The Kidney in Pregnancy

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Anatomic Changes in the Kidney during Pregnancy

Anatomical changes occur in the kidney during pregnancy. Renal length is increased by 1 to 1.5 cm [1]. A physiologic dilatation of the ureters gives rise to hydronephrosis, with urinary stasis of up to 300 cc in the ureters, a change which predisposes to urinary tract infection (UTI) [2]. The ureteral dilatation occurs as early as 12 weeks gestation in response to increased estrogen and progesterone as well as increased prostaglandin E_2 (PGE_2), which decreases ureteral peristalsis. Dilatation is later aggravated by the expansion of the uterus, and hydronephrosis may become more marked. The role of obstruction has been raised by the observation that dilatation is more marked after 4 months gestation and at distances greater than 5 – 10 cm above the ureterovesicular junction. The obstructive component of ureteral dilatation is aggravated by upright posture. By the third trimester, hydronephrosis graded as severe on ultrasound may be seen in normal pregnancy [3]. The increase in renal size usually reverses during the first week postpartum, but hydronephrosis may persist for 12 weeks postpartum. Stasis of urine in the dilated collecting system makes timed urine collections difficult, and it is important to verify the adequacy of collection by measuring total creatinine production. Establishing a brisk diuresis before starting a timed urine collection will minimize the likelihood of inaccuracy resulting from urine stasis. Methods of measuring glomerular filtration rate (GFR) that rely on radioisotopes such as iothalamate cannot be used in pregnancy.

Changes in Renal Physiology during Normal Pregnancy

Dramatic changes in renal function occur during pregnancy (Table 1). Renal plasma flow increases to 50 – 70% above normal during the first two trimesters and remains 40% above normal in the third trimester [4]. An increase in GFR begins by the fourth week of gestation, peaks at 150% of normal at 13 weeks, and continues almost until term. There is dilatation of both afferent and efferent arterioles, and increased renal blood flow is the major determinant of GFR. There is little pressure change across the glomerular basement membrane (GBM) [5]. Mean blood urea nitrogen (BUN) is 9 mg/dL and mean serum creatinine is 0.5 mg/dL. Despite an average decrease in serum albumin of 1.5 gm/dL

Table 1. Renal Changes in Normal Pregnancy

Anatomic
- 1 cm ↑ in length
- Dilatation of the collecting system

Physiologic
- 50% ↑ in GFR: normal
- BUN 9 mg/dL, creatinine 0.5mg/dL
- Respiratory alkalosis: normal PCO_2 27 – 32 mm Hg, HCO^-_3 18 – 21 mEq/L
- Decreased serum osmolality: normal 276 – 278 mOsm/L
- Doubling of uric acid clearance: normal 3 – 4 mg/dL
- ↓ Tubular reabsorption of glucose
- 40% ↑ in renal blood flow
- Decreased afferent and efferent arteriolar resistance
- Decreased BP: normal < 125/75 mm Hg 2nd trimester, < 125/85 mm Hg 3rd trimester
- ↑ Renin (8x), angiotensin (4x), aldosterone (10 – 20x)
- ↑ Prostacyclin and thromboxane

(from 4.7 to 3.2 g/dL), a significant decrease in the oncotic gradient across the glomerular basement membrane has not been found in animal models.

Tubular function also changes. The threshold for reabsorption of glucose increases, and glycosuria may occur without hyperglycemia [4]. Amino acid excretion is increased.

Uric acid clearance is increased in pregnancy from 6 – 12 mL/min to 12 – 20 mL/minute [6]. Increased glomerular filtration is the primary cause of increased uric acid clearance, but a role for decreased tubular reabsorption is suggested by an increase in the ratio of urate to inulin clearance. Normal uric acid in pregnancy is 3 – 4 mg/dL, and an increase in serum uric acid is a sensitive indicator of preeclampsia.

Salt and Water

Pregnancy is accompanied by retention of 900 mEq of sodium and 6 – 8 liters of water, of which 4 – 6 L is in the maternal intravascular and interstitial space. Plasma aldosterone begins to increase early in the first trimester and reaches 5 fold elevation by 16 weeks gestation and a 7–10 fold elevation by term. Early in the third trimester, serum aldosterone levels are 7–10 times greater than in the nonpregnant state, with greater elevations in urinary aldosterone [7]. Plasma renin activity (PRA) increases 4 fold early in pregnancy and then plateaus. Angiotensin II (Ang II) levels double early in pregnancy and rise to 3–4 times normal by term. Despite increased serum levels, pregnant women retain sodium and shut off aldosterone secretion in response to exogenous mineralocorticoid administration.

Osmolality

The osmostat is reset such that thirst is experienced at a level 10 mOsm below the nonpregnant normal, and serum sodium is about 5 mEq/L below nonpregnant normal. The set point for ADH release is decreased from a serum osmolality of 285 to 276 – 278 mOsm/L. While ADH is released at a lower serum osmolality, the rate of metabolic breakdown of ADH is increased because of vasopressinase produced in the placenta [8]. A short-lived diabetes insipidus (DI) secondary to excessive placental vasopressinase may occur in the third trimester. The syndrome is classified as neither central nor nephrogenic. It does not respond to ADH but does respond to synthetic desmopressin (DDAVP), which is not broken down by the enzyme [9]. Women with mild central DI suffer a worsen-

ing of their disease during pregnancy because they cannot increase vasopressin production.

Acid-base Metabolism

Pregnancy is accompanied by a chronic respiratory alkalosis caused by increased ventilation in response to progesterone [10]. Normal partial pressure of CO_2 (Pco_2) is 27 – 32 mm Hg, and normal serum bicarbonate is 18 – 21 mEq/L. The urine is usually alkaline. Changes in acid-base status should be kept in mind when evaluating maternal conditions associated with an increase in serum bicarbonate, such as vomiting and diuretic use. Increases in serum bicarbonate to the high 20s or low 30s may reflect critical alkalemia.

Hemodynamic Changes

Diastolic blood pressure decreases by 7 – 10 mm Hg during the first trimester and returns to prepregnancy levels in the third trimester. Changes in systolic blood pressure are less marked because the increase in cardiac output that occurs in normal pregnancy offsets the vasodilatation. The drop in blood pressure in normal pregnancy occurs despite sodium retention and increased levels of renin, angiotensin, and aldosterone. There is resistance to the hypertensive effects of both endogenously- and exogenously-administered angiotensin. The resistance has been attributed to production of prostacyclin by placental endothelial cells as well as other vasodilators, the relative importance of which is an area of intense study.

Hypertensive Disorders of Pregnancy

Hypertension complicates about 2 – 10% of pregnancies in the United States and is the most important cause of maternal morbidity [11]. In a previously normotensive woman, a rise in systolic blood pressure of 30 mm Hg or a rise in diastolic blood pressure of 15 mm Hg on 2 measurements taken 6 hours apart is considered hypertension. Women with a mean arterial pressure > 90 mm Hg in the second trimester have an increased frequency of stillbirth and neonatal death [12].

Classification

Most centers in the United States use the classification for hypertension in pregnancy proposed by the American College of Obstetricians and Gynecologists in 1972 [11]. This classification divides the hypertensive disorders of pregnancy into preeclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia, and gestational hypertension. The latter is a retrospective diagnosis. Hypertension occurs late in pregnancy without proteinuria and resolves postpartum. It may recur in subsequent pregnancies and is predictive of hypertension in later life.

Preeclampsia

Clinical Presentation

Preeclampsia is characterized by the triad of edema, hypertension, and proteinuria occurring after 20 weeks gestation. Risk factors for preeclampsia are listed in Table 2. Preeclampsia and eclampsia may develop post-

Table 2. Risk Factors for Preeclampsia

– Primigravida
– Different father in pregnancy for multigravida
– Diabetes
– Preexisting hypertension
– Renal disease
– Twin gestation
– Hydatidiform mole
– Fetal hydrops
– Family history

Table 3. Signs and Symptoms of Severe Preeclampsia

– Thrombocytopenia
– Microangiopathic hemolytic anemia
– Elevated transaminases
– Disseminated intravascular coagulation (DIC)
– Congestive heart failure (CHF)
– Retinal detachment
– Ascites
– Seizures
– Cortical blindness
– Acute renal failure (ARF)
– Hepatic rupture

partum, with 20% of the severe form of preeclampsia referred to as HELLP syndrome (see below) [13] and 4 – 10% of seizures [14] occurring postpartum.

Although the development of edema is part of the classic description of preeclampsia, clinically it can be difficult to interpret. Eighty percent of pregnant women develop edema during pregnancy, and, paradoxically, edema may be absent in some women with severe preeclampsia. Nonetheless, the first manifestation of preeclampsia is often a rapid weight gain that may precede the development of hypertension and proteinuria. The latter conditions usually appear after weight gain, and preeclampsia is unlikely in their absence. Symptoms of severe preeclampsia include headache, visual disturbances, and right upper quadrant pain. Objective observation of blood pressure or proteinuria is more important than subjective symptoms in making the diagnosis of preeclampsia because 59% of women who progress to eclampsia have no premonitory symptoms [15].

Severe preeclampsia is a multisystem disease (Table 3). The most common abnormalities are microangiopathic hemolytic anemia, elevated liver enzymes, and low platelets, giving rise to the acronym HELLP.

Hemolytic anemia is characterized by schistocytes on peripheral smear. The magnitude of hemolysis may be masked by intravascular volume contraction, which leads to a hematocrit higher than it otherwise would be. The platelet count may drop below 20,000 platelets/mm^3 as a result of platelet activation and consumption. There is consumption of clotting factors even in the absence of changes in prothrombin time (PT) and partial thromboplastin time (PTT). In approximately 20% of instances, frank disseminated intravascular coagulation (DIC) is seen [13]. There is an association of abruptio placentae with the development of DIC.

