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## PATERNAL AND MATERNAL COMPONENTS OF THE PREDISPOSITION TO PREECLAMPSIA

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### ABSTRACT

**Background** There is an inherited maternal predisposition to preeclampsia. Whether there is a paternal component, however, is not known.

**Methods** We used records of the Utah Population Database to identify 298 men and 237 women born in Utah between 1947 and 1957 whose mothers had had preeclampsia during their pregnancy. For each man and woman in the study group, we identified two matched, unrelated control subjects who were not the products of pregnancies complicated by preeclampsia. We then identified 947 children of the 298 male study subjects and 830 children of the 237 female study subjects who had been born between 1970 and 1992. These children were matched to offspring of the control subjects (1973 offspring of the male control group and 1658 offspring of the female control group). Factors associated with preeclampsia were identified, and odds ratios were calculated with the use of stepwise logistic-regression analysis.

**Results** In the group of men whose mothers had had preeclampsia (the male study group), 2.7 percent of the offspring (26 of 947) were born of pregnancies complicated by preeclampsia, as compared with 1.3 percent of the offspring (26 of 1973) in the male control group. In the female study group, 4.7 percent of the pregnancies (39 of 830) were complicated by preeclampsia, as compared with 1.9 percent (32 of 1658) in the female control group. After adjustment for the offspring's year of birth, maternal parity, and the offspring's gestational age at delivery, the odds ratio for an adult whose mother had had preeclampsia having a child who was the product of a pregnancy complicated by preeclampsia was 2.1 (95 percent confidence interval, 1.0 to 4.3;  $P=0.04$ ) in the male study group and 3.3 (95 percent confidence interval, 1.5 to 7.5;  $P=0.004$ ) in the female study group.

**Conclusions** Both men and women who were the product of a pregnancy complicated by preeclampsia were significantly more likely than control men and women to have a child who was the product of a pregnancy complicated by preeclampsia. (N Engl J Med 2001;344:867-72.)

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**A**N abnormal maternal–fetal interaction has been implicated as a cause of preeclampsia.<sup>1</sup> A familial predisposition to preeclampsia has been documented, confirming that genetic factors contribute to its development.<sup>2</sup> However, research to date has focused principally on the maternal genetic contributions, and little is known about the fetal or paternal contributions to this disease.

A maternal predisposition to preeclampsia has been described in studies in Australia, Iceland, and Sweden.<sup>2-4</sup> Possible explanations for this predisposition include genetically based hypersensitivity to vasoactive peptides, thrombophilia, or conditions that affect placental invasion of the uterus at the time of implantation.

The fetal genotype is a combination of maternal and paternal components. Therefore, the contribution of paternal genes to the fetus may be important in the pathophysiology of preeclampsia, and paternal genes may have a key role in placentation.<sup>5</sup> Incomplete invasion of the trophoblast or other abnormalities of placentation may be paternally derived characteristics. In fetal mice, a single renin gene inherited from the father may increase the risk of maternal hypertension during pregnancy.<sup>6</sup> Finally, the fact that preeclampsia occurs more often in a first pregnancy or after a change in partners suggests that there is an interaction between maternal antibodies and paternally derived fetal antigens.<sup>1</sup>

The single-gene model of inheritance that best explains the frequency of preeclampsia in a low-risk population (3 to 6 percent) is the presence of homozygosity for the same recessive gene in both the mother and the fetus.<sup>7</sup> In accordance with this model, the fetus must have one recessive paternally derived allele for

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preeclampsia to develop. Persons who were the product of a pregnancy complicated by preeclampsia would thus be homozygous for the recessive allele and in all cases would pass this allele to their offspring, thereby increasing the risk that their offspring would have a pregnancy complicated by preeclampsia. To test this hypothesis, we designed a study to determine whether the offspring of men and women who themselves were the product of pregnancies involving preeclampsia were more likely to be the product of pregnancies that were complicated by preeclampsia.

