Midterm eGFR and Adverse Pregnancy Outcomes: The Clinical Significance of Gestational Hyperfiltration

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Abstract

Background and objectives Although hemodynamic adaptation plays a crucial role in maintaining gestation, the clinical significance of midterm renal hyperfiltration (MRH) on pregnancy outcomes is unknown.

Design, setting, participants, & measurements This was an observational cohort study. Women with a singleton pregnancy and a serum creatinine measurement during their second trimester were followed at two university hospitals in Korea between 2001 and 2015. Those with substantial renal function impairment or who delivered during the second trimester were not considered. MRH was represented by the highest eGFR, which was calculated using the Chronic Kidney Disease Epidemiology Collaboration method. An adverse pregnancy event was defined by the composition of preterm birth (gestational age <37 weeks), low birth weight (<2.5 kg), and preeclampsia.

Results Data from 1931 pregnancies were included. The relationship between midterm eGFR and adverse pregnancy outcomes, which occurred in 538 mothers, was defined by a nonlinear U-shaped curve. The adjusted odds ratio and associated 95% confidence interval (95% CI) of an adverse pregnancy outcome for eGFR levels below and above the reference level of 120–150 ml/min per 1.73 m^2 were 1.97 (95% CI, 1.34 to 2.89; $P<0.001$) for ≥150 ml/min per 1.73 m^2; 1.57 (95% CI, 1.23 to 2.00; $P<0.001$) for 90–120 ml/min per 1.73 m^2; and 4.93 (95% CI, 1.97 to 12.31; $P<0.001$) for 60–90 ml/min per 1.73 m^2. Moreover, among mothers without baseline CKD, women with adverse pregnancy outcomes had less prominent MRH than those without ($P<0.001$).

Conclusions We identified a unique U-shaped relationship between midterm eGFR and adverse pregnancy outcomes, and the optimal range of midterm eGFR levels was 120–150 ml/min per 1.73 m^2. In those without evident functional renal impairment, the absence of prominent MRH might be a significant risk factor for poor pregnancy outcomes.

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Introduction

There are substantial alterations in hemodynamics in normal pregnancy, including increases in cardiac output, sodium, and water retention, leading to blood volume expansion and reduction in systemic vascular resistance (1). This physiologic adaption is impaired in women with risk factors for inappropriate hemodynamic responses, which increases the risk of adverse pregnancy outcomes (1,2). The Torino-Cagliari Observational Study demonstrated that the risk of adverse pregnancy outcomes is linked to CKD, even for stage 1 (2). Therefore, clinicians are recommended to monitor carefully the effect of renal disease on pregnancy in women with CKD (1–3). However, another common situation that clinicians encounter is the diagnosis of previously unrevealed kidney disease in pregnant women, which is present in non-negligible proportions (3). Yet renal function parameters are often measured just before delivery, which is too late to protect maternal and fetal safety. Instead of peri-gestational renal function, selected markers of systemic vascular adaptation, specifically soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), have been reported as predictors of preeclampsia and other adverse pregnancy outcomes (4–7). Nonetheless, these biomarkers are not yet used in daily practice. Hence, many studies have focused on more practical predictors, such as weight change or blood pressure (BP) (8–11).

Among physiologic changes that occur during gestation, midterm renal hyperfiltration (MRH) is a unique phenomenon of hemodynamic adaptation that develops early in gestation and persists until delivery (12,13). The increase in renal blood flow and involvement of several pathways, including the renin-aldosterone-angiotensin system or relaxin pathway, have been suggested as potential mechanisms of MRH (14–16). Although a definition of MRH has yet to be established, an increase of 30%–50% in the eGFR or an absolute eGFR value >120 ml/min per 1.73 m^2 is commonly defined as the criterion for normal MRH (17,18). It has been hypothesized that MRH provides a measure of the reserved kidney function available for

hemodynamic adaptation during pregnancy (19). To date, however, the clinical value of MRH as a predictor of pregnancy prognosis has not been validated (18,20).

In this study, we specifically investigated the relationship between midterm eGFR and adverse pregnancy outcomes, as MRH is known to peak during midgestation (12,13). Moreover, we assessed whether midterm eGFR and its change from baseline, as a surrogate marker for MRH, have clinical importance in mothers without underlying evidence of CKD to further evaluate its value as a prognostic factor of the eGFR during gestation.

Materials and Methods

Ethics Statement

This study was approved by the Institutional Review Boards of both Seoul National University Hospital and Bundang Seoul National University Hospital (H-1604–028–753). This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was an observational study without medical intervention, so informed consent was waived.

