

Pregnancy and early chronic kidney disease

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GUIDELINES

- a. Pregnancy generally does not affect the course of renal disease in women who have normal or near-normal renal function (plasma creatinine concentrations less than 200 µmol/L at conception or eGFR > 25 mL/min/1.73 m²) at conception provided blood pressure is well controlled. We recommend that these individuals should not be discouraged from conceiving purely on the basis of their renal disease (1C).
- b. CKD progression is probably accelerated by pregnancy in patients with poorly controlled hypertension or plasma creatinine concentrations of greater than 200 µmol/L at conception (equivalent to an eGFR < 25 mL/min/1.73 m² in a 30 year-old woman). The magnitude of this increase in risk compared to non-pregnant individuals with renal disease has not been established, but it is recommended that such patients be advised against falling pregnant (1C).
- c. Although foeto-maternal outcomes are generally favourable in pregnant patients with CKD, there is an increased risk of pre-eclampsia, pre-term delivery, need for neonatal intensive care and low birth weight babies compared with pregnant patients without CKD (1C).
- d. It is recommended that patients with CKD planning to fall pregnant should have their medications reviewed and modified prior to conception (1D). The anticipated benefits of each medication should be weighed against its potential risks. In particular, angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be discontinued. (1D).
- e. We recommend that pregnant patients with CKD should be carefully monitored for the development of pregnancy-induced hypertension, pre-eclampsia and renal functional deterioration, and should also be referred to a nephrologist (1D).
- f. The above recommendations also apply to women with functioning kidney transplants (1D).

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

IMPLEMENTATION AND AUDIT

Obstetric unit audits should examine foetomaternal outcomes for pregnancies in patients with pre-existing CKD (including impact on maternal kidney function).

BACKGROUND

Opinions vary markedly as to the frequency (or even the existence) of accelerated renal functional deterioration during and after pregnancy in women with chronic kidney disease. The available clinical evidence pertaining to the effect of pregnancy on the rate of GFR decline in CKD has been dealt with in the CARI Guidelines on the Prevention of Renal Failure Progression (http://www.cari.org.au/CKD_Prevent_List_Published/Pregnancy.pdf).

SEARCH STRATEGY

Databases searched: Text words for chronic kidney disease were combined with MeSH terms and text words for pregnancy. The search was carried out in Medline (1966 – 3 August 2009). No language restrictions were placed on the search. The conference proceedings of the American Society of Nephrology from 1994-2008 were also searched for trials.

Date of search/es: 25 August 2009.

WHAT IS THE EVIDENCE?

Recently, a population-based study [1] linking all 3405 women attending the Second Health Study in Nord-Trøndelag Norway 1995-1997 (HUNT 2 Study) and subsequent pregnancies in the Medical Birth Registry found that women with eGFR 60-89 ml/min/1.73 m² with or without albuminuria were not at increased risk for preeclampsia, small-for-gestational age (SGA) infants or preterm birth unless they were also hypertensive. Preterm birth risk in women with eGFR 60-74 ml/min/1.73 m² was significantly increased (OR 2.69, 95% CI 1.38-5.24, p=0.004). No significant interaction was seen between eGFR and albuminuria, but a significant additive interaction was seen between eGFR and hypertension. The probability of an adverse outcome increased significantly from 0.20-0.27 as GFR decreased from 105 to 65 ml/min/1.73 m², did not change significantly according to presence of albuminuria, but increased steeply from 0.25 to 0.48 for hypertensive women where GFR decreased from 105 to 70 ml/min/1.73 m². A major limitation of this study was that the event rates were exceedingly low (0 or 1) in women with eGFR values <60ml/min/1.73 m², raising uncertainties about the impact of a GFR < 60 ml/min/1.73 m² on outcomes. Moreover, the significant effect of blood pressure and eGFR on the composite adverse maternal outcome was primarily weighted by a significant effect on pre-term births in women with eGFR values between 60 and 74 ml/min/1.73 m². No significant independent effect of eGFR was observed on the individual outcomes of pre-eclampsia or SGA. Urine ACR was only available in a subgroup of the participants and the remaining values were replaced with multiple imputations. The possibility of misclassification/coding bias between pre-eclampsia and gestational hypertension could not be excluded.

A prospective, single centre study of 120 cases of pregnant mothers with CKD and 297 control patients (low-risk pregnancy without CKD) followed from the time of referral to 1 month after delivery during the period January 2000 to May 2009 demonstrated that foeto-maternal outcomes were generally favourable in CKD cases, although significantly increased risks were observed for pre-term delivery (44% vs 5%), caesarean section (58% vs 25%) and need for neonatal intensive care (26% vs 1%) compared with controls [2]. There was a tendency towards an increased risk of small for gestational age infants, although this did not reach statistical significance. No significant changes in serum creatinine or proteinuria were identified. The overall rate of pre-eclampsia was low. Pregnancy outcomes were correlated with hypertension, CKD stage and degree of proteinuria (above or below 1 g/day). The risks of caesarean section and pre-term delivery were increased even in pregnant patients with stage 1 CKD. The limitations of this study were its small sample size, single centre design and reliance on surrogate outcome measures with no reporting of patient-level outcomes (death and commencement of dialysis).