## METHODS

The Utah Population Database is a research resource that has been used to demonstrate familial predispositions to other complications of pregnancy, including preterm delivery, cesarean section, and forceps delivery.<sup>8,9</sup> This data base contains computerized genealogic records linking Utah residents and their descendants. The genealogic records are linked to other data sets, including birth and death certificates, cancer records, census records, and Health Care Financing Administration data, allowing comparison of medical conditions among several generations. The protocol for the study and the use of the data base were approved by the institutional review board at the University of Utah.

The study population consisted of two groups of subjects, all of whom had been born in Utah between 1947 and 1957 (the earliest available complete data set). The first study group consisted of men who had been born of pregnancies complicated by preeclampsia, and the second study group consisted of women who had been born of pregnancies complicated by preeclampsia. A single investigator reviewed the birth-certificate records to confirm the recorded diagnosis of preeclampsia. These subjects were then linked to the birth certificates of offspring who had been born to the subjects between 1970 and 1992. Each study subject was randomly matched to two control subjects according to sex, county of birth in Utah, maternal age, year of birth, and birth order. The controls were men and women who had been born between 1947 and 1957 of pregnancies not complicated by preeclampsia and who subsequently had at least one offspring born in Utah between 1970 and 1992. None of the sets of control subjects were siblings of either the study case subject or each other. Subjects were eligible for the study only if their mothers had not had a preexisting medical condition (e.g., hypertension, diabetes, or renal disease) during pregnancy or a complication of pregnancy associated with preeclampsia (e.g., multiple gestation, gestational diabetes mellitus, or chronic hypertension) or if they had at least one offspring within the data base.

For each study and control subject, we identified the outcomes of all pregnancies producing offspring using three different methods, depending on the year of birth. For births before 1978, pregnancies complicated by preeclampsia were identified from the section of the birth certificate covering complications of pregnancy. For births from 1978 through 1988, all medical complications listed on birth certificates in Utah were converted to the codes of the *International Classification of Diseases, 9th Revision*, by the Department of Health, and this data set was used to identify pregnancies complicated by preeclampsia. Since 1989, all birth certificates in Utah have contained a physician questionnaire regarding complications of pregnancy for each delivery, and the answers on this questionnaire were used to identify pregnancies complicated by preeclampsia.

The characteristics of the index pregnancies among the women or among the partners of the men in the study group and the control group were compared with the use of Student's t-test. We calculated an adjusted odds ratio for the development of preeclampsia during each of these pregnancies for the male and female cohorts using backward stepwise logistic-regression analysis involving an evaluation of 15 possible confounding variables: fetal sex, year of

birth, maternal age, paternal age, area of residence (urban or rural), maternal race, paternal race, maternal parity, number of previous live births, number of previous stillbirths, mother's level of education, father's level of education, marital status, gestational age at birth, and birth order. After eliminating covariates, we constructed a model to adjust for the statistically significant variables. The final model included the variables of paternal or maternal history of being the product of a pregnancy involving preeclampsia, the offspring's gestational age at birth, maternal parity, area of residence, father's level of education, and the offspring's year of birth. All statistical analyses were performed with Stata software (Stata, College Station, Tex.), with standard deviations adjusted to account for fathers or mothers who may have produced more than one offspring included in the study.

## RESULTS

From 1947 through 1957, a total of 210,313 live births in Utah were recorded in the Utah Population Database. During this period, 1900 women had pregnancies complicated by preeclampsia; 1011 of these women delivered male infants, and 889 delivered female infants. Two hundred ninety-eight of the males and 237 of the females subsequently had at least one offspring born in Utah between 1970 and 1992. A total of 947 offspring of the male study group and 830 offspring of the female study group met the criteria for inclusion.

