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Obstetric prognosis in sisters of preeclamptic women – implications for genetic linkage studies

Nonna Heiskanen*¹, Seppo Heinonen¹ and Pertti Kirkinen²

Address: ¹Department of Obstetrics and Gynecology, Kuopio University Hospital and ²Department of Obstetrics and Gynecology, Tampere University Hospital

Email: Nonna Heiskanen* - nonna.heiskanen@kuh.fi; Seppo Heinonen - seppo.heinonen@kuh.fi; Pertti Kirkinen - pertti.kirkinen@pshp.fi
* Corresponding author

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Abstract

Background: To investigate obstetric prognosis in sisters of preeclamptic women.

Methods: We identified consecutive 635 sib pairs from the Birth Registry data of Kuopio University Hospital who had their first delivery between January 1989 and December 1999 in our institution. Of these, in 530 pairs both sisters had non-preeclamptic pregnancies (the reference group), in 63 pairs one of the sisters had preeclampsia and the unaffected sisters were studied (study group I). In 42 pairs both sister's first delivery was affected (study group II). Pregnancy outcome measures in these groups were compared.

Results: Unaffected sisters of the index patients had uncompromised fetal growth in their pregnancies, and overall, as good obstetric outcomes as in the reference group. The data on affected sisters of the index patients showed an increased prematurity rate, and increased incidences of low birth weight and small-for-gestational age infants, as expected.

Conclusion: Unaffected sisters of the index patients had no signs of utero-placental insufficiency and they were at low risk with regard to adverse obstetric outcome, whereas affected sisters were high-risk. Clinically, affected versus unaffected status appears to be clear-cut in first-degree relatives regardless of their genetic susceptibility and unaffected sisters do not need special antepartum surveillance.

Background

Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality [1] and the disease carries a tendency towards familial clustering [2–6]. Although the pattern of inheritance is not yet resolved, investigations into the genetic etiology of preeclampsia have yielded intriguing results implying that genes are responsible for the disease rather than shared environment [7]. Current concepts favor the hypothesis, that preeclampsia results from interplay of multiple genes and the environment, the disease being a polygenic trait with a strong maternal contribution [8]. First-degree relatives are known to have

a fivefold increased risk of developing the disease compared with women with no family history of preeclampsia. Women above a certain threshold of this trait manifest the disease, whereas those below the threshold have a normal phenotype [9]. As far as we are aware of, studies looking at the obstetric outcome in unaffected sisters are still lacking. This study was undertaken to evaluate pregnancy outcome in unaffected sisters of preeclamptic women, to find out whether their genetic susceptibility is associated with adverse outcome. Such data is useful not only for scientific but also for counselling purposes.

Table 1: Maternal Risk Factors

risk factor	reference group N = 530	unaffected sisters of preeclamptic index patients N = 63	affected sisters of preeclamptic index patients N = 42
Age < 18 years	14 (2.64%)	2 (3.17%)	1 (2.38%)
Age > 35 years	11 (2.08%)	0 P = 0.617a	0 P = 1.00a
Miscarriage	39 (7.34%)	4 (6.35%) P = 1.00a	5 (11.90%) P = 0.358a
Pregavid body mass index > 25	73 (13.73%)	4 (6.78%) P = 0.134	10 (22.5%) P = 0.129
Unemployed	74 (13.94 %)	7 (11.11 %) P = 0.537	2 (4.76 %) P = 0.092
Not married	244 (46.04%)	21 (33.33%) P = 0.055	14 (33.33%) P = 0.111
IUD before pregnancy	4 (0.75 %)	0 P = 1.00a	0 P = 1.00a
Infertility	27 (5.09 %)	2 (3.17 %) P = 0.758a	3 (7.14 %) P = 0.476a
Smoking (> 5 cigarettes/day)	49 (9.23 %)	2 (3.17 %) P = 0.105	1 (2.38 %) P = 0.162a
Alcohol consumption	17 (3.20 %)	0 P = 0.240a	1 (2.38 %) P = 1.00a
Maternal diabetes	7 (1.32 %)	1 (1.59 %) P = 0.594a	0 P = 1.00a
Chronic illness	25 (4.71 %)	3 (4.76 %) P = 1.00a	1 (2.38 %) P = 0.712a

^a Fisher's exact test

Methods

The study was approved by the Research-Ethics Committee of Kuopio University Hospital.

The total number of deliveries during the study period was 23 772, and of those, 9576 women were primiparous and 14 196 women were multiparous. The study material comprised consecutive 635 sib pairs, both of whom had their first delivery in the Department of Obstetrics and Gynecology, Kuopio University Hospital, between January 1989 and December 1999. The data for this study were prospectively collected, and the case records were retrospectively analyzed. In 530 pairs both sisters had normotensive pregnancy and one sister of each sib pair (the one who gave birth later) was included in the analysis to constitute the reference group. In 63 sib pairs, one of the sisters had preeclampsia in her first pregnancy and study group I was derived from the unaffected sisters. In 42 pairs, both sisters had preeclampsia and one sister of each sib pair was incorporated (the one who gave birth later) to form study group II. All pregnant women were monitored in an identical manner as outpatients until the development of preeclampsia or another pregnancy complication requiring hospitalization. Basic clinical data were collected at prenatal visits and at delivery for all the target population by the team that took care of treatment.

