Effect of maternal pregnancy-induced hypertension on neonatal immunity

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Summary

Objective: To explore the effect of pregnancy-induced hypertension (PIH) on immune system of neonate. *Materials and Methods:* Sixty neonates whose mothers suffered from PIH were selected and divided into preeclampsia group (n=28) and gestational hypertension (GH) group (n=32) according to severity of mother's condition. Thirty neonates having healthy mothers were enrolled as control group. The base clinical characteristics of neonates were collected and umbilical vein blood was drawn to detect the distribution of T lymphocyte antigen, immune globulin, and complement level. *Results:* The gestational week, birth weight, head circumference, and one-minute Apgar score of both PIH groups were lower than those of control group, and preeclampsia group was lower than GH group ($p < 0.05$). There was significant difference between preeclampsia group and control group in blood routine and blood glucose levels. Concerning blood glucose levels, both PIH groups were lower than control group, and preeclampsia group was lower than GH group ($p < 0.05$). Content of IgG and complement C4 of GH group was lower than those of control group; IgG level of preeclampsia group was also lower than GH group ($p < 0.05$). *Conclusions:* PIH of pregnant mother affects the immunity of neonate, and more severe PIH will more negatively affect immunity of neonate.

Key words: Pregnancy-induced hypertension; preeclampsia; gestational hypertension (GH); immunity; neonate.

Introduction

Pregnancy-induced hypertension (PIH) is a common complication in the gestational period which frequently occurs after 20 weeks'. Main features include hypertension and proteinuria, which may be accompanied by functional lesion or non-function of multiple organs [1]. The incidence of PIH is quite high and causes great harm to pregnant women, fetus, and neonate. It is one of the important reasons leading to fetal growth restriction, fetal distress, perinatal death, and maternal death, and PIH, especially severe preeclampsia and eclampsia cause great harm to infants and mothers [2]. The basic pathological changes include decrease of blood perfusion of all organs caused by arteriolar spasm, ischemia, and hypoxia of organ and tissue, and increase of vascular permeability; the uterine placental vessel undergoes acute atherosclerosis, which causes the decrease of placental blood and placental function, and thus leads to intrauterine growth restriction and fetal distress. The pathogeny of PIH is not completely illustrated at present; some believe that vascular endothelial injury and immune imbalance are important links in the development of PIH [3, 4], while others uphold that inflammation participates in it [5].

Previous studies on this disease mostly focus on its effect on pregnant women, however, there are few reports on its effect on fetus and neonate. In recent years, some scholars have indicated that PIH may be related to the occurrence of newborn diseases, such as infection, septicemia, intracranial hemorrhage, and retinopathy. PIH will affect the neonate or fetus' blood pressure, hormone system, neuro-development system, as well as long-term physical strength, intelligence and living quality [6-8]. Through observing the basic clinical conditions and immune system indexes in neonates whose mothers suffered from PIH, the present authors investigated the effect of PIH on neonate's immune system.

Materials and Methods

Sixty neonates of mothers that suffered from PIH were admitted to the present hospital between June 2013 and June 2014 and enrolled in this study. They were divided into preeclampsia group (28 cases) and gestational hypertension (GH) group (32 cases) according to the severity of gestational hypertension. Inclusion criteria: (1) born in the Department of Gynecology and Obstetrics of the present hospital, gestational age of 28~41 weeks, birth weight < 4,000 grams (within 24 hours after birth); (2) single birth, live birth, spontaneous labor or cesarean section; (3) mother complicated with GH had an age between 20~35 years. Exclusion criteria: neonates whose mother suffered from anemia, primary hypertension, diabetes, liver and kidney disease, chronic diseases such as tuberculosis, or had a history of infection. Thirty full-term neonates whose healthy mothers had been hospitalized in the same period were selected as the control group. The family members of all enrolled neonates signed the informed consent.

