CEOG Clinical and Experimental Obstetrics & Gynecology

Primary glomerular diseases and pregnancy

M.S. Beksac[1], N.K. Ertürk[1], A.T. Beksac[2], G. Örgül[1], H.T. Celik[3], M. Yurdakök[3], T. Yildirim[4], A. Dolgun[5]

[1]Division of Perinatal Medicine, Department of Obstetrics and Gynecology, [2]Department of Urology, [3]Division of Neonatology, Department of Pediatrics, [4]Division of Nephrology, Department of Internal Medicine and [5]Department of Biostatistics, Hacettepe University, Ankara (Turkey)

Summary

Backround: Primary glomerular diseases (PGD) may represent wide spectrum of clinical presentations and pathological findings depending on the histopathological type and the severity/stage of the disease. The severity of PGD-related nephrotic syndrome (NS) predicts pregnancy outcome. The aim of the study to assess whether PGD has any effect on pregnancy and fetal outcome, as well as the effect of pregnancy on PGD. *Materials and Methods:* Retrospectively, ten pregnant women (11 pregnancies) with PGDs at Hacettepe University were investigated in terms of their pregnancy outcomes. The histopathological diagnosis was focal segmental glomerulosclerosis (FSGS), FSGS superimposed on immunglobulin A (IgA) nephropathy, membrano-proliferative glomerulonephritis (MPGN), and minimal change disease (MCD). *Results:* Nearly all pregnancies were complicated by nephrotic "signs and symptoms" and NS to a certain extend (mild-moderate to severe forms) and all cases were delivered by cesarean section. Eight cases (72.7 %) were complicated with IUGR, fetal distress and preterm delivery. *Conclusion:* In this case series, the authors have demonstrated that PGD has an adverse impact on perinatal outcome.

Key words: Pregnancy; Primary glomerular disease; Nephrotic syndrome; Perinatal outcome.

Introduction

One of the controversies in the field of perinatal medicine is the impact of pregnancy on the clinical course of primary glomerular disease (PGD) and the effect of PGD and related problems such as nephrotic syndrome (NS) on maternal/perinatal outcome [1, 2]. PGDs include a group of disorders (minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous glomerular nephropathy (MGN), Immunglobulin A nephropathy (IgAN), membranoproliferative glomerulonephritis (MPGN) and others, characterized by increased capillary wall permeability to serum proteins and altered glomerular structure/function [1-3].

Estimation of PGD prevalence in general population is difficult due to lack of well designed epidemiological surveys. However, the prevalence was found to be 6.9 in 1,000 in western France [4]. It has also been reported that there is a change in the pattern of glomerular disease and the annual incidence rates of IgAN, FSGS and MN are 2.1, 1.8, and 1.0 per 100,000/year, respectively in Olmsted County, USA [5].

PGD may represent a wide spectrum of clinical presentations and pathological findings depending on the histopathological type and the severity/stage of the disease [6, 7]. The severity of clinical signs, symptoms and laboratory parameters such as proteinuria, edema, decline in glomerular filtration rate (GFR), hypertension, hematuria, anemia, and abnormal urine sediments are critical in adverse perinatal outcome and maternal complications [8, 9]. In other words, the severity of PGD-related NS predicts pregnancy outcome [10].

Normal pregnancy is associated with increased renal plasma flow and GFR, together with decreased serum creatinine and hyperfiltration of amino acids, proteins, and water soluble vitamins [11]. All these shifts together with hemostatic and hormonal imbalances may aggravate NS occurrence in patients with PGDs but does not change the natural course of the disease [12,13]. On the other hand, PGD-related hypertension, hypoproteinemia, anemia. and other abnormal changes may induce obstetrical complications like gestational hypertension and result in adverse perinatal outcome [2, 8]. Thus, disturbed intrauterine perfusion and superimposed preeclampsia may be the reason of fetal hypoxia and intrauterine growth retardation (IUGR) which results in increased perinatal morbidity and mortality [2, 8, 14, 15].

In this paper, the authors retrospectively evaluated 11 pregnancy outcomes of ten pregnant women with PGD whose histopathological diagnoses were made before they became pregnant and who were under medical control.