The liver disease of preeclampsia presents with right upper quadrant pain and elevated bilirubin and transaminases. Preeclampsia is one of a handful of conditions that can result in transaminase levels > 1000 U/L. Pathology is characterized by periportal hemorrhage and deposition of fibrin and fibrinogen in the sinusoids. The most severe manifestation is hepatic rupture, which may result in exsanguination.

GFR is generally decreased in preeclampsia but may remain within the nonpregnant normal range. Severe preeclampsia may give rise to acute renal failure (ARF) with acute tubular

necrosis (ATN) and, rarely, cortical necrosis (see section below on acute renal failure).

Loss of vision has been described in preeclampsia. There are rare reports of retinal detachment [13]. A second uncommon cause of blindness is occipital ischemia, which gives rise to low-density areas on computed tomography (CT) scan and hyperintense lesions on magnetic resonance imaging (MRI) [16]. This occipital blindness is generally reversible.

Ascites occurs in as many as 10% of patients with HELLP syndrome and is associated with a 26% incidence of congestive heart failure (CHF) [17]. Although pulmonary edema may occur in severe preeclampsia, information about hemodynamic changes in preeclampsia is conflicting. There is a marked increase in peripheral resistance and a decrease in intravascular volume, despite sodium retention. Measurements of pulmonary capillary wedge pressure prior to treatment tend to be low normal but are increased in patients with CHF.

The risk of eclampsia in women with preeclampsia depends in great part on prenatal care and management once preeclampsia is present. Eclampsia occurs in < 1% of patients with preeclampsia in some large centers with extensive experience in managing such patients [18]. Severe preeclampsia has been defined by a blood pressure > 160/110, heavy proteinuria, or neurological symptoms, but making the distinction is fraught with hazard. While any one of the manifestations listed above is associated with a high risk of eclampsia, seizures may occur even without proteinuria and when the blood pressure is only mildly elevated or not elevated at all. Douglas and Redman reported on every instance of eclampsia occurring in England in 1992. Nine percent had neither proteinuria nor elevated blood pressure before seizure. Eighty-five percent of seizures occurred within 1 week of a prenatal visit, and only 26% were judged to have had substandard prenatal care. These data suggest that eclampsia cannot be anticipated in some instances. They also suggest that the distinction frequently made between mild and severe preeclampsia may lead to a false sense of security and decreased vigilance in caring for women thought to have mild preeclampsia.

Pathology

The characteristic pathologic changes in the kidney of women with preeclampsia include swelling of the endothelial cells (glomerular endotheliosis), ballooning of capillary loops into the tubule, fibrinogen and lipid in endothelial cells, and occasional foam cells. Rarely, changes similar to focal sclerosis occur, with reversal postpartum. Ischemic changes are less marked than in other organs. The renal pathologic changes resolve 2 – 4 weeks postpartum [19].

Pathophysiology

Preeclampsia is an endothelial cell disorder that may develop in response to placental ischemia resulting from an inadequate trophoblastic migration into the uterine spiral arteries [20]. In normal pregnancy at 16 weeks, the spiral arteries in the uterus lose their musculoelastic tissue and widen to allow an increase in uterine blood flow. In preeclampsia, this loss of musculoskeletal tissue may not occur and there may be necrosis, which gives the spiral arteries the appearance of acute atherosclerosis. Endothelial cell dysfunction leads to increased production of vasoconstrictors and activation of the clotting system. There is increased vascular permeability.

Much of the study of preeclampsia has centered on the pathophysiology of vasoconstriction. The study of the vasoactive substances is confounded by the difficulty of interpreting the effect of changes in the systemic levels of substances that have their greatest effect at the site of production. During normal pregnancy, production of both vasodilator (prostacyclin) and vasoconstrictor (thromboxane) by endothelial cells is increased, and the balance favors the effects of prostacyclin [21]. In preeclampsia, the ratio of thromboxane and prostacyclin production changes, with decreased prostacyclin production and increased thromboxane production, resulting in the predominance of thromboxane effect with diffuse vasoconstriction [21]. Resistance to the pressor effects of angiotensin decreases. In normal pregnancy, endothelin (ET) production by endothelial cells is decreased. Serum levels increase in women with preeclampsia, and because ET is a vasoconstrictor and facilitates platelet aggregation, the possibility that it plays a role in the pathogenesis of preeclampsia has been raised [22]. It is not clear whether increased ET production is a cause or effect of endothelial cell damage.

Decreased endothelial cell production of nitric oxide (NO) has also been suggested as playing a role in the development of preeclampsia. In animal models, blockade of NO production can produce a syndrome similar to preeclampsia [23]. However, serum from preeclamptic women does not change NO production by endothelial cells in vitro. Much of the end-organ disease seen in preeclampsia can be attributed to hypoperfusion resulting from vasoconstriction. Activation of platelets and the intrinsic coagulation pathway also plays a role, producing fibrin deposition and hemorrhage in the liver and generalized bleeding. The pathophysiology of seizures in this disorder is not known. Neurologic manifestations of preeclampsia may be from a combination of mechanisms, including hypoperfusion, bleeding, and cerebral edema. The decreased GFR appears to be caused by a combination of hypoperfusion and capillary occlusion by swollen endothelial cells.

Prevention of Preeclampsia

Numerous attempts have been made to develop a test which will identify women at high risk for the development of preeclampsia. All have been either too invasive for practical use or simply inaccurate. Two interventions have been extensively investigated to determine whether they prevent preeclampsia: low-dose aspirin and calcium supplementation. Despite initial promise, the effects of these two treatments have been disappointing in large trials.

Aspirin Prophylaxis of Preeclampsia

The discovery of the changes in prostacyclin and thromboxane ratios in preeclamptic pregnancies led to efforts to prevent preeclampsia in high-risk women by giving low-dose aspirin. Several small studies demonstrated the usefulness of low-dose aspirin in preventing preeclampsia in women identified as being at high risk [24 – 26]. A placebo-controlled study of 3135 healthy nulliparas found a rate of preeclampsia of 4.6% in the aspirin-treated group and 6.3% in the untreated group ($p = .05$) [27] The Low Dose Aspirin Study in Pregnancy [28] is the largest study of the efficacy of low-dose aspirin in the prevention of preeclampsia. Women ($n = 9364$) at risk for preeclampsia or intrauterine growth retardation (IUGR) were randomized to either low-dose aspirin (60 mg/day) or placebo. This study showed a 12% lower frequency of preeclampsia in the aspirin-treated group, a difference which was not statistically significant. Aspirin administration was associated with a

significant decrease in preterm delivery (19.7% vs. 22.2% for control.) Although the difference in the frequency of preeclampsia was not different for the two groups as a whole, aspirin did reduce the frequency of very early preeclampsia in which the risk of delivery to the fetus is greatest. In both these studies, the effectiveness of aspirin may have been diluted by the inclusion of low-risk women. Three other recent randomized, double-blind, placebo-controlled trials including over 11,000 high-risk women [29 – 31] have not found an effect, even in the subset of women with severe, early-onset preeclampsia. When the data in 2 of these studies were analyzed taking compliance into account, aspirin still had the effect of reducing preeclampsia [32].

The 1993 study found a slight increase in the frequency of abruptio placentae in the aspirin-treated group. The Collaborative Low Dose Aspirin Study in Pregnancy (CLASP) found that the use of low-dose aspirin in pregnancy carries a very low risk of dangerous bleeding, although there was a slight increase in the number of women requiring peripartum transfusions.

Even with the limitations of these studies and the suggested benefit of aspirin in some of the subanalyses, any dramatic benefit from aspirin should have been apparent in studies including >20,000 women. However, women with preexisting renal disease are among those at highest risk for preeclampsia, and the safety of aspirin in these large trials allows defending its use in this subgroup while awaiting the results of subanalyses.

Calcium Supplementation

The results of a prospective, randomized study involving 1194 nulliparous women were reported in 1991. A group receiving 2 g of elemental calcium was found to have a frequency of preeclampsia of 9.8% compared to 14.8% in a placebo-control group [33]. No effect on IUGR or perinatal death was noted. The findings were supported by several other small studies.

The US National Institute of Heath and Human Development has recently completed a prospective, randomized, double-blind, placebo-controlled study that found no difference in the frequency of preeclampsia in 2295 women taking 2 g of calcium daily and 2294 women taking placebo [34]. Nonetheless, pregnant women should routinely receive calcium supplements for bone protection and for calcification of the fetal skeleton.

Treatment of Preeclampsia

The definitive treatment for preeclampsia is delivery of the baby (see Table 4). The manifestations of preeclampsia must be managed until delivery can be effected, or when preeclampsia occurs very early in gestation and is mild enough to warrant an attempt to prolong the pregnancy.

A woman with suspected preeclampsia should be hospitalized because of the difficulty in predicting seizures. A number of pro-

Table 4. Treatment of Preeclampsia

– Admit to hospital
– Anticonvulsants: magnesium sulfate
– Antihypertensive drugs: hydralazine, labetolol
– Indications for delivery
≥ 36 weeks gestation
BP ≥ 160/110 after 24 hours of hospitalization
HELLP syndrome
≥ 3 g of protein in 24 hours
Rising serum creatinine
Headache, blurred vision, scotomata, right upper quadrant pain, clonus

tocols have been developed for intensive home monitoring of women with mild preeclampsia after initial hospitalization. The burden of proof of their safety in comparison to hospitalization rests with their advocates.