Table 1. — *Base characteristics of three groups.*

	Preeclampsia group	GH group	Control group	Statistics	*p* value
Maternal age (years)	26.61 ± 2.07	25.75 ± 2.90	26.97 ± 2.57	F= 1.863	0.161
Time of gravidity	1.29 ± 0.62	1.31 ± 0.47	1.33 ± 0.48	$H = 0.046$	0.997
Time of delivery	1.27 ± 0.46	1.28 ± 0.46	1.30 ± 0.46	$H = 0.028$	0.986
Neonatal sex (males/females)	20/18	16/16	17/13	$\chi^2 = 0.280$	0.870
Gestational weeks	30.31 ± 1.66*#	34.75 ± 2.16*	36.04 ± 1.93	F = 69.057	0.000
Birth weight (kg)	1.29 ± 0.45*#	2.02 ± 0.64*	3.03 ± 0.58	$H = 54.297$	0.000
Number of low birth weight infant [n (%)]	28 (100.00)	30 (93.75)	22 (73.33)	$\chi^2 = 11.616$	0.003
Head circumference of neonate (cm)	26.05 ± 1.90*#	29.69 ± 2.84*	33.14 ± 3.15	F = 30.657	0.000
One-minute Apgar score	3.32 ± 1.59*#	4.97 ± 1.53*	8.30 ± 1.34	$H = 47.125$	0.000
Five-minute Apgar score	6.68 ± 1.72*	7.47 ± 1.46*	8.93 ± 0.91	F = 19.593	0.000
Antenatal abnormalities [n (%)]					
Grade III infection of amniotic fluid	5 (17.85)	1 (3.12)	0 (0.00)	$\chi^2 = 8.139$	0.017
Placental abruption	11 (39.29)	9 (28.12)	1 (3.33)	$\chi^2 = 11.102$	0.004
Fetal distress in uterus	15 (53.57)	7 (21.87)	0 (0.00)	$\chi^2 = 22.682$	0.000
Neonate complications [n (%)]					
Severe infection	9 (32.14)	7 (21.87)	0 (0.00)	$\chi^2 = 10.807$	0.005
Myocardial injury	26 (92.86)	27 (84.37)	1 (3.33)	$\chi^2 = 60.656$	0.000
Polycythemia	12 (42.86)	6 (18.75)	1 (3.33)	$\chi^2 = 13.751$	0.001
Liver dysfunction	5 (17.86)	4 (12.50)	1 (3.33)	$\chi^2 = 3.190$	0.203
Kidney dysfunction	4 (14.29)	4 (12.50)	0 (0.00)	$\chi^2 = 4.449$	0.108
Hypoglycemia	14 (50.00)	10 (31.25)	0 (0.00)	$\chi^2 = 19.048$	0.000
Hypothyroidism	12 (42.86)	8 (25.00)	0 (0.00)	$\chi^2 = 15.612$	0.000
Respiratory failure	9 (32.14)	6 (18.75)	0 (0.00)	$\chi^2 = 10.929$	0.004
Pulmonary arterial hypertension	6 (21.43)	5 (15.62)	0 (0.00)	$\chi^2 = 6.735$	0.034

* *vs.* control group, $p < 0.05$; # *vs.* GH group, $p < 0.05$.

When the blood pressure (BP) of the pregnant women was no less than 140/90mm Hg after pregnancy and returned to the normal level within 12 weeks after delivery, proteinuria(-), and the patient suffered from epigastric discomfort or thrombocytopenia, she would be diagnosed with GH after delivery. Diagnosis of preeclampsia: (1) mild preeclampsia: BP ≥ 140/90mm Hg, urine protein ≥ 0.3 grams/24 hours or proteinuria (+) occurring after 20 weeks of pregnancy and perhaps accompanied by epigastric discomfort, headache, and so on; (2) severe preeclampsia: BP ≥ 160/110mm Hg; urine protein ≥ 2.0 grams/24 hours or proteinuria (++); serum creatinine > 106 μmol/L; platelets < 100×10⁹/L; microangiopathic hemolysis (blood LDH increase); serum ALT and AST increase; continuous headache or other cranial nerve disorder or dysopia; continuous epigastric discomfort.

After informed consent, routine prenatal examination was conducted and the information such as age, gravidity, parity, and history of disease during pregnancy was recorded. The data of all pregnant women after delivery was collected, including delivery condition, pregnancy outcome, relevant indexes of neonate which further included gestational age of neonate, delivery type, body mass, height, Apgar score, whether with amniotic fluid pollution, placental abruption, and fetal distress in uterus occurrence, and head circumference measured after 72 hours of birth.

