & NVP), decreased blood levels (due to changes in protein binding) and increased clearance (increased hepatic metabolism).
(2)-Other factors: stress, lack of sleep near term, and during labour (hyperventilation).

Effect of epilepsy on pregnancy

There is increased risk of congenital malformations (in 25-33% of cases) mostly due to anti-epileptic drugs (AEDs).

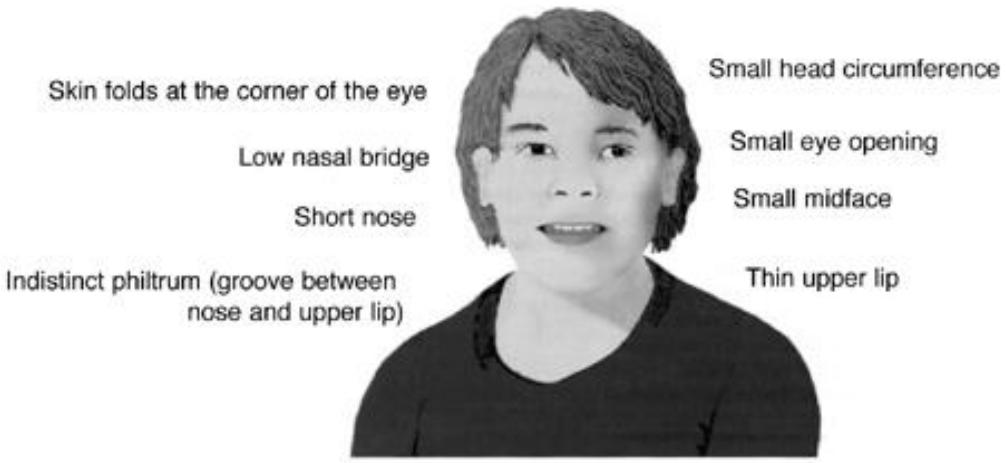
There is probably increased risk of cesarean delivery, but no increased risk of preterm labor. However, for women with epilepsy who smoke, there is possibly a substantially increased risk of preterm labour.

Increased the risk to the child of developing epilepsy (4%). if both parents are affected (10%) or previously affected sibling and both parents (15%).

Anti-Epileptic Drugs (AEDs):

Mechanism of Teratogenicity: phenytoin, carbmazepine and sodium valproate, all cross the placenta and interfere with folic acid metabolism. *The fetal hydantoin syndrome* described by Hanson and Smith in 1975 has been re-named *the fetal anticonvulsant syndrome* after the realization that AEDs other than phenytoin could also cause a similar abnormalities .

Major abnormalities	**Minor abnormalities**
Microcephaly. Cleft lip & palate. Neural tube defects. IUGR. Developmental delay.	*Face:* hypertelorism, epicanthus folds, low- set ears, flat nasal bridge and long philtrum.



Mechanism of vitamin k deficiency: AEDs perhaps by inducing liver enzymes responsible for vitamin K oxidative degradation. Vitamin K is required for carboxylation of factors II, VII, IX and X and deficiency in the neonate may cause hemorrhagic disease of the newborn with catastrophic bleeding.

Management of Epilepsy and pregnancy

Pre-pregnancy counseling:

-Consideration should be given to stopping AEDs in those women who have been seizure free for more than 2 years as the risk of relapse is 20-50%.

-When possible, treatment regimens should be simplified to a single AED with the lowest effective dose to minimize the risk of congenital abnormalities.

-The risks of AEDs on the fetus and its stoppage on the mother should be clarified.

Antenatal care:

-Care should be carried out by obstetrician and neurologist.

-Screening for congenital anomalies of all women on AEDs with fetal echocardiography at 22 weeks gestation.

-Drug level monitoring as a starting level then repeated as indicated.

-Oral vitamin K (10 mg/day orally) started at 36 weeks onwards to prevent hemorrhagic disease of the newborn.

-If steroids to be given for obstetric indications, women using enzyme-inducing AEDs should be given 48 mg in total (2 doses of 24 mg dexamethazone 24 hours apart).

Intrapartum care:

-Mode of delivery according to obstetric indications.

-Labour carries a higher risk of seizures due to hyperventilation and altered free levels of AEDs.

-Seizures during labour are best controlled by benzodiazepines (IV or rectal diazepam or clonazepam) as IV phenytoin may cause arrhythmias. Provided that FHR tracing remains reactive , otherwise cesarean section is indicated as well in cases of recurrent seizures or status epilepticus.

Postpartum care:

-The serum levels of AEDs may increase, so maternal observation with lowering of the dosage should be done.

-Breastfeeding should be encouraged with observation of withdrawal effects in the fetus as all AEDs reach breast milk.

-A single dose of 1 mg vitamin K by IMI should be given to the neonate to prevent hemorrhagic disease of the newborn.

Contraception:

The enzyme-inducing AEDs will decrease the efficacy of hormonal methods options include:

(1)-Combined oral pills containing 50 ug of estrogen with preferably a shorter pill-free interval (5-6 days instead of 7 days).Tri-cycling will further reduces the chances of ovulation.

(2)-Depo-Provera 150 mg should be given every 10 weeks instead of 12 weeks.

(3)-The mirena intrauterine system is ideal as the locally administered progestin will *not* be affected by enzyme-inducing AEDs as well as copper IUD.

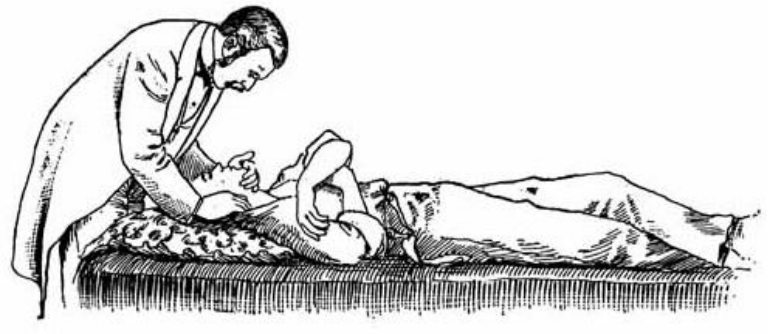
Special instructions to new mothers with epilepsy:

(1)-Ask for extra help if you are not getting enough sleep.

(2)-Ensure that someone else is present while bathing your baby.

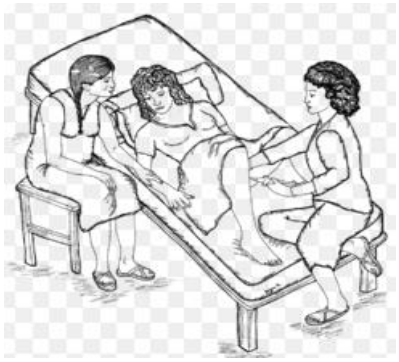
(3)-Surround yourself with cushions and pillows when you are holding your baby.

(4)-Feed and change your baby on the floor while leaning against a wall to prevent your falling onto the baby in the event of seizure.

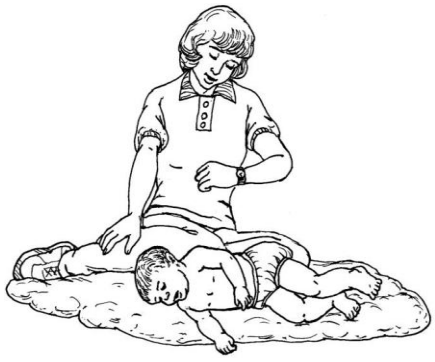


Pre-pregnancy counseling:
-Single drug with the least effective dose.
-Stop AEDs if seizure free for ≥ 2 years.
-Discuss risks of AEDs.

Antenatal care:
-Monitoring of AEDs blood levels.
-Screening for congenital fetal anomalies at 22 weeks.
-Give oral vit K 10mg/d from 36 weeks onwards.
-Double the dose of antenatal steroids (if indicated).



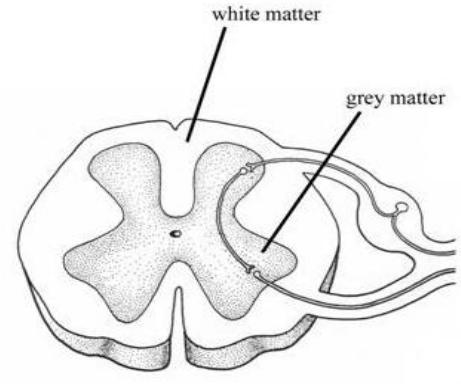
Vaginal delivery is preferred unless CS is indicated e.g. obstetric indications, recurrent seizures or status epilepticus.



Post-partum care:
-Adjust the dose of AEDs.
-Allow breast feeding.
-Give vit K to the newborn.
-Contraception: IUD is ideal, hormones (need special dosage) or tubal ligation.
-Give special instruction to the new mothers.

Multiple Sclerosis (MS)

-Multifocal autoimmune disease of the CNS (with myeline degeneration of the brain & spinal cord) characterized by remissions and exacerbations diagnosed by clinical features and MRI revealed white matter lesions.
-Pregnancy does *not* accelerate the course of MS and may have a protective effect (reduction in the number of relapses), but relapses are more common in the puerperium.



Myeline degeneration of the white matter of the brain & spinal cord

Visual symptoms:
Pain, blurred vision, loss of vision in one eye & disturbed colour vision.

Mental symptoms:
↓ concentration, attention & memory.

Psychic:
Depression & personal changes.

Sensory:
Numbness, pricking pain & loss of sensations.

Motor:
-Muscles spasms.
-Tremors.
-Limb weakness (paresis).

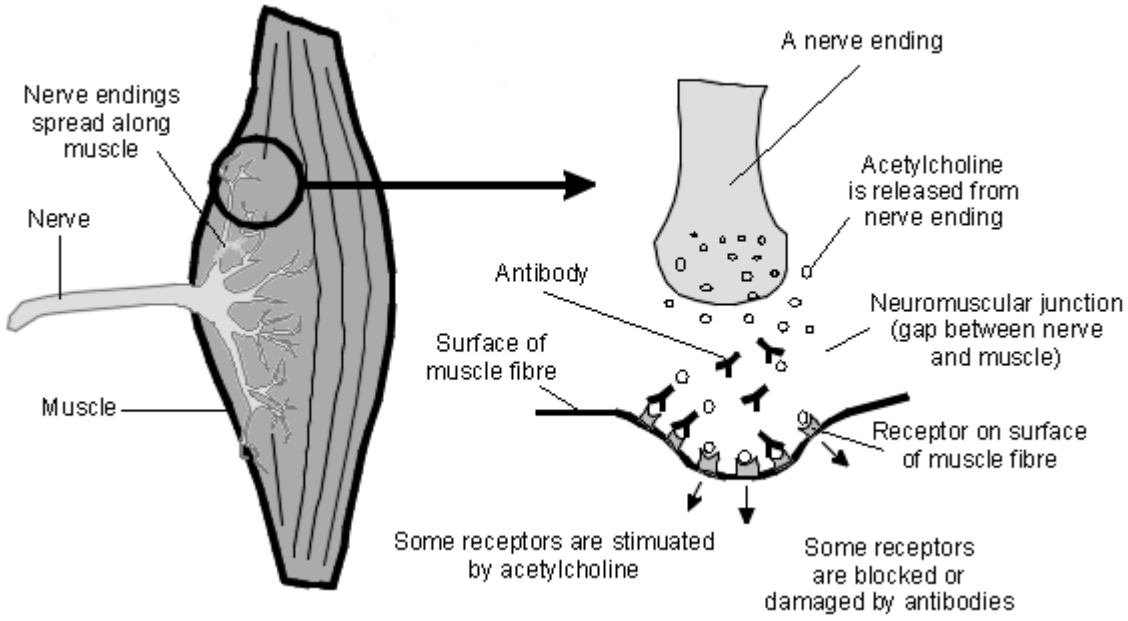
Autonomic:
-Bladder dysfunction (UI).
-Gut dysfunction.

