Pregnancy in chronic kidney disease and kidney transplantation

Philip Webster[1], Liz Lightstone[1], Dianne B. McKay[2] and Michelle A. Josephson[3]

[1]Section of Renal Medicine and Vascular Inflammation, Department of Medicine, Imperial College London, United Kingdom; [2]Division of Nephrology, Department of Medicine, University of California, San Diego, California, USA; and [3]Department of Medicine, University of Chicago Medicine, Chicago, Illinois, USA

Chronic kidney disease (CKD) affects up to 6% of women of childbearing age in high income countries, and is estimated to affect 3% of pregnant women. Advanced renal dysfunction, proteinuria, hypertension, and poorly controlled underlying primary renal disease are all significant risks for adverse maternal, fetal, and renal outcomes. In order to achieve the best outcomes, it is therefore of paramount importance that these pregnancies are planned, where possible, to allow the opportunity to counsel women and their partners in advance and to optimize these risks. These pregnancies should be deemed high risk and they require close antenatal monitoring from an expert multidisciplinary team. We discuss the effect of pregnancy on CKD, and also current guidelines and literature with specific reference to transplantation, autoimmune disease, and medication use in pregnancy. We also discuss the benefits of prepregnancy counseling and give practical recommendations to advise pregnant women with renal disease.

Kidney International (2017) **91,** 1047–1056; http://dx.doi.org/10.1016/j.kint.2016.10.045

KEYWORDS: acute rejection; chronic kidney disease; kidney transplantation; outcomes; pregnancy

Correspondence: *Michelle A Josephson, The University of Chicago Medicine, 5841 S. Maryland Ave, MC5100, Chicago, IL 60637, USA. E-mail: mjosephs@medicine.bsd.uchicago.edu*

Received 13 July 2016; revised 28 September 2016; accepted 6 October 2016; published online 13 February 2017

Impact of kidney function on pregnancy outcome

Chronic kidney disease stage and outcomes. The pregnancies of most normotensive women with mild or even moderate renal dysfunction succeed, but these pregnancies are prone to more complications than those of gravidas with normal renal function. However, pregnancy is much more hazardous when kidney dysfunction is advanced. Women with advanced chronic kidney disease (CKD) have a lower likelihood of conceiving because of the decreased fertility associated with the hormonal changes of worsening kidney function and end-stage renal disease (ESRD).[1] When they do conceive, advanced CKD predisposes to intrauterine growth restriction and preterm delivery[2]; pregnancy has been blamed for hastening the rate of decline of kidney function, increasing proteinuria, and hypertension.[3] However, such views are based on insufficient data. Thus, the level of kidney function and/or dysfunction and its effect on pregnancy remains a debated area.

An evolving state of understanding. Currently, there is controversy that reflects the swinging pendulum of attitudes related to pregnancy in women with CKD and the evolution of how the nephrology community assesses renal function. In 1975, an anonymously authored *Lancet* editorial noted that physicians in the past preferred women with any degree of CKD to avoid pregnancy: "Children of women with renal disease used to be born dangerously or not at all - not at all if their doctors had their way."[4] The editorial took the then provocative stance that because most pregnancies succeed in the setting of mild kidney dysfunction, this attitude should be changed. Davison and Lindheimer[5] noted in 2010 that studies in the decades after the *Lancet* editorial led to a better understanding of outcomes for pregnancy in women with kidney dysfunction. Observational studies indicated that outcomes depended on the degree of renal insufficiency before pregnancy, and the presence or absence of hypertension.[6] Based on these parameters, women were grouped into 3 categories: mild, moderate, or severe dysfunction. Normotensive women with preserved or mildly decreased but stable kidney function (defined as a serum creatinine [SCr] of $\leq$1.4 mg/dl) did well, with >95% live births, 75% of which were appropriate size for gestational age. However, prognosis worsened with moderate dysfunction (SCr $\geq$1.4 to 2.8 mg/dl) and more so with severe impairment (SCr level $\geq$2.8 mg/dl).[7] These estimates were based on a 26-year literature review (1984−2010) and the personal patient files of John Davison, which were recently published in a *Nephrology Self Assessment*

Program editorial by Drs. Lindheimer and Davison, in the issue devoted to renal disease and hypertension in pregnancy (reproduced with permission in Table 1).[8]

