Original Article Gestational proteinuria as a risk factor for the prognosis of pregnancy outcomes

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Received November 23, 2016; Accepted February 6, 2017; Epub August 15, 2017; Published August 30, 2017

Abstract: Objective: To analyze the factors that affecting the prognosis of gestational proteinuria and pregnancy outcomes, aiming to improve the prognosis of proteinuria and reduce the incidence rate of adverse pregnancy outcomes. Methods: The clinical data of 8241 pregnant women who were admitted to obstetrical department of Shanghai General Hospital from January 2012 to June 2014 were retrospectively analyzed. 83 patients were identified with gestational proteinuria according to antenatal care data, parturition records and follow-up data. Logistic regression analysis was used to analyze various risk factors for poor prognosis of proteinuria and adverse pregnancy outcomes including age, pregnant frequency, systolic blood pressure, diastolic blood pressure, edema, hemoglobin, plasma albumin, hepatorenal function, antenatal care, chronic kidney disease history, the occurrence time of proteinuria and the severity of proteinuria. Results: 83 patients with an average age (28.5±5.2) met the inclusion criteria. Chronic kidney disease (OR = 8.921, P = 0.027), the occurrence time of proteinuria (OR = 6.393, P = 0.001) and the severity of proteinuria (OR = 2.737, P = 0.024) were the risk factors of poor prognosis of gestational proteinuria. Systolic blood pressure (OR = 3.834, P = 0.011), diastolic blood pressure (OR = 2.132, P = 0.002), the severity of proteinuria (OR = 2.899, P = 0.015) were the risk factors of adverse pregnancy outcomes. Conclusion: Chronic kidney disease, the occurrence time of proteinuria and the severity of proteinuria were found to be risk factors for poor prognosis of gestational proteinuria. The severity of proteinuria was both the risk factor for poor prognosis of gestational proteinuria and adverse pregnancy outcomes.

Keywords: Pregnancy, proteinuria, kidney injury, pregnancy outcome

Introduction

Gestational proteinuria is a clinically common pregnant complication in obstetric department, the causes of it include eclampsia, HELLP syndrome, chronic kidney disease (CKD), renal dysfunction, and so on. Gestational proteinuria is closely related to adverse pregnancy comes, and the persisting proteinuria is one of the critical factors that leading to kidney injury. Urine protein may induce renal tubular epithelial cell apoptosis by the way of direct toxic effects and lead to kidney injury by immune-mediated mechanism or promote the produce of reactive oxygen species. All the pathogenesis above may worse the existed renal lesions before pregnancy and result in end-stage renal disease [1-3]. There has been a lack of study evaluating the risk factors for the prognosis of gestational proteinuria, controversy remains regarding the relationship between gestational proteinuria and adverse pregnancy outcomes. In the present study, we analyzed the relevant factors that may affect the prognosis of proteinuria and pregnancy outcomes in pregnancy women with gestational proteinuria, which aimed to provide useful information for clinicians to make early clinical intervention to control proteinuria, improve the prognosis of proteinuria, protect the renal function and reduce the incidence rate of adverse pregnancy outcomes.

Subjects and methods

Subjects

This retrospective study was conducted by a review of medical records. Between January 2012 and June 2014, 8241 pregnant women from obstetrical department of Shanghai General Hospital were admitted to our study.

We focused on singleton pregnancy of gestational proteinuria with integrated antenatal care data, parturition records and follow-up information that over twelve weeks since the termination of pregnancy in this hospital. To determine the risk factors that may be related to the poor prognosis of gestational proteinuria and adverse pregnancy outcomes, information of the patients that met the inclusion criteria were taken in consideration in the present study including age, pregnant frequency, antenatal care, pre-pregnancy CKD/renal dysfunction history (pp-CKD history), edema, systolic blood pressure (SBP), diastolic blood pressure (DBP), hemoglobin (Hb), hepatorenal function, the occurrence time of proteinuria, the quantity of proteinuria, serum albumin in pregnancy women. In addition, pregnancy outcomes and the follow-up of proteinuria after the termination of pregnancy were also taken in consideration. All procedures performed involving patient data in this study were in accordance with the ethical standards of the hospital and national research committee.

