Chronic Kidney Disease and Pregnancy

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Summary: Women with chronic kidney disease (CKD) are at risk for adverse pregnancy-associated outcomes, including progression of their underlying renal dysfunction, a flare of their kidney disease, and adverse pregnancy complications such as preeclampsia and preterm delivery. Earlier-stage CKD, as a rule, is a safer time to have a pregnancy, but even women with end-stage kidney disease have attempted pregnancy in recent years. As such, nephrologists need to be comfortable with pregnancy preparation and management at all stages of CKD. In this article, we review the renal physiologic response to pregnancy and the literature with respect to both expected maternal and fetal outcomes among young women at various stages of CKD, including those who attempt to conceive while on dialysis. The general management of young women with CKD and associated complications, including hypertension and proteinuria are discussed. Finally, the emotional impact these pregnancies may have on young women with a chronic disease and the potential benefits of care in a multidisciplinary environment are highlighted.
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Women with underlying renal disease are among the highest-risk patient populations for adverse maternal and fetal outcomes. Because the kidneys play such a significant role in the maternal accommodation to pregnancy, pregnancy-associated risks increase along with the stage of chronic kidney disease (CKD). Pregnancy is safer when women have only mild renal insufficiency as opposed to advanced renal dysfunction, and when associated hypertension and proteinuria are well managed and controlled. As such, nephrologists should be involved actively in pregnancy planning to assist young women with all types and stages of CKD find the optimal time to consider conception, to provide reproductive counselling, and to carefully prepare them for pregnancy.

In this article, we review the renal physiologic response to pregnancy and the literature with respect to both expected maternal and fetal outcomes in women at various stages of CKD, including those who attempt to conceive while on dialysis. Disease-specific reviews occur in other sections of this special issue. The general management of young women with CKD and associated complications, including hypertension and proteinuria are discussed. Finally, the emotional impact these pregnancies may have on young women with a chronic disease and the potential benefits of care in a multidisciplinary environment are highlighted.

PHYSIOLOGICAL ADAPTATION TO PREGNANCY

A healthy pregnancy requires significant structural, hemodynamic, and renal adaptations to ensure a successful outcome. These alterations, which are noted to begin as early as 6 weeks after conception, include dilatation of the urinary collecting system (calices, renal pelvis, and ureters), a decrease in systemic vascular resistance, as well as a remarkable increase in renal plasma flow (RPF), and hence, the glomerular filtration rate (GFR). Alterations in an array of hormones that govern both vasodilatation and vasoconstriction, including but not limited to nitric oxide, endothelin, and relaxin, as well as alterations to mediators of the renin-angiotensin-aldosterone system (RAAS), are responsible for the maternal accommodation to pregnancy, and the net effect of the pregnancy-associated physiological adaptation includes a vasodilated state. Maternal systemic vascular resistance decreases significantly, leading to a decrease in mean arterial pressure, which typically will decrease in the first trimester of pregnancy to reach a nadir by approximately 18 to 24 weeks' gestation, before returning back to baseline closer to term.[1,2] The resulting decreased afterload contributes to the increase in cardiac output that is characteristic of a healthy human pregnancy. In parallel, increments in renal hemodynamic function are notable with an increased RPF and an augmented GFR.

Glomerular Physiology

Glomerular hyperfiltration is the most notable physiological adaptation to a healthy pregnancy, which is

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manifested clinically by a decrease in the serum creatinine level. Both studies in animal models and human physiologic assessments have provided some insights into the key factors that contribute to the increments in the GFR, represented by the following equation:

$$GFR = \kappa_f \times (\Delta P - \pi_{GC})$$

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 (ie, the product of the surface area available for filtration and the permeability to ultrafiltrate across the three layers of the glomerulus).[3]

In animal models at least, these physiological changes occur irrespective of the presence of underlying kidney damage without any measured increase in intraglomerular pressure (ΔP), as shown in an array of studies that used elegant micropuncture techniques for direct pressure measurements.[4–7] Even in the presence of severely reduced renal mass, there is no evidence of increased intraglomerular pressure (ΔP).[8] Unfortunately, there is an extreme paucity of studies to better illuminate these necessary physiological processes in healthy young women, and none in women with varying degrees of renal insufficiency. Odutayo and Hladunewich[9] previously conducted a systematic review of all studies performed in human pregnancy that used either inulin or iothalamate and p-aminohippurate clearance methodology to assess GFR and RPF at different time points during gestation in relation to a baseline or control group. Studies identified were limited and difficult to compare because all were performed at different time points in gestation with significant differences in study methodology, including differences in patient positioning (semisupine, recumbent, sitting, and left lateral decubitus), inconsistent use of bladder catheterization, and different methods to correct for body surface area.

