Kidney Function Can Predict Pregnancy Outcomes

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Healthy pregnancy outcomes are dependent on important hemodynamic adaptations, including increased cardiac output, blood volume expansion with sodium and water retention, and reduced vascular resistance (1). In the kidney, pregnancy is associated with marked changes in intrarenal hemodynamic parameters, including increases in GFR and effective renal plasma flow (2). The failure of these physiologic changes carries an increased risk of adverse pregnancy outcomes (3,4). Even modestly impaired GFR in CKD stage 1 is associated with a worse prognosis (3,4). Midterm renal hyperfiltration is a recognized hemodynamic adaptation that develops early in gestation and persists until delivery (5). Although hyperfiltration in the nonpregnant setting is often linked to increased risk of nephropathy, midterm renal hyperfiltration is not necessarily accompanied by glomerular hypertension (6). The etiology of midterm renal hyperfiltration remains unclear, but proposed mechanisms include increased effective renal plasma flow because of decreased angiotensin II sensitivity and activation of vasodilatory pathways, such as relaxin and nitric oxide (7,8). Although midterm renal hyperfiltration has been proposed as a measure of kidney function reserve during pregnancy, less is known about midterm renal hyperfiltration as a predictor of pregnancy outcomes.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Park *et al.* (9) describe a retrospective cohort of 1931 singleton pregnancies with midterm serum creatinine data between 2001 and 2015 at two university hospitals in South Korea. The authors estimated midterm GFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (10), defined midterm renal hyperfiltration as >120 ml/min per 1.73 m^2, and stratified their cohort by eGFR: <90, 90–120, 120–150, and ≥150 ml/min per 1.73 m^2. Midterm eGFR values below and above the reference range of 120–150 ml/min per 1.73 m^2 conferred greater odds of adverse pregnancy outcomes (defined as premature birth, low birth weight, and preeclampsia). Their data suggest a U-shaped relationship between midterm eGFR and adverse pregnancy events. On the basis of the adjusted odds ratios, the 60 to 90 ml/min per 1.73 m^2 midterm eGFR group is clearly the most at risk, which is probably a result of baseline renal dysfunction. Notably, there were no mothers in this cohort with midterm eGFR <75 ml/min per 1.73 m^2. The authors also examined baseline eGFR and showed that a 1 ml/min per 1.73 m^2 increase in eGFR from baseline to midterm was associated with lower odds of gestational complications only in those mothers with healthy kidneys.

Although interesting, there are important limitations to the analyses, including the retrospective study design and reliance on serum creatinine to estimate GFR, which is inaccurate at normal and elevated GFR ranges (11). Serum creatinine is also confounded by muscle mass and diet (12), and defining hyperfiltration by serum creatinine has led to misclassification in other populations at risk of hyperfiltration (11,13), which may have also been an issue in this cohort. To our knowledge, there is only a single study validating CKD-EPI creatinine against a measured GFR in a South Korean cohort (14), and creatinine-based equations have not been validated in pregnant women as discussed in detail elsewhere (15). Additionally, the authors' decision to define the reference range for midterm eGFR as 120–150 ml/min per 1.73 m^2 may have been problematic, because this wide renal function range likely represents a heterogeneous group of mothers with risk for residual confounding. However, in a sensitivity analysis where mothers were stratified in increments of 15 rather than 30 ml/min per 1.73 m^2, the authors reported the lowest risk of gestational complications in the eGFR range of 120–135 ml/min per 1.73 m^2.

Although the epidemiologic finding of a U-shaped association between midterm eGFR and gestational complications is of merit, the underlying pathophysiology remains unclear. Midterm eGFRs <90 ml/min per 1.73m^2 and 90–120 ml/min per 1.73 m^2 likely reflects baseline CKD, and these kidneys are likely not able to mount the adaptive hemodynamic changes required for a healthy gestation. It is less clear why midterm eGFR ≥150 ml/min per 1.73 m^2 carries greater odds of adverse pregnancy outcomes. A plausible explanation could be that midterm eGFR ≥150 ml/min per 1.73 m^2 reflects a pathologic increase in GFR associated with intrarenal hemodynamic dysfunction and perhaps, early kidney disease. For example, eGFR≥150 ml/min per 1.73 m^2 may reflect underlying occult disease conditions, such as metabolic syndrome, obesity, endothelial dysfunction, or hypertension, which increase both the risk of hyperfiltration in the mother and the risk of adverse pregnancy outcomes. Importantly, in the cohort of Park *et al.*'s study (9), body weight,