The umbilical cord of neonate was immediately cut and the umbilical vein was punctured within five minutes to draw five ml umbilical cord blood. Of which, two ml was placed into anticoagulation tube for lymphocyte separation immediately, fixed by 70% alcohol, put in 4°C refrigerator, and used for T lymphocyte antigen (CD4, CD8, and CD4/CD8) determination. The remaining umbilical cord blood was placed in pro-coagulation tube. The serum was drawn after centrifugation for the determination of immune globulin (IgG, IgM, and IgA) and complement C3 and C4 content. The immune globulin and complement level were de-

tected by fully automatic biochemical analyzer. FACS Calibur flow cytometry was used to detect T lymphocyte level by ELISA.

Five to seven ml venous blood of neonate was collected after 72 hours of birth; two ml was used for blood routine examination and the remaining after centrifugation was used to detect the content of serum ALT, AST, creatinine, urea nitrogen, creatine kinase isoenzyme, blood sugar by fully automatic biochemical analyzer, free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) in serum. At 40 days after birth of neonate, head MRI inspection was conducted. If periventricular leukomalacia, cyst, dysplasia of corpus callosum, T1W1 or T2W2 signal abnormity existed, the head MRI result was recorded as abnormality.

SPSS 18.0 software was used to conduct data analysis. χ^2 test was adopted for comparisons of enumeration data. Measurement data was presented as mean ± SD. For data in normal distribution, one-way ANOVA or LSD *t*-test was adopted for comparisons; for data with abnormal distribution, Kruskal Wallis *H* test or Nemenyi test was adopted for comparisons. *P* < 0.05 was considered the statistical significance.

Results

The average age, time of gravidity and delivery, and neonatal sex distribution in preeclampsia group and GH group were similar to those in control group. Concerning gestational week, birth weight, head circumference, Apgar score, antenatal abnormalities, number of low birth weight infant, and neonate complications, there were significant differences among groups (*p* < 0.05). The results of pairwise comparison showed that gestational week, birth weight, head circumference, and one-minute Apgar score of

Table 2. — *Analysis on blood cell and thyroid hormone contents*

	Preeclampsia group	GH group	Control group	Statistic	p value
Blood routine examination					
RBC count ($\times 10^{12}$/L)	$6.60 \pm 0.91^{*\#}$	$5.64 \pm 1.14^{*}$	4.11 ± 1.02	F = 26.159	0.000
Hematocrit value (%)	$67.23 \pm 9.84^{*\#}$	56.87 ± 11.04	50.92 ± 9.55	F = 14.997	0.000
Hemoglobin (g/L)	$212.91 \pm 16.08^{*}$	$193.55 \pm 12.47^{*}$	148.85 ± 9.63	F = 43.154	0.000
WBC count ($\times 10^{9}$/L)	$12.23 \pm 1.50^{*}$	14.85 ± 1.62	15.71 ± 1.49	F = 18.673	0.000
PLT count ($\times 10^{9}$/L)	$132.47 \pm 6.04^{*}$	$160.05 \pm 6.76^{*}$	280.45 ± 23.64	F = 570.702	0.000
Blood glucose and thyroid function test					
Blood glucose (mmol/L)	$2.89 \pm 0.41^{*\#}$	$3.78 \pm 0.73^{*}$	5.00 ± 0.82	F = 11.912	0.000
FT_3 (pg/ml)	2.35 ± 0.20	2.51 ± 0.39	3.02 ± 0.76	F = 2.060	0.084
FT_4 (ng/dl)	1.11 ± 0.20	1.04 ± 0.33	0.92 ± 0.18	F = 1.575	0.142
TSH (μIU/ml)	$7.92 \pm 1.55^{*\#}$	5.32 ± 0.94	4.24 ± 0.61	F = 12.031	0.000
Head MRI of neonate					
MRI abnormality rate [n(%)]	$25\ (89.29)^{*\#}$	$15\ (46.87)^{*}$	$1\ (3.33)$	χ^2 = 180.00	0.000