Study Population

All delivery records were screened to identify women with measured serum creatinine (sCr) levels during the second trimester. Women with multifetal pregnancy were not considered. Additionally, women with substantially decreased maternal renal function, defined by an eGFR <60 ml/min per 1.73 m^2 even once during the peri-gestational period, were also excluded, allowing us to limit our analysis to mothers without advanced CKD. We did note in a large proportion of women that midterm sCr levels were obtained at the time of admission for a second trimester delivery, which we excluded as these eGFR measures were coincident with delivery rather than being predictive of pregnancy outcome. Next, we used the absolute values of the highest midterm eGFR value to classify our study group into four eGFR subgroups: 60–90 ($60 \leq$eGFR<90) ml/min per 1.73 m^2; 90–120 ($90 \leq$eGFR<120) ml/min per 1.73 m^2; 120–150 ($120 \leq$eGFR<150) ml/min per 1.73 m^2; and ≥ 150 ml/min per 1.73 m^2.

Peri-gestational Characteristics of Pregnancy

The following demographic and clinical variables were extracted from electronic health records: age, weight before pregnancy and at the time of delivery, height, body mass index, and history of hypertension and diabetes mellitus. The following pregnancy-related information was also collected: history of parity, including full-term birth, preterm birth, and miscarriage/stillbirth history; gestational age (GA); type of delivery (cesarean section or vaginal delivery); birth weight; and the mothers' systolic and diastolic BP at the time of admission for delivery.

The peri-gestational sCr levels from both hospitals were recalibrated to an isotope-dilution mass spectrometry assay (Roche Diagnostic). The eGFR values were calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, which is commonly used in practice and has been validated in women with relatively high eGFR (21). Dipstick urine albumin test results were reviewed.

When possible, baseline renal function was documented on the basis of several criteria. The date of conception was defined by subtracting the GA from the date of delivery. The last values from dipstick urine albumin tests and eGFR obtained within 3 years from the delivery date and before the estimated conception date were used as baseline parameters of renal function. Women with a baseline eGFR ≥ 60 ml/min per 1.73 m^2 and no documented albuminuria before conception were classified as having no evidence of CKD. Women with confirmed albuminuria at baseline were stratified according to their CKD stage (22). The available eGFR values were stratified by gestational trimester, with the second trimester defined as GA$\geq$12 weeks and $<$28 weeks, and the third trimester as GA$\geq$28 weeks. The follow-up eGFR was defined as the maximal eGFR value obtained before 3 years after the date of delivery.

As the indications for peri-gestational eGFR measurement varied widely between women, we stratified women on the basis of their status and cause of eGFR measurement: outpatient clinic, emergency department without admission, admission to the obstetric service, or admission for a nonobstetric reason.

Outcome Measurement

An adverse pregnancy outcome was defined by preterm birth, low birth weight, or preeclampsia, as well as by the composite of these three features. Following the International Classification of Diseases-10 criteria (23), preterm birth was defined as birth at GA$<$37 weeks, and further subdivided into moderate-to-late preterm birth (GA $\geq$32 and $<$37 weeks) and very preterm birth (GA $\geq$28 and $<$32 weeks) (23,24). The criterion for a low birth weight was birth weight of $<$2.5 kg and those $<$1.5 kg were further stratified as very low birth weight (22,25). The presence of preeclampsia was on the basis of the diagnosis provided by the obstetrician from findings of hypertension, proteinuria, and evidence of end organ damage.

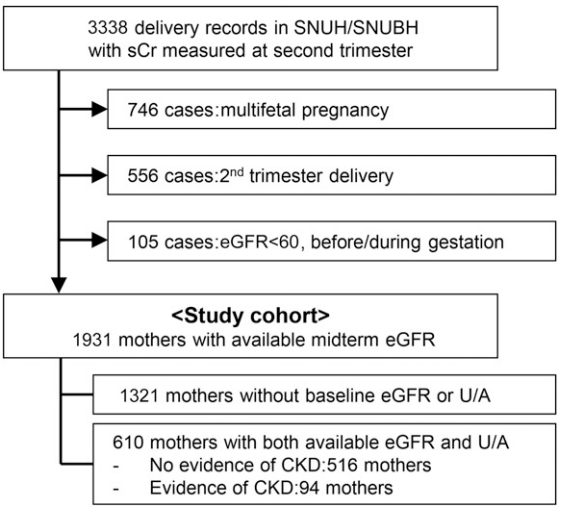

Figure 1. | Flow diagram of the study population. sCr, serum creatinine; SNUH, Seoul National University Hospital; SNUBH, Seoul National University Bundang Hospital; U/A, urinalysis.