-Drug therapy during pregnancy:
(1)-Corticosteroids during relapses: methylprednisolone IVI followed by tapering of the dose with oral prednisone.
(2)-Tricyclic antidepressants TCA in urinary urgency and depressive symptoms. (3)-Prophylaxis with cyclophosphamide, azathioprine and beta-interferons should be *stopped* during pregnancy.

-Mode of delivery: CS is reserved for obstetric indications except if there is severe relapse with exacerbations of urinary symptoms and limb spasm. Only Epidural anesthesia should be used as it does not cause disease progression.

Myasthenia Gravis

-A rare neuromuscular disease leading to fluctuating muscle weakness and fatiguability. It is an autoimmune disorder, in which weakness is caused by circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction, inhibiting the excitatory effects of the neurotransmitter acetylcholine on nicotinic receptors throughout neuromuscular junctions.



-It may present with double vision, dysphagia, ptosis and respiratory muscle failure.
-It is diagnosed with administration of edrophonium chloride (short acting anti-choline-estrase) which improves symptoms notably muscle strength.

-Treatment options: drug doses are gradually increased during pregnancy
(1)-First line: long acting anti-cholinesterase drugs as neostigmine and pyridostigmine.
(2)-Second line: immunosuppressive drugs as corticosteroids,azathioprine,cyclosporine A and methotrexate.
(3)-Plasmapharesis and IV immunoglobulins infusions are used for serious exacerbations.
-Myasthenic crises can be precipitated by infection, aminoglycosides, magnesium sulphate, beta blockers and agonists.

-Mode of delivery: CS for obstetric indications, instrumental delivery is mandatory due to muscle fatigue.
-The neonate is observed for neonatal myasthenia gravis.

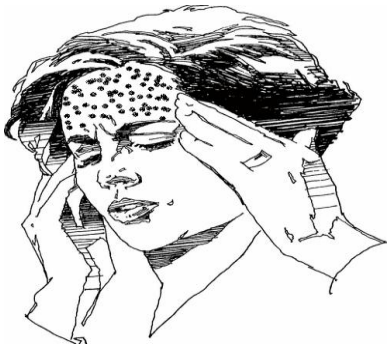
Affected muscles:
-Eye muscles.
-Muscles of swallowing.
-Respiratory muscles.
-Bulbar muscles.
-Limb muscles.

Myasthenia crisis by:
-Aminoglycosides.
-Beta blockers or agonists.
-Magnesium sulphate.
-Infections.

Migraine and Tension headache

-Tension headache is more common than migraine.
-Classic migraine attack is preceded by an aura of visual disturbance, aphasia and numbness for not more than one hour followed by a throbbing unilateral headache associated with nausea, vomiting and photophobia.

-Treatment include:
(1)-Non-phamacologic: relaxation technique, sleep, massage and ice packs.
(2)-Analgesics: paracetamol, codeine-based drugs with antiemetics and NSAIDs. Ergotamine and sumatriptan should be avoided during pregnancy.
-Prophylaxis during pregnancy is best achieved by low dose aspirin.



Tension headache:
Pain is like a band squeezing the head.

Sinus headache:
Pain is over the eyebrows and the maxilla (over sinuses).

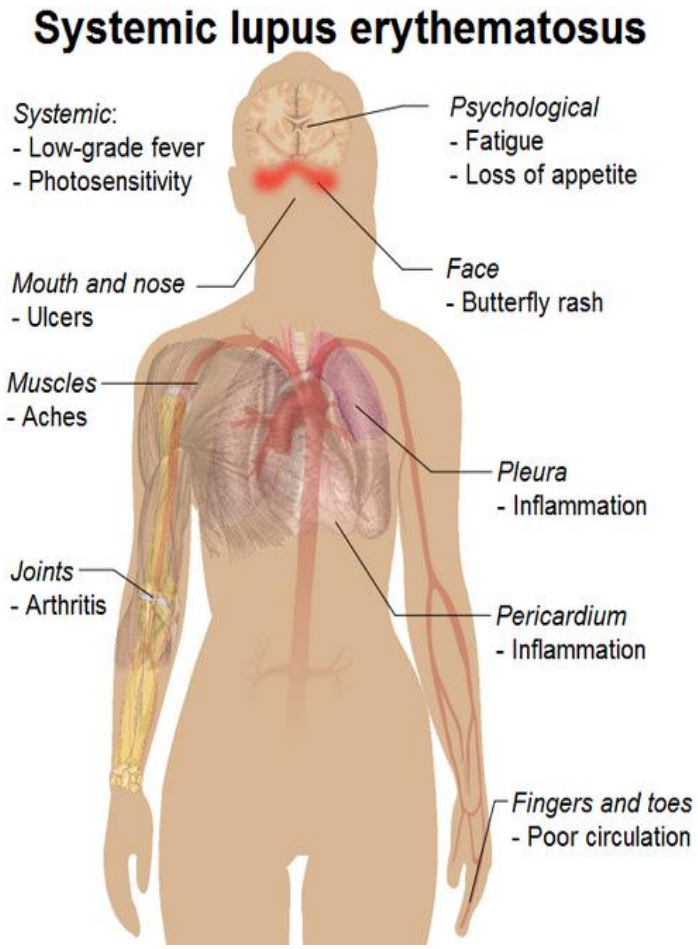
Migraine headache:
Pain affects half of the face preceded by an aura of visual symptoms & vomiting.

Autoimmune Connective tissue disease

	Systemic Lupus Erythematosus (SLE)	Rheumatoid arthritis (RA)
Incidence	1 in 2000 pregnancies	1 in 5000 pregnancies
Pathophysiology	Immunologic damage: **1.** The formation of (Ag–Ab) complexes, which, in turn, cause glomerulonephritides, arthritis, dermatitis, pericarditis & pneumonitis. **2.** Antibodies directed against cell-specific antigens (e.g. ITP, hemolytic anemia, APS and vasculitis).	An anti-IgM or IgG rheumatoid factor (RF) complex deposition **1.** Rheumatoid nodules: S.C. lumps over joints. **2.** Pleuritic and pericardial effusions: with low glucose. **3.** Felty's syndrome: splenomegaly and granulocytopenia **4.** Rheumatoid vasculitis.
Effect of SLE /RA on Pregnancy	The prognosis is dependent on four factors: the activity of the disease at conception, the occurrence of subsequent flares, the coexistence of lupus nephritis & development of APS antibodies. Patients with SLE have an increased risk of spontaneous abortion, PTL, IUGR, IUFD, CS and PE. The risk of PE in SLE patients is more increased with history of APS, nephritis, DM and hypertension.	There appears to be **no** increased rate of spontaneous abortion, perinatal mortality, or IUGR in the presence of RA uncomplicated by APS antibodies.
Effect of Pregnancy on SLE /RA	Pregnancy does not appear to alter the long-term prognosis of most SLE patients. These flares are usually mild and	75% will improve during pregnancy with a 90% postpartum exacerbation rate. Maternal immune response to

	involve primarily cutaneous and articular symptoms.	paternal HLA antigens may have a role in pregnancy-induced remission of RA.
Diagnosis	Patients generally present with intermittent, unexplained pyrexia, malaise, arthralgias, myositis, serositis, thrombocytopenia, nephritis, and/or CNS abnormalities. A positive antinuclear antibody (ANA) is found in 98% of patients when **four** or more of the followings: **1.** Butterfly rash. **2.** Discoid lupus. **3.** Photophobia. **4.** Oral ulcers. **5.** Arthritis. **6.** Serositis. **7.** Renal disease manifested by proteinuria greater than 500 mg/day, and/or cellular casts on urinalysis. **8.** Neurologic abnormalities often caused by cerebral vasculitis e.g. seizures, and psychosis. **9** Hematologic abnormalities, including HA, leukopenia less than 4000 cells/mL, lymphopenia less than 1500/mL, and thrombocytopenia less than 100,000/mL.	Affection of small joints (e.g. wrist and hand). An anti-IgM or IgG rheumatoid factor (RF) complex deposition is also noted in 90% of patients.

Treatment	Corticosteroids, Parecetamol, Immunosuppressive agents, Antimalarial Drugs, Antihypertensives.	Corticosteroids, Parecetamol , Immunosuppressive agents, Antimalarial Drugs,



Lupus panel:
Antinuclear antibody, anti-Ro &anti-La antibody titers, lupus anticoagulant levels, anticardiolipin antibody, anti-dsDNA antibody titers, C3 & C4 complements levels.

Management

Management of SLE in pregnancy consists of the following:

- **First Trimester**: Initial laboratory studies include CBC, serum creatinine, 24-hour urine collection for measurement of protein and creatinine, urinalysis, and a lupus panel (antinuclear antibody, anti-Ro and anti-La antibody titers, lupus anticoagulant levels, and anticardiolipin antibody, anti-dsDNA antibody titers, C3, and C4 complements).
  Evaluation for lupus flares should be done at each visit.
- **Second Trimester:** Repeated laboratory studies. Obstetric ultrasonography should be performed every 4 weeks after 20 weeks' gestation until delivery to monitor fetal growth. In women positive for anti-Ro or anti-La antibodies, fetal echocardiography should begin at 16 to 18 weeks' gestation to assess for possible heart block and be repeated weekly until delivery.
- **Third Trimester:** Fetal testing, with weekly non-stress tests and/or biophysical profile, may be initiated as early as 28 weeks based on clinical scenario. In the presence of IUGR, fetal Doppler ultrasonographic studies should be performed.
  Treatment with betamethasone or dexamethasone should be initiated in patients with poor fetal test results or worsening maternal disease in anticipation of a preterm delivery.
- **Postpartum:** Repeated labs, as recommended in the first trimester, should be repeated postpartum.

1st trimester: lupus panel & renal investigations.

2nd trimester: repeat labs, U/S: Anomalies scan ± fetal echocardiography.

3rd trimester: repeat labs, tests of fetal growth & well-being and antenatal steroids.

Lupus Flare

Most lupus flares are diagnosed clinically when patients present with fever, malaise, and lymphadenopathy. Laboratory findings include low C3 or C4 complement levels, active sediment on urine microscopic analysis elevation in anti-dsDNA antibody titer, and hemolytic anemia, thrombocytopenia, and leukopenia.

Distinguishing a lupus flare from pre-eclampsia in pregnant patients can be challenging. Factors that are useful include complement levels, which are low in lupus flare and usually normal in pre-eclampsia; serum hepatic transferase levels, which are generally normal in a lupus flare but may be elevated in pre-eclampsia; the presence of red blood cell casts in the urine implies active lupus; and very gradual onset of proteinuria (characteristic of lupus flare).

If differentiation between pre-eclampsia and a lupus flare becomes crucial to determine further management, renal biopsy may be performed.

Lupus flare versus Pre-eclampsia:
-↓↓C3 & C4 complement levels.
-Normal liver enzymes (ALT & AST).
-RBC casts in urine.

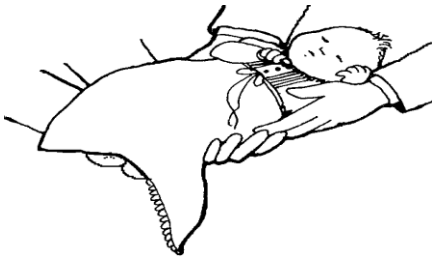
Treatment during Lupus Flare

- Corticosteroids can be used during a lupus flare. The usual dosage is prednisone 60 mg daily for 2 to 3 weeks, which is then tapered to the lowest dosage, ideally <10 mg/d, to control symptoms. Patients should be monitored closely for the development of glucose intolerance, hypertension, and pre-eclampsia. Patients on steroids should be on low salt diet, join an exercise program, and take calcium & vitamin D supplements.
- Immunosuppressive agents are used for only patients with significant organ involvement.
- Antimalarial drugs: hydrochloroquine is currently being used to treat SLE. Controversy exists over whether or not to continue hydrochloroquine during

pregnancy.
-Antihypertensives: Antihypertensive agents with good safety records in pregnancy include methyldopa and labetalol hydrochloride .
- In pregnant women, the presence of antiphospholipid antibodies or lupus anticoagulant is associated with fetal death, particularly in the second trimester. Treatment with low-dose aspirin and moderate-dose heparin improves fetal outcome but with more maternal complications.
Therapy with low-dose aspirin, heparin, or warfarin is usually recommended for approximately 3 months after delivery for women with history of thromboembolic events.

