

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

Nonna Heiskanen, M.D., Ph.D

Seppo Heinonen, M.D., Ph.D.

Pertti Kirkinen, M.D., Ph.D.

Department of Obstetrics and Gynecology¹

Kuopio University Hospital

Kuopio

Finland

Correspondence to: Nonna Heiskanen, M.D., Ph.D.
 Department of Obstetrics and Gynecology
 Kuopio University Hospital
 70211 Kuopio
 Finland
 Fax: 358-17-172 486

E-mail: nonna.heiskanen@kuh.fi

Running foot: Preeclampsia in sibpairs

Abstract

Objective: 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 1990 and December 1999 in our institution. Of these, in 530 cases both sisters had non-preeclamptic deliveries (the reference group), in 63 cases one of the sisters had preeclampsia and the unaffected sisters were studied (study group I). In 42 cases 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 chronic 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. Basically, sisters of preeclamptic women should be screened for hypertension and proteinuria, but otherwise there is no need to initiate special antepartum surveillance.

Background

Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality¹ and the disease carries a tendency towards familial clustering.²⁻⁵ 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.⁶⁻⁸ 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. First-degree relatives are known to have a fivefold increased risk of developing the disease compared with women with no family history of preeclampsia.⁹ This trait may be described as liability to develop preeclampsia. Women above a certain threshold of this trait manifest the disease, whereas those below the threshold have a normal phenotype.¹⁰ In other words, affected women fall at the extreme right end of the liability distribution and fulfil the diagnostic criteria defined on the basis of arbitrary cutoffs along a continuous distribution of blood pressure values and proteinuria. Unaffected relatives have a distribution of genetic liability shifted to the left in relation to the proband but to the right of the general obstetric population. 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. This data is useful not only for scientific but also for counselling purposes.

Materials and methods

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

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 1990 and December 1999. The data for this study were prospectively collected, and the case records were retrospectively analyzed. In 530 cases 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 cases, 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.

Preeclampsia was defined as the development of hypertension and new-onset proteinuria (> 300 mg of urinary protein in 24 h) in women with no proteinuria at baseline. Hypertension was defined along the current guidelines that accept 140 and/or 90 mmHg of systolic and diastolic pressure respectively, or higher, as hypertension, when measured on two consecutive occasions at least 24 h apart. Women with chronic hypertension were excluded from the study.

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 (below the normal 10th percentile according to our own records), low birth weight (newborn weight less than 2500 g),

prematurity (delivery before 37 completed weeks), low Apgar scores at 1 and 5 min (< 7), and fetal acidosis (venous pH < 7.15) at birth.

Differences between study subjects and the reference group were tested for significance by using X^2 statistics or Fisher's exact test, 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 (± 4.7 years) and it was 25.5 years (± 4.5 years) in the reference group ($P=0.04$). In study group II, the mean maternal age was 24.3 years (± 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 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. It is also noteworthy that only 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 (± 444 g) in the reference group, 3471 g (± 378 g) in study group I ($P=0.33$) and 3398 g (± 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 recorded in the reproductive risk factors of the groups studied. Among affected sisters, the prematurity rate and incidence of low birth weight and small-for-gestational age infants were increased, as expected. Although a trial of this size cannot be relied upon to detect differences in rare complications such as neonatal death ascribable to familial risk, the number of cases in the present study is high enough to make statistically valid comparisons with regard to commonly used outcome variables. Clinically, affected versus unaffected status appears to be clear-cut in first-degree relatives regardless of their genetic susceptibility to preeclampsia, although in affected pregnancies atherotic changes have been shown to be present in the placental bed early in the first trimester, before clinical onset of the disease.¹¹ In the current study, only one (1.59%) of the unaffected women with a first-degree relative affected by preeclampsia developed pregnancy-induced hypertension. Accordingly, Caruso et al. demonstrated in their study of pregnant women with gestational hypertension and preeclampsia that only the former were characterized by 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.¹² On the other hand, preeclampsia phenotypes defined by other criteria such as glomerular endotheliosis are difficult to assess in routine clinical work.¹³

Preeclampsia is a heterogeneous disorder and women with various underlying medical conditions are at risk of developing the disease.^{14,15} Many of these conditions are known to be governed by some genetic components, e.g. essential hypertension and diabetes mellitus, and mitochondrial abnormalities, which in turn, are characterized by microvascular disease.^{16,17} Nevertheless, in this study the contribution of chronic illness or diabetes was of little importance in the overall predisposition to preeclampsia or its occurrence in first-degree relatives.

The current data 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, routine prenatal 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,¹⁸ 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 further justification to stratify pregnant women into the categories of affected and unaffected individuals. Another point is that genetic linkage studies are otherwise enigmatic in a disease which is expressed only in one sex and only during pregnancy.

In summary, 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.¹⁹ However, in the present study genetic liability in unaffected first-degree relatives of preeclamptic index patients was not associated with any clinical phenotype.

Conclusion

Unaffected sisters of the index patients had no signs of chronic 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. Basically, sisters of preeclamptic women should be screened for hypertension and proteinuria, but otherwise there is no need to initiate special antepartum surveillance.

References

1. Kaunitz A, Hughes J, Grimes D, Smith J, Rochat R, Kafriksen M: **Causes of maternal mortality in the United States.** *Obstet Gynecol* 1985, **65(5)**: 605-612.
2. Chesley L, Cosgrave R, Annitto L: **Pregnancy in sisters and daughters of eclamptic women.** *Path Microbiol* 1961, **23**:662- 666.
3. Chesley L, Annitto L, Cosgrave R: **The familial factor in toxemia of pregnancy.** *Obstet Gynecol* 1968, **32**: 303-311.
4. Cooper D, Liston W: **Genetic control of severe pre-eclampsia.** *J Med Genet* 1979, **16**: 409-416.
5. Chesley L, Cooper D: **Genetics of hypertension in pregnancy: Possibly single gene control of preeclampsia and eclampsia in decendants of eclamptic women.** *Br J Obstet Gynaecol* 1986, **93**: 898-908.

