Seizures in Pregnancy

Seizure disorders complicate approximately 1% of all pregnancies. There is a two-fold increase in the incidence of congenital anomalies in children born to women with epilepsy. The risk is inherited from both the mother and the father. Anticonvulsive therapy does appear to further increase the incidence of congenital abnormalities in children of epileptics. Some increased risk is present regardless of therapy.

Despite the increased risk of congenital abnormalities that may be associated with anticonvulsant therapy, anticonvulsive therapy is warranted during pregnancy because of the danger that both the potential physical trauma and the periods of maternal apnea associated with seizures can present to the fetus.

Phenytoin (Dilantin), Carbamazepine (Tegretol), and Phenobarbital (Phenobarb) have all been used successfully to control seizures in pregnancy. They all appear to be associated with a similar increased risk of congenital anomalies. Congenital anomalies most commonly associated with phenytoin include facial abnormalities (such as cleft palate and cleft lip) and cardiac abnormalities (such as ventricular septal defects and atrial septal defects). Valproic acid (Depakote) has also been used to control seizures in pregnancy but carries with it a 1% risk of neural tube defects. The mildest form of neural tube defects is spina bifida occulta, but its most severe form is anencephathy. Although high dose folate in the range of 4 mg per day may decrease the risk of neural tube defects in mothers whose offspring are at risk, it is best, when possible, to avoid the use of valproic acid during the first trimester.

If a pregnant woman is maintained on the same dose of an anticonvulsant throughout pregnancy, total blood levels of the anticonvulsant will tend to go down during the pregnancy due to a pregnancy related increase in hepatic and renal clearance of the drug and a pregnancy related increase in the volume of distribution of the drug. This drop in total blood levels is partially counteracted by the fact that free (and, therefore, active) drug levels do not fall as much, or remain unchanged, due to a normal decrease in the concentration of serum proteins that occurs in pregnancy. Therefore, for any given total drug level there is likely to be more free drug available during pregnancy than there would be in a nonpregnant individual.

Because of the difficulty in interpreting serum drug levels of anticonvulsant during pregnancy, it is acceptable to take either one of two different approaches to the management of anticonvulsant during pregnancy: (1) Check total serum drug levels monthly in pregnant women and increase their dose accordingly; (2) Follow the patient clinically and increase drug doses if seizures occur with increased frequency. In the circumstance that seizures are occurring and there is concern about the meaning of particular total serum drug level, free drug levels can be obtained.

The acute management of the seizure during pregnancy is the same as for the nonpregnant individual. It is important to recognize that brief periods of hypoxia in a mother can be associated with dramatic fetal hypoxia (due to the uniqueness of the fetal hemoglobin oxygen dissociation curve).

It is very important to remember that not all seizures in pregnancy are from epilepsy. Epileptic women,

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1 Adopted from syllabus by Ray Powrie and colleagues at Women and Infants Hospital of Rhode Island presented at 1998 Society General Internal Medicine Meeting. Updated with the assistance of Michael Carson, MD, St. Peters University Hospital
although at no increased risk for an eclamptic seizure, will on occasion develop preeclampsia/eclampsia. Likewise, it is important to remember that not all first time seizures occurring in the third trimester are preeclampsia/eclampsia. It is said that up to 10% of epileptic women will present for the time during pregnancy.

Pregnancy appears to cause some depletion in maternal vitamin K stores and this depletion appears to be worse in women on the anticonvulsant. In patients taking Phenytoin, Primidone, and Phenobarbital, administration of Vitamin K administration to epileptic women is recommended.

**Preeclampsia And Pregnancy Induced Hypertension (PIH)**

Preeclampsia and pregnancy induced hypertension (PIH) are often used as interchangeable terms. Some clinicians are more strict in their definitions and use the term PIH to refer to only those patients with isolated hypertension occurring during pregnancy.

Pre-eclampsia is common and complicates at least 10% of first pregnancies. It is extremely rare prior to 20 weeks gestation and the vast majority of cases occur close to term (near 38-40 weeks gestation). The risk factors for preeclampsia include nulliparity (first pregnancy), chronic hypertension, in any pregnancy with a new father, women less than 18 years of age and greater than 35 years of age, diabetes, renal disease, systemic lupus erythematosus, family history of preeclampsia, prior history of preeclampsia, obesity, and any acquired or inherited tendency to thrombosis (especially the antiphospholipid antibody syndromes).