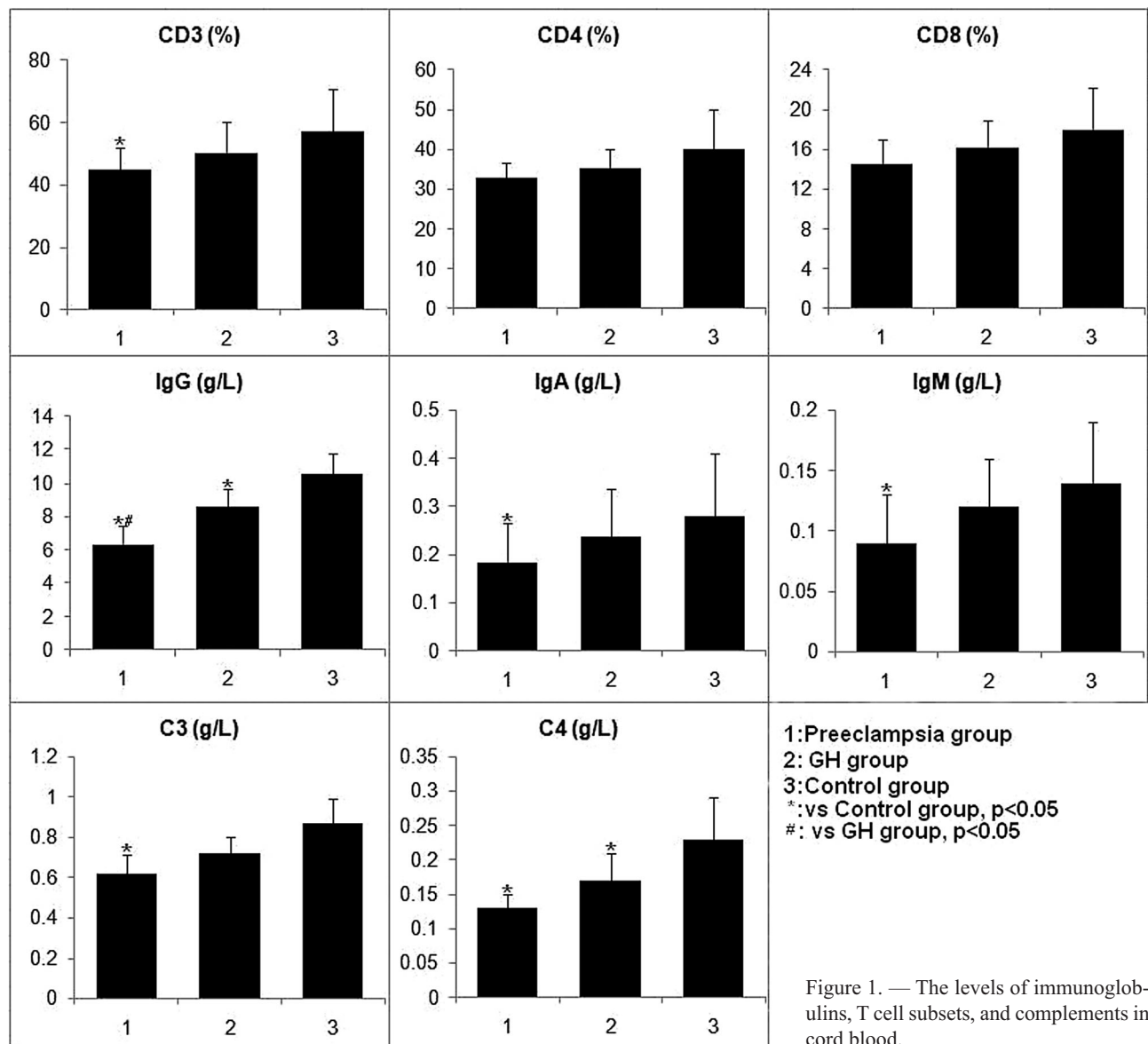* *vs.* control group, $p < 0.05$; # *vs.* GH group, $p < 0.05$.

Figure 1. — The levels of immunoglobulins, T cell subsets, and complements in cord blood.

preeclampsia group and GH group were obviously lower than those of control group, and preeclampsia group was lower than GH group ($p < 0.05$); one-minute Apgar score of preeclampsia group and GH group was also obviously lower than that of control group ($p < 0.05$).

