Maternal and Perinatal Outcomes in Pregnancy by Chronic Kidney Disease Stage Based on Midterm Glomerular Filtration Rate

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Objective: Chronic kidney disease (CKD) is a known risk factor of pregnancy that increases the rates of preterm birth, intrauterine growth restriction, and preeclampsia. And maternal CKD may worsen due to pregnancy itself. However, few studies have examined these problems in Korea.

Methods: The cases of 29 women with CKD who delivered singleton at our institute between 2006 and 2018 were retrospectively reviewed. Cases with major fetal malformation, intrauterine fetal death, a history of kidney transplantation, or insufficient information for the parameters were excluded. The subjects were divided into early-stage (stages 1 and 2) and late-stage (stages 3 to 5) groups according to the midterm glomerular filtration rate (GFR). Demographic profiles, renal function, perinatal complications, and changes in GFR from pre-conception to postpartum were compared and analysed.

Results: The incidence of preeclampsia (28.6% vs. 75.0%; $P=0.038$), anemia (28.6% vs. 75.0%; $P=0.038$), cesarean section (42.9% vs. 100.0%; $P=0.009$), small for gestational age (14.3% vs. 62.5%; $P=0.019$) and the need for neonatal intensive care unit (38.1% vs. 87.5%, $P=0.035$) were significantly higher in the late-stage group than those in the early-stage group. Gestational age at delivery (38.1 vs. 35.4 weeks, $P=0.021$) and birth weight (2,970 vs. 2,200 g, $P=0.006$) were significantly lower in the late-stage group than those in the early-stage group. GFR decreased significantly after delivery compared to pre-conception in both group ($P=0.028$, both).

Conclusion: Late-stage CKD is a poor prognostic factor for pregnancy outcomes. Pregnancy deteriorates renal function even in early-stage. Close monitoring and management are required for pregnant women with any stage of CKD.

Key Words: Pregnancy, Renal insufficiency, chronic, Glomerular filtration rate, Maternal health, Pregnancy outcome

Introduction

Chronic kidney disease (CKD) is defined as an abnormal renal structure or function that persists for more than 3 months. Specifically, patients are diagnosed as having CKD when a decreased glomerular filtration rate (GFR; $<60 \text{ mL/min/1.73 m}^2$) or one or more markers of kidney damage (albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, and history of kidney transplantation) are present for more than 3 months. CKD is stratified into five stages based on GFR level (mL/min/1.73 m^2) as Table 1.¹

The prevalence of CKD is 0.1–6% in women of childbearing age.^{2–7} Early-stage CKD (stage 1 and 2) affects 3.2% of pregnant women,⁶ while 1 of 750 pregnant women has late-stage CKD.⁴ It is well known that CKD adversely affects pregnancy, increasing the rates of miscarriage, stillbirth, preterm birth, fetal death, intrauterine growth restriction (IUGR),

Table 1. Classification of Chronic Kidney Disease by Stage 1 to 5 according to GFR

Stage	GFR (mL/min/1.73 m ²)	Terms
1	≥90	Normal and high
2	60-89	Mildly decreased
3a	45-59	Mildly to moderately decreased
3b	30-44	Moderately to severely decreased
4	15-29	Severely decreased
5	<15 or dialysis	Kidney failure

Abbreviation: GFR, glomerular filtration rate.

neonatal intensive care unit (NICU) admission, preeclampsia, and cesarean section (C/S).⁸⁻¹² According to a meta-analysis, the combined risk of gestational hypertension, preeclampsia, eclampsia, and maternal mortality was 2 to 10 times higher than that of the control group.⁸ The risk increases with worsening renal function, especially in late-stage CKD.^{9-11,13-20} Conversely, pregnancy alone may deteriorate maternal renal function.^{16,20} An estimated 50-75% of pregnant women with late-stage CKD experienced disease progression.²¹⁻²⁶

Although many studies have shown adverse effects of CKD on pregnancy outcomes and the aggravation of CKD in pregnancy, only a few studies in Korea have examined that issue. Therefore, we performed this retrospective study to evaluate whether late-stage CKD is a higher risk factor of adverse pregnancy outcomes than early-stage CKD and to what extent. We also analyzed the effect of pregnancy on early- and late-stage CKD progression in Korea.