Table 1. Baseline and pregnancy characteristics according to midterm eGFR

Characteristics	60≤eGFR<90 (*n*=26)	90≤eGFR<120 (*n*=534)	120≤eGFR<150 (*n*=1228)	eGFR≥150 (*n*=143)	*P* Value
Age, yr	33 (30–35)	34 (32–37)	32 (30–35)	31 (29–33)	<0.001
Body mass index, kg/m^2	20.6 (18.8–23.1)	21.5 (19.6–24.1)	20.9 (19.4–23.1)	21.0 (19.2–22.7)	0.08
Baseline sCr, mg/dl[a]	0.8 (0.7–0.9)	0.6 (0.6–0.7)	0.6 (0.5–0.7)	0.5 (0.4–0.6)	<0.001
Baseline eGFR, ml/min per 1.73 m^{2a}	92.5 (84.4–107.8)	113.6 (104.8–120.3)	120.6 (115.4–126.5)	129.0 (121.9–133.7)	<0.001
Multiparity	11 (42.3)	313 (58.6)	607 (49.4)	55 (38.5)	<0.001
No. of full-term births history					0.21
0	20 (76.9)	300 (59.2)	603 (57.0)	51 (58.6)	
1	6 (23.1)	164 (32.3)	388 (36.7)	30 (34.5)	
2	0 (0.0)	42 (8.3)	57 (5.4)	5 (5.7)	
≥3	0 (0.0)	1 (0.2)	9 (0.9)	1 (1.1)	
No. of preterm births history					0.16
0	25 (96.2)	435 (86.1)	944 (89.3)	79 (89.8)	
1	1 (3.8)	56 (11.1)	96 (9.1)	7 (8.0)	
2	0 (0.0)	12 (2.4)	1 (1.6)	2 (2.3)	
≥3	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.0)	
Presence of stillbirth/miscarriage history	9 (34.6)	221 (41.4)	376 (30.6)	27 (18.9)	<0.001
Previous history of hypertension	14 (53.8)	82 (15.4)	144 (11.7)	11 (7.7)	<0.001
Midterm sCr, mg/dl	0.7 (0.7–0.8)	0.5 (0.5–0.6)	0.4 (0.4–0.5)	0.2 (0.1–0.2)	<0.001
Midterm eGFR, ml/min per 1.73 m^2	84.0 (82.3–86.3)	114.6 (110.7–117.7)	130.5 (125.3–136.5)	163.0 (157.9–179.2)	<0.001
Weight gain until delivery, kg	11.2 (9.2–13.5)	12.0 (9.6–15.8)	12.3 (9.4–16.0)	12.0 (8.1–15.3)	0.19
Hypertension during pregnancy	11 (42.3)	45 (8.4)	66 (5.4)	9 (6.3)	<0.001
Systolic BP, mmHg[b]	130 (122–146)	119 (110–130)	120 (110–130)	120 (107–130)	0.06
Diastolic BP, mmHg[b]	90 (76–100)	74 (70–84)	74 (66–80)	69 (60–77)	<0.001
Albuminuria (dipstick)[c]					<0.001
(−)	14 (53.8)	399 (74.7)	1007 (82.0)	4 (78.3)	
1+	4 (16.7)	73 (13.7)	124 (10.1)	15 (10.5)	
≥2+	8 (30.8)	62 (11.6)	97 (7.9)	16 (11.2)	
Diabetes mellitus during pregnancy	1 (3.8)	28 (5.2)	31 (2.5)	0 (0.0)	0.003
Cesarean section	7 (26.9)	184 (34.5)	390 (31.8)	66 (46.2)	0.01
Gestational age when eGFR measured, wk	19 (15–22)	20 (15–24)	20 (16–24)	21 (17–25)	0.16
Causes of eGFR measured					<0.001
Routine outpatient visit	19 (73.1)	288 (53.9)	728 (59.3)	81 (56.6)	
Emergency room visit without admission	2 (7.7)	65 (12.2)	203 (16.5)	36 (25.2)	
Obstetrics ward admission	5 (19.2)	167 (31.3)	282 (23.0)	25 (17.5)	
Other ward admission	0 (0.0)	14 (2.6)	22 (1.8)	7 (4.9)	

Data are presented as median (interquartile range) or as *n* (%). sCr, serum creatinine.

[a]Available baseline sCr and eGFR values within 3 years of delivery date were identified in 719 women.

[b]BP values at the time of admission for delivery.

[c]Maximum values during pregnancy by urine dipstick method, the values were available in 1823 women.

