REVIEW ARTICLE

Pregnancy in women with renal disease. Yes or no?

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Abstract

Women with renal disease who conceive and continue pregnancy, are at significant risk for adverse maternal and fetal outcomes. Although advances in antenatal and neonatal care continue to improve these outcomes, the risks remain proportionate to the degree of underlying renal dysfunction.

The aim of this article, is to examine the impact of varying degrees of renal insufficiency on pregnancy outcome, in women with chronic renal disease and to provide if possible, useful conclusions whether and when, a woman with Chronic Kidney Disease (CKD), should decide to get pregnant.

This article, reviews briefly the normal physiological changes of renal function during pregnancy, and make an attempt to clarify the nature and severity of the risks, in the settings of chronic renal insufficiency and end stage renal disease, including dialysis patients and transplant recipients. Hippokratia 2011; 15 (Suppl 1): 8-12

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Pregnancy and kidney disease

Renal disease during pregnancy is relatively uncommon. Reviewing the available literature, it is difficult to define the exact incidence of chronic renal disease in pregnancy. In a population based study of pregnant women with kidney disease, the diagnosis of renal disease before pregnancy was only 0.03%[1]

Consequently it does seem reasonable to conclude that chronic renal disease in pregnancy is uncommon. For example, in a 18-year review from Parkland Memorial Hospital, there were only 37 women whose pregnancies were complicated by moderate- to-severe renal insufficiency for an approximate incidence of 2 per 10000 women[2].

In a more recent review by Trevisan and colleagues in 2004, the prevalence of moderate chronic renal insuffiency was 6 per 10.000 birth in their hospital from 1989 to 1999[3].

Fisher and colleagues, in a review of Colorado birth and death certificates from 1989 to 2001, found 911 births from women with the diagnosis of kidney disease out of 747.368 births for a frequency of 0,12%(12 per 10.000)[4].

There are several possible reasons for why renal insuffiency is uncommonly associated with pregnancy. First and more common is the fact that many women with significant renal insuffiency or renal failure are either beyond childbearing age or infertile[5,6].

Another important reason may be incomplete reporting or data collection and the fact that the incidence of mild renal disease is often not included in many of the reported series.

The mentioned rates can be justified more precisely when using the classification of chronic renal disease into five stages according to the level of renal function (Table 1). Stages 1 and 2 (normal or mild renal impairment with persistent albuminuria) affect up to 3% of women of child bearing age(20-39 years).Stage 3-5(glomerular filtration rate<60 ml/min) affect around one in 150 women of childbearing age, but because of reduced fertility and increase rate of early miscarriage, pregnancy in these women is less common[7].

Table 1: Stages of chronic kidney disease.

Stage	Description	Estimated GFR (ml/min/1.73m^2)
1	Kidney damage with normal or raised GFR	>90
2	Kidney damage with midly low GFR	60-89
3	Moderately low GFR	30-59
4	Severy low GFR	15-29
5	Kidney failure	<15 or dialysis

GFR=Glomerular filtration rate. (After permission from Williams D BMJ 2008; 336: 211-215).

Most women with chronic kidney disease who become pregnant have mild renal dysfunction and pregnancy does not usually affect renal prognosis (Table 2).

In a review by Bar and colleagues, among 46 pregnancies in 38 women with chronic renal insuffiency, 22% had preeclampsia, 22% preterm delivery, and 13% growth restriction, whereas the cesarean delivery rate was 24%[5].

Table 2: Estimated effects of pregnancy renal function on pregnacy outcome and maternal renal function. Values are the estimated percentage of women or neonates affected.

	Effects on pregnancy outcome				Loss of >25% of renal function		
Mean (SD) pregnancy serum creatinine value (mg/ml)	Fetal growth restriction	Preterm delivery	Pre-eclampsia	Perinatal deaths	During pregnancy	Persists pospartum	End stage renal failure after 1 year
<1.4	25	30	22	1	2	10	0
1.4-2	40	60	40	5	40	20	2
>2	65	>90	60	10	70	50	35
On dialysis	>90	>90	75	50*	N/A	N/A	N/A

N/A:Not applicable.
Estimates are based on literature from 1985-2007 with all pregnancies attaining at least 24 weeks gestation[4,8-10].
*If conceived on dialysis ,50% of infants survive;if conceive before introduction of dialysis, 75% of infants survive. (After permission from Williams D BMJ 2008; 336: 211-215).