Neonatal lupus syndrome

Neonatal lupus syndrome is a rare syndrome that occurs in a minority of infants delivered only to mothers who have antibodies to the Ro (SSA) or La (SSB) antigens, or both. Among infants at risk, fewer than 25% develop the cutaneous manifestations, and fewer than 3% develop congenital heart block. Although no treatment has been proven to be effective in reversing fetal heart block in utero, the administration of dexamethasone to the mother may be beneficial in preventing extension of the fetal myocarditis.



Neonatal lupus syndrome:
-25% cutaneous manifestations.
-3% congenital heart block.

Management of RA:

Initial treatment in pregnancy should include local steroid injections into the joint. If the response to local measures proves inadequate, begin prednisone, 5mg every morning and 2.5mg every evening. The utility and safety of other drugs are listed below.

1. *Paracetamol:* analgesic of choice
2. *Non-steroidal anti-inflammatories:* avoid after 30 weeks

3. *Intramuscular gold salts:* cross the placenta, may be useful in postpartum period to reduce exacerbations.
4. *Chloroquine:* useful, but possibly rare ocular side-effects in the fetus
5. *D-Penicillamine:* relatively contraindicated
6. *Methotrexate:* should be avoided
7. *Azathioprine:* use if refractory to steroids
8. *Cyclophosphamide:* avoid

Drugs to be stopped or avoided during pregnancy:
NSAIDs, Gold, Pencillamine, Cyclophosphamide, Methotrexate and Chlorambucil

Drugs to be given during pregnancy:
Paracetamol, Hydroxychloroquine, Sulfasalazine , Steroids and Azathioprine.

Contraception in SLE: COCs are contraindicated, Progestin only injectables can be used with no effect on flares, IUD is contraindicated if on immunosuppression and tubal sterilization is performed with renal and vascular disease.

Drugs to be stopped or avoided during pregnancy:
-NSAIDs. -Gold.
-Pencillamine. -Cyclophosphamide.
-Methotrexate. -Chlorambucil.

Drugs to be given during pregnancy:
-Paracetamol -Hydroxychloroquine.
-Sulfasalazine. -Steroids.
-Azathioprine.

Anemia and Pregnancy

Physiologic Consideration:

-Plasma volume increases by 50% while red cell mass by *only* 25%.
-There is a consequent fall in Hb concentration, hematocrit and red cell count because of hemodilution.
- Mean cell volume (MCV) increases secondary to erythropoiesis.
- Mean cell Hb concentration (MCHC) remains stable.
-Serum iron and ferritin concentrations decrease secondary to increased utilization.
-Iron requirements increase (due to expanding red cell mass and fetal requirements) from 2.5 mg elemental iron/day in the first trimester to 6.6 mg/day in the third trimester (700-1400 mg total pregnancy).
-There is a moderate increase in iron absorption and total iron binding capacity (TIBC) increases.
-Folate requirements increase in pregnancy (due to the fetus, placenta, uterus and expanded red cell mass).
-There is no major effect on B12 stores, although levels decrease (preferential active transport to the fetus).

Definition:

A pathological condition in which the oxygen carrying capacity of red blood cells is insufficient to meet the body's needs.
The WHO recommends that the Hb concentration should not fall below 11 g/dl. But CDC use the figures 11 g/dl in the first & third trimester and 10.5 g/dl in the second trimester.

Incidence:

Around 30-50% of women become anemic during pregnancy, with iron deficiency being responsible in more than 90% of cases. The incidence of folate deficiency is around 5% and this is almost always the cause of megaloblastic anemia in pregnancy, with vitamin B12 deficiency being rare.

Causes of anemias:

I. Decreased production of RBCs (Hemopoietic):

-Deficiency anemias: iron, folic acid, B12 and protein deficiency.

-Aplastic anemia.
-Bone marrow suppression secondary to chronic diseased e.g. renal failure, cancer therapy (chemotherapy & radiotherapy).

II. Blood loss (Hemorrhagic)

Chronic loss as in parasitic infestations & menorrhagia.

III. Hemolytic anemias

Increased destruction of RBCs.

Clinical features:

Anemia is very often asymptomatic in pregnancy, with the diagnosis being made on routine screening.
Clinical features include tiredness, dizziness, fainting, and lethargy. Pallor may be apparent.

Screening:

Anemia is routinely screened for in pregnancy by estimation of the Hb concentration by means of a full blood count at the beginning of pregnancy, at the start of the third trimester and again at term.

Risk factors:

In addition to nutritional deficiency, multiparity and increasing maternal age are the main causes of iron deficiency anemia.

Iron deficiency anemia
-Maternal: PTL, infections, PPH and increased need for blood transfusion.
-Fetal: IUGR and IUFD.

Folic acid deficiency
Those of anemia and increased incidence of neural tube defects and other anomalies if early, PE, abruption placenta, vesicular mole.

Deficiency anemia

	Iron deficiency anemia	Folic acid deficiency anemia
Incidence	> 90%	5%
Aetiology	Increased demand, decreased intake (NVP), decreased absorption (low HCl), chronic blood loss as in piles & bleeding during pregnancy.	Increased demand, decreased intake (NVP), patients on anticonvulsant therapy.
Consequences	Maternal: PTL, infections, PPH and increased need for blood transfusion. Fetal: IUGR and IUFD.	Those of anemia and increased incidence of neural tube defects and other anomalies if early, PE, abruption placenta, vesicular mole.
Diagnosis	1. CBC: Microcytic hypochromic anemia. 2. Ferritin conc.(diagnostic) less than 12 mg/L. 3. TIBC increased (N: 320 mgldL).	1. CBC: Macrocytic hyperchromic anemia (may be masked by iron def.). 2. Serum folate is decreased. 3. BM aspirate: megaloplastic hyperplasia.

Treatment:

I. Iron deficiency anemia:

diet (foods rich in iron and vitamin C), iron supplements.

IV iron is the most effective in improving the hematological indices , followed by IMI with oral supplementation being least effective.

(1)- Oral iron: effective if there is enough time for correction of anemia as maximum increase in Hb is 0.8 g/dl per week. The recommended dose is 120-240 mg of elemental iron per day. Ferrous salts are better than ferric salts and vitamin C taken simultaneously aids iron absorption.

(2)-Parenteral iron: for those with proven iron deficiency that cannot be managed with oral therapy because of lack of compliance, severe gastrointestinal side effects, malabsorption, or continuing significant blood

loss.

A-Intramuscular iron: iron sorbitol is administered by deep IMI. The dose is calculated depending on the degree of iron deficiency and patient's body weight.

B-Intravenous iron: iron sucrose is licensed for total dose iron replacement in the second and third trimesters. It is given as a single infusion over 4-6 hours.

Parenteral iron especially IV is a realistic alternative to blood transfusion when oral therapy has failed.

(3)-Blood transfusion: is the most rapid way to increase Hb concentration near term but has many risks.

(4)-Erythropoeitin: recombinant human erythropoietin is used for anemia associated with chronic renal failure.

II. Folic acid deficiency anemia:

Oral folate 5 mg/day or in severe cases parenteral folate or 5 mg oral pteroglutamic acid. Folic acid must be supplemented together with iron and vitamin B12 to avoid occurrence of nervous manifestations.

There is NO evidence to advice against a policy of routine iron and folic acid supplementation in pregnancy [A].*Cochrane Database Syst Rev , 2006.*

Oral iron: 120-240 mg/d of ferrous salts plus vit C if there is enough time.

↓

Parenteral iron (I.V.) is preferred if near term, GIT side effects or non-compliance.

↓

Blood transfusion as last resort or in emergency cases.

Hemolytic anemia and pregnancy

Definition:
Disorders in which the rate of RBCs destruction is increased and the ability of bone marrow (BM) to respond is not impaired.

Causes:
I. Corpuscular:
-Cell wall defect: as spherocytosis.
-Enzymatic defect : G6PD deficiency, Pyrovate kinase deficiency.
-Hemoglobinopathies : thalassemia and sickle cell anemia.
II. Extra-corpuscular:
-Immunologic: autoimmune hemolytic anemia.
-Non immunologic: toxins (drugs,snake venom),infections (malaria, clostridia).

Clinical manifestations:
(1)-Pallor & features of anemia as fatigue, palpitation, tachycardia and hemic murmurs.
(2)-Tinge of jaundice.
(3)-Dark stools and may be dark urine in acute hemolysis.
(4)-Hepatosplenomegaly (HSM) but shrunken spleen in sickle cell anemia.
(5)-Acute hemolytic crisis and other crises.

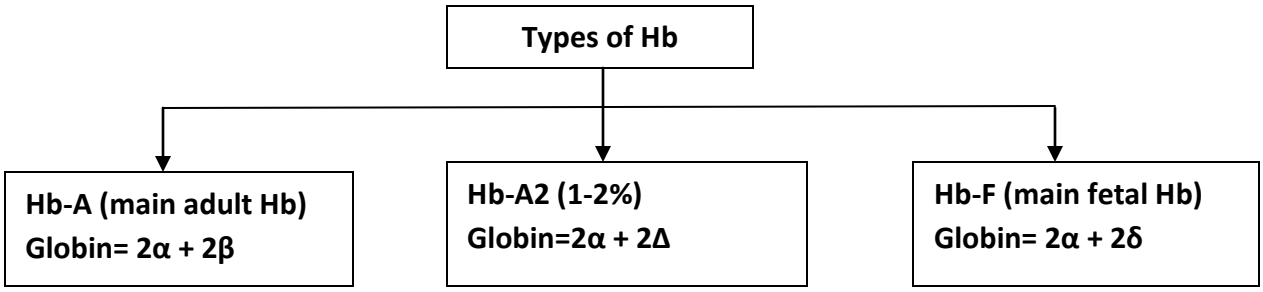
Investigations:

I. To diagnose hemolytic anemias:
(1)-Blood: Normocytic anemia (Microcytic in thalassemia), Reticulocytosis (> 2%), indirect hyperbilirubinemia, increased serum iron and decreased TIBC.
(2)-Urine and Stool analysis: increased uro-& stercobilinogen.
(3)-BM aspirate: erythroid hyperplasia.

II. To diagnose the cause:
(1)-Blood smear: RBCs shape: target cells in thalassemia, sickles in sickle cell anemia and spherocytes.
(2)-Enzymatic assay: for RBC G6PD.

(3)-Fragility test: rapid hemolysis in hypotonic saline in spherocytosis.
(4)-Sickling test: sickling of RBCs on addition of Na metabisulfite.
(5)-Hb electrophoresis (or spectrophotometry): for type of Hb, Hb-F in thalassemia & sickle cell anemia and Hb-S in sickle cell anemia.
(6)-Apt test: Hb-F resists denaturation by alkalies.
(7)-Coomb's test: for autoimmune hemolytic anemia.

Biochemistry of Hb molecule:
The Hb molecule is formed of:
(1)-Heme: iron proto-por-phyrin complex.
(2)-Globin: protein consisting of 4 polypeptide chains as follows:
-Hb-A: globin is formed of 2 alpha and 2 beta chains.
-Hb-A2: globin is formed of 2 alpha and 2 delta chains.
-Hb-F: globin is formed of 2 alpha and 2 gamma chains.
In the fetus, Hb-F is the most frequent at birth, it constitutes 70% of Hb which is gradually replaced by Hb-A.
In adults, Hb-A is the main Hb (97%), Hb-A2 (1-2%) and Hb-F (1-2%).
N.B. Alpha chain is responsible for oxygen carrying.



Effect of hemolytic anemia on pregnancy:

I. Maternal complications: anemia, heart failure, thrombo-embolism, PE, UTI, acute abdomen during pregnancy, hemolytic crises, abnormal uterine action, PPH and defective lactation.
II. Fetal complications: IUGR, IUFD and inheritance of the disease.

Common types:

Thalassemias: an autosomal inherited disorder results from failure of production of either alpha or beta chain of globin.