We identified in the data base 596 control men and 474 control women born between 1947 and 1957 who were subsequently linked to their offspring (1973 in the male control group and 1658 in the female control group). The characteristics of the offspring of the male study group and the male control group are shown in Table 1, and those of the offspring of the female study group and the female control group are shown in Table 2.

In the male study group, 26 of the 947 offspring (2.7 percent) were born of pregnancies complicated by preeclampsia, as compared with 26 of the 1973 offspring (1.3 percent) of the male control group. In the female study group, 39 of the 830 offspring (4.7 percent) were born of pregnancies complicated by preeclampsia, as compared with 32 of the 1658 offspring (1.9 percent) of the female control group (Fig. 1).

Among the offspring of the male study group, the frequency of maternal preeclampsia increased with each calendar year of birth (odds ratio, 1.1; 95 percent confidence interval, 1.0 to 1.2;  $P=0.03$ ) (Fig. 2). Preeclampsia was also associated with an increased risk of a lower gestational age at delivery (odds ratio for each decrease of one week, 0.8; 95 percent confidence interval, 0.8 to 0.9;  $P=0.001$ ). Maternal nulliparity (women having their first pregnancy resulting in a live birth), which is perhaps the most widely accepted risk factor for preeclampsia, was associated with a considerably increased risk of preeclampsia (odds ratio, 3.3; 95 percent confidence interval, 1.5 to 7.4;  $P=0.003$ ). Among the offspring of the male study group, having a father who was the product of a pregnancy complicated by preeclampsia was associated with an increased

**TABLE 1.** CHARACTERISTICS OF THE MOTHERS OF THE OFFSPRING OF THE MALE STUDY GROUP AND THE MALE CONTROL GROUP AND OF THE OFFSPRING THEMSELVES AT BIRTH.\*

CHARACTERISTIC	MALE STUDY GROUP (N=947)	MALE CONTROL GROUP (N=1973)	P VALUE
<b>Mothers</b>			
Age at birth of offspring (yr)	26±5	27±5	0.01
Parity	2.1±1.8	2.2±2.0	0.06
<b>Offspring</b>			
Gestational age at delivery (wk)	39.4±2.2	39.4±2.2	0.78
Birth weight (g)	3399±552	3422±544	0.27
Sex			0.84
Male	495	1040	
Female	452	933	
Birthplace			0.02
Urban	735	1603	
Rural	212	370	
Maternal race†			1.00
White	646	1408	
Other	9	21	
Paternal race†			0.46
White	649	1411	
Other	4	14	

\*Plus-minus values are means ±SD.

†Race was reported on the birth certificate as white or other by the parents; information on race was not available for all the subjects.

risk of being the product of a pregnancy complicated by preeclampsia (odds ratio, 2.1; 95 percent confidence interval, 1.0 to 4.3; P=0.04).

In the female study group, women who were the product of a pregnancy complicated by preeclampsia were three times as likely to have preeclampsia as women in the control group (odds ratio, 3.3; 95 percent confidence interval, 1.5 to 7.5; P=0.004) (Fig. 3). Nulliparity was also associated with a significantly increased risk of preeclampsia (odds ratio, 6.2; 95 percent confidence interval, 2.6 to 15.0; P=0.001) (Fig. 3).

To control for the possible effect of a maternal history of preeclampsia as a confounding variable, we identified the female partners of the men in the study group whose pregnancies were complicated by preeclampsia to determine the number who themselves had been born of a pregnancy complicated by preeclampsia. Information was available only for the women who were born in Utah. A total of 52 female partners of the men in the study group and the control group had pregnancies complicated by preeclampsia. Birth-certificate records were available for 41 (18 in the study group and 23 in the control group). None of these women were themselves the product of a pregnancy complicated by preeclampsia, making it unlikely that maternal history confounded our findings.

