3rd Edition

Textbook of NEPHROLOGY

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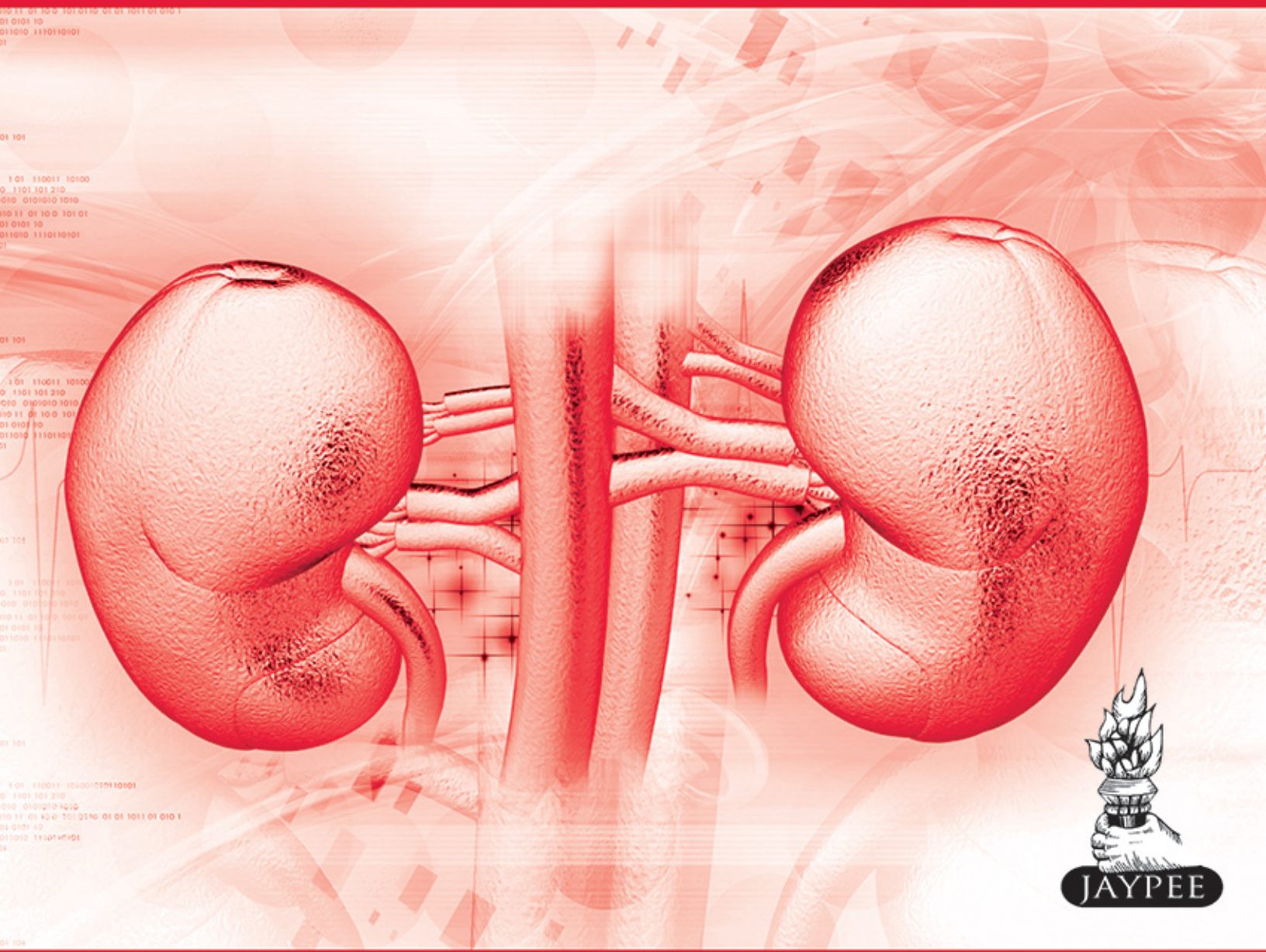

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INTRODUCTION

Pregnancy is associated with several physiological and hemodynamic changes. The kidney can be influenced by these changes as well as by certain pathological alterations which can occur during pregnancy. A clear understanding of these alterations is essential for the diagnosis and management of pregnancy related renal disease and hypertension.

The maternal changes start from the time of fertilization and continue throughout pregnancy and reverse almost completely to the pre-pregnant state within six to eight weeks of delivery. A pregnant woman gains approximately 12 to 14 kilograms of weight and is mainly contributed by retention of water distributed in the fetus, amniotic fluid, uteroplacental unit and maternal tissues. The weight gain is proportionally more during the second and third trimsters. Other factors contributing to weight gain include weight of the fetoplacental unit, maternal fat accumulation and increase in the uterine musculature. A pregnant woman also retains nearly 1,000 mEq of sodium and 350 mEq of potassium. Due to the accumulation of nearly seven liters of water, the levels of plasma proteins, sodium, potassium and osmolality decrease by approximately 3 percent. The resting heart rate increases by 10 beats per minute. Cardiac output and stroke volume are the highest when the woman remains in left lateral recumbency. Significant changes also occur in the structure and function of the urinary system in the course of a normal pregnancy. The increase in renal size of up to 1 cm is due to an increase in the renal parenchymal volume and water content. Ureteric peristalsis decreases by third month and dilatation of the pelvicalyceal system and ureters are noted in nearly 90 percent of women in the last trimester. The right ureter is more dilated than the left and the dilatation generally ceases at the pelvic brim. The mechanical theory postulates that pressure by the enlarged uterus on the ureter, and pressure from the dilated ovarian vein or iliac artery crossing the ureter at about the level of pelvic brim, causes dilatation of the ureter. A filling defect may be seen in the dilated ureter in intravenous urogram at the site of crossing of the iliac artery. This is called the "iliac sign". The hormonal theory suggests that different hormones acting on the smooth muscles of the pelvicalyceal system cause ureteral dilatation. In preeclampsia (PE), since blood flow to the placenta may be impaired, ureteric dilatation is also less frequent. Increased volume of residual urine in the urinary tract and a possible reduction in peristalsis may predispose to development of urinary tract infections.