Inclusion and exclusion criteria

Inclusion criteria: (1) singleton pregnancy; (2) integrated antenatal care data, parturition records and follow-up information (follow-up time ≥ 12 weeks since the termination of pregnancy); (3) twice urinary dipsticks \geq (1+), or urine protein quantitation ≥ 0.3 g/24 h in different days before the termination of pregnancy. Patients included in this study should fulfill all the criteria above at the same time.

Exclusion criteria: (1) multiply pregnancy; (2) nephrectomy, congenital unilateral renal agenesis, polycystic kidney, or deformity of kidney; (3) incomplete medical records of antenatal care data, parturition records and follow-up information (follow-up time < 12 weeks after the termination of pregnancy); (4) urinary dipsticks (-), or urine protein quantitation < 0.3 g/24 h during pregnancy. Patients met any one of the criteria above would be excluded.

Variables

In the present study, gestational proteinuria was defined as twice urinary dipsticks \geq (1+), or urine protein quantitation \geq 0.3 g/24 h in different days in pregnancy. Good prognosis of proteinuria defined as negative of urine protein

qualitative, or urine protein quantitation < 0.3g/24 h after twelve weeks since the termination of pregnancy. Poor prognosis of proteinuria defined as urinary dipsticks \geq (1+) and/or urine protein quantitation ≥ 0.3 g/24 h after twelve weeks since the termination of pregnancy. Adverse pregnant outcomes included stillborn foetus, abortion, preterm delivery, asphyxia neonatorum, neonatal death, oligohydramnios, premature rupture of membrane and placental abruption. In the present study, 24-hour urinary protein quantity resulted from the average of urine protein quantitation since the occurrence of proteinuria during pregnancy. The variables of physical measurements and laboratory tests included SBP, DBP, Hb, serum albumin, serum creatinine (Scr), blood urea nitrogen (BUN), uric acid (UA), serum glutamate pyruvate transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT) resulted from the average of twice highest records of medical examination in different days during pregnancy.

Groups

In the present study, patients were assigned into three groups according to the occurrence time of proteinnuria: (1) first trimester of pregnancy (gestational weeks \leq 12 W); (2) second trimester of pregnancy (12 W < gestational weeks < 28 W); (3) third trimester of pregnancy (gestational weeks \geq 28 w). The severity of proteinuria was also divided into three groups according to the urine protein quantitation or urinary dipsticks: (1) longitudinal proteinuria: 0.3 g/24 h \leq urine protein quantitation < 1.0 g/24 h, or urinary dipsticks (1+); (2) Moderate proteinuria: 1.0 g/24 h ≤ urine protein quantitation < 3.5 g/24 h, or urinary dipsticks (2+)~(3+); (3) massive proteinuria: urine protein quantitation \geq 3.5 g/24 h, or urinary dipsticks (4+).

Statistical analysis

Student's t test was used to analyze continuous data. The Chi-squared test and Fisher's exact test were used to analyze categorical data. Logistic regression analysis was used to analyze various risk factors for poor prognosis of proteinuria and adverse pregnancy outcomes including age, pregnant frequency, antenatal care, pp-CKD history, edema, SBP, DBP, Hb, serum albumin, Scr, BUN, UA, SGPT, SGOT, the occurrence time of proteinuria, the severity of proteinuria. For all analyses, *P* Value < 0.05

