

Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort

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Abstract

Objectives To assess the impact on risk of pre-eclampsia of genes that work through the mother, and genes of paternal origin that work through the fetus.

Design Population based cohort study.

Setting Registry data from Norway.

Participants Linked generational data from the medical birth registry of Norway (1967-2003): 438 597 mother-offspring units and 286 945 father-offspring units.

Main outcome measures Pre-eclampsia in the second generation.

Results The daughters of women who had pre-eclampsia during pregnancy had more than twice the risk of pre-eclampsia themselves (odds ratio 2.2, 95% confidence interval 2.0 to 2.4) compared with other women. Men born after a pregnancy complicated by pre-eclampsia had a moderately increased risk of fathering a pre-eclamptic pregnancy (1.5, 1.3 to 1.7). Sisters of affected men or women, who were themselves born after pregnancies not complicated by pre-eclampsia, also had an increased risk (2.0, 1.7 to 2.3). Women and men born after pre-eclamptic pregnancies were more likely to trigger severe pre-eclampsia in their own pregnancy (3.0, 2.4 to 3.7, for mothers and 1.9, 1.4 to 2.5, for fathers).

Conclusion Maternal genes and fetal genes from either the mother or father may trigger pre-eclampsia. The maternal association is stronger than the fetal association. The familial association predicts more severe pre-eclampsia.

Introduction

The heritable aspects of pre-eclampsia, which occurs in 3-5% of pregnancies, are complex.¹ The first pattern to be identified was the tendency for the risk of pre-eclampsia to be passed from mother to daughter.² This risk could reflect at least two genetic pathways: transmission to the daughter of genes that enhance maternal susceptibility to pre-eclampsia, or transmission from the daughter to her fetus of fetal genes that are capable of triggering pre-eclampsia.

Recent studies have shown an increased risk of pre-eclampsia could also be transmitted through the father.^{3,4} These findings support the hypothesis that the father's genes can be passed to the fetus and increase the risk of pre-eclampsia.

We explored these two pathways of genetic transmission of risk of pre-eclampsia using linked birth data between family members as recorded in the medical birth registry of Norway.

Methods

Population based generational data

We used data from the medical birth registry of Norway, a population based registry of all births in Norway since 1967. Up to 2003, 238 617 women born in Norway in 1967 or later had given birth to 438 597 singleton infants. Similarly, 158 340 men born in 1967 or later had fathered 286 945 singleton infants. The number of mothers is higher because mothers are generally younger than fathers and 4.4% of fathers were unknown.

We used these data to study whether women and men who themselves were born after a pregnancy complicated by pre-eclampsia have a higher risk of parenting a pre-eclamptic pregnancy, compared with those who had no family history of pre-eclampsia. We estimated risk related to their first pregnancy or to the second pregnancy if pre-eclampsia had not occurred in the first pregnancy.

We also assessed the risk of pre-eclampsia in any siblings born after an unaffected pregnancy, to study whether they could pass on an increased risk to the next generation (see bmj.com).

Definition of pre-eclampsia

We included pregnancies with a specified diagnosis of pre-eclampsia, and pregnancies with a combination of pregnancy induced hypertension and proteinuria (see bmj.com for definitions). We divided pre-eclampsia as either term (37-42 weeks) or preterm (before 37 weeks) and, since 1999, by clinical severity: mild or severe, and according to whether clinical signs were evident early (<34 weeks) in pregnancy.

Statistical analysis

For women born after a pre-eclamptic pregnancy, we estimated their own risk of pre-eclampsia in subsequent pregnancies compared with the risk in women who were not born after a pregnancy complicated by pre-eclampsia. We compared the risk of fathering a pre-eclamptic pregnancy in men who were born after a pre-eclamptic pregnancy and men who were not. For sisters and brothers who were born after another pregnancy without pre-eclampsia, we also estimated the risk of pre-eclampsia compared with the risk in women and men with no family history.

We used logistic regression and multinomial logistic regression analysis to estimate odds ratios.

Results

Pre-eclampsia related to first and second birth

Women born after a pre-eclamptic pregnancy had more than twice the risk of having pre-eclampsia in

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Table 1 Risk of pregnancy* affected by pre-eclampsia in women and men† who themselves were born after a pregnancy complicated by pre-eclampsia, Norway, 1967-2003

	Birth order	No of offspring	No (%) of affected pregnancies	Odds ratio (95% CI)‡
Women				
Maternal pre-eclampsia:				
Yes	First	2 768	299 (10.8)	2.2 (1.9 to 2.5)
No	First	91 338	4794 (5.2)	1.0§
Yes	Subsequent	1 977	200 (10.1)	2.1 (1.8 to 2.4)
No	Subsequent	142 288	7261 (5.1)	1.0§
Men				
Maternal pre-eclampsia:				
Yes	First	1 908	146 (7.7)	1.4 (1.2 to 1.7)
No	First	60 137	3274 (5.4)	1.0§
Yes	Subsequent	1 270	101 (8.0)	1.5 (1.2 to 1.8)
No	Subsequent	94 917	5154 (5.4)	1.0§

*Confined to first pregnancies of women and men.