Statistical Analyses

Categorical variables were reported as frequencies and percentages, with between-group differences evaluated using a chi-squared test. As continuous variables were non-normally distributed, measures were expressed as median values and associated interquartile ranges, with between-group differences evaluated using a Kruskal–Wallis test. The risks of adverse pregnancy outcomes were evaluated by univariable and multivariable logistic regression analysis using the subgroup with the lowest incidence of gestational complications as the reference group. Fractional polynomial models were constructed to investigate the relationship between the risk of an adverse pregnancy outcome as a binomial distribution and the midterm eGFR as the explanatory variable (22). For multivariable analysis, the following variables were adjusted: age, pregestational body mass index, gestational weight gain, diabetes mellitus, hypertension during/before pregnancy, previous history of stillbirth/miscarriage, multiparity, and the causes or status of the sCr/eGFR measurement. For analysis of preeclampsia risk, hypertension histories were not adjusted, as preeclampsia itself is a hypertensive disorder. As there were a substantial number of women with missing information for baseline body mass index (n=573, 29.7%) and weight gain during pregnancy period (n=446, 23.1%), missing value imputation by the classification and regression trees method was performed. To further demonstrate the predictive value of midterm eGFR, women in whom eGFR measurements were obtained during a routine outpatient visit at 4 weeks or more before delivery were subsequently assessed. Women without evidence of underlying CKD were analyzed to evaluate specifically the effect of the MRH on pregnancy outcome in women without underlying kidney function impairment using a linear mixed-model with fixed effects by the restricted estimated maximal likelihood method. All statistical analyses were performed using R software (version 3.2.5, the R Foundation). For all analyses, a two-sided P value <0.05 was considered significant.

Results

Study Population

A flow diagram of the study population is shown in Figure 1. From the two hospitals, 3338 delivery records with sCr values measured during the second trimester were identified. From this initial set of records, women with multifetal pregnancy (n=746) were excluded. After additionally excluding those with delivery during the second trimester (n=556) and substantial kidney functional impairment (eGFR<60 ml/min per 1.73 m^2) during or before gestation (n=105), 1931 delivery records ultimately formed our study group. Among them, 26, 534, 1228, and 143 mothers had midterm eGFR levels of 60–90, 90–120, 120–150, and ≥150 ml/min per 1.73 m^2, respectively.

Comparisons of Baseline and Pregnancy Characteristics According to Midterm eGFR

Baseline and pregnancy characteristics for the four different eGFR subgroups are summarized in Table 1. Significant between-group differences were identified regarding age, multiparity, and history of previous stillbirth/miscarriage. Baseline values of eGFR, although available in a limited number of mothers, were correlated with midterm eGFR levels. All mothers in the midterm eGFR range of 60–90 ml/min per 1.73 m^2 had midterm eGFR values >75 ml/min per 1.73 m^2. Of specific relevance for our analysis was the greater prevalence of a history of hypertension before gestation in women with lower midterm eGFR values. With regard to pregnancy-related characteristics, the incidence of hypertension during gestation was lowest in women with an eGFR of 120–150 ml/min per 1.73 m^2, with the incidence of hypertension during pregnancy higher for eGFR higher and lower than the 120–150 ml/min per 1.73 m^2 reference level. A similar U-shaped trend was identified between the midterm eGFR and the incidence of albuminuria during pregnancy.

Midterm eGFR and Adverse Pregnancy Outcomes

The incidence of a composite adverse pregnancy outcome, as well as the incidences of its individual features (preterm birth, low birth weight, and preeclampsia), was lowest in women with the reference midterm eGFR of 120–150 ml/min per 1.73 m^2 (Table 2). Regarding specific associations of a midterm eGFR below the reference range with pregnancy outcomes, women with a midterm eGFR of 60–90 ml/min per 1.73 m^2 experienced more frequent

Table 2. Maternofetal outcomes according to midterm eGFR

Adverse Pregnancy Outcomes	60≤eGFR <90 (n=26)	90≤eGFR <120 (n=534)	120≤eGFR <150 (n=1228)	eGFR≥150 (n=143)	P Value
Composite outcome	18 (69.2)	179 (33.5)	288 (23.5)	53 (37.1)	<0.001
Preterm birth, <37 wk	16 (61.5)	150 (28.1)	228 (18.6)	50 (35.0)	<0.001
Moderate to late preterm, 32 to <37 wk	10 (38.5)	93 (17.4)	143 (11.6)	34 (23.8)	<0.001
Very preterm, 28 to <32 wk	6 (23.1)	57 (10.7)	85 (6.9)	16 (11.2)	0.001
Gestational age, wk	35 (31–38)	38 (36–39)	38 (37–39)	37 (35–39)	<0.001
Low birth weight, <2.5 kg	11 (42.3)	106 (20.0)	195 (15.9)	39 (27.3)	<0.001
Very low birth weight, <1.5 kg	3 (11.5)	30 (5.6)	50 (4.1)	11 (7.7)	0.06
Birth weight, kg	2.46 (2.10–3.07)	3.02 (2.63–3.32)	3.10 (2.71–3.42)	2.96 (2.45–3.28)	0.001
Preeclampsia	8 (30.8)	41 (7.7)	53 (4.3)	8 (5.6)	<0.001

Data are presented as median (interquartile range) or as n (%).

adverse pregnancy outcomes than did those with a midterm eGFR of 90–120 ml/min per 1.73 m^2.