	Prognosis of proteinuria		Duchus
	Good	Poor	P value
Age (years)	27.94±5.44	29.17±4.93	0.292
Pregnant frequency	2.23±1.46	2.31±1.35	0.787
SBP (mmHg)	142.56±28.87	146.71±34.25	0.552
DBP (mmHg)	93.27±20.97	95.31±25.60	0.691
Hb (g/L)	114.32±20.48	111.28±23.73	0.538
Serum albumin (g/L)	29.60±4.96	27.60±5.31	0.080
Scr (umol/L)	67.54±28.30	79.35±45.17	0.156
BUN (mmol/L)	4.71±2.64	5.47±3.01	0.230
UA (umol/L)	393.26±111.66	413.21±116.26	0.444
SGPT (U/L)	37.73±25.38	36.47±29.53	0.674
SGOT (U/L)	42.91±38.69	37.40±29.53	0.509
Edema (n, %)	17 (35.42)	8 (22.86)	0.218
Pp-CKD history (n, %)	3 (6.25)	14 (30.00)	< 0.001*
Occurrence time of proteinuria (gestational weeks)			< 0.001*
≤ 12 w (n, %)	1 (9.09)	10 (90.91)	
12-28 w (n, %)	7 (41.18)	10 (58.82)	
≥ 28 w (n, %)	40 (72.73)	15 (27.27)	
Severity of proteinuria			0.003*
Longitudinal (n, %)	20 (83.33)	4 (16.67)	
Moderate (n, %)	18 (56.25)	14 (43.75)	
Massive (n, %)	10 (37.04)	17 (62.96)	
Total (n, %)	48 (57.83)	35 (42.17)	

Table 1. Clinical characteristics of pr	rognosis of proteinuria in patients	with gestational proteinuria
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Results are showed as mean \pm SD or as numbers with percentage. *Statistically significant (P < 0.05). SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; SGPT, serum glutamate pyruvate transaminase; SGOT, serum glutamic-oxaloacetic transaminase; pp-CKD history, pre-pregnancy CKD history.

was considered statistically significant. All data were processed by SPSS (Version 19.0. Armonk, NY: IBM Corp.).

Results

Of the 8241 patients admitted to our study from January 2012 to June 2014, 91 patients appeared gestational proteinuria, 8 of them were excluded from the study because of multiply pregnancy, nephrectomy or lacked on integrated medical data which were needed to analyze the risk factors for poor prognosis of proteinuria and adverse pregnancy outcomes. For the remaining 83 patients were enrolled in the study, 55 patients were primipara, 28 patients were multipara. Evident edema or progressive edema was found in 25 patients, hypertension was found in 43 patients, and pp-CKD history was found in 17 patients with disease course from two to ten years, the pathologic distribution of them were as follows: 11 chronic glomerulonephritis, 4 IgA nephropathy, 2 lupus nephritis. However, all the 17 patients with pp-CKD history were in normal state of renal function lasted over 1 year before pregnancy, 1 of them appeared acute renal failure during pregnancy. In addition, among the 66 patients without pp-CKD history, 6 developed in renal dysfunction during pregnancy, and 1 developed acute liver and kidney dysfunction with unknown reason. Of the 83 patients, the mean (median, range) pregnant frequency was 2.3 (2.0, 1-8), mean length of hospital stays was 9.7 (8.0, 1-33) days, mean SBP was 144 (140, 100-250) mmHg, mean DBP was 94 (90, 64-160) mmHg, mean occurrence time of proteinuria was 29.7 (30.3, 8-40) gestational weeks, mean 24-hour urinary protein quantity was 3.58 (2.94, 0.34-23.90) g/L, mean Hb was 113.0 (111.0, 61.4-162.0) g/L, mean Scr was 75.07 (62.00, 27.00-855.30) µmol/L, mean BUN was 5.39 (4.00, 1.90-34.57) mmol/L, mean UA was 416.11 (412.00, 181.00-726.80)



Figure 1. Occurrence time of proteinuria-related poor prognosis of proteinuria. The occurrence time of proteinuria negatively correlated with the poor prognosis of proteinuria. Earlier occurrence of porteinuria in pregnancy predicted higher incidence of poor prognosis.



