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Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 166–170

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Factors related to deterioration of renal function after singleton delivery in pregnant women with chronic kidney disease

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ARTICLE INFO

Article history:
Accepted 6 February 2015

Keywords:
chronic kidney disease
estimated glomerular filtration rate
pregnancy
receiver-operating characteristic curve analysis

ABSTRACT

Objective: This study is designed to evaluate which factors would relate to deterioration of renal function (DRF) after delivery in pregnant women with chronic kidney disease (CKD).
Materials and methods: This study included 156 singleton pregnancies of 139 women with CKD at our institution from 2001 to 2010. DRF was defined as the shift of CKD stage into another more severe stage. The relevant variables were compared between women who had DRF ($n = 39$) and the controls ($n = 117$).
Results: The number of transplantation or dialysis cases after delivery was 5.8%. DRF occurred in 25% of the study patients. From a logistic regression model, the factors that influence DRF were the presence of glomerulonephritis [odds ratio (OR) 3.56, 95% confidence interval (CI) 1.18–10.81], significant proteinuria prior to pregnancy (≥3 g/d or 3+ more dipstick; OR 3.43, 95% CI 1.14–10.33), and treatment with antiplatelet agents (OR 0.30, 95% CI 0.09–0.94). Receiver-operating characteristic curve analysis confirmed that the estimated glomerular filtration rate (eGFR) of 75 mL/min/1.73 m^2 or more before conception is not a risk factor for DRF after delivery (negative predictive value 0.788).
Conclusion: This was the first report to reveal a clear cutoff value regarding DRF in pregnant woman with CKD. There is an almost 78% risk of developing DRF after delivery in patients showing eGFR of 75 mL/min/1.73 m^2 or more before conception.

Introduction

Chronic kidney disease (CKD) is a healthcare problem that was only recently acknowledged in its full dimension and is often clinically silent until renal dysfunction enters advanced stages. In 2002, the redefinition of CKD led to development of the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for the diagnosis and staging of CKD and these disease classifications are now used worldwide [1]. The glomerular filtration rate (GFR) as assessed using the estimated GFR (eGFR) is also evaluated and the CKD stage is classified as follows: Stage 1 (eGFR > 90 mL/min/1.73 m^2), Stage 2 (89–60 mL/min/1.73 m^2), Stage 3 (59–30 mL/min/1.73 m^2), Stage 4 (29–15 mL/min/1.73 m^2), or Stage 5 (<15 mL/min/1.73 m^2 or dialysis) [1–3]. Stages 1 and 2 (normal or mild renal impairment with persistent albuminuria) affect up to 3% of women of childbearing age (20–39 years) [2,4]. Stages 3–5 (GFR < 60 mL/min/1.73 m^2) affect approximately one in 150 women of childbearing age, but because of reduced fertility and an increased rate of early miscarriage, pregnancy in these women is less common [2].

Pregnancy in women with CKD is considered to be high risk and the knowledge of this risk guides patient counseling and follow-up [3–9]. For example, Fink et al [5] concluded that women with renal disease were at an increased risk of preeclampsia [odds ratio (OR) 7.2, 95% confidence interval (CI) 4.2–12.5], preterm labor (PTL; OR 7.9, 95% CI 1.9–32.6), dysfunctional labor (OR 3.6, 95% CI 1.1–11.5), and cesarean section (OR 3.1, 95% CI 2.0–4.8). Although several studies have shown that women with CKD have an increased risk of developing adverse maternal and fetal outcomes, whether the long-term prognosis is influenced by pregnancy and delivery has remained unclear [6,8,10,11].

This study is designed to evaluate which factors would relate to deterioration of renal function (DRF) after delivery in pregnant women with CKD according to the CKD staging.

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http://dx.doi.org/10.1016/j.tjog.2016.02.003

Materials and methods

Study population

We evaluated 156 singleton pregnancies of 139 women who were recruited into this case–control study between January 1, 2001, and December 31, 2010. The study was conducted at the Maternal and Perinatal Center, Tokyo Women's Medical University Hospital. Patients' cases were singleton pregnancies of women with CKD between 22 and 41 weeks of gestation. Patients who showed multiple pregnancy or fetal anomaly or dialysis were excluded.