6. Lachmeijer A, Crusius J, Pals G, Dekker G, Arngrimsson T, ten Kate L: **Polymorphisms in the tumor necrosis factor and lymphotoxin alpha gene region and preeclampsia.** *Obstet Gynecol* 2001, **98(4)**: 612-619.
7. Lachmeijer A, Nosti-Escanilla M, Bastiaans E, Pals G, Sandkuij L, Kostense P, Aarnoudse J, Crusius J, Dekker G, Arbgrimsson R ten Kate L: **Linkage and association studies of IL1B and IL1RN gene polymorphisms in preeclampsia.** *Hypertens Pregnancy* 2002, **21(1)**: 23-38.
8. Francoual J, Audibert F, Trioche P, Chalas J, Capel L, Lindenbaum A, Labrune P, Frydman R: **Is a polymorphism of the apolipoprotein E gene associated with preeclampsia ?** *Hypertens Pregnancy* 2002, **21(2)**: 127-133.
9. Arngrimsson R, Björnsson H, Geirsson R: **Analysis of different inheritance patterns in preeclampsia/eclampsia syndrome.** *Hypertens Pregnancy* 1995, **14**: 27-38.
10. Falconer DS: **The inheritance of liability to certain diseases, estimated from the incidence among relatives.** *Ann Hum Genet* 1965, **2**: 51-76.
11. Nadji P, Sommers S: **Lesions of toxemia in first trimester pregnancies.** *Am J Clin Pathol* 1973, **59**: 344-349.
12. Caruso A, Ferrazzani S, De Carolis S, Lucchese A, Lanzone A, De Santis L, et al: **Gestational hypertension but not preeclampsia is associated with insulin resistance syndrome characteristics.** *Hum Reprod* 1999, **14(1)**: 219-223.
13. Fisher KA, Luger A, Spargo BH, Lindheimer MD: **Hypertension in pregnancy: clinical-pathological correlations and remote prognosis.** *Medicine* 1981, **60(4)**: 267-76.
14. Taylor DJ: **The epidemiology of hypertension during pregnancy:** Rubin PC, eds. *Handbook of Hypertension. V 10. Hypertension in Pregnancy.* Amsterdam: Elsevier, 1988, 223-240.
15. Thorbergesen T, Öian P, Mathiesen E, Borud O: **Pre-eclampsia, a mitochondrial disease?** *Acta Obstet Gynecol Scand* 1990, **68**:45 -48.

16. Roberts JM, Redman CWG: **Pre-eclampsia: more than pregnancy-induced hypertension.** *Lancet* 1993, **341**: 1447-1451.
17. Arngrimsson R, Hólmgeir B, Geirsson RT: **Analysis of different inheritance patterns in preeclampsia/eclampsia syndrome.** *Hypertens Pregnancy* 1995, **14(1)**: 27-38.
18. Arngrimsson R, Sigurardottir S, Frigge ML, Bjarnadottir RI, Jonsson T, Stefansson H, et al: **A genome wide scan reveals a maternal susceptibility locus for pre-eclampsia on chromosome 2p13.** *Hum Mol Genet* 1999, **8**: 1799-805.
19. Brosens I, Dixon HG, Robertson WB: **Fetal growth retardation and the arteries of the placental bed.** *Br J Obstet Gynaecol* 1977, **84**: 656-63.

TABLE 1. Maternal Risk Factors

RISK FACTOR	REFERENCE GROUP N=530	UNAFFECTED SISTERS OF PREECLAMPTIC INDEX CASES N=63	AFFECTED SISTERS OF PREECLAMPTIC INDEX CASES N=42
Age < 18 years	14/2.64 %	2/3.17 % P=0.683 ^a	1/2.38 % P=1.00 ^a
Age > 35 years	11/2.08 %	0 P=0.617 ^a	0 P=1.00 ^a
Miscarriage	39/7.34 %	4/6.35 % P=1.00 ^a	5/11.90 % P=0.358 ^a
Pregravid 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=1.00 ^a	0 P=1.00 ^a
Infertility	27/5.09 %	2/3.17 % P=0.758 ^a	3/7.14 % P=0.476 ^a
Smoking (>5 cigarettes/day)	49/9.23 %	2/3.17 % P=0.105	1/2.38 % P=0.162 ^a
Alcohol consumption	17/3.20 %	0 P=0.240 ^a	1/ 2.38 % P=1.00 ^a
Maternal diabetes	7/1.32 %	1/1.59 % P=0.594 ^a	0 P=1.00 ^a
Chronic illness	25/4.71 %	3/4.76 % P=1.00 ^a	1/2.38 % P=0.712 ^a

^a Fisher's exact test

TABLE 2. Pregnancy and Delivery Characteristics

CHARACTERISTICS	REFERENCE GROUP N=530	UNAFFECTED SISTERS OF PREECLAMPTIC INDEX CASES N=63	AFFECTED SISTERS OF PREECLAMPTIC INDEX CASES N=42
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
Meconium-stained amniotic fluid	73/13.75 %	9/14.29 % P=0.907	4/9.52 % P=0.440
Bloody amniotic fluid	11/2.07 %	2/3.17 % P=0.638 ^a	2/4.76 % P=0.246 ^a
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

TABLE 3. Obstetric Outcomes

OUTCOME	REFERENCE GROUP N=530	UNAFFECTED SISTERS OF PREECLAMPTIC INDEX CASES N=63	AFFECTED SISTERS OF PREECLAMPTIC INDEX CASES 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

^aFisher's exact test