Figure 2. Severity of proteinuria-related poor prognosis of proteinuria. The severity of proteinuria was positively correlated with the poor prognosis of proteinuria. The more severe of proteinuria in pregnancy predicted higher incidence of poor prognosis.

µmol/L, mean SGPT was 84.75 (20.10, 5.00-864.00) U/L, mean SGOT was 97.94 (29.00, 10.0-1259.00) U/L, and mean time of termination of pregnancy was 35.0 (36.5, 18-41) gestational weeks.

Prognosis of proteinuria distribution

Table 1 summarized the demographic data of all the characteristics of prognosis of protein uria distribution in the study. pp-CKD history, the occurrence time of proteinuria and the severity of proteinuria were significantly different between the two groups of good and poor prognosis of proteinuria (P < 0.05). The occurrence time of proteinuria negatively correlated with the poor prognosis of proteinuria which were from 90.91% for first trimester of pregnancy to 27.27% for third trimester of pregnancy (**Figure 1**). On the contrary, the severity of proteinuria was positively correlated with the poor prognosis of proteinuria which was from 16.67% for longitudinal proteinuria to 62.96% for massive proteinuria (**Figure 2**).

Risk factors for poor prognosis of gestational proteinuria

The risk factors for poor prognosis of gestational proteinuria were analyzed by a multiple logistic regression model. The results showed that pp-CKD history (OR = 8.921, P = 0.027), the occurrence time of proteinuria (OR = 6.393, P = 0.001), and the severity of proteinuria (OR = 2.737, P = 0.024) were independently associated with the poor prognosis of gestational proteinuria (**Table 2**).

Adverse pregnancy outcomes distribution

Among the 83 gestational proteinuria patients enrolled in the study, 51 of them appeared adverse pregnancy outcomes including 9 stillborn foetus, 3 neonatal death, 7 asphyxia neonatorum, 4 premature rupture of membrane, 3 placental abruption, 1 oligohydramnios and 24 preterm delivery respectively. Table 3 summarized the demographic data of all the characteristics of pregnancy outcomes in the study. The results revealed that SBP, DBP, serum albumin, Scr, BUN, UA, SGPT, SGOT, edema and the severity of proteinuria were significantly different between the two groups of gestational proteinuria patients with and without adverse pregnancy outcomes (P < 0.05). The severity of proteinuria positively and significantly affected the adverse pregnancy outcomes, which were from 37.50% for longitudinal proteinuria to 77.78% for massive proteinuria (Figure 3).

Risk factors for adverse pregnancy outcomes

The risk factors for the adverse pregnancy outcomes were analyzed using a multiple logistic regression model. The results revealed that

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Risk factors	B-coefficient	Std.err.	Wald statistic	P value	Odds ratio	95% CI
Pp-CKD history	2.188	0.989	4.896	0.027*	8.921	1.284~61.976
Occurrence time of proteinuria	1.855	0.582	10.159	0.001*	6.393	2.043~20.006
Severity of proteinuria	1.007	0.447	5.075	0.024*	2.737	1.140~6.573

Table 2. Multiple logistic regression analysis for poor prognosis of gestational proteinuria

*Statistically significant (P < 0.05). Std.err, standard error; B-coefficient, regression coefficient; Cl, confidence interval; pp-CKD history, pre-pregnancy CKD history.