All patients in this study provided verbal informed consent for study participation. This study was conducted after obtaining approval from the Institutional Review Board of Tokyo Women's Medical University (No. 2011-2299).

Study assessments

The gestational age was determined based on the last menstrual period and standard obstetric ultrasonography. All patients were permitted to continue the pregnancy by obstetricians and were managed in collaboration with nephrologist.

Clinical assessment was serially undertaken as follows: prior to the pregnancy, first check-up during pregnancy at 8–10 weeks' gestation, and thereafter, once in the first trimester, once in the second trimester, and once in the third trimester. Details such as mean arterial pressure; use of antihypertensive, immunosuppressive, and antiplatelet medication; and complications were documented at each visit.

PTL was defined as the demonstrated progressive dilation of the cervix with uterine contractions before 36 weeks of gestation [12]. Premature rupture of membranes (PROM) was defined as "leakage of a watery discharge" [13]. According to the criteria of the National High Blood Pressure Education Program, hypertensive disorders in pregnancy can be classified as follows: chronic hypertension, pregnancy-induced hypertension (PIH), preeclampsia, and superimposed preeclampsia [14]. The diagnosis of PIH was made in women whose blood pressure reached 140/90 mmHg or greater after the 20th week of gestation, but in whom proteinuria was not identified [15,16]. Significant proteinuria prior to pregnancy was defined as 24-hour urinary protein level of 3.0 g or more (or 3+ more) using a dipstick in random urine samples.

Delivery was allowed to occur with maternal indications such as onset of PIH or intractable hypertension, fetal indications such as nonreassuring fetal status, and gestational age more than 37 weeks. Cesarean sections were carried out for patients who had previously undergone cesarean section, as well as for those with dystocia, nonreassuring fetal status, fetal malpresentation, or maternal indications.

Recording of maternal characteristics

The obstetric notes of the mothers were reviewed by a researcher (Y.M). Nearly 10 variables were assessed, including demographic data, pregestational factors, and prenatal events. The pregestational factors were age, transplantation before conception, and maternal medical history (complications and previous obstetric history). The prenatal events were eGFR and obstetric complications such as preterm delivery (<37 weeks)/PROM and PIH. Details on the onset, duration, and clinical management of any relevant condition were also recorded.

The CKD staging

GFR was estimated using the Modification of Diet in Renal Disease-4 variable equation (based on the serum creatinine level, age, sex, and race) and expressed in milliliters/minute/1.73 m^2 of body surface area [10]. Patients were categorized into four groups according to GFR and the CKD stage was classified according to the K/DOQI guidelines [1–3]. The DRF was defined as the shift of CKD stage into another more severe stage [17]. The mean follow-up period and diagnosis of DRF was 3.8 years (13 years at most).

Statistical analysis

The results are expressed as the mean ± standard deviation. Statistical analysis was performed using the Chi-square test, Fisher exact probability test, Mann–Whitney *U* test, Kruskal–Wallis test, Student *t* test, and a multiple regression analysis (Artech Co., Ltd., Osaka, Japan). Receiver-operating characteristic (ROC) curve analysis was described with the Kaplan–Meier method. All *p* values less than 0.05 were considered significant. ORs, with 95% CI, were calculated to estimate the relative risk of the various risk factors for CKD in the cases compared with the controls. The results were compared using both univariate and multivariate analyses, and logistic regression models were used to assess the influence of confounding factors.

Results

The CKD lesions and the CKD staging in 156 singleton pregnancies of 139 women with CKD are shown in Table 1. Among the 156 pregnancies, before conception there were 39 pregnancies of women with CKD Stage 1, 59 with CKD Stage 2, 52 with CKD Stage 3, and six with CKD Stage 4. After delivery, there were 41 pregnancies with CKD Stage 1, 45 with CKD Stage 2, 52 with CKD Stage 3, nine with CKD Stage 4, and nine at CKD Stage 5.