Irrespective of these methodologic issues, our best understanding of the renal physiological accommodation to pregnancy includes an early gestational increase in both RPF and GFR above nongravid levels, with the former slightly surpassing the latter (41% and 37%, respectively). GFR remains increased until approximately a week postpartum, whereas RPF gradually decreases throughout pregnancy. Consistent with these changes, the filtration fraction decreases slightly in early pregnancy, but then increases consistently throughout pregnancy and remains increased in the early postpartum period (Fig. 1, Table 1). It has been suggested that the increase in GFR is solely a product of increments in RPF in the first and second trimesters,[10] but given the decrease in renal plasma flow in the later half of pregnancy and early postpartum, other changes must account for the maintenance of GFR. Without the ability to directly measure the determinants of GFR, one can only speculate that modest increments in either ΔP, K_f, or both are required because sufficient decrements in oncotic pressure have been excluded as the principal mechanism.[11] All values normalize between weeks 6 and 8 postpartum.[12]

Proteinuria

Alterations in the tubular handling of glucose, amino acids, and uric acid also have been noted in healthy human pregnancies, but the most clinically relevant are the changes noted in protein excretion, which often is attributed to hyperfiltration. In pregnancy, significant protein excretion usually is defined as 300 mg or more
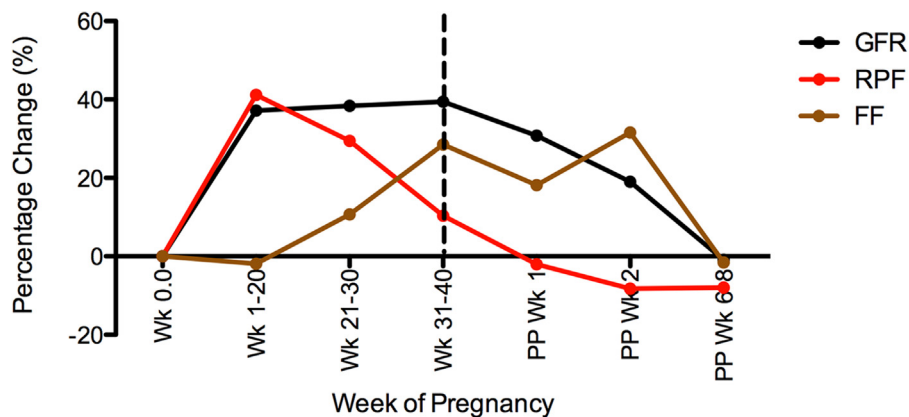

Figure 1. Increments in GFR, RPF, and filtration fraction (FF) as measured by inulin or iothalamate and p-aminohippurate clearance methodology, respectively, at different time points during gestation. Reprinted with permission from Odutayo and Hladunewich.[9]

Table 1. Increments in GFR, RPF, and Filtration Fraction as Measured by Inulin or Iothalamate And P-Aminohippurate Clearance Methodology, Respectively, at Different Time Points During Gestation

Gestational Age (wk)	Glomerular Filtration Rate (mL/min)	Renal Plasma Flow (mL/min)	Filtration Fraction
1-20	37.13	42.21	−1.89
21-30	38.38	29.44	10.68
31-40	39.46	10.37	28.52
PP week 1	34.48	2.44	19.05
PP week 2	19.05	−8.21	31.58
PP weeks 6-8	−0.91	−7.94	−1.59

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in a 24-hour period,[13] double the upper limit of normal in healthy adults. However, this upper limit in normal pregnancy is based on relatively small studies wherein urine protein or albumin excretion was measured serially throughout pregnancy. In one of the largest studies to date, the 24-hour urinary excretion of total protein and albumin were measured in 270 healthy pregnant women.[14] The reported mean 24-hour protein excretion was 116.9 mg (upper 95% confidence interval [CI], 259.4 mg) and the corresponding 24-hour albumin excretion was 11.8 mg (upper 95% CI, 28.7 mg), with no participants showing overt microalbuminuria (>30 mg/L).[14] Similarly, in a serial study of protein to creatinine ratios in healthy singleton and twin pregnancies, protein excretion increased gradually throughout gestation and was noted to be more pronounced in the twin pregnancies, but not impressively.[15] Another study showed the protein to creatinine ratio exceeded the albumin to creatinine ratio more than might be expected,[16] suggesting that the excretion of an alternate proteinaceous material may be responsible for the small augmentation in total proteinuria noted during a healthy pregnancy and that the method of choice for measurement of proteinuria may factor into this sometimes confusing literature. A study that measured the urine albumin-to-creatinine ratio (ACR) in 193 consecutive healthy pregnancies noted an incremental increase in the ACR with length of gestation, but only 6 women were noted to have an ACR greater than 15 mg/g.[17] As such, to date, studies have not provided evidence for a significant glomerular leak of urine protein in healthy pregnancy, and significant proteinuria or albuminuria should not simply be attributed to the hyperfiltration that accompanies the gravid state.

