CHAPTER

59 The Normal and Diseased Kidney in Pregnancy

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Of all medical disorders that add risk to pregnancy, renal disease is ranked among one of the most feared by physicians. Kidney disease during pregnancy, even when mild, can considerably increase both the maternal and fetal risk necessitating close follow-up by both specialists in nephrology and high-risk obstetrics. Risk increases with the degree of renal dysfunction and is further heightened by comorbid conditions like diabetes and hypertension, which are often now present for many years given the societal trends in developed countries to delay childbearing. In addition to advanced maternal age, risk is further exacerbated by the expanded use of reproductive technologies that often results in multigestational births. Thus, the role of the nephrologist must begin prior to conception to stabilize a woman's condition and provide an appropriate risk assessment. During pregnancy, close monitoring by both subspecialties likely improves outcome by providing early identification of both renal and fetal compromise.

The goal of this chapter is to provide practical clinical guidance to physicians consulted when such patients contemplate conceiving or are already pregnant. First, we briefly review the normal gestational anatomic and physiologic renal changes, as such knowledge permits early detection of abnormalities. We subsequently discuss an approach to risk stratification and optimization during prepregnancy counselling and, finally, management of renal disease in pregnancy including acute compromise secondary to preeclampsia and other causes of acute kidney injury specific to pregnancy.

PREGNANCY-INDUCED CHANGES IN RENAL ANATOMY AND FUNCTION

Anatomy

It is classically taught that kidney size increases in a normal human pregnancy likely due to a combination of increased renal weight, dilatation of the renal collecting system, and perhaps increased glomerular volume. Contemporary data utilizing imaging techniques or the assessment of human biopsy or autopsy tissue carefully delineating healthy renal accommodation to pregnancy, however, are truly limited. Older data that included 97 women dying during or shortly after pregnancy from causes other than preeclampsia suggested that the increased combined renal weight of "normal" kidneys to be greater than in nonpregnant women, but data for age-matched nonpregnant females was not presented.[1]

Radiologic estimation of kidney length shows an approximate 1-cm increase in renal size and notes dilatation of the collecting system—calyces, renal pelvis, and ureters—that is significantly more pronounced on the right side (Fig. 59.1).[2,3] In the largest study in the literature wherein over 1,000 women were followed serially during pregnancy, dilatation in the right kidney began in the sixth week of gestation and maximal dilatation progressed at a rate of 0.5 mm per week until week 24 to 26 and then slowed to 0.3 mm per week until term.[4] Dilatation on the left was less marked as in earlier studies. Although the majority of gravid women (>50%) demonstrate some degree of dilatation,[4–6] there is significant variability between patients and even serial variability within the same patient making the diagnosis of true obstruction challenging.[7] Resolution begins immediately postpartum, but return to the prepregnancy state likely takes a number of weeks.[6]

The mechanism of this dilatation of the urinary tract is not entirely clear and is most likely a combination of pregnancy-related hormonal factors and mild obstruction. Support for hormonal factors includes the evidence of early dilatation before the uterus has enlarged sufficiently to become an obstructive factor as well as persistence into the postpartum period after delivery.[4,6] One study, however, found no correlation between dilatation and either serum estradiol, serum progesterone, or urinary estradiol excretion, but perhaps other hormonal factors that have not been studied in relation to dilatation may be important.[5] The best evidence for the obstructive theory comes from studies in which intraureteral pressure was monitored in third trimester gravid patients utilizing a fluid-filled catheter connected to a strain gauge transducer.[8] Pressure was greatest in the supine or standing position, but decreased markedly in a lateral decubitus or knee-to-chest position as well as immediately

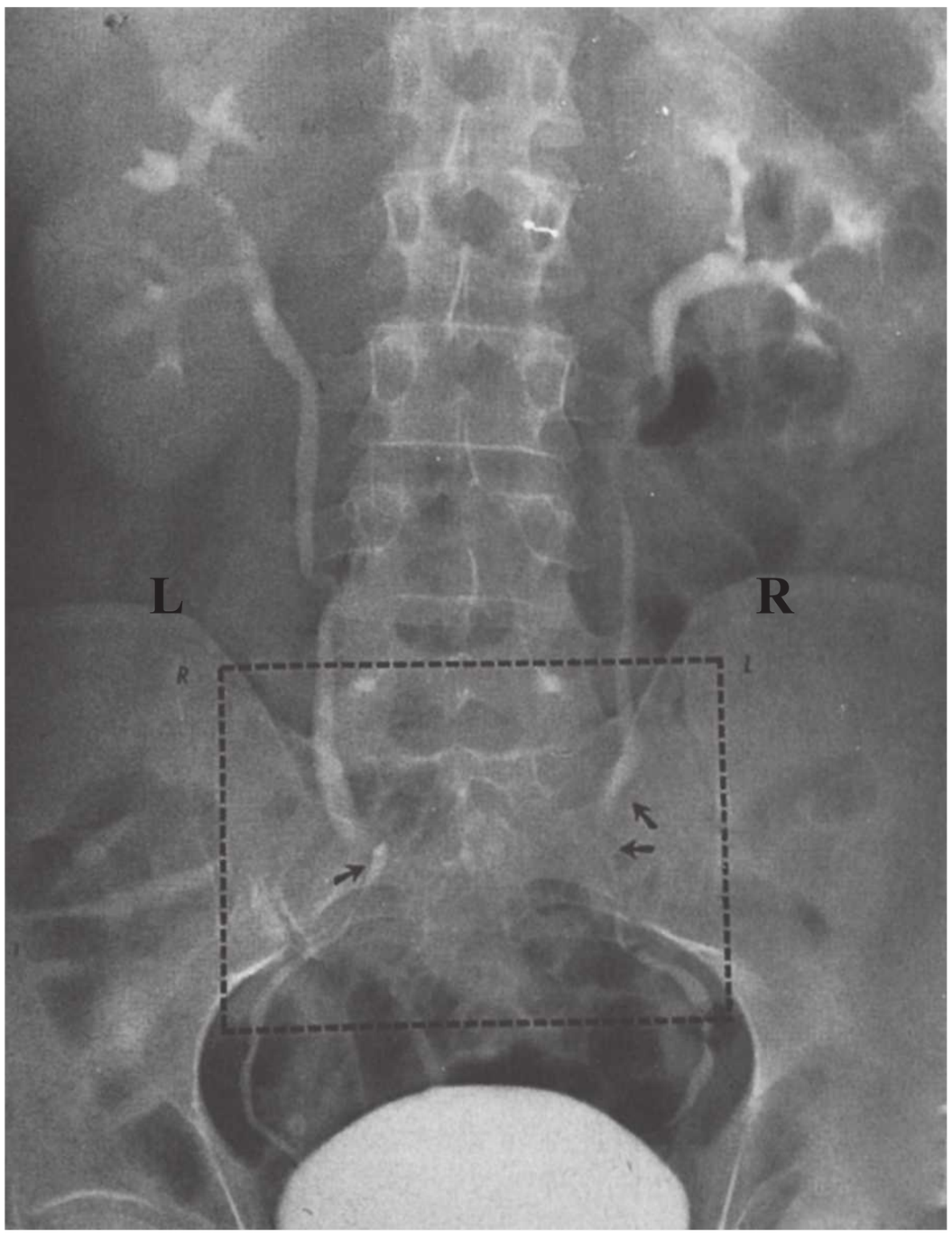

FIGURE 59.1 Normal physiologic dilatation of the urinary collecting system. Note the increased dilatation on the right side.

after cesarian delivery of the fetus, implying that the gravid uterus can obstruct the ureters. In addition, the increased pressure was present only above the pelvic brim where the ureters and the iliac arteries cross. Although this is consistent with the dilatation pattern in most gravid women,[9] the largest study to date did note at least some degree of dilatation in 10% to 15% of women in both kidneys before the uterus reached the pelvic rim. Thus, a combination of hormonal factors as well as obstruction is likely of physiologic importance.

In healthy pregnant subjects, the anatomic changes that occur at the level of the glomerulus are even less well described. There is data from 27 autopsy cases[1] and more recently from 12 third trimester biopsies[10] to suggest that glomerular diameter is greater than that measured in nonpregnant subjects. As already mentioned, the autopsy series conducted within 2 hours of death by the celebrated pathologist H.L. Sheehan between 1935 and 1946 at the Glasgow Royal Maternity Hospital did not include age-matched nonpregnant controls, but instead compared their data to even older autopsy studies wherein the timing and effect of autolysis was not clearly described.[1] The more recent biopsy series also failed to utilize careful stereologic techniques to carefully assess the glomerulus, but noted endotheliosis, albeit to a lesser degree, in healthy pregnant controls as well as in patients with preeclampsia.

Renal Function

Healthy pregnant women exhibit marked hyperfiltration. Both the glomerular filtration rate (GFR) and renal plasma flow (RPF) increase markedly during gestation. Unfortunately, however, there are few studies in which inulin or iothalamate and p-aminohippurate (PAH) clearance were measured serially and simultaneously throughout gestation in a sizable study population. Therefore, this knowledge comes from a synthesis of a small number of available studies that assessed renal physiology with proper clearance methodology at different time points during gestation (Fig. 59.2).

Hyperfiltration begins as early as the sixth week of gestation.[11] By the second half of pregnancy, GFR is elevated by

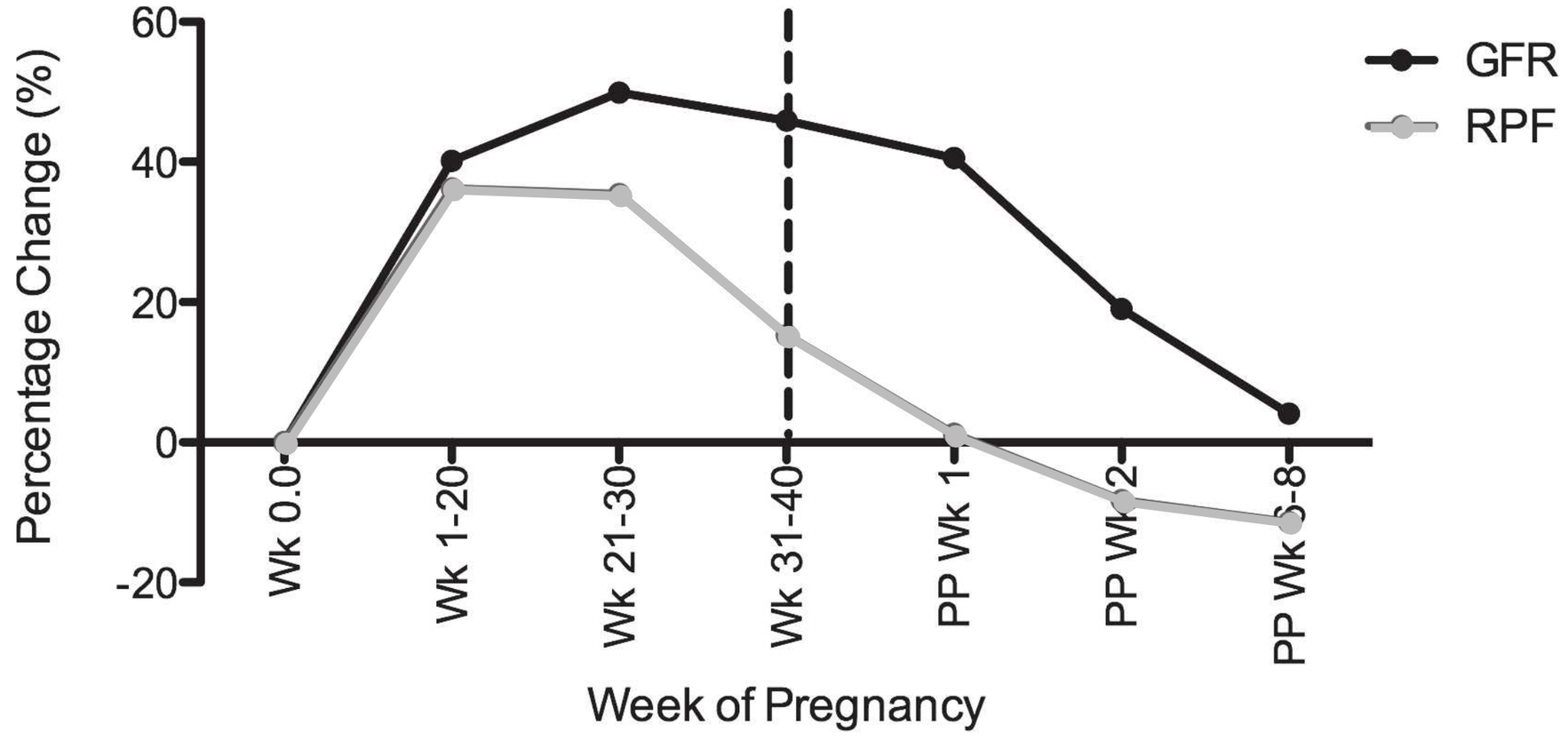

FIGURE 59.2 Glomerular filtration rate (GFR) and renal plasma flow (RPF) measured by inulin or iothalamate and p-aminohippurate clearance methodology, respectively, at different time points during gestation.[11,17,20,22,387]

40% to 60% above normal, nongravid levels, whereas the increase in RPF at least during the first trimester surpasses that of GFR with an increase in the order of 50% to as high as 80% in one study.[11–19] Thus, the filtration fraction is thought to fall in a pattern consistent with renal vasodilation. These high levels are maintained through gestational week 36, after which there is a decrease in GFR and a more pronounced decrease in RPF returning the filtration fraction to normal or a slightly elevated value compared to values observed in nonpregnant populations.[17,20,21] Despite normalization of RPF, the GFR remains elevated by approximately 41% on the first postpartum day[20] and by approximately 20% in the second postpartum week,[22] returning to baseline within the first postpartum month.[17,23]

The relationship between GFR and its determinants can be assessed using the following equation:

$$GFR = (\Delta P - \pi_{GC}) \chi K_f$$

where ΔP is the transcapillary hydraulic pressure difference or the pressure generated across the glomerulus; π_{GC} is the mean glomerular intracapillary oncotic pressure, the force that opposes the formation of glomerular filtration; and K_f is the glomerular ultrafiltration coefficient—that is, the product of the surface area available for filtration and the hydraulic permeability (k), which is the permeability to ultrafiltrate across the three layers of the glomerulus. As not all of these individual determinants can be directly measured in humans, and are instead inferred from complex mathematical modeling and theoretical analysis, the mechanisms of hyperfiltration during human pregnancy are not fully understood.[24]

The hyperfiltration that accompanies human pregnancy, however, appears to result primarily from depression of the oncotic pressure (π_{GC}) in the plasma that flows axially along the glomerular capillaries. The reduction of π_{GC} in pregnancy is attributable to two phenomena. The first is a hypervolemia-induced hemodilution that lowers the protein concentration and oncotic pressure of plasma entering the glomerular microcirculation.[25–28] The second is the elevated rate of RPF.[11,12,15,16] Hyperperfusion of glomeruli blunts the extent to which the axial protein concentration and oncotic pressure can increase along the glomerular capillaries during filtrate formation.[29]

Alternative explanations for increased GFR might include an increase in either K_f or ΔP. Utilizing a mathematical modeling of neutral dextran sieving coefficients to examine the determinants of the GFR in 13 healthy women late in pregnancy, investigators confirmed hyperfiltration was accomplished by an increase in RPF, but suggested perhaps a slight increase in K_f without any alteration in ΔP.[30] Our study that assessed determinants of GFR in the early postpartum period could not, with certainty, exclude a role for increased ΔP as an increment in either ΔP of 16% or an approximate increase in K_f of 50% would be necessary to account for the increased GFR in the postpartum period given the normalization of RPF and hence π_{GC}.[22] However, one must underscore the theoretical nature of these approaches in pregnant women, as direct micropuncture studies of the determinants of ultrafiltration are obviously not possible in humans. In rodent models, micropuncture studies consistently demonstrate a marked and parallel decrease in afferent and efferent vascular resistance resulting in an increased RPF without intraglomerular hypertension (increased ΔP).[31–33] Even following repeated pregnancies[34] or after a five-sixths reduction in renal mass[35] (an extreme example of compromised kidney function), the mechanism of renal accommodation to gestation did not change and there was no potential explanation for the pregnancy-associated renal damage often noted in young women with kidney disease. Further, no adequate human physiologic studies have been performed in diseased states and studies in humans that have utilized protein loading to assess potential renal reserve for accommodation have proven equivocal.[36,37] Thus, one cannot state with absolute certainty that the accommodation to pregnancy in a woman with advanced underlying renal disease does not involve an increase in intraglomerular pressure (ΔP) that could potentially have a long-term damaging effect on kidney function, and this is an area of renal physiology worthy of future study.

Tubular Function

Although precise mechanisms are not completely understood, the enhanced GFR that accompanies healthy pregnancy along with altered tubular reabsorption may be responsible for increased urinary levels of glucose, amino acids, uric acid, and protein. This classic teaching, however, is based on sparse data that in many scenarios lacks obvious clinical relevance.