Methods

This study was conducted in a tertiary medical center, Gachon University Gil Medical Center in Incheon, Korea. Women who were diagnosed as having CKD before or during pregnancy by a nephrologist were referred to the Department of Obstetrics and Gynecology of our center. Among them, patients delivered singleton baby at our institute between January 2006 and December 2018 were enrolled in this study. Seven patients were excluded from the study because of insufficient information for analysis (three patients), loss of follow-up (one patient), intrauterine fetal death (one patient) and a history of kidney transplantation before pregnancy (two patients). Finally, 29

cases were included in our study. Their medical records were obtained and retrospectively analyzed. This study had approval of Institutional Review Boards (IRB No. GAIRB2019-210).

Their GFRs were calculated using the CKD-Epidemiology Collaboration equation. The patients were categorized in five stages based on their GFR in the midterm of pregnancy because some patients were diagnosed as having CKD during pregnancy. The participants were divided into the early-stage (stages 1 and 2) and late-stage (stages 3 to 5) groups.

The baseline parameters of patients were obtained, including age, body mass index, pre-existing hypertension or diabetes mellitus, obstetrical history, gestational age (GA) at delivery, GA at first referral to the Department of Obstetrics and Gynecology, type of renal disease, CKD duration, dialysis, serum creatinine level, and hemoglobin level. To assess CKD progression during pregnancy, we used the GFRs based on the serum creatinine level before conception, in the midterm (the second trimester; between 14 weeks and 28 weeks), within 2 weeks before delivery, and within 6 weeks after delivery. When the serum creatinine level in the second trimester was not available, the level at the GA proximate to second trimester was used. Obstetrical outcomes were set as C/S, preterm birth (GA <37 weeks or <34 weeks), anemia and preeclampsia. Anemia was defined when the lowest hemoglobin level in pregnant period was below 11.0 g/dL (first or third trimester) or 10.5 g/dL (second trimester).²⁷ And preeclampsia was diagnosed when the baseline blood pressure rises newly or worsens with aggravated proteinuria, thrombocytopenia, elevated liver enzyme levels, cerebral symptoms or pulmonary edema.²⁸ Perinatal outcomes were birth weight, small for GA (SGA) which was defined in case that the birth weight was below the 10th percentile for the GA, IUGR defined when estimated fetal weight was below 10th percentile for the GA with oligohydramnios or abnormal Doppler findings in antenatal sonography, neonatal death, low 5-min Apgar score (<7), and NICU admission.

Descriptive statistics were performed to summarize the subjects' characteristics. Continuous data are shown as median and range and analyzed using the Mann-Whitney *U* test. GA converted to a decimal scale was used. Categorical data are presented as percentages, and the frequencies across categories were assessed using Fisher's exact test. To ascertain CKD progression during pregnancy, changes in GFR from pre-

conception to post-delivery were assessed using the Wilcoxon signed rank test. The statistically analyses were performed using SPSS version 22.0 (IBM Corp., New York, NY, USA), and values of $P < 0.05$ were considered statistically significant.

Results

The clinical profiles of 29 patients enrolled in the study are shown in Table 2. The median GA at delivery was 37.3 weeks; there was a significant difference in GA at delivery between the early-stage and late-stage groups (38.1 vs. 35.4 weeks, $P = 0.021$). Eleven patients (37.9%) had hypertension and six patients (20.7%) had diabetes mellitus. The prevalence of pre-existing hypertension was significantly high in the late-stage group (19.0% vs. 87.5%, $P = 0.001$). Regarding renal disease type, glomerulonephritis was the most common in the early-stage group (76.2%), while glomerulonephritis (37.5%) and diabetic nephropathy (37.5%) both were the most common type in the late-stage group. The serum creatinine levels and the calculated GFRs differed significantly between the early- and late-stage groups regardless of the measured time (Table 3). The

median hemoglobin level was 12.2 g/dL in the early-stage group and 10.5 g/dL in the late-stage group ($P = 0.028$).