Table 2 shows the maternal characteristics before conception. There were no differences across CKD stages from the standpoint of primipara, proteinuria prior to pregnancy, and the treatment by antiplatelet agents. eGFR before conception and after delivery is also presented. Thirty cases had hypertension. In CKD Stage 3, the number of hypertension cases increased significantly versus CKD Stage 1. Twenty-eight pregnancies suffered from PIH. In CKD Stage 4, the number of PIH cases was statistically significant versus CKD Stage 1. Fifty-four pregnancies suffered from preterm delivery (<37 weeks). In CKD Stages 3 and 4, the number of preterm delivery (<37 weeks) cases was statistically significant versus CKD Stage 1. The number of transplantation or dialysis procedures performed after delivery was nine (2 from Stage 2, 4 from Stage 3, and 3 from Stage 4). There was a shift from a lower to a higher CKD stage in 39 pregnancies and there was no statistical significance in any of the CKD stages. In the treatment, antihypertensive drugs and steroids of the CKD Stage 3 cases were statistically significant versus the Stage 1 cases. Immunosuppressive agents of the CKD Stage from 2 to 4 were statistically significant versus the CKD Stage 1. Antihypertensive drugs were as follows: alpha-methyldopa ($n = 19$); calcium-channel blocker ($n = 5$); and propranolol hydrochloride ($n = 2$).

Table 3 presents the relationship between DRF ($n = 39$; 10 from Stage 2, 17 from Stage 3, 9 from Stage 4, and 3 from Stage 5) and the controls (non-DRF; $n = 117$). By univariate analysis, glomerulonephritis, diabetic nephropathy, significant proteinuria prior to pregnancy (≥3 g/d or 3+ more dipstick), and treatment with antiplatelet agents were significant in DRF. Neither perinatal deaths nor maternal deaths were seen during the observation period.

From a logistic regression model, the factors that influenced DRF were the presence of glomerulonephritis (OR 3.56, 95% CI 1.18–10.81), significant proteinuria prior to pregnancy (≥3 g/d or 3+ more dipstick; OR 3.43, 95% CI 1.14–10.33), and treatment with antiplatelet agents (OR 0.30, 95% CI 0.09–0.94).

Table 1
Nature of the CKD lesions and CKD staging.

CKD lesions	Pregnant women, $N = 139$ (n)	Pregnancies, $N = 156$ (n)	Before conception					After delivery				
			CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 5	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD S tage 4	CKD Stage 5
			($N = 39$)	($N = 59$)	($N = 52$)	($N = 6$)	($N = 0$)	($N = 41$)	($N = 45$)	($N = 52$)	($N = 9$)	($N = 9$)
Immunoglobulin A nephropathy ($n = 54$)	46	54	7	29	17	1	0	13	18	19	3	1 (1 D)
Chronic renal failure [a] ($n = 16$)	16	16	0	1	12	3	0	0	4	9	2	1 (1 D)
Glomerulonephritis ($n = 17$)	16	17	3	7	6	1	0	2	4	8	0	3 (2 D, 1 T)
Nephritis ($n = 11$)	10	11	2	5	3	1	0	2	4	3	1	1 (1 T)
Nephrotic syndrome ($n = 12$)	11	12	9	3	0	0	0	10	1	1	0	0
Diabetic nephropathy ($n = 10$)	9	10	1	4	5	0	0	0	0	6 (1 T)	1	3 (3 D)
Congenital malformations and deformations ($n = 10$)	8	10	5	3	2	0	0	2	7	1	0	0
Renal agenesis ($n = 3$)	2	3	1	1	1	0	0	1	1	1	0	0
Polycystic kidney ($n = 2$)	1	2	0	2	0	0	0	0	2	0	0	0
Double renal pelvis and ureter ($n = 1$)	1	1	1	0	0	0	0	0	1	0	0	0
Cyst of kidney ($n = 1$)	1	1	1	0	0	0	0	0	1	0	0	0
Congenital hydronephrosis ($n = 1$)	1	1	0	0	1	0	0	0	1	0	0	0
Medullary sponge kidney ($n = 1$)	1	1	1	0	0	0	0	1	0	0	0	0
Noonan syndrome ($n = 1$)	1	1	1	0	0	0	0	0	1	0	0	0
Purpura nephritis ($n = 7$)	6	7	2	4	1	0	0	3	2	1	1	0
Membranous nephropathy ($n = 4$)	4	4	4	0	0	0	0	4	0	0	0	0
Systemic lupus nephritis ($n = 4$)	3	4	1	1	2	0	0	1	1	2	0	0
Renovascular hypertension ($n = 3$)	3	3	2	0	1	0	0	2	0	1	0	0
Focal glomerulosclerosis ($n = 2$)	2	2	1	0	1	0	0	1	0	0	1	0
Calculus of kidney and ureter ($n = 2$)	2	2	1	1	0	0	0	0	2	0	0	0
Hydronephrosis with ureteropelvic junction obstruction ($n = 2$)	1	2	0	1	1	0	0	0	2	0	0	0
Familial thin basement membrane disease ($n = 1$)	1	1	1	0	0	0	0	1	0	0	0	0
Gouty kidney ($n = 1$)	1	1	0	0	1	0	0	0	0	1	0	0