The low incidence of complications in this review, can be traced to the fact that nearly 90% of the women had only mild renal insuffiency. Only 2(4,4%) of the newborns required admission to the neonatal intensive care unit (NICU).

Jones and Hayslett found that among 82 pregnancies of 67 women with renal function stage three to five, 59% were premature, 37% presented fetal growth restriction, 59% underwent a cesarean delivery and the infant survival rate was 93%.[9] Jungers and colleagues in their review of 43 pregnancies in 30 women reported a success rate for live births of 82% after excluding first trimester abortions[10].

Holley and colleagues in their study of 43 pregnancies in 40 women, reported an overall pregnancy loss of 32.6%[11].

The reason for the variances in outcome in the literature is due to the different degrees of renal insuffiency and possibly various types of primary renal disease in the pregnant women studied. The presence of hypertension consists a significant factor indicating the poor prognosis of pregnancies outcome. As pointed out by Lindheimer and Katz pregnant women with minimal renal dysfunction and normal blood pressures have over a 90% chance of successful outcome. Moreover it is unlikely that pregnancy in this group will affect the progression of renal disease[12].

A population based study from Norway linking 3405 women who gave birth to 5655 singletons after 11 years follow up, concluded that women with GFR 60-89 ml/min/1.73 m2 were not at increased risk for preeclampsia,small gestation age or preterm birth unless they were also hypertensive[13]. Preexisting proteinuria and hypertension both increase this risk. Settler and Cunnigham, in a review of 65 pregnancies in 53 asymptomatic women with significant proteinuria (>500 mg/day), and no known preexisting renal disease or diabetes reported that 62% presented renal dysfunction and that in 40% chronic hypertension coexisted[14].They also reported that 93% of 53 pregnancies resulted in live newborns (excluding abortions) but almost one half delivered prematurely and one quarter had growth restriction. It is important to notice that 205 of the 53 women with follow up, progressed to end stage renal disease at median 5 years.

Small mainly uncontrolled retrospective studies have shown that women with the worst renal function before pregnancy are at greatest risk of an accelerated decline in renal function during pregnancy (Table 2).

Chronic hypertension, preeclamsia, anemia, fetal growth restriction and prematurity are common complications in pregnant women with moderate to severe renal insuffiency. A retrospective series of women with chronic kidney disease (87 pregnancies) found that those who initially had moderate renal impairment (serum creatinine 1,5-2,5 mg%) had a risk of a decline in renal function during pregnancy, which persisted after birth in about half of those affected[7].

In the observation study by Cunningham and colleagues, there were 37 pregnancies complicated by chronic renal disease that was moderate (serum creatinine level 1,5-2,5 mg%) to severe (serum creatinine level greater than 2,5 mg%). In the 26 women with moderate renal disease 62% had chronic hypertension, 58% had preeclampsia, and 73% had anemia. Moreover, 80% of the women with hypertension and moderate renal disease developed superimposed preeclampsia, versus 30% of the patients without hypertension and moderate renal disease[2].

The live birth rate of these 26 women was 88%,the fetal growth restriction rate 35% and the preterm birth rate 30%. Among the 11 women with severe renal insuffiency 82% were hypertensive, 64% had preeclampsia and all of them (100%) had anemia. These women with severe

renal insufficiency had a 64% of live birth rate, 43% of fetal growth restriction rate, and 86% of preterm birth rate. No stillbirths were reported in the 11 women with severe renal insuffiency. Six of the patients with moderate to severe renal insuffiency had 50% of worsening of their renal function during gestation.

A prospective study assessing the rate of decline of maternal renal function in 49 women with chronic kidney disease stages 3 to 5 before pregnancy confirmed these earlier observations[10].Women with both an estimated glomerular filtration rate <40 ml/min/1.73m^2 and proteinuria >1g/24h before pregnancy showed an accelerated decline in renal function during pregnancy[15].Chronic hypertension predisposes women to preeclampsia and this may explain why some women with milder renal dysfunction also have a gestational decline in renal function. The risk of such a decline is reduced when hypertension is controlled.