Renal plasma flow increases by nearly 70 percent in early pregnancy and stabilizes at 50 to 60 percent during the third trimester. The glomerular filtration rates (GFR) starts to increase by the first month after conception, reaches 50 percent in midpregnancy and returns to pre-pregnant levels near term. As a result of the increase in GFR, blood urea, serum creatinine and serum uric acid levels are lower than nonpregnant levels throughout normal pregnancy. Since the filtered load is high, the urinary excretion of amino acids, water-soluble vitamins, proteins and glucose are increased during normal pregnancy.

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Normal Blood Pressure Changes and Criteria for Diagnosis of Hypertension

A great deal of advancement has taken place in our understanding of the blood pressure (BP) variations in normal pregnancy. Blood volume and cardiac output are markedly increased by almost 50 percent during pregnancy. In addition, levels of renin substrate, renin, angiotensin I and angiotensin II are increased. In spite of this, the BP tends to fall. The uteroplacental unit which acts as a low resistance shunt leads to reduced vascular resistance. The cutaneous and renal circulations also contribute to the overall reduction in the peripheral vascular resistance. An increase in vasodilator prostaglandins or increase in angiotensinase enzymes may be responsible for neutralizing the effect of angiotensin II. Normal pregnant women do not respond to the pressor effect of exogenous angiotensin II. This may be due to increased level of endogenous angiotensin II and saturation of the receptors. An increased output of endothelium derived relaxing factor (nitric oxide) has been implicated for decreasing angiotensin II sensitivity. During early pregnancy, systolic and diastolic pressures are lower than pre-pregnant levels and the fall reaches a nadir by midpregnancy. Thereafter, it rises towards pre-pregnant levels at full term.

As there is no clear-cut dividing line between normal and abnormal BP during pregnancy, certain arbitrary BP levels have been established for clinical purposes. The Committee on Terminology of the American College of Obstetricians and Gynecologists suggested any one of the following criteria for the diagnosis of hypertension in pregnant women.

1. A sustained rise of 30 mmHg or more in systolic BP;
2. A sustained rise of 15 mmHg or more in diastolic BP;
3. A sustained systolic BP of 140 mmHg or more and;
4. A sustained diastolic BP of 90 mmHg or more.

"Sustained" refers to elevated BP observed on two different occasions, at least six hours apart.

These criteria have been largely abandoned because of the considerable variability of BP in normal women. In addition, to apply the above criteria, the BP in the prepregnant state or soon after conception must be known. Since these BP readings are often not available, the diagnosis of pregnancy-induced hypertension (PIH) becomes difficult. To overcome this difficulty, Lindheimer has suggested the upper limit of normal diastolic BP in pregnancy to be 75 mmHg in midtrimester and 85 mmHg in last trimester. A threshold diastolic BP of 90 mm Hg together with an increase of 25 mm Hg has also been suggested to improve the diagnosis.

HYPERTENSIVE DISEASES IN PREGNANCY

The most accepted clinical classification of the hypertensive disorders of pregnancy is that recommended by the Committee of the American College of Obstetricians and Gynecologists. This classification is presented in Table 1.

Preeclampsia

PE is characterized by a constellation of signs and symptoms including new onset of hypertension, proteinuria, often with edema and occasionally complicated by coagulation and liver function abnormalities. Hypertension occurs after 20 weeks of pregnancy. PE/eclampsia is a disease peculiar to pregnancy and was considered as one of the "toxemias" of pregnancy but the term toxemia is no longer used because no toxins have been identified in these women. The term PE, however, is used synonymously with PIH. Incidence of PE is estimated to range from 3 to 10 percent of all pregnancies. There are a number of predisposing factors for the development of PE. Higher incidence has been observed in women who are primigravida, extremes of age, multiple pregnancy, hydatidiform mole, diabetes, polyhydramnios, fetal anomalies, hydrops fetalis and family history of PE/eclampsia.

Chronic Hypertension of Whatever Cause

This group includes those patients with essential or secondary hypertension who subsequently become pregnant. Those who have hypertension before twenty weeks of pregnancy are more likely to fall into this group.

Table 1. Hypertensive disorders of pregnancy

1.	Pregnancy-induced hypertension (preeclampsia/eclampsia).
2.	Chronic hypertension of whatever cause.
3.	Chronic hypertension with superimposed preeclamspia.
4.	Late or "transient" hypertension.

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Chronic Hypertension with Super-imposed Preeclampsia

Almost three quarters of those with chronic hypertension develop superimposed PE in the second half of pregnancy. PE in this group is often more severe. Chronic hypertensive disease is independently associated with an increased incidence of not only PE but also gestational diabetes and placental abruption.

Late or Transient Hypertension

This group includes those who develop hypertension in the last trimester or immediate postpartum which normalizes by the tenth postpartum day.

PATHOPHYSIOLOGY OF PREECLAMPSIA/ECLAMPSIA

PIH is a multisystem disease characterized by vascular endothelial damage and dysfunction. There have been various postulates on its pathogenesis including the role of superficial placentation, immune maladaptation and reduced angiogenic factors. The placenta rather than the fetus seems to have a role in the pathogenesis of PE/eclampsia since it occurs in situations when the placenta is present but fetus is absent (e.g., hydatidiform mole). The placenta shows evidence of hypoperfusion and ischemia with scars. Normally, during pregnancy, the decidual part of spiral arteries invaded by the cytotrophoblast and replaced with fibrinoid material which transforms the vascular supply from a high pressure, low flow system to a low pressure, high flow system. This helps to meet the needs of the fetus and placenta. The loss of endothelium and muscle layer results in failure of the blood vessels to respond to vasomotor stimuli. In contrast, in PIH, the trophoblastic invasion is partially impaired. and preservation of the muscle layers makes the vessel sensitive to vasomotor stimuli resulting in reduced placental blood flow. The trophoblastic invasion of spiral arteries and remodeling of the vasculature in normal pregnancy are favored by angiogenic proteins produced by the normal placenta like vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). The receptor for these growth factors is called fms like tyrosine kinase (Flt1) which exists in two forms, a membrane bound form and a soluble secreted form (sFlt1). An excess of sFlt1 occurs in PE. This can bind to circulating VEGF and PlGF and can affect their binding to the endothelium receptors. This can result in a generalized endothelial damage and multiorgan involvement. Thus the endothelial damage which started in the placenta becomes generalized. The defective trophoblastic invasion may be due to the excess sFlt1 though various other antiangiogenic factors are also postulated. Asymmetric dimethyl arginine (ADMA), an endogenous endothelial nitric oxide synthase inhibitor may have a role. A decrease in nitric oxide, prostacyclin and release of procoagulant proteins like von Willebrand factor, endothelin, fibronectin and thrombomodulin may also have a role.