There is no reason to delay delivery if the pregnancy has reached 36 weeks gestation. Other indications for delivery include any manifestation of the HELLP syndrome, neurologic symptoms, rising serum creatinine, a blood pressure > 160/110 after 24 hours of hospitalization, and impending or actual seizures. Attempts have been made to manage severe preeclampsia at < 28 weeks gestation [35] and even to prolong pregnancy following a seizure, but we consider this approach too dangerous for general use.

Seizure prophylaxis is required while preparations for delivery are made. There has been a long-standing transatlantic difference in the approach to seizure prevention. Magnesium sulfate has been widely used in the United States, while European centers have favored other anticonvulsants, such as phenytoin and benzodiazepines. Magnesium sulfate appears to be preferable, based on a large, prospective, randomized study [18] in 1089 preeclamptic women assigned to treatment with phenytoin and 1049 assigned to treatment with magnesium sulfate. There were 10 instances of eclampsia in the phenytoin-treated group, but none in the magnesium-treated women. Magnesium sulfate was also more effective than phenytoin and diazepam for prevention of recurrent seizures in 1687 women who had had eclampsia [36]. The mechansim of action of magnesium sulfate has been attributed to its direct vasodilator effect and a possible effect in increasing prostacyclin production. It should be remembered, however, that magnesium sulfate is excreted by the kidneys, and oliguric women or women with preexisting renal insufficiency should be monitored carefully and treated with lower doses. Magnesium is a calcium channel blocker and its use with other calcium channel blockers may result in profound hypotension.

The combination of sodium retention and intravascular volume contraction have led to treatment of preeclampsia with both diuretics and with volume expansion. Both approaches are misguided. Diuretics aggravate hypoperfusion of vital organs and should be reserved for women with congestive heart failure. Volume expansion increases the risk of pulmonary edema. Hemodynamic monitoring by Swan-Ganz catheter is advised before using either of these interventions.

Treatment of hypertension does not reverse preeclampsia, and may even disguise progression, but is required to prevent the most severe complications of preeclampsia, including cerebral hemorrhage. Treatment is usually started when the diastolic blood pressure is 105 mm Hg but should be instituted earlier in women with very low blood pressures early in pregnancy. The drugs used to treat hypertensive emergencies in pregnancies are discussed below. The goal of blood pressure reduction is a diastolic blood pressure of 90 – 100 mm Hg.

Chronic Hypertension

Essential hypertension more often affects mothers in the later childbearing years. With the growing number of late pregnancies and even postmenopausal pregnancies, the importance of this problem can be expected to increase.

Almost half of the women with essential hypertension have a fall in blood pressure into

the normal range during the second trimester with a return to baseline elevated levels in the third trimester. This drop makes it difficult to determine whether a woman seen for the first time in the second trimester with normal blood pressure has essential hypertension or preeclampsia when the blood pressure rises in the third trimester.

Women with chronic hypertension have an increased risk of preeclampsia, perinatal mortality, small for gestational age (SGA) babies, premature delivery, and, in some series, gestational diabetes [37].

Women with severe essential hypertension (BP > 170/110) are at the greatest risk for preeclampsia and are also at risk for cerebral hemorrhage and abruptio placentae. The frequency of superimposed preeclampsia in this group is high: 52% in one group of 44 such women [38]. The perinatal mortality was 25% in the latter report. Seventy percent of infants were premature and 43% were SGA. Maternal complications included one instance of abruptio placentae, deterioration of renal function in 20 (permanent), and one episode of hypertensive encephalopathy. The frequency of superimposed preeclampsia in women with mild hypertension ranges from approximately 5.2 – 18.4%. Maternal and fetal morbidity are increased even with mild hypertension, but the efficacy of pharmacologic treatment in preventing complications in women with mild hypertension and the level of blood pressure at which treatment should be instituted are a matter of debate. There is conflicting evidence whether treatment of mild hypertension prevents worsening of hypertension later in pregnancy and whether treatment lowers perinatal mortality [39 – 43]. We take the position that safe medications are available for the treatment of hypertension during pregnancy, and treatment should begin at a blood pressure > 140/90.

Antihypertensive Medications

The effects of various antihypertensive medications in pregnancy are reviewed in Table 5. The Food and Drug Administration (FDA) designation (see appendix for explanation) is included, but does not adequately reflect the risks and safety of the various drugs.

Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors are contraindicated in pregnancy. Animal studies reported a high frequency of stillbirths in animals exposed to ACE inhibitors during pregnancy, resulting in a recommendation against their use in human pregnancy by a committee of the National Institutes of Health [44]. Exposure to ACE inhibitors in the second and third trimester has been associated with renal tubular dysplasia, hypocalvaria, hypoplastic lungs and limb contractures [45]. Renal tubular dysplasia has been attributed to fetal hypotension and decreased renal perfusion. ACE inhibitors are associated with decreased fetal urine output and oligohydramnios. Amniotic fluid is required for normal pulmonary development, and oligohydramnios is responsible for the instances of hypoplastic lungs. Many of the neonatal deaths in infants exposed to ACE inhibitors are the result of respiratory failure. Oligohydramnios also accounts for limb contractures. Direct pressure of the uterine muscle on the fetal skull is thought to result in abnormal calcification of the skull. Several instances of patent ductus arteriosus have been described. This effect is thought to be the result of the effects of ACE inhibitors on prostaglandin metabolism.

Two studies, involving 46 and 86 infants, respectively, showed no adverse effect of exposure to ACE inhibitors in the first trimester

Table 5. Antihypertensive Drugs in Pregnancy

Drug (Category)	Comments
Chronic hypertension	
ACE inhibitors(D)	Contraindicated. 2nd and 3rd trimester use associated with pulmonary hypoplasia, hypocalvaria, renal dysplasia, neonatal anuria, contractures. No known harm in 1st trimester.
Methyldopa (C)	Safe. 40-year use. Careful developmental testing of children at ages 4 and 7.
Beta Blockers (C)	Probably safe. Fetal bradycardia, hypoglycmia, respiratory depression at birth, intrauterine growth restriction
Labetolol (C)	Limited first trimester experience. Less bradycardia and growth restriction than β blockers.
Clonidine (C)	Probably safe. Limited 1st trimester exposure.
Calcium channel blockers (C)	Profound hypotension with when used magnesium. Limited experience. Reserve for severe hypertension.
Hydralazine (C)	Safe. Long experience with use in pregnancy. No increase in birth defects.
Minoxidil (C)	Very limited experience. Hypertrichosis in the infant.
Prazocin (C)	Limited experience. No problems noted.
Thiazide diuretics (D)	Increased congenital anomalies with chlorthaldone. Decreased intravascular volume expansion,neonatal thrombocytopenia, hemolytic anemia, electrolyte abnormalities
Hypertensive crisis	
Hydralazine (C)	Used for 40 years without serious side effects
Labetolol (C)	Shorter length of use. Appears safe.
Nitroprusside (C)	Fetal cyanide toxicity
Diazoxide (C)	Fatal maternal hypotension reported. Limit dose to 30 mg boluses. Decreased uterine contraction. Neonatal hyperglycemia.

[46]. In the latter report, there were 4 congenital anomalies, a number not significantly different from the 3 expected [46]. However, our understanding of the role of the renin-angiotensin system in early renal development is incomplete, and an as-yet unrecognized adverse effect of ACE inhibitors on this process is possible. The absence of demonstrated ill effects of ACE inhibitors following first trimester exposure is of considerable importance. Women with inadvertent first trimester exposure need not be advised to terminate the pregnancy. A more important issue is whether women with nephropathy taking ACE inhibitors for their renoprotective effect need to discontinue them in planning for pregnancy if there is some assurance that pregnancy can be diagnosed promptly and the drug stopped at that point. For women with normal renal function where conception can be expected to occur within a year, stopping ACE inhibitors in planning pregnancy is warranted. However, for women with moderately impaired renal function who may not conceive for years, discontinuation of ACE inhibitors may not be necessary.

There is less experience with Ang II receptor blockers, but it is expected that problems caused by decreased angiotensin effect will be similar.

Diuretics

The obstetric community is strongly averse to using diuretics during pregnancy. At one point, diuretics were widely used in the hope that by reducing edema and hypertension might prevent preeclampsia. These drugs did not prove to be effective for this purpose, and they aggravated the decreased intravascular perfusion seen with preeclampsia, possibly contributing to organ hypoperfusion [47]. The failure of diuretics to prevent preeclampsia now discounts the observation that their use in women with edema was rarely associated with adverse effects. A report documenting a subnormal expansion of intravascular volume in women with essential hypertension treated with diuretics did not show increased perinatal mortality [48]. For essential hypertension, other drugs are preferred, but diuretics may be useful in hypertension associated with renal insufficiency and salt-sensitive hypertension. There are some reports of neonatal thrombocytopenia, hemolytic anemia, jaundice, and electrolyte abnormalities with thiazides, but most of the concern about their use centers on their effects on intravascular volume [49, 50].

Beta Blockers

There have been several case reports of neonatal bradycardia, hypoglycemia and respiratory depression associated with beta blockers, but these problems are generally easily managed by the neonatologist [51]. Data are mixed concerning whether beta blockers are associated with IUGR and there are reports of SGA infants born to mothers treated with beta blockers for diseases not usually associated with growth restriction [52]. There are also data from animal models suggesting a decreased ability of the fetus to withstand anoxic stress [53]. None of these problems has turned out to be a major contraindication to the use of this category of drugs. Fetal bradycardia may make it difficult to interpret antenatal monitoring, which depends on changes in fetal heart rate.