	Pregnancy	P value	
	Good	Adverse	P value
Age (years)	28.53±5.48	28.41±5.13	0.920
Pregnant frequency	2.28±1.71	2.25±1.20	0.934
SBP (mmHg)	123.94±17.32	157.10±31.15	< 0.001*
DBP (mmHg)	79.91±11.34	103.06±23.88	< 0.001*
Hb (g/L)	111.11±22.26	114.18±21.74	0.541
Serum albumin (g/L)	30.84±5.39	27.4±4.62	0.003*
Scr (umol/L)	57.16±18.83	82.30±41.70	0.002*
BUN (mmol/L)	3.59±1.18	5.95±31.6	< 0.001*
UA (umol/L)	361.93±104.06	428.59±112.38	0.009*
SGPT (U/L)	14.76±9.22	51.96±12.74	< 0.001*
SGOT (U/L)	26.56±20.77	50.34±39.36	0.003*
Edema (n, %)	5 (15.63)	20 (39.22)	0.023*
Pp-CKD history (n, %)	6 (18.75)	11 (21.57)	0.757
Occurrence time of proteinuria (gestational weeks)			0.287
≤ 12 w (n, %)	5 (45.45)	6 (54.55)	
12-28 w (n, %)	9 (52.94)	8 (47.06)	
≥ 28 w (n, %)	18 (32.73)	37 (67.27)	
Severity of proteinuria			0.011*
Longitudinal (n, %)	15 (62.50)	9 (37.50)	
Moderate (n, %)	11 (34.37)	21 (65.63)	
Massive (n, %)	6 (22.22)	21 (77.78)	
Total (n, %)	32 (38.55)	51 (61.46)	

Results are showed as mean \pm SD or as numbers with percentage. *Statistically significant (P < 0.05). SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; SGPT, serum glutamatepyruvate transaminase; SGOT, serum glutamic-oxaloacetic transaminase; pp-CKD history, pre-pregnancy CKD history.

SBP (OR = 3.834, P = 0.011), DBP (OR = 2.132, P = 0.002) and the severity of proteinuria (OR = 2.899, P = 0.015) were independently associated with the adverse pregnancy outcomes (**Table 4**).

Discussion

The function of glomerular filtration, renal tubular reabsorption and secretion are closely related to the generation of proteinuria. For over 95% of protein filtered by glomerular is reabsorbed by renal tubule under normal conditions, a little of protein is excreted to the outside every day. But physiology may change during pregnancy, under this circumstance, glomerular experience high perfusion and high filtration station. This change arises later in the first month in pregnancy, and will get back to the base line twelve weeks after the termination of pregnancy [4, 5]. Glomerular filtration rate will increase about 50% in third trimester of pregnancy, and the secretion of urine protein is more than non-pregnant women to some extent, but less than 0.5 g every day in general



Figure 3. Severity of proteinuria-related adverse pregnancy outcome. The severity of proteinuria positively and significantly affected the adverse pregnancy outcomes. The more severe of proteinuria in pregnancy predicted higher incidence of adverse pregnancy outcomes.

[6, 7]. In general, this change will not result in pregnancy-related complications for those pregnant women with normal renal function before pregnancy. But for those women with CKD, especially with obvious decrease in kidney function, the kidney cannot compensate the change, as a result, massive proteinuria and serious pregnancy complications will be appear [4]. Persisting positive of urine protein last over twelve weeks after the termination of pregnancy may imply CKD. Many studies indicated that persisting positive of urine protein may lead to kidney injury and aggravate kidney disease by way of direct toxic effects, immunemediated mechanism, promote the produce of reactive oxygen species, addiment activation, and so on [1-3, 8, 9]. Jungers [10] indicated that the severity of gestational proteinuria was the independent risk factor leading to rapidly decline of renal function in CKD patients and one of the important elements affecting the pregnancy outcomes. Stettler [11] found that 20% (11/53) patients who without pre-pregnancy renal disease with persisting proteinuria after the end of pregnancy would progress to end-stage renal disease with long-term followup.

In the present study, multiple logistic regression analysis was used to analyze the factors that may be related to the prognosis of gestational proteinuria. The results revealed that the pp-CKD history, the occurrence time of proteinuria and the severity of proteinuria were independently associated with the poor prognosis of gestational proteinuria. The incidence rate for poor prognosis of gestational proteinuria was higher in pregnant women with pp-CKD history (82.4%) than those without pp-CKD history (31.8%). The reason may be that the change of physiology in pregnancy aggravate the existed lesion of kidney in pregnant woman with pp-CKD history, as a result, the pathophysiological change cannot get back to the condition before pregnancy, which lead to persisting proteinuria and higher rate of poor prognosis of gestational proteinuria after the termination of pregnancy [12, 13].

