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Intrauterine growth restriction in pregnant women after kidney transplantation as a marker of preeclampsia

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ABSTRACT

Objectives: Delayed motherhood is associated with an increasing number of comorbidities such as glomerulonephritis, systemic lupus erythematosus, and diabetic nephropathy. Women after renal transplant belong to the group of patients who require a highly individualized approach to treatment and diagnosis. The aim of the study was to validate the commonly used diagnostic criteria for preeclampsia which seem to be irrelevant in patients with chronic renal insufficiency.

Material and methods: The course of pregnancy and delivery were retrospectively analyzed in 48 renal transplant patients. Two patients were excluded. Group I included 23 patients with eutrophic neonates, while Group II consisted of 23 patients with fetal hypotrophy (birth weight of < 10[th] percentile).

Results: The duration of pregnancy was 34.5 and 35 weeks in Groups I and II, respectively. Mean birth weight in Groups I and II was 2608.64 g and 2046.30 g, respectively ($p = 0.002$). Mean weight percentile in Groups I and II was 36.57 and 2.91, respectively ($p < 0.000$). Proteinuria in the first half of pregnancy occurred in 16 and 14 patients from Groups I and II, respectively, and increased in the second half of pregnancy in 6 and 6 patients from Groups I and II, respectively. Patients from Group II were more prone to urinary tract infections (0.43 vs. 0.79; $p = 0.02$).

Conclusions: Current diagnostic criteria for preeclampsia are insufficient in case of pregnant women after kidney transplant. General criteria should be applied with special care in women with chronic kidney disease or in patients with systemic lupus erythematosus. As a predictive factor of neonatal morbidity, intrauterine growth restriction seems to be more valuable than typical markers of kidney function.

Key words: intrauterine growth restriction, kindey transplantation, preeclampsia, cyclosporine, tacrolimus

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INTRODUCTION

Recent years have witnessed significant changes in the classification of hypertension and preeclampsia in pregnant women. The 2014 recommendations of the International Society for the Study of Hypertension in Pregnancy (ISSHP) and the 2013 guidelines of the American Society of Obstetricians and Gynecologists (ACOG, the American College of Obstetricians and Gynecologists) have defined preeclampsia as hypertension occurring > 20 weeks of pregnancy, accompanied by one of the following symptoms: thrombocytopenia < 150 000/dL, deterioration of the liver function (doubled values of ALT and AST), renal failure (creatinine > 1.1 mg/dL), and neurological disorders or blurred vision. The difference between the two classifications is that according to the ISSHP guidelines, intrauterine growth restriction (IUGR) is an additional factor which allows to diagnose preeclampsia. Also, IUGR has been recognized a part of the diagnostic process for preeclampsia in the November 9, 2015 Regulation of the Minister of Health of the Republic of Poland on the management standards in pathological pregnancies [1].

None of the abovementioned classifications [2, 3] takes into account the specific characteristics of patients with chronic kidney disease. Due to delayed motherhood, women with glomerulonephritis, systemic lupus erythe-

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matosus and diabetic nephropathy are becoming increasingly common in the obstetric practice. Women after renal transplantation are among patients who require a highly individualized approach to both, treatment and diagnosis. Therefore, they were chosen to represent diversity in the diagnosis of preeclampsia in pregnant women with chronic kidney disease. IUGR is a complication of pregnancy whose occurrence may be affected by numerous factors, e.g. environmental conditions, such as smoking, anemia, hypertension, as well as chronic use of immunosuppressive drugs and the nature of the transplanted organ. It is impossible to identify one factor as the main cause of IUGR, but in patients after renal transplant at least two of them — hypertension and immunosuppressive therapy — are seen virtually in each case. Thus, our study was an attempt to validate the commonly used diagnostic criteria and support the hypothesis that intrauterine hypotrophy as a reflection of the materno-placental interaction should be an independent and important marker of preeclampsia in patients with chronic kidney insufficiency.

MATERIAL AND METHODS

We analyzed retrospectively the course of pregnancy and delivery in 48 renal transplant patients, who delivered at the First Department of Obstetrics and Gynecology between 2002 and 2015. Two patients were excluded from the study, because they had neither gestational nor pre-gestational hypertension. One of them delivered an eutrophic and the other a hypotrophic baby. The remaining 46 women with pre-gestational hypertension were divided into two groups: 23 patients who delivered eutrophic children (Group I) and 23 patients diagnosed with fetal hypotrophy defined as birth weight of < 10 percentile for the gestational age (Group II). The following factors were analyzed: occurrence of preeclampsia, duration of pregnancy, mode of delivery and postnatal state of the neonate, and compared for the two groups.