Hypertensive complications of pregnancy were classified as advocated by the U.S. National Institute of Health Working Group on Hypertension in Pregnancy [10]. Preeclampsia was defined as the development of hypertension and new-onset proteinuria (greater than 300 mg of urinary protein in 24 h) in women with no proteinuria at baseline. For those with a baseline diastolic pressure of

90 mmHg, hypertension was defined as a rise of at least 25 mmHg, measured on two consecutive occasions at least 24 h apart. For those with an initial diastolic pressure of 90 mmHg or above, an increment of at least 15 mmHg was required [11].

For data analysis, the following were used as evidence of fetal compromise: intrauterine death, admission to a neonatal intensive care unit, small-for-gestational-age delivery, low birth weight, prematurity, low Apgar scores at 1 and 5 min, and fetal acidosis at birth. Reference material values for the birth weight percentiles were obtained from own records [12].

Differences between study subjects and the reference group were tested for significance by using X² statistics or Fisher's exact tests, as appropriate. Student's t-test was used to analyze continuous variables. Differences were considered to be significant when P < 0.05.

Results

The mean maternal age in study group I (\pm SD) was 24.3 years (\pm 4.7 years) and it was 25.5 years (\pm 4.5 years) in the reference group (P = 0.04). In study group II, the mean maternal age was 24.3 years (\pm 3.4 years) (P = 0.04). Characteristics of women in study groups I and II, who gave birth at our hospital, during the 10-year period are compared against those of the reference group in Table 1. Apart from maternal age, the demographic data investigated in this study were comparable in the three groups.

Table 2. summarizes the frequencies of various pregnancy and delivery characteristics in the two study groups and in the control group. Preeclamptic women whose sisters also

Table 2: Pregnancy and Delivery Characteristics

	reference group	unaffected sisters of preeclamptic index patients	affected sisters of preeclamptic index patients
characteristics	N = 530	N = 63	N = 42
Pregnancy-induced hypertension	3 (0.57 %)	1 (1.59 %) P = 0.365 ^a	3 (7.14 %) P < 0.001 ^a
Placental abruption	2 (0.38 %)	0 P = 1.00 ^a	1 (2.38 %) P = 0.205 ^a
Placenta previa	4 (0.75 %)	2 (3.17 %) P = 0.126 ^a	0 P = 1.00 ^a
Prolonged gravidarum (>42 w)	39 (7.36 %)	6 (9.52 %) P = 0.612 ^a	1 (2.38 %) P = 0.346 ^a
Female fetus	261 (49.25 %)	30 (47.62 %) P = 0.807	23 (54.76 %) P = 0.491
Isoimmunization (Rh)	1 (0.19 %)	0 P = 1.00 ^a	0 P = 1.00 ^a
Low hemoglobin concentration (< 100 g/L)	7 (1.32 %)	0 P = 1.00 ^a	0 P = 1.00 ^a
Cesarean delivery	97 (18.30 %)	9 (14.29 %) P = 0.432	14 (33.33 %) P = 0.018
Forceps/vacuum	47 (8.87 %)	7 (11.11 %) P = 0.558	2 (4.76 %) P = 0.566 ^a
Bloody amniotic fluid	11 (2.07 %)	2 (3.17 %) P = 0.638 ^a	2 (4.76 %) P = 0.246 ^a
Meconium-stained amniotic fluid	73 (13.75 %)	9 (14.29 %) P = 0.907	4 (9.52 %) P = 0.440
Placental/fetal mass ratio (%)	16.6 %	16.2 % P = 0.51 ^b	17.8 % P = 0.46 ^b

^a Fisher's exact test, ^b Student's t-test

had preeclampsia in their first pregnancy underwent cesarean deliveries more often than the control women. However, the rate of vaginal operative deliveries did not differ between the groups. 1.59% of the women in study group I and 0.57% in the reference group had pregnancy-induced hypertension. Otherwise, the pregnancy characteristics were similar in these groups.

The mean birth weight (\pm SD) among those delivering at term (after 37 gestational weeks) was 3530 g (\pm 444 g) in the reference group, 3471 g (\pm 378 g) in study group I (P = 0.33) and 3398 g (\pm 494 g) in study group II (P = 0.12). Table 3. shows the pregnancy outcome measures in the reference and study groups. As expected, the incidence of prematurity (P < 0.001), low birth weight (P < 0.001) and small-for-gestational age infants (P = 0.06) was increased in sisters affected by preeclampsia (group II), whereas there was no difference in the rate of fetal death between the groups. Obstetric outcomes in study group I were comparable with those in the reference group.

