REVIEW ARTICLE

Pregnancy management and outcome in women with chronic kidney disease

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Abstract

An increasing number of pregnancies occur in the presence of chronic kidney diseases (CKD), mainly including chronic glomerulonephritis (GN), diabetic nephropathy (DN), and lupus nephritis (LN). The most important factor affecting fetal and maternal prognosis is the degree of renal function at conception. In the majority of patients with mild renal function impairment, and well-controlled blood pressure, pregnancy is usually successful and does not alter the natural course of maternal renal disease. Conversely, fetal outcome and long-term maternal renal function might be seriously threatened by pregnancy in women with moderate or severe renal function impairment. The last few years, advances in our knowledge about the interaction of pregnancy and renal function resulted in the improvement of fetal outcome in patients with chronic renal failure and also in the management of pregnant women with end-stage renal disease (ESRD) maintained on dialysis. However, women with impaired renal function and those on dialysis should be carefully counseled about the risks of pregnancy. Hippokratia 2013, 17, 2: 163-168

Keywords: chronic kidney disease, high-risk pregnancy, chronic glomerulonephritis, diabetic nephropathy, lupus nephritis, fetal outcome.

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Introduction

Pregnancy in women with chronic kidney disease (CKD) is relatively uncommon and there is a paucity of data on which to base clinical management and counseling recommendations[1]. In this non-systematic review (overview), we examine the effect of CKD on pregnancy outcome and fetal health. For this purpose, we have reviewed all English-language relevant publications identified through an electronic search in the major electronic databases (Medline, Embase) from 1984 to 2009. We also address the effect of pregnancy on the course of maternal renal disease.

Epidemiology of CKD during pregnancy

The prevalence of CKD in pregnancy cannot be ascertained from the available literature. From a large health maintenance organization in the southwestern United States during 1994 to 1997, 4% of childbearing-aged women have CKD, defined as serum creatinine (Scr) ≥1.2 mg/L (creatinine 1mg/L=88.4μmol/L)[2] or glomerular filtration rate (GFR) <90mL/min/1.73m^2. Given that a substantial increase in maternal (GFR) occurs regularly during pregnancy, including in women with CKD, the percentage of pregnant women with CKD must be even higher.

There are several possible reasons for the reported rarity of CKD in pregnancy. First, the pregnant population is usually young and relatively healthy. Second, pregnant women are not routinely screened for renal dysfunction. Third, many women with substantial renal insufficiency or renal failure are either beyond child-bearing age or infertile[3]. Finally, incomplete reporting of underlying CKD might also contribute. Reflecting its frequency in the population of childbearing-aged women, diabetic nephropathy is generally the most common cause of CKD during pregnancy. However, virtually any type of CKD can be found in the setting of pregnancy, including chronic glomerulonephritis, systemic lupus erythematosus, reflux nephropathy, polycystic kidney disease, and tubulointerstitial diseases.

Pregnancy outcomes

In reviewing this subject, it is important to distinguish between primary kidney diseases and systemic diseases affecting the kidneys, because the latter can contribute to maternal and fetal outcomes in ways beyond the presence of nephropathy. Most of the published studies represent small, retrospective series from single centers, thus compromising the generalizability of their conclusions[4]. Variation in the definitions of CKD as well as the maternal

and fetal outcomes used by authors limits comparisons between studies.

Nonetheless, the available data suggest that the degree of renal function impairment is the major determinant of pregnancy outcome. Besides the severity of CKD, clinical features such as hypertension and heavy proteinuria also figure as important prognostic factors[5].

Clinical features of renal disease

The development of hypertension during pregnancy increases the likelihood of GFR deterioration. Women with GFR-decline during pregnancy had a 3-fold higher prevalence of hypertension than those with stable GFR[6]. The overall fetal death rate is also 2 to 3 times higher in hypertensive than in normotensive pregnancies[7-10]. However, this adverse effect essentially manifests when hypertension is present at conception or develops early in pregnancy[10,11]. Hypertension developing late in pregnancy, even in the context of superimposed preeclampsia, usually has no deleterious effect on fetal outcome[10,11].