Furthermore, the risk of a composite adverse outcome was higher in all other eGFR subgroups in multivariable analysis, with the following adjusted odds ratios (aORs) and associated 95% confidence intervals (95% CI): aOR, 1.97 (95% CI, 1.34 to 2.89; $P<0.001$) for ≥150 ml/min per 1.73 m^2; aOR, 1.57 (95% CI, 1.23 to 2.00; $P<0.001$) for 90–120 ml/min per 1.73 m^2; and aOR, 4.93 (95% CI, 1.97 to 12.31; $P<0.001$) for 60–90 ml/min per 1.73 m^2 (Table 3). The risk for preterm birth and low birth weight exhibited a similar distribution, except for a comparable risk of low birth weight associated with an eGFR range of 90–120 ml/min per 1.73 m^2 and the reference range of 120–150 ml/min per 1.73 m^2. A significant risk for preeclampsia was identified for women with a midterm eGFR of 90–120 or 60–90 ml/min per 1.73 m^2. Additionally, a similar association was identified when we further divided our subgroups with smaller eGFR ranges of 15 ml/min per 1.73 m^2, and the lowest risk of gestational complications was observed in an eGFR range of 120–135 ml/min per 1.73 m^2 (Supplemental Tables 1 and 2). Overall, the risk of adverse pregnancy outcomes exhibited a nonlinear U-shaped relationship with midterm eGFR (Figure 2). In addition, the association between midterm eGFR and adverse pregnancy outcomes remained significant in a number of 1103 mothers in whom sCr measurements were obtained during a routine outpatient visit >4 weeks before delivery, further showing the predictive value of midterm eGFR (Supplemental Table 3).

MRH in Mothers without Evident CKD According to the Presence of Adverse Pregnancy Outcomes

For further analyses, we separately studied mothers within the study cohort with known underlying renal dysfunction (Supplemental Table 4). The pregnancy characteristics of the 610 women for whom both baseline eGFR and albuminuria information were available are summarized according to their CKD stages in Table 4 (26). Evidence of CKD was identified in 94 out of 610 women, with no evidence of underlying CKD in 516 out of 610 women. The risk of hypertension and significant albuminuria increased with a higher stage of CKD, both before ($P<0.001$) and during pregnancy ($P<0.001$). As expected, advanced CKD status was associated with the highest risk for composite adverse outcomes ($P<0.001$).

Lastly, 516 mothers without underlying evidence of CKD, shown in the first column of Table 4, were separately analyzed to assess the effect of MRH in those without preexisting CKD. In this group, the incidences of adverse pregnancy outcomes, both for composite and individual features, were significantly higher in those with lower midterm eGFR levels (Supplemental Table 5). Even a 1 ml/min per 1.73 m^2 higher increase in both eGFR rise from baseline to midterm (aOR, 0.98; 95% CI, 0.97 to 0.99; $P=0.01$) and absolute midterm eGFR levels (aOR, 0.98; 95% CI, 0.96 to 0.99; $P=0.01$) was associated with lower risk of gestational complications only when the analysis was limited to those without underlying CKD (Supplemental Table 6). Next, we plotted their median eGFR values at each period in Figure 3. When the eGFR change from baseline to midterm was compared between mothers with and without

Table 3. Risk of adverse pregnancy outcomes in each midterm eGFR subgroup

Adverse pregnancy outcomes	OR	95% CI	*P* Value	Adjusted OR[a]	95% CI	*P* Value
Composite outcome						
eGFR≥150	1.92	1.36 to 2.77	<0.001	1.97	1.34 to 2.89	<0.001
120≤eGFR<150		Reference			Reference	
90≤eGFR<120	1.65	1.32 to 2.06	<0.001	1.57	1.23 to 2.00	<0.001
60≤eGFR<90	7.34	3.16 to 17.07	<0.001	4.93	1.97 to 12.31	<0.001
Preterm birth						
eGFR≥150	2.36	1.63 to 3.42	<0.001	2.45	1.65 to 3.64	<0.001
120≤eGFR<150		Reference			Reference	
90≤eGFR<120	1.71	1.35 to 2.17	<0.001	1.63	1.26 to 2.11	<0.001
60≤eGFR<90	7.02	3.14 to 15.67	<0.001	4.84	2.00 to 11.74	<0.001
Low birth weight						
eGFR≥150	1.99	1.33 to 2.96	0.001	1.98	1.29 to 3.02	0.002
120≤eGFR<150		Reference			Reference	
90≤eGFR<120	1.32	1.02 to 1.72	0.04	1.27	0.96 to 1.68	0.09
60≤eGFR<90	3.88	1.76 to 8.58	0.001	2.49	1.03 to 5.99	0.04
Preeclampsia						
eGFR≥150	1.31	0.61 to 2.82	0.48	1.35	0.62 to 2.94	0.46
120≤eGFR<150		Reference			Reference	
90≤eGFR<120	1.84	1.21 to 2.81	0.004	1.77	1.14 to 2.76	0.01
60≤eGFR<90	9.85	4.10 to 23.69	<0.001	10.99	4.45 to 27.15	<0.001

eGFR measured in ml/min per 1.73 m^2. OR, odds ratio, 95% CI, 95% confidence interval.