Preeclampsia is a disease that is specific to the third trimester of pregnancy. Pathophysiology is characterized by diffuse vasospasm and endothelial damage. The main symptoms of pre-eclampsia are visual disturbances (scintillations and/or scotomas), headaches (the pattern can vary), epigastric discomfort, edema (30%) and rapid weight gain.

Signs of preeclampsia include retinal vasospasm, hypertension, right upper quadrant (hepatic) tenderness, facial and hand edema and clonus. Hypertension is an important manifestation of preeclampsia but is not always present in all patients. It is diagnosed when previously normal blood pressures exceed 140 systolic or 90 diastolic. It is important to remember when interpreting blood pressures in pregnant women that a rise of more than 30 systolic and 15 diastolic from baseline blood pressures during pregnancy are considered abnormal, but is no longer included as a criteria for diagnosis. Hepatic tenderness is due to capsular stretching from edema.

Laboratory manifestations of preeclampsia reflect the many systems involved in the process. An elevated hemoglobin is often seen because of relative intravascular volume depletion. The majority of pregnant women in the third trimester will have a hemoglobin around 10 g/dL. A finding of a hemoglobin of 14g/dL in a pregnant woman in the third trimester can be an early marker of preeclampsia. Thrombocytopenia is often seen and is from consumption. Proteinuria (> 300mg/dL) is one of the major manifestations and is due to a lesion known as glomerular endotheliosis. An elevated Creatinine is seen and is defined as greater than 0.8 mg/dL. Hyperuricemia is commonly seen in preeclampsia. Normal uric acid in pregnancy is lower than for the non-pregnant individual and should not be normally greater than 5 mg/dL. Elevated liver enzymes are seen. An elevated PT and PTT is due to disseminated intravascular coagulation (DIC), but this is rare.
The life threatening manifestations of pre-eclampsia that may lead to the involvement of internists are many. Seizures are the most well known manifestation of preeclampsia. In fact, the term preeclampsia literally means pre-seizure. Once a seizure has occurred, the diagnosis becomes eclampsia. Pulmonary edema is another life threatening manifestation of preeclampsia. It generally occurs due to pre-eclampsia related ventricular dysfunction and pulmonary endothelial damage. Ventricular dysfunction is seen in up to one third of severe cases of preeclampsia and echocardiographic studies have suggested that both systolic and diastolic dysfunction can be found. Cerebral hemorrhage is another important cause of death in preeclampsia. These cerebral hemorrhages can be unpredictable and are not necessarily due to severe elevations in blood pressure. Oliguric or anuric renal failure can occur in the setting of preeclampsia. Hepatic failure is also possible, although when this occurs serious consideration of the diagnosis of acute fatty liver of pregnancy needs to be made.

**Shortness of Breath in Pregnancy**

The normal \( \text{PaO}_2 \) in pregnancy averages to be 100 mmHg at sea level and \( \text{PCO}_2 \) is in the range of 28 and 32 mm Hg. A blood gas with a \( \text{PO}_2 \) of 80 and a \( \text{PCO}_2 \) of 40 mmHg in a pregnant woman is markedly abnormal. For optimal health the fetus requires that maternal oxygenation remains greater than a \( \text{PaO}_2 \) of 70 mmHg. The fetal hemoglobin has a different oxygen dissociation curve from adult hemoglobin and therefore the maternal oxygen saturation should be maintained greater than 95% at all times.

When evaluating pregnant patients with respiratory illness, chest x-rays should be done for the same indications that they would be in nonpregnant individuals. The abdomen is shielded to help protect the fetus and the amount of radiation involved in a routine chest x-ray is greatly below the minimal dose associated with any documented fetal effects. It is recommended that radiation dosages during pregnancy be kept below 5 rads in total. Below this level of radiation there has been no evidence of teratogenic or leukemogenic effects on the fetus. The average chest x-ray with modern equipment and abdominal lead shielding delivers approximately 0.001 rad of radiation to the maternal pelvis.

The most common chronic respiratory illness that we see during pregnancy is asthma. The management of asthma in pregnancy is basically unchanged from that of the nonpregnant individual. Inhaled beta agonists, inhaled steroids, systemic steroids (both oral and intravenous) and cromolyn sodium have all been used safely in pregnancy. There is no human data regarding the new leukotriene antagonists. The only asthma medication to be avoided in pregnancy is subcutaneous epinephrine which has been associated with placental ischemia.