In the nonpregnant state, healthy kidneys efficiently reabsorb glucose (>90%) and glycosuria is a clinical indicator of a filtered load that exceeds the maximal tubular reabsorption capacity (T_m). Despite the increased GFR that accompanies pregnancy, studies that utilized a continuous intravenous glucose challenge with inulin clearance techniques did not document a difference in GFR between women who displayed glycosuria and those who did not, suggesting instead that T_m was significantly decreased in pregnant women who displayed glycosuria.[38–40] The endogenous mechanism responsible is unclear, but the increased cortisol levels that accompany pregnancy have been postulated as a potential etiology based on observations in nonpregnant diabetic patients.[41]

The precise incidence of glycosuria in pregnancy is unclear with extensive variability noted between women and even in the same woman at different times during pregnancy.[40,42] During an oral glucose tolerance test, 26.9% of 104 patients in the second trimester and 42.8% of 205 patients in the third trimester developed glycosuria,[43] but a subsequent retrospective chart assessment of 17,647 pregnancies with normal carbohydrate screening noted an incidence of only 1.6% on routine clinical screening.[44] Further, no relationship of glycosuria to clinical diabetes has

been demonstrated, as the majority of women who demonstrate glycosuria have normal glucose tolerance, and even obviously diabetic patients do not consistently demonstrate glycosuria. A theoretical risk of the altered proximal tubular glucose reabsorption might apply to pregnant diabetic patients demonstrating increased susceptibility to hypoglycemia,[45] but this has never been proven.

A similarly confusing pattern has emerged for increased urinary excretion of amino acids and water soluble vitamins.[42,46] The few studies designed to determine mechanisms were inconclusive and noted patterns of excretion were not related to the biologic function or chemical structure of the compound.[46] However, it is likely that alterations in both GFR and tubular reabsorption would be needed to account for the magnitude of the some of the excretion rates noted.

Serum uric acid has been documented to be decreased in the first trimester, reach a nadir in the second trimester, and then gradually increase as pregnancy progresses and high renal clearance is necessary to clear the increased production that accompanies fetal and/or placental growth.[47,48] Uric acid has been noted to be elevated in pregnancies complicated by preeclampsia,[49] and even first trimester uric acid levels have been shown to be elevated prior to the diagnosis of preeclampsia.[50,51] In one study, uric acid levels in the highest quartile (>3.56 mg per dL) compared to the lowest three quartiles were associated with an increased risk of developing preeclampsia (aOR [adjusted odds ratio] 1.82; 95% CI [confidence interval], 1.03–3.21), but not gestational hypertension.[51] Thus, it is not clear if the noted increase in serum uric acid during pregnancies complicated by preeclampsia is solely due to decreased renal clearance secondary to glomerular endotheliosis or increased production caused by trophoblast breakdown. Cytokine release and ischemia might also contribute to increased serum levels.

In healthy adults, proteinuria is typically defined as a protein excretion rate two standard deviations above the mean or greater than 150 mg per day. Due to the aforementioned physiologic changes that accompany the gravid state, the upper limit for proteinuria in pregnancy has been increased and most obstetric guidelines define significant protein excretion as ≥300 mg in a 24-hour period.[52] To date, there have been limited efforts to carefully assess serial urine protein or albumin excretion. One of the largest studies wherein the primary attempt was to establish a range for proteinuria in normal pregnancy included 270 healthy women and noted a mean 24-hour urine protein excretion of 116.9 mg with a 95% upper confidence limit of 259.4 mg.[53] These levels corresponded to an albumin excretion rate of 11.8 mg with a 95% upper confidence limit of 28.7 mg with no participants exceeding 30 mg per L. Further, the increase in proteinuria did not mirror the increase in filtration, as it typically increased after 20 weeks' gestation. This later increase in urine protein was also noted in a study that followed protein-to-creatinine ratios in healthy singleton and twin pregnancies, noting a rise in the mean ratio between 34 to 38 weeks that was more pronounced in the twin pregnancies albeit still not impressively elevated (150 and 220 mg per g creatinine in the singleton and twin pregnancies, respectively).[54]

Of interest, other studies assessing only urine albumin suggest, in fact, no glomerular leak in the vast majority of healthy pregnancies.[55–57] In a study that assayed 193 consecutive uncomplicated pregnancies, an upward trend in the albumin-to-creatinine ratio was noted as the pregnancy progressed, but only six women had a ratio in excess of 15 mg per g creatinine.[55] A similar study that assayed 95 healthy pregnant women between 16 and 20 weeks' gestation demonstrated only four women with an albumin/creatinine (A/C) ratio greater than 17 mg per g creatinine, of which two proceeded to develop preeclampsia.[56] Another study confirmed the slightly higher levels of urine albumin in late pregnancy that further increased in labor, but again noted that the vast majority of the values did not exceed the upper limit of normoalbuminuria.[57] The presence of an alternative proteinaceous material is also possible, as one study did demonstrate the protein-to-creatinine ratio exceeded the albumin-to-creatinine ratio more than might be expected.[49] In summary, data establishing this well-subscribed higher upper limit for normal proteinuria in pregnancy is suspect at best by the sheer paucity of large, carefully conducted studies with serial measurements, and the presence of significant proteinuria cannot simply be ascribed to the hyperfiltration that accompanies the gravid state.

Electrolytes and Acid-Base Balance

An intricate balance of natriuretic and antinatriuretic factors governs gestational changes in electrolytes (Table 59.1). During pregnancy, total body sodium levels increase significantly by an average of 3 to 4 mEq per day to ultimately peak at an increase of approximately 900 to 1,000 mEq.[58] Elevations in GFR cause an increase in sodium filtration from 20,000 to 30,000 mEq per day, whereas increments in progesterone[59] and atrial natriuretic peptide (ANP)[60,61] levels blunt tubular reabsorption. Other factors that may promote natriuresis include decrements in serum albumin concentration and increments in prostaglandins and melanocyte stimulating hormone.[62] These changes are counteracted by the antinatriuretic effect of aldosterone and deoxycorticosterone, which increase drastically in the third trimester of pregnancy. Of interest, aldosterone is particularly responsive to volume levels, and volume expansion with saline has been shown to suppress aldosterone.[63] In contrast, deoxycorticosterone is produced through extra-adrenal hydroxylation of progesterone[64] and is not suppressible with dexamethasone.[65] Therefore, aldosterone may play a more important role in sodium homeostasis whereas deoxycorticosterone might represent an important mechanism to attenuate the natriuretic effects of progesterone. Glomerulotubular changes may also facilitate sodium resorption through increased reabsorption in the proximal and distal tubules.[66] Some authors have suggested that this may be mediated by

59.1 Major Physiologic Changes Associated with Sodium and Potassium Balance in Healthy Human Pregnancy

Physiologic Change	Effect During Pregnancy	Change During Pregnancy
Atrial natriuretic peptide	Natriuretic	Increased at 12 weeks/still elevated at 36 weeks
Progesterone	Natriuretic/Antikaliuretic	Increased after LH surge during ovulation/peak at 4 weeks before delivery
Glomerular filtration rate	Natriuretic	Increased in early pregnancy and sustained until delivery
Aldosterone	Antinatriuretic	Increased by 6 weeks gestation and sustained until delivery
Deoxycorticosterone	Antinatriuretic	Increased in first trimester/peak in third trimester
Na^+/K^+ transporters	Antinatriuretic	Increased in pregnancy

LH, luteinizing hormone.

increments in number of renal Na^+/K^+ ATPase,[67] but this is controversial.[68] Overall, the interplay of natriuretic and antinatriuretic factors is complex and varies during different periods of gestation.

Given the mineralocorticoid-induced retention of sodium, it is surprising that total body potassium increases by up to 320 mEq,[58] while serum potassium decreases.[47,69] Potassium balance was preserved in studies involving mineralocorticoid administration to gravidas,[70] while a similar maneuver in males produced decrements in potassium suggesting pregnancy may be responsible for attenuating the kaliuretic effects of mineralocorticoids.[70] These authors went on to identify progesterone as the key factor in facilitating potassium retention.[70] Pregnancy-induced alterations in potassium handling have important ramifications for the management of diseases associated with potassium processing. For instance, increments in potassium that are noted in sickle-cell anemia may be amplified in pregnancy.[71] Of interest, this amplification may not be secondary to potassium retention, but instead due to alterations in aldosterone release. It has also been hypothesized that the net potassium retention in pregnancy may attenuate the hypokalemia induced by diseases such as Bartter syndrome.[72] However, exacerbation of Bartter syndrome is more likely given the decrements in serum potassium that characterize normal pregnancy. In fact, complicated pregnancies with an increased need for potassium supplementation have been consistently reported in women with Bartter syndrome.[73,74] Altogether, it is imperative that health care providers consider pregnancy-induced alterations in electrolytes during clinical decision making. A recent report by Larsson et al. that details biochemical reference values in normal pregnancy can facilitate this process.[75]

Acid-base balance is also altered during pregnancy.[76] Respiratory alkalosis is induced by an increase in tidal volume[77,78] and a concomitant decrease in arterial partial pressure of carbon dioxide ($PaCO_2$).[79] A compensatory decrease in plasma bicarbonate is noted along with decrements in hydrogen ion levels.[79] Pregnancy-induced elevations in estrogen and progesterone have been implicated as the key factors in elevating minute ventilation, and therefore initiating these downstream changes.[80]

Blood Pressure and Volume Status in Pregnancy

In parallel with these absolute elevations in electrolytes, body water increases by approximately 8 L[81] and plasma volume increases by 1.2 L,[82] whereas plasma osmolality falls.[47,60,69,82] Such physiologic adjustments are in stark contrast to the nonpregnant state where sustained hypervolemia and decrements in plasma osmolality would result in high blood pressure and remarkable diuresis. Instead, blood pressure begins to decrease early in the first trimester and reaches a nadir between 18 and 24 weeks of gestation[11,83] due to significant systemic vasodilatation likely mediated through an altered balance of an array of vasodilatory and vasoconstricting hormones including, but not limited to, nitric oxide and endothelin, prostacyclin and prostaglandin, relaxin, as well as insensitivity to components of the renin angiotensin system (RAS).

The events initiating these changes are not completely understood, but human chorionic gonadotropin (HCG)-induced increased production of relaxin by the corpus luteum may facilitate vasodilation in normal pregnancy.[84] In animal models, relaxin upregulates vascular gelatinase

activity, thereby contributing to vasodilation and reduced myogenic reactivity of small arteries through activation of the endothelial endothelin B receptor–nitric oxide (NO) pathway.[84] A recent study noted a similar effect in small subcutaneous human arteries incubated with relaxin that was shown to be mediated through vascular endothelial growth factor (VEGF).[85] Thus, angiogenic factors may also have an important function in the increased production of NO and prostacyclin in pregnancy via pathways involving phospholipase C (PLC), mitogen-activated protein kinase (MAPK), and protein kinase C (PKC).[86] The importance of NO-mediated vasodilatation in the normal vascular adaptation to pregnancy has also been demonstrated in studies that utilize flow-mediated vasodilatation (FMD). In healthy pregnant women, an endothelial NO synthase Glu298Asp polymorphism was noted to be associated with differences in endothelium-dependent dilation at 12 weeks' gestation[87] and the concentration of l-homoarginine, another substrate for NO, has been shown to positively correlate with FMD ($r = 0.362$, $P = 0.006$).[88]

With respect to the RAS, it is the lack of vascular response that is integral for achieving decrements in blood pressure during pregnancy. In normal pregnancy, components of the RAS are upregulated. Prorenin, released from the ovaries, parallels the increase of β-HCG peaking at 10 times the usual blood level.[89] Angiotensinogen also increases gradually throughout pregnancy in response to increasing estrogen levels, as does plasma renin activity, possibly in response to progesterone. Increased plasma renin activity results in increased levels of ANG II,[90,91] but, as in the luteal phase of the normal menstrual cycle, resistance to its pressor effects characterizes normal pregnancy.[92] Vascular insensitivity to ANG II infusion has been demonstrated in healthy pregnant women[93,94] and reduced sensitivity of the renal circulation has been demonstrated in pregnant rats.[95] Although the mechanism of resistance to the effects of ANG II remains elusive, increased plasma levels and urinary excretion rates of ANG^{1-7} have been documented in human pregnancy.[90,96] The increased ANG^{1-7}-to-ANG II ratio may be critical for maintaining the decreased blood pressure that is characteristic of healthy human pregnancy.

Maintenance of hypervolemia is another important deviation from the nonpregnant state. The initial shift toward volume retention is dependent on the lowering of the osmotic threshold for AVP release thereby allowing for continued secretion of the hormone.[97] In mid to late pregnancy, AVP levels increase[97] in order to compensate for increments in vasopressinase-mediated clearance of the hormone.[98] Altogether the preservation of equilibrium is not a static process. Instead, there is a complex and dynamic interplay of increments and decrements in hormone control systems. It is, therefore, not surprising that three major hypotheses have emerged to explain the hypervolemia that attends the gravid state.[99] The "underfill" hypothesis is founded on the drastic depression in systematic vascular tone that is noted in early gestation.[60] This reduction in pressure results in a transient state of hypovolemia or underfill and the induction of compensatory hormones such as the RAS and vasopressin. Accordingly, there is a subsequent shift toward increased thirst and volume retention. In addition, investigators suggest that the threshold for AVP secretion is also lowered in an attempt to correct underfill. In contrast, the "normal fill" hypothesis suggests that hypervolemia is recognized as the new hemodynamic set point in pregnancy. Increments in β-HCG have been implicated as an initial and independent trigger for reductions in the AVP threshold,[100,101] and water intake and retention would increase until plasma osmolality decreases in parallel. Lastly, the "overfill" hypothesis stipulates that the primary change in pregnancy is fluid retention as opposed to decreased vascular tone and intravascular expansion.[99,102] The aforementioned elevations in natriuretic factors would, therefore, be consistent with an overfilled state.[99] Of interest, some authors have suggested that each of the three hypotheses are correct and all occur in gestation,[99] but the temporality of these events has not been clearly established.

A particularly important aberration in volume homeostasis during pregnancy is diabetes insipidus (DI). DI frequently occurs in the third trimester of pregnancy and is characterized by polydipsia and dilute polyuria. At a clinical level, DI during gestation can present as a resurgence of preexisting central or nephrogenic DI, transient DI of pregnancy, or a sequelae of Sheehan syndrome. Given the pregnancy-induced increments in vasopressinase, it is conceivable that AVP levels will further decrease and DI would be exacerbated by pregnancy. In fact, the resurgence of latent DI is documented in the literature.[103] Similarly, DI may be subclinical prior to gestation, but become symptomatic during pregnancy. As the increase in vasopressinase correlates with the timing of increments in trophoblastic mass,[98] it has been also speculated that women with multigestational pregnancies may have higher vasopressinase levels and therefore be at increased risk for DI.[104–106] However, this hypothesis has not been directly examined in the literature.

Accumulation or increased activity of vasopressinase may also underlie the development of a transient form of DI during pregnancy.[107] Although vasopressinase normally undergoes hepatic clearance during pregnancy, impairments in liver function increase circulating levels of the enzyme thereby leading to decrements in AVP, ultimately resulting in DI.[103] Of interest, the hepatic dysfunction noted in HELLP syndrome,[106,108] and acute fatty liver of pregnancy[109] may be associated with transient DI of pregnancy. Therefore, the diagnosis of DI should also prompt increased vigilance for preeclampsia and hepatic dysfunction. Current treatment for resurgence of latent DI, or transient DI of pregnancy, involves administration of desmopressin (DDAVP), a vasopressinase resistant analogue of AVP. DDAVP can be safely used in pregnancy[110] and its transfer to breast milk is limited.

Lastly, an uncommon, but important cause of DI is Sheehan syndrome, characterized by postpartum hemorrhage leading to avascular necrosis of the pituitary gland. It can

also produce diabetes insipidus if the posterior pituitary is affected.[111–113] However, the independent blood supply of the anterior and posterior pituitary may be protective.[112] Nevertheless, polyuria and polydipsia postpartum following significant hemorrhage should raise the appropriate suspicion.[112]

MONITORING RENAL FUNCTION DURING PREGNANCY

Glomerular Filtration Rate

The gold standard for determining GFR in pregnancy remains a carefully timed clearance utilizing either inulin or iothalamate plasma disappearance techniques or carefully timed urine clearances through a Foley catheter, but even in research settings these methodologies have become scarce. Further, clearance methodology, including a timed creatinine clearance, is hampered by the dilated urinary system and the potential bladder retention that accompanies the gravid state, resulting in an underestimation of the true GFR even when creatinine clearance is measured.[114] GFR equations, including the Cockcroft-Gault and the MDRD, can substantially overestimate or underestimate GFR and cannot be recommended for use in clinical practice.[114–116] A recent study that utilized Bland and Altman methodology noted the Cockcroft-Gault equation to underestimate GFR by 25% in 23% of the cases studied and to overestimate GFR by 25% in 16% of the cases studied.[114] The MDRD equation, on the other hand, underestimated GFR by 25% in 61% of the cases studied without any cases wherein there was a significant overestimation.[114] The newer CKD-EPI equation, which has been deemed superior to the MDRD when assessing patients with higher rates of GFR,[117] remains to be assessed in pregnancy.

Thus, trends in the serum creatinine are typically used to assess for renal insufficiency in pregnant women, but the inverse hyperbolic relationship between serum creatinine and GFR is blunted in the elevated range of the latter that is typically associated with pregnancy. A comparison of the serum creatinine and GFR as measured by inulin clearance revealed that the often profound depression in K_f that accompanies preeclampsia could not be appreciated by evaluation of the serum creatinine.[118] Although statistically significantly different, the serum creatinine remained in the normal range for both groups with a value of 0.85 ± 0.22 mg per dL in preeclamptic patients and 0.60 ± 0.10 mg per dL in healthy gravid controls, despite a loss of GFR in excess of 50%.

Cystatin C is a potential assay to detect subtle changes in GFR during pregnancy. However, to date, no serial longitudinal studies, spanning all three trimesters and utilizing a gold standard technique for GFR measurement, have been done to determine the value of cystatin C to reflect early changes in GFR. Further, there is evidence to suggest a placental source also exists and cystatin C may be released in response to placental ischemia. Cysteine-proteases are felt to be important for trophoblast invasion and are controlled by inhibitors such as cystatin C. Increases in placental expression of cystatin C at the mRNA and protein level have been noted in women with preeclampsia compared to women with normal pregnancies suggesting that an increase in placental production of cystatin C may contribute to the higher maternal levels seen in women with preeclampsia.[119] Although the process is not fully understood, an increase in the synthesis and secretion of cystatin C may be associated with poor placentation, consequently complicating interpretation of cystatin C as a marker of GFR.

