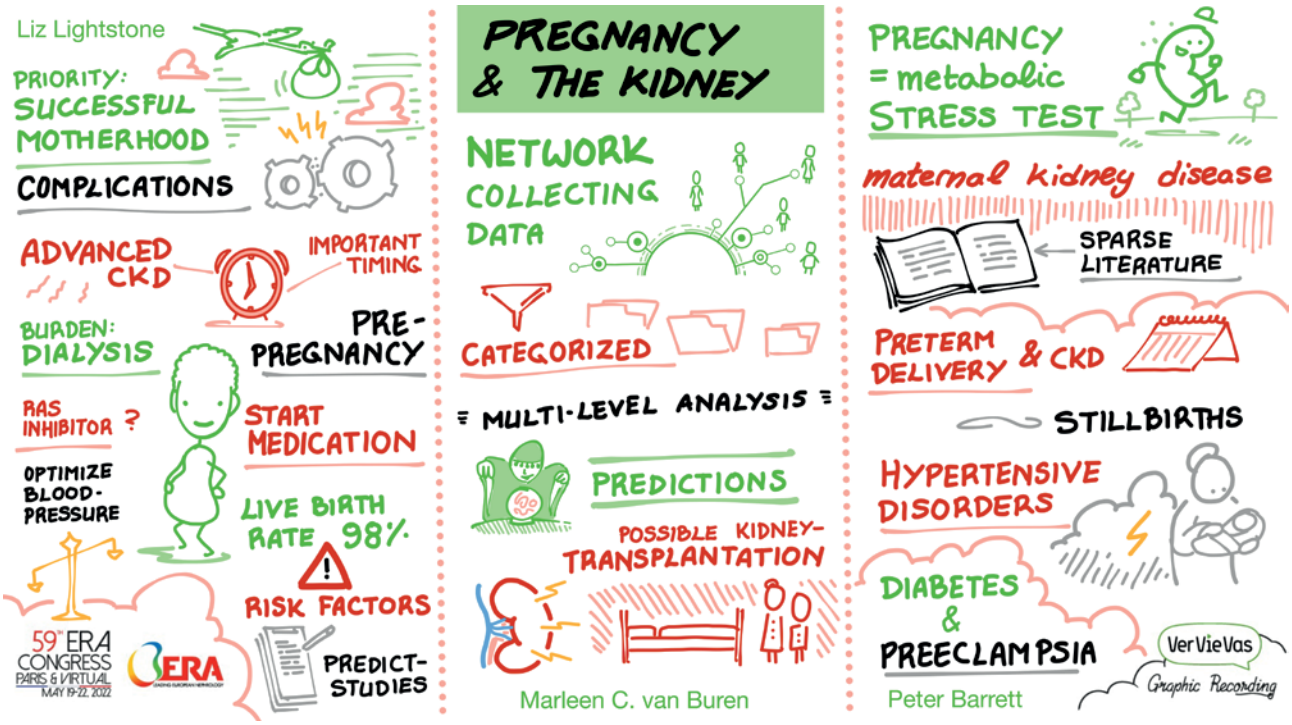
Symposium 2.5
Pregnancy and the kidney



Renal and pregnancy outcomes in advanced CKD patients

Liz Lightstone, United Kingdom

Chronic kidney disease (CKD) and other comorbidities in women of childbearing age are becoming more common, since the number of first-time births in women in their 30s and 40s has tripled and doubled, respectively. Fortunately, recent research enables medical professionals to provide better care for these patients before, during, and after pregnancy.

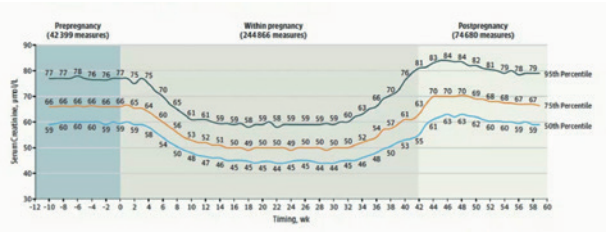


Figure 1.
Expected creatinine levels in pregnancy (from ref. 3)