Negative correlation was found between the occurrence time of proteinuria and the poor outcome of proteinuria in this study. The incidence rate of poor prognosis of proteinuria for the first trimester of pregnancy, second trimester of pregnancy and third trimester of pregnancy were 90.9%, 58.8% and 27.3% respectively, implying that earlier appearance of proteinuria in pregnancy resulted in higher incidence rate of poor prognosis of proteinuria. Reasons for the phenomenon maybe as follows: First, there are different renal physiological and renal function among women before pregnancy, some of them may exist potential renal lesions or renal insufficiency without clinical symptoms, the physiological change in pregnancy exacerbate the renal function, which result in early occurrence of proteinuria in pregnancy. However, the proteinuria appeared in the third trimester of pregnancy mostly due to acute physiological change and temporary of renal decompensation without renal lesions, which can rapidly recover to the baseline and the urine protein turn out to be negative after the termination of pregnancy. Second, there are different kinds and different severity of pregnancy complications among pregnant women, which may finally result in various degree of kidney injury and pathologic change [14], and the differences above will lead to different occurrence time of proteinuria during pregnancy and different prognosis of proteinuria after the termination of pregnancy.

In the present study, the severity of proteinuria was positively correlated with the poor progno-

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Risk factors	B-coefficient	Std.err.	Wald statistic	P value	Odds ratio	95% CI
SBP (mmHg)	1.344	0.562	6.412	0.011*	3.834	1.355~11.851
DBP (mmHg)	0.875	0.326	8.239	0.002*	2.132	1.942~4.271
Severity of proteinuria	1.603	0.435	5.966	0.015*	2.899	1.172~6.246

Table 4. Multiple logistic regression analysis for the adverse pregnancy outcomes

*Statistically significant (P < 0.05). Std.err, standard error; B-coefficient, regression coefficient; Cl, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure.

sis of proteinuria. The incidence rate of poor prognosis for longitudinal proteinuria, moderate proteinuria, and massive proteinuria were 16.7%, 43.8% and 63.0% respectively, indicating that severer of gestational proteinuria result in higher incidence rate of poor prognosis of proteinuria. Though the proteinuria is not the marker of renal function, the severity of proteinuria may indirectly reflect different degree of kidney injury to some extent. Some researches thought that there were some relationship between renal pathological types and the degree of urine protein in pregnancy women [14]. The severity of kidney injury or different renal pathological types, or both of them may be the reasons for the relationship between the severity of proteinuria and the prognosis of proteinuria, which needs further study to find the answer.

Gestational hypertension disease and proteinuria are common in pregnancy women from obstetrical department. In the present study, multiple logistic regression analysis revealed that SPB, DBP and the severity of proteinuria were independent risk factors of adverse pregnancy outcomes, which was similar to previous studies. North [15] noted that the probability of adverse pregnancy outcomes of gestational hypertension with proteinuria was three times to pregnant women with negative urine protein. Thornton [16] also discovered that the incidence rate of adverse pregnancy outcomes of gestational hypertension with proteinuria was higher than those women without proteinuria. Abo-Elnasr [17] performed a study which enrolled 124 patients with gestational proteinuria, the incidence rate for premature delivery (43.5%), newborn sent to ICU (40.3%), and neonatal death (15.3%) were significantly different with pregnant women without gestational proteinuria.

There may be some relationship between the severity of gestational proteinuria and adverse

pregnancy outcomes. In previous studies, Piccoli [18] considered that, the risks of preterm delivery and newborn sent to ICU in pregnant women with 24-hours proteinuria over 1.0 g were higher than others. Ferrazzani [19] hold a similar conclusion that the severity of proteinuria was negatively correlated with neonatal birth weight and delivery pregnancy week. In the present study, the severity of proteinuria was found positively correlated with the incidence rate of adverse pregnancy outcomes, the incidence rate of adverse pregnancy outcomes for longitudinal proteinuria, moderate proteinuria, and massive proteinuria were 37.5%, 65.6% and 77.8% respectively, which found further evidence to support the assumption. However, some studies hold different conclusions, considering there was no relationship between the perinatal outcomes and heavy proteinuria, only premature delivery itself could affect perinatal outcomes [20, 21].