Sickle cell anemia: an autosomal inherited disorder in which the A.A. glutamic acid in position 6 of the beta chain is replaced by valine leading to production of Hb-S which in exposure to hypoxia, RBCs become sickle-shaped with subsequent fragmentation. Abnormal cells increase the blood viscosity and may occlude blood vessels of various organs (vaso-occlusive crisis).Thus COCs are contraindicated.

Glucose-6-Phosphate Dehydrogenas (G6PD) deficiency: an X-linked disorder common in blacks. Hemolysis occurs on exposure to drugs as NSAIDs, sulpha drugs, anti-malarial drugs and nitrofurantoin or ingestion of fava beans.

Alpha thalassemia	Beta thalassemia	Sickle cell anemia
I. Major (homozygous): globin is formed of 4 gamma chains, the fetus is affected by hydrops (Bart's hydrops). **II. Minor (heterozygous):** globin is formed of 1 alpha & 3 gamma chains, live to adult life with no or mild anemia.	**I. Major (homozygous):** globin is formed of 2 alpha & 2 gamma chains, Hb-F 70-90% and Hb-A 10-30%. Usually dies during childhood or adolescence. **II. Minor (heterozygous):** Hb-F 10% and Hb-A 90 %. live to adult life with mild anemia. May be diagnosed during pregnancy when anemia failed to respond to iron therapy.	**I. Major (homozygous):** Hb-SS, sickle cell anemia or disease. On exposure to hypoxia or stress, hemolysis occurs. **II. Minor (heterozygous):** Hb-AS , sickle cell trait. only in severe hypoxia , hemolysis may occur.

Treatment:

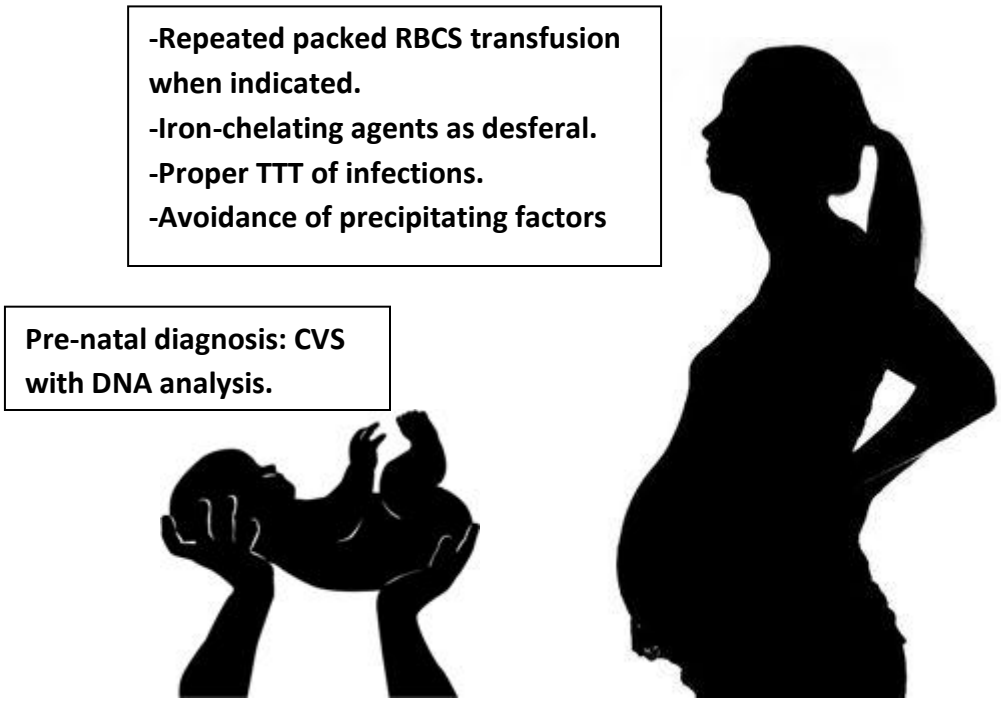
(1)-Repeated packed RBCS transfusion when indicated.
(2)-Splenectomy and folic acid supplementation.
(3)-Iron-chelating agents as desferal.
(4)-Proper TTT of infections.
(5)-Avoidance of precipitating factors of hemolysis as drugs, hypoxia……etc

Pre-conception counseling:

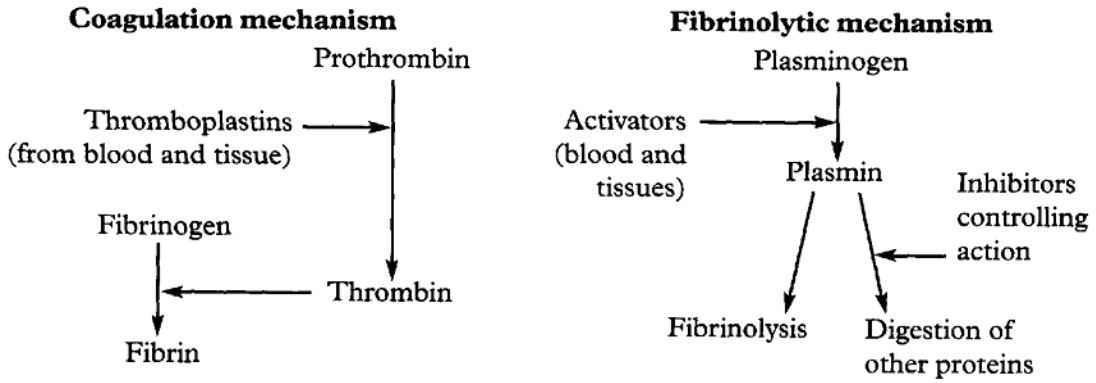
If a woman is found to be a carrier to hemoglobinopathy, her partner should be screened as early as possible and, if there is a risk of the fetus to have a major hemoglobinopathy, expert counseling for prenatal diagnosis and termination of pregnancy.

Pre-natal diagnosis:

Carried out by DNA analysis with chorionic villous sampling to allow early termination if the parents wish. Amniotic fluid sample is *not* preferred as it contains less free fetal DNA.



Blood Hemostasis



The hemostatic mechanism: 2 factors are involved:

(1)-Hemostasis:

Obliteration of the injured vessel (vasoconstriction, external pressure by hematoma or muscle contraction) and *platelet aggregation*.

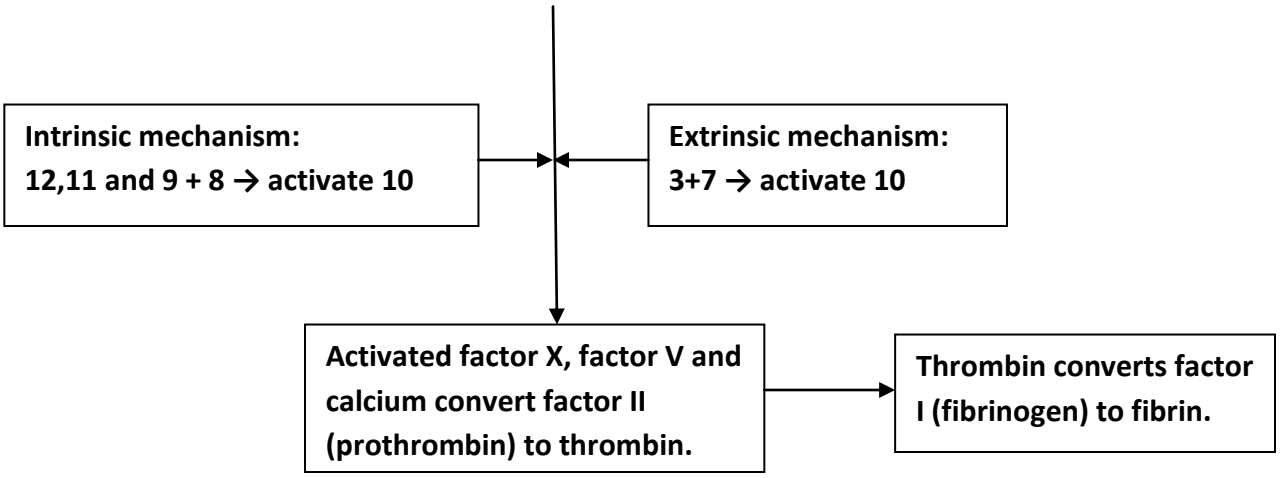
(2)-Coagulation:

a. Stage 1: *intrinsic mechanism:* activation of factors XII,XI and IX by vessel wall damage, then factor VIII activation in the presence of calcium causes activation of factor X. (12,11 and 9……10) and
extrinsic mechanism: tissue damage releases factors III and VII causing activation of factor X.(3+7=10).

b. Stage 2: Activated factor X, factor V and calcium convert factor II (prothrombin) to thrombin.

c. Stage 3: thrombin converts factor I (fibrinogen) to fibrin.

Pregnancy is a pro-thrombotic physiological state with increased platelets, coagulation factors (V, VII, VIII, IX, X, XII and fibrinogen). There is also increased antithrombin III, protein C, protein S and plasminogen activator inhibitor.



Hemophilias

-**Hemophilia A**: deficiency of factor VIII.
-**Hemophilia B (Christmas disease)**: deficiency of factor IX.
-Both are X-linked recessive disease, with females being carriers.
-Pre-pregnancy counseling is important.
-Non-invasive prenatal sexing include: free fetal DNA in maternal circulation or second trimester U/S assessment.
-Invasive prenatal testing includes chorionic villous sampling, amniocentesis and cordocentesis.
-Maternal factor levels should be checked at booking visit, at 28 and 34 weeks gestation.
-Intrapartum investigations should include CBC, coagulation profile, group and save of blood.
-If the fetus is at risk of a bleeding disorder: avoid IMI, fetal blood sampling and fetal electrodes.
-If the coagulation profile is normal and the levels of relevant factor activity are >50IU/dl, regional anesthesia can be used. If <50IU/dl or severe form of inherited bleeding disorder as vWD, regional anesthesia is contraindicated.
-Delivery should be by the least traumatic route, CS only for obstetric indications. If assisted, should be by forceps and not ventouse use.
-Factors levels should be kept above 50 IU/dl for 3-5 days after CS.
-The incidence of PPH (primary & secondary) is increased among hemophilia carriers and vWD between 20-30%.

-A cord blood sample should be collected from neonates at risk for coagulation studies and IMI should be avoided. Clotting factors in neonates only reach adult levels at 6 months of age.

Von Willebrand's disease (vWD)

Von Willebrand factor is a plasma protein that has 2 functions:
1. Stabilization of factor VIII.
2. Adherence of platelets to the injured vessel walls.

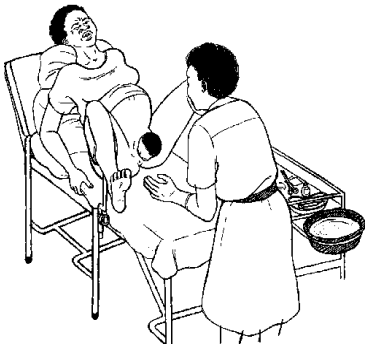
Von Willebrand's disease (vWD) is the commonest inherited bleeding disorder with prevalence of 0.8-1.3 %. Both sexes are affected as the vWF gene is on chromosome 12, and these patients have defective factor VIII and vWF.

Von Willebrand's disease (vWD) has 3 different types:
(1)-Type 1: the commonest (75%) and mildest form.it is associated with quantitative deficiency of vWF.
(2)-Type 2: is qualitative defect of vWF and is associated with thrombocytopenia.
(3)-Type 3: is the most severe form with marked decrease in vWF with bleeding similar to hemophilias.

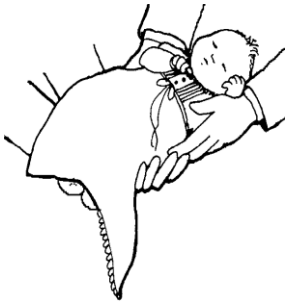
	Hemophilia carriers	**Von Willebrand disease**	**Factor XI deficiency**
Intrapartum	-Recombinant factors VIII & IX. -Factors VIII & IX concentrates. -Desmopressin : increase factor VIII only. -Tranexamic acid.	-Concentrates containing vWF. - Desmopressin in type 1 & 2. -Platelets in type 2. -Tranexamic acid.	-Factor XI concentrates. -Fresh frozen plasma. -Tranexamic acid.
Postpartum	-Desmopressin. -Tranexamic acid.	-Desmopressin. -Tranexamic acid.	-Tranexamic acid.