Data are presented as n (%).
CKD = chronic kidney disease; D = dialysis; T = transplantation.
[a] The diagnosis of chronic renal failure is without definite renal pathology proved.

Table 2
Clinical characteristics of the CKD patients before conception and after delivery.

	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	p
	($n = 39$)	($n = 59$)	($n = 52$)	($n = 6$)	
Before conception					
Maternal age (y) [a]	30.4 ± 5.1	32.9 ± 4.6	33.7 ± 4.4*	31.5 ± 4.7	<0.05*
Primipara (n)	32	43	36	5	n.s.
Transplantation before conception	0	10 *	28 *,**	3 *	<0.01* <0.01**
Maternal complications before conception					
Hypertension (n)	3	10	15 *	2	<0.05*
Significant proteinuria (≥3 g/d or 3+ more dipstick)	4	11	5	2	n.s.
Treatment before conception (n)					
Antihypertensive drugs	3	8	13 *	2	<0.05*
Steroids	12	22	28 *	3	<0.01*
Immunosuppressive agents	1	9*	27 *	3 *	<0.01*
Antiplatelet agents	8	18	14	2	n.s.
eGFR (mL/min) before conception [a]	109.6 ± 17.7	75.6 ± 7.7	45.1 ± 8.5	23.9 ± 3.9	<0.0001
After delivery					
eGFR (mL/min) after delivery [a]	103.4 ± 30.7	70.7 ± 20.1	43.2 ± 17.2	17.6 ± 17.7	<0.0001
Obstetrical complications (n)					
Pregnancy-induced hypertension	4	9	12	3 *	<0.05*
Preterm delivery (<37 wk)	8	17	24 *	5 **,#	<0.05* <0.01# <0.05**
The deterioration of renal function	10	17	9	3	n.s.

Data are presented as n (%) or mean ± standard deviation.
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; n.s. = not significant.
* (vs. stage 1) ** (vs. stage 2) # (vs. stage 1).
[a] Kruskal–Wallis test.

Figure 1 shows the ROC curve for eGFR as a predictor of the shift in CKD stage from a lower to a higher stage. The cutoff value of eGFR affecting the shift of CKD stage from a lower to a higher stage, determined with the ROC curve analysis, was 74.4 mL/min

Table 3
Clinical characteristics of the CKD patients between case and control.

