Hypertensive disorders in pregnancy: risk factors and epidemiologic analysis

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Summary

Objective: To measure the incidence of preeclampsia-eclampsia and its perinatal mortality as they appear in the two major ethnic groups in Thrace: Christian Orthodox and Muslims. *Study Design*: Incidence and perinatal mortality of preeclampsia-eclampsia were studied retrospectively on all women managed in our clinic for hypertensive disorders in pregnancy who were delivered of a stillborn or healthy neonate between 1986 and 1999. We also compared the prevalence of certain risk factors of the disease as they appear in the above-mentioned distinct ethnic groups. *Results*: The total incidence of preeclampsia-eclampsia in Thrace was 2.3% and the total perinatal mortality 6.4%. Both variables presented higher values and severe preeclampsia-eclampsia had greater prevalence in the Muslim population. Most risk factors presented statistically significant differences between Christians and Muslims (x^2 test, $p < 0.05$). *Conclusions*: There was an ethnic variation in most epidemiologic variables of hypertensive disorders in Thrace between Christians and Muslims.

Key words: Preeclampsia; Eclampsia; Hypertensive disorders in pregnancy; Perinatal mortality

Introduction

Preeclampsia, a syndrome unique to human pregnancy, is a major contributor to maternal and perinatal morbidity and mortality. Even if maternal deaths are rare in industrialized countries, a significant number are still caused by preeclampsia and eclampsia [1, 2]. It is reported that the annual average incidence of preeclampsia among all deliveries in the United States is 2.4% [3], while the incidence of eclampsia in Finland comes up to 2.4/10,000 deliveries [2] and in Colombia it is 8.1/1,000 deliveries [4].

Although preeclampsia has been studied extensively, the causes and risk factors for the disease remain so unclear that preeclampsia has been called "a disease of theories" [5]. Several preexisting characteristics of pregnant women have been proposed as potential risk factors for preeclampsia. Hypotheses have focused on numerous etiologic factors including the role of endogenous hormones, nutrition, immunologic factors, and family history of these conditions [6]. Extremes of maternal age, race, socioeconomic status, change of paternity, blood group and type, previous miscarriage or abortion, smoking and alcohol use during pregnancy, body mass index, systolic and diastolic blood pressure early in pregnancy, rate of weight gain during pregnancy and the presence of gestational diabetes have been considered risk factors for the development of preeclampsia [3]. Variation in the incidence of preeeclampsia in different ethnic groups has been described in many epidemiologic studies [3-8]. Some researchers have speculated that preeclampsia is a disease of the upper class; others more recently believe it is a disease of the impoverished and still others think all social classes are at equal risk [5]. Eclampsia is still commonly perceived as the end of a linear spectrum that extends from normal pregnancy through gestational hypertention, preeclampsia. However some authors [9, 10] have reported that eclamptic seizures appear in the two major ethnic groups (Christian Orthodox and Muslims) which make up the population of Thrace, a rural territory in Northern Greece. We also aimed at investigating whether variables reported as potential risk factors for preeclampsia-eclampsia differ within the above-mentioned ethnic subpopulations.

Patients and Method

The incidence of preeclampsia-eclampsia in Thrace from 1986-1999 was studied retrospectively. The study population consisted of all women who delivered a stillborn or healthy infant in the Department of Obstetrics and Gynecology, Democritus University of Thrace, which is the only tertiary referral center for the three prefectures of the region. Due to this reason we believe that our results, though preliminary, are reliable and indicate the prevalence of the disease in the area.

The women comprising the study population were of two distinct ethnic groups (Christian Orthodox and Muslims), with different demographic and socioeconomic characteristics.

We reviewed the charts of 9,563 women who gave birth to a single stillborn or healthy neonate during the 13-year study period. Incidence rates were calculated per 1,000 deliveries for mild preeclampsia, severe preeclampsia and eclampsia. Preeclampsia, according to the Committee on Terminology of the American College of Obstetricians and Gynecologists, was defined as hypertention induced by pregnancy after 20 weeks' gestation, concurrent with proteinuria or edema or both [12].

Revised manuscript accepted for publication March 30, 2007

Hypertension was defined as a rise in systolic blood pressure of ≥ 30 mm Hg, a rise in diastolic pressure of ≥ 15 mm Hg, or blood pressure ≥ 140/90. We also considered hypertension as a rise of the mean arterial pressure ≥ 20 mm Hg. The levels described had to be found at least twice, six hours or more apart, and were based on previously recorded blood pressure. Eclampsia was defined as the occurrence of at least one episode of convulsions unrelated to coincidental neurologic disease or coma between the 20th week of pregnancy and the end of the 6th week after delivery, in a patient with previous signs of preeclampsia.