RESULTS

No differences were found in terms of maternal age at delivery (30.8 vs. 29.17; p = 0.095), time from transplantation (5.41 vs. 4.6; p = 0.163), BMI (27.35 vs. 26.29; p = 0.17) or immunosuppressive drug regimen (p > 0.05) between the groups. Mean duration of pregnancy was similar: 34.5 and 35 weeks in Groups I and II, respectively (p = 0.235). Mean birth weight was 2608.64 g, and 2046.30 g in Groups I and II, respectively (p = 0.002). Mean weight percentile was 36.57 and 2.91 in Groups I and II, respectively (p < 0.000). Despite similar gestational age, APGAR score at 10 min. was statistically lower in Group II (9.7 vs. 8.65; p = 0.045), with no differences in the earlier scores. Despite the p-value of < 0.05, we are of the opinion that our sample size was insufficient to suggest the tendency to late respiratory and adaptive distress in hypotrophic neonates.

Cesarean section was performed in 18 and 18 patients from Groups I and II. The analysis revealed differences in the indications for this mode of delivery. In Group I, the main reason was a sharp increase in blood pressure, which was observed in 12 patients during childbirth or pregnancy. In Group II, this clinical situation occurred in 6 patients. Threatening intrauterine asphyxia was the reason for cesarean delivery in 2 patients from Group I and 6 from Group II. All patients received immunosuppressive drugs in two basic schemes. The first regimen consisted of prednisone with cyclosporine A, second of prednisone with tacrolimus. Two patients in Group II used azathioprine as a third drug. All data are shown in Table 1.

Other clinical problems affecting the diagnosis of preeclampsia were analyzed as well. Eclampsia occurred only in 2 patients, both from Group I. Proteinuria, which is defined

Table 1. Population data: sample size, pregnancy duration, mode of delivery, indications for cesarean section, and the use of immunosuppressive drugs

	Hypertension, eutrophy Group I	Hypertension, hypotrophy Group II
No. of patients	23	23
Duration of pregnancy	34.5 weeks	35 weeks
Mode of delivery cesarean/vaginal	18/5	18/5
Indications for cesarean section:		
• elective	–	–
• ↑ blood pressure	12	6
• imminent asphyxia	2	10
Immunosuppressive drugs	(P + C) – 5 (T + P) – 18	(P + C) – 4 – (P + T) – 17 (T + P + A) – 2

P + C — prednisone + cyclosporine A
P + T — prednisone + tacrolimus
P + T + A — prednisone + tacrolimus + azathioprine

Table 2. Clinical basis for the diagnosis of preeclampsia

	Hypertension — eutrophic fetus Group I	Hypertension + hypotrophy Group II
Eclampsia	2	0
Proteinuria before/after 20 weeks	16/22	14/20
Proteinuria > 20 weeks (de novo)	6	6
Increase in RR > 20 weeks	10	8
Creatinine < 1.2 before 20 weeks	15	9
Creatinine > 1.2 after 20 weeks	8 (*de novo* 5)	8 (*de novo* 4)
Preeclampsia	21	23

as the loss of > 300 mg of protein per day, was observed in the first half of pregnancy in 16 and 14 patients from Groups I and II, respectively. It has increased in the second half of pregnancy in 6 patients from Group I and 6 from Group II. The highest recorded loss of protein into urine was 3.8 g/day, and 9.1 g/day in Groups I and II, respectively.

Patients from Group II were more prone to urinary tract infections (0.43 vs. 0.79; p = 0.02). In 10 patients from Group I, a deterioration of blood pressure control was observed in the second half of pregnancy. It required increased doses of hypotensive drugs or the use of additional medications. A similar situation was observed in 8 patients from Group II.

In the first half of gestation, the concentration of creatinine in blood serum was < 1.2 mg% in 15 patients from Group I and in 9 from Group II. Higher creatinine concentration was observed in 8 patients from Group I, wherein in 5 the serum creatinine level increased *de novo* after 20 weeks of pregnancy. Similarly, also 8 patients from Group II presented elevated serum creatinine after 20 weeks of pregnancy, wherein the *de novo* increase was observed in 4 women.

Based on the abovementioned data, the diagnosis of preeclampsia was made in 21 and 23 patients from Groups I and II, respectively. In Group II, intrauterine hypotrophy was the only cause for the diagnosis in 2 cases, while signs of renal dysfunction were the basis for the diagnosis in the remaining 21 patients. Detailed data are shown in Table 2.