Many people and obstetrician care the risk of pregnant women with CKD. Pregnancy with CKD may result in higher incidence rate of adverse pregnancy outcomes such as spontaneous abortion, premature delivery and stillborn foetus [10, 18, 22, 23]. Even though, some studies didn't agree with the conclusion, which considered that a mild form of renal insufficiency would not increase the pregnancy complications [24]. In the present study, the incidence rate of adverse pregnancy outcomes of gestational proteinuria with CKD was 64.7%, while 60.6% for others without CKD, there was no significantly differences between the two groups, and CKD was not independent risk factor of adverse pregnancy outcome for pregnant women with gestational proteinuria according to logistic regression analysis. On the contrary, Fischer [25] study indicated that CKD was independent risk factor of adverse pregnancy outcomes, the study covered 911 pregnancy women with CKD and 4606 pregnancy women without CKD, showed that the incidence rate of adverse pregnancy outcome was almost twice in CKD group to non-CKD group (18.2% vs. 9.5%). The reasons for the different conclusion above may be that there were differences in inclusion criteria and group of people between the studies. However, nephrologist and obstetrician should pay more attention on pregnant women with gestational proteinuria.

In summary, pp-CKD history, the occurrence time of proteinuria, and the severity of proteinuria are risk factors of poor prognosis of gestational proteinuria. The severity of proteinuria is both the risk factor of poor prognosis of gestational proteinuria and adverse pregnancy outcomes. Obstetrician and nephrologist should cooperate with each other to make early effective intervention to improve the prognosis of gestational proteinuria and reduce the incidence rate of adverse pregnancy outcomes.

Acknowledgements

This study was funded by Shanghai Science and Technology Committee, China (No. 14411-963300).

Disclosure of conflict of interest

None.

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References

- [1] Caruso-Neves C, Pinheiro AA, Cai H, Souza-Menezes J, Guggino WB. PKB and megalin determine the survival or death of renal proximal tubule cells. Proc Natl Acad Sci U S A 2006; 103: 18810-18815.
- [2] Macconi D, Chiabrando C, Schiarea S, Aiello S, Cassis L, Gagliardini E, Noris M, Buelli S, Zoja C, Corna D, Mele C, Fanelli R, Remuzzi G, Benigni A. Proteasornal processing of albumin by renal dendritic cells generates antigenic peptides. J Am Soc Nephrol 2009; 20: 123-130.
- [3] Nakajima H, Takenaka M, Kaimori JY, Hamano T, Iwatani H, Sugaya T, Ito T, Hori M, Imai E. Activation of the signal transducer and activator of transcription signaling pathway in renal proximal tubular cells by albumin. J Am Soc Nephrol 2004; 15: 276-285.