Preeclampsia was classified as severe if the following criteria existed [13]: Blood pressure > 160 systolic or > 110 diastolic (at bed rest, on two occasions at least 6 hours apart, proteinuria > 5 g/24 h, oliguria (< 500 ml/24 h), cerebral or visual disturbances, epigastric pain, pulmonary edema or cyanosis.

We considered HELLP syndrome as an indication of fulminating toxemia of pregnancy and we estimated its incidence separately as well as with the severe preeclampsia group. HELLP syndrome was defined as: platelet count less than 150,000, elevated liver enzymes as an increased SGOT ≥ 72 IU/l and hemolysis on blood film or a lactic dehydrogenase of > 600 IU/l. Information abstracted included sociodemographic characteristics (maternal age, marital status, maternal occupation, education, and usual source of healthcare), past pregnancy history (previous episodes of toxemia, previous history of spontaneous abortions, week at first prenatal visit, weight gained by 20th week, season of birth, fetal sex), family history (family history of hypertension), pre-pregnancy weight and lifestyle habits (alcohol and tobacco).

Information was obtained mainly from the prenatal and pregnancy records, according to the discharge diagnoses. However, if certain information was not available (usually concerning maternal social status, personal habits, or family history), one of the team members was charged to communicate personally with the patient so as to complete all the missing details. Body mass index (BMI), calculated as weight (kg)/ height (m) 2 was categorized as follows: underweight was defined as BMI under 19.8; normal weight as BMI 19.8-26; and overweight and obese as BMI above 26 [14]. Perinatal mortality was defined as percentage of stillborns and neonatal deaths due to preeclampsia-eclampsia during the first week of all the children born to preeclamptic-eclamptic women within the study period.

The study group was categorized in two subpopulations – Christian Orthodox and Muslims. The prevalence of certain variables considered as risk factors for hypertensive disorders was estimated in each subgroup (percentage of the group members). We used the chi-square test and frequency tables to compare baseline characteristics (p was considered significant at .05 or below).

Table 1. — *Distribution of risk factors according to religion.*

	Christian Orthodox (n = 140)		Muslims (n = 80)		p (χ^2)
	n	%	n	%	
Maternal age					
< 19	6	5.7	14	13.7	
20-29	84	60	45	56.2	.005
> 30	50	34.2	21	30	
Parity					
0	41	29.2	17	21.2	NS
≥1	99	70.7	63	78.7	
*Previous history of SAB**					
Yes	32	22.8	9	11.2	
No	67	77.1	54	88.7	.005
Weeks at first prenatal visit					
≤ 13	118	84.2	28	35	.001
> 13	22	15.7	52	65	
Prepregnancy Quetelet index, kg/m²					
Low (< 18.9)	37	26.4	49	61.2	
Mid (18.9-25.8)	86	61.4	26	32.5	.001
High (> 25.8)	17	12.1	5	6.2	
Weight gained by 20th week					
< 5	27	19.2	26	32.5	
> 5	113	80.7	54	67.5	.05
Cigarette smoking					
Yes	43	30.7	58	72.5	.001
No	97	69.2	22	27.5	
Alcohol consumption					
Yes	34	24.2	2	2.5	.001
No	106	75.7	78	97.5	
*Previous history of toxemia**					
Yes	16	16.4	18	28.5	.01
No	83	83.8	45	71.4	
Family history of hypertension					
Yes	67	47.8	13	16.2	.001
No	73	52.1	67	83.7	
Marital Status					
Married	128	91.4	76	95	.05
Not married	12	8.5	4	5	
Usual source of healthcare					
Private	19	13.5	0	0	.001
Public	121	86.4	80	100	
Maternal education					
<6	16	11.4	67	83.7	
6-12	117	83.5	18	22.5	.001
> 12	7	5	0	0	
Maternal Occupation					
Specialized	35	25	0	0	
Not specialized	105	75	80	100	.001

SAB = spontaneous abortions.
* For multiparas only.