Overall, there is no evidence to suggest that the course of asthma is affected by pregnancy. It should be remembered that any asthmatic woman who has received steroids for greater than two weeks in the past year should be given stress dose steroids at the time of labor or cesarean section as would be done for any other perioperative patient.

Pulmonary thromboembolism is one of the leading medical causes of death in pregnant women. It occurs more frequently in pregnant women than in the nonpregnant population. Its presentation is often more subtle in pregnant women than it is in the general medical population. The diagnostic evaluation and investigation for a pulmonary embolism in pregnancy is the same as it is for the nonpregnant individual. Chest x-ray, venous compression ultrasound, ventilation perfusion scans and pulmonary angiograms all involve radiation levels which are well below accepted upper limits for the gravid woman.

Pregnant women have an increased propensity for a pulmonary edema because of the decrease in serum
Serum oncotic pressure decreases because the 50% increase in blood volume that occurs in pregnancy is predominantly achieved through an increase in plasma free water which has a dilutional effect on the serum albumin levels. The conditions which can precipitate pulmonary edema in pregnant women include pyelonephritis, other infections, tocolytics (medications which are used to stop preterm labor such as terbutaline) and pre-eclampsia.

Dyspnea of pregnancy is a specific entity that is quite common and characterized by an often dramatic increase in a patient's perceived shortness of breath that occurs during pregnancy. It usually begins sometime in the middle of gestation and can be very frightening for the patient. Investigations of these patients reveal a completely normal physical examination, oxygenation, chest x-rays, and pulmonary function testing. Once underlying pathology has been ruled out, reassurance is the mainstay of treatment.

Because of the increased cardiac work associated with pregnancy, heart disease can present for the first time during pregnancy as unexplained dyspnea. Typically, this will occur at around 24 to 28 weeks gestation when blood volume reaches its maximum. A classic example of this is mitral stenosis, which often presents for the first time in young, reproductive age women.

A dreaded cause of shortness of breath that is unique to pregnancy is amniotic fluid embolism. It is rare and often fatal. It has been reported to occur at anytime during the third trimester, but usually occurs at the time of delivery. It has been associated with precipitous delivery and the use of oxytocin. It is characterized by a rapid and progressive respiratory failure that is associated with hemodynamic instability and the rapid onset of disseminated intravascular coagulopathy (D.I.C.). Treatment is supportive as no specific treatment is available. Blood product and factor replacements should be given if the patient is bleeding. Mechanical ventilation and hemodynamic support with cardiac inotropes and vasopressors is often also necessary.

Cardiac Disease in Pregnancy

General principles

Three main changes in cardiac physiology occur during pregnancy. First, blood volume and cardiac output rise to a peak of 150% of normal at 24 to 28 weeks gestation that. After that point in pregnancy, blood volume and cardiac output remain stable until delivery. By the second week postpartum, non pregnant cardiac physiology has been re-established. Second, systemic vascular resistance decreases in pregnancy by 25%. This can improve the status of some cardiac lesions such as aortic insufficiency which may benefit from afterload reduction. Third, the gravid uterus can compress the inferior vena cava when the patient is in the supine position and thereby dramatically decrease venous return to the heart. This can precipitate hypotension especially in the presence of volume dependent lesion like aortic stenosis or very poor left ventricular function.

Because of the increased cardiac demands intrinsic to the gravid state, cardiac disease can be unmasked or worsen in pregnancy. A particular period of high risk for cardiac decompensation are at 24 to 28 weeks gestation (the end of the second trimester) when blood volume and cardiac output peak. A second period of high risk for cardiac decompensation during pregnancy is the work of labor. Every time the uterus contracts, about one in two units of blood is auto-transfused from the utero-placental circulation into the systemic circulation. When the contraction stops the "autotransfusion" returns to the utero-placental circulation. A compromised heart may not be able to compensate for such rapid volume shifts. A third high risk period is the postpartum. Cardiac stress in this period is due to a series of fluid
shifts that include the involution of the uterus (with loss of the low resistance circulatory unit of the placenta), the normal (or abnormal) postpartum blood loss, and the increase in preload that occurs because of release of the gravid uterus’ compression of the inferior vena cava.