Materials and Methods

In this study, the authors retrospectively evaluated 23,892 pregnancies delivered at the Department of Obstetrics and Gynecology, Hacettepe University Hospital between January 2001 and March 2015. The study protocol was reviewed and approved by the Ethical Committee of the Hacettepe University, Ankara, Turkey (Committee Decision: GO 16/24-03).

The authors found 32 patients whose pregnancies were com-

Revised manuscript accepted for publication December 7, 2016

Table 1. — *Clinical features and outcomes of 11 pregnancies with NS.*

Patient number	Age (years)	Obstetrical History	Type of glomerular disease	Comorbid Diseases	Gestational age at delivery (w-d)	Mode of delivery	DCS indications & complications	Birth weight (g)	Apgar score (5th min.)
1	29	G1P0	MPGN	-	31- 4	CS	IUGR, fetal distress, PD	1,310	9
2	37	G1P0	IgA nephropathy, secondary FSGS	-	38-5	CS	Breech presentation	3,500	10
3 (1)	21	G1P0	MPGN	HT	31-5	CS	IUGR, fetal distress preeclampsia, ablatio placenta, PD	1,230	8
3 (2)	25	G2P1L1	Secondary FSGS	HT	33-6	CS	IUGR, Fetal distress (+ repeat CS), PD	1,800	10
4	26	G2A1L0	IgA nephropathy, secondary FSGS	-	39-1	CS	Elective CS	3,600	10
5	29	G2P1L1	FSGS	HT	32-1	CS	IUGR, Fetal distress (+repeat CS) Preeclampsia, PD	1,340	9
6	32	G1P0	IgA nephropathy, secondary FSGS	HT	35-2	CS	IUGR, fetal distress, Preeclampsia, PD	2,310	8
7	35	G3P1A1L1	FSGS	-	37-0	CS	IUGR?, Fetal distress, PD repeat CS	2,700	10
8	26	G1P0	MCD	-	38-4	CS	Elective CS	2,900	10
9	19	G1P0	FSGS	-	31-3	CS	IUGR, AFD, PD	640	Intubated
10	33	G2P1L1	FSGS	HT	36-0	CS	IUGR, fetal distress (repeat CS)	2,280	10

HT: hypertension; w: weeks; d: days; g: grams; min: minutes; MPGN: membranoprolipherative glomerulonephritis; IgA: immunoglobulin A; FSGS: focal segmental glomerulosclerosis; MCD: minimal change disease; CS: cesarean section; IUGR: intrauterine growth restriction; AFD: acute fetal distress, G: gravida; P: parity; A: abortus; L: living, PD: preterm delivery.

plicated with NS (0.13 %) and they selected patients with PGDs, and excluded patients with secondary glomerular diseases and the cases without histopathological diagnosis. Eleven pregnancies of ten patients underwent further analysis. Of those ten pregnancies, six were primigravid and four multigravid. Furthermore, the pregnancies of those four multigravid patients (whatever the obstetric/perinatal outcome is) before the diagnosis of PGD were also excluded from the evaluation. In all cases, histopathological diagnosis of PGDs were already present before their pregnancies who were included to this study. All cases were under medical treatment and follow up and received pre-gestational counselling (patients with NS attack or impaired renal function were not given permission to become pregnant).

Patients' demographics such as duration of pregnancy, birth weight, laboratory values, APGAR scores, maternal and perinatal complications, pregestational, gestational and puerperal 24-hour urine-collection results, renal function tests, comorbid diseases, and neonatal outcomes were recorded.

Study subjects were under intensive antenatal care program and pre-pregnancy (1-4 months before the gestation), early-mid pregnancy (16-22 gestational week) and post-partum sixth week laboratory findings were especially recorded for comparison (Table I). Patients were at a different medical status in terms of renal function and NS (remission *vs.* relapse) at the time of blood samplings. As described above, all patients were already diagnosed with PGD together with NS pregestationally and nine of them demonstrated nephrotic findings at different gestational week of their current pregnancies and monitored extensively by laboratory tests.

Plasma kreatinine levels exceeding 0.80 (0.7-1.2) mg/dL are accepted as the sign of renal dysfunction. Proteinuria is accepted as nephrotic when 24-hour urinary protein levels exceed 3.5 grams [11]. All patients were under special antenatal care and perinatal surveillance program (genetic counselling, prenatal screening/diagnosis, ultrasonographic evaluation, Doppler velocimetry, non-stress test, as well as related maternal laboratory tests) and examined bi-weekly (more frequent when necessary) after 24th gestational week until delivery. Amniocentesis was performed in two cases due to advanced maternal age.