[a]Adjusted for age, pregestational body mass index, weight gain until delivery, baseline hypertension, diabetes mellitus and hypertension during pregnancy, previous history of stillbirth/miscarriage, multiparity, and hospitalization status at the time of eGFR measurement. For analysis of preeclampsia risk, hypertension during pregnancy was not adjusted. As a substantial number of women had missing information for baseline body mass index ($n=573$) and weight gain ($n=446$), missing value imputation by the classification and regression trees method was performed in multivariable analyses.

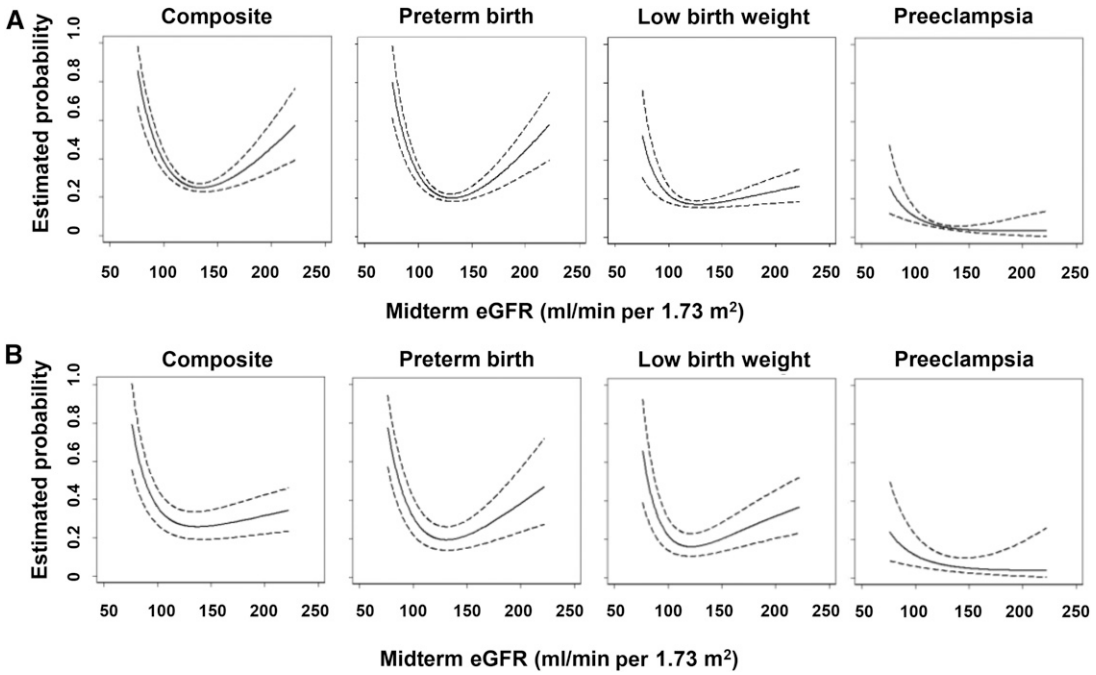

Figure 2. | **U-shaped relationship between midterm eGFR and adverse pregnancy outcomes.** Fractional polynomial models demonstrating the relationship between midterm eGFR and the risk of adverse pregnancy outcomes, including, from left to right: composite, preterm, low birth weight, and preeclampsia. The association between midterm eGFR and the estimated probability for each adverse pregnancy outcome is shown for (A) the univariable model and (B) the multivariable model. The dotted lines indicate the 95% confidence intervals of the estimated probability for each adverse pregnancy outcome.

adverse pregnancy outcomes in mothers without baseline CKD, women who did not experience gestational complications showed more prominent MRH ($P<0.001$).

Discussion

In this large observational study, we identified a nonlinear, U-shaped relationship between midterm eGFR and the risk of adverse pregnancy outcomes, with a midterm eGFR of 120–150 ml/min per 1.73 m^2 associated with the lowest risk. Moreover, women with a midterm eGFR <120 ml/min per 1.73 m^2 experienced more complications during gestation. We identified a higher risk for adverse pregnancy outcomes with midterm eGFR ≥150 ml/min per 1.73 m^2, which was an unexpected finding. Lastly, in mothers without evidence of kidney functional impairment, prominent MRH was associated with a better pregnancy prognosis.