Advanced CKD poses an increased risk of adverse outcomes, including, for the mother, preeclampsia, and possible accelerated loss of renal function, and for the fetus, fetal growth restriction and preterm delivery. Pre-pregnancy counseling should therefore include counseling on contraception, planning, and timing of pregnancy, review of current medications, and discussion about pregnancy and renal outcomes. Medications need to be reviewed carefully before pregnancy: some, such as those used in auto-immune medicine regimens, antihypertensives, and anti-diabetics, some should be discontinued even before planned conception (such as mycophenolate mofetil) or as soon as pregnancy is confirmed (such as ACE inhibitors), and alternative pregnancy safe medications started. In contrast, certain drugs should be introduced, such as hydroxychloroquine for patients with lupus nephritis and aspirin for all patients with CKD to reduce the risk of pre-eclampsia. During pregnancy, the dosage of some Immunosuppressants, most notably tacrolimus and cyclosporin, may also need to be revised due to altered handling of the drug during pregnancy. The retrospective and prospective cohort study led by Wiles and Webster followed 178 pregnancies in 159 women with CKD stages 3-5 – the live birth rate was high at 98% live birth rate but 56% of the babies were born pre-term. Early delivery

was more likely in women with hypertension and the risk doubled if they did not have a creatinine fall of at least 10% in early pregnancy. Proteinuria (urinary PCR) of more than 100mg/mmol was associated with an increased risk of having a baby with a lower than expected birthweight.

The fact that many women present to health professionals for the first time during pregnancy and that serum creatinine is not part of antenatal screening in most countries pose a considerable challenge to diagnosing kidney impairment in pregnant women. Therefore, it might be reasonable to include serum creatinine in routine prenatal testing and certainly in those women with known conditions that predispose to CKD such as diabetes or hypertension. Figure 1 highlights the range of creatinines to be seen in women of child bearing age pre, during and post partum. A creatinine of greater than 70, and certainly 77umol/l in pregnancy should raise concern about underlying kidney dysfunction. Multidisciplinary collaborative care during pregnancy is vital to ensure the mother's underlying disease, her blood pressure and proteinuria are adequately monitored and treated, and that the fetus is carefully reviewed to assessed fetal growth and development. Women with CKD are more likely to develop preeclampsia but it can be challenging to distinguish between worsening disease and superimposed pre eclampsia given both can present with hypertension and proteinuria. The recent advancement in measuring placental growth factor (PlGF), which is lower and declines precipitously in preeclampsia, has made this easier though the threshold at which PlGF is consider low may need to be higher in women with CKD. If kidney functioning is worsening due to underlying disease or the impact of pregnancy, but there is no preeclampsia and the fetus is not threatened, dialysis initiation can be considered when the urea is rising to 17mmol/l, rather than early delivery. If the woman is already on dialysis, the dialysis prescription should be increased at the onset of pregnancy, with previously optimized prescription pre-pregnancy. Decisions on delivery timing and mode should be guided by finding a balance between maternal health and the safety of the baby, the level of available neonatal care available, and avoiding acute kidney injury. Finally, post-partum care needs to take into consideration that pregnancy complications extend beyond the pregnancy, therefore proper follow-up must be conducted, not least to ensure that those women who presented for the first time in pregnancy, are fully diagnosed and have a proper treatment plan in place.

Effect of pregnancy on eGFR slope and predictors of pregnancy outcomes in kidney transplantation

Marleen C. van Buren, Netherlands

The nationwide cohort study from the PARTOUT (Pregnancy After Renal Transplantation OUTcomes) network from the Netherlands aimed to evaluate the pregnancy outcomes in kidney transplant recipients and to explore the effects of pregnancy on graft loss and eGFR after kidney transplantation. The study included 301 pregnancies in 202 patients, categorized by the value of pre-pregnancy eGFR.