†For men this is No (%) in their partners.

‡Pooled odds ratios (Mantel-Haenszel): 2.2 (2.0 to 2.4) for women and 1.5 (1.3 to 1.7) for men.

§Reference category.

their first pregnancy compared with other women (table). For men born after a pre-eclamptic pregnancy the risk of pre-eclampsia in the first pregnancy of their partner was moderately increased compared with men who were born after a pregnancy not complicated by pre-eclampsia (table 1). For both men and women these associations were remarkably stable, regardless of their own birth order.

Women who themselves were born after a pre-eclamptic pregnancy still had more than twice the risk (2.3, 1.8 to 2.9) of pre-eclampsia related to their second birth, when their first pregnancy was not affected, compared with other women (data not shown). The results were similar for men (1.5, 1.1 to 2.1).

Pre-eclampsia in brothers and sisters

Sisters who were not themselves born after a pregnancy complicated by pre-eclampsia were none the less at increased risk of pre-eclampsia compared with women with no family history of pre-eclampsia (2.0, 1.7 to 2.3, table 2). For brothers not themselves born after a pre-eclamptic pregnancy, the risk of fathering a pre-eclamptic pregnancy was similar to that in men with no family history (1.1, 0.9 to 1.4). Again, birth order did not influence these results. The figure illustrates the results shown in tables 1 and 2.

Clinical severity of pre-eclampsia

In the subgroup of women who had given birth since 1999, those who had clinically severe or early onset pre-eclampsia were much more likely to have been born after a pre-eclamptic pregnancy themselves compared with women born after an unaffected pregnancy (3.0, 2.4 to 3.7). Men who had fathered a pregnancy with severe or early pre-eclampsia were also more likely to have been born after a pre-eclamptic pregnancy themselves compared with men who had not fathered an affected pregnancy (1.9, 1.4 to 2.5).

Discussion

Men born after a pre-eclamptic pregnancy are apparently more likely to carry fetal alleles capable of triggering pre-eclampsia. These men then pass the

fetal risk alleles to their offspring, increasing their partner's risk of pre-eclampsia. The same presumably occurs for women born after pre-eclamptic pregnancies who can then pass susceptibility alleles to their own fetuses. In addition, women born after pre-eclamptic pregnancies may inherit from their mother genes that confer maternal susceptibility to pre-eclampsia. This maternal susceptibility can pass from mother to daughter but not from mother to son.

The purest expression of maternal genes would be among women not themselves born after a pre-eclamptic pregnancy but whose mothers had had pre-eclampsia in another pregnancy. Such women have twice the risk of pre-eclampsia in their own pregnancies compared with other women. The purest expression of fetal genes predisposing to pre-eclampsia would be among the offspring of men who had themselves triggered pre-eclampsia as fetuses. Such men have a 50% increased risk of fathering a pre-eclamptic pregnancy. Women who were born after a pre-eclamptic pregnancy potentially carry both types of genetic predisposition—maternal and fetal—and seem to be at highest risk (see figure).

Comparisons with other studies

Evidence for maternal predisposition to pre-eclampsia has been reported before.⁵⁻⁷ A population based case-control study from Utah, US, showed that women born after a pregnancy complicated by pre-eclampsia were more likely themselves to have pre-eclampsia.⁴

Another population based study in Norway, and the Utah study, both support the hypothesis that the father's genes contribute to the risk of pre-eclampsia.^{3 4}

Strengths and weaknesses

Among women and men who had a family history of pre-eclampsia, some were first born and others were born second or later. The familial association with pre-eclampsia was independent of birth order, strengthening the evidence of an association.

Table 2 Risk of pregnancy* affected by pre-eclampsia in sisters and brothers† who were born after a pregnancy not complicated by pre-eclampsia, Norway, 1967-2003

	No of siblings	No (%) with pre-eclampsia	Odds ratio (95% CI)‡
Younger sisters			
Mother had pre-eclampsia in first pregnancy:			
Yes	1 146	117 (10.2)	2.1 (1.7 to 2.5)
No	63 736	3327 (5.2)	1.0§
Younger brothers			
Mother had pre-eclampsia in first pregnancy:			
Yes	728	48 (6.6)	1.2 (0.9 to 1.5)
No	38 754	2251 (5.8)	1.0§
Older sisters			
Mother had pre-eclampsia in second pregnancy:			
Yes	580	54 (9.3)	1.9 (1.4 to 2.5)
No	59 205	3116 (5.3)	1.0§
Older brothers			
Mother had pre-eclampsia in second pregnancy:			
Yes	396	23 (5.8)	1.0 (0.7 to 1.6)
No	43 285	2461 (5.7)	1.0§

*Confined to first pregnancies of both siblings in first generation. Excludes families with recurrent pre-eclampsia in first generation.