Desmpressin is a synthetic analogue of anti-diuretic hormone and is given by IVI or intranasally under supervision with limitation of fluid intake to 1.5 L/24 hours. It can increase factor VIII levels and is used to cover delivery or surgical procedures in patients with hemophilia A and vWD.

Antenatal care:
-Maternal clotting factor levels at booking, 28, 34 weeks and at labour.
-Identification of the fetal sex by non-invasive or invasive methods.



Intrapartum care:
-Maternal CBC & coagulation profile.
-Cross matching of blood.
-Avoid fetal scalp electrodes & blood sampling.
-Avoid regional anesthesia & instrumentation.
-CS for obstetric indications.



Postpartum care:
-Guard against PPH.
-Cord blood sample for CBC & coagulation profile.
-Avoid neonatal IMI.

Thrombocytopenia in Pregnancy

Physiological Background:

Platelets are non-nucleated cells derived from megakaryocytes in the bone marrow and normally live in the peripheral circulation for *as long as* 7-10 days. Platelets play a critical initiating role in the hemostatic system.

Primary hemostasis begins when platelets adhere to the site of endothelial disruption, leading to platelet clumping. This is followed by platelet activation, which is characterized by release of granules containing von Willebrand factor, adenosine 5'-diphosphate (ADP), and serotonin. This serves to recruit other platelets into the growing platelet plug, which acts to stop the bleeding. Simultaneously, the synthesis of thromboxane A_2 and release of serotonin leads to vasoconstriction to reduce blood loss at the site of vascular injury.

The secondary hemostatic phase begins when the coagulation pathway is activated on the surface of the activated platelets to form a fibrin meshwork, which serves to reinforce the platelet plug.

Definition:

The normal range of platelets in non-pregnant women is 150,000 - 400,000/µL. Average platelet count in pregnancy is *decreased* by about 12% between 20-40 weeks gestation (213,000/µL versus 250,000/µL).

Thrombocytopenia can be defined as platelet count less than 150,000/ µL or platelet count *below* the 2.5th percentile for pregnant patients (116,000/µ L).

Incidence:

Thrombocytopenia, is encountered in 7-8% of all pregnancies.

Aetiology:

Thrombocytopenia can result from a wide range of conditions with several of them being pregnancy related.

The most common causes of thrombocytopenia in pregnancy are as follows:

- Gestational thrombocytopenia (70%).
- Hypertensive disorders of pregnancy (21%).
- Immune Thrombocytopenic Purpura, ITP (3%).
- Others: DIC, TTP, HELLP, acute fatty liver (6%).

Classification:

Classification of thrombocytopenia in pregnancy is arbitrary and not necessarily clinically relevant.
Mild thrombocytopenia is 100,000-150,000/μL.
Moderate thrombocytopenia is 50,000-100,000/μ L.
Severe thrombocytopenia is less than 50,000/μ L.

Manifestations:

Clinical assessment is the most important factor for the evaluation of a pregnant patient with thrombocytopenia.
Medical history may include the following:

- Current or previous bleeding problems.
- Family history of bleeding.
- Past obstetrical history.
- Transfusion history.

Examination findings suggestive of thrombocytopenia include the following:
-Petechiae, ecchymoses, nose and gum bleeding.
-Rare - Hematuria, gastrointestinal bleeding, intracranial bleeding.

History:
-Bleeding tendency.
-PH or FH of bleeding.
-H/ blood transfusion.
Examination:
-Petechiae.
-Ecchymoses.
-Orificial bleeding.

Gestational thrombocytopenia

Incidence:
The incidence of gestational thrombocytopenia (GT) is 8% of all pregnancies and accounts for more than 70% of cases of thrombocytopenia in pregnancy.

Pathophysiology:
The pathophysiology of gestational thrombocytopenia is unknown, but 2 main factors are associated with GT.
(1)-Accelerated platelet activation is suspected to occur at placental circulation.
(2)-Accelerated consumption of platelets is due to the reduced life-span of platelets during pregnancy.

Diagnosis:

- Asymptomatic patient with no history of abnormal bleeding.
- **Mild** thrombocytopenia (counts >70,000/μ L).
- Usually detected incidentally on routine prenatal screening.
- No specific diagnostic tests to definitively distinguish gestational thrombocytopenia from mild ITP.
- Usually develops in the third trimester.

Fetal/neonatal risks:
No pathological significance for the mother or fetus is noted. No risk for fetal hemorrhage or bleeding complications is observed.

Management Considerations
Pre-conceptional: Gestational thrombocytopenia can recur. Risk of recurrence is unknown.
Antepartum: Monitor platelet count periodically. No treatment is necessary for GT.
Labour and delivery: Antepartum anesthesia consultation should be obtained to discuss availability of regional analgesia.
Document return of maternal platelet count to normal levels after delivery.

Idiopathic Thrombocytopenic Purpura (ITP)

Incidence

Incidence is 1-3 per 1000 pregnancies, and it accounts for 3% of all thrombocytopenic gravidas.

Pathophysiology

Immunoglobulin G (IgG) antiplatelet antibodies recognize membrane glycoproteins and coat the platelets, which then are destroyed by the reticuloendothelial system, predominantly in the spleen.
Antiplatelet antibodies may cross the placenta and cause significant fetal thrombocytopenia (<50,000/μL), which could result in bleeding complications in the neonate.
Minor bleeding complications include purpura, ecchymoses, and melena.
Major bleeding complications include intracranial hemorrhage leading to neurologic impairment or death.

Diagnosis

ITP is *a diagnosis of exclusion*. The following may be noted:

- Persistent thrombocytopenia (<100,000/μL), increased number of megakaryocytes in the bone marrow, exclusion of systemic disorders or medications/drugs, absence of splenomegaly
- Approximately 80% of cases are associated with *antiplatelet antibodies*, although these are not required for the diagnosis.

Clinical manifestations

- Easy bruising, petechiae, epistaxis, and gingival bleeding, although some women are asymptomatic
- Significant hemorrhage is rare, even when counts fall to less than 20,000/μL.

- The rate of severe neonatal thrombocytopenia is approximately 12%.
- Intracranial hemorrhage is rare (approximately 1%) and appears to be unrelated to the mode of delivery.

- Vaginal delivery never has been proven to cause intracranial hemorrhage.
- Cesarean delivery should be reserved for obstetrical indications only.
- Neonatal platelet counts normally decrease, sometimes dramatically, for several days following delivery. This result may be due in part to the passage of IgG antiplatelet antibody in the breast milk, although breastfeeding is not contraindicated. Neonatal thrombocytopenia may lead to delayed postnatal intracranial hemorrhage. Notifying pediatrics of any parturient with maternal ITP is important so that neonatal platelet counts can be monitored closely.

Maternal treatment for ITP

No treatment is necessary if platelet counts remain above 50,000/μL and the patient is asymptomatic. However, many physicians will treat for asymptomatic platelet counts of less than 50,000/μL, abnormal bleeding, or prior to invasive procedures such as cesarean delivery or regional anesthesia.

With steroids (e.g. prednisone), the following is noted:
-Response time is 3-7 days; maximum effect occurs by 2-3 weeks.
-Approximately 70% of patients will respond, and 25% will enter complete remission.
-Risks include hyperglycemia, fluid retention, and bone calcium loss.

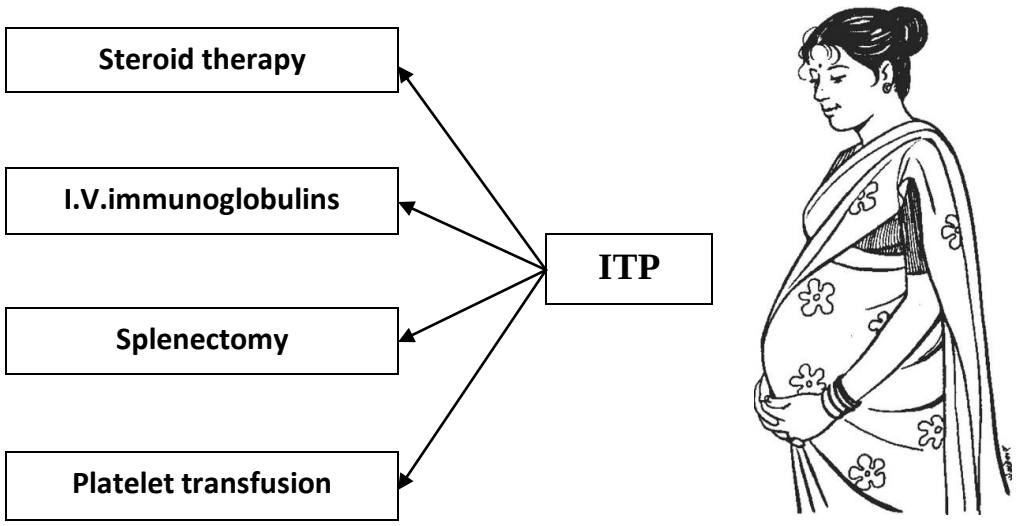
With intravenous immune globulin (IVIG), the following is noted:
-IVIG works by binding to platelets, blocking the attachment of antiplatelet antibodies.
-IVIG is ideal when time is inadequate for steroids to take effect (prior to surgery or low platelet counts with bleeding).
-Response time is 6-72 hours.
-Approximately 70% of patients will return to pretreatment levels within 30 days.
-This treatment is very expensive.

With splenectomy, the following is noted:
-Splenectomy usually is avoided during pregnancy for technical reasons,

although it remains an option in the first and second trimesters when ITP is severe (counts <10,000/μL) and the patient does not respond to steroids or IVIG.
-Complete remission occurs in two thirds of cases.
-Splenectomy does not have an impact on circulating antibodies that may still cross the placenta and cause neonatal thrombocytopenia.

With platelet transfusion, the following is noted:
-This is a temporary measure, which should be administered for life-threatening hemorrhage and should be available prior to surgery for patients with severe thrombocytopenia.
-Six to 10 units of platelets are usually administered at one time.
-Platelet counts normally rise by 10,000/μL for each unit of platelets transfused, but in ITP the rise is less pronounced due to destruction of donor platelets.

N.B. **Aquired Glanzman's disease**
Rarely in some cases of ITP,the circulating immune complexes can bind to the platelets and inhibit their function.In this situation,the hemorrhagic history is in excess of that expected from the platelet count,and patients may give a history of excessive bruising or bleeding even with a platelet count of more than 50,000/μL. (platelet function is inadequate).
Diagnosis is by platelet function tests and bleeding time.
Treatment consists of immunosuppression and platelet transfusion.



Microangiopathies

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are characterized by thrombocytopenia, hemolytic anemia, and multi-organ failure.

Incidence

Incidence is 1 in 25,000 births. Microangiopathies are often mistaken for preeclampsia/HELLP, often leading to delay in diagnosis and treatment. Delay in diagnosis may result in significant maternal morbidity and mortality.

Pathophysiology

Etiology is unknown, but endothelial damage is suspected as the initiator. Abnormal intravascular platelet aggregation leads to microthrombi formation, which results in thrombocytopenia, intravascular hemolysis from the breakage of red blood cells through partially occluded vessels, and end organ ischemia.
TTP is known for central nervous system involvement, while HUS predominantly affects the kidneys.
Significant overlap exists in the clinical manifestations of TTP and HUS.

Diagnosis

Both TTP and HUS are clinical diagnoses. Tissue biopsy is not required.
Obligate findings for either TTP or HUS include hemolytic anemia (hematocrit <30% with schistocytes on peripheral smear) and thrombocytopenia under 100,000/μ L (50% of patients will have counts <20,000/μ L).

- **TTP** - Severe thrombocytopenia, hemolytic anemia, neurologic abnormalities (headache, altered consciousness, seizures, hemiparesis), fever
- **HUS** - Thrombocytopenia, hemolytic anemia, acute renal failure (rising blood urea nitrogen [BUN] and creatinine with proteinuria, hematuria, or oliguria/anuria).