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body mass index, gestational weight gain, BP, and hypertension history were not elevated in the hyperfiltration group. It, therefore, seems unlikely that traditional risk factors associated with hyperfiltration were responsible for the elevation in eGFR. The hyperfiltration group did, however, have more emergency room visits leading to the index eGFR measurement compared with the other groups—an observation that remains unexplained. The midterm renal hyperfiltration group also had higher Caesarian section rates. If the eGFR measurements were collected during periods of physiologic stress or with fluid administration, such as preoperatively for a Caesarian section, then this may have influenced effective renal plasma flow and/or glomerular pressure, leading to changes in renal function. Finally, in terms of additional metabolic confounders, midterm eGFR above the midterm renal hyperfiltration range (*i.e.*, ≥150 ml/min per 1.73 m^2) could be attributed to hyperglycemia or a protein or fructose load if serum creatinine was drawn postprandially (16). Data on simultaneous glucose and whether serum creatinine was drawn postprandially would have been helpful when interpreting the eGFR data due to acute effects of these metabolic parameters on intrarenal hemodynamic function.

Creatinine clearance is used to estimate GFR during pregnancy, but this method remains inaccurate in the setting of impaired renal function, because creatinine is secreted by the kidney tubules (17). Cystatin C, which may have less bias (18) in nonpregnant, hyperfiltering populations (19,20), shows poor agreement with measured GFR in pregnancy due to placental production of cystatin C (21,22). Further work is, therefore, required to determine how to optimally measure GFR and define hyperfiltration to avoid misclassification in pregnancy. Physiologic studies with measured GFR are needed to understand the intrarenal hemodynamic mechanisms underlying the relationship between midterm eGFR and gestational complications described by Park *et al.* (9).

Measuring GFR by inulin and effective renal plasma flow is feasible and safe in human pregnancy. In fact, several studies have shown a progressive increase in both GFR and effective renal plasma flow in pregnant women, such as the study by Dunlop (5). Subsequent analyses by Hladunewich *et al.* (23) and Odutayo and Hladunewich (24) have suggested that only a portion of the rise in GFR in pregnancy is related to increased effective renal plasma flow and that increased transcapillary pressure gradients or increases in the ultrafiltration coefficient are likely involved. To our knowledge, there are no data relating measured GFR and effective renal plasma flow to gestational complications. Such studies are important to validate the epidemiologic data reported by Park *et al.* (9) and examine the relationships between gestational complications and changes in glomerular hemodynamics. To gain additional insight into the intrarenal circulation *in vivo* in humans, mathematical equations developed by Gomez can be applied (25). These equations use measurements of GFR, renal blood flow, effective renal plasma flow, renal vascular resistance, hematocrit, and serum protein to calculate afferent and efferent arteriolar resistances, glomerular hydrostatic pressure, and filtration pressure (25). These data could further define the intrarenal hemodynamic profile of pregnancy and elucidate the role of neurohormonal mediators that are responsible for these alterations (23,24). Such data would advance our understanding of the intrarenal hemodynamic adaptation—and dysfunction—that occur in both health and disease.

Should the results of the study by Park *et al.* (9) influence current clinical practice? On the basis of available evidence, it seems premature to recommend that women with midterm renal hyperfiltration should be considered at elevated risk of adverse maternal or neonatal outcomes or that women should be followed more intensively in high-risk obstetric clinics. Park *et al.* (9) reported increases in premature birth—both "moderate to late preterm" and "very preterm"—although only 16 of the latter events occurred in the midterm renal hyperfiltration group (9). Moderate to late preterm deliveries and Caesarian section outcomes were more common in the midterm renal hyperfiltration group but are subject to iatrogenic and practice pattern influences. Preeclampsia, however, was not associated with midterm renal hyperfiltration, and the risk of very low–birth weight gestations did not differ between the groups. Park *et al.* (9) did not report other important end points, including neonatal outcomes, which will ultimately be important to better understand the study's future clinical implications. Given the study's limitations, these interesting findings need to be substantiated and replicated to establish the effect of midterm renal hyperfiltration on hard maternal and neonatal outcomes.

In conclusion, midterm renal hyperfiltration is a hallmark renal physiologic change that defines a healthy gestation. Epidemiologic data from Park *et al.* (9) suggest that midterm eGFR deviating from the expected midterm renal hyperfiltration range may carry risk for adverse pregnancy outcomes. Further research is needed to understand the pathophysiology underlying intrarenal hemodynamic dysfunction in pregnancy and how it contributes to gestational complications. The study of renal reserve in pregnancy and how it relates to intrarenal hemodynamic function and pregnancy outcomes will also be particularly relevant to better understand if midterm renal hyperfiltration has adverse prognostic importance for obstetric or pediatric outcomes.

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Disclosures

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