In summary, there are no RCTs or prospective controlled studies. Most of the literature addressing this subject is limited to retrospective studies and case series, which have suffered from many limitations including:

- a) case selection bias, since retrospective analyses often in tertiary institutions are likely to be biased in terms of selecting more severely diseased cases;
- b) recall bias
- c) small numbers with a low event rate (ie progression to end-stage renal failure);
- d) short follow-up times;
- e) collection of data from several decades ago when maternal and obstetric care (particularly with respect to anti-hypertensive treatment) were not as advanced as presently;

- f) lack of data prior to the index pregnancy, making it difficult to determine whether the natural history of a patient's renal disease was actually altered by pregnancy;
- g) failure to use controls or the selection of inappropriate controls (eg unaffected family members where maternal surveillance may have been altered by knowledge of the proband);
- h) lack of a secure histologic diagnosis in involved patients;
- i) infrequent or sub-optimal measures of renal function.

SUMMARY OF EVIDENCE

Data are conflicting, although the bulk of studies have suggested that when kidney function is normal or near-normal and hypertension is well-controlled at conception, the natural course of maternal renal disease due to a variety of causes is usually not adversely affected by pregnancy. Although the numbers of patients progressing to end-stage kidney disease (stage 5 CKD) in each of the studies are very small, the bulk of reports also suggest that the risk of deterioration in maternal renal function is increased mainly when conception has occurred at a plasma creatinine concentration in excess of 200 µmol/L or in the setting of poorly controlled hypertension. Whether such deterioration represents an acceleration of renal failure progression or merely the natural history of the underlying chronic kidney disease has not been conclusively established.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcome Quality Initiatives: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Case-control study examining the impact of CKD (including levels of albuminuria/proteinuria and eGFR) on foetomaternal outcomes of pregnancy (including development of end-stage renal failure within 12-18 months of completion of pregnancy).

CONFLICT OF INTEREST

David Johnson has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

REFERENCES

1. Munkhaugen J, Lydersen S, Romundstad PR et al. Kidney function and future risk for adverse pregnancy outcomes: a population-based study from HUNT II, Norway. *Nephrol Dial Transplant* 2009; **24**: 3744-50.
2. Piccoli GB, Attini R, Vasario E et al. Pregnancy and chronic kidney disease: a challenge in all CKD stages. *Clin J Am Soc Nephrol* 2010; **5**: 844.

APPENDICES

Table 1. Characteristics of included studies

Study ID	N	Study design	Participants	Follow up	Comments and results
[1] Munkhaugen et al. (2009)	3,405	Population-based	Women aged ≥ 20 years, attending the Second Health Study in Nord-Trondelag Norway (1995 – 1997). Data was linked with pregnancies registered in the Medical Birth Registry.	11 years	<ul style="list-style-type: none"> • Hypertensive women with eGFR 60 – 74 ml/min/1.73m² and eGFR 75 – 89 ml/min/1.73m² had significantly increased risk for: pre-eclampsia, small for gestational age (SGA) infant or pre-term birth OR 10.09 (95% CI: 2.38 - 42.87, P<0.001) and 2.58 (95% CI: 1.40 – 4.75, P<0.001) respectively, compared to women with eGFR ≥ 90 and no hypertension • Women with eGFR 60 – 89 ml/min/1.73m² with or without albuminuria were not at increased risk for preeclampsia, SGA infants or preterm birth, unless they were also hypertensive. • The probability of adverse outcomes associated with decreased eGFR increased from 0.20 to 0.27 as eGFR decreased from 105 to 65 ml/min/1.73m². The risk increased steeply from 0.25 to 0.48 for hypertensive women when eGFR decreased from 105 to 70 ml/min/1.73m².
[2] Piccoli et al (2010)	120 cases 297 controls	Prospective cohort	Cases: Women with kidney disease with singleton pregnancies. Controls: singleton low-risk pregnancies. Single centre, Italy	9 years	<ul style="list-style-type: none"> • Most outcomes, including gestational age at delivery, foetal weight, and need for NICU admission, were better in CKD stage 1 than in all other stages. However increased risks were observed in all CKD Stages when compared with controls: Caesarean section 58% vs 25% (P=<0.0001); Pre-term delivery 44% vs 5% (P<0.0001); Foetal weight 2631.7g \pm 786.5 vs 3268.3 g \pm 500.4 (P<0.0001); Admission to NICU 27% vs 1% (P<0.0001)