- [4] Krane NK, Hamrahian M. Pregnancy: kidney diseases and hypertension. Am J Kidney Dis 2007; 49: 336-345.
- [5] Karumanchi SA, Maynard SE, Stillman IE, Epstein FH, Sukhatme VP. Preeclampsia: a renal perspective. Kidney Int 2005; 67: 2101-2113.
- [6] Robson RC, Dunlop W, Hunter S. Haemodynamic change during early pregnancy loss. Br J Obstet Gynaecol 1998; 95: 1134-1136.
- [7] Sturgiss SN, Dunlop W, Davison JM. Renal haemodynamics and tubular function in human pregnancy. Ballieres Clin Obstet Gynaecol 1994; 8: 209-234.
- [8] Tang S, Sheerin NS, Zhou W, Brown Z, Sacks SH. Apical proteins stimulate complement synthesis by cultured human proximal tubular epithelial cells. J Am Soc Nephrol 1999; 10: 69-76.
- [9] Theilig F. Spread of glomerular to tubulointerstitial disease with a focus on proteinuria. Ann Anat 2010; 192: 125-132.
- [10] Jungers P, Chauveau D, Choukroun G, Moynot A, Skhiri H, Houillier P, Forget D, Grünfeld JP. Pregnancy in women with impaired renal function. Clin Nephrol 1997; 47: 281-288
- [11] Stettler RW, Cunningham FG. Natural history of chronic proteinuria complicating pregnancy. Am J Obstet Gynecol 1992; 167: 1219-1224.
- [12] Eardley KS, Zehnder D, Quinkler M, Lepenies J, Bates RL, Savage CO, Howie AJ, Adu D, Cockwell P. The relationship between albuminuria, MCP-1/CCL2, and interstitial macrophages in chronic kidney disease. Kidney Int 2006; 69: 1189-1197.
- [13] Sung SS, Bolton WK. T cells and dendritic cells in glomerular disease: the new glomerulotubular feedback loop. Kidney Int 2010; 77: 393-399.
- [14] Yue RZ, Zhang L, Fu P, Xu H. Clinical and pathological features in patients with renal damage of serious pregnancy hypertension syndrome. Med J West China 2010; 22: 231-234.
- [15] North RA, Taylor RS, Schellenberg JC. Evaluation of a definition of preeclampsia. Br J Obstet Gynecol 1999; 106: 767-773.
- [16] Thornton CE, Makris A, Ogle RF, Tooher JM, Hennessy A. Role of proteinuria in defining preeclampsia: clinical outcomes for women and babies. Clin Exp Pharmacol Physiol 2010; 37: 466-470.
- [17] Abo-Elnasr M, Alhalaby A, Zahran A, Badr H. Maternal and fetal outcome in women with gestational hypertension in comparison to gestational proteinuria: a 3-year observational study. Hypertens Pregnancy 2016; 24: 1-8.
- [18] Piccoli GB, Attini R, Vasarion E, Conijn A, Biolcati M, D'Amico F, Consiglio V, Bontempo S, Todros T. Pregnancy and chronic kidney dis-

ease: a challenge in all CKD stages. Clin J Am Soc Nephrol 2010; 5: 844-855.

- [19] Ferrazzani S, Caruso A, De Carolis S, Martino IV, Mancuso S. Proteinuria and outcome of 444 pregnancies complicated by hypertension. Am J Obstet Gynecol 1990; 162: 366-371.
- [20] Hall DR, Odendaal HJ, Steyn DW, Grové D. Urinary protein excretion and expectant management of early onset, severe pre-eclampsia. Int J Gynaecol Obstet 2002; 77: 1-6.
- [21] Schiff E, Friedman SA, Kao L, Sibai BM. The importance of urinary protein excretion during conservative management of severe preeclampsia. Am J Obstet Gynecol 1996; 175: 1313-1316.
- [22] Davison JM, Lindheimer MD. Pregnancy and chronic kidney disease. Semin Nephrol 2011; 31: 86-99.

- [23] Bramham K, Briley AL, Seed PT, Poston L, Shennan AH, Chappell LC. Pregnancy outcome in women with chronic kidney disease: a prospective cohort study. Reprod Sci 2011; 18: 623-630.
- [24] Munkhaugen J, Lydersen S, Romundstad PR, Widerøe TE, Vikse BE, Hallan S. Kidney function and future risk for adverse pregnancy outcomes: a population-based study from HUNT II, Norway. Nephrol Dial Transplant 2009; 24: 3744-3750.
- [25] Fischer MJ, Lehnerz SD, Hebert JR, Parikh CR. Kidney disease is an independent risk factor for adverse fetal and maternal outcomes in pregnancy. Am J Kidney Dis 2004; 43: 415-423.