Proteinuria

As in the nonpregnant population, issues exist with all the methods used to quantify urine protein. The accuracy of the urine dipstick for predicting meaningful proteinuria is poor with numerous false-negative and false-positive results due to either dilute or concentrated samples, respectively. A systematic review identified only six studies of adequate methodologic quality producing a pooled positive likelihood ratio of 3.48 (95% CI 1.66–7.27) and a negative likelihood ratio of 0.6 (CI 0.45–0.8) for predicting 300 mg per day of urine protein at the 1+ or greater threshold on urinalysis.[120] Despite this lack of accuracy, urinalysis as an initial screen is still frequently utilized by the obstetrical community to assess for abnormal proteinuria.

To date, a multitude of studies have correlated either the protein-to-creatinine or the albumin-to-creatinine ratio to the 24-hour urine collection or shorter timed collections typically demonstrating highly positive correlations as might be expected[121–123] and larger systematic reviews do confirm the ability of ratios to identify clinically meaningful urine protein,[124] irrespective of the time of collection,[125] making it a tool that can be utilized in the outpatient clinic setting. Correlation, however, would not be the optimal assessment tool to compare two obviously related measures. To date, only a single study utilized the appropriate Bland Altman test to confirm agreement between the 24-hour urine protein and the protein-to-creatinine ratio.[126] These authors confirmed the correlation between the two measures and examination of the plots suggests (like the systematic reviews) that at lower levels of urine protein, there is a high level of agreement, but the ratio is less precise at higher levels of urine protein not unlike the nonpregnant state.

Thus, a carefully timed urine protein collection along with an assessment of creatinine excretion to ensure adequacy of the collection remains the most commonly used test for the quantification of urine protein in pregnancy. The potential for inadequate collection due to significant dilatation of the urinary tract system, however, is an issue that remains to be adequately addressed and clarified. One study noted a high error rate (13%–54%) when the adequacy of the collection was assessed based on the predicted creatinine excretion for prepregnancy maternal weight.[127] In a recent excellent review on the topic, the author recommended adequate hydration and maintaining the lateral recumbent

position for an hour prior to initiating and completing the collection to reduce the potential errors from retention.[128] Although rarely practiced clinically, such techniques should at least be utilized in future studies wherein the careful assessment of proteinuria is required.

Kidney Biopsy

As mentioned, significant proteinuria in a pregnant woman should not simply be attributed to the hyperfiltration of pregnancy. If the clinical presentation includes nephrotic syndrome or deterioration in renal function early in pregnancy without an established diagnosis, a kidney biopsy can be done to assist with the diagnosis and guide treatment. Data is limited with respect to the safety of kidney biopsy in pregnant women. An early study noted bleeding complications to be almost three times more common in pregnant women with serious complications arising including a patient death.[129] However, this study predated ultrasound guidance and the diagnosis on a number of the biopsies was preeclampsia with significant hypertension that should have precluded the procedure. The only sizable series was published in 1987 reporting a low complication rate of 4.5% based on 111 renal biopsies in 104 women over 20 years.[130] A smaller subsequent case series confirmed safety in women <30 weeks' gestation.[131] Most guidelines, therefore, come from expert opinion recommending a cutoff of approximately 32 weeks' gestation,[132] as the further along in gestation, the more likely that preeclampsia may be factoring into the presentation. In the presence of possible preeclampsia, a kidney biopsy should not be applied indiscriminately, given that the safety of the procedure can be further compromised by evolving hypertension, abnormal coagulation indices, and a low hemoglobin.[129] On the other hand, the initiation of steroid or immunosuppressive therapy on the speculation of a potential glomerular-based disease is also not without risk.

PREPREGNANCY RISK STRATIFICATION AND OPTIMIZATION

Prognostication of an individual woman's pregnancy-associated risk in the setting of chronic kidney disease (CKD) remains profoundly challenging. The literature is complicated and incomplete, and therefore divergent opinions arise with respect to the impact of kidney disease on pregnancy outcome as well as the impact of pregnancy on future CKD progression. The many issues including nonhomogeneity in the classification of the maternal condition (renal function, proteinuria, and hypertension), the frequent absence of preconception baseline data, and the many different definitions of relevant pregnancy outcomes—particularly the nearly impossible task of diagnosing preeclampsia superimposed on CKD wherein hypertension and proteinuria are often already present—are beautifully summarized in a recent excellent systematic review of the literature.[133] Suffice to say, prepregnancy renal insufficiency, proteinuria, and hypertension all likely factor toward untoward maternal and fetal outcomes in an additive manner.

Early studies tended to utilize the serum creatinine to stratify pregnancy risk. A typical stratification schema defined mild renal insufficiency as a serum creatinine less than 123 μmol per L (1.4 mg per dL), moderate renal insufficiency as 124–220 μmol per L (1.4–2.4 mg per dL), and severe renal insufficiency as a serum creatinine exceeding 221 μmol per L (2.5 mg per dL). As the grade of renal insufficiency increased, the healthy accommodation to pregnancy (GFR increase with a simultaneous drop in the serum creatinine) was documented to occur in only approximately 50% of women within the moderate category and in none in the severe renal insufficiency category.[134,135] In a classic paper by Jones and Hayslett published over two decades ago, they assessed pregnancy outcome in women with mild, moderate, and severe renal insufficiency as defined above and noted pregnancy-related loss of kidney function in a staggering 43% of pregnancies of which 10% rapidly progressed to end-stage renal disease (ESRD).[136] Of interest, not all the accelerated loss occurred only in those with the most severe renal compromise (Fig. 59.3). Both proteinuria and hypertension

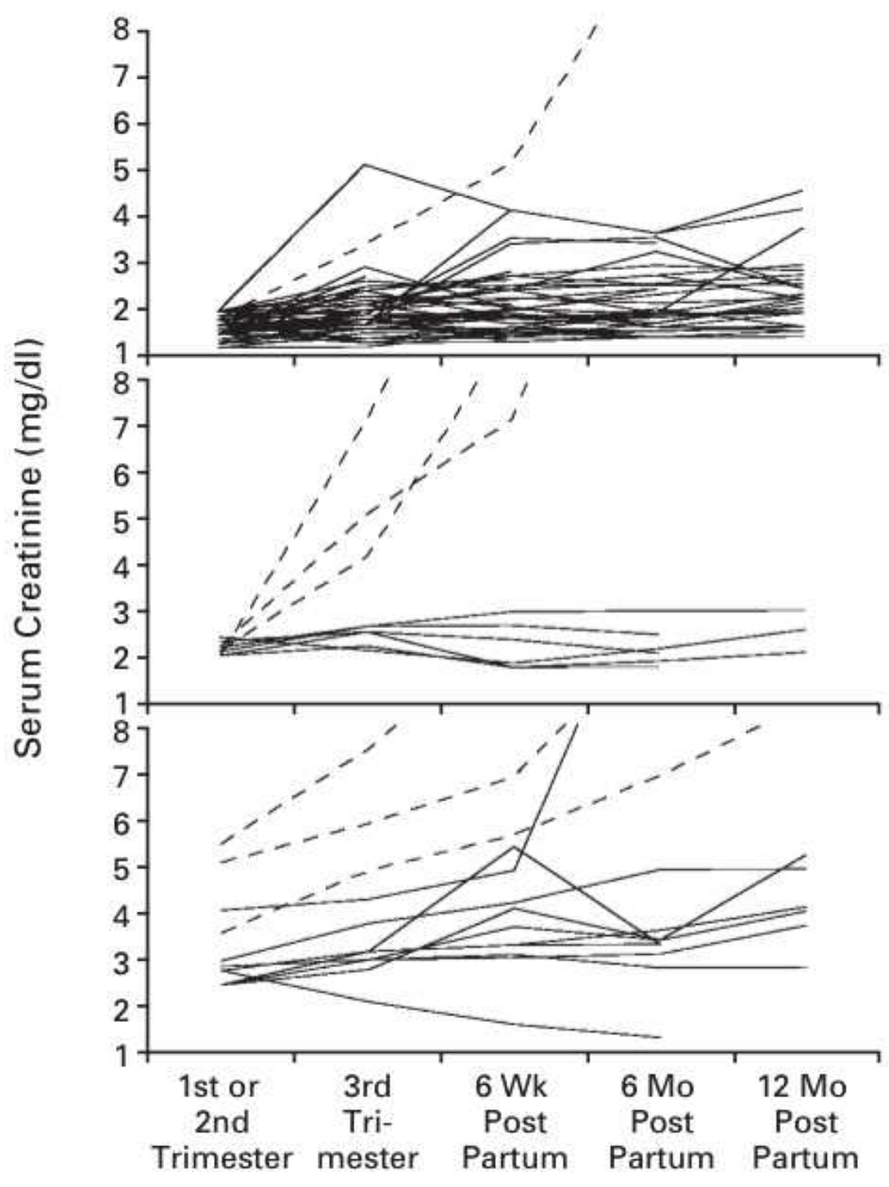

FIGURE 59.3 Pregnancy-related loss in women with renal insufficiency as determined by the serum creatinine level where mild renal insufficiency is <123 μmol/L (1.4 mg/dL), moderate renal insufficiency is 124 to 220 μmol/L (1.4 to 2.4 mg/dL), and severe renal insufficiency is >221 μmol/L (2.5 mg/dL), respectively. (Reprinted with permission from Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. *N Engl J Med.* 1996;335:226–232.)

are also important factors with respect to the risk for progression that are difficult to examine simultaneously in small single center experiences.[135] Further, the serum creatinine is likely too imprecise to be utilized to stratify women prior to pregnancy as it does not take into account patient size and muscle mass, and in young women serum creatinine is often inadequately reflective of the actual degree of histologic renal damage. Tubulointerstitial changes involving in excess of 20% of the cortical area, glomerulosclerosis, and severe arteriolar hyalinosis have all been deemed important with respect to pregnancy outcome.[137,138]

More recently, therefore, studies have prognosticated pregnancy outcome on the basis of a calculated GFR, which has served to increase the reported prevalence of CKD in pregnancy significantly from <1% to 3% as women with more subtle renal insufficiency are identified.[133,139] A recent study assessed pregnancy outcome in women with stage 3–5 CKD, excluding women with diabetes and lupus.[140] They utilized the MDRD formula to calculate the GFR and stratified women into four groups based on GFR (>40 or ≤40 mL/min/1.73 m^2) and the baseline level of proteinuria (<1 or ≥1 g per d). In women with a GFR in excess of 40 mL/min/1.76 m^2, there was no change in the rate of progression before and after pregnancy irrespective of the degree of urine protein. In women with a GFR ≤40 mL/min/1.73 m^2, the change in the rate of the postpartum decline in renal function was governed by the presence or absence of proteinuria, wherein the rate of progression increased from −0.55 mL/min/month to −1.17 mL/min/month. Gestational age decreased across the four groups as did birth weight. They concluded that only women with advanced kidney dysfunction and proteinuria need be counselled aggressively with respect to pregnancy, but their study overall was small (n = 49) and requires confirmation specifically in the group with GFR >40 mL/min/1.73 m^2 and with significant proteinuria as there were only six women in this group. Further, a subsequent study did note adverse outcomes even at early stages of CKD that associated with the degree of proteinuria and hypertension, but was limited by the fact that a first trimester serum creatinine was utilized in quite a number of cases, which could have served to reclassify more severe renal insufficiency to stage I CKD following accommodation to pregnancy.[133] The most recent study utilized the CKD-EPI equation to calculate eGFR from a preconception serum creatinine and noted an odds ratio for a composite maternal complication (worsening kidney function or preeclampsia) to be 6.75 (95% CI 1.8–24.8) and an odds ratio for a fetal complication (intrauterine growth restriction [IUGR], preterm birth, and fetal death) to be 2.91 (95% CI 1.19–7.09) when eGFR ranged between 60 and 89 mL/min/1.73 m^2.[141] A large study that utilized data from the HUNT II cohort, however, noted that the increased risk of preeclampsia in women with an eGFR between 60 and 89 mL/min/1.73 m^2 occurred only in women who also had hypertension and that there was a significant interaction between reduced kidney function and hypertension.[142] Although interesting, only a fraction of these women had microalbuminuria and therefore this is not the population likely to present to a renal clinic for prepregnancy consultation. Instead, women with identified kidney disease of various histologic types along with varying degrees of renal insufficiency, proteinuria, and hypertension will deserve guidance with respect to preconception planning and existent data suggests caution be exercised in women with established kidney disease. Multicenter efforts with larger numbers of patients will be necessary to refine counselling strategies particularly in the large group of women with moderate disease and to better understand the impact of different types of kidney disease along with current available treatment regimens. Available data for specific disease entities, as well as ESRD, are discussed in later text.

Diabetic Nephropathy

Due to increasing rates of obesity, diabetes mellitus is becoming a growing public health concern. Prepregnancy assessment and optimization can be effective[143] and it is, therefore, mandatory to improve pregnancy outcomes. Adequate prepregnancy optimization includes achieving a glycosylated hemoglobin (HbA1c) of ≤7.0%[144] and is typically achieved with multiple daily injections of insulin or an insulin pump. In addition to minimizing potential congenital abnormalities,[145] meticulous glycemic control improves pregnancy outcomes. In fact, for each 1% increment in HbA1c the adjusted odds ratio for preeclampsia is 1.6 (95% CI 1.3–2.0) whereas it is 0.6 (95% CI 0.5–0.8) for every 1% decrement during the first half of pregnancy.[146] The trend to delay childbirth, however, is resulting in more end-organ damage, including diabetic nephropathy, even prior to the consideration of pregnancy, thereby mandating early involvement of nephrology as well as endocrinology in prepregnancy counselling and optimization. The exact manner in which to counsel and optimize a young woman with significant nephropathy, however, is remarkably less clear based on the sparse and often controversial existing literature. Although most series note approximately a 90% live birth rate,[147–149] risks inherent to a pregnancy complicated by diabetic kidney disease are twofold. Significant fetal risks include poor growth and preterm delivery. Frequent maternal complications include acceleration of hypertension and preeclampsia as well as the potential to hasten progression of underlying nephropathy.

Like other forms of kidney disease, pregnancy outcome is affected by the prepregnancy kidney function, proteinuria, and blood pressure, but the rates of untoward outcomes are likely higher than described in other forms of kidney disease. One study assessing pregnancy outcome categorized women according to their urinary albumin excretion rate.[150] Compared to women with normal albumin excretion wherein the rate of preeclampsia was 6%, the rate increased to 42% and 64% in women with microalbuminuria and diabetic nephropathy, respectively. A similar pattern emerged for extreme preterm delivery (<34 weeks' gestation) wherein the rate was 6% in women with normal urine albumin excretion, 23% in women with microalbuminuria, and finally

45% in women with diabetic nephropathy, defined as urine protein excretion >500 mg daily. However, there were also differences between the groups in both baseline HbA1c and blood pressure. Irrespective, the strong relationship between microalbuminuria and preeclampsia has been noted in other studies,[151–154] including one that noted no additive predictive value of blood pressure[151] and in another that adjusted for both baseline hypertension and glycemic control.[153] Unfortunately, baseline serum creatinine was rarely reported and never adjusted for as a potential contributor to untoward pregnancy outcome in any of these studies, but has been shown to be an independent predictor of delivery before 32 weeks' gestation and very low birth weight independent of proteinuria and glycemic control in any trimester.[155] Although microalbuminuria and proteinuria are a reflection of established endothelial dysfunction, a well-described correlate of preeclampsia and preterm delivery,[156] HbA1c, blood pressure, and baseline kidney function are likely additive with respect to adverse pregnancy outcomes.

In addition to pregnancy-related complications, the potential for progression of nephropathy and accelerated loss of kidney function is serious and deserves careful consideration given the poor outcome of patients with ESRD secondary to diabetes mellitus. Proteinuria has been described to increase throughout pregnancy with nephrotic syndrome (>3 g per day) developing in the vast majority (>70%) who enter pregnancy with diabetic nephropathy (>500 mg per day) and tends to occur along with some increase in blood pressure in the third trimester.[157–160] In those studies that followed urine protein well into the postpartum period significant improvements were noted and in many women the value returned to prepregnancy levels.[157,158] The rates of late gestation nephrotic range proteinuria being higher than the quoted rate of preeclampsia in this population reflects the difficulty of diagnosing the syndrome in a population that already has significant proteinuria as well as lack of understanding of the pathophysiologic mechanisms of preeclampsia in this particularly high risk population (see later section, Pathophysiology of Preeclampsia).

Despite the almost uniform worsening of urine protein during pregnancy in women with diabetes mellitus, the literature has been conflicting with respect to pregnancy impact on progression of renal dysfunction. Early studies concluded that pregnancy did not hasten disease progression in diabetes,[147,157,158,161–163] but these early studies were small with variable follow-up periods and included a spectrum of baseline kidney function with the majority of patients having well preserved kidney function at conception. Those with significant renal insufficiency and nephropathy certainly did deteriorate during pregnancy, but the overall slope toward ESRD, which was already steep, did not change significantly reflecting the overall poor outcome of diabetic nephropathy prior to more widespread use of blockade of the RAS. Studies that more effectively stratified women based on baseline renal function noted that women with well-preserved kidney function at conception had better outcomes whereas moderate to severe renal insufficiency predicted more rapid deterioration in kidney function during and after pregnancy.[159,160,164,165] One such study noted a baseline creatinine clearance of 70 mL per min to be a potentially meaningful value with respect to outcome.[164] Women who entered pregnancy with a creatinine clearance >70 mL per min were more likely to have an appropriate early pregnancy renal accommodation and stable kidney function after pregnancy whereas women with lower baseline clearance values had a significant decline in renal function at 3 months postpartum (36% lower). Another study that assessed women with more significant baseline renal dysfunction (mean creatinine 1.8 mg per dL) found a significant deterioration in kidney function that was transient in 27% and permanent in 45%.[159] It is distinctly possible that superimposed preeclampsia manifesting as worsening proteinuria and kidney function during pregnancy is damaging over the long term. A health administrative study from the Norwegian Renal Registry that identified 2,204 women with pregestational diabetes whose pregnancy was complicated by either preeclampsia, preterm delivery, or a low birth weight baby and noted higher future rates of nephropathy, ESRD, and death.[166] Another study noted the median age of children to be 9 (3–17) when the mother expired secondary to complications of renal or cardiac disease,[167] reminding us that this is a very vulnerable, high-risk group that is not to be taken lightly.