Plasma volume was found to be significantly decreased in patients with PIH compared to pregnant women with normal BP. The lowest intravascular volumes were found in pregnant women who developed severe PIH and evidence of uteroplacental insufficiency. Despite contracted plasma volume, women with PE are characterized by relatively greater BP sensitivity to exogenous Angiotensin II than normotensive pregnant women. Evidence suggests that this is due to an alteration in angiotensin II receptor sites.

Thromboxane A2 production is more in those having more severe forms of preeclampsia and coagulopathy. Low-dose aspirin selectively inhibits the synthesis of platelet thromboxane by acting on the cyclooxygenase enzyme without affecting the production of endothelium-derived prostacyclin or nitric oxide. This may be the basis for the beneficial role of low-dose aspirin in some cases of PE. Oxidative stress may also have a role with increased levels of reactive oxidation species being detected in PE. This may suggest a role for antioxidants.

The salient pathological changes in the kidneys include enlargement of the glomeruli with no increase in the number of cells. The endothelial cells are swollen and fill up the capillary loops. These changes have been termed "glomerular endotheliosis".

Diagnosis

PE can be suspected clinically by noting BP elevation which may be associated with headache, epigastric or right upper quadrant abdominal pain, visual abnormalities such as scotoma and cortical blindness. Visual disturbances are due to spasm of retinal arterioles and suggest generalized increase in vascular tone. Symptoms like epigastric discomfort and visual disturbances may precede the development of generalized convulsions.

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If convulsions occur, the diagnosis is eclampsia. Fifty percent of cases of eclampsia occur before labor, 25 percent during labor and 25 percent in the postpartum period. Severe dysfunction of pulmonary, renal, hepatic and central nervous systems may occur.

Some laboratory parameters may be helpful in the diagnosis. Examination of urine reveals proteinuria which may be heavy even in the nephrotic range, and nonselective with excretion of high molecular weight proteins. The urinary sediment is generally unremarkable but may show only granular casts. Presence of red blood cells, red blood cell casts or other findings suggestive of nephritic illness indicates undetected preexisting renal diseases. The important hematologic abnormalities are increased hematocrit and hemoglobin due to reduction of plasma volume, thrombocytopenia and increased thrombin time. Blood levels of aspartate aminotransferase, alanine aminotransferase and lactic dehydrogenase enzymes may be elevated, but they return to normal within 10 days of delivery. Renal function may be decreased with elevation of blood urea nitrogen (BUN) and serum creatinine. Due to the marked increase in GFR, BUN and serum creatinine levels are much lower in pregnant compared to nonpregnant women. The normal levels of urea nitrogen in nonpregnant and pregnant women are 10 to 16 mg/dL and 5 to 8 mg/dL, respectively. The corresponding normal values of serum creatinine are 0.8 to 0.9 mg/dL and 0.4 mg/dL respectively. Therefore if BUN and serum creatinine during pregnancy are at or above the pre-pregnant levels, it indicates impairment of GFR. Similarly, serum uric acid is low (2.5 mg/dL) due to enhanced GFR. Elevation of serum uric acid to 4.5 mg/dL is an indication of enhanced proximal tubular reabsorption of uric acid caused by volume contraction and consequently decreased GFR. Hyperuricemia is of diagnostic importance, as it helps to distinguish women with PIH from those with chronic hypertension. There is a postulate that the hyperuricemia could independently contribute to the hypertension. Intrauterine growth retardation can be quantified by serially monitoring the fetal growth clinically and by ultrasound scan.

It may be difficult to differentiate between pre-eclampisa and chronic hypertension complicating pregnancy. Presence of hypertension before conception or detection of hypertension before 20 weeks of gestation is not suggestive of PE. However, new onset of hypertension early in pregnancy, especially in primigravida signifies PE. Severe PE is invariably associated with hypertension but uncommon in multiparous women. The BP usually decreases dramatically following termination of pregnancy in PE. Severe PE may be confused with acute fatty liver of pregnancy, thrombotic microangiopathy, glomerulonephritis or systemic lupus erythematosus. A combination of development of hypertension during pregnancy, proteinuria and elevated serum uric acid supports a diagnosis of preeclampisa. Although the onset of hypertension frequently is abrupt and rapidly progressive, the mean BP of women destined to develop PE is higher in the first and second trimesters than the mean BP of those who do not develop PE.

Management

An important step in prevention of PE is to avoid teenage pregnancy or consider first pregnancy after the age of 35 years. In the antenatal checkup, care is taken to restrict maternal weight gain to less than 12.5 kg, and to avoid aggressive salt restriction or diuretic therapy. The preeclamptic women is hospitalized early and encouraged to rest on the left lateral position. Fetal growth parameters are monitored clinically and by ultrasound scans. The fetal prognosis has improved considerably by judicious and deliberate preterm delivery combined with the skill of the neonatologist and a good premature nursery. Doppler flow velocimetry has been used to monitor abnormalities in uterine and umbilical circulation. Calculation of the systolic/diastolic ratio of the uterine or umbilical artery provides an indirect evidence of the impedance of these circulations. A first stage test with uterine Doppler ultrasound at 20 to 24 weeks of gestation followed by a second stage test with ambulatory 24-hour BP monitoring in patients with abnormal uterine Doppler might indicate women at risk of developing PIH. The Doppler flow study should be repeated once at 32 to 34 weeks. If umbilical artery flow remains abnormal, attention should be focused on the fetus using ultrasonography to evaluate the possibility of chromosomal abnormalities, fetal growth assessment, fetal heart rate monitoring and the biophysical profile for development of hypoxia. Absent or reversed diastolic flow is an indication for daily fetal surveillance. The presence of any sign of fetal hypoxia should warrant delivery.

Depending on the facilities in the premature baby unit, labor is induced when the fetal weight is 1.5 to

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1.8 kg, since the infant has more chances of survival in a good premature nursery than the womb of a mother with uncontrolled hypertension. It is suggested that delivery can be planned by 37th week in mild cases and by 34th week in more severe cases. Treatment should be instituted if diastolic BP is 85 mmHg in mid-pregnancy and 95 mmHg in late pregnancy. BP above 95 mmHg in mid-pregnancy or 100 mmHg in late pregnancy should be considered an emergency. If the fetal maturity and weight are satisfactory at the time of detection of hypertension, labor may be induced. Great caution must be exercised in prescribing antihypertensive drugs to hypertensive pregnant women. While centrally acting alpha-2 receptor agonists (methyldopa), vasodilators (hydralazine), beta-blockers (atenolol), combined alpha-beta receptor blocking agents (labetalol) and calcium channel blockers (nifedipine) are safe, other antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists are unsafe. There is a great deal of controversy about the use of diuretics in PIH.