†For brothers, this is No (%) in their partners.

‡Pooled odds ratios (Mantel-Haenszel): 2.0 (1.7 to 2.3) for sisters and 1.1 (0.9 to 1.4) for brothers.

§Reference category.

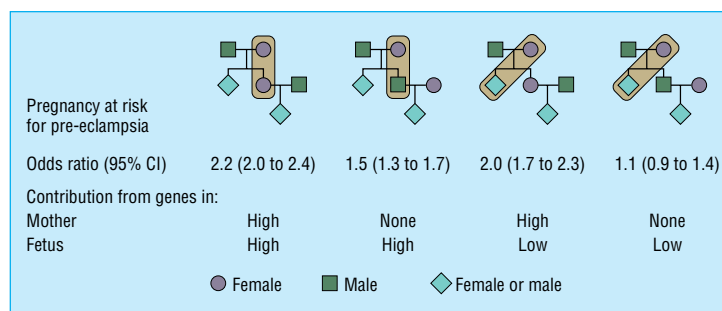
The large study size and the standardised collection of data provide high precision in the estimates of effect. The cohort design, comprising a whole population, reduces the possibility of selection bias. We cannot exclude potential confounding by other risk factors, for example obesity. In Norway, however, obesity of the degree that increases the risk of pre-eclampsia was relatively uncommon over the time of the study. Obesity may be limited to the relatively mild type of pre-eclampsia with term delivery, but we found a stronger familial association for clinically severe than for mild pre-eclampsia.

Confounding by one of a number of other factors, such as interval between births, change of partner between births, chronic hypertension, and smoking in pregnancy cannot be excluded. Supplementary analysis of potentially confounding factors in the subgroup of women who had given birth since 1999, on whom we had more detailed information, did not substantially influence the results.

Maternal or fetal genes

It seems reasonable to attribute the observed patterns of familial predisposition to genetic inheritance. Daughters born after a pre-eclamptic pregnancy may carry their mothers' susceptibility genes, as well as genes from either parent that operate through the fetus.³⁻⁴ Their sisters who were born after pregnancies not complicated by pre-eclampsia would be at lower risk as they are less likely to be carrying the genes that operate through the fetus. Still they are just as likely to be carrying their mothers' susceptibility genes. Thus, sisters of affected men and women have about twice the risk of women with no family history of pre-eclampsia.

For men who were born after an affected pregnancy, an increased risk of fathering a pre-eclamptic pregnancy can be attributed solely to paternal factors. Brothers who were born after a pregnancy without pre-eclampsia



Risk of parenting a pregnancy with pre-eclampsia

would have a low probability of carrying fetal risk genes, which is confirmed by the near baseline risk of pre-eclampsia among pregnancies they father.

Mild or severe pre-eclampsia

Recent studies have supported the hypothesis that pre-eclampsia comprises several pathogenetic entities with varying degrees of severity. The familial association is stronger for preterm than for term pre-eclampsia. When we confined analysis to preterm pre-eclampsia in the first generation, the odds ratios were 2.6 (2.0 to 3.4) and 1.7 (1.2 to 2.5) for women and men, respectively. For preterm pre-eclampsia in the second generation the odds ratios were 2.8 (2.3 to 3.3) and 1.7 (1.3 to 2.2). This may suggest that genetic susceptibility to pre-eclampsia, either through maternal or paternal genes, is more likely to cause clinically severe disease.⁸

Conclusions

Both maternal and paternal factors contribute to the risk of pre-eclampsia. The risk through affected mothers is higher, presumably because these mothers carry susceptibility genes and also transmit independent genetic risk factors to their fetus. The risk through affected fathers is lower because fathers transmit only fetal risk factors. Also, the differences that we observed between sisters and brothers suggest that genes that determine maternal susceptibility to pre-eclampsia differ from the paternal genes that may trigger pre-eclampsia through the fetus. Finally, familial associations are stronger for the clinically more severe types of pre-eclampsia.

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What is already known on this topic

Maternal susceptibility to pre-eclampsia can be passed from mother to daughter

Less is known about fetal propensity to trigger pre-eclampsia and the transmission of such propensity through the father or mother

What this study adds

Men and women who were born after pre-eclamptic pregnancies contribute to increased risk of pre-eclampsia in the next generation

The risk through affected mothers is higher, presumably because these mothers carry susceptibility genes and also transmit independent genetic risk factors to their fetus

Risk through affected fathers is lower, presumably because fathers transmit only fetal risk factors

Other familial patterns are consistent with independent genetic risk in the mother and the fetus, and the associations seem to be stronger for the clinically more severe types of pre-eclampsia