In summary, the mechanisms governing gestational hyperfiltration in human pregnancy are incompletely understood and increased intraglomerular pressure

(ΔP) cannot be excluded as a potential contributor. Whether intraglomerular hypertension factors into the clinical deterioration noted as pregnancy progresses in many women with underlying kidney disease is unknown. Carefully designed physiological investigations assessing glomerular hemodynamics in both normal pregnancy and in women with underlying renal disease are needed to further our understanding of the hemodynamics of normal pregnancy and inform the processes that may result in the progression of renal dysfunction during pregnancy. Furthermore, there are no studies that attempt to illustrate the mechanisms of increasing proteinuria in women with underlying CKD and proteinuric renal disease, which is a frequent occurrence in this patient population. This remains a diagnostic dilemma for clinicians.

PREGNANCY RISK ASSESSMENT AND COUNSELING BY CKD STAGE

Although the mechanisms for the progression of renal insufficiency and the contributors to adverse pregnancy outcomes are poorly understood, it is well known that pregnancy becomes more hazardous to both the mother and the baby as women progress through each stage of CKD, especially in the presence of significant proteinuria and/or hypertension as well as comorbidities such as diabetes and lupus (reviewed separately in detail in other sections of this issue entitled Diabetic Nephropathy and Pregnancy and Lupus Nephritis and Pregnancy: Concerns and Management). Although not always possible or practical, it is preferable that pregnancy be undertaken early in a woman's journey with kidney disease. In early stage CKD, both the potential for loss of kidney function as well as pregnancy-associated complications are fewer, increasing significantly at more advanced stages of CKD.

Effect of Pregnancy on Kidney Function

CKD is defined variably in the literature with earlier studies using a serum creatinine cut-off value and more recent studies assigning a CKD stage based on a measured creatinine clearance or calculated GFR. As such, early stage CKD can be defined as a serum creatinine level less than 1.4 mg/dL (124 μmol/L), a creatinine clearance level greater than 70 mL/min or stage 1 to 2 CKD, whereas advanced CKD has been defined as a serum creatinine level in excess of 1.4 mg/dL (124 μmol/L), further subclassified into moderate 1.4 to 2.4 mg/dL (124-220 μmol/L) or severe renal insufficiency greater than 2.4 mg/dL (>220 μmol/L). More recently, moderate and severe renal insufficiency have been defined as a clearance between 40 and 70 mL/min (CKD stages 2-3) and a creatinine clearance level less than 40 mL/min (CKD stages 4-5), respectively.

There is reasonable evidence to suggest that women with underlying kidney disease, but only mild renal impairment, normal blood pressure, and no/minimal proteinuria, have much lower risks for accelerated progression during pregnancy and long term. This has been best studied in women with IgA nephropathy because of the prevalence of that disease in young women,[18–21] but also has been confirmed in women with diabetes,[22,23] autosomal-dominant polycystic kidney disease,[24] and other glomerular diseases.[25] In fact, the potential for pregnancy to hasten progression has been noted only in women with hypertension or histologic damage on renal biopsy.[26] A recent analysis, however, did note progression to a more advanced stage of CKD in 7.6% of 370 women with stage 1 CKD,[27] but potential characteristics of these patients who shifted from CKD stages 1 to 2 in pregnancy, including concomitant hypertension, proteinuria, type of renal disease, or renal pathology, were not reported. As such, women with preserved kidney function before pregnancy can be informed that significant renal function loss is unlikely, but further multicenter efforts are needed to identify at-risk women who may represent a particular type of renal disease, a combination of comorbidities, or a particular renal histologic pattern.