Specific Cardiac Complaints and Lesions

Palpitations are commonly experienced by pregnant women. Increased ectopy (especially premature atrial contractions and premature ventricular contractions) is generally believed to occur during pregnancy, possibly due to increased atrial and ventricular stretch from increased blood volume. Also, increased body awareness among many pregnant women coupled with increased exposure to health care providers may contribute to an increased reporting of palpitations during pregnancy.

Acute supraventricular tachycardia can be safely treated with adenosine in pregnancy. Use of digoxin and verapamil is also acceptable although there are case reports of fetal cardiovascular collapse following the use of verapamil. If the patient is hemodynamically unstable, cardioversion can be safely carried out in pregnancy.

For assessing the risk of pregnancy associated with structural cardiac disease, the New York Heart Association functional Classification for congestive heart failure is very useful. Class I and Class II patients generally tolerate pregnancy very well. Class III patients are at moderate risk with a pregnancy and often need hemodynamic monitoring during labor and delivery. Class IV patients do very poorly with pregnancy and should be cared for by a multi-disciplinary team. Hemodynamic monitoring should be considered, but the utility is controversial.

In addition to the NYHA classification, some general comments about particular lesions can be made. Stenotic valves tend to have increased symptoms in pregnancy because of the difficulty in moving the increased blood volume across the stenotic valve. Also, stenotic valves may be volume dependent and therefore lying on the back (which leads to IVC compression by the uterus) should be avoided in these women. Incompetent or regurgitant valves tend to have improvement in their symptoms during pregnancy. The decrease in systemic vascular resistance associated with pregnancy favors forward flow across these valves, much in the same way that ACE inhibitors improve hemodynamic function in these patients.

Subacute bacterial endocarditis (SBE) prophylaxis is not officially recommended by the American Heart Association for vaginal deliveries or routine cesarean sections.

Ischemic heart disease, although uncommon in pregnancy, can manifest itself during pregnancy especially in those women who have had diabetes for over 20 years. However, the majority of acute ischemic heart disease in pregnancy is not related to atherosclerosis. About 50% of ischemic heart disease in pregnancy is related to idiopathic dissections of the coronary. Other reported causes of ischemic heart disease in pregnancy are cocaine, antiphospholipid antibody associated arterial thrombosis and arterial vasospasm. Clinicians should be aware that CK-MB has been shown to rise above normal levels after routine cesarean section. The explanation is that CK-MB is released from the uterus or placenta and it is present in these organs at levels >3% of the total CK.

Peripartum cardiomyopathy can occur any time in the third trimester and up to 6 months following delivery. It presents with congestive heart failure. The etiology is poorly understood. About one third of patients with this diagnosis will have a complete recovery, one third will have chronic cardiac
insufficiency and one third will have progressive cardiac failure ending in either cardiac transplant or death. A risk of recurrence of peripartum cardiomyopathy in subsequent pregnancies is thought to exist, although poorly quantified.

Deep Venous Thrombosis And Pulmonary Embolism in Pregnancy

Pulmonary embolism is the major, non-obstetric cause of maternal mortality in the United States and Canada. Risk factors for thromboembolic disease in pregnancy include immobilization, obesity, smoking, surgery (including cesarean section), and presence of an inherited or acquired hypercoagulable state.

There are two important physiologic changes that occur in pregnancy that help explain the predisposition of pregnant women to venous thrombosis. The first is "stasis" or slowed flow of blood in the large vessels of the pelvis and leg resulting from the gravid uterus pressing against the large pelvic vessels, partially obstructing flow in the deep venous system of the leg. The second change is levels of all of the coagulation factors involved in clot formation ( except Factors XI and XIII ) increase during pregnancy. At the same time, the levels of protein S which act to inhibit clot formation within blood vessels has found to decrease during pregnancy. Free and Total levels of Protein S decrease during pregnancy, while Protein C and Antithrombin III levels remain unchanged or increase slightly.

Pulmonary embolism and deep venous thrombosis occur at a similar rate throughout all three trimesters. The risk for thromboembolic disease does peak in the first 48 hours after delivery and continues from between six weeks to three months postpartum.