Despite the great potential for both untoward maternal and fetal outcome, there are precious little data to guide prepregnancy preparation outside of optimization of HbA1c. In one study, for example, hypertension was not treated unless the diastolic blood pressure exceeded 105 mm Hg.[157] There is, however, some data to suggest that adequate blood pressure control is important. Although no randomized data exists, one retrospective cohort study compared outcomes in women with a mean arterial pressure either ≥100 mm Hg or <100 mm Hg and noted patients with higher blood pressures were significantly more likely to deliver before 32 weeks' gestation (38.1% versus 4.6%, P =.007) even after adjusting for duration of diabetes and glycemic control.[168] A second prospective study targeted a blood pressure of <135/85 mm Hg in 117 pregnant women with type 1 diabetes mellitus and noted a trend toward longer gestation and higher birth weight as compared to historical data published prior to theirs from the same geographical region in Europe.[169] However, it is difficult to draw comparisons between these small single-centered studies, and the vast majority of the women included in their study did not have even microalbuminuria, a group one might overall expect to do better. Only one group has assessed the potential for prepregnancy optimization in women with significant diabetic nephropathy. They have published two articles advocating for aggressive prepregnancy blockade of the RAS with captopril to lower proteinuria prior to pregnancy along with aggressive glycemic control.[170,171] They recommend stopping captopril at the time of conception and effectively demonstrated the ability to lower proteinuria from

a mean value in excess of a gram to a mean value <300 mg. Although proteinuria still increased throughout pregnancy, the rate of increase was not as dramatic as what might be expected from the previous literature and kidney function was stable at 2 years postpartum. Of note, the patients in these two small series had well-preserved kidney function, which likely also factored into favorable long-term outcomes. Irrespective, there are data outside of pregnancy that speak to the potential for prolonged renoprotective effect after cessation of RAS blockade.[172]

Of course, anyone prescribing RAS blockade to a woman of child-bearing potential needs to be cognizant of the potential for teratogenicity.[173] Second and third trimester teratogenicity secondary to angiotensin-converting enzyme (ACE) inhibition is well described and includes oligohydramnios, neonatal anuria and renal failure, limb contractures, craniofacial abnormalities, pulmonary hypoplasia, and patent ductus arteriosus. Children that survive ACE inhibition/angiotensin receptor blocker (ARB) fetopathy are left with renal insufficiency and profound impairment in the urine concentrating ability likely due to papillary atrophy and disturbed formation of the medullary concentration gradient.[174] A more recent publication, however, suggests the potential as well for first trimester teratogenicity.[175] This study has a number of issues such as the inclusion of defects not previously described in risk estimates as well as the inability to control for other potential confounders including maternal age, obesity, and diet-controlled diabetes. ARBs may very well be more teratogenic with case reports of significant malformations emerging after first trimester exposure.[176–178] There are no case reports as yet of teratogenicity after exposure to the newer direct renin inhibitors, but there is no reason to expect they will not be equally or even more teratogenic, and this class of medication also should be used with extreme caution in young women. The risk of teratogenicity must be carefully balanced against the need to prevent progression of diabetic nephropathy. It is, therefore, imperative that physicians educate young diabetic women as to the risks of an unplanned pregnancy as opposed to denying them a potentially renoprotective therapy. Unintentional first trimester exposure does not require termination, but careful fetal imaging is recommended.[179] In the postpartum period, there is also no need to deny RAS blockade while breastfeeding. Captopril, enalapril, and quinapril have all been tested and noted to be absent in breast milk and, therefore, can be used if necessary to treat diabetic nephropathy in the early postpartum period.[180,181]

IgA Nephropathy

Although IgA nephropathy is the most common glomerular-based disease diagnosed in women of childbearing age, there is a remarkable paucity of data in the literature to assist with prepregnancy counselling and management. Most studies, being small and decades old, could not simultaneously assess the impact of kidney function, blood pressure, and proteinuria on pregnancy outcome or potential impact of treatment prior to conception with either immunosuppression or blockade of the RAS.[137,182–184] Due to the slow insidious nature of the disease, a large proportion of women first come to medical attention during pregnancy without a careful prepregnancy assessment of blood pressure, proteinuria, and kidney function to assist with the understanding of the impact of these variables on the prognostication of pregnancy outcome. The follow-up time used to determine if pregnancy ultimately has an impact on progression is likely inadequate with only 5 years of long-term follow-up in most studies.[182,183,185–187] Finally, in studies that attempt to assess the impact of histology, older classification systems were used and the baseline clinical correlates of disease were not consistently reported, therefore making this area of literature very difficult to interpret.[188,189]

Early data would suggest that even mild disease associated with preserved renal function might significantly increase the risks of untoward pregnancy outcomes and worsening maternal condition. In a large analysis of 116 pregnancies, the fetal loss was noted to be 22%.[190] Maternal renal function declined transiently in 26%, and was progressive and irreversible in 2%. Proteinuria and hypertension increased in 52% and 62% of women, respectively, and did not resolve after delivery in 13% and 10%, respectively. This study, however, was retrospective with the vast majority of women formally diagnosed by biopsy either during or after pregnancy limiting the collection of careful prepregnancy data.

Also supporting the notion that even mild disease may have consequences in pregnancy are studies that assessed women with isolated hematuria, a marker perhaps of even milder glomerular disease. A study that assessed 276 women, of which 44 had isolated hematuria on their first prenatal visit, noted significantly increased rates of preeclampsia (OR 9.1, 95% CI 2.5–33.7).[191] That odds ratio was mitigated albeit still statistically significant in a larger dataset wherein the same authors utilized data from the trial of Calcium for Preeclampsia Prevention (CPEP) noting idiopathic hematuria in 132/4307 (3%) of participants. An almost twofold increased risk was observed for the development of preeclampsia after adjustment for blood pressure, race/ethnicity, and medical center (aOR = 1.89; 95% CI 1.12–3.18).[192] However, the most recent and largest study to date (n = 1,000) noted that dipstick positive hematuria was common (20%) and typically did not signify any meaningful renal disease, as 60% of these patients were carefully assessed in the nephrology clinic.[193] In this more comprehensive study, microscopic hematuria did not increase the likelihood of preeclampsia, gestational hypertension, or delivery of a small for gestational age baby. Further, a sizable study that assessed women with known thin basement membrane disease, another potential explanation for hematuria, also failed to note rates of pregnancy-related complications that differed significantly from those of the general population.[194]

The absence of prepregnancy baseline data and the use of serum creatinine to determine baseline renal function likely hampered the interpretation of pregnancy risk in

many of the early studies. In studies wherein the creatinine clearance was calculated, a better understanding of pregnancy risks emerged. Women with preserved kidney function as defined by a creatinine clearance over 70 mL per min were demonstrated to have reasonable pregnancy outcomes.[137,186,195] Exceptions were noted in women with difficult to control prepregnancy hypertension (blood pressure [BP] >140/90 mm Hg)[66,69,77] or worsening of hypertension early in pregnancy[183,196] as well as in women with significant renal scarring on biopsy that perhaps was not appropriately reflected by clinical measures of renal function. Specifically, worse pregnancy outcomes have been noted in women with sclerosed glomeruli,[188,189,195] tubulointerstitial damage that involves in excess of 20% of the cortical area,[137,195] or significant arteriosclerosis.[137] Whether the biopsy findings might be better reflected in the baseline proteinuria is not known as the impact of that variable on pregnancy outcome cannot be assessed without much larger multicenter efforts due to the inherent variability and issues with quantifying urine protein that are not unique to the pregnancy literature.

Although, as mentioned, the literature does note exceptions, in general, pregnancy does not hasten progression of renal dysfunction as long as kidney function prepregnancy is well preserved. A recent study that compared 136 pregnant women with IgA to 87 matched controls noted an overall rate of progression of 1.31 (95% CI, 0.99–1.63) mL/min/year that was impacted by levels of proteinuria, but not affected by pregnancy.[187] Of note, all women in this study had well-preserved kidney function with a creatinine clearance of 92 ± 17 mL/min/1.73 m^2 in the pregnancy group. Although not as high as quoted in the earlier studies, pregnancy complications still exceeded what might be expected in the general population including a perinatal death rate of 3%, premature delivery rate of 10%, low birth weight in 11%, and 21% of the pregnancies were complicated by hypertension. Data with respect to more moderate or severe disease with renal dysfunction was poorly addressed in this study due to inadequate numbers, but the limited existing data does suggest these women should approach pregnancy with due caution as both poor fetal and maternal outcomes have been noted.[182,195,196] As women delay childbearing and are more likely to approach pregnancy with more moderate degrees of renal impairment, this is an area in need of further study.

Urinary Tract Infections, Pyelonephritis, and Reflux Nephropathy

Urinary tract infections (UTIs) are among the most common complications noted in pregnancy and Escherichia coli is the most frequently cultured bacterial organism.[197,198] Patients commonly present with asymptomatic bacteriuria that can progress to cystitis or even pyelonephritis if not promptly treated given the dilation of the urinary tract that accompanies the gravid state.[199] The classification of patients into either of these clinical categories has implications for medical management, which must be hastened in pregnancy due to the risk of progression to more severe maternal complications such as septicemia[200] and renal insufficiency.[200,201]

With respect to asymptomatic bacteriuria, current guidelines support the screening for bacteriuria using urine dipstick followed by urine culture when positive.[197] Subsequent initiation of antibiotic therapy based on culture sensitivity is also recommended as this practice reduces progression to cystitis and, more importantly, to pyelonephritis and its associated complications.[202] Safe, empiric antibiotic choices in pregnancy include trimethoprim-sulfamethoxazole, nitrofurantoin, and cephalexin.[197] However, controversy currently exists regarding the duration of antibiotic administration. Recent meta-analyses comparing the 1-day to 4- and 7-day regimens demonstrated that 1-day regimens resulted in fewer side effects and increased compliance at the expense of a decreased cure rate.[198,203] Accordingly, current guidelines support the use of a 3-day regimen in healthy women[197] or a 7-day regimen to increase the likelihood of definitive cure in women with comorbidities.[198] Successful treatment must also be assured by the acquisition of a negative follow-up urine culture after completion of the antibiotic regimen and periodic screening throughout the remainder of the pregnancy.[197]

Cystitis or symptomatic bacteriuria resides further along the continuum of UTI severity. Cystitis is a clinical diagnosis based on the presence of bacteriuria and the clinical symptoms of dysuria, frequency, lower abdominal or suprapubic pain, but not fever.[199] In contrast to asymptomatic bacteriuria, urine culture and sensitivity results are often unavailable at the time of diagnosis and empiric therapy is required.[197] Selection of the appropriate antibiotic regimen was previously a contentious issue, but a recent Cochrane Review found few significant differences in cure rates and recurrence between the various empiric antibiotic regimens examined in the literature.[199] Similar to asymptomatic bacteriuria, a follow-up urine culture and periodic re-screening must occur throughout the pregnancy.

Pyelonephritis is the most severe manifestation of a UTI and is significantly more prevalent in young nulliparous women.[200] Clinically, patients often present in the third trimester of pregnancy with irritative urologic symptoms as well as fever and costovertebral tenderness,[199] but an increasing prevalence of pyelonephritis has recently been noted in earlier trimesters.[200] As such, health care providers must be vigilant for pyelonephritis at all stages of pregnancy and administer prompt empiric treatment until culture and sensitivity results are available. The importance of aggressively managing pyelonephritis cannot be overstated. Recent data from a cohort of 440 inpatients with antepartum pyelonephritis demonstrated a decrease in the prevalence of renal dysfunction (20% to 2%)—a finding the authors attribute to early treatment.[200] However, respiratory insufficiency within the context of pyelonephritis remained common in this cohort (10%), and one in five women with pyelonephritis were diagnosed with septicemia based on blood culture results.[200] It has been suggested that pyelonephritis can be managed in the outpatient setting,[204] but this decision

should be individualized based on the patient and available outpatient resources. Based on available data,[244,250] current recommendations for chronic suppressive prophylactic antibiotics include women with frequent prepregnancy UTIs, persistent asymptomatic or symptomatic infection despite two courses of antibiotics, and women who have recovered from pyelonephritis or may be at particular risk for pyelonephritis (e.g., diabetic patients or immunosuppressed patients). Emergence of resistance in the face of decreased safe antibiotic options remains a theoretical concern.

Reflux nephropathy is a common condition with a female preponderance that is typically diagnosed in childhood and, therefore, is another condition that can affect young women of childbearing age. Reflux nephropathy can be an incidental finding during standard pregnancy screens for bacteruria, UTI, or pyelonephritis (17%–28%).[205–208] However, the impact of reflux nephropathy on maternal and fetal health is certainly not benign and, like other renal conditions, complications include preeclampsia, deterioration of renal function, and fetal loss.[206,207,209] Unique to this condition, however, is the predisposition to UTIs (17%–65%) and pyelonephritis (3%–37%) that can cause significant maternal morbidity.[210] Further, the genetic preponderance of the condition necessitates assessment of the newborn for vesicoureteral reflux.[211] Pregnancy outcome can be largely prognosticated by prepregnancy renal function and hypertension as a reflection of the degree renal parenchymal scarring. A recent systematic review noted primary vesicoureteral reflux without renal scarring was not associated with an increased incidence of gestational hypertension, preeclampsia, and fetal morbidity,[210] but persistent reflux during pregnancy does increase the likelihood of pyelonephritis.[205]

The majority of data on reflux nephropathy in pregnancy comes from three older, but sizable retrospective case series[205,206,209] and a more recent prospective series,[211] examining just over 1,000 pregnancies in women with reflux nephropathy. All studies assessed the prognostic value of prepregnancy renal function as a reflection of parenchymal scarring, typically utilizing a serum creatinine cutoff of 110 μmol per L (1.3 mg per dL) to distinguish preserved kidney function from renal impairment. An increased serum creatinine of ≥110 μmol per L (>1.3 mg per dL) significantly increased the risk of maternal complications including preclampsia and loss of kidney function as well as fetal loss. Preeclampsia, in one series, was 36% in women with renal insufficiency compared to 13% in women with preserved kidney function and the presence of parenchymal scarring was noted to be positively correlated with prevalence of preeclampsia.[206] Further, in another study, preeclampsia was noted to be higher in women with bilateral as opposed to unilateral scarring (24 versus 7%; P <.001).[205] The difference was more dramatic in a second series at 56.7% compared to 6.4%, respectively,[209] and preexisting hypertension has been noted to further increase the risk.[211]

Similarly, at a prepregnancy serum creatinine threshold of ≥110 μmol per L (>1.3 mg per dL), 8% of women with reflux nephropathy experienced a decline in renal function whereas only 2% of women with preserved renal function exhibited a similar deterioration.[206] Again, the results were more striking in the second series wherein an increase in serum creatinine above the preconception value was observed in all cases with renal insufficiency, reversing partially in most with the exception of cases also complicated by hypertension and increased proteinuria that proved progressive.[205,209] Thus, the relative risk of renal function deterioration was determined to be 12.7 (95% CI 1.6–98.5) in women with mild renal insufficiency (90–120 μmol per L or 1.0–1.4 mg per dL) and 19.8 (95% CI 2.6–155) in women with moderate to severe renal insufficiency (130–350 μmol per L or 1.5–4.0 mg per dL).[211] The large confidence intervals reflect the small number of patients assessed in the prospective cohort (n = 54 pregnancies).[211]

Fetal outcomes are also governed by the degree of renal impairment, and, likely to be of even more significance, the presence of significant first trimester hypertension. In the series published by Jungers et al.,[208] maternal blood pressure at early gestation was the only significant prognostic marker for adverse fetal outcomes after adjustment for covariates, including serum creatinine and proteinuria, with the relative risk of fetal loss in hypertensive patients being 4.8 times higher than in normotensive patients wherein there were no fetal losses.[209] Of note, there was no correlation between the degree of renal dysfunction and hypertension. Moreover, in the subset of women with early gestational hypertension, adequate control of blood pressure resulted in significantly lower rates of fetal loss (11% vs. 74%) and no fetal deaths occurred in late-gestational hypertension.[208,209] Although serum creatinine was noted to be a significant predictor of fetal outcome in this study, fetal loss has been demonstrated to be significantly more likely in women with impaired renal function (serum creatinine ≥110 μmol per L or 1.3 mg per dL).[205,209] Similarly, the birth weight of living neonates was significantly lower in this cohort.[209]

Given these risks, women with reflux nephropathy and diminished renal function require careful coordinated nephrologic and obstetric care such that manageable renal complications such as UTIs can be immediately diagnosed and treated and hypertension can be aggressively controlled. Efforts toward this endeavor have been successful as the prevalence of UTIs has been documented to be lower in women with reflux nephropathy and diminished renal function as compared to women with preserved function presumably due to differences in the intensity of follow-up.[206,208] Further, fetal outcomes have been demonstrated to be more favorable in planned and carefully monitored pregnancies despite the presence of renal insufficiency and hypertension.[208]