First, the PARTOUT group looked at maternal outcomes per eGFR category and observed that the likelihood of development of gestational hypertension also rises with lower eGFR, while the probability of preeclampsia remains stable throughout the different eGFR groups, but rises to 100% at eGFR <30 mL/min. The combined adverse pregnancy outcomes (cAPO) were defined as low birth weight (<2500g), preterm birth (<37 weeks), severe hypertension in the 3rd trimester (>160mmHg systolic, >110mmHg diastolic blood pressure), and 3rd-trimester serum creatinine higher than preconception levels. The study concluded that overall pregnancy outcomes after kidney transplantation are positive, with a live birth rate of 93%, a mean gestational age of 35 + 4 weeks, and a mean birth weight of 2383 grams. The most important predictors of cAPO are high pre-pregnancy serum creatinine and the absence of a second-trimester decrease in serum creatinine or mean arterial pressure. Also, cAPO is a significant risk indicator for death-centered graft loss. (ref 4)

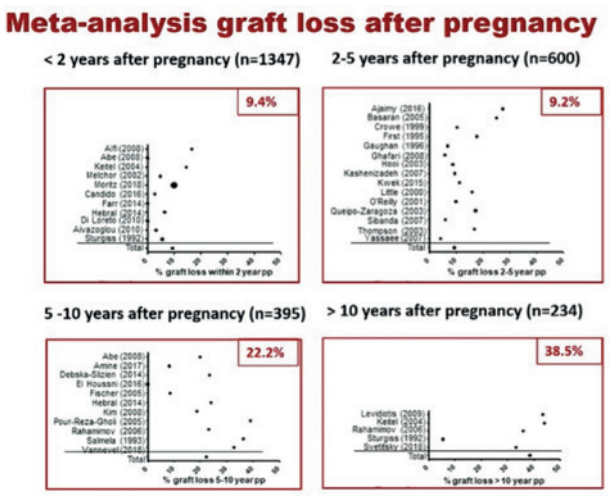


Figure 2.
Kidney graft loss after pregnancy

Furthermore, the PARTOUT group performed a meta-analysis on graft loss after pregnancy (ref 5 and figure 2). Ten of these studies used control groups to compare graft loss rates with women who did not get pregnant after kidney transplantation. The matched control groups

were heterogenic but most often for age and creatinine levels. No significant difference in graft loss was shown between the pregnant group and the control group. At last the PARTOUT group presented the multilevel analyses of pregnancy on eGFR slope. Results showed that pregnancy after kidney transplantation had no significant effect on eGFR, did not accelerate its slope, and did not amplify the negative effect of significant univariate predictors of worse eGFR. Also, multivariate generalized estimating equations analysis showed that transplant vintage, rejection before firs.t pregnancy, pre-pregnancy eGFR, and shorter transplant-to-conception interval are predictors of worse eGFR after kidney transplant, and not pregnancy itself. Graft survival after first delivery was significantly better in women with midterm hyperfiltration (>15% decrease in serum creatinine) during the first pregnancy (ref 6)

Adverse pregnancy outcomes and long-term maternal kidney disease

Peter Barrett, Ireland

There is increasing evidence that adverse pregnancy outcomes are associated with a higher risk of CKD later in life. Recent research by Peter Barrett aimed to assess whether post-pregnancy maternal CKD and end-stage kidney disease (ESKD) in previously healthy women may be associated with adverse pregnancy outcomes such as hypertensive disorders of pregnancy, preeclampsia and gestational hypertension, preterm delivery, delivery of a small for gestational age infant, gestational diabetes and pregnancy loss. Upon systematic review of the literature, research continued by conducting several original population-based cohort studies. The population of interest included women who had ever been pregnant and experienced at least one of the relevant adverse pregnancy outcomes. The control group included women who only had uncomplicated pregnancies. The data were obtained from the Swedish Medical Birth Register and included 1.9 million women and 3.8 million deliveries. The median follow-up period was 20.6 years and the outcomes observed were CKD and ESKD.

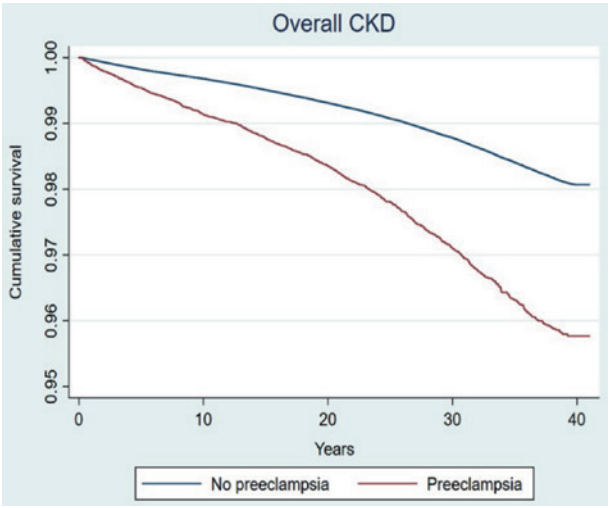


Figure 3.
The risk of developing CKD is related to the presence of preeclampsia during pregnancy