Women with more advanced CKD must be counselled about the potential for loss of kidney function during pregnancy, which at the most advanced stages of CKD may be severe enough to require dialysis during pregnancy. Furthermore, pregnancy termination does not reliably reverse the decrease in renal function. In the largest study in the literature published to date, 59 pregnancies with moderate renal insufficiency (125-220 µmol/L) and 15 pregnancies with severe renal dysfunction ($>$220 µmol/L) were assessed, noting that significant pregnancy-related loss of kidney function during pregnancy or within 6 weeks postpartum occurred in 43% of pregnancies with 23% progressing to end-stage kidney disease (ESKD) by 6 months postpartum.[28] Of interest, not all women who progressed were among those with the most severe renal dysfunction. In the aforementioned Italian cohort study, 16.2% of women with stage 3 CKD and 20% of women with stages 4 to 5 CKD progressed to a more advanced stage of CKD or required dialysis,[27] but patient numbers were small. A prospective study assessed the rate of renal function decrease before and after pregnancy in 49 women with a calculated estimated GFR (eGFR) less than 60 mL/min stratified by the degree of proteinuria.[29] Only women with an eGFR less than 40 mL/min and more than 1 g of proteinuria showed significantly hastened renal loss postpartum (0.21 ± 0.20 increased to 1.17 ± 1.23 mL/min/mo before and after pregnancy, respectively). Again, the study was limited by a small sample size, particularly in the group with a higher eGFR ($>$40 mL/

min) and more than 1 g of proteinuria (n = 6). As with milder forms of CKD, the ability to precisely predict renal demise is lacking because none of the studies were of adequate size to assess other potential contributing factors such as hypertension, proteinuria, cause of CKD, and/or renal histologic findings.

Pregnancy Outcomes

Overall, the risks of adverse pregnancy outcomes are higher in women with CKD compared with the general population. A recent systematic review and meta-analysis was able to identify 1,342 patients in 23 studies to assess the risk of adverse pregnancy outcomes, noting an approximately 10-fold increased risk of preeclampsia, a 5-fold increased risk for preterm delivery and small for gestational age (SGA) babies, as well as an odds ratio of almost 3 for cesarean section.[30] Study heterogeneity, however, was significant with effect modifiers, including the level of proteinuria and type of renal disease, limiting the use of these data for individualized counseling. Data from other studies noted differing rates of preeclampsia dependent on the type of renal disease, with much higher rates noted among women with diabetic nephropathy[31] than IgA nephropathy[32] and lupus nephritis.[33] Still, there is a reasonably well-documented stepwise worsening in pregnancy outcomes as women progress through the stages of CKD.

Even women at the earliest stages of CKD have been noted to have worse pregnancy outcomes than the general population. A sizable cohort from Italy noted significantly higher rates of caesarean section, preterm delivery before 37 and 34 weeks and need for neonatal intensive care unit (NICU) care, along with a shorter gestational age and lower birth weights among stage 1 CKD patients compared with 297 singleton low-risk pregnancies in the general population.[34] This increased risk among women with stage 1 CKD relative to the general population was confirmed in a subsequent larger study,[27] which also made it possible to assess the independent impact of stage 1 CKD on a combined outcome of preterm delivery ($<$37 weeks' gestation), SGA, and NICU admissions. After controlling for the presence of systemic disease, proteinuria greater than 1 g/d, hypertension, and timing of the first obstetric visit, stage 1 CKD still was independently associated with an adverse pregnancy outcome (odds ratio, 1.88; 95% CI, 1.27-2.79). Other investigators, however, have not noted an independent effect of CKD stage, suggesting comorbidities such as hypertension may be an important risk modifier. A population-based study from Norway used the Nord-Trøndelag Health Study (HUNT) II cohort and linked these data to the medical birth registry to assess the risk of adverse pregnancy-related outcomes in 5,655 singleton pregnancies at different levels of renal function defined by the

Modification of Diet in Renal Disease (MDRD) equation, and did not show an increased risk for the combined outcome of preeclampsia, SGA, or preterm delivery in women with eGFR levels greater than 75 mL/min (1.25; 95% CI, 0.96-1.62; $P = .091$) unless these women also had hypertension.[35] Given the increasing numbers of women with stage 1 CKD, a better understanding of exactly who is at risk is needed urgently given the burden of high-risk care to both the health care system and patients. Presently, women with stage 1 CKD and hypertension and/or proteinuria should be followed more closely during pregnancy pending further data.