Typically deep venous thrombosis in pregnancy presents with unilateral leg edema, leg pain and tenderness. However, the accuracy of diagnosis of deep venous thrombosis by history and physical exam is notoriously unreliable. Interestingly, 90% of deep venous thromboses in pregnancy occur on the left side, The reason for this is not well understood but likely has to do with the position of the uterus with respect to the left iliac vein. To investigate a patient for deep venous thrombosis, all of the usual tests including compression ultrasound of the lower limbs, impedance piethysmography, and contrast venography can be safely done with reliable results. It is also important to remember that a significant proportion of deep venous thrombosis in pregnancy occur in the pelvic veins and therefore may not always be picked up by routine testing such as compression ultrasound or even lower limb venogram. In those cases where a high index of suspicion is met with a negative lower limb compression ultrasound, a skilled ultrasonographer can examine the iliac and femoral veins with considerable accuracy.

Pulmonary embolism in pregnancy may have a more subtle presentation than in the general medical population. The most common feature is dyspnea. Chest x-rays, ventilation perfusion scan and pulmonary angiograms can all be done safely during pregnancy and involve a dose of radiation that is well below the general accepted maximum recommended radiation exposure in pregnancy. (An angiogram via the femoral route involves 0.2-0.4 rads of fetal radiation exposure). In the situation that a low or intermediate probability scan is obtained, a pulmonary angiogram is often necessary to rule out pulmonary embolism. The life threatening nature of pulmonary embolism and the lifelong clinical implications of making the diagnosis of thromboembolic disease in a young person almost always warrants getting a definitive answer. Computed tomography for the diagnosis of pulmonary embolism has not been studied in pregnancy, but data in the non-pregnant population do not support its use.

The acute treatment of deep venous thrombosis and pulmonary embolism in pregnancy is identical to non-pregnant patient. Heparin is a large molecule which does not cross the placenta and therefore does
not have any effect upon the fetus. After five to seven days of intravenous heparin, the patient with DVT and / or pulmonary embolism is eventually discharged on twice daily subcutaneous injections of heparin. Full anticoagulation with subcutaneous heparin is monitored with the goal of achieving a mid-interval (6 hours after a q 12h dosing), PTT of 60 - 80 seconds. The total amount of units of heparin required over a 24 hour period is estimated from the total number of units of intravenous heparin given divided by two to determine the initial dose to be given every 12 hours. Heparin should be administered throughout pregnancy.

Warfarin is contraindicated during pregnancy. Warfarin readily crosses the placenta and has deleterious effects on the fetus. It acts as a teratogen in the first trimester and later in pregnancy coumadin is associated with an increased incidence of cerebral bleeding in the fetus. Inferior vena cava filters can be placed safely in pregnancy.

The role of low molecular weight heparin in pregnancy is yet to be defined. Like unfractionated heparin, it does not appear to cross the placenta. It would appear to be a reasonable alternative to unfractionated heparin.

Women who have had a previous deep venous thrombosis or pulmonary embolism, regardless of its etiology, may require prophylactic heparin during their pregnancy and for six weeks postpartum. The risk of thrombosis in a pregnant women with a previous thrombotic event is not known, nor is the exact effect that prophylactic heparin has on this recurrence risk. This is an area in need of a large multicenter investigation. If prophylaxis is used the dose should be administered q 12 subcutaneously and the dose increased as pregnancy progresses: 5000 u, in the first trimester, 7500 u in the second trimester, and 10,000 in the third trimester. The increased doses of heparin used in the second and third trimester are needed because of the increased volume of distribution of heparin during the latter two trimesters. When the patient goes into labor, the heparin is stopped and resumed approximately 12-24 hours postpartum.

Heparin is continued 5000 u q 12 for six weeks postpartum because the increased risk of thrombosis. Alternatively, warfarin may be given postpartum. Both warfarin and heparin are considered to be compatible with breast feeding.

Gastrointestinal Disorders

Nausea and vomiting occur in up to half of all pregnancies. This should be considered part of the normal course of a pregnancy. However, the term "morning sickness" is a misnomer as the nausea and vomiting of pregnancy can occur at any time of day. The "normal" nausea and vomiting experienced by many pregnant women should be distinguished from hyperemesis gravidarum. Hyperemesis is defined as an intractable nausea and vomiting, severe enough to cause dehydration. It occurs in less than 1% of all pregnancies. The present understanding of hyperemesis gravidarum suggests that elevated levels of human chorionic gonadotropin (hCG) has a central nauseant effect in susceptible women. Hyperemesis gravidarum generally is an illness only of the first trimester and tends to resolve in most patients around the time that hCG levels begin to fall off during a pregnancy. Contributing to the illness of hyperemesis gravidarum is the decreased tone of the lower esophageal sphincter. Delayed gastric emptying that is a normal part of pregnancy also contributes. This delayed gastric emptying is a manifestation of the progesterone effects upon gastrointestinal smooth muscle.