Regarding pregnancy outcomes, 42.9% of patients delivered by C/S in the early-stage group versus 100% in the late-stage group (Table 4). The most common indication of C/S in the early-stage group was prior C/S (four cases), which was followed by breech presentation, severe IUGR, preeclampsia with uncontrolled blood pressure, fetal anomaly and maternal request (one case each). Eight patients in the late-stage group delivered by C/S due to prior C/S (four cases), fetal distress (two cases), preeclampsia with uncontrolled blood pressure (one case), and aggravation of CKD (one case). The rates of preterm birth before GA 37 weeks (33.3% vs. 62.5%) and before 34 weeks (9.5% vs. 12.5%) did not differ significantly between the two groups. The incidence of preeclampsia was 28.6% in the early-stage group and 75.0% in the late-stage group (odds ratio, 7.5; $P = 0.038$). There were no cases of eclampsia. The rate of anemia was significantly higher in the late-stage group than that in the early-stage group (odds ratio, 7.5; $P = 0.038$). The median birth weights were 2,970 g and 2,200 g in the early- and late-stage groups, respectively, which showed significantly low in late-stage ($P = 0.006$). The incidence of SGA was significantly

Table 2. Clinical Characteristics of Women with CKD

Characteristic	Overall (n=29)	Early-stage (n=21)	Late-stage (n=8)	P-value
Age (years)	31.0 (24.0-47.0)	31.0 (24.0-37.0)	31.5 (25.0-47.0)	0.487
Body mass index (kg/m ²)	21.7 (18.8-28.3)	21.5 (18.8-28.3)	22.1 (21.3-24.9)	0.301
Nulliparity	15 (51.7)	12 (57.1)	3 (37.5)	0.427
Abortion history	9 (31.0)	6 (28.6)	3 (37.5)	0.675
GA at delivery (weeks)	37.3 (29.1-40.7)	38.1 (30.4-40.7)	35.4 (29.1-37.4)	0.021
GA at referral (weeks)	9.0 (4.0-36.0)	8.0 (4.0-36.0)	12.0 (7.0-29.0)	0.793
Hypertension	11 (37.9)	4 (19.0)	7 (87.5)	0.001
Diabetes mellitus	6 (20.7)	3 (14.3)	3 (37.5)	
CKD duration (years)	4.0 (0.0-17.0)	2.0 (0.0-10.0)	4.5 (1.0-17.0)	0.093
Dialysis	4 (13.8)	0 (0.0)	4 (50.0)	
Type of renal disease				
Glomerulonephritis	19 (65.5)	16 (76.2)	3 (37.5)	-
Diabetic nephropathy	5 (17.2)	2 (9.5)	3 (37.5)	-
Hypertensive nephropathy	1 (3.4)	0 (0.0)	1 (12.5)	-
SLE	2 (6.9)	2 (9.5)	0 (0.0)	-
Unknown	2 (6.9)	1 (4.5)	1 (12.5)	-

Values are presented as median (range) or number (%). Analyzed by Mann-Whitney *U* test and Fisher's exact test. Abbreviations: CKD, chronic kidney disease; GA, gestational age; SLE, systemic lupus erythematosus.

Table 3. Laboratory Characteristics of Women with CKD

	Overall (n=29)	Early-stage (n=21)	Late-stage (n=8)	P-value
Serum creatinine (mg/dL)				
Pre-conception	0.8 (0.4-11.6)	0.7 (0.4-1.5)	3.0 (1.4-11.6)	<0.001
Midterm	0.7 (0.4-10.2)	0.6 (0.4-1.2)	4.0 (1.3-10.2)	<0.001
2 weeks before delivery	0.9 (0.3-9.4)	0.7 (0.3-2.0)	4.2 (1.6-9.4)	<0.001
6 weeks after delivery	0.9 (0.4-11.8)	0.8 (0.4-1.9)	5.0 (1.6-11.8)	<0.001
GFR (mL/min/1.73 m ²)				
Pre-conception	99.0 (4.0-136.0)	115.0 (48.0-136.0)	23.5 (4.0-49.0)	<0.001
Midterm	116.5 (4.0-142.0)	122.0 (61.0-142.0)	16.0 (4.0-54.0)	<0.001
2 weeks before delivery	86.0 (5.0-149.0)	116.0 (33.0-149.0)	14.0 (5.0-42.0)	<0.001
6 weeks after delivery	85.0 (4.0-133.0)	100.0 (35.0-133.0)	11.5 (4.0-42.0)	<0.001
Hemoglobin (g/dL)	11.3 (7.1-15.2)	12.2 (7.1-15.2)	10.5 (8.6-11.6)	0.028

Values are presented as median (range). Analyzed by Mann-Whitney *U* test.
Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

