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Pregnancy in Women With CKD: A Success Story

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In women with chronic kidney disease (CKD), pregnancy outcomes have improved over the last 50 years, particularly in the developed world. Maternal mortality is now extremely low, fetal survival has markedly increased (even in women with CKD stages 4-5), and it is now the exception for women with CKD to be advised against embarking on a pregnancy. However, pregnancies are rarely free from complications, and there are unanswered questions about the longer term effects on maternal and infant health. The developments have led to a more optimistic attitude to pregnancy in women with CKD not requiring renal replacement treatment. The remaining problems are described in this World Kidney Forum.

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In 1963, Mackay[1] published the outcomes of pregnancy for 150 pregnant women with chronic kidney disease (CKD) in the 1950s, reporting overall fetal survival of only 66%. In women with an initial serum urea nitrogen level > 60 mg/dL (>21.4 mmol/L), fetal survival was zero.[1] Some 50 years later, the Torino-Cagliari Observational Study described a series of more than 500 pregnancies in women with CKD and reported fetal survival of 99%, including 47 pregnancies in women with CKD stages 3 to 5.[2] Almost more remarkable is the report of Hladunewich et al[3] in Toronto reporting fetal survival rates of 86% in pregnant women maintained by hemodialysis.

What has led to these remarkable improvements? Progress in medicine occurs in 3 ways: a radical change in approach, availability of new effective drugs or devices, or gradual improvement in the individual components of management, sometimes referred to as the aggregation of marginal gains. For obstetric nephrology, published series suggest it is the latter that has brought about the improved results (Table 1). With the exception of some notable developments in maternal and neonatal care medicine,[7,8] most changes have been progressive rather than stepwise, and there have been no revolutionary pharmaceutical developments in the field.

This World Kidney Forum discusses how the reciprocal impact of established CKD and pregnancy on each other has evolved. Acute kidney injury, kidney transplantation, and dialysis in pregnancy are not included.

PLANNING A PREGNANCY

In 1975, *The Lancet* described recent practice as follows: "Children of women with renal disease used to be born dangerously or not at all–not at all, if their doctors had their way."[9p801] It soon became apparent that a diagnosis of CKD should not lead to "one-size-fits-all" advice. In 1980, Katz et al[4] reported on 121 pregnancies in women, almost all of whom had only mildly decreased kidney function (creatinine < 1.2 mg/dL [<106 μmol/L]). Infant survival was 87%.[4] Women with heavy proteinuria were less likely to have successful pregnancies. Preconception kidney function was a strong determinant of outcome.[4,10] Except for lupus nephritis and diabetes mellitus, the cause of kidney disease had less impact on pregnancy outcome than its severity at the time of conception.[10]

The early reports recognized that "the presence of high blood pressure is often of serious import."[1] Subsequent series consistently emphasized that women with poor control of hypertension before or in early pregnancy had a more

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Table 1. Infant Survival in Selected Series of Women With CKD and Pregnancy

Publication Year (Years of Pregnancies)	Patient Population (No. of Pregnancies)	Infant Survival[a]
1963 (1950-1960)[1]	CKD (n = 150)	66%
	Baseline SUN > 20 mg/dL (n = 33)	43%
	Baseline SUN > 40 mg/dL (n = 21)	37%
	Baseline SUN > 60 mg/dL (n = 13)	0%
1980 (1956-1979)[4]	CKD; biopsy or angiographic diagnoses (n = 121)	87%
	CKD; baseline SUN > 20 mg/dL (n = 1)	100%
	CKD, baseline Scr > 1.2 mg/dL (n = 3)	100%
1996 (1971-1993)[5]	CKD; baseline Scr > 1.4 mg/dL (n = 82)	93%
	CKD; baseline Scr 1.4-2.5 mg/dL (n = 67)	91%
	CKD; baseline Scr > 2.5 mg/dL (n = 15)	100%
2007 (1977-2004)[6]	CKD stages 3-5 (n = 49)	96%
	Baseline GFR ≥ 40 mL/min/1.73 m^2 (n = 22)	100%
	Baseline GFR < 40 mL/min/1.73 m^2 (n = 27)	93%
2015 (2000-2013)[2]	CKD stages 1-5 (n = 504)	99%
	CKD stages 1-2 (n = 457)	99%
	CKD stages 3-5 (n = 47)	100%