Centrally Acting Alpha-2 Receptor Agonists

Methyldopa, has been used most extensively for the control of BP during pregnancy. It is safe and effective, but may cause transient BP fall in the neonate. The dose is titrated depending on the response in individual cases. A dose of up to 4 gm per day can be given.

Vasodilators

Hydralazine is a vasodilator antihypertensive drug and can be used alone or in combination with methyldopa. It is quite safe but may produce transient tachycardia in the infant. It improves the uteroplacental circulation. It can be used intravenously in emergency. The usual oral dose is 50 mg four times daily. This drug is relatively less expensive and can be used as the first-line drug. It may produce headache and tachycardia in some patients.

Beta-Blockers

Beta-blockers were initially condemned because of fetal growth retardation, persistent neonatal hypoglycemia, respiratory depression and bradycardia. Studies have also noted poor development of the spiral arteries and intrauterine growth retardation. However, with careful use, beta-blockers such as atenolol and oxprenolol have been found to be effective during the latter part of pregnancy.

Combined Alpha-Beta Receptor Blockers

Labetalol belongs to this group and is being increasingly used in the management of hypertension in pregnancy in a dose of 100 to 200 mg orally twice daily. It has a number of advantages like insignificant maternal and fetal side effects, improved fetal lung maturity and improved uteroplacental circulation. A total dose up to 1,200 mg orally per day can be given. Some studies have noted an increase in retroplacental clots in a few cases. This drug is beneficial for the treatment of severely elevated BP or resistant hypertension during pregnancy.

Calcium Channel Blockers

Among the calcium channel blocking drugs, only nifedipine has been used successfully. Nifedipine 10 to 20 mg orally three to four times daily lowers BP in patients with severe hypertension during pregnancy and may be even preferable to hydralazine. Nifedipine has been used successfully to postpone delivery in patients with preterm labor. We have observed that in some women on nifedipine therapy, induction of labor with pitocin is attenuated or fails and uterine contraction is not satisfactory after cesarean section. If nifedipine is discontinued 48 to 72 hours prior to the induction of labor or cesarean section, uterine inhibition is reversed (unpublished personal observation). Although nifedipine has been used to prevent preterm labor, it does not arrest the process of labor once it is well established. Diltiazem can decrease proteinuria and can be used in patients with renal disease, hypertension and pregnancy.

Diazoxide

Diazoxide is a parenteral vasodilator agent used in emergencies. When given in bolus doses of 300 mg, it produces uterine atony. Therefore, small repeated doses are generally recommended. Since nifedipine can bring about rapid reduction of BP when given through the buccal route, intravenous diazoxide is not commonly used now.

Other Drugs

Alpha-receptor blocking agents such as prazosin, central alpha agonists such as clonidine, ACE inhibitors and angiotensin II receptor blockers like losartan are not recommended. Oligohydramnios and neonatal renal failure has been reported in a premature infant whose mother received enalapril in 32 to 35 weeks of her pregnancy.

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Diuretics

As mentioned earlier, prevailing controversies are deterrent to the use of diuretics in the treatment of hypertension during pregnancy. Based on available data, it may be safer to control hypertension in pregnancy with other antihypertensive drugs and using diuretics judiciously in resistant cases with edema. In case of hypertensive emergency, intravenous or intramuscular hydralazine, methyldopa or diazoxide may be used. However, oral Labetalol or Nifedipine also act quickly. Sodium nitroprusside is not generally recommended since thiocyanate blood levels increase causing cyanide toxicity and reduced placental blood flow. It may be employed only if the mother's life is at risk or fetal outcome is inconsequential.

Once PE is confirmed, the expectant mother is hospitalized and severity is assessed as mild, moderate or severe. In mild and moderate cases, termination of pregnancy is recommended if pregnancy is close to term (36 weeks or later) and fetal maturity is acceptable. If the period of gestation is less than 36 weeks, the mother is closely observed and parameters like BP, urine output, proteinuria, optic fundi, neurologic status, BUN, serum creatinine, serum uric acid, lactic dehydrogenase, platelet count and aspartate aminotransferase are monitored. Fetal lung maturation can be assessed by determination of lecithin/sphingomyelin ratio or phosphatidylglycerol in the amniotic fluid. However, since the decision to deliver the baby preterm depends on maternal deterioration, this test should not be performed routinely. A favorable fetal lung maturity can help in a decision to terminate pregnancy earlier than 36 weeks with good results.

Under careful observation, the mother and fetus can continue to coexist with benefit to the fetus and relatively slight risk of immediate or remote harm to the mother. The maternal health and fetal growth are closely monitored, and a judicious and deliberate preterm delivery is conducted, if the fetus is viable and the maternal environment is hostile for further growth of the fetus. The presence of chorionic villi in some women incites development of vasospasm and hypertension which revert to normal following the expulsion/removal of the chorionic villi.

If the welfare of the mother is at risk and the fetus is severely growth retarded, or the mother has imminent eclampsia or convulsions, immediate termination of pregnancy remains the only alternative.

Treatment

In the event of development of eclampsia, the main objectives of treatment are the following:

Arrest/Prevent Convulsions

Early detection of hypertension and adequate control of BP with antihypertensive drugs can prevent development of eclampsia. Convulsions can be arrested and further occurrence is prevented by the timely use of parenteral magnesium sulfate. It can also decrease risk of eclampsia by more than half. The usual protocol followed is as follows: 20 ml solution of 20 percent magnesium sulfate ($MgSO_4$, $/7H_2O$, 4 gms) is given intravenously in five minutes followed by 10 ml solution of 50 percent magnesium sulfate given by deep intramuscular injection into each buttock (total = 10 gm intramuscularly). The convulsions are usually arrested by this regime. Subsequently, the patient is closely monitored for patellar jerk, urine flow rate and respirations. The loss of patellar jerk is the earliest warning sign of impending magnesium toxicity. If the patellar jerk is present, urine output is more than 100 ml in the previous four hours and respirations are adequate, a further dose of 10 ml 50 percent magnesium sulfate (5 gm) is administered into alternate buttocks every four hours. Administered in the above fashion, the plasma magnesium often increases to 7 to 9 mEq/L but stabilizes at a serum level of 4 to 7 mEq/L. Administration of magnesium sulfate is often continued for 24 hours postpartum.