Table 4. Comparison of Pregnancy Outcomes by CKD Stage

Obstetric and perinatal outcomes	Overall (n=29)	Early-stage (n=21)	Late-stage (n=8)	OR (95% CI)	P-value
Obstetric outcomes					
Cesarean section	17 (58.6)	9 (42.9)	8 (100.0)	-	0.009
Preterm birth (<37 weeks)	12 (41.4)	7 (33.3)	5 (62.5)	3.33 (0.61-18.15)	0.218
Preterm birth (<34 weeks)	3 (10.3)	2 (9.5)	1 (12.5)	1.36 (0.11-17.42)	1.000
Preeclampsia	12 (41.4)	6 (28.6)	6 (75.0)	7.50 (1.17-48.15)	0.038
Anemia	12 (41.4)	6 (28.6)	6 (75.0)	7.50 (1.17-48.15)	0.038
Perinatal outcomes					
Birth weight (g)	2,658 (820-4,275)	2,970 (1,470-4,275)	2,200 (820-2,545)	-	0.006
SGA	8 (27.6)	3 (14.3)	5 (62.5)	10.00 (1.52-65.68)	0.019
IUGR	7 (24.1)	3 (14.3)	4 (50.0)	6.00 (0.95-38.08)	0.068
Anomaly	1 (3.4)	1 (4.8)	0 (0.0)	-	1.000
Neonatal death	0 (0.0)	0 (0.0)	0 (0.0)	-	-
5-min Apgar score <7	1 (3.4)	1 (4.8)	0 (0.0)	-	1.000
Admission in NICU	15 (51.7)	8 (38.1)	7 (87.5)	11.38 (1.27-110.42)	0.035

Values are presented as median (range) or number (%). Analyzed by Mann-Whitney *U* test and Fisher's exact test.

Abbreviations: CKD, chronic kidney disease; OR, odds ratio; CI, confidence interval; SGA, small for gestational age; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit.

high in late-stage group ($P=0.019$), whereas, the incidence of IUGR did not differ significantly between the two groups ($P=0.068$). There were no cases of neonatal death in either group. The NICU admission rate was 38.1% in the early-stage group versus 87.5% in the late-stage group (odds ratio, 11.4; $P=0.035$). There was one baby in the early-stage group who was born at GA 34.7 weeks and 1,500 g in weight had a low 5-min Apgar score below 7 points. Another baby in the early-stage group had anomalies of mild pulmonary artery stenosis and tricuspid

valve regurgitation with no other complication. He was born by C/S due to antenatal detection of those anomalies and expected need for neonatal resuscitation, however his 5-min Apgar score was 10 and the anomalies were mild.

To assess changes in kidney function regarding CKD stage, the median GFR was compared among measurement points (Table 5). In early-stage CKD, the midterm GFR increased compared to the pre-conception GFR, decreased again before delivery, and decreased further postpartum. On the other hand, the median

Table 5. Changes in GFR Over Time in Early- and Late-stage CKD (mL/min/1.73 m²)

Stage	Pre-conception	Midterm	2 weeks before delivery	6 weeks after delivery	P-value*
Early	115.0 (48.0-136.0)	122.0 (61.0-142.0)	116.0 (33.0-149.0)	100.0 (35.0-133.0)	0.028
Late	23.5 (4.0-49.0)	16.0 (4.0-54.0)	14.0 (5.0-42.0)	11.5 (4.0-42.0)	0.028

Values are presented as median (range). Analyzed by Wilcoxon signed rank test.

Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease.

*Pre-conception vs. 6 weeks after delivery.

GFR declined steadily from pre-conception to postpartum in the late-stage CKD. There was significant decrease in GFR pre-conception (115.0 mL/min/1.73 m²) versus postpartum (100.0 mL/min/1.73 m²) in early-stage group ($P=0.028$). In late-stage group, the change of GFR between pre-conception (23.5 mL/min/1.73 m²) and postpartum (11.5 mL/min/1.73 m²) was also significant ($P=0.028$).