Discussion

The main finding of this study was, that unaffected sisters of preeclamptic index patients had normal outcomes in their first pregnancy, the course of pregnancy being comparable to that in the general obstetric population. Basically, no differences were noted in the reproductive risk factors of the groups studied. Among affected sisters, the rate of prematurity, low birth weight, and small-for-gestational age infants were increased, as expected [13]. Although a trial of this size cannot reliably detect differences in rare complications, such as neonatal death ascribable to familial risk, the number of cases in the present study is sufficient to make statistically valid comparisons with re-

gard to commonly used outcome variables. However, it is not known whether similar changes are present in unaffected first-degree relatives during pregnancy because of their genetic susceptibility to preeclampsia which in turn would adversely affect their pregnancies. Any adverse effect was undetectable in the present study, since only one (1.59%) of the unaffected women with a first-degree relative with preeclampsia developed pregnancy-induced hypertension and there were no signs of chronic uteroplacental insufficiency.

Caruso et al. demonstrated in their study of pregnant women that preeclampsia, but not gestational hypertension, was characterized by atherogenic metabolic features similar to those of patients with insulin resistance syndrome, such as lower insulin sensitivity, and higher levels of triglycerides and nonesterified fatty acids [14]. Thus, the clinical definition seems appropriate, and in clinical work, preeclampsia phenotypes defined by other criteria such as glomerular endotheliosis are too difficult to assess routinely [15].

Preeclampsia is a heterogeneous disorder, and women with various medical problems are at risk of developing the disease [16–18]. Many of these conditions are known to be governed by some components which may have genetic origin, e.g. genetic risks associated with essential hypertension and diabetes mellitus, and mitochondrial abnormalities, which in turn, are characterized by microvascular disease [19–21]. Our results may be useful in counselling patients and their first-degree relatives. Genetic susceptibility to preeclampsia has minor effects, if any, on pregnancy outcome in first-degree relatives of index patients, if they do not develop the disease. Basically, rou-

Table 3: Obstetric Outcomes

outcome	reference group N = 530	unaffected sisters of preeclamptic index patients N = 63	affected sisters of preeclamptic index patients N = 42
Admission to a neonatal intensive care unit	34 (6.42 %)	3 (4.76 %) P = 0.786 ^a	9 (21.43 %) P = 0.002 ^a
Intrauterine fetal death	3 (0.57 %)	0 P = 1.00 ^a	0 P = 1.00 ^a
Prematurity (delivery before 37 weeks)	25 (4.72 %)	1 (1.59 %) P = 0.344 ^a	10 (23.80 %) P < 0.001
Low birth weight (<2500 g)	16 (3.02 %)	0 P = 0.398 ^a	12 (28.57 %) P < 0.001
Small for gestational age (< 10 th percentile)	61 (11.51 %)	8 (12.70 %) P = 0.781	9 (21.43 %) P = 0.059
Low Apgar score (<7 at 1 min)	31 (5.85 %)	4 (6.35 %) P = 0.780 ^a	5 (11.90 %) P = 0.173 ^a
Low Apgar score (<7 at 5 min)	7 (1.32 %)	0 P = 1.00 ^a	0 P = 1.00 ^a
Fetal venous pH <7.15 at birth	11 (2.1 %)	3 (4.76 %) P = 0.175 ^a	2 (4.76 %) P = 0.250 ^a

^a Fisher's exact test

tine antenatal care in which blood pressure and urine dipstick are checked each visit is sufficient for women with an affected sister and there is no need to initiate special fetal monitoring in these pregnancies. Accordingly, the results may have implications in genetic linkage studies [22], since the phenotype in unaffected sisters of preeclamptic women can be considered normal in terms of clinical outcome measures. In other words, this observation provides justification to stratify pregnant women into the categories of affected and unaffected individuals which is the current practice in clinical work [23].

Conclusions

The sisters of preeclamptic women are at low risk with regard to adverse pregnancy outcome if they do not develop preeclampsia. They have pregnancy outcomes comparable to that of the general obstetric population, and routine antenatal follow-up and management is sufficient in these cases. Although the etiology and pathogenesis are as yet unresolved, the complexity of the disease phenotype supports the theory of a polygenic trait. Women belonging to the liability group could have considerable pathological changes in their placental tissue without developing the maternal syndrome, and this might explain, why such changes are occasionally observed in fetal growth retardation, which has also been called normotensive preeclampsia [24]. However, in the present study genetic liability in unaffected first-degree relatives of preeclamptic index patients was not associated with any clinical phenotype

Competing interests

None declared.

Authors' contributions

NHE participated in the design of the study and performed the statistical analysis and drafted the manuscript.

SHE participated in the design of the study, drafted the manuscript and coordination.

PKI conceived of the study and participated in its design and coordination.

All authors has read and approved the final manuscript.

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