Table 2 shows that there was significant difference between GH group and control group with regards to red blood cell, hemoglobin, and platelet content ($p < 0.05$). The blood glucose level of two PIH groups was lower than that of control group, and preeclampsia group was lower than GH group ($p < 0.05$). Concerning thyroid function, preeclampsia group had a significantly higher TSH content than the other groups ($p < 0.05$). With regards to head MRI abnormality rate, GH group was higher than control group, and preeclampsia group was higher than GH group ($p < 0.05$).

Figure 1 indicates that the content of CD3 cells, IgG, IgA, and IgM, and the levels of complement C3 and C4 in preeclampsia group were lower than those of control group; IgG content in preeclampsia group was also lower than that in GH group ($p < 0.05$); the content of IgG and complement C4 in GH group was also lower than that in control group ($p < 0.05$).

Discussion

PIH, especially preeclampsia, may lead to premature delivery and intrauterine growth retardation, increase the proportion of low birth weight infant, or damage the cardiovascular, blood, and endocrine systems, etc. The chronic injury caused by it is a major potential risk of certain childhood and adult disease [9-12]. In a retrospective cohort study, Phad *et al.* [13] showed that the median weight and median birth weight of the infants was significantly lower in the study group than that in the control group, and accelerated villous maturation, placental infarcts, and decidual vessel vasculopathy were more common in the study group ($p < 0.01$). Nahar *et al.* [14] also found the placental weight, surface area, number of cotyledons of placenta, and the weight of neonate were all related to PIH.

The results of the present study indicated that PIH had direct adverse effect on gestational week, birth weight, head circumference, Apgar score, blood routine, blood glucose level and thyroid function, and increased the occurrence of antenatal abnormalities, number of low birth weight infant, as well as the occurrence rate of neonate complications. The adverse effect was more obvious with the increase of severity of this disease. The study of Cantu *et al.* [15] found that laboratory abnormalities increased with severity of hypertension: mild hypertension alone (4.9%), severe hypertension alone (8.9%), and mild or severe hypertension with clinical signs of end-organ dysfunction (12.2%) ($p < 0.001$).

It is known that maternal PIH could influence the im-

munological effects of the neonates. In a study on preeclampsia transgenic rat model, Przybyl *et al.* found that under the premise of not influencing hypertension and proteinuria of pregnant rats, the intervention of regulatory T cells can obviously promote growth and development of fetus, and improve the immunity of fetal rat [16]. Sohlberg *et al.* [17] found that neonates born to pre-eclamptic mothers had an inflammatory serum cytokine profile and cord blood NK cells from pre-eclamptic pregnancies had higher NKp30 expression; therefore they concluded that pre-eclamptic pregnancies might influence specific NK cell functions in newborns.

In the present study, the CD3 cell content and level of complement C3 and C4 of preeclampsia group were lower than those of control group, and the complement C4 level of GH group was also lower than that of control group. These results show that PIH has a certain influence on cellular immunity and humoral immunity of neonate. The effect of PIH will be more obvious with the increase of severity [18]. IgG level of preeclampsia group was lower than that of GH group and control group, which indicated that preeclampsia has obvious adverse effect on IgG level of pregnant mother suffering from preeclampsia, leading to low IgG level of cord blood of neonate [19, 20]. Meanwhile, the result also suggested that the influence of PIH on GH patient was weaker than the influence on preeclampsia patient.

In summary, PIH seriously affected immunity and multisystem function of neonates. More severe PIH will more negatively affect immunity of neonate.

References

[1] Jun Z., Jonathan Z., Maureen C., Gertrud B.: "Epidemiology of pregnancy induced hypertension". *Epidemiol. Rev.*, 1997, *19*, 218.

[2] Kintiraki E., Papakatsika S., Kotronis G., Goulis D.G., Kotsis V.: "Pregnancy-Induced hypertension". *Hormones (Athens)*, 2015, 14, 211.

[3] Kocyigit Y., Atamer Y., Atamer A., Tuzcu A., Akkus Z.: "Changes in serum levels of leptin, cytokines and lipoprotein in pre-eclamptic and normotensive pregnant women". *Gynecol. Endocrinol.*, 2004, *19*, 267.

[4] Moreno-Eutimio M.A., Tovar-Rodríguez J.M., Vargas-Avila K., Nieto-Velázquez N.G., Frías-De-León M.G., Sierra-Martinez M., *et al.*: 'Increased serum levels of inflammatory mediators and low frequency of regulatory T cells in the peripheral blood of preeclamptic Mexican women". *Biomed. Res. Int.*, 2014, *2014*, 413249.