The first retrospective cohort study focused on pre-term delivery and found that women who had at least one preterm delivery before the 37th gestation week had a 39% higher risk of developing CKD during follow-up and more than double the risk of developing ESKD. These associations were stronger for women who had at least one extremely pre-term delivery (before 28 weeks gestation) or if they experienced pre-term preeclampsia. The next cohort study sought to measure whether women who experienced stillbirth have an increased risk for future kidney disease. The results showed that women who had at least one stillbirth had a modestly increased risk for CKD during follow-up and more than double the risk for ESKD over time. The third study investigated whether women who experienced hypertensive disorders during pregnancy have an increased risk of developing CKD, including subtypes of kidney disease. It concluded that women who had preeclampsia exhibited almost four times higher risk of developing diabetic or hypertensive CKD during follow-up compared to women who never had preeclampsia. More modest associations were observed for tubular interstitial disease and non-specific forms of CKD.

The most recent epidemiological study conducted by Barrett et al. focused on gestational diabetes and the long-term risk of CKD and ESKD, including subtypes of renal disease. It showed that subjects who had gestational diabetes alone and never developed type 2 diabetes had no significant risk of future kidney disease. On the other hand, women who went on to develop type 2 diabetes following pregnancy had a significantly higher risk of both CKD and ESKD, suggesting that gestational diabetes itself is not an independent risk factor.

Further research is needed to determine whether adverse pregnancy outcomes would add incremental value to existing clinical risk prediction tools. Also, some research gaps remain in terms of the risk profile of women who experience multiple adverse pregnancy outcomes concurrently. Finally, the effects of intermediate variables like post-pregnancy hypertension, hyperglycemia, or dyslipidemia need further consideration.

Further readings

1. Wiles K, Webster P, Seed PT, et al. The impact of chronic kidney disease Stages 3-5 on pregnancy outcomes. Nephrol Dial Transplant. 2021;36(11):2008-2017. doi: 10.1093/ndt/gfaa247. PMID: 33313680; PMCID: PMC8577624
2. Wiles KS, Bramham K, Vais A, et al. Pre-pregnancy counselling for women with chronic kidney disease: a retrospective analysis of nine years' experience. *BMC Nephrol.* 2015;16:28. doi:10.1186/s12882-015-0024-6
3. Harel Z, McArthur E, Hladunewich M, et al. Serum Creatinine Levels Before, During, and After Pregnancy. *JAMA.* 2019;321(2):205-207. doi:10.1001/jama.2018.17948
4. van Buren MC, Schellekens A, Groenhof TKJ, et al. Long-term Graft Survival and Graft Function Following Pregnancy in Kidney Transplant Recipients: A Systematic Review and Meta-analysis. *Transplantation.* 2020;104(8):1675-1685. doi: 10.1097/TP.0000000000003026.
5. Barrett PM, McCarthy FP, Evans M, et al. Risk of long-term renal disease in women with a history of preterm delivery: a population-based cohort study. *BMC Med.* 2020;18(1):66. doi:10.1186/s12916-020-01534-9
6. Barrett PM, McCarthy FP, Evans M, et al. Hypertensive disorders of pregnancy and the risk of chronic kidney disease: A Swedish registry-based cohort study. PLoS Med. 2020;17(8):e1003255. doi: 10.1371/journal.pmed.1003255.
7. Barrett PM, McCarthy FP, Evans M, et al. Stillbirth is associated with increased risk of long-term maternal renal disease: a nationwide cohort study. *Am J Obstet Gynecol.* 2020;223(3):427.e1-427.e14. doi:10.1016/j.ajog.2020.02.031
8. Barrett PM. Editorial: Adverse Pregnancy Outcomes-A Missed Opportunity to Prevent Chronic Disease?. *Int J Public Health.* 2021;66:582810. doi:10.3389/ijph.2021.582810

Written by Jasna Trbojevic-Stankovic.
All the speakers reviewed and approved the content.