Labetolol

Labetolol is not associated with fetal bradycardia and IUGR and it is widely used in preference to beta blockers. Nonetheless, data on first trimester effects of the drug are still limited. Moreover, controlled studies have not shown it to be superior to other antihypertensive agents [41, 46, 54].

Methyldopa

Methyldopa has been used in pregnant women for over 40 years and is still the drug of choice for essential hypertension. Careful developmental studies have been done in children at 4 and 7 years of age exposed to the drug in utero, and no problems have been found [55]. One study of 242 women with diastolic blood pressures of 90 – 110 mm Hg randomized to treatment with methyldopa versus placebo showed decreased fetal loss in the methyldopa-treated group [56].

Clonidine

Clonidine is a centrally acting α2-agonist reported in one study to have efficacy and safety similar to methyldopa [57]. In view of the limited experience with it, there is no reason to use it in preference to methyldopa.

Calcium Channel Blockers

Nifedipine, nicardipine, and verapamil have been used in severe hypertension. They do not appear to be associated with any increase in congenital anomalies when used in the first trimester. These drugs have been used for tocolysis in the third trimester. There is limited experience with diltiazem. Calcium channel blockers may potentiate the hypotensive effects and neuromuscular blockade of magnesium, and the interaction should be kept in mind when the drugs are used in women at risk for preeclampsia [58, 59]. Because of limited experience, their use is best restricted to severe hypertension unresponsive to other drugs.

Prazocin

No adverse effects on the fetus have been demonstrated with prazocin drugs, but the experience with it is more limited than with labetolol, methyldopa, and β blockers, and it does not appear to offer any advantage. The drug can be continued in women whose blood pressure is well controlled on it at the time of conception.

Hydralazine

Hydralazine has been used safely during pregnancy for 40 years. It is ineffective as a single oral agent but can be added to a first-line drug if the latter is ineffective alone.

Minoxidil

The more potent vasodilator, minoxidil has been associated with hypertrichosis and congenital anomalies in one case report [60]. It is ineffective unless combined with a diuretic and a sympatholytic agent.

Drugs for Hypertensive Emergencies

Hydralazine

Intravenous hydralazine in doses of 5–10 mg every 20 – 30 minutes is the drug of first choice for hypertensive crisis in pregnancy. A single study has shown a higher frequency of malignant ventricular arrhythmias in eclamptic women treated with hydralazine than in women treated with labetolol [61]. Nine studies comparing hydralazine with other drugs, most often intravenous labetolol, have found no advantage of one drug regimen over another [62].

Labetolol

Intravenous labetolol given either as a 20 mg loading dose followed by 20 – 60 mg every 30 minutes, or a 1 – 2 mg/min drip is the second most commonly used regimen for treating hypertensive emergencies in pregnant women. There are occasional reports of fetal bradycardia, and the newborn should be monitored for hypotension.

Diazoxide

There is extensive experience with the use of diazoxide in pregnancy, but the drug is now primarily of historic interest. In doses of 150 – 300 mg, it has been associated with at least one maternal fatality from hypotension. It is also associated with decreased uterine contractions and neonatal hyperglycemia. Its only

advantage is a long duration of action, which may make it useful in a woman who must be transported with minimal monitoring capability, or when other drugs have failed. It should be used only in 30 mg boluses every 1 – 2 minutes until the desired blood pressure is reached.

Nitroprusside

Nitroprusside carries the risk of fetal cyanide toxicity, and it should be used with caution, especially in women with renal insufficiency.

Nifedipine

Because of its interaction with magnesium sulfate and the general movement away from using short-acting nifedipine for hypertensive emergencies in nonpregnant patients, nifedipine should not be used as a first-line drug in hypertensive emergencies of pregnancies.

Chronic Hypertension with Superimposed Preeclampsia

Ten percent of women with mild hypertension and up to 50% of women with severe hypertension develop superimposed preeclampsia. The diagnosis depends on an increase in blood pressure over baseline levels and development of proteinuria. Since there is frequently a modest increase in blood pressure in hypertensive women in the third trimester, proteinuria is more important to the diagnosis. The absolute level of blood pressure is frequently higher in these women than in women with isolated preeclampsia. It is the group of women with superimposed preeclampsia in whom the frequency of abruptio placentae and cerebral hemorrhage is increased.

Secondary Hypertension in Pregnancy

Secondary hypertension in pregnancy is generally uncommon, but several causes bear discussion.

Pheochromocytoma

Pheochromocytoma is exceedingly rare, but is associated with a 50% maternal mortality rate if it is undiagnosed, and it should be excluded if the suspicion arises [63]. The maternal mortality rate is 11%, even if the diagnosis is made antepartum. Catecholamines do not cross the placenta and the fetus is not exposed to high levels, but there may be placental hypoperfusion secondary to vasoconstriction. Hypertension can be precipitated by labor. Urine and plasma norepinephrine and epinephrine are unchanged in normal and preeclamptic pregnancy, and the usual biochemical screening can be used. Surgery is generally the treatment of choice after two weeks of treatment with α blockers. An unusual complication of pregnancy is compression of an extra-adrenal pheochromocytoma located at the aortic bifurcation in the organ of Zuckerkandl by the expanding uterus.

Cocaine

Cocaine use is a common cause of secondary hypertension in young women and may

have a similar clinical presentation to pheochromocytoma. Serum and urine screening usually makes the diagnosis and α blockers are required for treatment. Cocaine use is associated with an increased risk of abruptio placentae [64].

Hyperaldosteronism

Hyperaldosteronism is uncommon in pregnancy. Basal aldosterone levels in pregnancy are elevated but are suppressible by salt loading and exogenous mineralocorticoid [63]. Plasma renin is usually but not always, suppressed rather than showing the usual pregnancy-associated elevation. Progesterone counteracts the potassium-wasting effect of aldosterone, and hypokalemia may be absent. Bilateral disease is treated medically. Spironolactone, used in nonpregnant individuals, is an antiandrogen and may cause abnormal genital development in male fetuses. Amiloride can be used in pregnancy to treat primary hyperaldosteronism.

Renal Artery Stenosis

Renal artery stenosis is uncommon, and its effect on pregnancy is related to the severity of the hypertension. Management is complicated by the inability to use ACE inhibitors, but other medications are frequently effective. Angioplasty has been successfully carried out during pregnancy [65].

Long-Term Prognosis of Hypertensive Disorders

Studies of the long-term effects of hypertensive disorders of pregnancy have been confounded by the failure of many reports to distinguish preeclampsia from chronic hypertension. Chesley followed 270 women who had survived eclampsia in a landmark study of the long-term consequences of the disease. Only one-third of the women who had subsequent pregnancies developed hypertension. In a separate study of 354 subsequent pregnancies in 151 nulliparous women who survived eclampsia, severe preeclampsia recurred in 5.3% and eclampsia recurred in 2% [66]. The risk of recurrence of the HELLP syndrome is approximately 20% [67]. Chesley followed 197/206 nulliparous women with eclampsia for an average of 33 range (23 – 42) years, by which time > 81% of the women were older than 50 years of age [68]. The frequency of hypertension, mortality (16.6%) and cardiovascular mortality (4.8%) in white women was similar to the general population. Mortality in 19 nulliparous black women who survived eclampsia was twice that of white women, but was not increased compared to the general black population. The mortality rate for the 59 multiparous white women was 56%, but 100% and for the 5 black multiparous women surviving eclampsia. By using eclampsia to define the group, Chesley excluded women with simple chronic hypertension, while including women with preeclampsia superimposed on chronic hypertension. The conclusion is that preeclampsia is a predictor of mortality and cardiovascular disease only when it is superimposed on essential hypertension.

Renal Infections in Pregnancy

Asymptomatic bacteriuria, defined as > 10^5 colony-forming units (CFU) of a single organism cultured from a clean-catch midstream urine specimen, occurs in 5% to 10% of pregnancies. While this frequency is no higher than for normal nonpregnant women, the consequences are greater, as up to 30% of pregnant women with asymptomatic bacteriuria will go on to develop pyelonephritis if untreated [69]. In recent years, screening programs and treatment of asymptomatic bacteriuria have led to a decline in the frequency of pyelonephritis in pregnant women. In one report, the incidence of pyelonephritis declined from 1.8% – 0.6% of pregnancies [70]. Screening by urine culture should be done at the first prenatal visit. Other tests for bacteriuria, such as urine dipstick for nitrate and leukocyte esterase, have not proven to be sensitive enough for use in screening [71], and the urine sediment may contain an increased number of white blood cells during pregnancy, even in the absence of infection.

A positive urine culture should be treated for 7 – 10 days with antibiotics chosen on the basis of sensitivity of the organism and safety in pregnancy. Surveillance cultures should be done a week after the completion of treatment and every 4 – 6 weeks thereafter to monitor for relapse. A second positive culture warrants another course of treatment, and a relapse within a week of the initial antibiotic therapy should be treated with a different drug. For patients who relapse a second time, the usual course of antibiotics is followed by suppressive therapy for the rest of the pregnancy. Women with 2 or more relapses should undergo urologic evaluation when they are 12 weeks postpartum, i.e. after pregnancy-induced changes in the urinary tract have had sufficient time to revert to normal [69, 72]. Patients who have a negative urine culture at initial evaluation and no other risk factors for urinary tract infection do not need additional testing unless symptomatic. In most cases, asymptomatic bacteriuria represents a preexisting condition, because the risk of acquiring asymptomatic bacteriuria during pregnancy peaks near term at 2% [73].