Creatinine versus estimated glomerular filtration rate. In 2002, the Kidney Disease Outcomes Quality Initiative released a new CKD classification that designated 5 categories based on the estimated glomerular filtration rate (eGFR).[9] Ignoring the question of whether this classification system overdiagnosed kidney disease and dysfunction in some, the eGFR-based system provided another filter through which to consider pregnancy outcomes. Piccoli *et al.*[10] used the classification system, and looked at pregnancy outcomes in 504 pregnancies in women with CKD compared with 836 low-risk pregnancies in women without CKD. They considered whether hypertension, proteinuria (>1 g/d), systemic disease, or CKD stage at baseline affected pregnancies. Outcomes assessed were cesarean section, preterm delivery, early preterm delivery, small for gestational age, need for neonatal intensive care unit, new onset of hypertension, new onset and/or doubling of proteinuria, CKD stage shift, and a combined outcome. Most patients in the study were classified as CKD stage 1. The authors concluded that adverse outcomes increased with increasing stage of CKD, including surprisingly stage 1, even in the absence of hypertension, baseline proteinuria, and systemic diseases. The eGFR was calculated based on the Cockcroft-Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas. Because CKD-EPI and Modification of Diet in Renal Disease have been found to underestimate GFR in pregnancy,[11,12] and Cockcroft-Gault has been demonstrated to both underestimate and overestimate GFR in hypertensive pregnant women,[13] it is possible that some of the patients in the study by Piccoli *et al.* had lower GFRs than the group in which they were classified. Therefore, some of the individuals reported to have CKD stage 1 could have had a higher stage. Although the findings by Piccoli *et al.* were primarily in women with mild and moderate dysfunction, Imbasciati *et al.* studied 49 women with preconception stage 3 to 5 CKD who were observed for a mean of 39 months after delivery. In the latter study, only individuals with both GFR <40 ml/min/1.73 m^2 and >1 g/d of proteinuria were noted to have poor fetal outcomes and accelerated kidney function loss.[14] A meta-analysis by Zhang *et al.* of 23 studies that included 1514 pregnancies in women with CKD found no significant difference in renal outcomes in pregnant women with CKD compared with nonpregnant women with CKD. However, the study did find that adverse pregnancy outcomes, including preeclampsia, premature births, small for gestational age and/or low birth weight, cesarean section, stillbirth, fetal death, and neonatal death, were increased in women with CKD compared with those without CKD. The conclusions that can be drawn from the meta-analysis must be put into context because the literature review focused on patients with CKD stages 1 to 3, thus excluding those with stage 4 or 5, who are the most vulnerable for progression of disease.[15]

In their review and recent editorial, Davison and Lindheimer[5,8] underscore that most eGFR formulas correlate poorly with measured GFR in pregnant women, and that obstetricians familiar with absolute values of creatinine may be unfamiliar with the nephrology community's CKD system. However, despite the seeming differences between those who are considering pregnancy outcomes through an eGFR-based CKD stage filter and those who are more comfortable with the serum creatinine–based assessment, proponents of both agree that the degree of kidney function plays an important role in outcome. Neither group advocates returning to the pre-1975 mindset of avoiding pregnancy in women with mild kidney dysfunction, however it is defined.

Additional contributing factors. Although clearly important, kidney function alone does not uniformly predict pregnancy outcomes. There are likely to be additional contributing factors to pregnancy outcomes, such as active systemic disease or endothelial injury. For example, certain specific diseases, such as systemic lupus erythematosus, may exert a greater adverse effect on the pregnancy, making it impossible to isolate the role of kidney function per se on outcomes.[16] Similarly, kidney transplantation does not present a pristine model to look at kidney function alone because of the effects of immunosuppression.

Kidney transplantation and outcomes. A national UK cohort study demonstrated that most pregnancies after renal transplantation are successful, although the risks of

Table 1 | Prepregnancy kidney function in patients with CKD with estimates of problems in pregnancy[a]

Renal status (dysfunction)	SCr (mg/dl) (μmol/L)	Problems in pregnancy (%)	Successful obstetric outcome (%)	Compared with prepregnancy a permanent PP loss of kidney function (>25% increment in SCr) (%)	ESRF within 1 yr PP (%)
Mild	≤1.4 (≤125)	26	96	<2	—
Moderate	≥1.4 (≥125)	50	90	25	3
Severe	≥2.8 (≥250)	86	74	55	40
Mild	≤1.4 (≤125)	26	96	<2	—
Moderate	≥1.4 (≥125)	42	95	15	1
Severe	≥2.0 (≥180)	79	78	50	38

ESRF, end stage renal failure; PP, post-partum; SCr, serum creatinine.
Estimates are on the basis of a 26-year literature review (1984–2010) of pregnancies that attained ≥24 weeks' gestation.
[a]Fetal growth restriction, preeclampsia, preterm delivery, and significant kidney function loss in pregnancy (>25% SCr increment), obstetric outcome, and loss of kidney function: the effect of altering thee cutoff between moderate and severe dysfunction from 2.8 mg/dl (≥250 μmol/L) to 2.0 mg/dl (≥180 μmol/L), respectively.
(Adapted with permission from Lindheimer MD, Davison JM. Editorial: pregnancy and the kidney managing hypertension and renal disease. *Nephrol Self Assess Program.* 2016;15:109–114.)