Signs and symptoms of TTP and HUS may overlap. Renal involvement occurs in 80% of cases of TTP; neurologic involvement occurs in 50% of cases of HUS

Clinical manifestations

-Presenting symptoms are often non-specific (e.g. lethargy, nausea, vomiting, headaches, weakness, fever, shortness of breath), although 67% present with bleeding.

-Hypertension may be observed in as many as 75% of cases.

-Hemolysis and anemia may be absent at presentation in 50% of cases.

-Fibrinogen levels are within the reference range, and DIC is rare.

-Long-term sequelae, such as hypertension and chronic renal failure, are observed in 44% of patients with TTP or HUS.

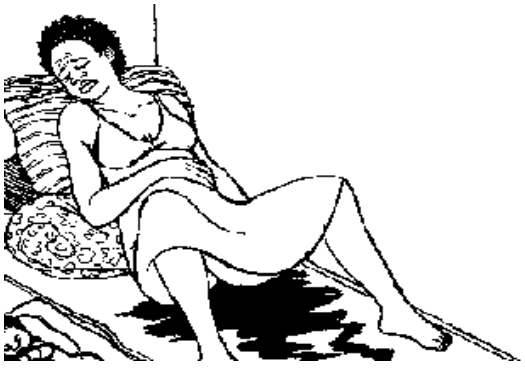
-The maternal mortality rate is 15%.

-Recurrences are common (50%).

Fetal/neonatal risks

The perinatal mortality rate is as high as 30% because of preterm delivery, growth restriction, and intrauterine fetal demise.

Differentiation between TTP, HUS, and HELLP can be difficult or even impossible, especially when the onset is in the second or third trimester. **Delivery** leads to resolution of preeclampsia, but the condition may continue or worsen after delivery with TTP/HUS. If suspected preeclampsia/HELLP does *not* improve within 48-72 hours after delivery, consider TTP/HUS.



Hypertension, 75%

Bleeding, 67%

Non-specific symptoms

Features and laboratory findings	TTP	HUS	HELLP
Fever	++	+/-	-
Neurologic features	+++	+/-	+/-
Hypertension	+/-	+/-	+/-
Renal dysfunction	+/-	+++	+/-
Skin-purpura	+	-	-
Platelets	↓↓↓	↓↓	↓
PT and aPTT	-	-	↑ or ⇔
Fibrinogen	-	-	↓ or ⇔
BUN/creatinine	↑	↑↑↑	↑ or ⇔
AST & ALT	-	-	↑
LDH	↑	↑↑↑	↑

TTP	HUS	HELLP
		
Neurologic features. **Fever.** **Skin-purpura.**	**Renal dysfunction.** **↑BUN/creatinine.**	**Liver dysfunction.** **↑AST & ALT.** **DIC**

Treatment

Plasmapheresis *is the first-line therapy*. Plasmapheresis removes platelet-aggregating substances causing TTP and HUS. Treatment is 90% successful with TTP but is less successful with HUS.

Steroids have been used, often in conjunction with plasmapheresis. However, steroids are less effective than plasmapheresis (25% response rate).

Platelet transfusions should be avoided when possible because they can cause a clinical deterioration. Use platelet transfusions only for uncontrolled bleeding or intracranial hemorrhage.

Other therapies include
Immunosuppressive agents (vincristine, azathioprine, cyclosporine).
Splenectomy for TTP.
Hemodialysis for HUS.

Premature termination of pregnancy has been associated with relapse. Delivery should be considered only when no response to other therapies occurs.

Other causes of Thrombocytopenia

Infections:
Many infectious diseases are associated with thrombocytopenia e.g. viruses as HIV, EBV, CMV-mycoplasma and malaria.

Drugs:
Heparin, quinine, rifampicin and trimethoprim are some of the drugs that can cause thrombocytopenia.

Disseminated Intravascular Coagulation (DIC)

Aetiology:

1-Abruptio placenta: the commonest cause.

2-Pre-eclampsia and eclampsia.

3-IUFD and missed abortion (if retained more than 6 weeks) due to release of thromboplastin from the degenerated fetus &/or the placenta which enters into the maternal circulation causing intravascular coagulation as it converts prothrombin into thrombin.

4-Amniotic fluid embolism.

5-Sepsis as septic abortion, puerperal sepsis and severe pyelonephritis. The endotoxins of Gram-negative organisms leads to damage of vascular endothelium, clumping of platelets and activates factor XII.

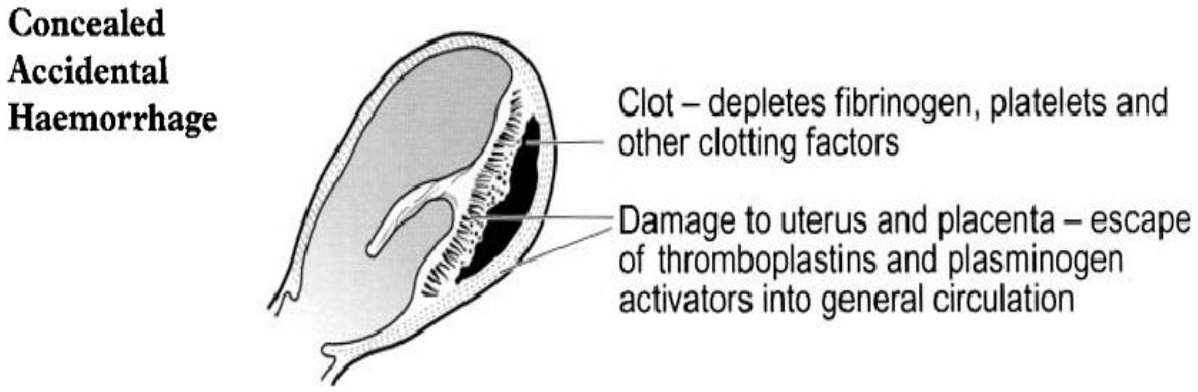
6-Induction of abortion by intra-amniotic injection of hypertonic saline or urea.

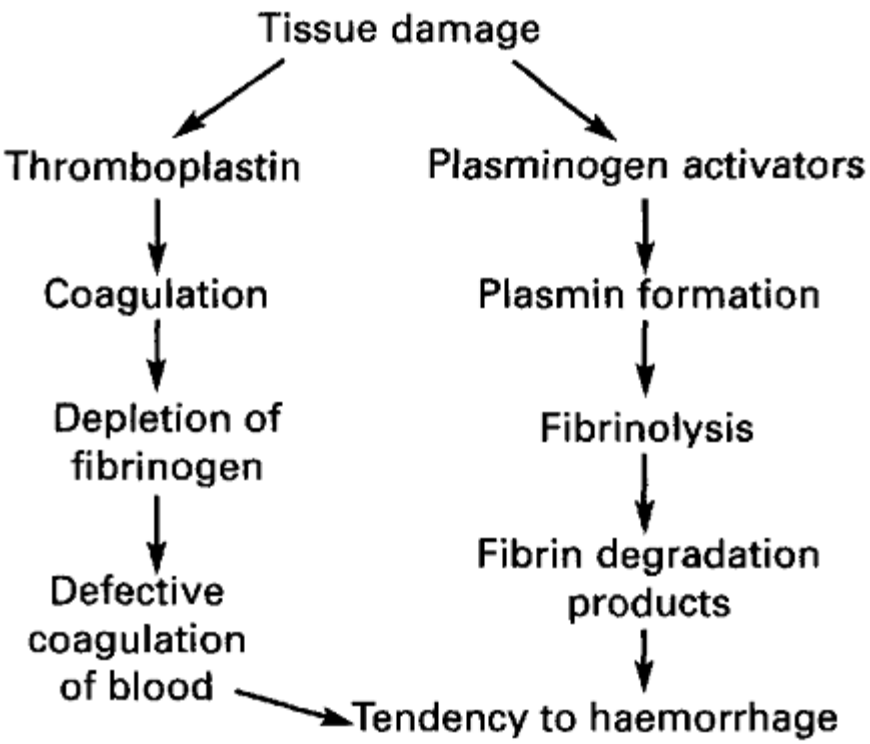
Pathogenesis:

Consumption of platelets and other clotting factors occur with DIC, this is accompanied by increased activity of the fibrinolytic system to produce lysis of fibrin thrombi to maintain the patency of the microcirculation with increased fibrin degradation (split) products.

FDPs prevent formation of fibrin clots, inhibit myometrial contractility and cause toxic myocarditis with further worsening of bleeding and shock.

Bleeding occurs when plasma fibrinogen falls below 100 mg%.





Diagnosis:

I. Presentation: failure of the blood to coagulate may give rise to epistaxis , hematuria , bleeding from the needle puncture sites and PPH. The patient will show the clinical features of the cause as abruption and IUFD.

II. Clot observation test (Weiner test): it is rapid bedside test in which 5 ml of venous blood are withdrawn in a test tube, failure of any clot to form within 10 minutes indicates that fibrinogen is less than 100 mg%. If a clot forms , the tube is incubated at 37°C, if clot dissolves after 30 minutes it means excessive fibrinolytic activity.

III. A coagulation profile is ordered:
(1)-CBC: platelets are decreased.
(2)-Plasma fibrinogen: decreased less than 100 mg% (N: 400-600 mg%).
(3)-Prothrombin time (PT): prolonged (N: 12-14 seconds).
(4)-Activated partial thromboplastin time (aPTT): prolonged (N: 30-45

seconds).

(5)-Fibrin degradation products (FDPs): increased more than 40 ug/ml.

(6)-D-dimers: increased more than 0.5 ug/ml. It is more specific than FDPs.

Treatment:

-Treatment of the cause.

-Transfusion of blood products.

One unit	Volume per unit	Contains per unit	Effects
Whole blood	500 ml, Hct 40%	RBCs, plasma, fibrinogen 600-700 mg, NO platelets.	Restores TBV & fibrinogen. ↑ Hct by 3-4%.
Packed RBCs	250 ml & additives , Hct 55-80%.	RBCs only.	↑ Hct by 3-4%.
Fresh Frozen Plasma, FFP	250 ml, 30 minutes thaw before use.	Colloid, fibrinogen 600-700 mg.	2500 ml needed to restore fibrinogen > 150 mg/dL.
Cryoprecipitate	About 15 ml.	About 200 mg fibrinogen plus other clotting factors.	3000-4000 mg total to restore fibrinogen > 150 mg/dL.
Platelets	About 50 ml	5000-10,000 platelets.	6-12 units are usually needed.

Thrombophilias and Pregnancy

Definition:

A thrombophilia is defined as a predisposition to thrombosis, secondary to any persistent or identifiable hypercoagulable state. This can be inherited or acquired.

Incidence:

Thrombophilia is present in 15% and can be identified in up to 50% of women with a history of venous thromboembolism (VTE).

Type	Incidence	Pathology	Features
Protein C deficiency	1 in 500 people - autosomal dominant	Thrombin activates this vit K-dependant protein. Activated protein C & its Co-factor protein S will inactivate factors Va & VIIIa.	Thrombosis occurs in 25% of untreated patients, mostly in the postpartum period.
Protein S deficiency	Unknown	Protein S levels decrease in pregnancy, COCs users.	-
Antithrombin III deficiency	1 in 5000 people - autosomal dominant	AT-III inactivates thrombin & factors IXa, Xa,Xia & XIIa. Its activity is amplified by heparin.	Thrombosis occurs in 70 % of untreated patients
Factor V Leiden	2-15% in Caucasians.	Associated with protein C deficiency.	20 folds increased risk of thrombosis.
Prothrombin gene mutat.	2-6% in Europe autosomal dominant	Elevated plasma prothrombin levels.	5 folds increased risk of thrombosis.
Hyper-homo-cysteinemia	Above 15 umol/L	Produced from AA methionine.	Arterial & venous thrombosis.
APS		Positive ACL or LAC. Primary or secondary.	thrombosis.