Lupus Nephritis and Other Connective Tissue Diseases

Because of the female preponderance and the typical young age of onset, lupus is another disease that frequently requires

management during a woman's reproductive years. Even prior to considering a pregnancy, treatment of the condition requires mindfulness of the reproductive potential of this patient population while imparting an understanding to the patient that an unplanned pregnancy can be hazardous. Lupus itself does not impact female fertility, but some of the medications frequently prescribed to treat the renal manifestations of the disease may impact fertility and have proven teratogenicity. Thus, sexually active women initiating either cyclophosphamide or mycophenolate mofetil should have a negative pregnancy test prior to starting these therapies, and young women initiating cyclophosphamide need to be informed that fertility may be compromised. Amenorrhea secondary to cyclophosphamide use is related to the age of the patient and the number of prescribed treatment cycles. Rates of sustained amenorrhea have been documented to be 12% in women ≤25 years old, 27% in women between the age of 26 and 30, and rise sharply to 62% in women ≥31 ($P = 0.04$).[212] There are limited data to suggest a gonadotropin-releasing hormone analog (GnRH-a) may provide ovarian protection, decreasing the rates of premature ovarian failure from 30% to 5% in one study.[213]

Historically, lupus patients did poorly in pregnancy, but outcomes have improved over time, presumably as new treatment strategies for the disease emerge to induce remission prior to a pregnancy attempt. As in all chronic kidney diseases, renal insufficiency and chronic hypertension cause poor pregnancy outcomes. However, lupus is unique in that active nephritis predicts a particularly poor pregnancy outcome, and pregnancy itself has been demonstrated by some to increase the potential of a disease flare during any trimester or in the early postpartum.[214] The literature on maternal and fetal outcomes has been recently summarized in a systematic review and meta-analysis that included 2,751 pregnancies in women with lupus from 37 studies wherein adequate outcome data was reported.[215] Significant study heterogeneity was noted due to variable definitions of active lupus nephritis and a disease flare. Twenty-two cited studies did not meet study validity criteria. Irrespective, useful outcome data was synthesized and reported, and areas in need of future study were elucidated. Overall, 23.4% (95% CI 19.5–27.3%) of pregnancies were unsuccessful. The most frequent maternal complications included a disease flare in 26% that included nephritis in 16% of cases along with hypertension (16%) and preeclampsia (8%). Fortunately, severe maternal complications, including stroke, ESRD, and death, were rare (approximately 1%). Fetal complications included spontaneous abortion (16%), premature birth rate (37%), IUGR (13%), stillbirth (4%), and neonatal death (2.5%). Active lupus nephritis and positive antiphospholipid antibodies were significantly associated with maternal hypertension and premature birth. Antiphospholipid antibodies also correlated with an increased risk of spontaneous pregnancy loss. Of interest, there was no statistically significant association between antiphospholipid antibodies and active nephritis. A history of nephritis predicted maternal hypertension and preeclampsia and this finding was confirmed by a recent Toronto study comparing pregnancy outcomes in patients with renal involvement within 6 months prior to pregnancy to those without renal involvement.[216]

This study also confirmed disease flares during pregnancy to be more common in patients with active nephritis.[216] Therefore, 6 months of sustained disease quiescence prior to considering a pregnancy has been recommended based on studies that show the disease flared in 7% of patients with inactive disease as compared to 61% of patients wherein there was active disease at the time of conception.[217] Despite the knowledge that an unequivocal clinical remission is necessary prior to consideration of a pregnancy, judging disease activity in a clinical setting can prove very challenging for the practicing clinician. Although, for example, hypocomplementemia and abnormal serology have been demonstrated to be associated with poor pregnancy outcomes,[218] many patients' clinical presentations are not concordant with their serology. In many studies >500 mg of proteinuria was defined as active nephritis, but available data are inadequate to definitely determine the impact of histologic subtype or level of kidney function and degree of proteinuria on outcome.[215] Thus, further study is needed to assist the many young women with lupus who attain a partial remission to make an informed choice with respect to pregnancy.

A reasonable approach based on current data includes treatment with appropriate immunosuppression to attain remission for at least 6 months prior to converting a young woman to pregnancy safe treatment, which can include prednisone, azathioprine, and the calcineurin inhibitors (see section on Renal Transplantation). Hydroxychloroquine does not appear to be associated with any increased risk of congenital defects, spontaneous abortions, prematurity, or fetal death, and therefore can be used safely in pregnancy.[219] A repeat biopsy may prove necessary in select cases wherein it is difficult to clinically confirm absence of active nephritis in pregnant women receiving safe immunosuppression therapy. Baseline laboratory assessment of serology including antiphospholipid antibody levels and lupus anticoagulant as well as anti-Ro and La antibodies can help predict the rate of spontaneous fetal loss with pregnancy complications[220] and the rate neonatal lupus, respectively. Women with positive antiphospholipid antibody titers in conjunction with a history of thrombosis, fetal loss, or untoward pregnancy complications require assessment and management by physicians who are expert in the area of thromboprophylaxis and pregnancy. Even in the presence of positive anti-Ro and La antibodies, fetal heart block is rare. Recent studies suggest that the titer is more predictive than just simply the presence of antibodies and should guide referral for serial fetal echocardiography. Cardiac complications were diagnosed in the presence of moderate to high maternal anti-Ro levels (50–100 U/mL or 15%–85%) independent of anti-La levels.[221]

Other connective tissue diseases of relevance to the practicing nephrologist include renal ANCA-associated vasculitis, Goodpasture syndrome, and scleroderma renal

disease. Of these, ANCA-associated vasculitis will be encountered most frequently, but there is still inadequate data from which to provide definitive pregnancy counseling with the exception that women conceiving while their disease is active do poorly.[222] The literature notes a number of cases either presenting in pregnancy or relapsing during pregnancy to suggest the possibility that, like lupus, pregnancy might result in disease activation.[222] Even in the presence of inactive disease, approximately 25% of patients have been noted to relapse irrespective of the presence or absence of maintenance immunosuppression.[223] Despite an approximate 75% live birth rate, there are numerous complications with preeclampsia complicating approximately 25% of the reported cases in the literature and preterm delivery occurring is just over 40%.[222] Outcome will depend on severity of the presentation and nephrologists will likely be involved in the most severe presentations necessitating treatment decisions. Steroids remain first line therapy, but will likely be inadequate as a single agent. Azathioprine can be used safely, but in at least one case proved inadequate and resulted in maternal death,[224] and in another there were a number of relapses during pregnancy.[222] Intravenous immunoglobulin and plasmapheresis are safe options in pregnancy for this disease and have been used with some success.[225–227] Cyclophosphamide has rarely been used with success,[228] and as a rule is contraindicated at least in the first trimester wherein it has been noted to cause spontaneous pregnancy loss, growth deficiency, developmental delay, craniosynostosis, blepharophimosis, flat nasal bridge, abnormal ears, and distal limb defects including hypoplastic thumbs and oligodactyly.[229] At present, there are some limited data on the use of rituximab primarily from the oncology literature, which might be an option. To date, no fetal malformations have been noted, but CD19 B cells were either undetectable or severely decreased in exposed neonates returning to normal levels by 3 to 6 months' gestation without documented serious infections.[230] Also of interest to the neonate is the report of placental transport of myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA) resulting in neonatal pulmonary hemorrhage.[231]

Goodpasture syndrome is a rare disease wherein antiglomerular basement membrane (GBM) antibodies result in pulmonary hemorrhage and crescentic renal disease. There are only a handful of cases presented in the literature and those suggest overall poor maternal and fetal outcomes.[232–236] Given that women diagnosed and treated prior to conception have better outcomes,[232,236] one can postulate that the infrequency of the condition likely delays appropriate diagnosis and expeditious treatment when it presents during pregnancy.[234,235] Further, in some cases, the anti-GBM antibody was negative until the postpartum period and it has been postulated that the placenta might act as an absorbent.[233,235] Overall, there is inadequate data in the literature to make any formal recommendations short of having high clinical suspicion in women presenting with symptoms suggestive of pulmonary-renal syndrome.

Fortunately, scleroderma is rare and presents in older age groups. However, as women delay childbearing, there is more potential for a pregnancy to be affected by this disease. Although women whose disease is limited to the skin may do reasonably well with the exception of increased rates of preeclampsia (22.9%) and IUGR (5.3%) compared with the general population,[237] those with underlying vascular involvement can have devastating outcomes with maternal morbidity and mortality due to accelerated hypertension, renal failure, and pulmonary hypertension.[238–240] Thus women with progressive disease complicated by renal involvement and/or significantly increased pulmonary pressures should be cautioned against pregnancy. Of interest, prompt institution of captopril in the postpartum period resulting in partial renal recovery and cessation of hemodialysis has been described.[240]

Other Glomerular-Based Diseases

There are limited published data with respect to the pregnancy outcomes for less frequently encountered glomerular-based diseases including minimal change disease (MCD), focal segmental glomerular sclerosis (FSGS), membranous nephropathy (MN), and hereditary nephritis or Alport disease. Trends have emerged to suggest perhaps pregnancy outcomes are best in MN and the worst in MPGN and FSGS,[185] but the study numbers are too small and too varied with respect to the definition of a poor outcome and timing of biopsy in relation to the pregnancy to definitively make these conclusions. If one examines studies wherein hard outcomes including spontaneous abortion and fetal or neonatal death were reported independently then the live birth rates for MCD, FSGS, MN, MPGN, and hereditary nephritis are approximately 74%, 71%, 96%, 80%, and 85%, respectively (Table 59.2).[183,185,241–244] These live birth rates may be dependent on the status of the disease and may vary significantly in treated as compared to untreated disease. Further, issues with respect to potential side effects from nephrotic syndrome in pregnancy, including difficult to manage edema and potential thrombosis, are not adequately reported in the literature. Suffice to say, treatment and maintenance of nephrotic syndrome with pregnancy safe immunosuppression where indicated and possible should be the prepregnancy goal.

Polycystic Kidney Disease

Despite the potential presence for ovarian cysts in women with polycystic kidney disease, fertility is not impaired, but there are data to suggest ectopic pregnancies might be more common and should be considered in the differential of abdominal pain in young women.[245] Unlike other forms of kidney disease, women with autosomal dominant polycystic kidney disease (ADPKD) need to be educated that there is a 50% chance of transmission of their renal disease to their offspring. Prenatal diagnosis is possible, but not always readily available and typically not desired by a patient who is

59.2 Pregnancy Outcome in Glomerular-Based Disease

Disease	Cases	Spontaneous Loss	Fetal/Neonatal Death	Live Birth Rate (%)
MCD[137,183]	19	3	2	74
FSGS[137,183,241,244]	74	5	16	72
MN[137,183,241,242]	51	1	1	96
MPGN[137,183,241]	40	4	4	80
Alport disease[183]	33	2	3	85

MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis.

otherwise well.[245,246] For the most part, pregnancy outcomes in young women with ADPKD are quite good largely because kidney function is still well preserved with minimal proteinuria during the reproductive stage of life, but there are notable exceptions.

The largest series to date compared 605 pregnancies in women with ADPKD to 244 pregnancies in their unaffected family members.[245] No significant differences were noted in the live birth rate between women with ADPKD and unaffected controls: 77% of 605 pregnancies and 82% of 244 pregnancies, respectively. However, age >30 years predicted increased fetal complications and preexisting hypertension predicted both increased fetal and maternal complications in women with ADPKD. Maternal complications occurred in 35% of women with ADPKD compared to 19% of unaffected controls ($P < .001$) and included new or worsening hypertension (25%) and superimposed preeclampsia (11%) complicated by placental abruption and acute kidney injury (AKI) (0.8%). Similar to other forms of kidney disease, prepregnancy renal impairment (serum creatinine > 106 μmol per L or 1.2 mg per dL) may hasten progression to ESRD as these women progressed to ESRD on average 15 years earlier than the general female ADPKD population, but the numbers were too small to assess for a potential independent effect of pregnancy-induced hypertension or preeclampsia. Of interest, normotensive women with ADPKD who developed either pregnancy-induced hypertension or preeclampsia were at greater risk for the later development of chronic hypertension.

Finally, in this same study,[245] mean renal volume measurements did not differ in women with four or more pregnancies compared to age-adjusted measurements for women with fewer than three pregnancies suggesting that the hormonal changes that occur during pregnancy do not promote cyst growth in the kidneys as has been demonstrated in the liver.[247] Liver cysts, fortunately, are rarely of clinical significance, but should be mentioned during counselling of these young women prior to pregnancy.

End-Stage Renal Disease

Pregnancy, once on dialysis, is difficult due to the decreased fertility that accompanies ESRD and is historically associated with poor outcomes. Data are emerging, however, to suggest that pregnancy while on intensive renal replacement therapy may result in better outcomes for both mother and baby and, therefore, may prove a viable option for a large number of young women whose reproductive years are lost to ESRD.

The ovulatory menstrual cycle reflects normal function and physiology of the hypothalamic-pituitary-gonadal axis, which is known to be affected on multiple levels in women with advanced renal disease. Menstrual irregularities, infertility, and sexual dysfunction are known to occur in patients with ESRD and worsen in parallel with the renal disease. Even in those dialysis patients who menstruate, their cycles are often anovulatory.[248] There are numerous documented endocrine abnormalities that affect fertility in young women with ESRD. During the follicular phase, FSH levels are comparable or slightly lower than nonuremic controls, whereas luteinizing hormone (LH) levels are elevated.[249,250] Despite the elevated baseline LH levels, women on hemodialysis fail to have the luteal surge in LH.[250] Both progesterone and estradiol levels are extremely low[249] and prolactin levels are higher due to prolonged plasma half-life from decreased clearance.[251,252] In fact, levels have been found to correlate with serum creatinine.[252] Compounding the hormonal alterations, which can render these women infertile, medications, anemia, fatigue, and depression can contribute to a lack of libido.[253,254]

Given the many reasons for impaired fertility and sexual dysfunction in patients with ESRD on dialysis, it is not surprising that conception is uncommon. There is, however,

emerging data that does suggest the conception rate might be improving over time. Representing approximately 10% of the U.S. dialysis population, a slightly higher rate of 2.4% of hemodialysis patients became pregnant over a 4-year period (1992 and 1995)[255] in contrast to earlier data from the same group wherein a 1.5% rate of pregnancy in hemodialysis patients was described over a 2-year period (1990–1992).[256] In the last decade, higher pregnancy rates of 5% to 7.9% were noted on questionnaire data collected from dialysis units in Saudi Arabia.[257,258] Most recently, clearance augmented by intensive nocturnal hemodialysis has resulted in higher conception rates. Seven pregnancies occurred in 45 women of childbearing age on nocturnal hemodialysis for a pregnancy rate of 15.9%.[259] All these women were previously on conventional hemodialysis, but none conceived, suggesting fertility can be improved with more intensive clearance.

With fewer case reports of pregnancy occurring in peritoneal dialysis as compared to hemodialysis patients, the potential to conceive actually appears significantly lower on peritoneal dialysis. However, to date, there are very few studies that attempted to systematically collect this data. In Saudi Arabia, wherein the highest rates of conception were noted in conventional hemodialysis patients, data was also collected on peritoneal dialysis and no patients conceived.[257] In the U.S. dialysis registry that reported data from 930 dialysis centers including 1,699 women of child-bearing age on peritoneal dialysis, the pregnancy rate was only 1.1%.[255] In addition to the hormonal and functional causes of infertility described in ESRD patients, experts in the field have hypothesized additional etiologies for decreased conception rates in peritoneal dialysis patients might include damage to fallopian tubes from peritonitis or interference with ovum transport from the ovaries to the fallopian tubes from the presence of hypertonic solutions in the intraperitoneal space.[260]

The first successful pregnancy reported in a patient on chronic hemodialysis occurred in 1970.[261] However, initial enthusiasm was tempered following the first registry report from the European Dialysis and Transplant Association published a decade later.[262] Of the original 115 reported pregnancies, 45 were electively terminated and there were only 16 viable pregnancies of the remaining 70 women for a live birth rate of 23%. The majority of those whose pregnancies succeeded were noted to have residual renal function and four pregnancies occurred prior to the initiation of hemodialysis. They described very difficult to manage hypertension in most cases, and note a mean birth weight of 1,900 g with a mean gestational age of 33.2 weeks.

One might presume the high rates of termination influenced the poor live birth rate, but subsequent data from the United States[256] and the Saudi Arabian Registry,[263] wherein termination was unlikely, did not reflect a much better outcome with a live birth rate of only 37%. However, even in this early data, the relationship between time on dialysis and outcome began to emerge. Those cases that progressed beyond 28 weeks had their weekly dialysis time increased from an average of 9.4 ± 2.3 to 12.0 ± 2.6 hours, whereas unsuccessful pregnancies did not have their dialysis time increased after conception. The importance of enhanced clearance was also noted in the second registry study from the United States wherein infant survival was 40.2% in women who conceived on hemodialysis compared to 73.6% in women who conceived prior to initiating hemodialysis.[255] Still, overall maternal and fetal outcomes were poor with documented maternal deaths, high rates of severe uncontrolled hypertension, and prematurity. A similar discrepancy in outcome between established dialysis patients (live birth rate 50%) and those who started dialysis after conception (live birth rate 80%) was noted in the Belgian registry.[264] In addition, this study also noted a correlation between birth weight and dose of dialysis. Still, the incidence of prematurity was 100% with high rates of complications adding growth restriction and polyhydramnios to the list of potential adverse outcomes.

