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 4 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.

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**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.”\(^9\) 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 \([<106\) \(\mu\)mol/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.\(^4,10\) 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 complicated course, with higher rates of preterm delivery, preeclampsia, and fetal death. 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.

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. 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.

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.

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.

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 m²) after delivery. About one-third of women starting pregnancy with eGFRs < 30 mL/min/1.73 m² should expect to require renal replacement treatment within a year of delivery (Table 3).

Women contemplating pregnancy with severely decreased kidney function should weigh the options of delaying pregnancy until after successful transplantation against trying to keep a pregnancy while function is poor or actually starting dialysis therapy during pregnancy.

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.

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

<table>
<thead>
<tr>
<th>Publication Year (Years of Pregnancies)</th>
<th>Patient Population (No. of Pregnancies)</th>
<th>Infant Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963 (1950-1960)¹</td>
<td>CKD (n = 150)</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>Baseline SUN &gt; 20 mg/dL (n = 33)</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>Baseline SUN &gt; 40 mg/dL (n = 21)</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td>Baseline SUN &gt; 60 mg/dL (n = 13)</td>
<td>0%</td>
</tr>
<tr>
<td>1980 (1956-1979)⁴</td>
<td>CKD; biopsy or angiographic diagnoses (n = 121)</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>CKD; baseline Scr &gt; 2.0 mg/dL (n = 1)</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>CKD; baseline Scr &gt; 1.2 mg/dL (n = 3)</td>
<td>100%</td>
</tr>
<tr>
<td>1996 (1971-1993)⁵</td>
<td>CKD; baseline Scr &gt; 1.4 mg/dL (n = 82)</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>CKD; baseline Scr 1.4-2.5 mg/dL (n = 67)</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>CKD; baseline Scr &gt; 2.5 mg/dL (n = 15)</td>
<td>100%</td>
</tr>
<tr>
<td>2007 (1977-2004)⁶</td>
<td>CKD stages 3-5 (n = 49)</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>Baseline GFR ≥ 40 mL/min/1.73 m² (n = 22)</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Baseline GFR &lt; 40 mL/min/1.73 m² (n = 27)</td>
<td>93%</td>
</tr>
<tr>
<td>2015 (2000-2013)²</td>
<td>CKD stages 1-5 (n = 504)</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td>CKD stages 1-2 (n = 457)</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td>CKD stages 3-5 (n = 47)</td>
<td>100%</td>
</tr>
</tbody>
</table>

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.

¹Excludes data for spontaneous and therapeutic abortion as incomplete; includes stillbirths and neonatal deaths.

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Matthew Hall
For example, simply providing iron and folic acid supplementation in early pregnancy reduced neonatal mortality by >50% in Nepal. In the United Kingdom, giving up cigarette smoking during pregnancy is associated with a 28% decreased risk for preterm delivery.

The early case series identified the 2 most common barriers to successful pregnancy in women with early CKD; namely, urinary tract infection and hypertensive disorders of pregnancy. The term chronic pyelonephritis, the most common cause of CKD described in pregnancy case series, includes recurrent urinary tract infections, congenital structural abnormalities of the kidney and urinary tract, and acquired obstructive urologic disease. Pregnancy increases the propensity for all women and particularly those with a previous history to develop bacteriuria and overt infection. More than 50 years ago, trials of antibiotic prophylaxis during pregnancy showed a reduction in the incidence of pyelonephritis from 36% to 0%. Asymptomatic bacteriuria was shown to progress to pyelonephritis more frequently in pregnant women. Furthermore, pyelonephritis in pregnancy not only leads to maternal morbidity, but may provoke the onset of preterm labor. Treatment of asymptomatic bacteriuria has therefore become standard practice for women at risk, with a 34% reduction in the incidence of low-birth-weight infants.

Preeclampsia remains the dominant determinant of pregnancy outcomes for women with CKD. Mackay reported that fetal survival decreased from 90% in women with proteinuric CKD alone to 40% when preeclampsia was superimposed. However, there was caution in describing women with CKD as having developed “preeclampsia” because of a history of chronic hypertension or proteinuria confused diagnostic criteria. Ambiguity in defining preeclampsia in this population had been clearly identified some 30 years earlier by Gibberd, who wrote the following:

A chronic nephritic who becomes pregnant is suffering from albuminuria which is almost entirely “nephritic”. At the other extreme...is a healthy patient who develops albuminuria during pregnancy. She is suffering from “toxaemia” [preeclampsia]...Between these two extremes come all shades of the two elements.

