

Challenges of kidney function evaluation in pregnancy

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Introduction/Context

The kidney plays a central role in maintaining physiological homeostasis during pregnancy. Since the 1950s, it has been known that measured glomerular filtration rate (mGFR), assessed by inulin clearance, increases during pregnancy, in parallel with an increase in renal plasma flow (RPF) measured by para-aminohippurate clearance.¹

According to the meta-analysis by Lopes Van Balen, inulin clearance increases by 37.7% before 14 weeks of gestation, by 46.6% between 15 and 21 weeks, by 40.2% between 22 and 28 weeks, by 35.6% between 29 and 35 weeks, and by 55.6% between 36 and 41 weeks compared with reference baseline values.²

Creatinine clearance rises significantly at the end of the luteal phase in non-pregnant women (~20%), followed by a sharp increase from early pregnancy (4 weeks gestation), until reaching 40–65% by mid-gestation, after which it stabilizes. Renal plasma flow increases by 50–85% during the first half of pregnancy, then gradually decreases from 26 weeks onward. Plasma volume expansion, which occurs primarily in the second half of pregnancy, contributes minimally to this increase; it has been demonstrated that systemic and renal vasodilation, mediated by hormones such as relaxin and, to a lesser extent, progesterone, explains this phenomenon. The filtration fraction ($[FF] = mGFR/RPF$) therefore decreases during pregnancy because the increase in renal plasma flow exceeds that of glomerular filtration. Due to the decline in plasma flow in late pregnancy without a concomitant decrease in GFR, the filtration fraction rises again in late pregnancy (36 weeks' gestation). It has been demonstrated in experimental models of rats that the increase in single-nephron GFR was secondary to the augmented renal plasma flow resulting from equivalent vasodilation of the pre- and post-glomerular arterioles without an increase in hydrostatic pressure.^{1,3}

The decline in renal plasma flow in late pregnancy was initially attributed to vascular compression by the gravid uterus in the supine position; however, it was later demonstrated that maternal position has no effect on creatinine or para-aminohippurate

clearance. The late-pregnancy decrease in renal plasma flow without a decrease in GFR is instead due to increased post-glomerular arteriolar resistance.¹

Tubular function and water/electrolyte handling are also modified physiologically during pregnancy, with modest increases in proteinuria and glycosuria, low osmolality, and hyponatremia. There are no data available on the impact of pregnancy on tubular creatinine secretion.^{1–3}

Monitoring kidney function in pregnancy

Monitoring kidney function during pregnancy is particularly important in women with pre-existing chronic kidney disease or acute functional decline, as this may necessitate preterm delivery to reduce maternal-fetal morbidity and mortality.

The gold standard for GFR determination requires inulin or radioisotope infusion, which is time-consuming and costly. Furthermore, administration of radioisotopes (I-iothalamate, Technetium-99 m Diethylene Triamine Penta-Acetic acid or Chromium-51 Ethylenediaminetetraacetic acid) is relatively contraindicated during pregnancy.

Plasma creatinine decreases during pregnancy mainly due to hyperfiltration and hemodilution. Average serum creatinine values during pregnancy are approximately 84% of non-pregnant levels in the first trimester, 77% in the second trimester, and 80% in the third trimester. According to Wiles' systematic review, serum creatinine above 77 $\mu\text{mol/L}$ (0.87 mg/dL) should be considered abnormal in pregnant women. Wiles concluded that using trimester-specific thresholds—85% of the upper reference limit in the first trimester, 80% in the second, and 86% in the third—provides clinically relevant guidance. Similarly, intra-individual comparison of pre-conception and longitudinal creatinine changes can be informative.⁴

Due to the difficulties in measuring and estimating GFR during pregnancy (see below), creatinine clearance remains the most commonly used method to assess GFR in clinical practice;