Results

From 1986 to 1999 a total of 9,563 single pregnancies (7,301 Christian Orthodox women and 2,262 Muslim women) were registered in our clinic records. During the same period 220 cases with hypertensive disorders (140 Christian Orthodox and 80 Muslims) fit the study criteria and were reviewed. This is translated into a total preeclampsia-eclampsia incidence of 2.3 per 100 deliveries. In the Christian sub-group the incidence of hypertensive disorders in pregnancy comes up to 1.9% while in the Muslim subgroup the disease presents an incidence of 3.5%. Eight patients (2 Christians and 6 Muslims) developed eclamptic seizures before, during, or after delivery. This corresponds to a total rate of eclampsia of 0.8 per 1,000 deliveries (0.27% for Christians and 2.6% for Muslims). All cases were treated for mild or severe preeclampsia. Four patients (2 Christians

and 2 Muslims) presented laboratory findings of HELLP syndrome which gives an incidence rate of 0.4% for the whole population (0.3% for the Christian and 0.9% for the Muslim population).

The age distribution of hypertensive disorders in pregnancy for both study groups and for the whole study population is presented in Figure 1. We observed that the peak incidence rate of the disease for Christians is found at the age of 26-30 years while for Muslims the disease presents its highest rate five years earlier and then decreases significantly by almost 10%. For ages below 20 Muslims with hypertensive disorders are more than two-fold compared to Christians.

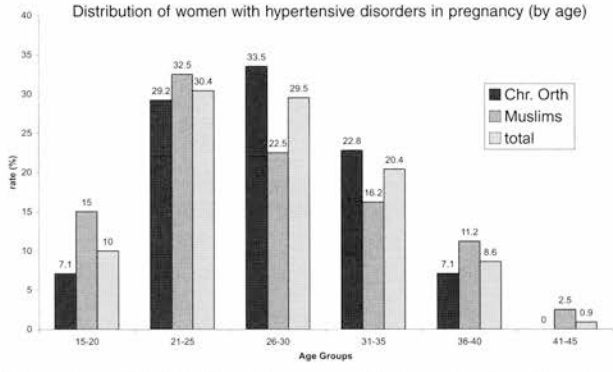

Figure 1. — Distribution of women with hypertensive disorders in pregnancy by age.

Figure 2 shows the time distribution of hypertensive disorders in the study period. The annual incidence rate of the disease in the Christian population remains almost steady, without remarkable fluctuations. In the Muslim population the same variable shows an increasing inclination from 1997 and on, with the rate in 1999 being almost two-fold the one in 1997.

The average incidence rates of hypertensive disorders in the two half-study periods is presented in Figure 3. The parameter shows a small but insignificant decrease in the Christian subgroup and a slight insignificant increase in the Muslim subgroup, while the total incidence remains practically stable.

In Figure 4 there is a comparative presentation of the incidence of each type of hypertensive disorder between Christian Orthodox and Muslims. It appears that mild forms of preeclampsia are more frequently found in Christians, while all other severe types of hypertensive disorders in pregnancy present a higher prevalence in Muslims.

A comparative chart of the way of delivery in all cases of pregnancies with hypertensive disorders is shown in Figure 5. Christians had only 10% fewer normal deliveries than cesarean sections while cesarean sections in Muslims were two-fold higher than normal deliveries.

Figure 6 depicts the distribution of fetal birthweights in all cases of preeclampsia-eclampsia. The majority of Muslim neonates had birthweights below 2,500 g. On the contrary, the majority of Christian neonates presented birthweights over 2,500 g.

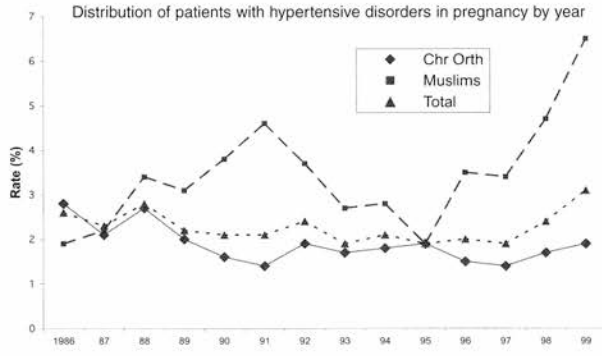

Figure 2. — Distribution of patients with hypertensive disorders in pregnancy by year.