To our knowledge, this is the largest study to date to have evaluated the clinical significance of midterm eGFR as a prognostic factor for adverse pregnancy outcomes. Therefore, evaluation of renal function could provide a novel biomarker to predict adverse pregnancy outcomes. As methods for measuring sCr levels and calculating eGFR are widely available, clinicians should consider monitoring these variables during gestation. Of clinical importance is our finding of a significant risk of adverse pregnancy outcomes associated with midterm eGFR values of 60–90 ml/min per 1.73 m^2, and even 90–120 ml/min per 1.73 m^2, an eGFR range regarded as normal in nonpregnant women. Therefore, careful interpretation of renal function tests is necessary during pregnancy.

Several factors may have contributed to the U-shaped association between midterm eGFR and adverse pregnancy outcomes and, in particular, with the increased risk in women with a midterm eGFR ≥150 ml/min per 1.73 m^2. Foremost, considering that both gestational hypertension and significant albuminuria were more prevalent in women with midterm eGFR ≥150 ml/min per 1.73 m^2, it is possible that this range of eGFR may be indicative of an early CKD status, in which compensatory hyperfiltration and albuminuria are representative features (26). Additionally, when we assessed those with known baseline renal function, a greater eGFR increase or midterm eGFR was associated with better pregnancy outcomes, but only in those without baseline CKD. Therefore, similar to results of several previous studies (27–30), a certain portion of mothers with midterm eGFR ≥150 ml/min per 1.73 m^2 might have an early stage of underlying kidney disease, in which hyperfiltration would not reflect the appropriate hemodynamic adaptation, as it is itself one of the features of early CKD. Next, the codependence of eGFR values on measured sCr should be considered, in that a high eGFR value may be the result of low sCr levels. So, a low muscle mass or inappropriate dietary intake could have contributed to our identified higher relative risk for adverse pregnancy outcomes in women with excessive MRH. However, as this association remained significant after adjusting for baseline body mass index and gestational weight gain, we favor our prior hypothesis that women

Table 4. Baseline and pregnancy characteristics according to baseline renal function

Characteristics	No CKD[a] (*n*=516)	CKD Stage 1 (*n*=87)	CKD Stage 2 (*n*=7)	*P* Value
Age, yr	32 (30–35)	34 (32–37)	33 (30–33)	0.43
Body mass index, kg/m^2	20.1 (18.8–22.6)	21.1 (19.4–23.8)	18.2 (16.9–23.5)	0.004
Baseline sCr, mg/dl	0.64 (0.58–0.73)	0.62 (0.52–0.65)	0.91 (0.91–0.94)	<0.001
Baseline eGFR, ml/min per 1.73 m^2	117.0 (105.5–122.2)	120.4 (114.1–127.4)	82.4 (81.7–82.7)	<0.001
Baseline albuminuria (dipstick)	0 (0–0)	1$^+$ (1$^+$–2$^+$)	2$^+$ (2$^+$–2$^+$)	<0.001
Multiparity	309 (59.9)	56 (64.4)	6 (85.7)	0.18
No. of full-term births history	1 (0–1)	0 (0–1)	1 (0–1)	0.14
No. of preterm births history	0 (0–0)	0 (0–0)	0 (0–0)	0.40
Presence of stillbirth/miscarriage history	178 (34.5)	32 (36.8)	6 (85.7)	0.08
Previous history of hypertension	98 (19.0)	40 (46.0)	6 (85.7)	<0.001
Midterm sCr, mg/dl	0.49 (0.45–0.54)	0.44 (0.35–0.54)	0.73 (0.72–0.79)	0.002
Midterm eGFR, ml/min per 1.73 m^2	123.5 (114.6–141.2)	124.2 (113.8–131.7)	92.5 (88.3–102.2)	0.001
Weight gain until delivery, kg	11.6 (9.2–13.6)	10.0 (8.0–14.2)	10.0 (7.0–11.3)	0.07
Hypertension during pregnancy	45 (8.7)	20 (23.0)	5 (71.4)	<0.001
Albuminuria (dipstick)[b]				<0.001
(−)	412 (79.8)	43 (49.4)	2 (28.6)	
1+	69 (13.4)	11 (12.6)	0 (0.0)	
≥2+	35 (6.8)	33 (37.9)	5 (71.4)	
Diabetes mellitus during pregnancy	13 (3.7)	3 (3.4)	1 (14.3)	0.53
Cesarean section	171 (33.1)	33 (37.9)	1 (14.3)	0.82
Composite outcome	113 (21.9)	33 (37.9)	4 (57.1)	<0.001
Preterm birth, <37 wk	84 (16.3)	29 (33.3)	3 (42.9)	<0.001
Moderate to late preterm, 32 to <37 wk	68 (13.2)	21 (24.1)	1 (14.3)	0.02
Very preterm, 28 to <32 wk	16 (3.1)	8 (9.2)	2 (28.6)	<0.001
Gestational age, wk	38 (36–39)	38 (35–40)	37 (33–39)	0.14
Low birth weight, <2.5 kg	73 (14.1)	18 (20.7)	2 (28.6)	0.06
Birth weight, kg	3.00 (2.52–3.34)	2.86 (2.12–3.08)	2.95 (2.89–2.98)	0.05
Preeclampsia	20 (3.9)	14 (16.1)	1 (14.3)	<0.001

Data are presented as median (interquartile range) or *n* (%). Baseline sCr and eGFR values were available in 718 women and, combining urinalysis results, 610 women were stratified into each CKD stage group in the table. sCr, serum creatinine.