Magnesium sulfate potentiates the hypotensive action of calcium channel blockers. It is believed to act at the neuromuscular junction. A comparative study between magnesium and phenytoin showed a better efficacy with the former. Magnesium toxicity can be counteracted by intravenous calcium administration.

Long-term use of diazepam as an anticonvulsant is not favorable for the fetus, since it may cause hypotonia, drowsiness and apnea for several hours after birth. The Apgar score may also be low. However, diazepam can be used to terminate a fit. The generalized central nervous system depression of mother and fetus discourages the use of morphine in this condition.

Terminate Pregnancy with Least Amount of Trauma to Mother and Fetus

In most cases, the termination of pregnancy can be easily accomplished by the use of oxytocin, 10 units in 250 ml of 5 percent dextrose in water as a controlled infusion.

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Deliver an Infant Who may Subsequently Thrive

If the maternal health is not jeopardized, pregnancy may be continued under close monitoring of maternal and fetal parameters until the fetus is sufficiently mature to survive in the premature nursery.

Restore Mother's Health Completely

This requires close monitoring of the mother, particularly the BP during puerperium. Clinicians often make a mistake by abruptly stopping all drugs immediately after delivery or shortly thereafter. The mother may require a variable dose of antihypertnesive drugs for a few weeks. All cases of hypertension in pregnancy are not PE. Cases with undetected renal disease or essential hypertension may not come back for observation and diagnosis of hypertension is made for the first time during pregnancy. It is likely that such mothers need long-term administration of antihypertensive drugs.

Prognosis and Predictability

The long term prognosis of PE is controversial, particularly because the clinical diagnosis of PE may be confused with latent hypertension, preexisting renal disease or essential hypertension. Women with essential hypertension may have a significant fall of BP during pregnancy and may remain in the "normotensive" range throughout most of the pregnancy. Women with recurrent gestational hypertension should be considered to have preexisting hypertensive disease.

Pregnancy is now thought to act as a stress test and those who develop PE may be predisposed to endothelial injury and have an eightfold increased risk of cardiovascular disorders as well as hypertension and stroke in later life. They could also have an increased risk of dyslipidemia, insulin resistance and mortality, besides anemia and lung diseases. They should hence be advised lifestyle changes to decrease this risk. Those with recurrent hypertension or when hypertension occurs before 30 weeks may also have an increased incidence of subsequent chronic hypertension. It has been noted that if hypertension persists on the tenth postpartum day, the possibility of recurrence is higher. If the average systolic BP is more than 160 mmHg, the probability of recurrence is higher.

Roll-over test is a simple but nonspecific noninvasive test performed between 28 to 32 weeks. It can be used to detect patients at risk, since it has a higher negative predictive value. The BP is recorded 15 minutes after the subject assumes lateral recumbent posture or until the recordings are stable. Then the subject rolls over to a supine position and BP is checked after one minute. Any increase in diastolic BP of more than 20 mmHg is considered as positive. The gold standard in predicting those who are likely to develop PE in later pregnancy is the angiotensin infusion test based on the increased sensitivity to angiotensin. Antiplatelet agents would be expected to have theoretical advantage in view of the generalized endothelial damage. Low-dose aspirin was found to be beneficial in several initial trials. However, the optimism has been moderated following large scale randomized trials where a statistically significant reduction is hypertension and fetal morbidity and mortality was not seen. It would need to treat almost 90 patients with aspirin to prevent one case of PE. Thus, while aspirin may have a role in high-risk individuals, it cannot be recommended as routine prophylaxis. The following guidelines may be used for selecting pregnant women for low dose aspirin therapy:

1. Positive family history of PIH.
2. Previous history of PE.
3. Teenage pregnancy and pregnancy after 35 years.
4. Preexisting renal disease with hypertension.
5. Multiple pregnancy.
6. Rh negative mother.
7. Diabetic mother.
8. Positive roll-over test.
9. Positive AII infusion test.

Calcium supplementation was reported to be useful in preventing eclampsia, but subsequent trials did not reveal any significant beneficial effects.

The syndrome of hemolysis, elevated liver enzymes and thrombocytopenia (HELLP) has been recognized as a complication of PE for many years. This complicates 0.1 percent of pregnancies and could be associated with eclampsia. Most patients (90 percent) give a history of malaise for a few days prior to presentation. Nausea or vomiting and right upper quadrant pain are also common. Renal dysfunction is common. The typical hepatic lesion associated with HELLP syndrome is periportal or focal parenchymal necrosis, in which large hyaline deposits of fibrin-like materials can be seen in the sinusoids. Prompt delivery is advised, usually within 24 hours of the diagnosis.

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ACUTE RENAL FAILURE IN PREGNANCY

Acute renal failure (ARF) is becoming an increasingly rare complication of pregnancy in industrialized countries because of a decrease in illicit abortions, improved prenatal care, and better management of maternal complications potentially leading to ARF. In the developing countries also, the occurrence of obstetric ARF is progressively declining in parallel to the improvement of social and economic status. The incidence of ARF in pregnancy has a bimodal pattern. During the first trimester, illegal abortion practices induced by crude methods like use of phenol, soap, quinine, other nephrotoxic abortifacients or introduction of foreign bodies into the uterine cavity result in sepsis (septic abortion) and ARF. Other factors like dehydration and shock due to hyperemesis gravidarum, bleeding, urinary infection and septicemia may be responsible. During the third trimester, ARF may develop from severe PE/eclampsia. Almost 8.9 percent of patients with severe PE can develop ARF, usually associated with HELLP syndrome and abruptio placenta. Other important causes of ARF include uterine hemorrhage with hypotension, prolonged intrauterine fetal death, amniotic fluid embolism and disseminated intravascular coagulation. Multiple factors may operate in the same patient and result in severe ARF. Bilateral renal cortical necrosis occurs more frequently in women with placental abruption. Preexisting nephrosclerosis, renal ischemia, disseminated intravascular coagulation or Schwartzman reaction may predispose to development of renal cortical necrosis.