Pregnancy and Dialysis

Pregnancies outcome among women undergoing dialysis is markedly increased over the last years. Okundaye and colleagues have reported the data from a large registry of pregnancy in dialysis patients .In a survey of 2299 dialysis units involving 6230 women aged 14-44 years (1699 peritoneal dialysis and 4531 hemodialysis), they found 184 pregnancies (2%),in women who were on dialysis before conception and 57 who were initially dialysed during pregnancy. The infant survival was better (73,6%) ,in those women who began dialysis during pregnancy, than in those who conceived after dialysis was initiated (40,2%)[16].

There was a trend toward better infant survival in women who received dialysis ≥ 20 hours per week and a weak correlation between numbers of hours of dialysis and gestational age(p=0.05).Seventy-nine persent of women had some degree of hypertension, and 32 persent had blood pressure higher than 170/110 mm Hg .Eleven infants had congenital abnormalities, 11 had long term medical problems. Eighty-four percent of infants born to women who conceived after starting dialysis, were premature. The authors concluded, that increasing dialysis time may improve outcome, but prematurity remains a major cause of morbidity and likely contributes to a high frequency of long-term medical problems in surviving infant[16].

In a review of six studies from 1992 through 2002 of dialysis patients in pregnancy, Holley and colleagues reported a pregnancy rate of 1-7% and an infant survival rate of 30-50%[11].The spontaneous abortion rate from three of the studies ranged from 12% to 46%. Informations of complications were provided by four studies. Polydramnios was present in 42% to 79% (three studies), cesaerian delivery rate 46% to 53% (two studies) and hypertension in 42% to 79% (three studies).

Polyhydramnios occurs usually between 19 and 20 weeks of gestation, it is associated with peak frequency of spontaneous second trimester abortion and with the onset of premature contraction and labor, and it is related to changes in fetal epidermal and renal function. It has been hypothesized that fetal skin may act as diffusing membrane permitting the extension of the fetal extracellular fluid space to the amniotic fluid causing biochemical changes of the amniotic fluid[17].

The review of the literature supports the theory that intensive dialysis provides better results on pregnancy outcome (ie live birth). However a defined statement on the advantages or disadvantages of intensive dialysis cannot be ascertain because of the lack of data on the effect of dialysis on maternal or fetal outcome. The proposed method over the last decade was to increase the frequency of dialysis and maintain blood urea levels<100 mg/ml in order to decrease the risk of developing polyydramnios and concequently the risk of preterm labor and preterm delivery. Several case reports, small observation and retrospective studies supporting intensive dialysis (>20 h/week) in pregnant women, were proposed or recommended and the results showed an improvement in maternal outcome but as it was stated before in this article the presence of gestation age (32 weeks) and the birth weight (<1500 gr) remains significantly low[16,18-21].

Table 3: Neonatal outcomes, of RFH, UKTPR and NTPR 2001.

Preterm delivery(<37 weeks)	RFH	NTPR 2001	UKTPR
Mean gestation age	56.5%	52%	49%
Meanbirth age	34,9 weeks	36 weeks	
Mean birth weight	2204 g	2493 g	
Low birth weight(<2500g)	50%	45%	54%
Very low birth weight weight(1500g)	20%		18%
Fetal growth restriction	40.7%		8%
Small for gestation age(<10th percentile)	33%		

RFH (Royal Free Hospital)[26], NTPR 2001 National Transplatation Pregnancy Registry[27], UKTPR (UK Transplant Pregnancy Registry)[28]. (After permission from Thomson BC. Q J Med 2003; 96: 837-844).

Pregnancy and Transplantation

Transplantation usually provokes lost fertility in women suffering of end stage kidney disease. Pregnancy is then common, occurring in 12% of women at childbearing age[22]. Pregnancy success rate exceeds 90% after first trimester and the recovery of fertility is less common in women who undergo transplantation close to the end of their childbearing years[8]. The first reported successful pregnancy occurred in a recipient of a kidney transplant from an identical twin sister performed in 1958[23]. Since then, a great number of successful pregnancies has been reported in renal transplant recipients[24-26].

The three most important registries concerning pregnancy in transplant recipients include United States National Transplantation Registry (NTPR), a voluntary registry initiated in 1991 that relies on transplant center of patient self-reporting[27], the United Kingdom Registry (UKTPR), which has collected information on the majority of transplantation units in the United Kingom from 1997 to 2002[28], and the European Dialysis and Transplant Association Registry, which collected information on outcomes from European countries[29].

