Pregnancy in CKD Stages 3 to 5: Fetal and Maternal Outcomes

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Background: Prognostic criteria to inform women with moderate to severe renal insufficiency who wish to bear children are not well established.

Study Design: Longitudinal multicenter cohort study.

Settings & Participants: Nondiabetic white women with pregnancies proceeded beyond the 20th week and estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 (<1 mL/s/1.73 m^2) before conception.

Predictors: Baseline GFR and proteinuria (exposure); other clinical characteristics at conception (covariates).

Outcomes & Measurements: Difference in GFR decreases before conception versus after delivery (mixed linear models); low birth weight (<2,500 g), and maternal renal survival (logistic and Cox regressions).

Results: 49 women were studied. Mean serum creatinine and GFR at conception were 2.1 ± 1 (SD) mg/dL (186 ± 88 μmol/L) and 35 ± 12 mL/min/1.73 m^2 (0.58 ± 0.2 mL/s/1.73 m^2), respectively. Overall mean GFR after delivery was less than before conception (30 ± 13.8 versus 35 ± 12.2 mL/min/1.73 m^2 [0.50 ± 0.23 versus 0.58 ± 0.20 mL/s/1.73 m^2]; $P < 0.001$), but the rate of GFR decrease did not change (0.55 ± 0.8 versus 0.50 ± 0.3 mL/min/mo [0.0092 ± 0.013 versus 0.0083 ± 0.005 mL/s/mo]; $P = 0.661$). Independent of potential confounders, the combined presence of baseline GFR less than 40 mL/min/m^2 (<0.67 mL/s/m^2) and proteinuria with protein greater than 1 g/d, but not either factor alone, predicted faster GFR loss after delivery compared with before conception (1.17 ± 1.23 versus 0.55 ± 0.39 mL/min/mo; difference, 0.62 mL/min/mo; 95% confidence interval [CI], 0.27 to 0.96 mL/min/mo [0.020 ± 0.021 versus 0.0092 ± 0.007 mL/s/mo; difference, 0.10 mL/s/mo; 95% CI, 0.005 to 0.016 mL/s/mo]). The presence of both risk factors, but not either alone, also predicted shorter time to dialysis therapy or GFR halving (N = 20; hazard ratio, 5.2; 95% CI, 1.7 to 15.9) and low birth weight (N = 29; odds ratio, 5.1; 95% CI, 1.03 to 25.6).

Limitations: Generalizability to other settings; study power.

Conclusion: In women with renal insufficiency, the presence of both GFR less than 40 mL/min/1.73 m^2 (<0.67 mL/s/m^2) and proteinuria with protein greater than 1 g/d before conception predicts poor maternal and fetal outcomes.

Am J Kidney Dis 49:753-762.

INDEX WORDS: Angiotensin-converting enzyme (ACE) inhibitors; chronic kidney disease; fetal outcome; pregnancy; proteinuria; renal disease progression.

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It generally is accepted that pregnancy in women with chronic kidney disease (CKD) and mild renal function impairment, ie, CKD stages 1 to 2, corresponding to an estimated

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Received October 20, 2006; accepted in revised form March 27, 2007.

Support: P.R. holds a young investigator award from the Italian Society of Nephrology for 2005 to 2006 and received funding from the European Union (Marie Curie Actions-OIF, proposal #021676) for 2006 to 2007. Potential conflicts of interest: None.

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0272-6386/07/4906-0006$32.00/0
doi:10.1053/j.ajkd.2007.03.022

glomerular filtration rate (GFR) of 60 mL/min/1.73 m^2 or greater (≥1 mL/s/1.73 m^2),[1] is successful and does not alter the course of renal disease.[2] However, this view derives from retrospective studies that were not always consistent. Some investigators claimed an adverse effect of pregnancy on the natural course of renal disease for women with such specific renal diseases as focal and segmental glomerular sclerosis or immunoglobulin A nephropathy, even when renal function was normal or only mildly impaired and especially when arterial hypertension or severe proteinuria was present at conception.[3] Conversely, progressive deterioration in renal function, apparently related to pregnancy, was estimated to occur in a considerable proportion of women with moderate to severe CKD, ranging from 23% to 43%.[4-8] Such estimates are a matter of major concern for women with CKD who wish to give birth, although these estimates are not supported by long-term follow-up or by comparison of rates of progression before and after pregnancy.[4,6,8] In addition, fetal and maternal outcomes may vary not only as a function of baseline GFR, but also by the presence of other factors, such as proteinuria, hypertension, and required therapies. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are avoided because of their fetotoxicity[9] and potential teratogenic effect.[10] It is possible that changes in treatment schedules and/or worsening of proteinuria and hypertension control may negatively influence the course of renal disease.