Ninety years later, despite a better understanding of the pathophysiology of preeclampsia, women with CKD continue to be classified by variable and indistinct criteria under the umbrella of “superimposed preeclampsia.” Nevertheless, the association between CKD and preeclampsia, however defined, was clear, and a correlation between severity of decreased kidney function and risk for preeclampsia emerged. In the review by Williams and Davison of the 1985 to 2007 literature, reported rates of preeclampsia were 22% in women with CKD and a baseline creatinine level <1.4 mg/dL (<125 μmol/L), 60% in women with creatinine levels >2.0 mg/dL (>177 μmol/L), and 75% in women on dialysis therapy compared to ~5% in the general population. In a recent Italian CKD cohort, a looser definition of new-onset hypertension was identified in 5.5% of controls, 9% in women with CKD stages 1 and 2 and 48% in women with CKD stages 3 to 5. Evidence for using measurements of angiogenic factors to differentiate preeclampsia from progressive CKD is growing. Pilot data for dextran sulfate apheresis to remove the antiangiogenic protein sFlt1 (soluble fms-like tyrosine kinase, or sVEGFR1) in women with early preeclampsia (<32 weeks) show promise. Despite decades of research and innovation, there is no reliable test to predict who will develop the condition and there is no cure for it other than delivery of the infant and placenta. Of all the potential interventions, only low-dose aspirin has become established in clinical practice and included in international guidelines for women at high risk for

<table>
<thead>
<tr>
<th>Year (Years of Pregnancies)</th>
<th>Patient Population</th>
<th>Early Preterm (&lt;34 wk)</th>
<th>Late Preterm (34-36 wk)</th>
<th>LBW (1,500-2,500 g)</th>
<th>VLBW (&lt;1,500 g)</th>
<th>SGA</th>
<th>PE</th>
<th>CS</th>
<th>NICU Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980 (1956-1979)⁴</td>
<td>CKD; Scr &lt; 1.2 mg/dL³  (n = 85)</td>
<td>15%</td>
<td>18%</td>
<td>29%</td>
<td>8%</td>
<td>NA</td>
<td>15%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1996 (1971-1993)⁵</td>
<td>CKD; Scr &gt; 1.4 mg/dL (n = 82)</td>
<td>59%</td>
<td>NA</td>
<td>NA</td>
<td>37%</td>
<td>NA</td>
<td>59%</td>
<td>37%</td>
<td>NA</td>
</tr>
<tr>
<td>2007 (1977-2004)⁶</td>
<td>CKD stages 3-5 (n = 49)</td>
<td>63%</td>
<td>NA</td>
<td>NA</td>
<td>39%</td>
<td>20%</td>
<td>73%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2015 (2000-2013)²²</td>
<td>CKD stages 1-2 (n = 457)</td>
<td>10%</td>
<td>19%</td>
<td>NA</td>
<td>14%</td>
<td>NA</td>
<td>52%</td>
<td>14%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>CKD stages 3-5 (n = 47)</td>
<td>39%</td>
<td>42%</td>
<td>NA</td>
<td>26%</td>
<td>NA</td>
<td>77%</td>
<td>50%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note: Conversion factor for Scr in mg/dL to μmol/L, ×88.4.
Abbreviations and definitions: CKD, chronic kidney disease; CS, cesarean section; NA, not available; NICU, neonatal intensive care unit; PE, preeclampsia; Scr, serum creatinine; SGA, small for gestational age (<10th percentile); VLBW, (very) low birth weight.

⁴Scr < 1.2 mg/dL in 82 of 85 pregnancies.
focussing on maternal kidney function to baseline values.4,6,7,10,11