Discussion

Delivery by C/S occurs more frequently in women with CKD than in those with a normal pregnancy.^{11,12} Piccoli et al.¹¹ reported a higher C/S rate in patients with CKD versus controls (54.8% vs. 27.2%, respectively). This result is similar to that in our patients with CKD (56.7%). In our study, the rate of C/S in the late-stage group was significantly higher than that in the early-stage group (100% vs. 42.9%, respectively), which is thought to be due to the more unfavourable maternal and fetal condition of late-stage CKD including preeclampsia, fetal distress, and worsening renal function. A cohort study reported a 9.1% incidence of preeclampsia in early-stage CKD, which is significantly higher than that in the normal population.²⁹ Our study showed a higher prevalence of 28.6% in patients with early-stage CKD and a much higher rate of 75.0% in the late-stage group ($P=0.038$). This significant difference in the incidence of preeclampsia between early- and late-stage CKD is consistent with preceding data.^{16,20,23} An erythropoietin deficiency in CKD patients induces anemia, which is associated with fetal growth restriction, especially in the late-stage.²⁶ The incidence of anemia was significantly higher in patients with late-stage CKD (28.6% vs. 75.0%) as reported by preceding studies.^{20,30} Several studies demonstrated a diverse prevalence of preterm birth of 22.4–44% in CKD patients versus 4.9% in the normal population.^{9,19,29} In our study, there was a 41.4% preterm birth rate in overall CKD

patients, which is consistent with other studies. More than 75% of patients with stage 3 CKD and almost all patients with stage 4–5 CKD gave birth to a premature baby.^{8,13,26,31} However, a study in India reported a comparable incidence of preterm birth rate in both stages (45.4% in early-stage, 56.5% in late-stage).²⁰ Similar to the result of an Indian study, there was no significant difference in the preterm birth rate between two stages in our study, whereas the significant gap of the median GA at delivery (38.1 vs. 35.4 weeks, $P=0.021$). This is thought to be because of the early intervention to unfavourable fetal and maternal condition in late-stage CKD. The median birth weight was 2,970 g in the early-stage group and 2,200 g in the late-stage group, which showed a significant difference ($P=0.006$). The result is probably due to earlier GA at delivery with late-stage CKD. The adverse effect of CKD stage on SGA remains disputable with various results of preceding studies.^{9,20,30} In this study, the incidence of SGA was 14.3% in the early-stage group and 62.5% in the late-stage group, which showed significant difference ($P=0.019$). However, the incidence of IUGR had no significant difference ($P=0.068$). Piccoli et al.²⁶ reported that more than 40% of babies born to women with late-stage CKD required NICU admission. In our study, the NICU admission rate in the late-stage group was 87.5%, which was significantly higher than 38.1% of rate in early-stage group ($P=0.035$).

The risk of CKD progression differed among several studies (22–75%) and remains controversial.^{20,23–26} According to the results of preceding studies, there was a significant decrease in GFR 6 weeks after delivery versus before conception at all CKD stages.^{16,20} A study by Davidson et al.³⁰ reported a significant difference in GFR between before conception and 6 weeks and 12 months postpartum only in the late-stage group. On the other hand, a meta-analysis showed no association between pregnancy and deterioration of renal function.¹⁸ In our study, comparison of pre-conception and 6 weeks postpartum revealed a significant decrease in GFR in both stage group

($P=0.028$, both). The changing pattern of GFR in the early-stage resembled the physiological change in renal blood flow and hyperfiltration in pregnancy peaking in midterm, while the GFR value decreased steadily over time in the late-stage. Furthermore, the decline in GFR was faster and a greater proportion of patients progressed to a higher CKD stage in the late-stage group.^{16,20} Four out of 16 patients in stage 1 CKD, three out of five patients in stage 2, one out of two patients in stage 3, and two out of two patients in stage 4 progressed to the next stage 6 weeks after delivery in our study, supporting that higher initial stage is adverse factor of CKD aggravation.

This is the largest study to assess pregnancy and renal outcomes in pregnant women with CKD in Korea by comparing those with early- and late-stage disease. However, its size is too small to evaluate other factors known to affect adverse pregnancy outcomes and deterioration of renal function such as CKD pathology, proteinuria, hypertension, and required therapies.^{6,11,32-36} Another limitation is that our study was retrospective, so missing data could not be controlled for. Further multivariate analyses with larger populations are needed to more clearly verify the outcomes. The new attempt to set mid-term GFR as the baseline value can be a limitation, but it can be a good basis for identifying new useful predictors.

In conclusion, late-stage CKD raised the risk of many adverse maternal and perinatal outcomes compared with early-stage CKD. Renal function deterioration induced by pregnancy was influenced regardless of CKD stage. Therefore, women with CKD, even in early-stage, must plan for pregnancy, and when they conceive, adequate and close multidisciplinary monitoring should be performed by obstetricians, nephrologists, and neonatologists to ensure better pregnancy and renal outcome.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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