Initial Assessment:

I. History: personal & family with past history of VTE.
II. Thrombophilia screen:
(1)-Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT) and Clotting Time.
(2)-Functional assays to determine Antithrombin III, protein C levels and antiphospholipid antibodies.
(3)-Immunoreactive assays for protein S antigen.
(4)-PCR-based testing for prothrombin gene mutation and factor V Leiden.

Management of pregnancy:

I. Preconception care:
Women with identifiable heritable thrombophilias should be given information about risks of VTE and risks of drugs.

II. Antenatal care:
The general consensus is that special groups should receive both antepartum and postpartum thromboprophylaxis , some advocate low dose aspirin during pregnancy. Those at high risk include:
(1)-Women on long-term anticoagulation.
(2)-Women with antithrombin III deficiency.
(3)-Women with previous history of VTE and have a thrombophilic defect.
(4)-Women without history of VTE but, with protein C deficiency, prothrombin gene mutation and factor V Leiden mutation.

III. Postnatal care:
If the patient does not want to continue heparin injections throughout the puerperium, oral warfain may be introduced on the first or second postpartum day and heparin withdrawn when the INR is in the recommended range.

Pregnancy outcome and inherited thrombophilias
There is an increased association with:
I. Recurrent miscarriage.
II. IUGR and IUFD.

III. Pre-eclampsia.
IV. Placental abruption.

There is NO good evidence available regarding the management of pregnant women with a previous VTE or with an inherited thrombophilias. Guidelines are based on expert opinion.

Maternal risks:
-Recurrent miscarriage.
-IUGR & IUFD.
-Preeclampsia.
-Placental abruption.

Antiphospholipid Antibody Syndrome (APS)

Definition:
The antiphospholipid syndrome (APS) is an autoimmune disorder characterized by a high-risk of obstetrical complications affecting both mother and fetus. A diagnosis of APS requires the presence of both clinical and laboratory criteria.

Classification:
APS is classified as primary or secondary depending on its association with other autoimmune disorders.
Primary antiphospholipid syndrome is diagnosed in patients demonstrating the clinical and laboratory criteria without other recognized autoimmune disease.
Secondary antiphospholipid syndrome is diagnosed in patients with other autoimmune disorders such as SLE.

Diagnosis:

APS is diagnosed when at least one of the following clinical criteria and one of the following laboratory criteria are met according to the guidelines of the **International Society onThrombosis and Haemostasis (2006)**

Clinical criteria	Laboratory criteria
(i)-3 or more consecutive spontaneous abortions before the 10th week, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. **(ii)-One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week**, with normal fetal morphology documented by ultrasound or by direct examination of the fetus. **(iii)- One or more premature births of a morphologically normal neonate before the 34th week** of gestation because of eclampsia or severe preeclampsia or recognized features of placental insufficiency.	**(i)-Lupus anticoagulant (LA)** present in plasma, on two or more occasions at least 12 weeks apart. **(ii)-Anticardiolipin (aCL) antibody of IgG and/or IgM isotype** in serum or plasma, present in medium or high titer, on two or more occasions, at least 12 weeks apart, measured by standardized ELISA. **(iii) Antiβ2glycoprotein-1 antibody of IgG and/or IgM isotype** in serum or plasma (in titer >99th percentile), present on two or more occasions, at least 12 weeks apart, measured by standardized ELISA.

Diagnostic criteria (ACOG, 2005)

I. Clinical Criteria:

Thrombosis: arterial, venous or small vessels.

Obstetrical complications:

-Fetal loss at 10 weeks or later, without apparent fetal abnormalities.

-One or more premature birth (<34 weeks) due to pre-eclampsia or placental insufficiency.

-3 or more consecutive unexplained spontaneous abortions (less than 10 weeks).

II. Laboratory criteria:

-Lupus anticoagulants (LA).
- Anticardiolipin antibodies (aCL): Antibodies (IgG or IgM)

- The diagnosis of APS requires at least one of the clinical criteria plus the presence of either a LA or an aCL.
- The LA or aCL must be shown to persist for at least 6-12 weeks before the diagnosis of APS may be made.

Pathogenesis:
Antiphospholipid (aPL) antibodies belong to the large family of antibodies that react with negatively charged phospholipids (PLs) including cardiolipin, phosphatidyl-glycerol, phosphatidyl-inositol, phosphatidyl-serine, phosphatidyl-choline, and phosphatidic acid.
The pathogenesis of APS involves a co-factor, beta 2 glycoprotein. aPL reduce hCG release and inhibit trophoblastic invasion in vitro-a potential explanation for the association with preeclampsia and IUGR. However, the typical APS fetal loss occurs in the second trimester and is associated with severe IUGR, oligohydramnios and early onset PE. The commonest feature is defective or abnormal placentation, possibly related to thrombosis. APS is a form of acquired thrombophilia, thrombosis may affect unusual sites such as the axillary or retinal veins or affect small arteries causing for example stroke or renal disease.
Pregnancy also increases the risk of, or exacerbate pre-existing thrombocytopenia.

Treatment:
For women with APS-associated complications of pregnancy, prophylaxis with LMWH or heparin, with or without aspirin, can be recommended.

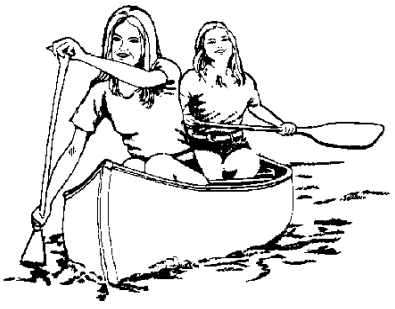
Although APS may be associated with a number of other manifestations such as thrombocytopenia and livedo reticularis, there is no evidence to support treatment with anticoagulants for those conditions. Anticoagulants are indicated for the treatment of thrombosis and prevention of pregnancy loss.

Management recommendations for APS pregnancies (NICE, 2009):

Antiphospholipid antibodies - No thrombosis or pregnancy loss.	Aspirin 75 mg or nothing.
Previous thrombosis.	LMWH and aspirin.
Previous recurrent (> 3) miscarriage (<10 weeks).	Aspirin +/- LMWH (? stop LMWH at 13-20 weeks).
Fetal loss or severe PE, IUGR, neonatal death.	LMWH and aspirin.

Those women with previous thrombosis will usually be on long treatment with warfarin. This should be converted to aspirin and high prophylactic doses of LMWH as soon as pregnancy is confirmed (before 6 weeks gestation to avoid warfarin embryopathy). LMWH is continued throughout pregnancy and postpartum for 6 weeks or until warfarin is recommenced.

ACOG guidelines, 2005 recommend the use of low-dose aspirin 81 mg orally per day, along with unfractionated heparin 5,000 units subcutaneously, twice daily. *This therapy, begun when pregnancy is diagnosed, is continued until delivery*. Although this treatment may improve overall pregnancy success, these women remain at high risk for preterm labour, premature rupture of membranes, fetal growth restriction, preeclampsia, and placental abruption.



Venous Thromboembolism (VTE)

Physiological considerations:

Pregnancy is a pro-thrombotic physiological state with increased platelets, coagulation factors (V,VII,VIII,IX,X,XII and fibrinogen). There is also increased antithrombin III ,protein C, protein S and plasminogen activator inhibitor.

Incidence:

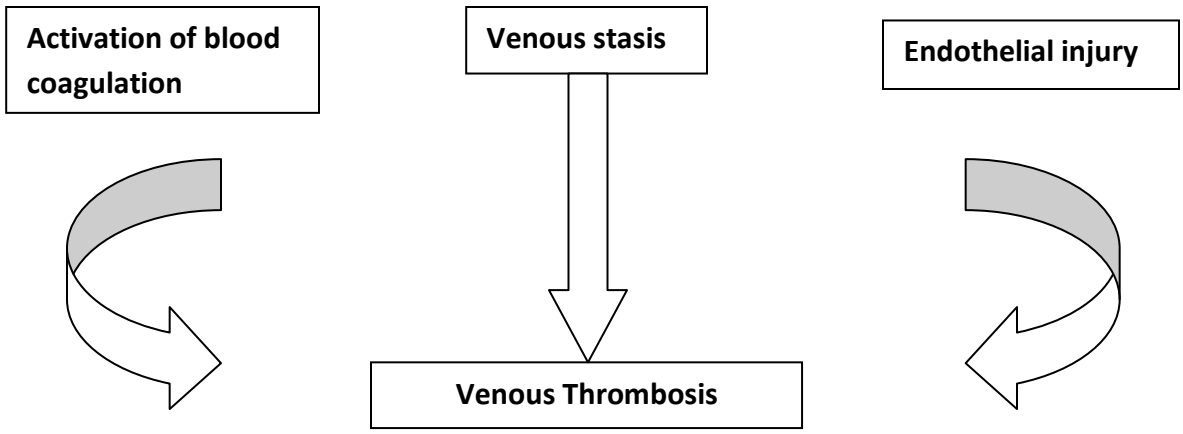
The risk of VTE increased with pregnancy to 1/1000 pregnancies and is greater in the postpartum period.

Aetiology:

Virchow's triad: activation of blood coagulation, venous stasis and endothelial injury.

The pregnancy associated increase in coagulation factors with venous stasis due to enlarging uterus which diminishes venous return from the legs combined with immobilization , prolonged labour, dehydration, excessive blood loss and possible surgery explain the increased risk of VTE.

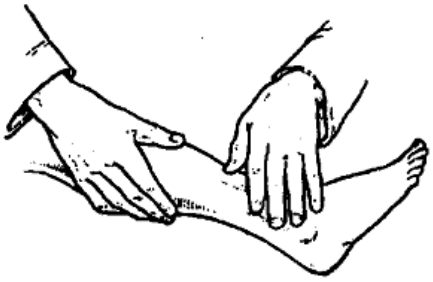
Wonen with a previous VTE should have a careful history taken and undergo screening for both inherited and acquired thrombophilias.



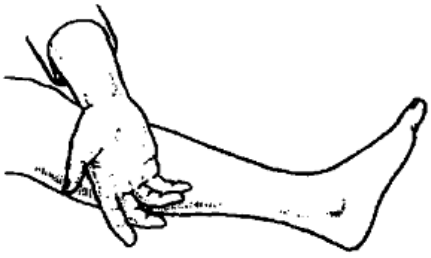
Deep Venous Thrombosis (DVT)

Symptoms and Signs

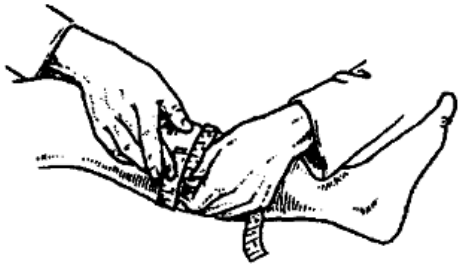
The majority of DVT occurring during pregnancy are in the left leg. Symptoms include pain in the affected leg, swelling, fever, erythema and increased heat of the affected leg. A positive Homan's sign is unreliable.



Palpation of the calf demonstrates tenderness and oedema



The affected leg may feel warmer to the back of the hand



Careful measurement may reveal some swelling compared with the other leg

Investigations

Any woman with signs and symptoms suggestive of VTE should be treated with low-molecular-weight heparin (LMWH) until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated.

(1)-D-dimers: low levels of D-dimer in pregnancy suggests there is no VTE.

(2)-Duplex ultrasound: it is non-invasive and has high sensitivity and specificity in proximal DVT but less sensitive in calf DVT. if negative with stong clinical suspicion, it may be repeated in a week or venography is done with initiation of anticoagulant therapy.

(3)-Venography: this adequately visualizes calf and deep veins. Disadvantages include the use of radiation, allergic reaction to the dye and 5% risk of thrombosis.

(4)-Before commencing anticoagulant therapy: CBC, coagulation profile, liver and kidney function tests with screening for thrombophilias.