### DISCUSSION

We found that men and women who were the product of a pregnancy complicated by preeclampsia were

**TABLE 2.** CHARACTERISTICS OF THE WOMEN IN THE FEMALE STUDY GROUP AND IN THE FEMALE CONTROL GROUP AND OF THEIR OFFSPRING AT BIRTH.\*

CHARACTERISTIC	FEMALE STUDY GROUP (N=830)	FEMALE CONTROL GROUP (N=1658)	P VALUE
<b>Women</b>			
Age at birth of offspring (yr)	28±5	28±5	0.60
Parity	2.3±0.07	2.5±0.05	0.10
<b>Offspring</b>			
Gestational age at delivery (wk)	39.5±2.1	39.4±2.3	0.10
Birth weight (g)	3444±535	3445±536	0.96
Sex			0.84
Male	429	845	
Female	401	813	
Birthplace			0.40
Urban	617	1259	
Rural	213	399	
Maternal race†			0.20
White	525	1050	
Other	11	13	
Paternal race†			0.003
White	524	1022	
Other	2	25	

\*Plus-minus values are means ±SD.

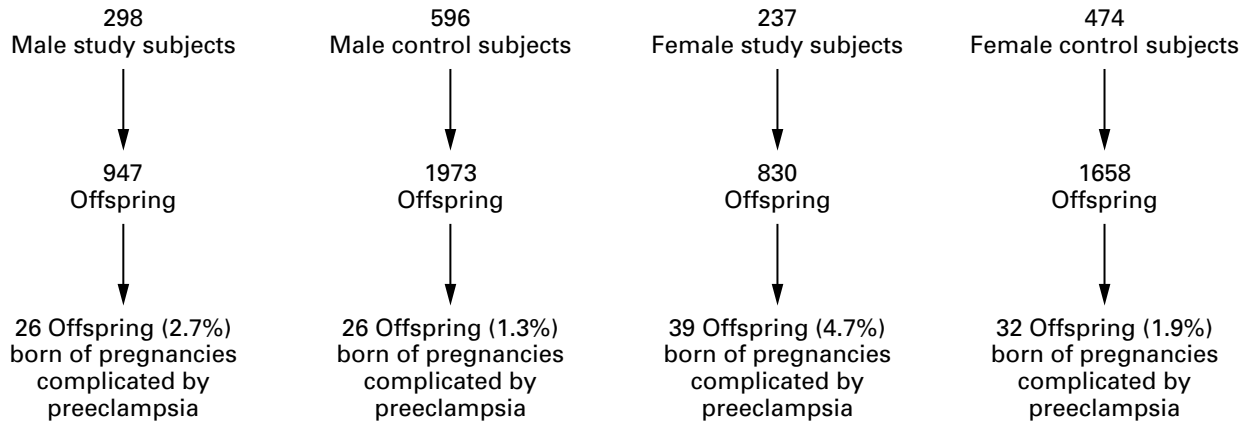
†Race was reported on the birth certificate as white or other by the parents; information on race was not available for all the subjects.

significantly more likely than those without such a history to have a child who was the product of a pregnancy complicated by preeclampsia. These findings support the hypothesis that the genotype of the fetus contributes to the overall risk of preeclampsia.