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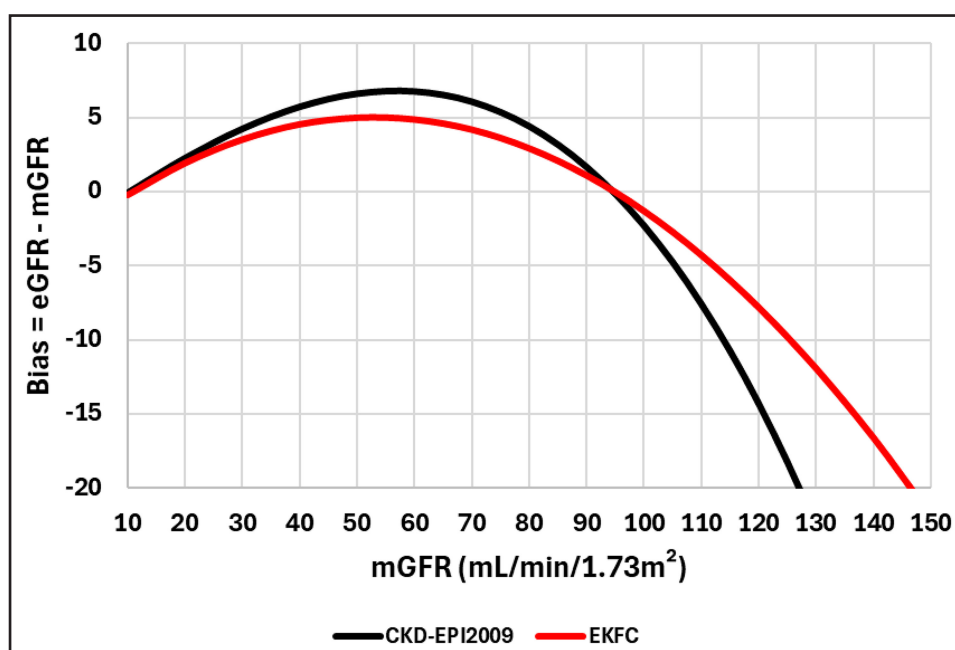


Figure 1 Bias of the CKD-EPI and EKFC equations in the general population according to GFR (adapted from⁶). CKD-EPI, Chronic Kidney Disease Epidemiology equation; EKFC, European Kidney Function Consortium Equation; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate.

however, this method has limited precision and several well-recognized limitations. Indeed, urine collection can be challenging and inaccurate, which is why most reported clearances are performed in hospital settings. Interestingly, 6-hour urine collections, which are more practical, showed good correlation with 24-hour collections. Therefore, repeated collections over shorter time periods could be of interest. Daily urinary creatinine excretion can also vary and be influenced by medications.⁵

Kidney function estimation formulas are commonly recommended to monitor GFR in the general population.^{6,7} However, data on estimating GFR equations in the specific population of pregnant women remains scarce, primarily due to inherent challenges of measuring GFR during pregnancy. Consistent with literature on non-pregnant hyperfiltrating patients, creatinine-based equations, including the currently validated European Kidney Function Consortium (EKFC) and Chronic Kidney Disease Epidemiology (CKD-EPI) equations, would tend to underestimate mGFR and exhibit low precision, as illustrated in Figure 1 (data from the EKFC cohorts).⁶ A strong underestimation of GFR by creatinine-based equations is also observed with diverse, non-validated equations.⁵ Beyond these systematic underestimations, the fundamental relationship between serum creatinine and GFR appears to differ significantly in pregnant women in comparison to the general population. While a pregnancy-specific equation is clinically necessary, no satisfactory model has been established to date.

Cystatin C, a cysteine protease inhibitor produced by all nucleated cells, might be a reliable endogenous marker of GFR, especially in combination with creatinine and/or in specific populations where serum creatinine is inaccurate in non-pregnant women.⁷ It initially appeared to be a promising candidate in pregnant women because it is independent of body weight and muscle mass. However, measurements of plasma cystatin C have unfortunately demonstrated a poor correlation with inulin

clearance during pregnancy. Akbari *et al.* observed an unexpected increase in cystatin C levels during the third trimester, whereas inulin clearance remained stable during the same period.⁸ The proposed explanations for this rise in cystatin C remain hypothetical and include a certain degree of glomerular endotheliosis at the end of pregnancy, even in normal pregnancies, increased cystatin C production by placenta cells, and hormonal changes occurring in late gestation. Albeit there is doubt about the role of cystatin C in estimating GFR during pregnancy, some data suggested a role for this biomarker in predicting preeclampsia and/or risks associated with preeclampsia, like preterm delivery.⁹

Conclusion and Clinical Implications

Hyperfiltration is a physiological status during pregnancy. For this reason, serum creatinine physiologically decreases in pregnant women. Validated equations based on creatinine should not be used in pregnant women. In chronic kidney disease or pathological pregnancies, serum creatinine must be longitudinally followed and a serum creatinine which does not decrease must be considered abnormal. Using cystatin C does not seem to be an accurate way to estimate GFR in pregnant women but could have a role in the prediction of preeclampsia.

Further large-scale studies are required to determine which biomarkers should be utilized and how they should be applied across the different stages of pregnancy. This remains a significant challenge because, particularly during the third trimester, the volume of distribution increases. This physiological change calls into question the accuracy of plasma clearance and necessitates the use of urinary clearance measurements as a reference method, which are more difficult to obtain in practice.

Furthermore, the principle of precaution remains paramount in obstetric care, even though the use of contrast agents to measure GFR is generally considered advisable during pregnancy.

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Author contributions

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Conflicts of interest

Pierre Delanaye is a consultant for Nephrolyx.

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Ethical disclosure

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Informed consent

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