	DRF ($N = 39$)	non-DRF ($N = 117$)	p
CKD lesions			
Immunoglobulin A nephropathy ($n = 54$)	10	44	0.243
Chronic renal failure ($n = 16$)	2	14	0.361
Glomerulonephritis ($n = 15$)	8	9	0.037
Nephritis ($n = 11$)	2	9	0.732
Nephrotic syndrome ($n = 12$)	2	10	0.732
Congenital malformations and deformations ($n = 10$)	5	5	0.068
Diabetic nephropathy ($n = 10$)	6	4	0.020
Purpura nephritis ($n = 7$)	2	5	>0.99
Others ($n = 8$)	2	17	0.203
Maternal age (y)	32.0 ± 4.9	32.7 ± 4.8	0.446
Primipara (n)	33	83	0.137
Maternal complications prior to pregnancy			
Hypertension (n)	9	21	0.488
Significant proteinuria (≥3 g/d) or 3+ more dipstick	10	12	0.016
Obstetrical complications (n)			
Pregnancy-induced hypertension	8	20	0.635
Transplantation before conception	9	32	0.678
Treatment (n)			
Antihypertensive drugs	8	18	0.463
Steroids	11	54	0.061
Immunosuppressive agents	9	31	0.832
Antiplatelet agents	5	37	0.003
Mode of delivery: cesarean section (n)	22	48	0.060
Mean gestational week at delivery	35.3 ± 4.7	36.6 ± 3.7	0.075
Mean birth weight (g)	2236.1 ± 892.0	2513.1 ± 761.6	0.062
Apgar score < 7			
5 min (n)	3	4	0.368

Data are presented as n (%) or mean ± standard deviation.
CKD = chronic kidney disease; DRF = deterioration of renal function.

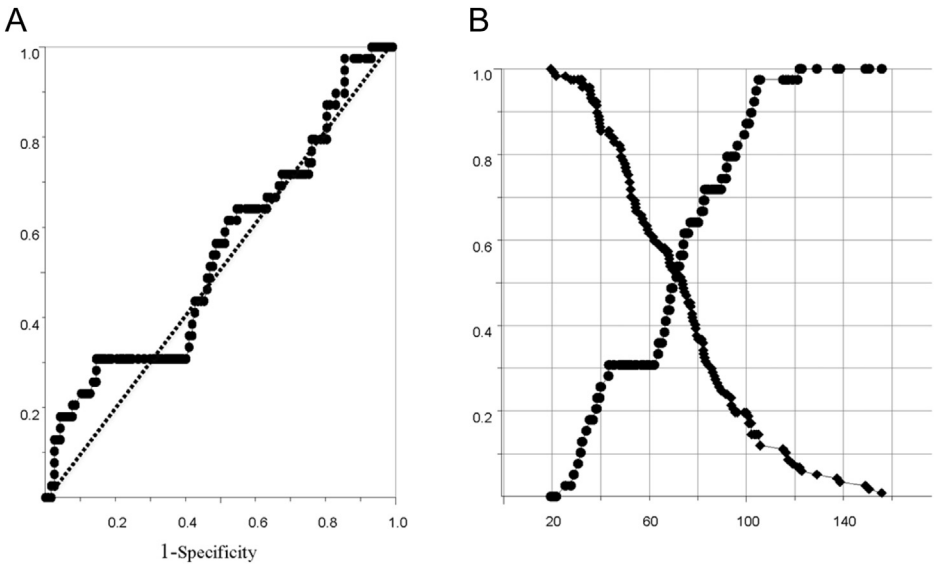

Figure 1. (A) Receiver-operating characteristic (ROC) curve for the estimated glomerular filtration rate (eGFR) before conception as a predictor of the shift of chronic kidney disease (CKD) stage from a lower to a higher stage. The cutoff value (74.4), sensitivity (0.615), specificity (0.479), positive predictive value (0.282), negative predictive value (0.788), and the area under the curve (0.720) were obtained from an analysis of the ROC curve. (B) Sensitivity and specificity curve for eGFR before conception predicting renal dysfunction in pregnant women with CKD. Each curve crossed at 74.4 mL/min/1.73 m^2 before conception.

(sensitivity = 0.615, specificity = 0.479, positive predictive value = 0.282 and negative predictive value = 0.788, and the area under the curve = 0.720).

Discussion

Persistent studies of CKD before or after pregnancy primarily classified patients on the basis of serum creatinine values in women with CKD [8]. However, the accuracy of the serum creatinine level as a marker of renal function is limited due to its nonlinear association with the GFR that varies according to age, sex, and lean body mass [18]. By contrast, the choice of GFR as a marker of renal function has the obvious advantage of revealing a population with normal serum creatinine level, but with significant renal functional impairment [19]. With this background, we examined the impact of CKD staging, based on a new formula for eGFR, on outcomes in pregnant women with CKD [1–3].