The most commonly occurring organisms in asymptomatic bacteriuria are gram negative bacteria, with *Escherichia coli* responsible for up to 90% of positive cultures, followed by the *Klebsiella Enterobacter* group (5 – 15%), *Proteus* species (1 – 10%), and gram positives such as coagulase-negative *Staphylococcus* (1 – 11%), *Streptococcus faecalis* (1 – 4%), and group B *Streptococcus* (1 – 4%). Antibiotics should be chosen carefully in pregnancy. Ampicillin is safe in pregnancy; however, up to 30% of E. coli are resistant to it [69], and antibiotic sensitivities are continuously changing. First-generation cephalosporins, e.g. cefazolin and cefalexin, are safe in pregnancy. Cephalosporins with a methyltetrathiazole moiety (cefoperozone, cefotetan, moxalactam, and cefamandole) are usually avoided in pregnancy because studies have shown infertility in animals [74]. Nitrofurantoin, an antibiotic specific for the urinary tract, is safe in pregnancy and effective against the most common causative organisms. It cannot be used in women with renal insufficiency. It can cause hemolysis in the male fetus of a woman who carries glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, and patients should be screened for this history prior to use. Sulfa drugs, such as sulfamethoxazole, can be used in the early part of pregnancy but should be avoided in the latter part because of the risk of kernicterus. Trimethoprim and trimethoprim-sulfamethoxizole combinations are generally avoided because of the

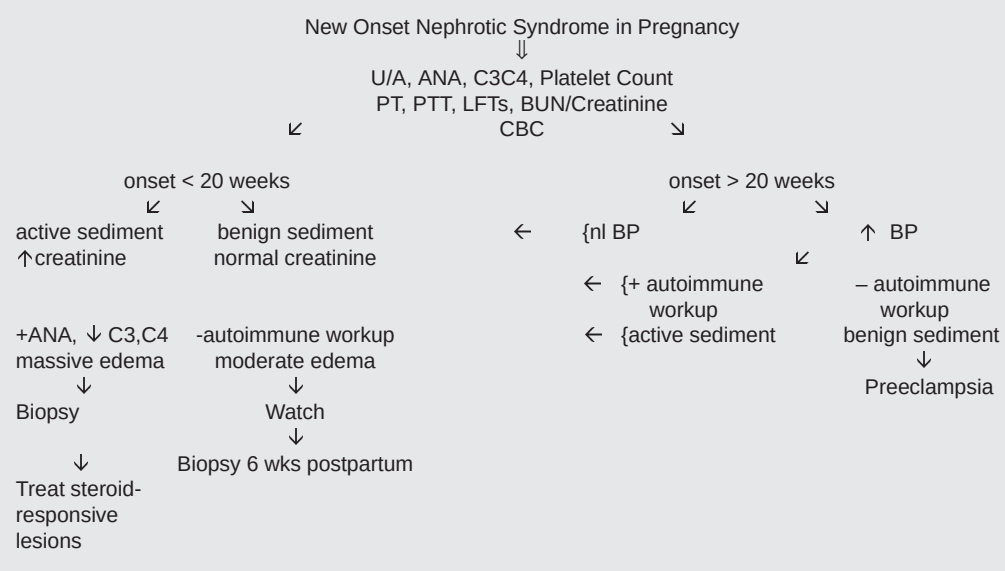

Figure 1. New Onset Nephrotic Syndrome in Pregnancy.

teterogenicity of folic acid antagonists. In practice, significant increases in congenital anomalies have not been noted with these drugs. The quinolone antibiotics should be avoided in pregnancy because they have been associated with weakened cartilage in young animals. Aminoglycosides should also be avoided because of their association with eight nerve damage [74].

Pyelonephritis in pregnancy is a severe infection associated with bacteremia, hypotension, premature labor, and, in 2% of patients with respiratory failure. Pyelonephritis during pregnancy is often associated with a decline in GFR. In a study of 220 women hospitalized for pyelonephritis, Whalley and colleagues observed that 25% of women had a creatinine clearance < 80 cc/min [75]. On reevaluation 3 – 8 weeks after treatment, 18 women whose creatinine clearance had fallen to < 70 mL/min had had a return to normal or near-normal renal function. Pregnant women with pyelonephritis should be treated aggressively with antibiotics and fluid resuscitation. Hospitalization and initiation of intravenous antibiotics have been the traditional standard of care. Relatively stable pregnant patients with pyelonephritis treated on an outpatient basis with intramuscular ceftriaxone showed recurrence rates similar to those of women treated with intravenous cefazolin. Antibiotic therapy should be continued for 2 weeks, and suppressive therapy may be continued for the remainder of the pregnancy. Women who fail to improve within 3 days of antibiotic therapy should undergo ultrasound evaluation to rule out nephrolithiasis. Ultrasound may be difficult to interpret because of hydronephrosis and, if suspicion is high, additional radiographic tests may be needed.

Nephrolithiasis in Pregnancy

Several changes in pregnancy might be expected to lead to increased stone formation. Urinary stasis in the dilated collecting system is accompanied by hypercalciuria, increased supersaturation levels of calcium, oxalate, and phosphate, and an alkaline urine. However, there is an increased excretion of magnesium citrate as well as the glycoprotein nephrocalcin, which inhibit stone formation [76]. Nephrolithiasis is a common cause of abdominal pain in pregnant women and may be overlooked when evaluation focuses solely on obstetric problems. The seriousness of infection associated with stone disease outweighs any potential adverse fetal effect of radiation required to diagnose and treat stone disease. Stones may be difficult to visualize on plain abdominal films because they may be obscured by the fetal skeleton late in pregnancy, and ultrasound is difficult to interpret. Intravenous pyelography (IVP) or spiral CT scan can be used to diagnose and locate the stone. Retrograde pyelography for diagnostic purposes or stent placement can be performed but requires considerable urologic finesse late in pregnancy. The effects of lithotripsy during pregnancy are not known, and it should not be used.

Development of Proteinuria

When proteinuria develops de novo in a woman receiving regular prenatal care, much of the diagnostic evaluation has already been done: glucose tolerance testing, screening for infectious causes of nephrotic syndrome, e. g. HIV, hepatitis B and C, and syphilis, and a history of prescription, over-the-counter and illicit drug use. The remaining crucial issues that need to be addressed are presented in Figure 1.

Diagnosis of Preeclampsia

Preeclampsia is the most common cause of proteinuria in pregnant women, and most women are presumed to have preeclampsia unless there is some atypical feature that points to another renal disease. The likelihood of another renal disease is very high if the onset of proteinuria occurs before 20 weeks gestation, if there is no hypertension, if there is an active urine sediment, or if serum complements are depressed. Only 25% of multigravidas with proteinuria have uncomplicated preeclampsia [77], but previous pregnancy is not as strong an indicator of other renal disease as are the other factors mentioned previously.

When to Biopsy for Proteinuria

Diagnosis of Systemic Lupus Erythematosis (SLE)

SLE is the other most important cause of proteinuria which presents more frequently during pregnancy. Usually SLE can be distinguished from preeclampsia by an active urine sediment or positive lupus serologies. Both SLE and preeclampsia can be multisystem diseases, and there is some overlap in their extrarenal manifestations. Thrombocytopenia and hemolytic anemia are common manifestations of both. In preeclampsia, hemolytic anemia is distinguished by microangiopathic changes on peripheral smear. Both SLE and preeclampsia may be characterized by hyper-

tension, rapidly progressive renal failure, and seizures. The pulmonary hemorrhage of SLE may appear similar on chest X-ray to pulmonary edema in preeclampsia. However, pericarditis, joint pain, and skin rash are not characteristic of preeclampsia, and markedly elevated transaminases are not common in SLE. If thrombocytopenia occurs before hypertension and proteinuria, the possibility of SLE arises. When the diagnosis of SLE is made or strongly suspected during pregnancy, a renal biopsy is warranted. SLE that develops during pregnancy frequently has the histology of diffuse proliferative glomerulonephritis and may require the prompt initiation of aggressive treatment.

Loss of Renal Function (See Acute Renal Failure)

When there is a deterioration of renal function during pregnancy and the cause is not apparent, biopsy should be done. Usually the diagnosis of preeclampsia or hemolytic uremic syndrome (HUS) as a cause of proteinuria and rising serum creatinine can be made without biopsy. Acute glomerulonephritis may require biopsy to determine whether treatment is indicated or likely to be effective.

Severe Nephrotic Syndrome

When renal function and blood pressure are normal in a patient who appears to have a primary renal disease, it is not usually necessary to make a specific histologic diagnosis. Occasionally the edema and hypoalbuminemia associated with nephrotic syndrome are so severe that treatment with steroids is considered. In this situation, renal biopsy is helpful. High-dose steroids have been used extensively in pregnancy for a wide variety of conditions, but are associated with an increased risk of hypertension and glucose intolerance as well as adrenal suppression in the infant. Their use should be confined to minimal change disease (MCD) or focal sclerosis where there is a substantial chance of response. In patients with focal sclerosis, treatment should be continued only in women who have an early response (within a month) rather than using a prolonged trial that might be undertaken in a nonpregnant patient.

Differentiating Preeclampsia from Primary Renal Disease

In some situations, it is difficult to distinguish between primary renal disease and preeclampsia. Since the definitive treatment for preeclampsia is delivery, certainty about the diagnosis has therapeutic implications. Practically, it is rarely possible to take advantage of a brief window of opportunity when proteinuria is heavy enough to raise the question of another renal disease and before the blood pressure is too high to do the biopsy safely.

In some women, pregnancy is the first occasion for a urinalysis in adult life, and the discovery of proteinuria at the first prenatal visit may reflect preexisting renal disease. The distinction between preeclampsia and primary renal disease is made on the basis of the same diagnostic features that differentiate the two diseases when the onset of proteinuria is known to have occurred during pregnancy.