Patients were encouraged to have necessary precautions before their pregnancies to control hypertension and optimize renal functions. All necessary consent forms were signed by the patients before their clinical interventions.

Mean ± standard deviation (SD) and median values were used to describe the quantitative variables. Also, frequency and percentages were given for the nominal data. Normality assumption was checked by Shapiro Wilk's test and it was found that data do not conform to normal distribution. Serum creatinine levels and 24-hour urinary protein levels were compared before, during, and after the pregnancy with the non-parametric Friedman test. Conover-Dunn test was used for post-hoc comparisons. For all analyses the SPSS version 21.0 was used, and the statistical significance was set at $p < 0.05$.

Results

The histopathological diagnosis was FSGS, FSGS superimposed on immunglobulin A (IgA) nephropathy, MPGN, and MCN in four, three, one, and one patients, re-

Table 2. — *Renal functions of the patients.*

	Before pregnancy		During pregnancy		After pregnancy	
Patient number	Serum creatinine (mg/dL)	Proteinuria (mg/24 h)	Serum creatinine (mg/dL)	Proteinuria (mg/24 h)	Serum creatinine (mg/dL)	Proteinuria (mg/24 h)
1	1.20	3443	2.20	10730	2.60	692
2	0.80	1213	0.90	1670	0.90	591
3 (1)	0.30	5289	0.50	6455	0.50	689
3 (2)	0.60	5266	0.60	3791	0.60	632
4	0.50	876	0.60	2749	0.60	987
5	2.70	3456	4.30	5213	3.10	1556
6	1.00	4576	1.40	7234	1.30	2504
7	1.70	375	2.10	1751	1.60	1108
8	0.50	79	0.30	374	0.50	24
9	0.50	522	0.60	5297	0.50	103
10	0.60	9000	0.80	4125	0.80	3478

mg: milligrams; h: hours; dL: deciliter.

Table 3. — *Mean serum creatinine and proteinuria levels of patients with NS.*

	Before pregnancy mean ± SD (median)	During pregnancy mean ± SD (median)	After pregnancy mean ± SD (median)	*p* value
Serum creatinine level mg/dL	0.95 ± 0.71^{a} (0.6)	1.30 ± 1.18^{b} (0.8)	$1.19 \pm 0.90^{a,b}$ (0.8)	0.013
Proteinuria level mg/24 hrs	$3099.5 \pm 2800.9^{a,b}$ (3443)	4489.9 ± 2958.9^{a} (4125)	1124.0 ± 1039.5^{b} (692)	0.001

[a,b]: Different superscript letters indicate statistically significant difference at α= 0.05 level according to the Conover-Dunn post-hoc comparison test.

spectively. In the tenth patient who delivered twice, the diagnosis was MPGN in her first pregnancy and FSGS superimposed on MPGN in her second pregnancy. The median age of the study subjects was 28.3 (ranging between 19 and 37) years. The mean gestational week at delivery was 34 weeks and two days and all patients delivered by cesarean section

Five patients were hypertensive (45.5%) at the beginning of their pregnancies and three of them were superimposed with preeclampsia (27.3%). Although nephrotic signs and symptoms were observed in all cases, only nine pregnancies were complicated with moderate to severe NS and in three cases preeclampsia was superimposed. These three preeclamptic pregnancies [one MPGN, one FSGS, and one FSGS superimposed on immunglobulin A (IgA)] were also complicated with IUGR and fetal distress, and delivered prematurally by cesarean section. Three of the 11 pregnancies were delivered at term (two of the three FSGS superimposed on immunglobulin A (IgA) nephropathy" cases and one MCD). Eight (72.7%) cases were complicated by IUGR, fetal distress, and preterm delivery.

Three of these ten patients (ten patients 11 pregnancies) had IgA nephropathy diagnosis prior to their pregnancies and all these three patients' pregnancies were complicated with superimposed FSGS (Table 1). Two patients' renal biopsies showed MPGN; one of these patients had two pregnancies within the 14-year study period. The second pregnancy of that patient was complicated with superimposed FSGS. Table 1 shows the details of the demographic and clinical characteristics of the patients.

