Pregnancy across the spectrum of chronic kidney disease

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Management of the pregnant woman with chronic kidney disease is difficult for both nephrologists and obstetricians. Prepregnancy counselling with respect to risk stratification, optimization of maternal health prior to pregnancy, as well as management of the many potential pregnancy-associated complications in this complex patient population remains challenging due to the paucity of large, well-designed clinical studies. Furthermore, the heterogeneity of disease and the relative infrequency of pregnancy, particularly in more advanced stages of chronic kidney disease, leaves many clinicians feeling ill prepared to manage these pregnancies. As such, counselling is imprecise and management varies substantially across centers. All pregnancies in women with chronic kidney disease can benefit from a collaborative multidisciplinary approach with a team that consists of nephrologists experienced in the management of kidney disease in pregnancy, maternal-fetal medicine specialists, high-risk pregnancy nursing staff, dieticians, and pharmacists. Further access to skilled neonatologists and neonatal intensive care unit support is essential given the risks for preterm delivery in this patient population. The goal of this paper is to highlight some of the data that currently exist in the literature, provide management strategies for the practicing nephrologist at all stages of chronic kidney disease, and explore some of the knowledge gaps where future multinational collaborative research efforts should concentrate to improve pregnancy outcomes in women with kidney disease across the globe.

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Pregnancy is characterized by renal physiological alterations, including changes to kidney size as well as glomerular and tubular function with both renal plasma flow and the glomerular filtration rate (GFR) increasing markedly during gestation.[1,2] These changes are not only critical for an optimal pregnancy outcome, but cognizance of these expected physiological changes are necessary to assist with the proper interpretation and identification of worsening kidney dysfunction and/or superimposed preeclampsia. As such, kidney disease during pregnancy, even when mild, can considerably increase both the maternal and fetal risk necessitating close follow-up by both nephrologists and high-risk obstetricians. Risk increases with the degree of renal dysfunction and is further heightened by comorbid conditions such as 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 well before conception to identify the safest "window of opportunity" for childbearing along the spectrum of chronic kidney disease (CKD), to stabilize a woman's condition and provide an appropriate risk assessment, and finally to provide close monitoring during pregnancy to identify early both maternal and fetal compromise, all of which can prove extremely challenging given the available literature. With respect to prepregnancy counselling based on the degree of renal dysfunction, the existing literature is contradictory and difficult to synthesize due the variable means used to define the level of CKD that has also changed over time, making studies from different eras difficult to compare; prepregnancy baseline renal function is often not available, resulting in stage misclassification in the face of the known physiological changes that accompany pregnancy; most studies are single-center experiences and therefore subject to local obstetrical practices that may differ between sites; and all of the studies include a very heterogeneous mix of patients with different types of renal disease as well as varying degrees of hypertension and proteinuria. Typically studied pregnancy-associated outcomes include preterm delivery and caesarean section rates, which may have an iatrogenic component; the rate of preeclampsia, which is profoundly difficult to diagnose in this patient population that often already has underlying

hypertension and proteinuria; and small for gestational age or intrauterine growth restriction, which is also variably defined throughout the literature, relies on ultrasonogram assessments that are not universally available and finally can be impacted by the timing of delivery, which may vary between centers.[3] Irrespective of these many limitations, the goal of this review is to highlight some of the pertinent data that currently exist in the literature, provide management strategies for the practicing nephrologist at all stages of CKD, and explore some of the knowledge gaps where future multinational collaborative research efforts should concentrate to improve pregnancy outcomes in women with kidney disease across the globe.

Early stage CKD

Early stage CKD is defined variably in the literature, including a serum creatinine <1.4 mg/dl (124 μmol/l), a creatinine clearance >70 ml/min or stage 1/2 CKD, and includes variable degrees of proteinuria and a heterogeneous mix of underlying renal lesions. As the risks for both loss of kidney function and adverse pregnancy outcomes increase with the degree of baseline renal insufficiency, it makes intuitive sense that pregnancy is safer in women with earlier stages of CKD, and 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 good maternal and fetal outcomes, with much lower risks for accelerated progression. That being said, the risk for pregnancy complications have been documented to exceed those noted in the general population,[4] so these women may still require specialized care.