Note: Conversion factors for units: Scr in mg/dL to μmol/L, ×88.4; SUN in mg/dL to mmol/L, ×0.357.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; Scr, serum creatinine; SUN, serum urea nitrogen.

[a]Excludes data for spontaneous and therapeutic abortion as incomplete; includes stillbirths and neonatal deaths.

complicated course, with higher rates of preterm delivery, pre-eclampsia, and fetal death.[10] Achieving control of blood pressure before conception is therefore recommended, and "pregnancy-safe" agents, including nifedipine or labetalol, are usually sufficient but require titration. Despite this, there are some series that describe women with treated hypertension who fared as poorly as those with uncontrolled hypertension, perhaps reflecting a state of generalized maternal endothelial dysfunction that manifests as utero-placental insufficiency.[11-13]

The improvements in pregnancy outcomes for women with CKD mean that advising against it is the exception, provided there has been adequate counseling and an opportunity for discussion. Counseling should be encouraged for all women with CKD contemplating pregnancy. Unfortunately, those who seek counseling are not always those at the greatest risk.

Embarking on a pregnancy should be deferred in those with active systemic lupus erythematosus, nephrotic syndrome, or systemic vasculitis because outcomes are better for those in stable remission.[14-18] Drug treatments, particularly with statins, renin-angiotensin system antagonists, or mycophenolic acid derivatives, need to be altered and a period of stabilization using pregnancy-safe agents needs to be achieved before attempts to conceive.[19-21]

Advising women with advanced CKD when to embark on a pregnancy is complicated. Fertility rates diminish with increasing severity of kidney disease, and assisted fertility options both are high risk for maternal health and have a low success rate.[22]

Despite the recent improvements in fetal survival in women with CKD stages 3 to 5, pregnancy complication rates remain high (Table 2). Reliable data for rates of first-trimester miscarriage are not available, but they are certainly higher than for healthy mothers. Most infants born to women with CKD stages 3 to 5 are delivered before term and often by cesarean section. Half the babies will require special neonatal care.[2]

The potential adverse effect of pregnancy on kidney function is also an issue. A lack of comparative data from nonpregnant controls in maternal outcome series means that loss of kidney function after pregnancy could be no more than the natural history of the CKD. Data from the last 20 years continue to show irreversible loss of kidney function in 30% to 50% of women with moderate to severe CKD (defined either as baseline creatinine > 1.4 mg/dL [>125 μmol/L] or estimated glomerular filtration rate [eGFR] < 45 mL/min/1.73 m^2) after delivery. About one-third of women starting pregnancy with eGFRs < 30 mL/min/1.73 m^2 should expect to require renal replacement treatment within a year of delivery (Table 3).[1,4-6,23,24]

Women contemplating pregnancy with severely decreased kidney function should weigh the options of delaying pregnancy until after successful transplantation[25,26] against trying to keep a pregnancy while function is poor or actually starting dialysis therapy during pregnancy.[2,3] The decision will depend on the acceptability of delay imposed by the rate of progression to end stage, availability of a live donor, and maternal age and consequent fertility.

DURING PREGNANCY

Developments in obstetric medicine per se have contributed most to the improved fetal outcomes seen in women with CKD. Iron and folic acid supplementation, eschewing cigarette smoking, alcohol avoidance, antenatal screening of infants, antenatal clinical supervision by specialist midwifery teams, and the advances in neonatal intensive care have all reduced fetal mortality.