Bilateral renal cortical necrosis has been observed in 27 to 38 percent of pregnant women with ARF. Some patients with patchy cortical necrosis recover sufficient renal function to survive without dialysis. Since renal biopsies are not done in many cases of ARF, some of these cases go undiagnosed.

ARF Peculiar to Pregnancy

Idiopathic Postpartum ARF

This condition is also known as postpartum malignant nephrosclerosis and postpartum hemolytic uremic syndrome. This follows an apparently normal pregnancy and manifests usually between one day to several weeks after delivery. The onset is a "flu-like" illness followed by rapidly developing renal failure. The BP is usually normal. Congestive cardiac failure and convulsions may occur in some cases. The cause of the syndrome is not clear. Retained placental fragments, oral contraceptives, oxytocin, ergot alkaloids, prostaglandin deficiency and immunologic basis had been postulated as possible causes. Endothelial cell damage is now thought to be the primary abnormality and is associated with unusually large von Willebrand factor multimers which form platelet thrombi in the renal circulation. This resembles a generalized Schwartzman-like reaction. The management is aimed at reducing the BP, if elevated, and supportive measures. The renal function may never recover or do so partially. Although several therapeutic strategies like anticoagulants, antiplatelet drugs, exchange transfusion and antithrombin III supplementation have been tried, there is no convincing evidence that these therapeutic manipulations confer any benefit. Plasma exchange daily or on alternate days for the initial two weeks has been found to be effective, probably by removing the von Willebrand factor multimers. Those who receive kidney transplants do well in the post-transplant period.

ARF in Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy is a condition characterized by rapid development of jaundice, normal alkaline phosphatase and microvesicular steatosis usually presenting in the third trimester. More than 50 percent of these patients also develop ARF. The cause of ARF is obscure and may be due to hemodynamic factors as in the hepatorenal syndrome. The mortality is high and often the result of hepatic failure rather than renal failure. Prompt delivery usually improves liver function. Women surviving acute fatty liver of pregnancy have gone through uneventful pregnancies subsequently.

ARF due to Hyperemesis Gravidarum

Persistent vomiting and inadequate fluid replacement may lead to volume contraction and/or hypotension resulting in prerenal failure followed by acute tubular necrosis. This can be prevented by early rehydration and maintenance of intravascular blood volume.

ARF due to Septic Abortion

The pathogenesis of ARF in septic abortion is multifactorial. Bleeding, shock, coagulopathy, septicemia, drugs and nephrotoxic abortifacients are the important pathogenetic factors. In some places, abortifacient paste containing

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mercury is instilled into the uterus together with a foreign body. Such crude methods result in multiple pathogenetic factors which lead to acute tubular necrosis or renal cortical necrosis.

ARF due to Obstetric Bleeding

Blood loss, hypotension, and volume contraction are the important factors leading to ARF. It may occur in antepartum hemorrhage, placenta previa or post-partum hemorrhage In abruptio-placentae, in addition to the above factors, coagulopathy with disseminated intravascular coagulation may play a very significant role. This may lead to a more severe ARF where the clinical course is more prolonged and recovery of renal function is partial or negligible due to the development of patchy or total renal cortical necrosis. This condition is often suspected if ARF does not recover in 4 to 6 weeks and a renal biopsy provides a definite proof.

ARF from Amniotic Fluid Embolism

Entry of amniotic fluid in the maternal blood may lead to redistribution of body fluids, intravascular volume contraction and hypotension. Protracted hypotension can lead to ARF.

ARF from Obstructive Uropathy

Obstructive uropathy leading to anuria may develop, if the ureter from a single kidney or ectopic kidney is obstructed. Bilateral ureteric obstruction may occur due to tissue trauma and edema of ureter during surgical procedures in the broad ligament. Rarely, accidental ureteric ligation during pelvic surgery may lead to anuric ARF.

ARF from Super-imposed Preeclampsia

The chances of ARF are greater if PE supervenes on a preexisting renal disease.

ARF from Acute Pyelonephritis

While acute pyelonephritis is seldom associated with ARF in the nonpregnant subjects, it is more common is pregnancy, probably due to increased sensitivity of the vasculature to bacterial endotoxin.

Management

The management of ARF per se in pregnant and nonpregnant subjects is essentially similar. However, certain specific conditions which may accompany pregnancy may need attention. In early pregnancy, a retained intrauterine foreign body used for inducing abortion is a consideration particularly if there is infection. Some abortifacients contain nephrotoxic substances like mercury paste, etc. During the third trimester, the extent of concealed hemorrhage may be large and prompt transfusion of adequate quantities of blood is essential. Replacement of fluid or blood must be closely monitored to prevent overcorrection or under-correction. Since infectious complications may be more common during pregnancy than in the nonpregnant state, the mother should be treated with appropriate antibiotics which are not toxic to the fetus or kidney. Early or prophylactic dialysis is advocated since urea and creatinine cross the placenta and may reduce the chances of fetal survival. If the fetus is viable, termination of pregnancy should be attempted as soon as the maternal condition improves. Since urea and creatinine cross the placenta, the neonate may have higher blood levels of these substances at birth. The osmotic diuresis due to accumulated urea in the neonate must be recognized and managed with prompt rehydration. Both peritoneal and hemodialysis have been advocated in women with ARF in pregnancy. The choice of dialysis therapy has to be individualized. Care is taken to prevent excessive fluid shifts during dialysis. In cases of septic abortion with ARF, aggressive surgical management combined with antibiotic therapy and dialysis support was more useful compared to conservative management combined with dialysis.

URINARY TRACT INFECTIONS IN PREGNANCY

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is characterized by absence of symptoms of urinary tract infection at a time when significant bacteriuria exists. Significant bacteriuria is confirmed when a single suprapubic aspirated sample of urine shows bacterial growth or when two consecutive samples of freshly passed urine yield more than 100,000 colonies per ml of the same organism on culture.