[a]Alteration in eGFR according to time phases of mothers without CKD evidence (*n*=516) are separately analyzed in Figure 3.

[b]Maximum values during pregnancy by urine dipstick method.

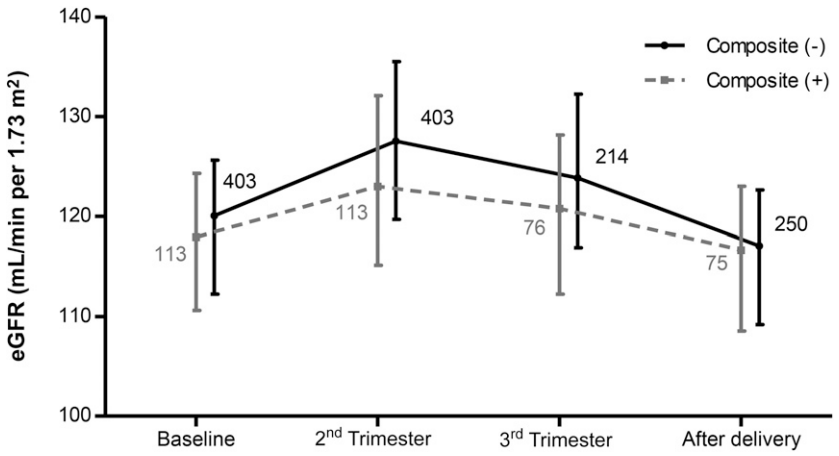

Figure 3. | **More prominent midterm renal hyperfiltration is observed in mothers without adverse pregnancy outcomes.** The *x*-axis represents each period of pregnancy, with the eGFR values shown along the *y*-axis. The black circles with connecting lines indicate the median maximal eGFR values in each measured period for women without composite adverse pregnancy outcomes. Gray squares with dotted connecting lines indicate the median eGFR values in each measured period for women with adverse pregnancy outcomes. Vertical lines indicate the interquartile ranges, with the number of available women with eGFR measurements in each period reported as a count beside the squares and circles.

with early CKD were included in our subgroup of midterm eGFR ≥150 ml/min per 1.73 m^2.

Appropriate systemic vasodilation and consequent hyperfiltration play an important role in safely maintaining gestation (14,16,17). In those without underlying kidney functional impairment, MRH, even excessive MRH, was significantly apparent in women with safe pregnancies. Therefore, sCr measurement and eGFR calculation could be considered as screening tools to assess hemodynamic adaptation during pregnancy. In contrast, the clinical effect of hyperfiltration in those with underlying CKD warrants further study.

There are several limitations in this study, foremost, by its retrospective nature. We observed that midterm sCr levels were not routinely obtained in the majority of women. Consequently, our study group included a large number of high-risk women in whom the midterm sCr level was obtained during a hospital visit for other medical conditions, which may have contributed to the relatively higher incidence of gestational complications in our study group. Therefore, further prospective study in healthy pregnant women with routine sCr measurements is warranted for more confirmatory results. Second, the possibility of inaccuracy in the calculation of eGFR from measured sCr because of pregnancy-related changes in physiologic volume and weight (31,32) should be considered. However, considering the significant relationship between eGFR and pregnancy outcomes in our study and the availability of sCr measurements in practice, we propose that eGFR should be monitored to predict gestational complications. Additional studies using 24-hour urine collection for creatinine clearance could provide a more reliable predictor of pregnancy prognosis, but the limited availability of the test should be considered. Lastly, the absolute eGFR values, not the changes, were used to define subgroups because of the small proportion of mothers with known baseline renal parameters. However, it should be noted that the relative eGFR increase itself was a protective marker in mothers without kidney functional impairment, even after adjustment for baseline levels.

In conclusion, we identified a unique U-shaped relationship between midterm eGFR and pregnancy outcomes, and an optimal range for MRH included eGFR levels of 120–150 ml/min per 1.73 m^2. We confirmed the prognostic value of eGFR even for women with no evidence of underlying CKD, in whom the absence of adequate MRH was associated with the presence of gestational complications. On the basis of our results, it might be beneficial to measure eGFR during midterm gestation to assess risk for pregnancy complications, and clinicians should be mindful to apply different standards for interpretation of levels than for a general population.

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Disclosures

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