There are several reports in which CKD was redefined according to the K/DOQI guidelines in pregnant women with CKD

[2,3,10,19,20]. For example, Imbasciati et al [10] evaluated fetal and maternal outcomes of 49 pregnancies in 49 patients with CKD Stages 3–5 followed up for a mean period of 39 months after delivery. The authors reported that the combined presence of baseline GFR less than 40 mL/min/1.73 m^2 (<0.67 mL/s/m^2) and proteinuria with protein levels greater than 1 g/d, but not either factor alone, predicted faster GFR loss after delivery compared with before conception [1.17 ± 1.23 mL/min/mo vs. 0.55 ± 0.39 mL/min/mo; difference, 0.62 mL/min/mo; 95% CI 0.27–0.96 mL/min/mo (0.020 ± 0.021 mL/s/mo vs. 0.0092 ± 0.007 mL/s/mo; difference, 0.10 mL/s/mo; 95% CI 0.005–0.016 mL/s/mo)]. Moreover, the presence of both risk factors, but not either alone, also predicted shorter time to starting dialysis therapy or GFR halving ($N = 20$; hazard ratio 5.2; 95% CI 1.7–15.9) [10]. By contrast, we showed that patients showing eGFR of 75 mL/min/1.73 m^2 or more before conception were at an almost 78% risk of developing DRF after delivery in ROC curve analysis. Our study is the first report to reveal the clear cutoff value regarding DRF in pregnant woman with CKD.

In this study, we showed that glomerulonephritis, significant proteinuria prior to pregnancy (≥3 g/d or 3+ more dipstick), and treatment with antiplatelet agents were the factors that affected DRF in pregnant women with CKD. First, we revealed a 3.56-fold increase in risk of DRF in pregnant woman with glomerulonephritis. Glomerulonephritis usually shows no adverse effect if renal function is preserved and hypertension is absent before gestation [7]; however, an increase in cortisol and lactogen originating from the placenta may affect renal function and severity of nephritis and glomerular hypertension, and hyperfiltration could become prominent; these changes may damage the glomeruli during pregnancy [3]. In addition, as the blood pressure increases, relaxation and constriction of the import arteries occur repeatedly, damaging the endothelial cells of the glomerular arterioles and capillaries during pregnancy. These factors cause changes in the edematous endothelium of the glomeruli, the penetration of mesangial cells, and ischemia of the loop and focal segmental glomeruli [21–23]. From these findings, glomerulonephritis may be a risk factor for DRF in pregnant women with CKD. Second, we revealed a 3.43-fold increase in the risk of DRF in pregnant woman with significant proteinuria prior to pregnancy (≥3 g/d or 3+ more dipstick). Piccoli et al [19] also revealed that proteinuria and hypertension were correlated with outcomes in CKD. Third, we revealed a 0.30-fold decrease in risk of DRF in pregnant woman treated with antiplatelet agents that has not been reported previously. Thrombotic abnormalities may be present in all stages of CKD, and CKD is characterized as a state with a prothrombotic tendency where platelet dysfunction plays a pivotal role. Platelet activation is heavily implicated in the prothrombotic state observed in CKD patients, and oral antiplatelet agents have been extensively used in these patients [24]. According to these findings, antiplatelet agents are useful in the treatment of pregnant women with CKD.

Some limitations should be considered when interpreting the results of this study. First, there are several limitations such as a small sample size leading to inadequate assessment, short duration of therapy, and selection of a heterogeneous group of patients with CKD. Second, data were retrospectively collected as compared with a prospective study and more prospective studies are needed to confirm the results.

Conclusion

In conclusion, our findings demonstrate that glomerulonephritis, significant proteinuria prior to pregnancy (≥3 g/d or 3+ more on a dipstick), and treatment with antiplatelet agents are factors that affect DRF in pregnant women with CKD. Moreover, the ROC curve analysis confirmed that there is an almost 78% risk of developing DRF after delivery in patients showing eGFR of 75 mL/min/1.73 m^2 or more before conception.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

We thank Dr Satoru Shimizu (Medical Research Institute, Tokyo Women's Medical University, Tokyo, Japan) for advising on the analysis.

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