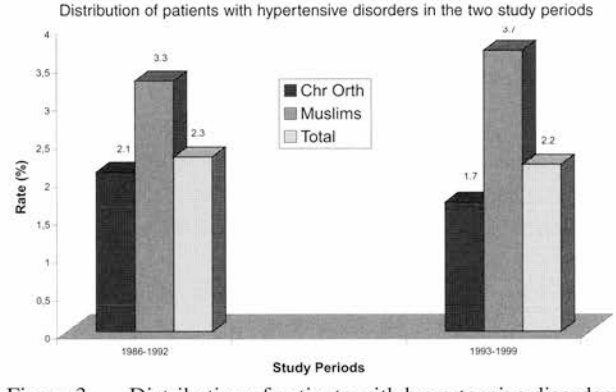

Figure 3. — Distribution of patients with hypertensive disorders in the two study periods.

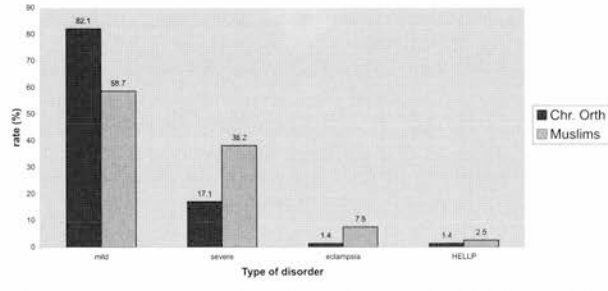

Figure 4. — Comparative values of hypertensive disorders in pregnancy between Christians and Muslims.

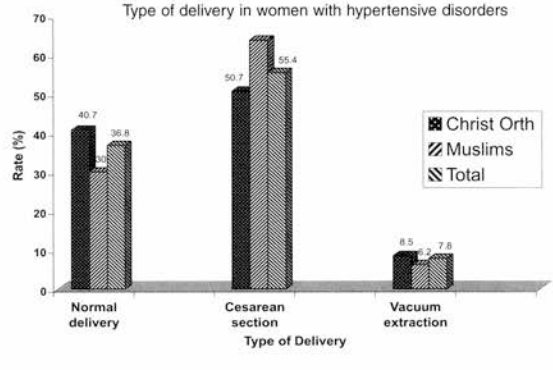

Figure 5. — Type of delivery in women with hypertensive disorders.

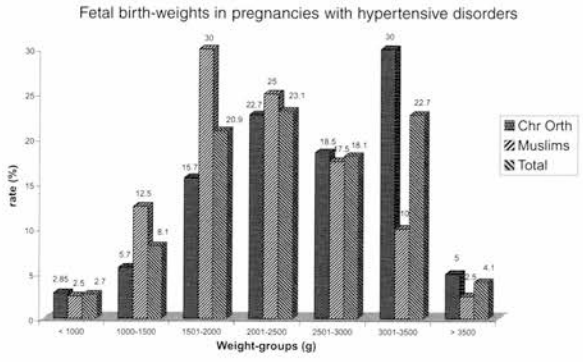

Figure 6. — Fetal birthweights in pregnancies with hypertensive disorders.

Perinatal death occurred in 14 cases of preeclampsia-eclampsia (6 perinatal deaths in Christians and 8 perinatal deaths in Muslims). This corresponds to a total perinatal mortality in preeclampsia-eclampsia of 6.4% (4.3% in Christians and 7.5% in Muslims).

We noticed that there were statistically significant differences in most risk factors of the disease between Christians and Muslims (Table 1). Muslims had more than twice as many patients below 19 years of age as Christians had ($p < .005$), the majority of them had their first prenatal visit after the 13th week of pregnancy ($p < .001$) and were smokers ($p < .001$), none had private healthcare ($p < .001$) or did any specialized job ($p < .001$), and most of them did not go to school for more than six years ($p < .001$).

On the other hand, Christians presented a larger proportion of patients with history of previous spontaneous abortions ($p < .05$), the majority of which were of a mid to high pre-pregnancy Quetelet index ($p < .001$) and gained more than 5 kg in the first 20 weeks of pregnancy ($p < .05$), and almost half of them had a family history of hypertension ($p < .001$). Parity, previous history of toxemia and marital status did not differ significantly among the two study populations.