Remarkably, worse outcomes are noted in women with advanced CKD with much higher rates of caesarean section (70%), preterm delivery less than 37 (89%) and less than 34 (44%) weeks, SGA less than 10% (50%) and less than 5% (25%), as well as an increased need for NICU care (70%).[27] Women with more advanced CKD also tend to have higher rates of concomitant hypertension and proteinuria, which also has been shown to increase the risk of adverse outcomes.[34] The aforementioned prospective cohort[29] noted a stepwise decrease in gestational age and birth weight with successive worsening in eGFR and amount of proteinuria. Women with less than 40 mL/min of eGFR and more than 1 g/d of proteinuria compared with those with an eGFR greater than 40 mL/min and less than 1 g of proteinuria delivered their babies at 33.5 ± 3.5 weeks gestation, weighing 1,864 ± 806 g and 36.7 ± 2.5 weeks' gestation, weighing 2,519 ± 670 g, respectively. As such, advanced CKD necessitates multidisciplinary care that includes nephrologists, high-risk obstetricians, and neonatologists, with the availability of specialized neonatal intensive care units.

OPTIMIZATION AND MANAGEMENT STRATEGIES

It is ideal to diagnose the type of renal disease and optimize management before pregnancy, including the management of hypertension with safe pregnancy options, stabilization of any progression of kidney dysfunction, as well as treatment of proteinuria and the nephrotic syndrome (Fig. 2).

Kidney Biopsy

Although a kidney biopsy is possible in pregnancy, it typically is feasible only earlier in gestation because later in gestation both technical issues and the potential for superimposed preeclampsia become more common, and evolving hypertension and abnormal coagulation indices can hamper the safety of the procedure. A recent meta-analysis of 39 studies, including 243 antepartum and 1,236 postpartum kidney biopsies, showed a significantly higher complication rate with antepartum compared with postpartum biopsies (7% versus 1%; $P = .001$), but fortunately most complications were minor such as loin pain and macroscopic hematoma.[36] Where possible, a biopsy before pregnancy is favored,

Emotional Support

Medications for Preeclampsia Prevention
- Folic acid 4 mg daily
- Low dose Aspirin (75 - 81 mg) daily to be continued or started after conception and continued until 34 - 36 weeks gestation.
- Calcium supplementation

Fetal Surveillance
- Biophysical profiles
- Fetal growth assessments
- Placental function studies
  - Monthly (1st trimester) then alternate week (2nd trimester) then weekly (3rd trimester)

BP Management
- Target <140/90 mm Hg
- Blood pressure should be monitored and logged using a home device validated in early pregnancy. Otherwise, blood pressure should be documented at each visit.
- Acceptable agents include long acting nifedipine, labetalol and/or methyldopa.

Management of Proteinuria/ Nephrotic Syndrome
- Safe immunosuppresive options include prednisone, calcineurin inhibitors and azathioprine.
- RAAS blockade is used in some women preconception wherein there are no immunosuppresive options, but must be stopped at the time of conception.
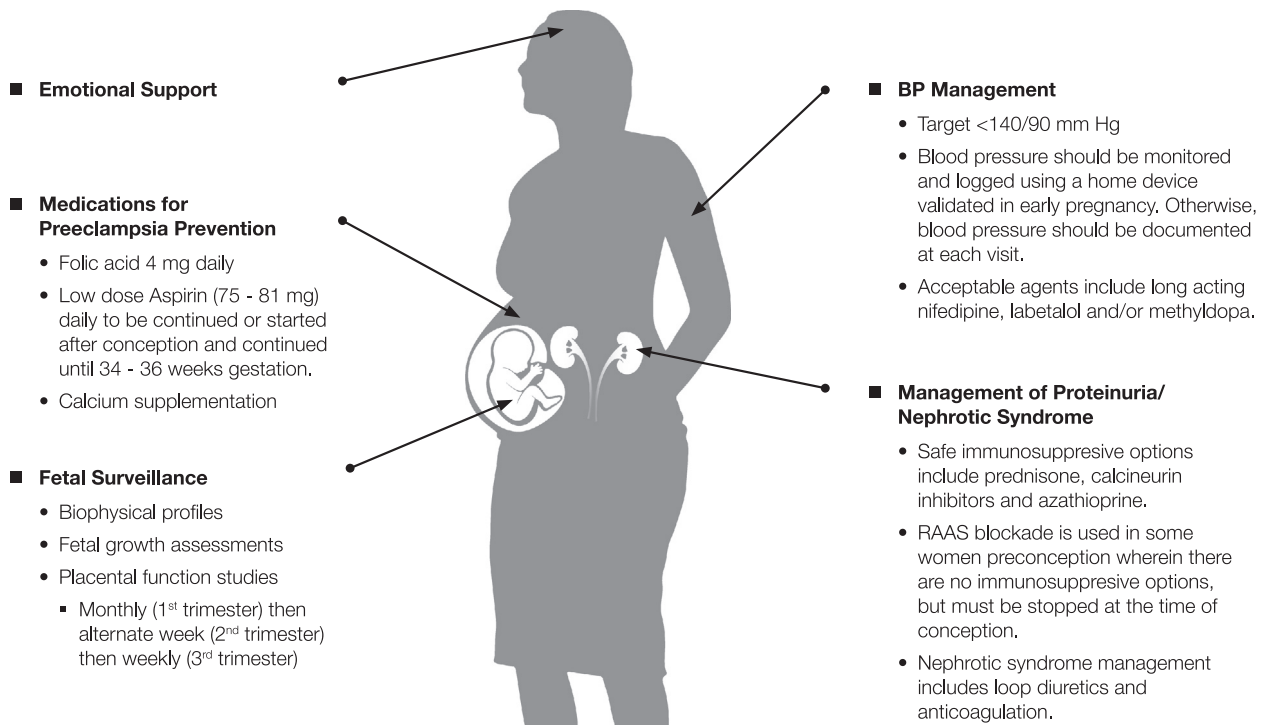- Nephrotic syndrome management includes loop diuretics and anticoagulation.