Because of the anatomical and functional changes in the urinary tract and the high urinary nutrients in pregnant women, asymptomatic bacteriuria may occur in 5 to 10 percent of all pregnancies. It is commonly seen in old multiparous women from low socioeconomic

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background. It is more common when preexisting conditions like diabetes mellitus, sickle cell disease, renal diseases or hypertension are present. Although asymptomatic bacteriuria may be a relatively benign disorder in nonpregnant subjects, 30 to 50 percent of pregnant women with asymptomatic bacteriuria may go on to develop symptomatic urinary tract infection. Asymptomatic bacteriuria may be associated with increased incidence of PE, premature delivery, anemia and low birth weight. Therefore, routine screening of all pregnant mothers during the first trimester for bacteriuria is advocated. If asymptomatic bacteriuria is detected, it is advisable to eradicate the infection with a 14-day course of appropriate antibiotics. Ampicillin, amoxicillin, cephalosporins or kanamycin can be safely used. Short course of ciprofloxacin, nitrofurantoin, nalidixic acid or cotrimoxazole may be used cautiously in pregnancy. These patients should be followed up with serial urine cultures. In women in whom asymptomatic bacteriuria is difficult to eradicate, continuous antibiotic therapy during pregnancy and detailed investigations to rule out urinary tract obstruction in the postpartum period are warranted.

Acute Pyelonephritis

Symptomatic renal parenchymal infection with fever, rigors, chills, loin pain and pyuria may occur in about 1 percent of all pregnancies. Severe infections may lead to sepsis, shock, fetal loss, renal cortical abscess, renal carbuncle and other maternal complications. Asymptomatic bacteriurics, those with previous urinary tract infections or congenital anomalies of the urinary tract, are more prone to develop acute pyelonephritis. A significantly greater pelvicalyceal dilatation has been noted in those developing acute pyelonephritis. The management of acute pyelonephritis in pregnancy should be promptly instituted and performed in the hospital. Urine and blood samples are sent for culture, and treatment with intravenous fluids, antipyretics, and antibiotics are begun. In severe infections, antibiotics which reach high renal parenchymal concentration and have no adverse effects on the fetus should be started immediately. After fever has remitted for several days, antibiotics may be continued by oral route. It may be advisable to give a three-week course of antibiotics to ensure complete eradication of infection. Intermittent urinalysis and cultures are essential to guide control of infection. Tetracyclines are avoided during pregnancy. Co-trimoxazole may cause kernicterus in the neonatal period and hence is avoided near term. In view of ototoxicity, aminoglycosides are preferably avoided. Of the aminoglycosides, kanamycin may be used for severe infection with susceptible organisms. *E. coli* is the commonest organism in more than 70 percent, though Gram positive pathogens can occur later in pregnancy.

PREGNANCY IN PRE-EXISTING RENAL DISEASE

Renal diseases may become manifest during the course of pregnancy or pregnancy may supervene on preexisting renal disease. When proteinuria is first discovered after the twentieth week of pregnancy, an obvious question comes up whether the patient has PE or underlying renal disease, because the clinical features of proteinuria, hypertension, edema and renal insufficiency occur in both settings. The degree of proteinuria does not help in distinguishing between PE and underlying renal disease. Elevated serum uric acid out of proportion to the severity of renal insufficiency is supportive of the diagnosis of PE. Percutaneous renal biopsy may be helpful as glomerular capillary endotheliosis is considered to be specific for PE and almost invariably present, even in mild cases. However, in view of increased vascularity, renal biopsy is usually deferred unless considered essential.

Kidney diseases during pregnancy can affect both the mother and fetus. Hence when a person with preexisting renal disease contemplates pregnancy or conceives, the following questions will be considered:

1. Is conception or continuation of pregnancy advisable?
2. What will be the effect of the renal disease on the pregnancy?
3. Will gestation aggravate renal disease?

Women with moderate or advanced renal failure generally have anovulatory cycles or amenorrhea. If they conceive, it is usually unsuccessful and ends in abortion, intrauterine death or preterm delivery of a severely growth retarded fetus. Women with mild renal failure (serum creatinine < 2.3 mg/dL) may conceive and may be able to go through the pregnancy successfully, if the BP is normal upon conception and maintained at normal level throughout pregnancy. The overall fetal outcome depends on the degree of renal function impairment, degree of control of hypertension and extent

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of proteinuria on conception. The outlook for the fetus in women who become pregnant despite the presence of renal disease seems favorable as long as significant hypertension is absent and serum creatinine is less than 1.4 mg/dL. The majority of investigations indicate that pregnancy does not influence the natural course of renal disease, if renal function is relatively well preserved and hypertension is absent at conception, though worsening of renal functions are common in moderate to severe renal failure. It was reported that in lupus nephritis, IgA nephropathy, membranous glomerulopathy or focal and segmental glomerulosclerosis further deterioration of the original disease may occur. However, it now appears that risk factors like nephrotic range proteinuria, hypertension and impaired renal function have a more important role. If the serum creatinine is more than 1.5 mg/dL, pregnancy can accelerate renal damage and if it exceeds 2 mg/dL, more than one third can worsen their renal functions. Renal disease complicated by pregnancy must hence be considered "high risk" pregnancy and must be managed with close fetal and maternal monitoring by an experienced team of nephrologists and obstetricians. They will require more frequent visits and monthly renal function test. It is generally recommended that the BP should be kept below 140/90 mm Hg.

Acute Glomerulonephritis

Women who conceive during the resolving phase of acute glomerulonephritis may not need any aggressive management. Those who develop acute nephritis in pregnancy also may be managed as in nonpregnant state.

Chronic Glomerulonephritis

Although superimposed PE and hypertensive complications may occur more frequently in women with chronic glomerulonephritis, pregnancy may be successful if hypertension is adequately controlled and renal function is normal.

Polycystic Kidneys

When one of the spouses has autosomal dominant polycystic kidney disease, the couple should undergo counseling. The high chances of transmitting the disease to the offspring and its implications are explained to them and the decision to conceive is left to them. Women with asymptomatic polycystic kidneys usually have an uneventful pregnancy. If the enlargement of the kidneys is massive, it may cause mechanical hindrance for the enlargement of the uterus during the later stages of pregnancy.

Nephrotic Syndrome

Woman with proteinuria less than nephrotic range may develop increased proteinuria in the nephrotic range during pregnancy due to increased GFR, changes in the filtration mechanism or a rise in venous pressure. Women with nephrotic syndrome but in remission may relapse during pregnancy. Nephrotic syndrome is managed by appropriate fluid restriction. Normal salt intake is permitted but diuretics are avoided. Although a protein-restricted diet has been advised in nonpregnant subjects with nephrotic syndrome, this is not followed during pregnancy. The fetal development may be affected and small for date babies are common, if fetal development takes in the unfavorable environment of hypoalbuminemia. Regular albumin infusions are advocated until delivery. Specific treatment with corticosteroids can be given if indicated, whereas other immunosuppressive drugs are usually commenced after delivery.