Treatment of Nephrotic Syndrome

Treatment of nephrotic syndrome unresponsive to steroids is problematic during pregnancy. Proteinuria increases during pregnancy and edema may become massive, lead-

ing, in some cases, to skin breakdown and bladder outlet obstruction. Low doses of diuretics have been shown to be fairly low risk in the absence of preeclampsia, and the use of low-dose diuretics in women with disabling edema is reasonable. Unfortunately, patients with nephrotic syndrome frequently require doses much higher than those shown to be safe in studies of pregnant women. When furosemide is used in pregnant women, fetal urine output increases, and high doses might be expected to carry the risk of volume contraction and electrolyte abnormalities in the fetus. Pregnancy may aggravate the hypercoagulability associated with nephrotic syndrome. Women with previously documented renal vein thrombosis should be fully anticoagulated with heparin throughout pregnancy. Although there are no clear data, it is reasonable to give low-dose heparin (5000 U subcutaneously twice daily) to women with membranous nephropathy and profound hypoalbuminemia (albumin < 2 g/dL). Treatment of elevated cholesterol should be deferred until after delivery because lovostatin has been associated with congenital anomalies.

Chronic Renal Disease

Hypertension

Hypertension is a common complication of pregnancy in women with renal disease even with good renal function. Worsening hypertension is usual. The diagnosis of preeclampsia can be difficult because all manifestations of preeclampsia can occur from the renal disease itself. The approach to the control of blood pressure in women with preexisting renal disease is similar to that in women with chronic hypertension, but control of blood pressure should be initiated early and an attempt should be made to keep the blood pressure < 140/90. We recommend teaching women with underlying renal disease to measure their own blood pressure at home between obstetric visits because increases in blood pressure can be abrupt.

Proteinuria

Proteinuria generally increases in women with glomerular disease and preexisting proteinuria who become pregnant, but pregnancy does not precipitate a relapse in women whose nephrotic syndrome is in remission [78]. Heavy proteinuria early in pregnancy has been associated with an increased rate of fetal loss, prematurity, and IUGR, an observation that provides support for steroid treatment of susceptible lesions. Nephrotic-range proteinuria occurring later in pregnancy does not adversely affect fetal outcome.

Accelerated Decline in Renal Function

The most important determinant of the effect of pregnancy on underlying renal disease is the level of renal function at the time of conception rather than the nature of the underlying renal disease. If a woman with renal disease conceives when her renal function is normal or only mildly decreased, the progression of her renal disease is not usually accelerated, although her pregnancy is still likely to be complicated by hypertension and increased proteinuria [79]. Three retrospective studies examined the course of renal disease in women who had a least one pregnancy compared with concurrent controls [80 – 82]. The largest study included 171 women with a

variety of glomerular diseases who became pregnant and 189 women who did not become pregnant after the onset of glomerulonephritis. There was no difference in the frequency of ESRD with a mean follow-up of 15 years [81].

In contrast, decline in renal function accelerated in women with moderate to severe renal insufficiency who become pregnant. There is disagreement about the level of renal function at which pregnancy becomes a factor in the acceleration of the disease, but the most widely used marker is a serum creatinine of 1.4 mg/dL. Multiple studies support this observation [83 – 86], but are flawed because of small numbers and the absence of controls. A larger report published in 1996 included 82 pregnancies in 67 women with primary renal disease and serum creatinine of 1.4 mg/dL. prior to conception or in the first trimester [87]. Twenty percent of women had a deterioration in renal function during pregnancy, and 23% had a deterioration in the first 6 weeks postpartum. At 6 months postpartum, 8% had recovered renal function and an additional 10% had deteriorated. The likelihood of an accelerated decline in renal function was greater in women whose first measured serum creatinine was > 2 mg/dL. One of 49 women with serum creatinine between 1.4 and 1.9 mg/dL. experienced accelerated decline, in contrast to 7/ 21 pregnancies in women with serum creatinine of ≥ 2.0 mg/dL. Eight women progressed to ESRD within a year of pregnancy, including 7 women with pregnancy-associated decline in renal function.

With the obstetric and neonatal care currently available, fetal survival in the setting of chronic renal disease is high. The fetal prognosis even for women who conceive with impaired renal function has improved over the last 2 decades. Several recent outcome studies have reported fetal survival > 90% in such pregnancies [87, 88] and infant survival > 70% even in pregnancies in women whose renal function deteriorated to the point of needing dialysis [89]. Prematurity and IUGR, however, are still common. Over 70% of infants are born prematurely in some series [84, 85, 87], and the frequency of IUGR from 43 – 57% [84, 87].

Arguments have been made that the outcome of pregnancy and the effect on maternal disease is worse in certain glomerular diseases, including IgA nephropathy, focal segmental glomerulosclerosis (FSS), and membranoproliferative glomerulonephritis (MPGN) [78]. However, there is no solid evidence that the risk factors for poor outcome in these diseases, specifically hypertension and renal insufficiency, are different from other renal diseases.

Diabetic Nephropathy

At least 4 reports involving 136 women with diabetes mellitus (DM) and nephropathy conclude that pregnancy does not have an adverse effect on the progression of the disease [90 – 93]. Most of the reports investigating the effect of pregnancy on established diabetic renal disease included very few women with impaired renal function. Only 12 of the 90 women in the reports that gave individual baseline renal function had initial serum creatinine > 1.4 mg/dL. At least 6 of these women experienced an accelerated progression of renal disease during pregnancy. In one study in which 12 women had ESRD at follow-up, it was unclear whether these were women with preconception serum creatinine ≥ 1.4 mg/dL. Purdy and colleagues recently reported on 14 pregnancies in 11 women with

diabetic nephropathy and serum creatinine of ≥ 1.4 mg/dL prior to pregnancy or in the first trimester. Forty-five percent of the women showed accelerated progression of renal disease [94], as determined by a change in the slope of 1/Cr during pregnancy and postpartum, and by comparison with a nonpregnant control group. Another report of 7 pregnancies in 6 patients with preconception serum creatinine of 1.5 mg/dL found no change in the slope of 1/Cr, but 3 women had reached ESRD at 30-month follow-up [95]. In diabetic nephropathy, as in other renal diseases, the level of renal function at conception is the most important determinant of the effect of pregnancy on the progression of the disease.

Patients with diabetic nephropathy, with or without severe renal insufficiency, have a high frequency of hypertension during pregnancy (53 – 97%). Hypertension is common before pregnancy, frequently worsens during gestation, and often develops in previously normotensive women. DM is a recognized risk factor for preeclampsia, but even low level proteinuria (190 – 499 mg/24 hours) identifies a group at higher risk for preeclampsia than women with diabetes alone [96]. Coombs and colleagues followed pregnancies in 311 women with DM with varying degrees of first trimester proteinuria. For women with 24 hours urine protein < 190 mg/day, the risk of preeclampsia was 10%, only slightly higher than the general population. The risk of preeclampsia in the groups with 190 – 499 mg/day and ≥ 500 mg/ day was 40% and 47%, respectively.

Proteinuria increases during pregnancy in women with diabetic nephropathy, as it does in women with other renal diseases. The frequency of nephrotic-range proteinuria in the 5 reports cited above ranged from 41 – 73%. Nephrotic-range proteinuria develops in > 50% of women who have lower levels of proteinuria before conception.

Despite serious maternal problems, long-term infant survival was > 95% with no stillbirth or neonatal death in the two reports of women with moderate renal insufficiency. However, approximately half of the infants were born prematurely and 15% had long-term developmental problems, often related to congenital anomalies resulting from poor glucose control during organogenesis.

Lupus Nephritis

Course of Lupus Nephritis in Pregnancy

Although some investigators argue that pregnancy per se does not aggravate lupus nephritis, the bulk of the data supports the contention that pregnancy has an adverse effect on the course of the disease, and there is a risk of renal failure and even death in women with lupus nephritis who become pregnant. In 276 women reported in 19 studies who had a diagnosis of lupus nephritis at conception, 133 (48%) experienced a worsening of renal disease during pregnancy [97 – 115]. Thirty exacerbations were characterized by ARF and, of these, 18 progressed to ESRD or resulted in maternal death. An additional 8 had a decline in renal function that was permanent but did not lead rapidly to ESRD. At least 44 women became nephrotic. Even in the absence of evidence of a lupus flare, hypertension and preeclampsia were common, and episodes of eclampsia were reported. While the majority of studies were uncontrolled, several studies using both nonpregnant women and the index subjects before and after

pregnancy as controls showed an increase in the frequency of SLE flares during pregnancy. In studies where renal histology was known, the frequency of exacerbations during pregnancy was higher for women with membranous nephropathy than for those with diffuse proliferative glomerulonephritis, even though membranous lupus is generally thought to have a more indolent course. Women with lupus nephritis were also at risk for severe extrarenal manifestations of SLE, including cerebritis, pericarditis, and mesenteric vasculitis. The risk of exacerbation is lower in women whose disease has been in remission for > 6 months before conception [101].

Effects of SLE on the Fetus

Several characteristic problems occur in the infants of women with SLE. Women with anticardiolipin antibody have an increased risk of fetal loss [116]. Several studies of prednisone treatment for this disorder show no benefit from steroid treatment. Many lupus-associated autoantibodies are IgG and cross the placenta. Neonatal lupus may be associated with skin rashes, thrombocytopenia, and hemolytic anemia [117]. These manifestations resolve over 6 months as maternal antibody disappears. Anti-SSA is deposited in the conducting system of the fetal heart and is associated with irreversible congenital heart block [118 – 120]. Some infants die in childhood from related myocardial fibrosis and heart failure, and others require long-term pacemakers.