Maternal Outcomes in Selected Series of Women With CKD and Pregnancy

<table>
<thead>
<tr>
<th>Publication Year</th>
<th>Baseline Maternal Kidney Function</th>
<th>Peripartum Loss of 25% Kidney Function</th>
<th>Accelerated/Persistent Loss of Kidney Function</th>
<th>RRT</th>
<th>Maternal Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963 (1950-1960)</td>
<td>CKD; SUN 1.2 mg/dL (n = 135)</td>
<td>NA</td>
<td>27%</td>
<td>NA</td>
<td>4% within 2 y</td>
</tr>
<tr>
<td>1980 (1956-1979)</td>
<td>CKD; Scr 1.2 mg/dL (n = 85)</td>
<td>17%</td>
<td>NA</td>
<td>1%</td>
<td>1 y</td>
</tr>
<tr>
<td>1996 (1971-1993)</td>
<td>CKD; baseline Scr 1.4 mg/dL (n = 82)</td>
<td>43%</td>
<td>31%</td>
<td>10%</td>
<td>5% within 5 y</td>
</tr>
<tr>
<td>1980 (1956-1979)</td>
<td>CKD; Scr 1.4-2.0 mg/dL (n = 49)</td>
<td>10%</td>
<td>33%</td>
<td>2%</td>
<td>1 y</td>
</tr>
<tr>
<td>1996 (1971-1993)</td>
<td>CKD; baseline Scr 2.0-2.4 mg/dL (n = 9)</td>
<td>33%</td>
<td>33%</td>
<td>1 y</td>
<td></td>
</tr>
<tr>
<td>1980 (1956-1979)</td>
<td>CKD; baseline Scr &gt; 2.4 mg/dL (n = 12)</td>
<td>50%</td>
<td>33%</td>
<td>1 y</td>
<td></td>
</tr>
<tr>
<td>2007 (1977-2004)</td>
<td>CKD stages 3-5 (n = 49)</td>
<td>NA</td>
<td>24%</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>2008a,b</td>
<td>CKD; Scr 1.4 mg/dL</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
<td>NA</td>
</tr>
<tr>
<td>2008a,b</td>
<td>CKD; Scr 1.4-2.0 mg/dL</td>
<td>2%</td>
<td>2%</td>
<td>1 y</td>
<td></td>
</tr>
<tr>
<td>2008a,b</td>
<td>CKD; Scr &gt; 2.0 mg/dL</td>
<td>2%</td>
<td>0%</td>
<td>1 y</td>
<td></td>
</tr>
<tr>
<td>2011 (2003-2011)</td>
<td>CKD stage 3a (n = 17)</td>
<td>11%</td>
<td>6%</td>
<td>0%</td>
<td>1 y</td>
</tr>
<tr>
<td>2011 (2003-2011)</td>
<td>CKD stage 3b (n = 9)</td>
<td>33%</td>
<td>56%</td>
<td>0%</td>
<td>1 y</td>
</tr>
<tr>
<td>2011 (2003-2011)</td>
<td>CKD stages 4-5 (n = 6)</td>
<td>33%</td>
<td>67%</td>
<td>33%</td>
<td>1 y</td>
</tr>
</tbody>
</table>

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; NA, not available; RRT, renal replacement therapy; Scr, serum creatinine; SUN, serum urea nitrogen.

aScr < 1.2 mg/dL in 82 of 85 pregnancies.

Preeclampsia (including women with CKD). The benefits are modest: a 25% relative risk reduction in high-risk women, resulting in a 10% reduced risk for small-for-gestational-age infants and preterm delivery, and 14% reduced relative risk for perinatal death. The intervention is inexpensive, safe, and well tolerated. Despite limited progress in preventing or predicting the condition, the outcomes for women who develop preeclampsia have improved. For example, the United Kingdom Confidential Enquiry Into Maternal Deaths has shown a reduction in deaths related to preeclampsia from 1.2/100,000 to 0.4/100,000 pregnancies in the 16 years following the introduction of national guidelines for early identification and management.

Pregnancies in women with more advanced CKD (defined as baseline creatinine > 2.0 mg/dL [>177 µmol/L] or eGFR < 30 mL/min/1.73 m²) were commonly associated with poor fetal growth, preterm labor, declining kidney function, and hypertensive complications. This led to management plans that proactively search for these problems throughout pregnancy so that at best, prompt changes to medication can be initiated to prolong gestation, or at worst, timing of delivery can be optimized. This was clearly shown in an Italian series of 91 pregnancies in women with CKD. Although preterm delivery rates were high at 44%, only 3 (3%) cases were spontaneous preterm labor; the rest were interventions for impending maternal or fetal distress predictive of adverse events. Infant survival was 100%.