Proteinuria commonly reflects the degree of kidney damage but also holds prognostic value for progression of kidney disease. In a review of asymptomatic pregnant women with proteinuria >500 mg/day, not previously known renal disease and no evidence of preeclampsia, 20% of them progressed to ESRD at a median time of 5 years[12]. When proteinuria exceeds 1 g/day, there is a greater tendency for accelerated GFR-decline and nearly a 2-fold higher incidence of ESRD[8,10,13]. The impact of proteinuria on fetal outcome is equally important. In the previously described series of asymptomatic pregnant women with substantial >500 mg/day proteinuria, although 93% of pregnancies resulted in live newborns, almost one half delivered prematurely and almost one quarter had growth restriction[12]. When present from the first trimester of gestation, nephrotic-range proteinuria is an important risk factor of spontaneous abortion, prematurity, and growth restriction. Similarly to hypertension, no significant impact on fetal outcome was noted when the nephrotic syndrome developed later in pregnancy[10,11,14].

Severity of CKD and pregnancy outcome

Mild CKD (Scr <1.3 mg/dl or GFR 60-89 mL/min/1.73m^2)

Worsening of hypertension and proteinuria, and development of preeclampsia occur in as many as one third of pregnant women with mild CKD. Prematurity, low birth weight, and fetal death are slightly higher in women with mild CKD than in normal women[7-9,11,15-24]. Recent data suggest a successful fetal outcome in 98% of pregnancies, while 65% of the pregnancies resulted in no fetal complication, such as preeclampsia, intrauterine growth retardation (IUGR), or preterm delivery[19].

In a review of the outcome of 906 pregnancies in 558 women with histologically proven primary kidney disease and mild renal insufficiency (60-89mL/min/1.73 m^2), the kidney function showed a reversible deterioration in 8% of women and a progressive decline in only 3%[7-9,11]. Long-term follow up suggests that pregnancy has no deleterious effect on maternal renal disease when renal function is near normal GFR>90mL/min/1.73 m^2 or Scr<1.3 mg/dl at conception[6]. In a case-control analysis provided by Jungers et al, pregnancy did not emerge as a risk factor for ESRD[10].

Moderate CKD (*Scr 1.3-1.9 mg/dl or GFR 30-59 mL/min/1.73m^2)*

The rate of complications is clearly higher in pregnant women with moderate CKD than in those with mild CKD[25]. The rate of preterm delivery is higher (50-55%) compared with mean rates of 10% among pregnant women in developed countries, as well as, fetal mortality is also higher (up to 6%) and 34-37% of infants are small for gestational age[9,11,13,19,21-23,25-27].

Hypertension and proteinuria are more common and often worsen during gestation[26]. Approximately, 25-38% of pregnant women with moderate CKD had an increase in Scr during pregnancy[25,26]. This decline in kidney function can persist in one third of the women for 6 months postpartum, and in 10% of the total cohort can reach ESRD. Women with moderately decreased GFR (59 to 40 mL/min/1.73m^2 corresponding to Scr between 1.4 and 1.6-1.7 mg/dl) can have a successful pregnancy without substantial risk of progression of their renal disease. Contrariwise, women with a more severe renal functional impairment (GFR<40 mL/min/1.73m^2) and proteinuria exceeding 1 g/day had poorer outcomes, the combination resulting in worse outcomes than either factor alone[13].

Severe CKD (Scr >1.9 mg/dl or GFR 15-29 mL/min/1.73m^2*)*

Complications are even higher in women with more severe kidney disease at conception. A consistent observation is that severe CKD is associated with severe proteinuria and combined with severe edema might reflect placenta edema and results in more (73%) preterm deliveries and lower (57%) birth weights. The fetal outcome in these women included a live birth rate of 64% but the neonatal survival was impressive at 100%[25].

In the study of Cunningham et al., 82% of women with severe CKD had chronic hypertension and 64% developed preeclampsia[27]. Substantial declines in maternal kidney function can occur in over 25% of women in this setting[13,25-27]. The risk of accelerated progression to ESRD is highest when Scr is greater than 1.9 mg/dl at the beginning of the pregnancy[13,16,25].