Pregnancy in Renal Transplant Recipients

Over 6,000 pregnancies have been reported in women of childbearing age who have received a renal transplant. Transplant recipients are advised to wait 2 years after transplantation before contemplating pregnancy. Pregnancy should be undertaken only if blood pressure is controlled and renal function is stable with a serum creatinine of < 2.0 mg/dL.

Effect of Pregnancy on Graft Function

The question has been raised whether the hyperfiltration that occurs during pregnancy might have a detrimental effect in women with renal transplants whose GFR is lower at conception than in healthy women. Permanent loss of graft function during or after pregnancy in women with renal transplants is approximately 10% in a large number of reports. Several case-control studies have attempted to determine whether decline in renal function was caused by pregnancy [121 – 124].

First and colleagues reported on graft function in 18 women who underwent 25 pregnancies, compared with 26 female controls and 23 male controls [121]. Mean follow-up for the women who became pregnant was 11.8 years after transplantation and 6.9 years after pregnancy, with similar periods of follow-up for the control groups. At last follow-up, graft survival was 77.8% in women who had become pregnant, 69.2% in the female controls, and 69.8% in the male controls (NS). Both women who had become pregnant and the female controls had had an increase in serum creatinine over time. However, only 3 women

had serum creatinine > 1.5 mg/dL at conception, and in only one was it > 2.0 mg/dL. Only 5 of the 18 women who became pregnant were treated with cyclosporine.

A single controlled study suggests that graft function is adversely affected by pregnancy [122]. Salmela et al. reported on long-term graft function in 22 female transplant recipients with 29 pregnancies, compared to 38 female controls matched for cause of renal failure, kidney source, immunosuppression, time from transplantation, and serum creatinine. During the follow-up period, 8 of the women who became pregnant lost their grafts, one at one month postpartum. The remainder of the grafts were lost between one and 11 years postpartum, but deterioration of graft function began during pregnancy in 3 women. At 10-year follow-up, graft survival was 100% for the control group and 69% for the group who had had pregnancies ($p < .005$). Graft loss could not be correlated with elevated serum creatinine at the time of conception. The general applicability of the conclusions drawn in this report is limited by the paucity of centers achieving 100% 10-year graft survival similar to what was seen in the control group.

Infection

UTIs are the most common bacterial infections in pregnant transplant recipients, occurring in 40% of pregnancies [125]. Monthly urine cultures and prompt treatment of asymptomatic bacteriuria are needed. The pathogenic organisms occurring in immunosuppressed patients that are of particular concern for pregnant women are Listeria, Herpes, Cytomegalovirus (CMV) and Toxoplasma. Transplant recipients should be evaluated for previous infection with the latter 3 before pregnancy or at the first prenatal visit.

Immunosuppressive Drugs in Pregnancy

Cyclosporine

There are a number of theoretical concerns about cyclosporine metabolism in pregnancy. The increase in plasma volume and interstitial fluid, as well as increase in red cell mass would be expected to decrease the cyclosporine levels at a given dose. Because there is a greater increase in plasma volume than in red cell mass, a greater portion of any increase in cyclosporine dose would be distributed in the plasma and less would be red cell bound. It is not known whether sex steroids might slow the metabolism of cyclosporine through their inhibition of hepatic microsomes [125].

Although predictions about the effect of cyclosporine suggest forces working in opposite directions, the clinical observation is that cyclosporine levels drop and an increase in dose may be required to maintain the same plasma levels.

The most striking finding in transplant recipients treated with cyclosporine compared to those treated with other immunosuppressive regimens is an increase in SGA babies. The American Registry for Pregnancy in Transplant Recipients noted a low birth weight (< 2500 g) in 49.5% and a very low birth weight (< 1500 g) in 17.8% of 107 infants born to mothers treated with cyclosporine [126] during pregnancy. The frequency of low and very low birth weight for 207 infants born to mothers treated with prednisone and azathioprine was 39.1% and 7.7% respectively. The difference in gestational age was not significant (35.6 vs. 36.2 weeks.)

There was a higher frequency of maternal comorbid conditions in women treated with cyclosporine; 51.7% of cyclosporine-treated women were hypertensive prior to conception

compared to 18.5% of women treated with other regimens. More women in the cyclosporine-treated group had prepregnancy serum creatinine > 1.5 mg/dL (23.6% vs. 14.3%). It is not known whether hypertension and renal insufficiency before pregnancy account for the increase in IUGR.

The use of cyclosporine raises the question of its effect on the renal response to pregnancy in a renal transplant recipient. In transplant recipients treated with prednisone and azathioprine who have good renal function prior to conception (serum creatinine < 1.3 mg/dL), GFR, as measured by creatinine and inulin clearance, increases by a third by the tenth week of gestation and remains at an increased level until the third trimester when it returns to baseline [127]. The increase in GFR is less in women with lower prepregnancy GFR. It has not been determined whether cyclosporine, either by a direct effect or by virtue of the higher prepregnancy serum creatinine in cyclosporine-treated women, interferes with this response to pregnancy.

Experience with tacrolimus (FK 506) in pregnancy is extremely limited. It crosses the placenta and dose adjustment does not appear to be required for pregnancy. Severe IUGR was observed in one infant exposed to tacrolimus [128]. In one study of 9 pregnancies, hyperkalemia was seen in 5/ 7 surviving infants and one infant was anuric for 36 hours [129]. A recent report of 25 infants born to liver transplant recipients did not find IUGR, however neonatal hyperkalemia and renal insufficiency occurred [130]. Experience with the use of mycophenolate mofetil in pregnancy is even more limited.

Long-term survival of infants whose mothers were treated with cyclosporine during pregnancy is no different than for infants whose mothers were treated with azathioprine and prednisone alone. At present, taking cyclosporine out of the regimen is not warranted. Unless there is a clear indication for using tacrolimus or mycophenolate mofetil, the better studied combination of cyclosporine, azathioprine, and prednisone is preferable.

Pregnancy in Dialysis Patients

Fertility is decreased in dialysis patients. The American Registry for Pregnancy in Dialysis Patients reports a frequency of conception of 0.5% per year in women under the age of 44. For unclear reasons, conception is two to three times more common in hemodialysis patients than in peritoneal dialysis patients [89]. In 1980, the European Dialysis and Transplant Association reported on 115 pregnancies in women on dialysis [131]. Twenty-three percent of pregnancies not electively terminated resulted in surviving infants. The outcome was somewhat better in 344 pregnancies reported by the American Registry for Pregnancy in Dialysis Patients [89]. In the 187 pregnancies not electively terminated occurring in women receiving dialysis at conception, the likelihood of a surviving infant was about 40%. In contrast, the prognosis for the 59 pregnancies in women who began dialysis during gestation was better, with a fetal survival of approximately 70%.

Both hemodialysis and peritoneal dialysis have been used during pregnancy. There is no advantage of one modality over the other, either in fetal survival or in degree of prematurity.

When hemodialysis is used, it is common practice to increase the intensity of dialysis, based on the observation that women with residual renal function have a better outcome than women with no residual renal function. There is a suggestion of increased survival and less prematurity in pregnancies where the mother was dialyzed ≥ 20 hours per week [89].

Technical problems are not markedly increased with peritoneal dialysis, and catheters can be placed at any time during pregnancy. In the third trimester, abdominal discomfort usually makes it necessary to decrease exchange volume. There are few data on the effects of peritonitis on pregnancy outcome.

A substantial percentage of fetal loss occurs late in pregnancy, with 16.5% of pregnancies ending in second trimester spontaneous abortion and 6.4% in stillbirth. Of live-born infants, 18.2% die in the neonatal period, mostly from complications of prematurity. Little long-term follow-up is available on the surviving infants, but 11 of 49 infants where follow-up was available had developmental problems [89].

The frequency of complications is high, with > 75% of women suffering from hypertension, often severe. A drop in hematocrit is almost inevitable unless erythropoietin doses are increased 2 – 4 fold early in pregnancy. Almost all women not treated with erythropoietin require transfusion [89]. Two maternal deaths have been reported.

Acute Renal Failure (ARF)

ARF in pregnancy is largely a preventable problem resulting from obstetric complications and not intrinsic renal disease. Pregnancy-related ARF can thus be viewed more as a public health problem than a nephrologic problem. Historically, ARF in pregnancy once represented 20 – 40% of all cases of ARF and was responsible for 50% of cases in women [132]. In 1958, the estimated incidence of ARF in pregnancy was as high as 1 in 1400. Today, in industrialized countries, the approximate incidence is 1 in 20,000 [133]. In pregnancy, ARF occurs with a bimodal distribution. A peak in early pregnancy is associated with septic abortion, while a third trimester peak is associated with late obstetric complications, such as preeclampsia, abruptio placentae, postpartum hemorrhage, amniotic fluid embolism, and retained dead fetus [134, 135].

In industrialized countries where most women have access to high-quality prenatal care and where abortion has been legalized, there has been a marked decline in pregnancy-related ARF, with near elimination of the first peak [133]. The legalization of abortion in France was followed by a decrease in the percentage of cases of ARF attributable to obstetric causes, from 40% in 1966 to 4.5% in 1978 [133]. When abortion was made illegal in Romania in 1966, complications of illegal abortion became a major cause of ARF. In a report of 653 patients dialyzed for ARF between 1966 and 1989, 131 cases (20%) ARF resulted from complications of illegal abortion [136]. Between 1990 and 1992 after legalization of abortion, obstetric ARF accounted for only 1.52% of the total.