More recently, however, live birth rates have improved as it has become standard practice to increase the dose of delivered dialysis after conception. In 2005, Haase and colleagues described a systematic approach wherein intensive hemodiafiltration 6 days a week was prescribed for five pregnant patients with ESRD.[265] They received an average of 28.6 ± 6.3 hours per week and were able to maintain urea levels consistently <50 mg per dL. All had a live birth and the mean gestational age was 32.8 ± 3.3 weeks with a mean birth weight of 1,765 ± 554 g. The authors felt convective clearance was important to outcome by enhancing both the clearance of large and small solutes. However, in another study wherein intensified clearance was provided by increasing the amount of nocturnal hemodialysis from a weekly mean of 36 ± 10 to 48 ± 5 hours, six live births after seven pregnancies (one pregnancy was electively terminated) were documented with a mean gestational age of 36.2 ± 3 weeks and a mean birth weight of 2,417.5 ± 657 g.[259] Complications were minimal and included two babies that were small for gestational age, a single preterm birth (<32 weeks), and a single shortened cervix. Hypertension was either absent or easily managed.

The success of intensified regimens appears to be directly related to enhanced clearance of urea and likely other solutes. An early study prior to the use of widespread dialysis noted fetal mortality to be directly related to the blood urea nitrogen (BUN) level with no documented successful pregnancies once the BUN exceeded 21.4 μmol per L (60 mg per dL).[266] More recently, in a series of 28 pregnant women receiving hemodialysis with 18 surviving infants, a significant negative relationship was noted between BUN and birth weight ($r = -0.533$, $P = .016$) as well as gestational age ($r = -504$, $P = .023$).[267] A birth weight of at least 1,500 g was achieved at a BUN <17.9 μmol per L (49 mg per dL) and a gestational age of at least 32 weeks was achieved at a BUN <17.1 μmol per L (48 mg per dL). Thus, the authors recommended adequately intensified dialysis to maintain the BUN <48 mg per dL. In the most recent and largest series to date wherein dialysis was increased from three to four

59.3 Series Reporting on Greater than 20 Pregnancies in Hemodialysis Patients

Year	Geographic Region	Terminations	Losses	Live Births
1980[262]	Europe	39%	38%	23 %
1992[263]	Saudi Arabia	0%	63%	37%
1994[256]	United States	8%	52%	37%
1998[255]	United States	11%	46%	42%
1999[386]	Japan	19%	24%	49%
2009[267]	Japan	–	36%	64%
2010[268]	Brazil	–	13%	87%

to six times weekly, 52 pregnancies with an 87% overall successful birth rate was described.[268] Mean gestational age was noted to be 32.7 ± 3.1 weeks and birth weight was 1,554 ± 663 g. A summary of pregnancy outcomes from studies with >20 pregnancies is displayed in Table 59.3. Obvious trends include the decreased rate of therapeutic abortions likely reflecting a change in counselling practices over time secondary to an observed improved live birth rate as the decades pass and dialysis is routinely intensified.

In the early 1980s, the first reported outcomes of pregnant women on chronic ambulatory peritoneal dialysis (CAPD) were mixed with a successful pregnancy delivering at 33 weeks' gestation[269] as well as a reported intrauterine fetal death at 30 weeks' gestation.[270] The largest, early series by Redrow et al. concluded peritoneal dialysis to be superior to hemodialysis, and therefore, the preferred option for young pregnant women, but their own data did not clearly support that conclusion.[271] They described 14 pregnancies of which four ended in spontaneous abortion. The spontaneous losses occurred in one woman on established CAPD and in another woman on established hemodialysis, but the other two losses occurred in hemodialysis patients who were switched to peritoneal dialysis to potentially improve their pregnancy outcome. Another patient had three failed attempts to switch from hemodialysis to peritoneal dialysis due to drainage failure, eventually delivering a preterm, small for gestational age baby weighing 780 g. Of the remaining nine pregnancies, four were patients approaching ESRD who were started on either peritoneal dialysis (n = 2) or hemodialysis (n = 2), and therefore had significant residual renal function whereas established peritoneal and hemodialysis patients accounted for only five patients. Of interest, the three established peritoneal dialysis patients delivered babies weighing 1,065 to 1,720 grams between 32 and 34 weeks' gestation whereas the hemodialysis patients delivered at 35 and 36 weeks' gestation babies weighing 2,044 and 2,218 g, respectively. Subsequent case reports and series continued to demonstrate mixed results with the vast majority of patients conceiving prior to the initiation of peritoneal dialysis, and therefore having residual renal function.[272–283] Although early registry data from the United States did not document a statistically significant live birth rate in peritoneal versus hemodialysis patients,[255,284] a later single-center series noted worse outcomes in peritoneal versus hemodialysis patients.[285] Numbers of peritoneal dialysis patients, however, are typically few in single-center experiences.[285,286]

In addition to the potential maternal and fetal complications already described in hemodialysis patients, a number of maternal complications are unique to peritoneal dialysis. Abdominal fullness, discomfort, catheter drainage difficulties, and polyhydramnios necessitating a progressive decline in fill volumes have been described.[287] Bloody dialysate can herald an obstetrical catastrophe including placental abruption[275] or can be secondary to trauma to the expanding uterus from the peritoneal dialysis catheter,[282,288] and has been documented to be severe resulting in significant maternal morbidity with fetal demise.[288,289] Preterm delivery, premature rupture of membranes, and stillbirth have also been documented to occur secondary to acute peritonitis.[278,280,290]

A pregnant woman on either intensive hemodialysis or peritoneal dialysis requires meticulous follow-up. Fetal follow-up includes careful screening for congenital anomalies and follow-up of fetal growth. Amniotic fluid and cervical status also need careful assessment and follow-up. Issues for maternal care include the careful follow-up and supplementation of electrolytes, vitamins, and minerals as well as the management of anemia, volume status, and blood pressure.

Thus, care is best delivered by a dedicated team including nephrologists, obstetricians, and a full multidisciplinary staff.

Renal Transplantation

The first successful pregnancy in a renal transplant recipient occurred in 1958 with the birth of a 3,300-g, term, male infant.[291] Since that first successful pregnancy, there have been over 15,000 more reported in the literature. Similar to native kidneys, allografts accommodate to pregnancy with an increase in kidney volume[292] as well as an increase in GFR and enhanced creatinine clearance, 34% on average ranging from 10% to 60% with better allograft function prepregnancy predicting more robust pregnancy accommodation.[293] The anatomic increase in renal size is also associated with a better pregnancy outcome.[292] Pregnancy outcomes in women with renal allografts, therefore, are also dependent on baseline kidney function, the degree of proteinuria, and the frequent coexistence of hypertension and diabetes, which governs the kidney's ability to accommodate to pregnancy. Other additional issues that must also be carefully considered to ensure a successful outcome include the timing of pregnancy to minimize the risk of rejection, the careful management of various immunosuppressive agents, and the careful monitoring and treatment of potential infectious complications.

Outcome data, by and large, come from a multitude of single-center experiences that span the globe[294–301] along with a number of sizable registries including the National Transplantation Pregnancy Registry (NTPR),[302] the United Kingdom (UK) Transplant Pregnancy Registry,[303] and the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry.[304] Each has their own potential sources of bias and is incomplete with respect to capturing the entire population and/or relevant variables. The National Transplantation Pregnancy Registry includes data from over 1,200 subjects. Although the largest of the three registries, the data is self-reported. The other two registries are smaller, but are reported by health care practitioners and therefore are more complete and less prone to reporting errors of possible adverse outcomes. Regardless, as summarized in Table 59.4, all three report a similar live birth rate ranging from 73% to 79%, and pregnancy-related complications remain more common than the general population with the UK Transplant Pregnancy Registry reporting approximately half of all pregnancies ending preterm (<37 weeks' gestation) with a low birth weight (<2.5 g). The vast majority of untoward outcomes are secondary to superimposed preeclampsia with rates that range from approximately 25% to 30%.

Risk factors for poor outcome do not differ drastically from those that hamper a favorable outcome in women with native kidney disease. Further, the literature is similarly flawed by the use of serum creatinine to predict pregnancy outcome and cognizance is required to counsel women who may have more significant renal dysfunction than evident from serum creatinine alone. Regardless, the worst pregnancy outcomes are noted in women with poor

TABLE 59.4 **Pregnancy Outcome Data from Transplant Registries**

	NTPR	UK	ANZDATA
Live births	882 (73%)	149 (79%)	444 (76%)
Spontaneous abortions	NA	21 (11%)	52 (9%)
Stillbirths	NA	6 (4%)	14 (2%)
Mean gestational age	36.5 ± 2.7	35.6 ± 0.3	NA
Birth weight	2668 ± 784	2316 ± 80	NA
Preterm delivery (<37 weeks)	NA	61 (50%)	NA
Preeclampsia	≈29%	18 (36%)	27%
Deterioration in SCr	NA	14 (24%)	NA
Low birth weight (<2.5 g)	NA	53 (52%)	NA
Rejection	2%–4%	NA	NA

NTPR, National Transplantation Pregnancy Registry[302]; UK, United Kingdom Transplant Pregnancy Registry[303]; ANZDATA, Australian and New Zealand Dialysis and Transplant Registry[304]; NA, not available; SCr, serum creatinine.

allograft function prior to conception as defined by a serum creatinine >150 μmol per L (>1.7 mg per dL) and urine protein >500 mg per day.[302–304] Further, comorbidities, including hypertension, that necessitate more than a single therapeutic agent, and diabetes can further compromise outcome. A recent acute rejection episode is deemed a relative contraindication to pregnancy. These same risk factors that compromise pregnancy outcomes also predict accelerated postpartum deterioration in graft function, but prepregnancy baseline graft function and a rising serum creatinine during pregnancy appear to be the most important predictors of accelerated postpartum graft loss after adjustment for immunosuppressive therapy, hypertension before and during pregnancy, and preeclampsia.[302] In women who experienced postpartum graft loss, the mean prepregnancy serum creatinine was 1.5 ± 0.6 mg per dL and the creatinine during pregnancy was 1.7 ± 0.9 mg per dL compared to 1.3 ± 0.4 mg per dL and 1.2 ± 0.4 mg per dL, respectively, among women who did not have postpartum graft loss.[302] Thus, these women need to thoroughly understand the potential for both a poor pregnancy outcome along with the potential for graft compromise if pregnancy is considered in the presence of compromised graft function.

Repeated pregnancies in healthy women with a well-functioning graft do not hasten graft loss and can be encouraged.[302] At present, there is very limited data with respect to in vitro fertilization in renal transplant recipients and preliminary results are not encouraging, but this is gathered from self-reported data and therefore poor outcomes might be over-represented.[302]

Similar to intensive hemodialysis, successful kidney transplantation restores ovarian function and fertility. However, a recent report from USRDS data detailing 16,195 female transplant recipients noted decreasing pregnancy rates, and therefore live birth rates, over time that did not parallel the general population.[305] A variety of potential explanations for this finding exist including the introduction of mycophenolate mofetil and the realization of its teratogenic potential, prompting both physicians and patients to use appropriate contraception. Another possibility is the longer waiting times for cadaveric transplantation that could result in the loss of a woman's reproductive window or damage from other underlying comorbidities like hypertension and diabetes. In this same study, risk factors for increased rates of fetal loss included African American race, diabetes, and a lower socioeconomic status. An aging female recipient population with other comorbidities, therefore, has important implications for pregnancy timing.

Historically, the optimal timing for pregnancy post-transplantation was stated to be 2 years. This allowed for stabilization of graft function and the lowering of immunosuppression doses. However, the data from the USRDS noted only a borderline increase in pregnancy loss during the first as compared to the third year after transplantation, suggesting the historical 2-year waiting period might be overly conservative.[305] Another small study of 74 patients compared pregnancy outcomes in women who conceived within the first year after transplantation (n = 11) and compared them to women conceiving after 1 year (n = 63) noting no difference in the live birth rate.[306] In fact, there was a trend toward higher rates of preterm delivery and smaller babies in the women further out from transplantation suggesting that timing of pregnancy has to be carefully balanced by maternal age and comorbidities. We typically recommend women wait a year after transplantation prior to initiating a switch to pregnancy safe immunosuppression, but this warrants careful case by case consideration. Pregnancy itself does not cause acute rejection, but changing to pregnancy-safe immunosuppression requires cautious surveillance. Although there are no immunosuppressive medications adequately tested in pregnancy to be designated by the U.S. Food and Drug Administration (FDA) as pregnancy category A, there are a number of medications wherein the risk-benefit ratio is appropriate for use in pregnant women. These include prednisone, azathioprine, and the calcineurin inhibitors, but not mycophenolate mofetil.[307]

Only a fraction of the oral dose of prednisone reaches the fetus and, therefore, at the low doses that one would expect to be using in a stable transplant recipient, prednisone is considered a safe option. Higher doses, however, may not be completely without risk, as first trimester exposure may be associated with an increased risk of cleft palate (approximately 3/1,000 compared to 1/1,000 in the general population) and exposure later in pregnancy can be associated with an increased potential for the development of gestational diabetes and exacerbation of hypertension. Azathioprine requires the enzyme inosinate pyrophosphorylase for conversion to its active metabolite, an enzyme lacking by the fetal liver. Both cyclosporine and tacrolimus can be safely used in pregnant women, but the metabolism of these medications can change, necessitating close follow-up of blood levels. Cyclosporine metabolism tends to increase and therefore higher doses may be required whereas tacrolimus metabolism may be decreased by inhibition of hepatic cytochrome P450 enzymes. Although smaller babies have been reported in conjunction with use of these medications, it is not clear if this is a direct drug effect or secondary to the underlying disease state that necessitated use of these medications. The calcineurin inhibitors do have the potential to exacerbate hypertension and can be nephrotoxic even at therapeutic levels in our experience. Mycophenolate mofetil has now clearly emerged as a human teratogen with an identifiable pattern of malformations—craniofacial (microtia or anotia, absent auditory canal, cleft palate, hypertelorism) and limb anomalies (Fig. 59.4).[308] In pregnant transplant recipients (n = 48) exposed to a wide range of doses of mycophenolate mofetil, birth defects were noted in 11 women resulting in an incidence of 22.9%.[302] Thus it is recommended women initiating mycophenolate mofetil have a negative pregnancy test and utilize appropriate contraception. Those who desire pregnancy should be off mycophenolate mofetil at least 6 weeks prior to conception. Although human data

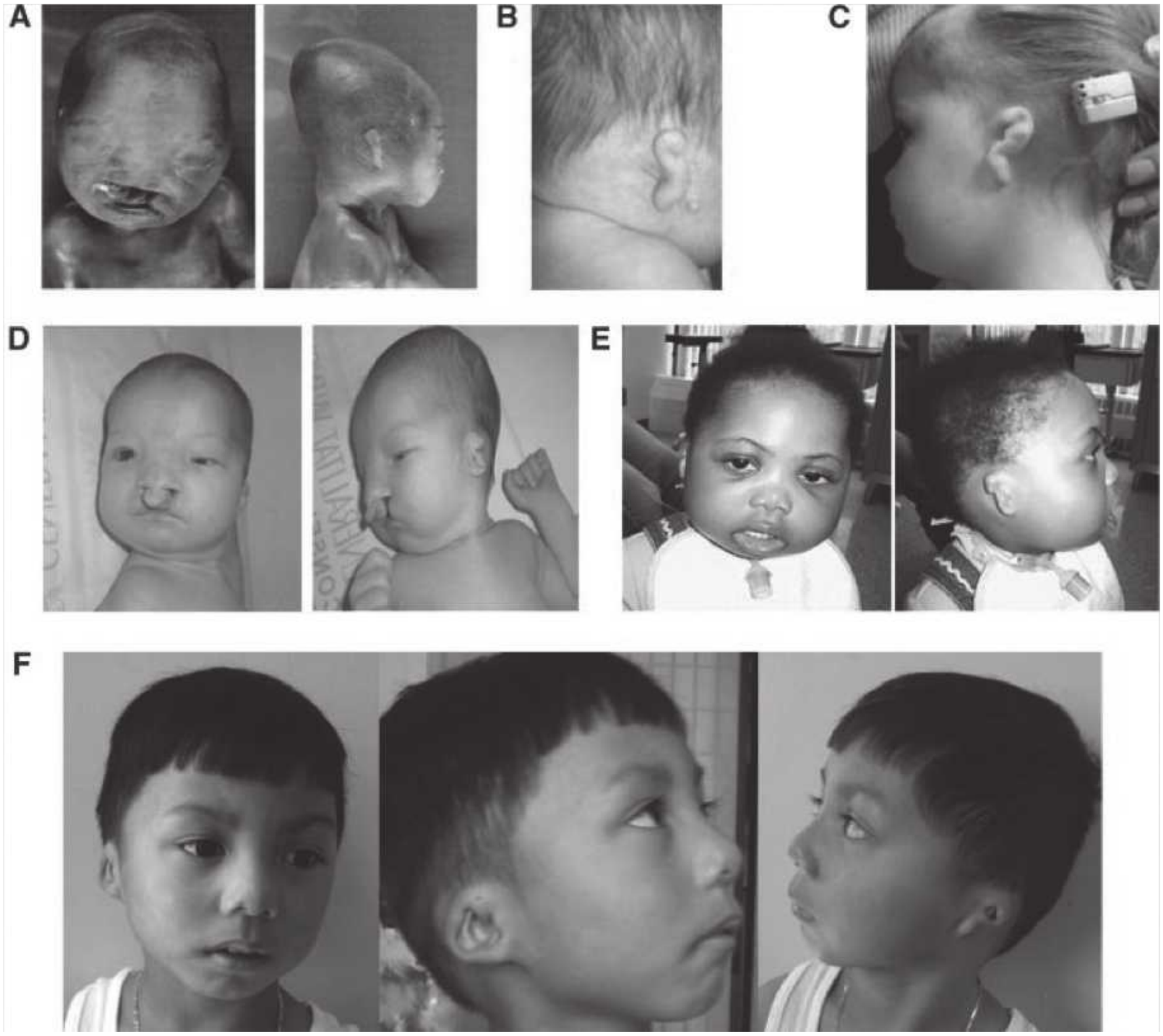

FIGURE 59.4 Characteristic fetal malformations following exposure to mycophenolate mofetil include microtia or anotia, absent auditory canal, cleft palate, hypertelorism, and limb anomalies. (Reprinted with permission from Anderka MT, Lin AE, Abuelo DN, et al. Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature. *Am J Med. Genet A* 2009;149A:1241–1248.)

are lacking, rapamycin is highly teratogenic in animals and is therefore contraindicated in pregnancy.