Diabetic Nephropathy

The problem of diabetic nephropathy and pregnancy is particularly relevant in juvenile diabetics. If the diabetes has been present for many years at the time of conception, microscopic changes may have developed in the kidneys. These women have greater chances of developing bacteriuria or PE. Although proteinuria may become severe during pregnancy, it returns to the prepregnant levels after delivery and the gestation does not seem to alter the course of maternal diabetic nephropathy.

Systemic Lupus Erythematosis

The effect of gestation on lupus and the effect of lupus on gestation are variable. If the woman has no lupus activity for at least one year before conception and renal function is normal, she has a good chance of an uneventful pregnancy with no apparent aggravation of lupus activity postpartum. If the woman had active lupus at the time of conception or the symptoms develop during pregnancy for the first time, the outcome may be unfavorable. Flares can occur during pregnancy, especially in those having thrombocytopenia and

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hypertension, but are usually mild to moderate. In about 10 percent of patients, there may be an exacerbation of lupus activity postpartum leading to ARF. For this reason, some centers still increase the dose of steroids prophylactically after delivery and reduce it over the next three months. The autoantibodies may cross the placenta and result in repeated abortions. Such patients may need drug therapy for control and may be able to go through a successful pregnancy while on low-dose steroid therapy. The presence of antinuclear antibodies may be responsible for the lupus syndrome in the neonate characterized by transient skin rash, pancytopenia or heart block. Lupus nephritis class III to IV is a risk factor for hypertensive disease during pregnancy, but it does not contraindicate gestation. Pregnancy is safe for the majority of mothers if it is planned when SLE is quiescent. Although fetal risk has been progressively reduced in the last 40 years, it continues to be higher than that occurring in pregnancies of healthy women. In particular, the presence of antiphospholipid antibodies considerably worsen the fetal outcome. Some feel that the deterioration of renal function seen in some pregnant lupus patients may not be influenced by pregnancy and could be the natural course.

Vascular Disorders

Polyarteritis nodosa, scleroderma and Wegener's granulomatosis are associated with hypertension and significant vascular involvement. Hence the outcome of pregnancy is uniformly poor. Even maternal deaths have been reported and such patients should be advised against pregnancy.

Chronic Tubulointerstitial Nephritis, Reflux Nephropathy and Urolithiasis

In all these conditions, the chances of developing symptomatic urinary tract infections are high. Such women are monitored closely by frequent urine cultures and suitable antibiotics used at the appropriate time. If the BP and renal functions are in the acceptable range, the outcome of pregnancy is favorable. Prophylactic ureterovesical reimplantation in women with repeated pyelonephritic episodes may be advisable in women with persistent vesicoureteric reflux contemplating pregnancy. In urolithiasis, adequate hydration is maintained and analgesics used, if necessary.

PREGNANCY AND DIALYSIS

To optimize pregnancy outcome in the pregnant lady with renal failure, it is recommended to initiate hemodialysis when the serum creatinine exceeds 5 mg/dL or the BUN exceeds 60 mg/dL with the goal being a predialysis BUN below 50 mg/dL with normalization of systemic pH, calcium, phosphorus and potassium. Five to seven hemodialysis sessions per week may be required with bicarbonate buffer. Intensive nocturnal hemodialysis may give a better outcome. Fluid balance should be maintained and abrupt fluid shifts during dialysis avoided. The BP should be closely monitored and hypotension avoided. Anticoagulation should be very carefully planned to avoid hemorrhagic complications. In women who develop ARF during pregnancy, early dialysis is advocated and continued till renal function recovers or improves. Both hemodialysis and peritoneal dialysis can be used. Women on maintenance hemodialysis may conceive. Nearly 50 percent may abort spontaneously. In view of the risks and overall poor outcome, most women prefer therapeutic abortion. However, there are reports of successful pregnancy in women who have been on maintenance hemodialysis for months or years. Successful pregnancies have also been reported in diabetic women on continuous ambulatory peritoneal dialysis.

PREGNANCY FOLLOWING RENAL TRANSPLANTATION

Renal transplantation is the best treatment for fertile women with end-stage renal disease who want to become pregnant. Women who are keen to conceive after successful transplantation may be advised to do so only around two years after transplantation provided renal function and BP are normal and there is no significant proteinuria. The patient should be monitored closely by a team of nephrologists and obstetricians in a high risk pregnancy unit. Although the graft functions are rarely affected, there is an increased risk of spontaneous abortions, premature deliveries, low birth weight, PE and cesarean sections. The incidence of fetal malformations due to immunosuppressive drugs does not seem to be a significant problem with prednisolone, azathioprine or cyclosporine, though there is little experience with the newer drugs. However, the urinary protein excretion and

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Textbook of NEPHROLOGY

Diabetes has constituted a large part of nephrology practice. Diabetes-related renal disease including end-stage renal disease makes up the considerable volume of patients in nephrology offices throughout the world. Therefore, the editor feels deeply that including several chapters on diabetes will educate the readers with comprehensive knowledge of the pathophysiology of diabetes in this text unlike other textbooks on the subject of nephrology. The pathophysiology such as what does high glucose do to body function is written on the platform of fundamental research in the editor's laboratories. The more we know about the fundamentals of diabetes, the safer the care we will be able to provide to our patients. In other words, it is the editor's conviction that physicians should pay utmost attention to enabling a productive and healthy life for our diabetes patients rather than dictating a therapy which leads to dialys is and the burden it imposes on the patient and the family.

The chapter on logical management of diabetes should help the readers to accomplish this defined task. The focus of this third edition of the book is a conservative nephrology practice directed toward healthy living, clear of artificial means of prolonging life.



Anil K Mandal is a native of India and a naturalized citizen of the Unites States. He graduated from Calcutta National Medical College and is a Diplomate of the American Board of Internal Medicine and in Nephrology (Kidney Disease and Hypertension). He is the author of many books and articles on research in diabetes and kidney disease. He is a two-time Fulbright Scholar to India and Visiting Professor to 24 countries where he has lectured on diabetes, high blood pressure, and kidney disease.

He began the Mandal Diabetes Research Foundation for the prevention and treatment of diabetes based on his knowledge that diabetes is the most common cause of kidney failure worldwide.

His convictions are that—in the office, patients come first and, in the home, children come first. He is dedicated to helping diabetic patients live a good life and not enter dialysis.

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