Medications used for the management of hyperemesis gravidarum include promethazine (Phenergan), prochlorperazine (Compazine) and metoclopramide (Reglan).
Hyperemesis can be associated with hyperthyroidism, hyperparathyroidism and elevated transaminases. In those cases of hyperemesis severe enough to require hyperalimentation a free T4, TSH, calcium, and liver enzymes should be checked. The free T4 may be elevated in up to 40% of women with true hyperemesis. Liver enzymes elevations related to hyperemesis should not usually be greater than ten times normal.

Gastroesophageal reflux disease is nearly universal in pregnancy due to the altered GI motility that occurs in pregnancy. Both delayed gastric emptying and decreased gastroesophageal sphincter tone occur due to the progesterone effects on smooth muscle. Treatment options include such things as lifestyle modification and antacids. For patients with symptoms despite such interventions, medications such as sucralfate, ranitidine and metoclopramide (Reglan) can be used. Sucrefate is an excellent choice because it is not absorbed systemically and, therefore has no fetal effects.

Biliary disease is seen with increased frequency in pregnancy. This is both because of the altered smooth muscle activity of the gallbladder (again due to progesterone effects) and an increased lithogenicity of bile during pregnancy. Mild symptoms of biliary tract disease can be managed conservatively in pregnancy but, for those patients with persistent symptoms or significant complications, cholecystectomy, can be performed safely throughout pregnancy. However, the ideal time during pregnancy is the second trimester. In the first trimester cholecystectomy, has an increased risk of miscarriage and in the third trimester has an increased risk of preterm labor as well as being technically more difficult. However, necessary cholecystectomy should never be delayed because of a woman's gravid status.

Cholestasis of pregnancy presents as severe itching in a gravid woman. This entity is very similar to other forms of cholestasis such as is seen in relation to medications. Liver enzyme elevations are generally not more than 4-5 times above the normal range. Alkaline phosphatase may also be elevated but may be difficult to interpret as alkaline phosphatase is normally elevated in pregnancy. Ultrasound of the liver and gallbladder show no abnormalities. Fasting serum "bile salts" levels are markedly elevated. There is an increased risk of sudden fetal demise in this condition. Medical treatments for cholestasis in pregnancy include cholestyramine, phenobarbital and ursodeoxycholic acid.

It is important to remember that preeclampsia and the HELLP syndrome are causes of elevated liver function tests during pregnancy. HELLP syndrome stands for hemolysis, elevated liver enzymes, and low platelets and is believed to be a severe form of preeclampsia.

Acute fatty liver of pregnancy is an uncommon illnesses that carries a mortality that may be as high as 50%. It presents as a progressive hepatic failure that occurs in the third postpartum period and usually occurs in association with preeclampsia. Progressively rising liver enzymes are complicated by jaundice and coagulopathy and treatment includes both delivery and supportive management. Liver biopsy, if performed, will show extensive fatty infiltration of the liver.

Viral hepatitis is not an uncommon complication of pregnancy. Hepatitis A has no fetal effects and is not transmitted from mother to fetus. Hepatitis B and C however have significant rates of vertical transmission. All infants born in the US receive hepatitis B vaccine. Infants born to mothers who are hepatitis B service antigen positive should receive a higher dose of the vaccine and also be given hepatitis B immune globulin. There is presently no treatment available to decrease the maternal fetal transmission of hepatitis C.
The course of inflammatory bowel disease is not significantly affected by pregnancy. However, if the disease is active at the time of conception, it is likely to remain so. Steroids, sulfasalazine, antibiotics and 5’ASA have been used safely in pregnancy. Metronidazole, however, should be avoided in the first trimester. For patient women requiring TPN (total parenteral nutrition) during pregnancy, close monitoring of the blood glucose is required because of the increased insulin resistance seen in pregnancy.

Indicated endoscopy, sigmoidoscopy, colonoscopy and biopsies can and should be performed during pregnancy with the same indications as would occur in the non-pregnant individual. There is no evidence of any increased complication rate related to any of these procedure occurring during pregnancy.