Figure 2. Antenatal care in women with CKD. BP, blood pressure.

but indications for renal biopsy during pregnancy include a sudden deterioration in renal function and/or de novo nephrotic syndrome if there is suspicion of significant glomerular disease in which the diagnosis will alter therapy. As gestation progresses, the risks often outweigh the benefits of establishing a diagnosis after approximately 30 weeks of gestation.

Hypertension Management

Poorly controlled hypertension adds significantly to the risk of pregnancy, including the risk for early pregnancy loss, superimposed placental ischemia and preeclampsia, as well as premature delivery and fetal growth restriction.[37] As such, blood pressure control should be established before conception, ideally with pregnancy safe options, including but not limited to long-acting nifedipine, labetalol, and methyldopa. Although there are no randomized studies that have included women with kidney disease or proteinuria, it is reasonable to extrapolate that the lower blood pressure targets established by the recently published Control of Hypertension in Pregnancy Study, which randomized women to a diastolic blood pressure of 85 or 100 mm Hg and confirmed that treating hypertension in pregnancy to a lower diastolic blood pressure target is not associated with adverse neonatal effects or pregnancy outcomes.[38] Furthermore, women with less tight control more frequently developed a blood pressure of 160/110 mm Hg or greater, so a blood pressure goal less than 140/90 mm Hg has been recommended for women with kidney disease during pregnancy.[39]

Treatment of Proteinuria and the Nephrotic Syndrome

Proteinuria also has been implicated as an additive factor for progression of underlying renal disease during pregnancy[29] and adverse pregnancy outcomes.[34] Ideally, proteinuria should be minimized with treatment with pregnancy safe immunosuppression where appropriate or decreased by suppression of the RAAS if the medication can be stopped safely at the time of conception based on data extrapolated from patients with lupus nephritis and diabetic nephropathy, respectively. Safe immunosuppressive options that can be used during pregnancy and while breastfeeding include prednisone, azathioprine, calcineurin inhibitors, and likely rituximab. Pulse steroids and plasmapheresis also can be considered for flares during pregnancy where appropriate. Blockade of the RAAS with enalapril, captopril, or quinapril also can be re-instituted safely during breastfeeding to lower proteinuria[40,41] because these medications do not appear to pass into breast milk.

The nephrotic syndrome that accompanies significant proteinuria can be particularly difficult to manage during pregnancy. Peripheral edema can be severe because serum albumin levels also decrease as part of a normal pregnancy.[42] Conservative treatments include compression stockings and elevation of extremities. Judicious use of loop diuretics is appropriate for severe edema when conservative measures fail, and supportive albumin infusions have been reported in case reports of women with severe nephrosis.[43,44] Pregnancy itself also is a prothrombotic state, and nephrotic syndrome with severe hypoalbuminemia (albumin < 25 g/L) is associated with an increased risk of venous thromboembolic disease.[45] Because there are no available published data to guide the use of anticoagulation in this patient population, expert opinion suggests that women with severe proteinuria and a serum albumin level less than 20 g/L should receive thromboprophylaxis throughout pregnancy continued for at least 6 weeks postpartum because the postpartum period carries a particularly high risk of thrombosis.[46] Anticoagulation, however, also should be considered in those with less severe nephrotic syndrome with additional risk factors, including immobility, obesity, or types of renal disease with known high rates of thrombosis (eg, membranous nephropathy or vasculitis). Subcutaneous low-molecular-weight heparin is the anticoagulant of choice in pregnancy. Finally, lipid profiles also are altered by pregnancy with significant increases in total cholesterol, low-density lipoprotein, and serum triglyceride levels, but presently statins are considered teratogenic (Food and Drug Administration pregnancy category X), and are not yet acceptable for use in pregnancy.