Comparative outcome

Our analysis of all series on the outcome of pregnancy in women with CKD published until 2009 revealed 2190 pregnancies in women with CKD and normal or near normal renal function (Scr <1.3 mg/dl or GFR>89 mL/min/1.73m^2) and 378 pregnancies in women with substantially impaired renal function (Scr ≥1.3 mg/dl or GFR≤89 mL/min/1.73m^2). A comparison of the pooled

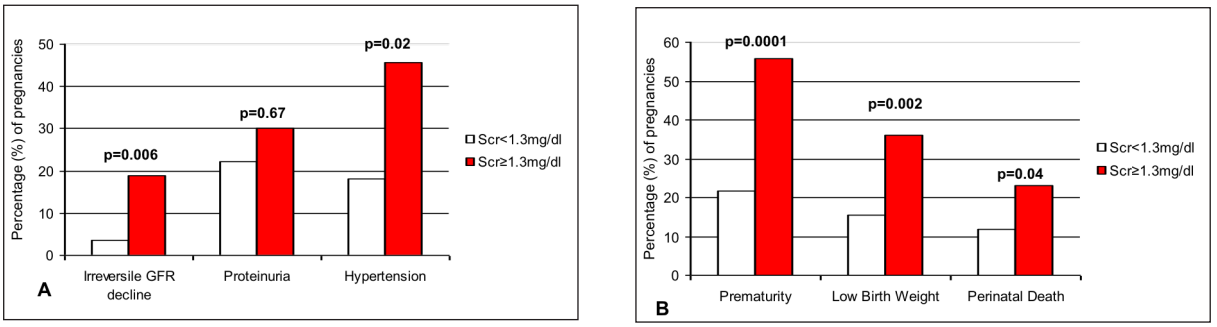

Figure 1: Maternal and fetal outcomes in women with CKD. Figure is based on our analysis of data from references 13-15, 18-27 and 31-36. The risks of irreversible decline in maternal renal function (19% vs 4%) and the development or worsening of arterial hypertension (46% vs18%) were significantly higher in women with more severe renal functional impairment. Proteinuria was not significantly different between the two groups (Panel A). The rates of premature fetal births (56% vs 22%), low-birth weight infants (36% vs 15%) and perinatal deaths (23% vs 12%) were significantly higher in women with more severe renal functional impairment (Panel B).

Scr denotes serum creatinine. To convert the values of serum creatinine to micromoles per liter multiply by 88.4
The Mann-Whitney U test was used for the analysis of the data.

data regarding maternal and fetal outcomes between the two groups is illustrated in figure 1. However, as there are many different causes of CDK, each with its own pathophysiology, it is beyond the scope of this review to discuss each entity separately.

Pregnancy in women with ESRD

Conception is not common in women on dialysis but its true frequency is unknown. Most pregnancies probably end in early spontaneous abortion[28]. Incidence of conception in ESRD appears to be increasing from 0.9% in earlier studies to 1-7% in more recent publications[29,30,31]. Since 1990, 52% of pregnancies in women on dialysis resulted in surviving infants, a much better result than in earlier years[30]. The available literature indicates that the percentage of surviving infants born to women on dialysis has improved from 27% before 1994 to 65% in more recent report. The overall infant survival rate is similar in women treated with hemodialysis or with peritoneal dialysis (37% vs 39.5%)[31]. Despite improved infant survival, the proportion of perinatal deaths (14.1%) remains higher than in the general population. Maternal mortality is low on the order of 1%[31]. Prematurity is seen in 80% of pregnancies. The mean age of pregnancy at delivery is 32 weeks and birth-weights of the infants are usually less than 2,000 g[28,30]. Hypertension is the most frequently reported maternal complication in this population occuring in 56% of women . Polyhydramnios (47.3%) is common and likely originates from the elevated placental blood urea that results in fetal solute diuresis and increased amniotic fluid volume[30].

Prepregnancy counseling and management

Whenever possible, pregnancy in women with CKD should be planned at a time when potential risks are minimized. Pregnant women with CKD should be cared jointly by an obstertrician familiar with fetal medicine and a nephrologist [13,14.] Women with CKD and preserved renal function are rarely to be cautioned against pregnancy. By contrast, women with known CKD and renal function impairment should be informed that the renal disease might progress during pregnancy, especially in those with moderate to severe disease[32,33]. Most pregnancies associated with moderate to severe renal insufficiency will result in a premature birth[33]. Moreover, women with a Scr level greater than 2.0 mg/dl or GFR less than 30mL/min/1.73m^2 should be counseled that they have an one-in-three chance of progressing to ESRD within 1 year post partum[34]. However, the ultimate decision of becoming pregnant is made with the woman, as long as we inform her about the risks and reassure her that all medical staff are there to support her decision.