Effect of pregnancy on kidney function. The potential for pregnancy to hasten the progression of renal dysfunction has been studied most extensively in young women with IgA nephropathy, given the prevalence of this glomerular disease among young women.[5–8] In women with preserved kidney function, the potential for pregnancy to hasten progression has only been noted in women with hypertension or significant histological damage on renal biopsy.[9] Similar encouraging long-term renal outcomes have been noted in women with diabetes,[10,11] autosomal dominant polycystic kidney disease,[12] and other glomerular diseases.[13] However, a very recent analysis of a large cohort of women with stage 1 CKD ($n = 370$) did note progression to a more advanced stage of CKD in 7.6% of patients.[14] Other potential characteristics of these patients who shifted from CKD stage 1 to 2 in pregnancy, including concomitant hypertension or proteinuria, was not reported. An earlier study by the same group that included 127 women with stage 1 CKD did show an upward trend in serum creatinine over the course of pregnancy from a baseline creatinine of 0.62 mg/dl (55 μmol/l) to 0.67 mg/dl (59 μmol/l); $P = 0.003$,[15] but the clinical significance of this change is questionable given that many women in the study did not have preconception data and the upward shift noted toward the end of pregnancy may simply reflect a return to the prepregnancy baseline creatinine as opposed to any meaningful loss of kidney function. In general, women with preserved kidney function before pregnancy can be informed that significant renal function loss is unlikely so long as blood pressure and proteinuria are managed prior to conception.

Pregnancy outcomes. Pregnancy complications, on the other hand, may be more common even in women with preserved kidney function. In the Italian study described, significantly higher rates of caesarean section, preterm delivery prior to 37 and 34 weeks, and need for neonatal intensive care unit care along with a shorter gestational age and smaller birth weight were noted in the stage 1 CKD patients compared with 297 singleton low-risk pregnancies in the general population.[15] Of interest, the more robust outcome of small for gestational age was not significantly different between the groups. Irrespective, this increased risk among women with stage 1 CKD relative to the general population was confirmed in a subsequent larger study.[14] The larger sample size made it possible to assess the independent impact of stage 1 CKD on a combined outcome of preterm delivery (<37 weeks' gestation), small for gestational age, and neonatal intensive care unit admissions. After controlling for the presence of systemic disease, proteinuria >1 g/day, hypertension, and timing of the first obstetrical visit, stage 1 CKD was still independently associated with an adverse pregnancy outcome (odds ratio, 1.88; 95% confidence interval, 1.27–2.79).

In contrast, a recent population-based study from Norway that utilized the Nord-Trøndelag Health Study (HUNT) II cohort and linked this data to the medical birth registry to assess the risk of adverse pregnancy-related outcomes at different levels of renal function defined by the Modification of Diet in Renal Disease (MDRD) equation did not confirm these results.[16] This study included 3405 women who had 5655 singleton pregnancies and did not show an increased risk for the combined outcome of preeclampsia, small for gestational age, or preterm delivery in women with estimated GFR (eGFR) levels above 75 ml/min (odds ratio, 1.25; 95% confidence interval, 0.96–1.62; $P = 0.091$) unless these women also had hypertension. Furthermore, reduced eGFR and hypertension were synergistic risk factors. Interestingly, microalbuminuria in the context of a preserved eGFR did not augment the pregnancy risk, but given this was a general population study and not a study that specifically identified women with CKD, numbers with microalbuminuria (3.2%) were too limited and imputation was necessary for significant portions of missing data.

This is an important discrepancy in the literature that requires further study and confirmation from other centers as the numbers of women with stage 1 CKD are increasing and high-risk care in all these patients will prove both a burden to health care systems and the patients. The studies from Italy are hampered by a lack of preconception data, which may have resulted in stage misclassification. Furthermore, the outcomes are driven by local obstetrical practices. The HUNT II cohort was a healthy population study that lacked adequate numbers of women with proteinuric renal disease. Suffice it