Typically, drugs that can be used safely during pregnancy can also be used during breastfeeding. Minimal amounts of prednisone and azathioprine are actually found in breast milk. Thus, the potential for neonatal immunosuppression and future carcinogenesis is largely theoretical. Cyclosporine is now deemed compatible with breastfeeding as a completely breastfed infant would likely receive no more than 2% of the mother's weight-adjusted dose.[309] Although breastfeeding on tacrolimus is often discouraged, even less is passed to the infant (0.5% of the mother's weight adjusted dose).[310] Regardless, there are rare case reports that describe detectable and even therapeutic levels in the neonate.[311] Not surprisingly, there are no data to guide the safety of mycophenolate mofetil or rapamycin use during breastfeeding and therefore this practice should be avoided.

The mandated immunosuppressed state of pregnant women with renal allografts places these women at increased risk for infections. Ongoing close surveillance for bacterial infections, including regular urine cultures, for example, along with prompt treatment is necessary. A number of potential infectious complications can also result in serious neonatal compromise, the most common and significant of which is primary or reactivated cytomegalovirus (CMV) infection during pregnancy.[312] Primary maternal infection has a 30% to 40% risk of intrauterine transmission and a 20% to 25% risk for the development of fetal sequelae including microcephaly, hearing loss, visual impairment, mental retardation, as well as more subtle learning disabilities.[313]

The transmission rate to the fetus is significantly lower in reactivated CMV disease. The diagnosis of primary maternal CMV infection is based on the de novo appearance of viral specific IgM or IgG if previously known to be IgG seronegative. The prenatal diagnosis of fetal infection should be based on presence of the virus in amniotic fluid. The diagnosis of secondary infection is based on a significant rise in IgG antibody titre and the risk–benefit ratio of amniocentesis in cases of secondary infection must be considered more carefully given the lower rate of transmission. The incidence of primary or reactivated infections in transplant recipients, however, is largely unknown with very few cases reported to the National Transplant Registry.[302] Further, it is not clear if rates of transmission perhaps are higher given the immunosuppressed state of these patients. It is our practice to establish antibody status at the outset of pregnancy and follow titers during each trimester and in women who develop an influenza-like infection during pregnancy. Ganciclovir has been noted to be teratogenic in high doses in animal studies and to date there are only case reports to guide its use in humans.[314]

Renal Donation

Although renal donation is universally encouraged as a safe and altruistic endeavor, confusing data has emerged with respect to future pregnancy complications in young female donors that warrants further investigation. In a study utilizing the Norwegian Birth Registry, 326 kidney donors were identified and pregnancy outcome before (n = 620) and after (n = 106) were compared.[315] Although no significant difference was noted in the incidence of preeclampsia between the groups, a generalized linear mixed model demonstrated a significantly higher incidence of preeclampsia in postdonation pregnancies compared to predonation pregnancies (5.7% versus 2.6%, P =.026). A second study that collected survey data from 1,769 female donors identified 98 donors with pregnancies both before and after donation.[316] They noted that postdonation pregnancies were significantly less likely to have gone to term (73.7% versus 84.6%, P = .0004) and significantly more likely to have resulted in fetal loss (19.2% versus 11.3%, P <.0001) likely due to increased rates of gestational hypertension (5.7% versus 0.6%, P <.0001) and preeclampsia (5.5% versus 0.8%, P <.0001). As these studies are not without limitations, such as the confounder of advancing age between pregnancies, kidney donation in young women of childbearing potential warrants further research.

ACUTE KIDNEY INJURY IN PREGNANCY

The approach to and assessment of AKI should not differ from the nonpregnant population with attention paid to potential prerenal, renal, and postrenal etiologies. However, there are conditions that can impair kidney function that are either unique to pregnancy or worsened by the gravid state, and therefore, warrant further discussion. The main etiologies of AKI in a recent assessment of 55 obstetric cases requiring dialysis included pregnancy-related hypertensive conditions and the thrombotic microangiopathies.[317] Other potential pregnancy-specific etiologies of AKI include acute fatty liver of pregnancy and rarely acute cortical necrosis secondary to shock from obstetrical hemorrhage, severe sepsis, or an amniotic fluid embolus.

Preeclampsia

Affecting 5% to 7% of pregnancies, preeclampsia is easily the most common glomerular-based disease and remains the leading cause of infant and maternal morbidity and mortality worldwide.[318] Preeclampsia is a disease of the glomerular endothelial cell characterized by decreased GFR, proteinuria, and hypertension that can evolve to include coagulopathies and affect liver function (HELLP syndrome) as well as cause seizures (eclampsia). The pathophysiology of preeclampsia is best understood at the level of the kidney wherein novel insights into the release of antiangiogenic factors from an abnormal placenta that are injurious to the maternal endothelium as well as abnormalities in the RAS have elucidated the mechanisms responsible for the clinical syndrome. With very rare exceptions, preeclampsia is limited to the second half of the gestation and the early postpartum period. Hypertension, GFR depression, and proteinuria typically resolve rapidly after delivery of the placenta.

As compared to the healthy gravid state, preeclampsia presents with variable degrees of renal insufficiency. A study that utilized precise physiologic measurements in conjunction with morphometric analysis of postpartum biopsies to examine the determinants of the GFR in 13 women with preeclampsia and 12 healthy gravid controls noted GFR to be significantly depressed in women with preeclampsia compared to healthy controls (91 versus 149 mL/min/1.73 m^2, respectively; P <.0001) without detected differences in either RPF or π_{GC}.[319] As compared to tissue obtained from healthy female kidney transplant donors, the morphometric analysis revealed numerous significant ultrastructural differences including swelling of the endothelial cells, the presence of subendothelial fibrinoid deposition, and mesangial cell interposition (Fig. 59.5). Scanning electron microscopy was utilized to characterize the endothelial fenestral dimensions wherein a substantial decrease in endothelial permeability was noted (Fig. 59.6). The authors concluded that a reduction in density and size of the endothelial fenestrae and subendothelial accumulation of fibrinoid deposits lowered glomerular hydraulic permeability whereas mesangial cell interposition also likely decreased available surface area for filtration in patients with preeclampsia compared to controls, resulting in a depression of K_f that was proportional to the decrease in GFR without a hemodynamic basis.

These findings were confirmed by a more recent study that used a semiquantitative scale to grade the endotheliosis present on biopsy specimens taken from women with

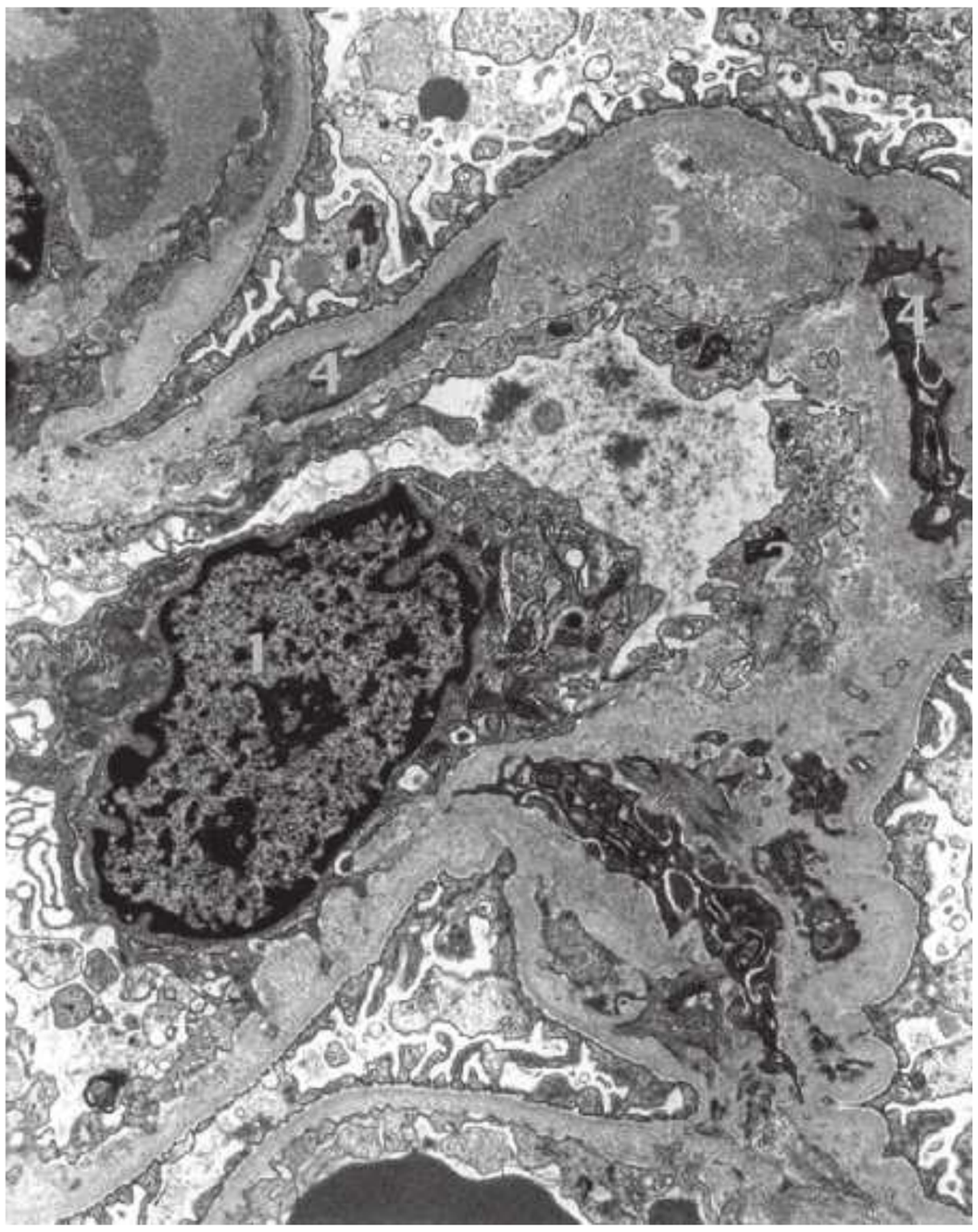

FIGURE 59.5 Kidney biopsy specimen revealing the characteristic findings associated with preeclampsia including swelling of the endothelial cells, the presence of subendothelial fibrinoid deposition, and mesangial cell interposition. (Reprinted with permission from Lafayette RA, Druzin M, Sibley R, et al. Nature of glomerular dysfunction in pre-eclampsia. *Kidney Int.* 1998;54(4):1240–1249.)

preeclampsia approximately 1 week prior to delivery.[10,320] The authors noted moderate to severe endotheliosis in all women with significant hypertension and proteinuria prior to delivery and found a strong linear trend between the degree of endotheliosis and cystatin C. Although, as discussed, issues do exist with the use of cystatin C as a marker for GFR in pregnancy, this study also supports the notion that the basis for hypofiltration in preeclampsia is largely secondary to structural changes in the glomerulus as opposed to renal vasoconstriction. Others, however, have suggested a modest decrease in renal plasma flow in women with preeclampsia compared to normotensive women in the third trimester.[321,322]

Given preeclampsia is largely understood as an endothelial disease, the mechanism of nephrotic range proteinuria was difficult to reconcile prior to the discovery of soluble antiangiogenic factors released from an ischemic placenta, as well as the understanding of crosstalk between the glomerular endothelial cell and the podocyte. Recent studies have described the release of soluble fms-like tyrosine kinase 1 (sFlt-1), which binds placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), potent angiogenic factors that play critical roles in the maintenance of a healthy vascular endothelium, preventing their interaction with receptors located on the vascular endothelial cells.[323]

In the kidney, podocytes have been shown to be the site of VEGF production in vivo. VEGF receptors are expressed on the endothelial cells suggesting that the VEGF produced by the podocyte travels against the flow of filtrate to its receptor. More recently, VEGFR-1 and neuropilin-1 have been shown to be present on podocytes, both in vitro and in vivo. Thus, paracrine and autocrine pathways could very well exist that promote fenestration formation and govern the integrity of the glomerular filtration barrier,[324,325] and tight regulation of VEGF signalling is necessary to maintain a healthy glomerulus. Mice with a homozygous deletion in podocyte specific VEGF fail to develop a filtration barrier, a uniformly lethal condition.[326] Podocyte-specific heterozygosity, on the other hand, resulted in glomerular endotheliosis and proteinuria, a lesion reminiscent of human preeclampsia. In another rat model wherein adenoviral overexpression of sFlt-1 produced hypertension, proteinuria, and glomerular endotheliosis, VEGF121 treatment improved the clinical symptoms as well as renal histology.[327] Human data linking endothelial injury with enhanced glomerular permeability in preeclampsia includes two studies. The first study noted decreased glomerular expression of podocyte-specific proteins, nephrin, and synaptopodin in renal tissue from autopsies of women who died from preeclampsia compared to women who died from trauma.[328] The same authors then went on to demonstrate that podocyturia was associated with preeclampsia and correlated with the degree of proteinuria.[329] One can therefore postulate that in preeclamptic women,

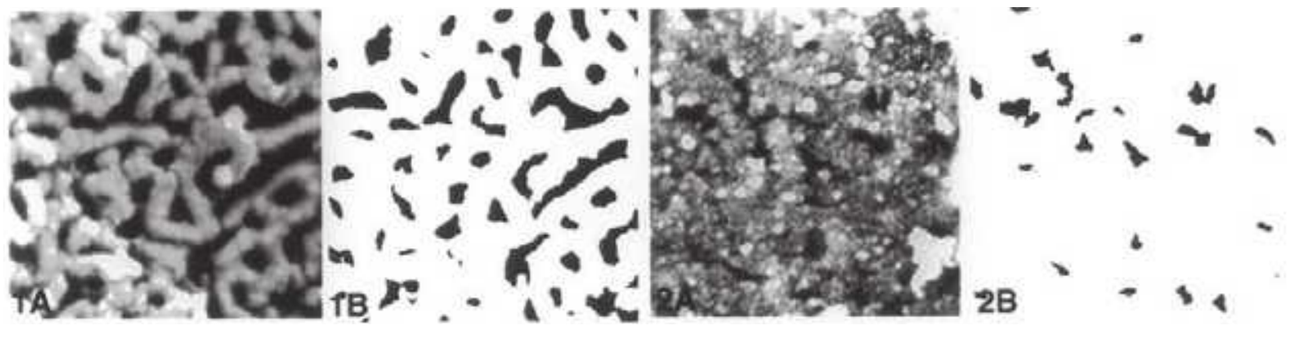

FIGURE 59.6 Scanning electron microscopy comparing the endothelial fenestral dimensions in a healthy transplant donor and a woman with severe preeclampsia. (Reprinted with permission from Lafayette RA, Druzin M, Sibley R, et al. Nature of glomerular dysfunction in pre-eclampsia. *Kidney Int.* 1998;54(4):1240–1249.)

high levels of circulating sFlt-1 systematically deprive the glomeruli of local VEGF signalling. sFlt-1 molecules displace locally derived VEGF produced by the podocyte reducing both size and density of fenestrations to cause endotheliosis and damage the fenestral glycocalyx, a potentially important part of the barrier to albumin permeability.