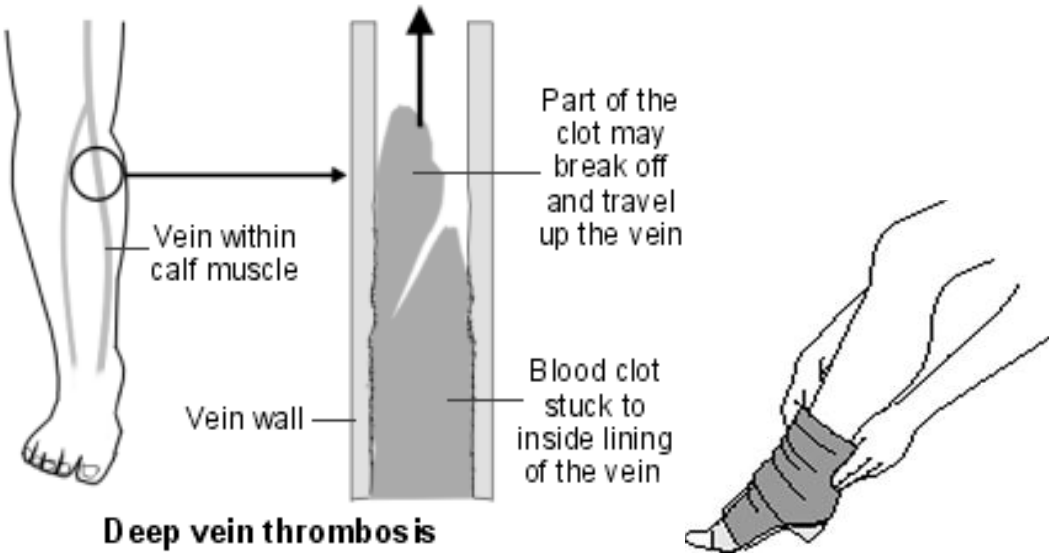
Management:

(1)-Graduated compression stockings should be worn in the acute period and for 2 years on the affected leg to reduce the incidence of post-thrombotic syndrome [A].

(2)-Low molecular weight heparin (LMWH) by SCI is the treatment of choice.

Treatment in relation to pregnancy should continue for 6-12 weeks after delivery or 6 months after the initial episode-whichever is the longer.

A recent Cochrane review concluded that LMWH was at least as effective as unfractionated heparin in preventing recurrent VTE and signifacntly reduced the occurance of major hemorrhage during the initial treatment and overall mortality at the end of follow-up [A].



Pulmonary Embolism

This can occur with or without preceding DVT. Symptoms range from minimal disturbance to sudden collapse and death, depending on the size ,number and site of emboli.

Symptoms and Signs

These include dyspnea, chest pain, cough, hemoptysis, tachycardia, tachypnea, cyanosis, raised jugular venous pressure, pleural rub, pleural effusion and right ventricular failure.

Investigations of PE

(1)-Arterial blood gases (ABG) analysis: hypoxia and hypercapnia.
(2)-ECG: inverted T wave and atrial arrhythmia are suggestive.
(3)-Chest X-ray : abnormal findings in 60-80% in patients with PE.
Where there is clinical suspicion of acute PE a chest X-ray should be performed. Compression duplex Doppler should be performed where this is normal. If both tests are negative with persistent clinical suspicion of acute PE, a ventilation–perfusion (V/Q) lung scan or a computed tomography pulmonary angiogram (CTPA) should be performed.
(4)-Computed Tomography Pulmonary Angiogram (CTPA) is the gold standard for the diagnosis of PE and is necessary if other pulmonary pathology is present or if a V/Q is inconclusive.
Women with suspected PE should be advised that V/Q scanning carries a slightly increased risk of childhood cancer compared with CTPA (1/280,000 versus less than 1/1,000,000) but carries a lower risk of maternal breast cancer (lifetime risk increased by up to 13.6% with CTPA, background risk of 1/200 for study population).

Treatment:

(1)-Intravenous unfractionated heparin is the preferred treatment in massive PE with cardiovascular compromise.Platelet count should be checked at least every other day for 2 weeks or until heparin is stopped.
(2)-LMWH may be used for smaller, minimally symptomatic clots. Dosage is based on the patient's body weight.
(3)-Warfarin has a minimal place in the treatment of pregnant women with

acute VTE but, suitable in the postpartum period.
(4)-Inferior vena cava (IVC) filters are reserved for patients with recurrent PE despite adequate anticoagulation or who cannot received anticoagulation.
(5)-Thrombolytic therapy: limited data about the use of streptokinase during pregnancy but it does not cross the placenta and its major side effect can be severe genital bleeding therefore its use is reserved for patients who are hemodynamically unstable.
(6)-Surgical embolectomy.
Intravenous unfractionated heparin is the traditional method of heparin administration in acute VTE and remains the preferred treatment in massive PE because of its rapid effect and extensive experience of its use in this situation.

One regimen for the administration of intravenous, unfractionated heparin is:
● Loading dose of 80 units/kg, followed by a continuous intravenous infusion of 18 units/kg/hour
● If a woman has received thrombolysis , the loading dose of heparin should be omitted and an infusion started at 18 units/kg/hour.
● It is mandatory to measure activated partial thromboplastin time (APTT) 4–6 hours after the loading dose, 6 hours after any dose change and then at least daily when in the therapeutic range. The therapeutic target APTT ratio is usually 1.5–2.5 times the average laboratory control value.
● Using this weight-adjusted regimen, the infusion rate should be adjusted according to the APTT.

N.B. Anticoagulant therapy during labour and delivery ,RCOG 2009

The woman taking LMWH for maintenance therapy should be advised that once she is established in labour or thinks that she is in labour, she should *not* inject any further heparin.
Where delivery is planned, LMWH maintenance therapy should be discontinued 24 hours before planned delivery.
Regional anaesthetic or analgesic techniques should not be undertaken until at least 24 hours after the last dose of therapeutic LMWH.
A thromboprophylactic dose of LMWH should be given by 3 hours after a

caesarean section (more than 4 hours after removal of the epidural catheter, if appropriate).

The epidural catheter should not be removed within **12 hours** of the most recent injection.

In women receiving therapeutic doses of LMWH, **wound drains** (abdominal and rectus sheath) should be considered at caesarean section and the skin incision should be closed with staples or interrupted sutures to allow drainage of any haematoma.

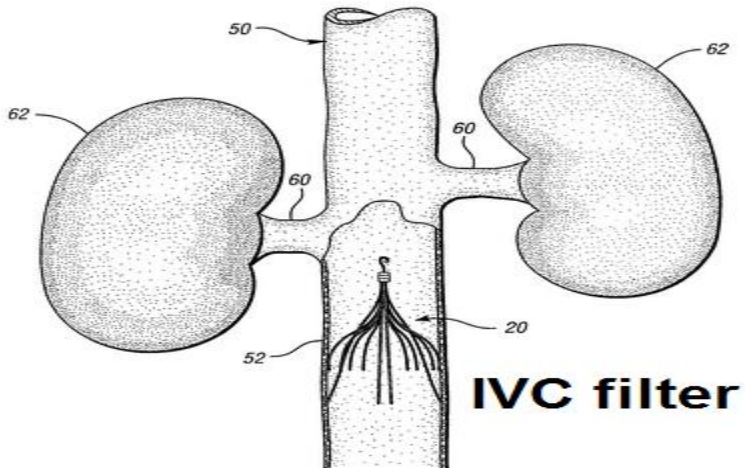
Any woman who is considered to be at high-risk of haemorrhage and in whom continued heparin treatment is considered essential should be managed with intravenous, unfractionated heparin until the risk factors for haemorrhage have resolved.

Therapeutic anticoagulant therapy should be continued for the duration of the pregnancy and for at least 6 weeks postnatally and until at least 3 months of treatment has been given in total.

Women should be offered a choice of LMWH or oral anticoagulant for postnatal therapy after discussion about the need for regular blood tests for monitoring of warfarin, particularly during the first 10 days of treatment.

Women should be advised that neither heparin (unfractionated or LMWH) nor warfarin is contraindicated in breastfeeding.

Postpartum warfarin should be avoided until **at least the third day** and for longer in women at increased risk of postpartum haemorrhage.



VTE prophylaxis

High Risk:	-Single previous VTE (+ Thrombophilia Or positive family history of VTE). -Previous recurrent VTE.
Moderate Risk:	-Single previous VTE with no family history of VTE or thrombophilia. -Thrombophilia + no VTE. -MEDICAL COMORBITIES, e.g. heart or lung disease, SLE, cancer, imflammatory conditions, nephrotic syndrome, sickle cell disease, intravenous drug users.
Additional Risk factors:	● Dehydration. ● Immobility, e.g. paraplegia. ● Current systemic infection. ● Gross varicose veins. ● Smoker. ● Parity ≥ 3. ● Obesity (BMI > 30kg/m2). ● Age > 35 years. **The presence of 3 or more risk factors = Moderate risk.** **The presence of less than 3 = low risk.**

Level of Risk	Prevention Strategies
Low	No specific prophylaxis; early and "aggressive" mobilization.
Moderate	Low-dose unfractionated heparin (5,000 units every 12 hours), low molecular weight heparin (2,500 units dalteparin or 40 mg enoxaparin daily), graduated compression stockings, or intermittent pneumatic compression device.
High	Low-dose unfractionated heparin (5,000 units every 8 hours), low molecular weight heparin (5,000 units dalteparin or 40 mg enoxaparin daily), or intermittent pneumatic compression device.

Low-dose unfractionated heparin as Calheparine and Heparine sodium.

Low molecular weight heparin as Dalteparin (Fragmine) & Enoxaparin (Clexane).

Anticoagulant therapy

	Heparin	Warfarin
Mechanism of action	Heparin and its low molecular weight derivatives bind to the enzyme inhibitor antithrombin III (AT) causing its activation. The activated AT then inactivates thrombin and other factors involved in blood clotting, most notably factor Xa.	Warfarin inhibits the vitamin K-dependent synthesis of biologically active forms of the calcium-dependent clotting factors II, VII, IX and X, as well as the regulatory factors protein C and protein S.
Indications	• Atrial fibrillation. • Deep-vein thrombosis and pulmonary embolism. • Cardiopulmonary bypass for heart surgery.	People with an increased tendency for thrombosis or as secondary prophylaxis (prevention of further episodes) in those individuals that have already VTE. Warfarin treatment can help prevent formation of future blood clots and help reduce the risk of embolism.
Administration	Heparin is given parenterally because it is not absorbed from the gut, Because of its short biologic half-life of approximately one hour, heparin must be given frequently or as a	When administered, these drugs do not anticoagulate blood immediately. Instead, onset of their effect requires about a day

	continuous infusion. However, the use of LMWH has allowed once-daily dosing, If long-term anticoagulation is required, heparin is often used only to commence anticoagulation therapy until the oral anticoagulant warfarin takes effect.	before clotting factors being normally made by the liver have time to naturally disappear in metabolism, and the duration of action of a single dose of warfarin is 2 to 5 days. Under normal pharmacological therapy the drugs are administered to decrease the action of the clotting factors they affect by 30 to 50%.
Contraindications	Risk of bleeding (especially in patients with uncontrolled blood pressure, liver disease and stroke), severe liver disease, severe hypertension.	Pregnancy and as heparin.
Side effects	Hemorrhage, thrombocytopenia, increased potassium levels and osteoporosis.	Hemorrhage, Warfarin necrosis and Osteoporosis.

Control	The effects of heparin are measured in the lab by the partial thromboplastin time (aPTT), (the time it takes the blood plasma to clot). With LMWH, there is a reduced risk of osteoporosis and heparin-induced thrombocytopenia (HIT). Monitoring of the aPTT is also not required and indeed does not reflect the anticoagulant effect, as aPTT is insensitive to alterations in factor Xa.	The effects of wafarin are measured in the lab by the INR of prothrombin time.
Antagonism	The effects of heparin can be reversed with pratamine sulphate (1 mg IV for every 100 U of heparin).	The effects of warfarin can be reversed with vitamin K, when rapid reversal is needed by fresh frozen plasma and IV vitamin K.

Methods:

(1)-Unfractionated heparin 5000-10,000 u every 12 hours SCI.

(2)-LMWH: Enoxaparin (Clexane): 40 mg once or twice daily by SCI.

(3)-Calciparin (calcium salt of heparin): 10,000 u once or twice daily by SCI.