In a retrospective analysis from Royal Free and University College Scool of Medicine London.Thomson BC and colleagues,identified all pregnancies in their transplant recipients between 1976 and 2001. Among 48 pregnancies in 24 transplants, 32 (68%) resulted in live births including one twin pregnancy. The obstetric and maternal outcomes are recorded in Table 3[26]. The authors compared their results of neonatal and pregnancies outcomes (Table 4), with those of NTPR and UKTPR and their discussion emphasize the decisive role of the prepregnancies on kidney graft failure. With serum creatinine >1,5 mg/dl, pregnancies outcome is associated with obstetric complications. However a recent analysis of the University of British Columbia Vancouver, reports that pregnancy rates in kidney recipients are notably lower than those of general population, and live birth rates in kidney transplant recipients are also much lower than previously estimated. In this observation study Gill J and colleagues found that among 16195 female kidney transplant recipients aged 15-45 years in the United States between 1990 and 2003, pregnancy rate was 33 per thousand and progressively declined from 59 in 1990 to 20 in 2000. The pregnancy rate in kidney transplant recipients was markedly lower, and declined more rapidly than reported in the American population during the same period. The live birth rate between 1990 and 2003 was 19 per thousand female transplant recipients and decline in parallel with the pregnancy rate. The live birth rate was substantially lower than reported in voluntary registries of transplant recipients and the proportion of pregnancies resulting in unexpected fetal loss increased over time. Gill et al conclude that the reasons for the low birth rate are unclear and require further study and added why the pregnancy rate, declined over should be pursued in future studies[30].

A report of the AST Consensus Conference on Reproductive Issues and Transplantation state that many

Table 4: Comparative outcomes and data, of RFH, UKTPR and NTPR 2001.

	RFH (n=48)	UKTPR (n=117)	NTPR 2001 (n=487)
Live births	68%(32)	80%(93)	76%
Miscarriages	12%(6)	12%(14)	12%
Terminations	12%(6)	8%(9)	8%
Ectopics	4%(2)	<1%(1)	1.00%
Stillborn	4%(2)	0%	3%
	(n=27)		(n=313)
Pre-existing hypertension	77%(21)	75%	63%*
Pre-eclampsia	29%(8)	5%	30%
Diabetes during pregnancy	2%		12%
Delivery by caesarian section	59%	63%	52%
	(n=30)		
Graft dysfunction during pregnancy	16%	16%	11%**
Rejection during pregnancy	0%		4%
Graft loss <2 years post-partum	3.30%		9%

*Hypertension during pregnancy, **NTPR 1999-CsA data, CsA: Cyclosporine/Neoral, RFH: Royal Free Hospital, UKTPR: UK National Transplant Pregnancy Registry, NTPR 2001: National Transplant Pregnancy Registry. (After permission from Thomson BC. Q J Med 2003; 96: 837-844).

uncertainties exist including the risk that the pregnancy presents to the graft, the patient herself, and the long term risks to the fetus. It is also unclear how to best modify immunosuppressive agents or treat rejection during pregnancy ,especially in light of newer agents available where pregnancy safety has not been established[31,32].

Conclusions

The level of renal insuffiency is more important than the type of renal disease in predicting pregnancy outcome. Women with chronic kidney disease and mild renal insuffiency (Stages 1-2) with normal or controlled arterial pressure have an uneventful pregnancy and good renal outcome. The presence of uncontrolled hypertension and proteinuria (>500mg/day), have a detrimental effect on the outcome of pregnancy. Women with moderate to severe renal disease are at higher risk of complications during pregnancy. The presence either or both arterial hypertension or proteinuria in this group predisposes poor maternal and fetal outcome and accelerated decline in renal function. The likehood of a surviving infant resulting from pregnancy in dialysis patients is higher than previously observed. The increase dialysis time ameliorates the rate of maternal complications and improve outcome but prematurity remains a major cause of morbidity and contributes to a high frequency of long-term medical problems in survival infants. Kidney transplant recipients have been conceiving for more than 50years yet, and the results coming out of limited data concerning the short and long-term outcome for the mother and the infant seem to be contradictory. Further retrospective studies need to evaluate in order to base treatment recommendations and on which to offer advice to prospective parents.

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