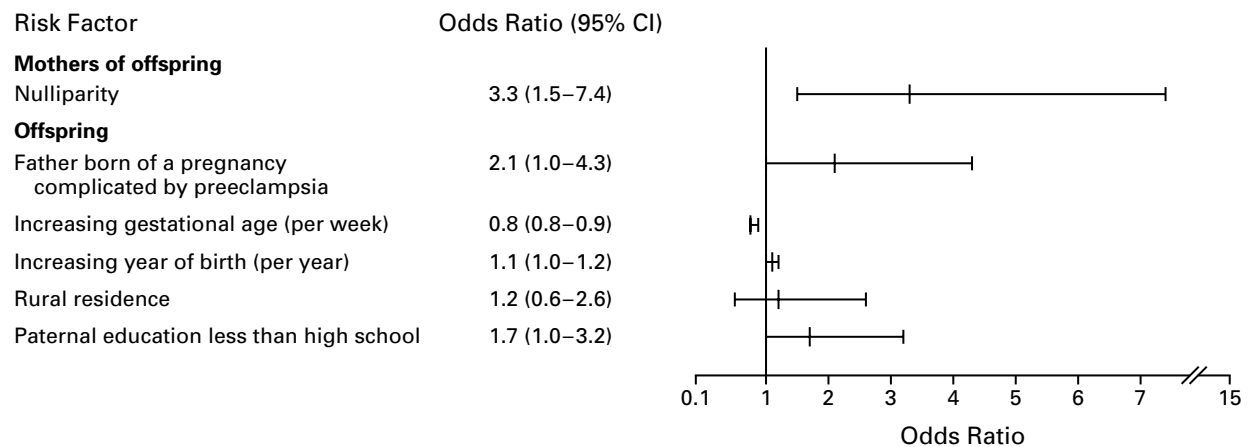
Our results confirm and extend the findings of other studies that have suggested that there is a paternal component to the predisposition to preeclampsia. In a population-linked data base in Norway, among men who had fathered children with more than one woman, men who had fathered a child with a woman whose pregnancy was complicated by preeclampsia were nearly twice as likely as men without such a history to father a child with another woman who also had preeclampsia during the pregnancy.<sup>10</sup>

Our findings are also consistent with the results of studies in mice with a preeclampsia-like condition. Specifically, transgenic mice that inherit human renin genes from their fathers had high levels of human renin in their placentas. Human renin was secreted into the maternal circulation, resulting in hypertension, morphologic renal changes associated with proteinuria, and generalized convulsions in late pregnancy.<sup>6</sup> In these animals, a paternally derived gene expressed in the placenta is responsible for the development of pregnancy-associated hypertension.

We did not attempt to clarify the mechanism underlying the way in which the paternal component of the predisposition to preeclampsia is expressed. The importance of paternally derived genes in the process of placentation has been described. Insulin-like growth



**Figure 1.** Overview of the Study Groups and the Control Groups. The members of the study and control groups (top row) were born in Utah between 1947 and 1957. The offspring of these subjects (middle row) were born in Utah between 1970 and 1992. The study subjects were the product of pregnancies complicated by preeclampsia.



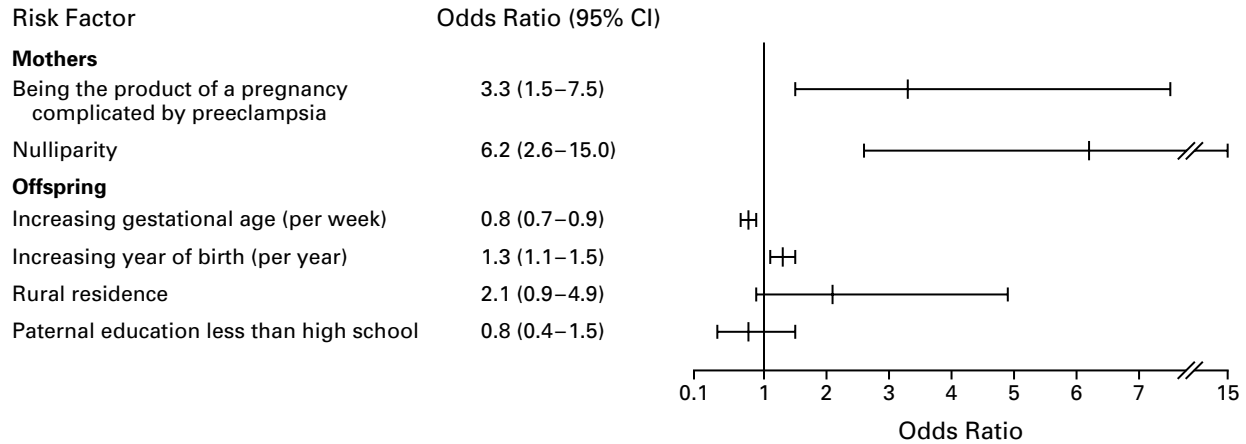
**Figure 2.** Odds Ratios for Preeclampsia among the Partners of the Male Study Group as Compared with the Partners of the Male Control Group. CI denotes confidence interval. The scale on the abscissa is different on either side of unity.