Preeclampsia Prevention and Diagnosis

All women with CKD should receive strategies for preeclampsia prevention, including adequate prenatal vitamin supplementation, calcium supplementation for those with inadequate intake,[47] and low-dose aspirin.[48] High- risk obstetric follow-up evaluation is needed for careful surveillance of fetal growth and well-being, while placental Doppler assessments can assist with the diagnosis of superimposed preeclampsia.[49]

Emotional Support

Finally, the importance of emotional support for these women cannot be overstated. Qualitative studies have noted a number of themes that all would require a number of prepregnancy counselling sessions to address, including fear about birth defects as a result of the various medications required, the potential for disease exacerbation, perceptions of failing to fulfil social norms, and lack of control over the situation.[50] A multidisciplinary clinic has been noted as a supportive environment to address these concerns and provide much needed reassurance.[51]

PREGNANCY AND END-STAGE KIDNEY DISEASE

For the unfortunate young women who reach the most advanced stages of CKD or end-stage kidney disease during their reproductive years, a pregnancy on dialysis may need to be considered especially if the potential for a kidney transplant is not imminent. Although historically considered a very poor idea, recent increases in both the incidence of pregnancy on dialysis as well as better outcomes have made many clinicians re-think their previous advice to seriously consider termination in women who conceived while on dialysis, and some programs now even facilitate conception on hemodialysis.[52]

Although a pregnancy on dialysis remains very rare in every age group when compared with renal transplant recipients or the general population, there is evidence to suggest it is becoming more common in recent years, likely owing to the use of biocompatible membranes, widespread use of erythropoietin-stimulating agents, and the intensification of dialysis dose in many centers. Data from the Australia and New Zealand Dialysis and Transplant registry documented that 43 of 49 pregnancies occurred after 1996.[53] Similarly, a recently published meta-regression analysis noted a large increase in the number of reported cases of pregnancy in women on hemodialysis (n = 616 pregnancies from 2000 to 2014)[54] compared with a similar systematic review completed less than a decade earlier (n = 90 pregnancies from 2000 to 2008).[55] Emerging from the literature, however, is a consistent difference between hemodialysis and peritoneal dialysis wherein conception on hemodialysis is approximately twice as likely as on peritoneal dialysis

for unclear reasons, but perhaps related to the presence of fluid in the abdominal cavity or inadequate dialysis intensity.[53,56] To date, the highest documented pregnancy incidence is 15.6% in eligible intensively dialyzed home dialysis patients conceiving between 2001 and 2006.[57]