In developing countries, obstetric ARF remains a serious problem. Randeree et al. described the changing picture of obstetric ARF as the health care system in South Africa improved [137]. Between 1978 and 1991, the frequency of ARF in a hospital serving an impoverished community fell from one in 450 pregnancies to one in 900 pregnancies. With improvement in prenatal care, the proportion of obstetric ARF secondary to septic abortion decreased from 65% to 19%, while the percentage of obstetric ARF from preeclampsia increased from 10% in 1978 to 48% in 1991. With further improvement in obstetric care and early recognition of preeclampsia, the frequency of ARF from this cause would be expected to decrease.

ARF can occur after postabortal sepsis from any organism but is most common and dramatic with infection by *Clostridium welchii*, which produces a toxin that causes hemolysis and renal failure [138]. The infection may follow a fulminant course, characterized by severe abdominal pain and vascular collapse. *Clostridium welchii* is difficult to culture, and clostridia species are part of normal vaginal flora, but characteristic gas in the uterine wall on x-ray is highly suggestive. Care is supportive and is aimed at fluid resuscitation and infection control. The need for hysterectomy has been debated but can often be avoided with early aggressive conservative treatment [139, 140].

ARF in the Third Trimester

Bilateral Cortical Necrosis

In a majority of instances, ARF secondary to preeclampsia or peripartum hemorrhage follows a course typical of ATN with recovery. In obstetric ARF, a substantial minority of patients develop bilateral cortical necrosis, in which renal function may fail to recover or recovery may be partial with later progression to ESRD. Bilateral cortical necrosis may occur in any type of ischemic ARF, but a disproportionate number of cases occur in obstetric patients. In a report of 38 instances of cortical necrosis that occurred at Necker Hospital between 1953 and 1972, obstetric patients accounted for 26 (68%) [141]. The incidence of cortical necrosis was 2% in the nonpregnant adults with ARF and 21% of obstetric patients with ARF. There may be a vulnerability of the renal vasculature which is peculiar to pregnancy. It is notable that the Schwartman reaction can be induced in pregnant animals after one exposure to endotoxin, whereas nonpregnant animals develop it only after a second exposure [142]. Cortical necrosis can be diagnosed by CT scan or angiography [143]. The diagnosis is made primarily for prognostic purposes.

ARF in Preeclampsia

Decreased GFR, renal blood flow and sodium excretion are characteristic of preeclampsia, but frank renal failure is unusual. ARF in preeclamptic women occurs most often when another obstetric complication such as abruptio placentae is present, or when preeclampsia has progressed to the HELLP syndrome [144 – 146]. In the largest series of patients with HELLP, 7.7% suffered ARF. In one report of 17 preeclamptic women with ARF, 80% of women who developed cortical necrosis had abruptio placentae compared to one third of those who recovered renal function [145]. When ARF follows preeclampsia, there is substantial risk of maternal mortality (9.6% in one study) [144]. Pulmonary edema occurs in > 50% of women with ARF secondary to preeclampsia, emphasizing the need for judicious fluid administration in women with preeclampsia. Women who survive ARF in the setting of preeclampsia without essential hypertension or underlying renal disease have normal renal function at long-term follow-up. When ARF occurs in women with underlying chronic renal disease and renal insufficiency, as many as 80% are dialysis dependent at follow-up [144]. In these women, it is frequently difficult to distinguish between ARF secondary to preeclampsia and the poorly understood acceleration of renal failure in women with preexisting renal insufficiency, particularly because these women are frequently hypertensive when they lose renal function.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy is an obstetric emergency. If left untreated, it may progress to fulminant hepatic failure which is life threatening for both mother and fetus. The disease most often presents in the third trimester, with complaints of headache, fatigue, malaise, nausea, and abdominal pain. Late signs include jaundice, bleeding, seizures, and hepatic encephalopathy that may progress to frank coma. Liver biopsy shows microvesicular fatty infiltration of hepatocytes in a centrilobular distribution [147]. The maternal mortality rate for the disease has improved from 80 – 85% in the 1970s to less than 20% in recent series, with the lowest mortality rate reported being 6.6% [148 – 150]. The improvement in outcome can be attributed to earlier recognition and treatment, the recognition of milder cases, and better supportive care of fulminant hepatic failure. Acute fatty liver is frequently accompanied by preeclampsia, and there may be a link between the 2 syndromes. The etiology of the syndrome is unknown, but recent investigations have found a familial metabolic defect in fatty acid metabolism [151 – 153].

Some degree of ARF occurs in up to 90% of women with acute fatty liver of pregnancy [148, 149]. Renal biopsy findings in acute fatty liver of pregnancy include ATN, fatty vacuolization of tubular cells, and occlusion of capillary lumens by fibrin-like material. Clinically, the ARF in this syndrome may resemble hepatorenal syndrome, with low fractional excretion of sodium (FE_{NA}) and benign sediment. Treatment includes delivery of the baby and supportive care. ARF usually resolves postpartum, as does the liver failure. The availability of orthotopic liver transplant offers a life-saving treatment to women who do not recover postpartum. The timing of liver transplant is difficult. Waiting may result in the patients' deterioration and increase transplantion mortality. A transplant done prematurely may commit a woman to life-long immunosuppression when she might have had a complete recovery.

Postpartum Hemolytic Uremic Syndrome (HUS)

Initially described in children with antecedent diarrheal illness and in association with verotoxin, HUS is characterized by a microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. It is also recognized in adults in association with diarrheal illnesses, certain forms of adenocarcinoma, medications, and pregnancy. Early reports of postpartum HUS refer to the syndrome as postpartum renal failure. Although it usually occurs between one day and 3 months postpartum, HUS may occur before delivery as well [154, 155]. Thrombotic thrombocytopenic purpura (TTP), considered to be related to HUS along a continuum, typically occurs during, but occasionally after pregnancy. Renal failure in both HUS and TTP is often severe enough to require temporary dialysis, and patients may suffer residual renal damage, some severe enough to require chronic dialysis or transplant [156].

In a review of 68 adults with HUS/TTP of various etiologies diagnosed between 1980 and 1982, Conlon found a normal urinalysis at presentation in only 3%. Eighty-six percent had microscopic hematuria and 89% had proteinuria [157]. In one study of 11 women with pregnancy-associated HUS, 81% had impaired renal function at presentation.

The mainstay of treatment for HUS/TTP is plasma exchange. Before the advent of plasmapheresis, the maternal mortality rate was 90%. With this treatment, maternal survival has increased to 70 – 80%. Plasma exchange

during pregnancy has not shown adverse effects on the fetus [158, 159]. It is thought to work by removing factors that promote platelet aggregation and replacing inhibitory factors that may be lacking in the serum of patients with HUS/TTP. The number of treatments necessary varies among patients, ranging from 5 – 47 days in one study of 67 women [160]. The duration of treatment is determined by monitoring hematologic, neurologic, and renal parameters. Other treatments have included prednisone, aspirin, dipyridamole, heparin, immunoglobulin, vincristine, and splenectomy. These should be considered only as adjuncts to plasma exchange.

Recurrence of HUS has been described both in subsequent pregnancies and in response to other inciting factors, including oral contraceptives, infections, and drugs such as cyclosporine.

It is sometimes difficult to distinguish between HUS/TTP and severe preeclampsia accompanied by the HELLP syndrome. Thrombocytopenia, microangiopathic hemolytic anemia, renal insufficiency, proteinuria, and hypertension may occur in both. Some distinguishing features include isolated elevation of lactate dehydrogenase (LDH) in HUS/TTP, as opposed to elevation of transaminases in preeclampsia/HELLP. Elevations of PT and PTT are unusual in HUS/TTP and suggest preeclampsia. Preeclampsia generally improves after delivery, although there may be transient worsening for 48 hours. TTP/HUS is not improved by termination of pregnancy. The distinction is important because preeclampsia resolves with supportive care after delivery, but HUS/TTP is generally irreversible without plasma exchange.

Biopsy findings in HUS/TTP include glomerular capillary endothelial swelling and subendothelial deposition of fibrinoid material that may cause occlusion of capillaries [157]. Thrombi composed of fibrin and platelets are found within capillaries and arterioles [157].

The pathophysiology of microthrombus formation in HUS/TTP is thought to involve endothelial injury along with other factors contributing to enhancement of platelet aggregation or a decrease in inhibitors to platelet aggregation. Among those factors, abnormally large multimers of von Willebrand factor have been observed in TTP, and these can cause aggregation of activated platelets. Calpain, a cysteine protease capable of causing aggregation of normal platelets and enhancing platelet binding by von Willebrand factor, has been found in some patients with active TTP. Decreased fibrinolysis may play a role. Plasminogen activator inhibitor type 1, the major inhibitor of plasminogen activator, is increased in some cases of postdiarrheal HUS. Decreased synthesis and increased degradation of prostacyclin have been suggested on the basis of studies using plasma from individuals with TTP [161]. There may also be some genetic predisposition to HUS/TTP. There are known familial occurrences, and pregnancy-associated HUS has been reported in sisters [162 – 164].

Although advances in treatment have dramatically increased patient survival in obstetric HUS/TTP, it still poses a significant threat to both mother and child, particularly if not diagnosed and treated promptly. Patients with pregnancy-associated HUS/TTP should be aware of the possibility of recurrence in future pregnancies and with estrogen-containing oral contraceptives, although at present there is no method to identify those who will be affected a second time.

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Appendix

Food and Drug Administration categories evaluating the risk of drugs to the fetus.

A. Controlled studies fail to demonstrate risk to the fetus even in the first trimester and the possibility of fetal harm appears remote.

B. Either animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).

C. Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or others) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may justify the risk.

X. Studies in animals or human beings have demonstrated fetal abnormalities, and the risk of using the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.