Nine patients had nephrotic proteinuria (more than 3,500 mg/24 hours) and/or increased serum creatinine levels during the course of their pregnancies. The details and mid-pregnancy values are given in Table 2. Mean serum creatinine levels were 0.95 mg/dL, 1.30 mg/dL, and 1.19 mg/dL before, during and after pregnancy, respectively. The present authors have demonstrated a statistically significant increase in creatinine levels during pregnancy ($p = 0.043$). The creatinine levels were decreased after delivery though this decrease was not statistically significant (all $p > 0.05$) in the puerperal period (Table 3).

In this series, the authors have shown that urinary protein levels were generally increased but not to nephrotic range in all cases before pregnancy (mean 24-hour urinary protein level was ≤ 3.5 grams). Mean 24-hour urinary protein levels were 3,099.5 mg, 4,489.9 mg, and 1,124.0 mg before, during, and after pregnancy, respectively. Twenty-four-hour urinary protein levels were increased during pregnancy, but this increment was not statistically significant (all $p > 0.05$). On the other hand, 24-hour urinary pro-

tein levels were found to be statistically significantly decreased after delivery ($p = 0.001$) (Table 3).

In this series, nephrotic manifestations were observed in all cases and nine cases were complicated by mild-moderate to severe NS. The signs and symptoms regressed almost in all cases after the delivery and the patients were reevaluated by their physicians.

All of the babies were delivered by cesarean section. Only one baby had a low APGAR score, although she was born at the 31st gestational week, her birth weight was 640 grams because of IUGR and she was intubated immediately after birth. This neonate died during neonatal period. All neonates were monitored in the neonatal intensive care unit and ten of them were discharged without any important complication. Gestational weeks at delivery, birthweights, APGAR scores, and related data are shown in Table 1.

Discussion

Although PGD-pregnancy interaction is controversial, it has been reported that gestational process does not have an adverse impact on the natural course of the disease [2, 13]. On the other hand, impaired maternal GFR and NS activation are critical clinical conditions on the impact of pregnancy on PGDs [2, 13]. In the present case series, all cases were complicated by nephrotic signs and symptoms or NS (nine out of 11) at different gestational weeks of their pregnancies. The natural course of PGDs seems to be influenced by gestational changes although the authors did not observe an adverse impact of pregnancy on the disease itself at the end of puerperal period. The wide spectrum and unclear biological rationales behind PGDs create difficulties in the prediction of prognosis. However, careful pregnancy planning is essential and patients should be in remission for a minimum of six months not to have increased maternal and perinatal morbidity [10, 12, 16].

In this study, the authors demonstrated that PGD has an adverse impact on pregnancy. Nearly all pregnancies were complicated by NS to a certain extent (mild-moderate to severe forms) and delivered by cesarean section. Eight cases (72.7 %) were complicated with IUGR, fetal distress, and preterm delivery. Three of the five hypertensive cases (three out of 11 pregnancies; 27.3%) were also superimposed by preeclampsia, although all cases were under special prenatal care. There is no randomised prospective study investigating the incidence of preeclampsia among pregnant women with PGDs or kidney diseases together with NS.

There are several publications about successful pregnancies in PGDs [2, 3], but most of them are case reports, case series, or review-type publications [3, 16]. The rarity and lack of clear knowledge about the etiological factors behind PGDs together with time dependent changes in medical approaches create difficulties in the organisation of prospective clinical trials [4, 5]. In the present clinical series, the authors showed that clinical manifestations (in all cases) and NS (nine out of 11) are induced to a certain extent in different modalities and influence intrauterine fetal perfusion. Five of the 11 pregnancies were hypertensive early in pregnancy and three of them were consecutively superimposed by preeclampsia as mentioned above.

Gestational process is complicated by IUGR and fetal distress in 72.7 % of cases (eight out of 11 cases) and one neonate died during neonatal period. Prematurity (eight out of 11 cases) is an important issue in the management and necessitates intensive neonatal care. There are limited number of case series related to maternal and fetal outcomes in chronic kidney diseases, and furthermore, wide spectrum of etiologies make interpretations more difficult to be understood [16].

The present authors believe that pregnant women with PGDs must be under intensive antenatal care program and serious perinatal surveillance is necessary to avoid serious adverse maternal and perinatal outcomes.