AFTER PREGNANCY

Following delivery, the hemodynamic changes of pregnancy resolve within 6 weeks. For most women, this results in normalization of blood pressure, proteinuria, and kidney function to baseline values. However, for women with more advanced kidney disease, the physiologic “stress” of pregnancy can challenge the remaining nephrons beyond their tipping point, limiting recovery. There are few prospective studies of pregnant women with CKD that extend beyond the peripartum. Jones and Hayslett reported that 90% of women with modest decreased kidney function (baseline creatinine of 1.4-2.0 mg/dL [124-177 µmol/L]) returned to their baseline kidney function by 12 months postpartum, but rates decreased to 67% for those with creatinine levels of 2.0 to 2.5 mg/dL (177-221 µmol/L) and 50% for those with creatinine levels > 2.5 mg/dL (>221 µmol/L). Data from the United Kingdom showed a persistent loss of kidney function at 1 year postpartum in 12% of women with baseline eGFRs of 45 to 59 mL/min/1.73 m² but 73% in women with eGFRs < 45 mL/min/1.73 m². Conversely, a meta-analysis of studies in which almost all women had only mildly decreased kidney function did not show that pregnancy was a risk factor for progression of disease.

There are anecdotal data describing a pattern of steady decline in kidney function during pregnancy followed by a more abrupt deterioration to end stage requiring renal replacement treatment in the months following delivery. Studies to elucidate the pathophysiology of pregnancy-associated loss of kidney function...
have not provided an explanation. Possible mechanisms include the effect of increased blood pressure and proteinuria during pregnancy or the withholding of renoprotective agents such as angiotensin-converting enzyme inhibitors during pregnancy. An altered balance between angiogenic and antiangiogenic factors in pregnancy may aggravate glomerular injury and, in women with already damaged nephrons, lead to glomerular loss. This is supported in part by autopsy and urine chemistry studies. As shown in Table 3, regardless of the pathophysiology, there has been a consistent and unchanged statistic for 20 years; namely, that 1 in 3 women with CKD stage G4 will require renal replacement therapy within a year of delivery. It is still difficult to predict which women are at the greatest risk.

What of the infants born to mothers with kidney disease? Is there an effect of the uremic milieu on fetal development? Data are scant and confounded by the impact of placental insufficiency and the sequelae of prematurity. Animal models suggest that prematurity may affect nephron density and structure. Epidemiologic studies have linked prematurity with decreased kidney function in later life, but an independent effect of maternal kidney disease on these outcomes has not been proved, even in children born to mothers maintained by dialysis. Fortunately, there does not appear to be an increased incidence of congenital abnormalities in children born to women with CKD, above that expected from known hereditary conditions such as cystic kidney diseases.

More recently, attention has turned to the potential effect of maternal kidney disease on the incidence of neurodevelopmental defects. Interpretation is confounded by prematurity, which is known to have a negative impact on school performance and behavior, even in “late preterm” (34-36 +6 weeks’ gestation) infants. Piccoli et al compared the behavioral and emotional development of children born to mothers receiving dialysis to children born to mothers with thalassemia major or sickle cell disease and controls. Despite marked differences in rates of prematurity, birth weight, and neonatal care unit admission, no differences were found over controls except for a slight increase in pervasive developmental disorder scores, which were not significant after correction for multiple comparisons.

WHAT NEXT?

Table 1 summarizes the data showing that stillbirth and neonatal death are now rare events in pregnancies to women with kidney disease, but data in Table 2 remind us that such pregnancies remain high risk for complications, particularly for mothers with CKD stages 3 to 5. Supervision of these pregnancies must be regular and close. How can we predict the risk for poor outcomes with greater accuracy? We will have to rely on data from future observational studies, such as those currently being performed in Italy and the United Kingdom.

Advice to women with CKD has changed over the decades from recommending avoidance of pregnancy to offering support through a sometimes stormy gestation. What advice should be given to women with CKD stages 4 or 5 requesting assisted conception? Is it ethical to pursue assisted conception when the risks to maternal health are high and the likelihood of success is low? How low and high do these risks need to be to refuse? A woman’s right to not have a child is enshrined in many nations’ laws, but the right to have a child is not. The response will vary depending on the availability of resources, funding structures, and cultural and religious opinions.

Finally, women with CKD (and those who supervise their health) should take some confidence from the most recent published results, although these series come from developed nations. International infant mortality rates vary by a factor of 70 (from 1.5/1,000 births in Monaco to 107/1,000 births in Afghanistan). Provision of dialysis varies from 66 per million in Indonesia to 3,021 per million in Taiwan. It is therefore obvious that the most effective way of diminishing kidney disease as a barrier to motherhood worldwide is by achieving global equality of maternal and pediatric medical care.

ACKNOWLEDGEMENTS

Support: None.

Financial Disclosure: The author declares that he has no relevant financial interests.

Peer Review: Evaluated by 3 external peer reviewers, the Feature Editor, and the Editor-in-Chief.

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