Pregnancy outcomes also are improving for young women who conceive while on dialysis. Data from Europe in the 1980s noted a live birth rate of only 23%,[58] which has improved dramatically to in excess of 85% in more recent case series.[59,60] As with pregnancy incidence, clearance is also likely associated with improved live birth rates. Residual renal function improves the live birth rate as noted in another study that used the Australia and New Zealand Dialysis and Transplant registry, reporting a live birth rate of 91% in patients who conceived before starting hemodialysis compared with 63% in those who conceived on hemodialysis, with a median difference in clearance of 12 versus 5 mL/min, respectively.[61] Other studies have shown a negative correlation between the blood urea nitrogen level and birth weight as well as gestational age,[62] whereas the number of hours of hemodialysis provided weekly was noted to be significantly and inversely correlated with preterm delivery (<37 weeks' gestation) and delivery of babies weighing less than the 10th percentile.[54] In a recent comparison of the intensively dialyzed Toronto Pregnancy and Kidney Disease Registry and the American Registry for Pregnancy in Dialysis Patients, the live birth rate was 83% in the Canadian as compared with 53% in the American patients who were dialyzed on average 43 ± 6 and 17 ± 5 hours per week, respectively.[60] Furthermore, it was shown that the live birth rate increased
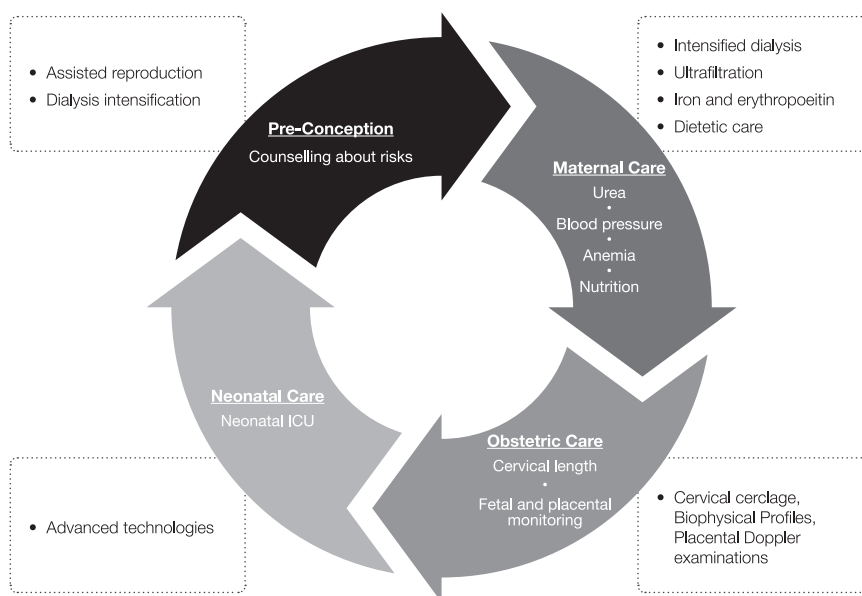
Figure 3. Multidisciplinary care of women on intensive hemodialysis. BPP, _____.

from 48% in patients dialyzed fewer than 20 hours a week, to 75% in patients dialyzed between 21 and 36 hours a week, to 85% in patients dialyzed in excess of 36 hours per week, along with improvements in both gestational age and birth weight in more intensively dialyzed pregnancies.[60] As such, it is becoming the standard of care to increase dialysis intensity significantly during pregnancy.

Despite improvements in live birth rates, these remain high-risk pregnancies with increased rates of complications,[59,60] requiring meticulous follow-up evaluation and management by a multidisciplinary team that includes nephrologists, high-risk obstetricians, and neonatologists (Fig. 3). Nephrology care ensures the delivery of an adequate dose of hemodialysis tailored to any residual renal function along with the appropriate supplementation of water-soluble vitamins and management of electrolytes, as well as calcium-phosphate balance. Most often, a higher dose of vitamins and a higher dialysate concentration of potassium and calcium are required along with phosphate and magnesium supplementation. Anticoagulation with heparin remains safe, although anemia needs to be followed closely and avoided by adequate supplementation of iron along with typically much higher doses of erythropoietin-stimulating agents. Blood pressure requires careful follow-up evaluation to avoid both hypertension, which may be a sign of placental compromise, as well as hypotension, which can affect placental perfusion adversely. Frequent assessments of volume status are needed to determine the appropriate ultrafiltration goals. Obstetric follow-up evaluation includes ensuring all teratogenic medications have been stopped, careful screening for fetal anomalies, as well as regular surveillance of fetal growth and placental well-being. Particular obstetric concerns in this population include cervical incompetence and polyhydramnios.[59,60] Polyhydramnios may be secondary to either inadequate ultrafiltration or clearance of uremic toxins; both necessitating an adjustment to the hemodialysis prescription. Because preterm delivery is common, delivery in a facility with access to a NICU is mandatory.

CONCLUSIONS

In summary, women at all stages of CKD can benefit from careful prepregnancy counselling and optimization as well as careful follow-up evaluation during pregnancy and in the postpartum period. Furthermore, more women with end-stage kidney disease are also now conceiving, and although still a rare occurrence, nephrologists need to be familiar with the special challenges of this vulnerable population. As such, nephrologists need to be actively involved in pregnancy planning throughout a young woman's life cycle to educate all young women with kidney disease with respect to the risks of unplanned pregnancy, to treat the disease before conception and during pregnancy, and to identify windows of opportunity along the CKD continuum because pregnancy at earlier stages of CKD is safer than in later stages of CKD. For all these women, the emotional strain of preparing for a high-risk pregnancy and then caring for a child while also managing a chronic illness need to be carefully considered and supported.

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