[5] Matias M.L., Romão M., Weel I.C., Ribeiro V.R., Nunes P.R., Borges V.T., *et al.*: "Endogenous and uric acid-induced activation of NLRP3 inflammasome in pregnant women with preeclampsia". *PLoS One*, 2015, *10*, e0129095.

[6] Sibai B.M.: "Diagnosis, prevention and management of eclampsia". *Obstet. Gynecol.*, 2005, *105*, 402.

[7] Davis E.F., Lewandowski A.J., Aye C., Williamson W., Boardman H., Huang R.C., *et al.*: "Clinical cardiovascular risk during young adulthood in offspring of hypertensive pregnancies: insights from a 20-year prospective follow-up birth cohort". *BMJ Open*, 2015, *5*, e008136.

[8] Zugna D., Galassi C., Annesi-Maesano I., Baïz N., Barros H., Basterrechea M., *et al.*: "Maternal complications in pregnancy and wheez-

ing in early childhood: a pooled analysis of 14 birth cohorts". *Int. J. Epidemiol.*, 2015, *44*, 199.

[9] Perveen S.: "Frequency and impact of hypertensive disorders of pregnancy". *J. Ayub. Med. Coll. Abbottabad.*, 2014, *26*, 518.

[10] Tuovinen S., Eriksson J.G., Kajantie E., Räikkönen K.: "Maternal hypertensive pregnancy disorders and cognitive functioning of the offspring: a systematic review". *J. Am. Soc. Hypertens.*, 2014, *8*, 832.

[11] Ulanovsky I., Diab K., Makhoul I.R., Blazer S., Smolkin T.: "The effect of maternal medications, hypertension/pre-eclamptic toxemia and diabetes mellitus on neonatal hearing screening". *Harefuah*, 2014, *153*, 511.

[12] Herrera-Garcia G., Contag S.: "Maternal preeclampsia and risk for cardiovascular disease in offspring". *Curr. Hypertens. Rep.*, 2014, *16*, 475.

[13] Phad N., Dahlstrom J.E., Ellwood D., Kent A.L.: "The effect of pregnancy-induced hypertensive disorders on placental growth along short and long axes and neonatal outcomes". *Aust. N. Z. J. Obstet. Gynaecol.*, 2015, *55*, 239.

[14] Nahar L., Nahar K., Hossain M.I., Yasmin H., Annur B.M.: "Placental changes in pregnancy induced hypertension and its impacts on fetal outcome". *Mymensingh. Med. J.*, 2015, *24*, 9.

[15] Cantu J., Clifton R.G., Roberts J.M., Leveno K.J., Myatt L., Reddy U.M., *et al.*: "Laboratory abnormalities in pregnancy-associated hypertension: frequency and association with pregnancy outcomes". *Obstet. Gynecol.*, 2014, *124*, 933.

[16] Przybyl L., Ibrahim T., Haase N., Golic M., Rugor J., Luft F.C., *et al.*: "Regulatory T cells ameliorate intrauterine growth retardation in a transgenic rat model for preeclampsia". *Hypertension*, 2015, *65*, 1298.

[17] Sohlberg E., Saghafian-Hedengren S., Bachmayer N., Hamad R.R., Bremme K., Holmlund U.: "Pre-eclampsia affects cord blood NK cell expression of activation receptors and serum cytokine levels but not CB monocyte characteristics". *Am. J. Reprod. Immunol.*, 2014, *71*, 178.

[18] Ramdenee G.R., Matah M., Bhatia B.D., Sen M.R., Swain S.: "Immunoglobulin G and complement C3 levels in pregnancy induced hypertension". *Indian Pediatr.*, 1995, *32*, 179.

[19] Arinola G., Arowojolu A., Bamgboye A., Akinwale A., Adeniyi A.: "Serum concentrations of immunoglobulins and acute phase proteins in Nigerian women with preeclampsia". *Reprod. Biol.*, 2006, *6*, 265.

[20] Das S., Sanyal S., Banerjee U., Basu K.: "Humoral immunity status in neonates born to pre-eclamptic toxaemia mothers". *J. Indian Assoc.*, 1998, *96*, 77.

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