In the presence of nephrotic syndrome, pregnancy should be delayed until appropriate treatment has been given[14,32]. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) should be withdrawn, if possible, before conception[35].

Women with DN should undergo a thorough evaluation of their nephropathy and achieve optimal glycemic control prior to becoming pregnant. Pregnancy should be discouraged in women with DN who have a Scr above 1.5 to 1.7 mg/dl or a GFR <60 ml/min/1.73m^2, especially in the presence of uncontrolled hypertension[36]. In women with LN, conception should preferably be planned for a period of stable, sustained remission of at least 6 months[37].

Women on dialysis should be informed of the possibility of fertility and the risks of pregnancy, including fetal outcomes and maternal complications. Finally, these women should be counseled that renal transplantation affords the best chances for pregnancy and a viable birth[32].

Management guidelines of pregnancy in women with CKD and those on dialysis are summarized in Tables 1 and 2 [38,39]. Maintenance immunosuppression is often required for a substantial number of women with underlying

Table 1: Guidelines for the management of pregnant women with CKD.

1) Blood pressure control:	-Avoid or stop ACEI or ARB; drugs of choice: methyl-dopa, calcium channel blockers, hydralazine, beta-blockers, and labetalol. -Diuretics (if needed) used cautiously to prevent hypovolemia. -Maintain blood pressure below 140/90mmHg.
2) Anemia:	-Maintain hemoglobin levels of 100-110g/L. -Iron and folic acid supplementation -Higher doses of rhEPO might be needed.
3) Acid-base and electrolyte balance:	-Maintain serum HCO_3^-≥24 mEq/L and avoid hypocalcemia. Use sodium bicarbonate, calcium carbonate, and vitamin D analogs.
4) Nutrition:	-Provide daily protein intake of 1g/kg with an additional 20 g for fetal growth.
5) Renal biopsy:	-Avoid after 32 weeks of pregnancy;Indications before 32 weeks include:unexplained deterioration in GFR or or symptomatic nephrotic syndrome.
6) Initiation of supplemented dialysis:	-When BUN >50 mg/dl or serum creatinine >5- 7mg/dl, or for treatment of metabolic acidosis, electrolyte imbalance and volume overload.

(Adapted from references 28,30,32), Abbreviations: CKD: chronic kidney disease, ACEI: angiotensin-converting enzyme imhibitors, ARB: angiotensin receptor blockers, rhEPO: recombinant human erythropoietin, GFR: glomerular filtration rate, BUN: blood urea nitrogen.

Table 2: Guidelines for the management of pregnant women on dialysis.

1)Hemodialysis(HD) prescription:	-4-6 dialysis sessions per week should be performed; non-reuse, biocompatible, smaller surface area dialyzer, slow-rate ultrafiltration - At least 20 hours per week -Predialysis BUN less than 45-50 mg/dl -Target fluid removal less than 1.5 kg/day
2) Peritoneal dialysis(PD):	Increase the number of exchanges Dialysate volumes from 7.5 to 12 L daily
3) Anemia:	Maintain hemoglobin levels of at least 10-11 g/dl Increase rhEPO dose by 50%-100% Iron and folic acid should be supplemented
4) Hypertension:	-Diastolic BP should range between 80 and 90 mmHg -Avoid maternal hypotension or volume depletion on dialysis -Avoid ACEI or ARB
5) Nutrition:	Protein intake 1.5 g/kg/day in HD and 1.8 g/kg/day in PD Calories: 30-35 kcal/kg/day Fluids: 0.75-1.5 L/day Calcium: 1500 mg/day; usually achieved with 2.5 mEq/L calcium dialysate. If indicated, vitamin D preparations can be continued.
6) Preterm labor:	Consider progesterone for prevention; tocolysis with beta-agonists, indomethacin (limited duration,) calcium channel blockers ,or magnesium (keep serum level <5 mg/dl)
7) Obstetric/fetal monitoring:	Close follow-up and fetal monitroring as soon as viability is reached.