DISCUSSION

Preeclampsia is one of the most frequently reported complications in pregnancies after kidney transplantation [4, 5]. This complication is up to 8 times more common in that group of women than in the general population [5]. Due to the fact that the etiology of preeclampsia remains to be fully elucidated, every few years its classification changes, making it difficult to compare patients from the past, especially after 2014.

Furthermore, proper qualification and diagnosis, relevant to the clinical symptoms, present a challenge also in other groups of patients. Similar problems have been reported about patients with chronic kidney disease and systemic lupus erythematosus (SLE). Preeclampsia affects up to 30% of pregnancies in these women [6, 7]. Out of these all conditions, clinical diagnosis of preeclampsia is much more difficult because most of these patients had hypertension and proteinuria before pregnancy [8, 9]. The diagnosis is based on deterioration of hypertension control and increased proteinuria, combined with lowered platelet count, elevated liver enzymes, or intrauterine fetal hypotrophy [10, 11]. Worsening of hypertension and proteinuria may reflect worsening of the underlying disease or the physiological changes in pregnancy. Differentiation between these symptoms is very important because the course of action in each of these cases is different [10]. Sometimes preeclampsia is the first sign of chronic kidney disease [12].

In our study, no significant differences in pregnancy duration (35 weeks in Group I vs. 34.5 weeks in Group II), time from transplant to delivery, or BMI were found, which is consistent with the findings of other authors [13]. Mode of delivery was similar in both groups, with the majority of cesarean sections, although indications for the procedure were different: mainly a sudden increase in blood pressure during pregnancy or childbirth in Group I and threatening intrauterine fetal asphyxia in Group II.

Chronic immunosuppressive therapy constitutes an important factor, which undoubtedly has an impact on the fetal and neonatal outcome. The most frequently used immunosuppressive drugs in pregnant after kidney transplantation include prednisone, azathioprine, cyclosporine A, and tacrolimus. Prednisone passes through the placenta but owing to its rapid metabolism by placental 11β-hydroxysteroid dehydrogenase, fetal serum concentration reaches only 10% of the maternal levels. Azathioprine and 6-methylmercaptopurine (the active metabolite of azathioprine) also pass through the placenta. Azathioprine concentration in the placenta is relatively high, reaching 64–93% of the concentration in the maternal serum. However, the concentration in fetal blood is much lower, and is 1–5% of that in the maternal serum [14–16]. Cyclosporine A cross the placenta, reaching about 5% fetal blood concentration compared to

the concentration in the maternal serum [14–18]. Systematic literature review published in 2016 by the European League Against Rheumatism shows compatibility with pregnancy and lactation for azathioprine, cyclosporine, tacrolimus and glucocorticosteroids [19].

Notably, out of 48 pregnancies, pregestational hypertension and proteinuria < 20 weeks of gestation were found in most patients (46:16 in Group I and 14 in Group II). Both of these factors are known risk factors for intrauterine growth retardation [20]. Deteriorated blood pressure control was found in 10 patients from Group I and in 8 from Group II. Proteinuria has markedly increased in the second half of pregnancy in 6 patients from Group I and 6 in Group II. Based on the existing criteria, preeclampsia should be diagnosed in all of these patients. Analyzing other clinical parameters, there was no difference in the increase of serum creatinine levels > 20 weeks of pregnancy (> 1.2 mg%) (8 patients from Group I and 8 from Group II). Taking into account all of the abovementioned parameters, if we strictly abide by the recommendations, preeclampsia should be recognized in the vast majority of patients after kidney transplant — according to our observations in 46 from 48 patients. Noteworthy, none of the preeclampsia markers mentioned above had any effect on the condition of the neonate delivery.

Three factors seem to have a significant impact on the possibility of intrauterine growth retardation and preeclampsia in post-transplant patients. The exact etiopathogenesis of eclampsia is still a topic of much debate, but recently researches have been paying more attention to the role of damage to the vascular endothelium [21], which is especially true about the vulnerable patients with chronic kidney disease. Hypertension and proteinuria are found in the majority of the affected subjects, while immunosuppressive therapy is observed in all patients. In our study, no differences in these factors have been noted. Therefore, intrauterine hypotrophy in these patients proves to be an independent factor, sufficient for the recognition of preeclampsia. Neonatal outcomes have been correlated more directly with the intensity of hypotrophy than with gestational age alone.

CONCLUSIONS

Current diagnostic criteria for preeclampsia are insufficient in pregnant women after kidney transplantation. General criteria should be applied with special care in women with chronic kidney disease or with systemic lupus erythematosus. In those patients, intrauterine growth restriction seems to be a better predictive factor for neonatal morbidity than typical markers of kidney function.

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