Discussion

The reported incidence of hypertensive disorders in pregnancy shows great variation all over the world, which may be attributed to differences in definition, population composition, demographic and obstetric characteristics, or actual disease incidence [15]. Saftlas *et al.* [6] report that preeclampsia complicated 2.6% of all births in the United States from 1979 to 1986. Eclampsia complicated 0.56 per 1,000 deliveries over this 8-year period. On the other hand, the US Collaborative Perinatal Study [16] reports an incidence of preeclampsia of 4.5% and 11.2% for whites and blacks, respectively, and an eclampsia rate of 0.61 cases per 1,000 deliveries for whites and 0.75 cases per 1,000 deliveries for black women. Samadi *et al.* [17] describe a 4.5% preeclampsia incidence among normotensive women. Preeclampsia in the Netherlands is estimated at about 1.4% [8]. Ekholm *et al.* [2] reported an eclampsia incidence of 2.4 per 10,000 deliveries in Finland in the years 1990-1994. Eclampsia in Sweden comes up to 2,7 per 10,000 births, in Iceland 3.0 per 10,000 deliveries and in Great Britain 4.9 per 10,000 deliveries [10, 18].

Most authors agree that there is racial differentiation in the incidence of hypertensive disorders, with black women being more likely to develop hypertensive disorders in pregnancy than whites [1, 3, 6, 8]. Other reports are dubious about race increasing the risk of developing hypertensive disorders [6, 7, 19]. The results obtained from our study on the incidence rates of hypertensive disorders in pregnancy are comparable to the ones found in many developed countries of Northern Europe and America and they are lower than the ones reported for developing countries all over the world. Especially for preeclampsia, our results are lower compared to those found in most studies because we are not referring to a high-risk population (e.g., nulliparous women) like most studies. The Muslim population presents a greater possibility of developing hypertensive disorders in pregnancy, which confirms the racial-ethnic differences in the prevalence of the disease reported in other studies.

Some authors suggest that there has been a decrease in the incidence of hypertensive disorders the last 20 years (preeclampsia has decreased mainly among black women and other minority races but varies little among white women and eclampsia in all racial-ethnic groups in developed countries [2,18], reflecting the improved antenatal management of women with preeclampsia). Increasing incidence rates of the disease have been reported for certain developing countries, which suffer special political or socioeconomic conditions, like Colombia [4]. The estimated incidence rates of the disease in our study for the two half-study periods correspond with the above-mentioned studies as far as the decreased incidence in the Christian population is concerned. The slight increase in the incidence of the disease in Muslims is not consistent with the decreased rates presented in other minority ethnic groups and could probably be attributed to improved medical information, antenatal care and hospitalization of affected Muslim women.

Friedman *et al.* [20] reported a perinatal mortality due to preeclampsia of 5.6% for deliveries < 35 weeks of gestation and a total perinatal mortality of 3.4% in cases of preeclampsia with antenatal glucocorticiod exposure. Fitzpatrick *et al.* [21] reported a total perinatal mortality in Ireland of 0.71 per 1,000 deliveries between 1981-1987. Copper *et al.* [22] reported that perinatal mortality in black women with preeclampsia is 1.6 times greater than for white women.

The total perinatal mortality estimated in our study is comparable to the one mentioned by the previous authors, bearing in mind that all preeclamptic neonates benefit from an immediate approach to a well organized neonatal intensive care unit [20-22]. Moreover, the majority of preeclamptic patients undergo a full course of glucocorticoid exposure. The increased perinatal mortal-

ity due to preeclampsia in the Muslim population might possibly be attributed to defects still existing in the prenatal care of these patients. Cesarean delivery in patients with hypertensive disorders ranges from 25.4% [21] to 63.7% [20] in various studies. The percentage of cesarean sections performed in our study is within this range. Muslims had higher rates of cesarean delivery, which correlates with the more severe forms of the disease found in this population. This also explains the lower birth weights of Muslim neonates.

Our study results suggest that risk factors for hypertensive disorders in pregnancy show differences in prevalence among women of different ethnic groups and their effects vary within ethnic groups (Christians and Muslims). Considering that the baseline socioeconomic characteristics do not differ greatly, the significant difference in the prevalence of most risk factors among the study populations indicates that ethnicity results in differences in genetic predisposition and everyday life which, in turn, form distinct risk profiles for each population. This is in agreement with other reports [8,23] which suggest that ethnicity seems to be a reasonable factor of etiologic heterogeneity among populations. Our data support the hypothesis that women from distinct ethnic groups should be analyzed separately in order to improve prediction of hypertensive disorders in pregnancy.

References

[1] Stone J.L., Lockwood C.J., Berkowitz G.S., Alvarez M., Lapinski R., Berkowitz R.L.: "Risk factors for severe preeclampsia". *Obstet. Gynecol.*, 1994, *83*, 357.