The hypertension associated with preeclampsia can also certainly be explained by the presence of soluble antiangiogenic factors. Abnormally increased levels of sFlt-1 have been demonstrated in women with gestational hypertension albeit with levels not as high as in women with preeclampsia.[330] Further, soluble Endoglin (sEng), also released from an ischemic placenta, deleteriously affects vascular tone by blocking the activation of endothelial nitric oxide synthase.[331] Recently, the role of the RAS in blood pressure control in pregnancy has received more attention. In contrast to the healthy gravid state, RAS components in preeclampsia are depressed, yet enhanced vascular sensitivity to angiotensin has been noted. Angiotensin infusions have resulted in a more dramatic hemodynamic response in women destined to develop preeclampsia as compared to healthy pregnant controls.[332,333] The exact mechanism underlying the angiotensin resistance in normal pregnancy is still unclear, but studies have shown that plasma and urine levels of ANG(1-7) are increased in pregnancy.[90,334] This potential counter regulator of angiotensin is also significantly decreased in preeclamptic women as compared to healthy gravid women.[90] Alternatively, upregulation of the AT1 receptor has been demonstrated on the decidual or maternal side of the placenta.[335] Finally, recent studies in women with preeclampsia have also identified circulating autoantibodies belonging to the fraction of IgG antibodies that are capable of stimulating the angiotensin 1 receptor.[336,337] In preeclamptic women, they may induce heterodimerization between the angiotensin I receptor for the vasopressor angiotensin II and the bradykinin 2 receptor for the vasodilator bradykinin. Expression of these heterodimers may result in an increased responsiveness to angiotensin II.[338]

New insights into the pathogenesis of disease also provide novel diagnostic opportunities (Fig. 59.7). Both the soluble antiangiogenic factors and the AT1 autoantibody have been shown to predate the clinical syndrome, but the

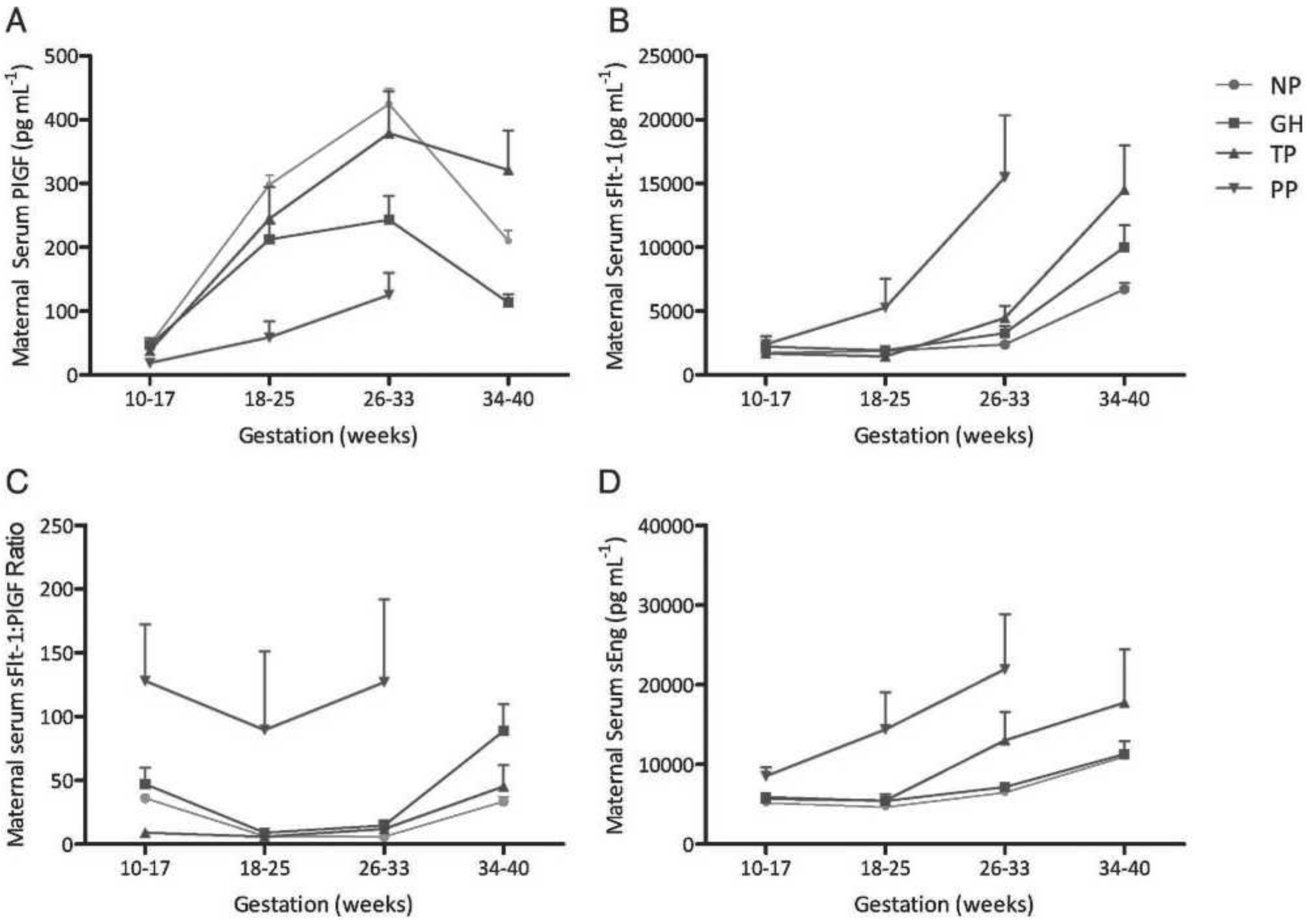

FIGURE 59.7 Gestational changes of maternal serum PlGF, sFlt-1, Flt-1/PlGF ratio, and sEng in normotensive pregnancies (NP), gestational hypertension (GH), term preeclampsia (TP), and preterm preeclampsia (PP). (Reprinted with permission from Noori M, Donald AE, Angelakopoulou A, et al. Prospective study of placental angiogenic factors and maternal vascular function before and after preeclampsia and gestational hypertension. *Circulation*. 2010;122(5):478–487.)

soluble antiangiogenic factors provide more accurate discrimination between cases and healthy gravid controls.[339] Increased sFlt-1 and sEng along with decreased serum and urine PlGF and VEGF levels results in an adjusted odds ratio of 31.6; 95% CI 10.7–93.4 for the development of early onset preeclampsia.[340] The antiangiogenic factor assays can be used to discriminate preeclampsia from other etiologies of renal compromise and have proven useful in a variety of clinical scenarios including presumed glomerulonephritis,[341] lupus,[342] and in patients on hemodialysis.[343] Most recently, a small pilot study utilized dextran sulfate cellulose apheresis treatments to reduce circulating sFlt-1 levels in a dose-dependent fashion.[344] Treatments in three women with severe early onset preeclampsia lowered circulating sFlt-1 levels, reduced proteinuria, and stabilized blood pressure without apparent adverse events to mother or fetus. Further studies will determine the feasibility of using clearance techniques to possibly prolong pregnancy and improve fetal outcomes.

Chronic kidney disease is a risk factor for the development of preeclampsia. Further, preeclampsia may be the disorder revealing the existence of underlying renal disease that is often diagnosed when proteinuria and hypertension fail to subside postpartum, and has been noted to be as high as 20% in some series wherein women developed preeclampsia prior to 30 weeks' gestation.[345] Abnormalities in glomerular VEGF expression have been linked to glomerular diseases other than preeclampsia and may specifically increase susceptibility in diseased populations. Di Marco and colleagues assayed sFlt1 levels in 130 patients with CKD, stages 3 to 5, and in 56 age and gender matched controls.[346] The sFlt1 levels were higher in patients with CKD and exclusively associated with renal function. A reverse transcription/polymerase chain reaction assessment of glomerular and tubular VEGF expression in patients with type II diabetes revealed progressive decline in VEGF expression with more severe glomerular and tubulointerstitial disease.[347] One can easily conceptualize based on such data why women with diabetic nephropathy are at a substantially increased risk for the development of preeclampsia. However, the levels of VEGF expression likely vary between different glomerulopathies and can vary with the stage of progression. Further, a distinction has to be made between circulating VEGF levels and glomerular VEGF bioactivity. Moreover, regulation of the bioactivity of glomerular VEGF may be dependent on other factors such as TGF-beta, NO, mechanical strain, and hyperglycemia.[348] Future research should attempt to elucidate the levels of angiogenic and antiangiogenic factors that underlie the complex interaction between preeclampsia and kidney disease as these interactions are necessary to better understand the physiologic basis for the increased risk of preeclampsia noted in women with kidney disease, and may allow for the measurement of antiangiogenic factors to play a role in the often complex diagnostic dilemmas that practicing clinicians regularly face.

The clinical syndrome of preeclampsia resolves with delivery of the placenta, but recently is has become clear that placental disease is associated with long-term health consequences. The first study to describe the relationship between preeclampsia and cardiovascular disease utilized the Norwegian Medical Birth Registry.[349] Although this study did not show an increased risk of death among women with preeclampsia who delivered at term, it did show almost a threefold increased risk of death with an eightfold increased risk of cardiovascular death in women who delivered prior to 37 weeks, interpreted as a surrogate marker for more severe disease. These findings have been confirmed and expanded by other studies where, in addition to an increased risk of cardiovascular disease, an increased risk of cerebrovascular disease, peripheral vascular disease, and ESRD was also noted.[350,351] Of interest to nephrologists is the concept of whether preeclampsia as a secondary insult hastens the progression of underlying glomerular-based disease. The variable etiologies of kidney disease preceding ESRD in the aforementioned study suggests that it might,[351] but a subsequent study did not confirm this hypothesis.[351] Clearly further data that examine the impact of expectant management in women with kidney disease and superimposed preeclampsia prior to delivery is necessary.

Thrombotic Microangiopathies

The thrombotic microangiopathies include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), disorders characterized by disseminated occlusion of arterioles and capillaries by agglutinated platelets with resultant ischemia. Both disorders present with hemolytic anemia, thrombocytopenia, and renal insufficiency, whereas neurologic abnormalities and fever may also accompany TTP. With recent insights into the pathophysiology, TTP is becoming well understood in the context of pregnancy and, more recently, the pregnancy outcomes in atypical HUS associated complement gene mutations have been described.

TTP is a rare condition with incidence rates across the globe ranging from 2.2 to 6.5 per million in the United Kingdom and the United States, respectively.[352] It is more common in women who represent approximately 70% of cases.[353] Black race and obesity also appear to be risk factors, and pregnancy is a well-described precipitant[353] with TTP occurring in approximately 1 in 25,000 pregnancies.[354] As pregnancy in some way incites the cascade of endothelial disruption resulting in microthrombi, a significant percentage of young women present for the first time during pregnancy even in the presence of congenital or familial disease.[355,356]

It is now understood that the pathophysiology involves either a congenital absence of, or an immunoglobulin G (IgG) autoantibody inhibitor to ADAMTS13 (A Disintegrin And Metalloproteinase with ThromboSpondin type 1 motifs 13) normally produced by the liver, platelets, vascular endothelial cells, and the renal podocytes. This metalloproteinase specifically cleaves unusually large multimers of von Willebrand factor (ULVWF) preventing interaction of these

large multimers with platelets and the subsequent vascular occlusion characteristic of the syndrome. Plasmapheresis inhibits platelet aggregation, replenishes absent ADAMTS13, and/or removes pathogenic antibodies. There are a number of theories why pregnancy might pose a heightened risk for the development of TTP including the procoagulant state that accompanies pregnancy as well as the potential effect of estrogen on the level of ADAMTS13, which progressively decreases throughout pregnancy to a nadir in the early postpartum period. In the largest, most complete patient registry of TTP-HUS from Oklahoma City, pregnancy accounted for 26 of the 352 cases collected over approximately 15 years and the vast majority presented in the third trimester and early postpartum period.[353]

Establishing a diagnosis of TTP with rapid initiation of treatment is critical to decrease morbidity and mortality. Its typical presentation in the later stages of pregnancy and the early postpartum period can result in a diagnostic dilemma as preeclampsia complicated by the HELLP syndrome presents with similar features. Further, the two entities are not mutually exclusive and may very well coexist. A systematic review of the literature that summarized the outcome in 166 reported cases spanning 1955 to 2006 noted the coexistence of TTP with preeclampsia/HELLP syndrome in 28 cases without obvious laboratory discriminants[357] and other careful case series reported a true association as opposed to a mistaken diagnosis.[358] Further, placental pathology in cases of TTP describes similar features as noted in preeclampsia including small placental size, vascular thrombosis, infarction, and accelerated villous maturation in conjunction with zones of vascular dilatation and constriction consistent with aneurysmal dilatation of the spiral arteries on the maternal side of the placenta, a finding distinctive of TTP.[359] Finally, ADAMST13 levels do fluctuate significantly between and within patients,[360] levels have been demonstrated to be lower in patients with HELLP syndrome than in healthy gravid patients[361] and severe deficiency ($<5\%$), wherein one is confident with respect to the diagnosis, is certainly not uniform in reported pregnancy cases.[74,358,362] Thus, without useful laboratory assays to definitively diagnose these entities it is difficult to definitively distinguish them and it is not entirely clear how often they coexist. Although more common in the later stages of pregnancy, TTP can certainly occur at any stage of pregnancy as fatal and nonfatal cases in the first trimester have been documented,[353,363] as have cases following a molar pregnancy[364] and first trimester therapeutic abortion.[365] Thus, a high level of clinical acumen with mindfulness of this rare disease as a possibility is necessary irrespective of the timing in pregnancy as misdiagnosis is common and improved outcome has been demonstrated with the shortest latency from diagnosis to therapy.[366]

Prior to modern treatment with plasmapheresis mortality approached 100%. Despite better outcomes with treatment, TTP remains a serious condition with significant potential morbidity and mortality for both mother and fetus. Maternal morbidity has been documented in case reports and case series, but the exact incidence is unclear. In the systematic review that spanned six decades, maternal morbidity decreased over time, but remained substantially higher in women experiencing an initial TTP compared to women with recurrent disease (26% versus 10.7%, respectively) as well as in women diagnosed with coexistent preeclampsia/HELLP syndrome.[357] Maternal morbidity is also not negligible with significant renal insufficiency and even subtle cognitive deficits noted in survivors.[354,367] The stillbirth rate was not significantly different in patients with a first presentation of TTP compared to recurrent disease (32 versus 44%, respectively),[357] and both fetal growth restriction and preterm delivery are common.[354] However, documented successful outcomes with therapy have been documented even with congenital[356] and early onset disease.[363] Thus, clinicians are often in the position of counselling with respect to risk of pregnancy flare in idiopathic disease and recurrence in cases where the first presentation occurred during pregnancy.

The most comprehensive study with respect to the potential occurrence during pregnancy comes from the Oklahoma TTP-HUS Registry wherein they compared their data to the existing literature.[362] In women who recovered from idiopathic TTP, recurrences were reported, but none in association with a subsequent pregnancy. In women with pregnancy-associated TTP, the overall risk of recurrent TTP is reported to be infrequent (14%).[368] The risk of recurrence in congenital TTP, on the other hand, is reported to be 100%,[362] and therefore the detection of severe deficiency of ADAMTS13 levels may assist with pregnancy planning.[369] Overall, the rates in the Oklahoma TTP-HUS Registry are more optimistic than the older literature in general, and differences could be explained by misdiagnosis or a bias to the publication of more severe and complicated cases. There are insufficient data in the literature to comment on the benefit or lack thereof associated with the prophylactic use of maintenance plasmapheresis, immunosuppression, antiplatelet agents, or anticoagulation with respect to pregnancy outcomes.[361,362]

Although more often seen secondary to acute infection (Shigatoxin-producing Escherichia coli O157), HUS can rarely be induced by genetic mutations involving the activation or regulation of the alternative complement pathway triggered by pregnancy. These disorders present clinically with low serum complement levels and predominant renal involvement. Currently, data are limited, but overall maternal outcome appears to be quite poor. Documented HUS cases most frequently present in the postpartum period with severe renal involvement, necessitating dialysis during the acute phase of the disease in 81% with 62% reaching ESRD within a month despite therapy.[370] However, given the late onset of disease, fetal outcomes are reasonable with the vast majority proving uneventful (74.7%). Preeclampsia and fetal loss complicated 7.7% and 4.8% of pregnancies, respectively. Further studies will be needed to better understand these rare presentations of atypical HUS.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is a serious, but rare complication with an estimated incidence between 1 in 7,000 and 1 in 13,000 births.[371,372] With respect to pathophysiology, AFLP is characterized by accumulation of lipids in hepatocytes.[373] Recently, investigators have demonstrated that the fetus may be the source of increased fatty acids due to inherited autosomal recessive genetic mutations from heterozygous parents.[374] Clinically, the management of AFLP must be swift and decisive given the risk of fetal and maternal mortality, 19% and 12% respectively.[375] Yet, a common challenge in prompt identification of AFLP is distinguishing it from preeclampsia or HELLP syndrome. Recently, investigators have highlighted important clinical findings that can aid in clinical decision-making.[376] Although epigastric pain, nausea/vomiting, and jaundice were noted in 60% of women in AFLP, these signs and symptoms were only identified in 5% of women with HELLP syndrome.[376] Furthermore, albumin phosphatase, total bilirubin, and white blood cell count were significantly more elevated in the context of AFLP, whereas glucose, cholesterol, triglycerides, fibrinogen, and antithrombin III were significantly more elevated in the context of HELLP syndrome. However, the conditions were similar with respect to the presence of hypertension and proteinuria.[376] The syndromes can also be distinguished based on complications associated with the disease course. In particular, renal failure is a common complication in AFLP (>70%) and tends to present earlier.[376–378] Altogether, prompt termination of pregnancy (which is the treatment of choice for HELLP syndrome as well) is an important aspect of the management of AFLP as time to termination can affect maternal outcomes.[379] Further interventions including liver transplantation may also be required.[375,380]

Renal Cortical Necrosis

Renal cortical necrosis is an uncommon complication of pregnancy that is primarily noted in developing countries.[381,382] Recently, decrements in the prevalence were reported by investigators in India, citing improvements in medical management of obstetrical complications.[381,383] Commonly reported causes of renal cortical necrosis include septic abortion and hemorrhage from placental abruption.[381,384] The exact pathophysiology is not known, but it is widely accepted that the final common pathway involves renal ischemia. In particular, disseminated intravascular coagulation, a potential source of ischemic injury, has been reported to occur concurrently with renal cortical necrosis.[385] However, previous studies suggest that DIC does not predispose to renal cortical necrosis.[244] Given the low incidence, it is not surprising that there are no recent studies examining this relationship. Although mortality from renal cortical necrosis has decreased,[381] outcomes are still not favorable. In a general cohort of patients with obstetrical and nonobstetrical causes, mortality was 19%, whereas partial recovery of renal function and ESRD occurred in 33% and 50%, respectively.[381]

CONCLUSION

The kidney and its many functions undergo profound physiologic alterations to support a healthy pregnancy so women with significant renal disease may prove higher risk as impaired renal function, proteinuria, and hypertension can compromise this healthy accommodation. Thus, these women require meticulous prepregnancy assessment and effective optimization by nephrologists along with careful pregnancy follow-up by both nephrology and a high risk obstetrician. Further research is necessary to better understand the diseased kidney's ability to accommodate pregnancy and to better understand disease-specific risks. Intensive dialysis regimens may make possible pregnancy in a subset of patients wherein previously that was most unlikely. Finally, recent insights into the pathophysiology of preeclampsia should yield novel diagnostic and treatment opportunities for the most common pregnancy-related complications experienced by women with underlying renal disease.

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