Renal Disorders

Anatomic changes associated with pregnancy include that hydronephrosis and ureteral dilatation. Glomerular filtration rate increases by 50% during pregnancy so that the average creatinine clearance of a pregnant woman is 150 mL/minute and the average creatinine in pregnancy is 0.5 to 0.6 mg/dL. Normal urinary protein excretion also increases during pregnancy from normal pre-pregnant level of 150 mg per 24 hours to 300 mg per 24 hours. The normal plasma bicarbonate level in pregnancy is decreased by approximately 4 meq/L due to the physiologic mild respiratory alkalosis that occurs during pregnancy.

The most common renal disease to occur in pregnancy is pyelonephritis. All pregnant women require a urine culture at the beginning of pregnancy to screen for asymptomatic bacteriuria. Asymptomatic bacteriuria should be treated with the appropriate antibiotic. The recurrence rate of pyelonephritis during pregnancy in women who do not receive prophylactic antibiotics is approximately 10%. Pyelonephritis during pregnancy is associated with a dramatic increase in the incidence of preterm labor and a 10% incidence of pulmonary edema.

The approach to the patient with acute renal failure during pregnancy is the same as it would be for the nonpregnant individual. Acute tubular necrosis can occur in pregnant women related to septic abortion or significant postpartum hemorrhage. Acute fatty liver of pregnancy has been associated with acute renal failure, much in the same way as any causes of acute hepatic failure can lead to hepatorenal syndrome. Severe preeclampsia can cause acute renal failure both through causing a lesion known as glomerular endotheliosis and also through acute tubular necrosis occurring as a result of severe renal artery vasospasm. Hemolytic uremic syndrome seems to occur at an increased incidence in the postpartum period and needs to be considered in the woman with progressively decreasing renal function and hemolysis after a delivery. A specific entity known as idiopathic postpartum renal failure has been described and is felt by some to be related to the HUS/TTP spectrum of disease.

Chronic renal failure can have significant effects on the course of a pregnancy. In general, women whose creatinine is less then 1.5 can expect a good maternal and fetal outcome can be expected. For women whose creatinine range between 1.5 and 3 mg, pregnancy can lead to deterioration in renal function during gestation that may be only partially reversible after delivery. For some individuals with this range of creatinine, acceleration of the underlying renal disease may also continue to occur postpartum. Intrauterine growth restriction, an increased risk of fetal morbidity and mortality, and preeclampsia will occur in up to one third of patients with this degree of renal insufficiency.

Women with a creatinine > 3 mg/dl are often infertile and when conception does occur in such individuals, the fetal loss rate exceeds 50%. Patients with proteinuric renal disease but a preserved
creatinine clearance may have marked increases in urinary protein excretion during pregnancy without any progression of the underlying parenchymal disease. Therefore worsening proteinuria during gestation in these patients should not be automatically attributed to worsening glomerular disease or pre-eclampsia and can be a difficult diagnostic and management challenge.

Renal biopsy, and dialysis may be performed during pregnancy. Women who have had successful renal transplants are candidates for pregnancy. If renal function has been stable and there are no signs of rejection for 2 years then the risk of graft failure during pregnancy is low. Antirejection drugs need to be continued during the pregnancy and are surprisingly well tolerated by the fetus. It is important to remember that renal calculi are seen with an increased incidence during pregnancy. In fact, nephrolithiasis and urolithiasis are among one of the most common non-obstetrical causes of abdominal pain requiring hospitalization during gestation.

THYROID DISEASE IN PREGNANCY

Thyroid disease is often seen in women of reproductive age. In the past, the diagnosis was challenging because thyroid binding globulin increased in pregnancy and routine tests such as total total T4 and T3RU were affected. However, now free T4 levels can be ordered and unaffected by pregnancy.

Significant hypothyroidism is unusual in pregnancy as untreated hypothyroid patients rarely conceive and carry a pregnancy. For patients with treated hypothyroidism, dose adjustments of thyroxine replacement are not usually necessary. Thyroid function tests are obtained once per trimester. If this frequency of testing shows that a patient requires some increase in thyroxine replacement, then begin checking the patient's thyroid function monthly.