Acknowledgements

The authors would like to thank Prof. Dr. Ergun Karaağaoglu for his help in statistical analysis.

References

[1] Katz A.I., Lindheimer M.D.: "Does pregnancy aggravate primary glomerular disease?" *Am. J. Kidney Dis.*, 1985, *6*, 261.
[2] Barceló P., López-Lillo J., Cabero L., Del Río G.: "Successful pregnancy in primary glomerular disease". *Kidney Int.*, 1986, *30*, 914.
[3] Cote A.M., Sauve N.: "The management challanges of non-preeclampsia-related nephrotic syndrome in pregnancy". *Obstet. Med.*, 2011, *4*, 133.
[4] Simon P., Ramee M.P., Boulahrouz R., Stanescu C., Charasse C., Ang K.S., *et al.*: "Epidemiologic data of primary glomerular diseases in western France". *Kidney Int.*, 2004, *66*, 905.
[5] Swaminathan S., Leung N., Lager D.J., Melton L.J. 3rd., Bergstralh E.J., Rohlinger A., Fervenza F.C.: "Changing incidence of glomerular disease in Olmsted County, Minnesota: a 30-year renal biopsy study". *Clin. J. Am. Soc. Nephrol.*, 2006, *1*, 483.
[6] Chávez Valencia V., Orizaga de La Cruz C., Becerra Fuentes J.G., Fuentes Ramírez F., Parra Michel R., Aragaki Y., et al.: "Epidemiology of glomerular disease in adults: a database review". *Gac. Med. Mex.*, 2014, *150*, 403. [Article in Spanish]
[7] Zaza G., Bernich P, Lupo A.: "'Triveneto' Register of Renal Biopsies (TVRRB). Renal biopsy in chronic kidney disease: lessons from a large Italian registry". *Am. J. Nephrol.*, 2013, *37*, 255.
[8] Singh R., Prasad N., Banka A., Gupta A., Bhadauria D., Sharma RK., Kaul A.: "Pregnancy in patients with chronic kidney disease: Maternal and fetal outcomes". *Indian J. Nephrol.*, 2015, *25*, 194.
[9] Morken N.H., Travlos G.S., Wilson R.E., Eggesbø M., Longnecker M.P.: "Maternal glomerular filtration rate in pregnancy and fetal size". *PLoS One*, 2014, *9*, e101897.
[10] Smyth A., Radovic M., Garovic V.D.: "Women, kidney disease, and pregnancy". *Adv. Chronic Kidney Dis.*, 2013, *20*, 402.
[11] Hnat M., Sibai B.: "Renal disease and pregnancy". *Glob. Libr. Women's Med.*, 2008. Available at: http://editorial.glowm.com/ch075/framesets/005f.html?p=glowm.cml/section_view&articleid=157
[12] Sebestyen A., Varbiro S., Sara L., Deak G., Kerkovits L., Szabo I., Kiss I., Paulin F.: "Successful management of pregnancy with

nephrotic syndrome due to preexisting membranous glomerulonephritis: a case report". *Fetal Diagn Ther.*, 2008, *24*, 186.
[13] Hayslett J.P.: "Pregnancy does not exacerbate primary glomerular disease". *Am. J. Kidney Dis.*, 1985, *6*, 273.
[14] Parlakgümüş H.A., Şimşek E., Çok T., Tarım E.: "The relationship between proteinuria in severe preeclampsia and maternal and fetal outcomes". *Gynecol. Obstet. Reprod. Med.*, 2012, *187*, 11.
[15] Beşe E., Devran Bıldırcın F., Malatyalıoğlu E.: "The effects of preeclampsia severity and thrombocytopenia on the prognosis of the hypertensive pregnant women". *Gynecol. Obstet. Reprod. Med.*, 2013, *19*, 12.
[16] Feng Z., Minard C., Raghavan R.: "Pregnancy outcomes in advanced kidney disease". *Clin Nephrol.*, 2015, *83*, 272.

Corresponding Author:
H.T. CELIK, M.D.
Hacettepe University Faculty of Medicine
İhsan Doğramacı Children's Hospital,
Department of Pediatrics, Division of Neonatology
Sıhhiye, 06100, Altındağ, Ankara (Turkey)
e-mail: htcelik@gmail.com