[2] Ekholm E., Salmi M.M., Erkkola R.: "Eclampsia in Finland in 1990-1994". *Acta Obstet. Gynecol. Scand.*, 1999, *78*, 877.

[3] Sibai B.M., Ewell M., Levine R.J. *et al.*: "Risk factors associated with preeclampsia in healthy nulliparous women". *Am. J. Obstet. Gynecol.*, 1997, 177, 1003.

[4] Conde-Agudelo A., Kafury-Goeta A.C.: "Epidemiology of eclampsia in Colombia". *Int. J. Gynecol. Obstet.*, 1998, *61*, 1.

[5] Eskenazi B., Fenster L., Sidney S.: "A multivariate analysis of risk factors for preeclampsia". *JAMA*, 1991, *266*, 237.

[6] Saftlas A.S., Olson D.R., Franks A.L., Atrash H.K., Pokras R.: "Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986". *Am. J. Obstet. Gynecol.*, 1990, *163*, 460.

[7] Williams P.K., Wilson S.: "Ethnic variation in the incidence of HELLP syndrome in a hypertensive pregnant population". *J. Perinat. Med.*, 1997, *25*, 498.

[8] Knuist M., Bonsel G.J., Zondervan H.A., Treffers P.E.: "Risk factors for preeclampsia in nulliparous women in distinct ethnic groups:a prospective cohort study". *Obstet. Gynecol.*, 1998, *92*, 174.

[9] Sibai B.: "Matenal-perinata outcome in 254 consecutive cases". *Am. J. Obstet. Gynecol.*, 1990, *163*, 1049.

[10] Douglas K.A., Redman C.W.G.: "Eclampsia in the United Kingdom". *Br. Med. J.*, 1994, *309*, 1395.

[11] Martin J.N., Blake P.J., Perry K.G. *et al.*: "The natural history of HELLP syndrome:patterns of disease progression and regression". *Am. J. Obstet. Gynecol.*, 1991, *164*, 1500.

[12] National High Blood Pressure Education Program Working Group. Report on High Blood Pressure in Pregnancy. *Am. J. Obstet. Gynecol.*, 1990, *163*, 1691.

[13] Gavert G., Bolger P.M.: "Benson and Pernolls Handbook of Obstetrics and Gynecology". Hypertensive Disorders During Pregnancy. Singapore, McGraw Hill, 1994.

[14] Parker J.D., Abrams B.: "Prenatal weight gain advice: An examination of the recent prenatal weight gain recommendations of the Institute of Medicine". *Obstet. Gynecol.*, 1992, *79*, 664.

[15] World HealthOrganization. Geographic variation in the incidence of hypertension in pregnancy. World Health Organization International Collaborative Study of Hypertensive Disorders in Pregnancy. *Am. J. Obstet. Gynecol.*, 1988, *158*, 80.

[16] The Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. The women and their pregnancies. Washington, DC: U.S. Department of Health, Education, and Welfare, 1972; DHEW publication no (NIH) 73.

[17] Samadi A., Mayberry R.M.: "Maternal hypertension and spontaneous preterm births among black women". *Obstet. Gynecol.*, 1998, *91*, 899.

[18] Geirsson R., Arngrimsson R., Apalset E. *et al.*: "Falling population incidence of eclampsia". *Acta Obstet. Gynecol. Scand.*, 1994, *73*, 465.

[19] Sibai B.M., Gordon T., Thom E. *et al.*: "Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study". *Am. J. Obstet. Gynecol.*, 1995, *172*, 642.

[20] Friedman S.A., Schiff E., Kao L., Sibai B.M.: "Neonatal outcome after preterm delivery for preeclampsia". *Am. J. Obstet. Gynecol.*, 1995, *172*, 1785.

[21] Fitzpatrick C., Connolly R., Stronge J.M.: "Epidemic pre-eclampsia?". *Lancet*, 1987, *2*, 6940.

[22] Copper R.L., Goldenberg R.L., DuBard M.B., Davis R.O.: "Risk factors for fetal death in white, black, and Hispanic women. Collaborative Group on Preterm Birth Prevention". *Obstet. Gynecol.*, 1994, *84*, 490.

[23] Ness R.B., Roberts J.M.: "Heterogenous causes constituting the single syndrome of preeclampsia: a hypothesis and its implications". *Am. J. Obstet. Gynecol.*, 1996, *175*, 1365.

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