(Adapted for references 5,16,26,32), Abbreviations: BUN: blood urea nitrogen, BP: blood pressure, ACEI: angiotensin- converting enzyme inhibitors, ARB: angiotensin receptror blockers, rhEPO: recombinant human erythropoietin.

chronic GN. Corticosteroids and azathioprine can be used safely during pregnancy, because they are not associated with major developmental abnormalities[40]. Cyclosporine does not appear to be a major teratogen, as suggested by a meta-analysis of 15 studies[41]. Registry data suggest that dose adjustments are required in the majority of pregnant women who receive cyclosporine to maintain therapeutic levels established before conception as pregnancy is associated with alterations in cyclosporine metabolism and distribution[42]. There is a paucity of data concerning the

effect of tacrolimus on pregnancy. As with cyclosporine, patients taking tacrolimus require frequent monitoring of drug levels[43]. Mycophenolate mofetil (MMF) is contraindicated in pregnancy. According to the European Best Practice Guidelines, MMF should be discontinued at least six weeks prior to attempted conception and patients switched to another agent (such as azathioprine)[44].

Women with incipient or overt DN who are receiving ACEI or ARB should be changed to other agents[35]. Dihydropyridine calcium channel blockers can be useful in such women..Strict blood pressure control is recommended in pregnant women with DN, goal blood pressure being 110-129/65-79mmHg[45].

In pregnant women with LN, distinguishing between preeclampsia and LN flare is important. Flares of LN are likely to be associated with hypocomplementemia and increased titers of anti-DNA antibodies[46]. All women with LN should be tested for the presence of anticardiolipin antibodies and lupus anticoagulants. Women with such antibodies should either receive low dose aspirin (75-100 mg/day) or low-dose subcutaneous heparin from the beginning of pregnancy[47]. Fetal heart block is a serious complication that occurs in babies born to mothers with anti-Ro/SSA or anti-La/SSB antibodies, who might derive benefit from serial fetal echocardiographic monitoring[47]. Patients with severe LN first developing or relapsing in pregnancy should be aggressively treated with high-dose corticosteroids. Azathioprine is also safe to use during pregnancy. Cyclophosphamide can be used to treat acute worsening of LN unresponsive to other therapy[48]. By contrast, MMF and methotrexate should not be used during pregnancy[49]. Non-steroidal anti-inflammatory drugs are generally safe during the latter part of the first trimester as well as during the second trimester but they should not be used in the last trimester due to increase risk of miscarriage and premature closure of fetal ductus arteriosus. Women without any signs of active LN require no specific treatment during pregnancy[50].

Patients with lupus in stable remission during pregnancy but with a history of proliferative LN should receive preferably a course of corticosteroids in late pregnancy or at least for 2-3 months post partum to prevent late renal flares. Women who show evidence of increased serologic activity but remain asymptomatic should be monitored more closely. No therapy for serologic findings alone is indicated, with the possible exception of the development of antiphospholipid antibodies. Treatment of postpartum women with active LN is the same as in non pregnant women[47,49].

In conclusion: An increasing number of pregnancies is complicated by CKD. The most important factor affecting fetal and maternal prognosis is the degree of renal functional impairment at conception. In the majority of patients with CDK who have mild renal disease, preserved renal function and well-controlled blood pressure, pregnancy is usually successful and doesn't alter the natural course of maternal renal disease. Conversely, fetal outcome and long term maternal renal function might be seriously threatened by pregnancy in women with impaired renal function. Advances in our knowledge have improved the management and fetal outcome of pregnant women with ESRD maintained on dialysis. However women with impaired renal function and those on dialysis should be carefully counseled about the risks of pregnancy.

Conflict of Interest

BE has a conflict of interest to declare: travel grants by Merck Sharp & Dohme.
TD has no conflict of interest to declare.
SM has no conflict of interest to declare.
TB has conflict of interests to declare: Unrestricted research grants, travel grants and honorarium by Merck Serono and Merck Sharp & Dohme as well as travel grants and honoraria by IBSA & Ferring.

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