factor 2, an insulin homologue with mitogenic activity, is present in high levels in invasive cytotrophoblasts but is absent in syncytiotrophoblasts.<sup>11</sup> Because of imprinting, insulin-like growth factor 2 is expressed solely by the paternal allele in many adult and fetal tissues, including the placenta.<sup>12–14</sup> In fetal mice, inactivation of the paternal copy of the gene for insulin-like growth factor 2 results in severe intrauterine growth restriction, supporting a role for this growth factor in placentation.<sup>15</sup> An alteration in fetal-placental transport or metabolism of essential nutrients, resulting in decreased fetal growth, could also be responsible.

Other genes implicated in the development of pre-

eclampsia, such as the T235 allele of angiotensinogen, the factor V Leiden mutation, and variants of the methylenetetrahydrofolate reductase gene, may be of paternal origin.<sup>3,16,17</sup> A paternally derived antigen or an immunogenic alteration inherited by the fetus is also a potential explanation for the increased incidence of preeclampsia in our study group.

The maternal predisposition to preeclampsia that we identified confirms the results of several other studies. In addition, the fact that commonly accepted factors associated with preeclampsia, such as maternal nulliparity, were associated with an increased risk in our study provides reference values that are useful for comparing the relative strengths of the associations. The



**Figure 3.** Odds Ratios for Preeclampsia in the Female Study Group as Compared with the Female Control Group. CI denotes confidence interval. The scale on the abscissa differs on either side of unity.

incidence of preeclampsia among primigravid women with a family history of preeclampsia was three times that among primigravid women who had no such family history.<sup>2</sup> In another study the daughters of women with preeclampsia had nearly twice as high a risk of having preeclampsia themselves during their first pregnancy as did the daughters of women with no history of preeclampsia.<sup>4</sup> Finally, the prevalence of preeclampsia and eclampsia was significantly higher among the daughters of women who had a history of preeclampsia (23 percent) than among their daughters-in-law (10 percent).<sup>3</sup>

The cohort design of our study minimizes ascertainment bias, and the objective nature of the birth-certificate data also eliminates the bias that may confound a study that is based solely on maternal recall. The accuracy of birth-certificate records may be questioned, but there is no reason to believe that such limitations would affect the study group more than the matched control group. Although the accuracy and reliability of information obtained from birth certificates may vary, some have found the accuracy of information obtained from birth certificates to be as high as 90 percent.<sup>18,19</sup> Furthermore, information obtained from linked data sets is more accurate and reliable than that obtained from patient questionnaires.<sup>20</sup> The heterogeneous nature of preeclampsia may explain differences between our findings and those of others. Previous studies that failed to identify a paternal contribution to the risk of preeclampsia included only women with severe preeclampsia or eclampsia.<sup>3,21</sup> Severe preeclampsia and eclampsia may represent a different subgroup of disease from milder forms of preeclampsia. In the present study, we were not able to determine the severity of preeclampsia.

The relatively low prevalence of preeclampsia in our study is not surprising, given the racial homogeneity of the subjects, almost all of whom were white. The study design resulted in the selection of healthy subjects without preexisting medical conditions and, thus, a relatively low-risk group. An overall rate of preeclampsia of 1.3 to 4.7 percent is reasonable in such women. The results may not be applicable in more racially diverse subjects.

In conclusion, we found evidence of both paternal and maternal components of the predisposition to preeclampsia, supporting the theory that genetic contributions from both parents are important in the development of the disorder.

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