Untreated hyperthyroidism is associated with decreased fertility and an increased risk of a miscarriage. Symptoms and signs of hyperthyroidism in pregnancy are the same as they are for the nonpregnant individual. Treatment of hyperthyroidism in pregnancy involves the use of beta blockers and propylthiouracil (PTU). Although PTU does cross the placenta, it appears not to significantly affect the fetal thyroid unless the mother is taking doses greater than 450 mg/day. Grave's disease, the most common cause of hyperthyroidism, often goes into remission in the third trimester and relapses after delivery. This frequently observed phenomena is attributed to immune changes in pregnancy. In general, treatment goals should favor keeping the patient mildly hyperthyroid rather than hypothyroid, as mild hyperthyroidism has a better pregnancy outcome associated with it than hypothyroidism.

Hyperemesis gravidarum is associated with abnormal thyroid function tests in a significant number, (about 40%) of cases. Hyperthyroidism is caused by the hyperemesis itself. Beta HCG, the placental hormone which is believed to be partially responsible for the nausea and vomiting of hyperemesis, is only one amino acid different from Thyroid Stimulating Hormone (TSH). It is therefore believed that in some cases of hyperemesis, the high levels of Beta HCG may stimulate the thyroid. Hyperthyroidism associated with hyperemesis usually resolves at the end of the first trimester when the beta HCG levels start to decline and the symptoms of hyperemesis tend to resolve.

Postpartum thyroiditis resembles subacute or Dequervain's thyroiditis. It occurs postpartum, and usually begins with a period of acute inflammation in the thyroid that manifests itself as a mildly tender goiter associated with intermittent episodes of hyperthyroidism. Over the course of time, the hyperthyroidism is often followed by many months of hypothyroidism. This hypothyroidism usually resolves within a year following delivery. This is an important diagnosis to be aware of because it may mimic and be
misdiagnosed as postpartum depression. It is also important to be aware of because although there is usually complete recovery, a risk of recurrence exists with subsequent pregnancies.

**DIABETES**

The most important aspect of the management of the type I diabetic with respect to pregnancy is preconception counseling. Studies have repeatedly shown that hyperglycemia in the first trimester is a teratogen and increases the risk of cardiac and neurologic malformations in the children of type I diabetics. However, studies have also shown that if euglycemia is achieved throughout the first trimester, pregnant type I diabetics do not have an increased risk of fetal malformation as compared to the non-diabetic population. It is very important type I diabetic patients of reproductive age plan their pregnancy and attempts at conception should occur in a context of tight glucose control.

Type I diabetics planning to conceive and those who are already pregnant will require insulin three times a day to maintain the tight euglycemic control that optimizes fetal outcome. This tight glucose control is advocated even after the teratogenic potential has passed after the first trimester. Euglycemia in the second and third trimester is also associated with an improved pregnancy outcome. In general, monitor the postprandial glucose rather than the preprandial glucose in pregnant diabetics and aim to keep these levels between 70 and 120 mg/dL. Postprandial monitoring is done to try to avoid marked glucose fluctuations following meals.

Type I diabetics are at an increased risk for preeclampsia. Up to 50% of type I diabetics with nephropathy will develop preeclampsia during their pregnancy. Management of the type I diabetic in labor almost always requires an insulin drip.

Type II diabetics also need tight blood sugar control in the first trimester as hyperglycemia in this context is also teratogenic. It is present practice to stop oral hypoglycemics in patients wanting to conceive and to use insulin in all type II diabetics throughout the course of their pregnancy. This is done not so much because oral hypoglycemics are contraindicated, but because they do not provide the tight control necessary to the diabetic gravida.

Gestational diabetes is an illness of the third trimester which occurs because of the antiinsulin effects of many of the hormones associated with pregnancy. These high sugars can cause fetal macrosomia (large babies) and therefore are associated with an increased risk for delivery. Risk factors for gestational diabetes include a family history of type II diabetes, obesity and previous history of a large baby. It is controversial whether all, some or no pregnant woman should be tested for gestational diabetes. Screening for gestational diabetes occurs by a 1 hour 50 gram glucose tolerance test. If this screening test is positive, the more formal 3 hour 100 g oral glucose tolerance test is performed. If this test is positive, the woman is placed on dietary restrictions.

An important point for internists to know about gestational diabetes is that the majority of gestational diabetics will eventually develop type 2 diabetes. Therefore, all women who have a history of gestational diabetes should probably have a yearly fasting glucose screen to help identify the new onset of type 2 diabetics early.