The aims of this multicenter study are to: (1) establish whether pregnancy per se may accelerate the rate of renal function decrease when baseline GFR is less than 60 mL/min/1.73 m^2 (<1 mL/s/1.73 m^2) independent of other risk factors, and (2) identify prognostic criteria to inform women who wish to bear children and their caregivers of the likelihood of pregnancy complications and worsening of their renal disease. Specifically, we want to shed light on the impact on maternal and fetal outcomes of levels of renal function and proteinuria at conception, taking into account differences in renal disease diagnosis, the presence of hypertension, and use of ACE inhibitors or ARBs before pregnancy.

METHODS

Inception Cohort Assembled

Patients were enrolled from 1977 to 2004 by centers participating in the "Rene e Gravidanza" initiative of the Italian Society of Nephrology (http://www.sin-italy.org). The main purpose of the study group is to define categories of risk for poor pregnancy outcomes in women with CKD. Information for 7 women included in the cohort was collected retrospectively before the prospective study was planned in 1987. Per protocol, inclusion criteria were: (1) preexisting CKD, (2) serum creatinine level of 1.4 mg/dL or greater (≥124 μmol/l) or GFR less than 60 mL/min/1.73 m^2 (<1 mL/s/1.73 m^2) recorded within 3 months before conception or within the first month of pregnancy, (3) a gestation proceeded up to the 20th week, and (4) follow-up with adequate renal function assessment of at least 1 year after delivery or until dialysis treatment. Pregnancies that ended in the first trimester spontaneously or because of therapeutic abortion were excluded. Patients with diabetes or other systemic diseases also were excluded. Data for 5 pregnancies were included in a previous report.[8]

Definitions and Measurements

GFR was estimated using the Modification of Diet in Renal Disease 4-variable equation (based on serum creatinine level, age, sex, and race) and expressed in milliliters per minute per 1.73 m^2 of body surface area.[11] Rate of progression was assessed before and after pregnancy as loss of GFR in milliliters per minute per month. Reference points used for the assessment of progression rate were the first GFR less than 90 mL/min/1.73 m^2 (<1.5 mL/s/1.73 m^2) and GFR at conception, at 2 to 4 weeks after delivery, and at the end of follow-up. Serum creatinine measurements, used to establish reference points for the rate of GFR loss, were checked at least twice, and in the case of discrepancies, the mean value was adopted. Proteinuria was assessed by means of 24-hour urine collection after careful patient instruction and was checked at least twice. Per protocol, patients were categorized into 4 groups according to GFR (≥40 versus <40 mL/min/1.73 m^2 [≥0.067 versus <0.067 mL/s/1.73 m^2]) and proteinuria (protein ≥ 1 versus <1 g/24 h) at conception. The 4-level exposure resulting from the combinations of the two 2-level categories of baseline GFR and proteinuria with their interaction was the main predictor of interest in all analyses (GFR ≥ 40 mL/min/1.73 m^2, proteinuria with protein < 1 g; GFR ≥ 40 mL/min/1.73 m^2, proteinuria with protein ≥ 1 g; GFR < 40 mL/min/1.73 m^2, proteinuria with protein < 1 g; and GFR < 40 mL/min/1.73 m^2, proteinuria with protein ≥ 1 g [to convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667]). During pregnancy, all patients had at least 1 visit per trimester with clinical and laboratory assessment. Serum creatinine was measured in different laboratories, ensuring quality control.

Hypertension was considered present if systolic blood pressure was greater than 140 mm Hg and/or diastolic blood pressure was greater than 90 mm Hg in a sitting