Assessment of Genetic Contributions to Risk of Preeclampsia in Ecuadorean Women

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Aim: To identify the immunogenetic factors that trigger the beginning of preeclampsia and eclampsia. Methods: A retrospective, case-control study of 142 pregnant women in Obstetrics and Gynecological Hospital Isidro Ayora in Quito, who are grouped into two different groups, diseased and healthy. The study analyzed ethnicity, age, gynecological history, contraception, immunizations, blood type and Rh factor, and family history of preeclampsia-eclampsia of each of the pregnant women; and gestational age, sex, weight, and blood type and Rh factor of the progeny. Results: Age, ethnicity, history of pregnancy, abortions, contraception, and blood type and Rh factor were similar for both groups (p > 0.05). Gestational age and weight of the progeny was lower in cases compared with controls (p < 0.05). There was no statistical difference when comparing the blood type and Rh factor of the two groups (p > 0.05). Male gender was predominant in both groups for cases 69.01 and 87.32% for controls (p < 0.05). Conclusions: There was a higher predisposition for inherited cases (26%) versus controls (9.85%), p < 0.05, for the occurrence of preeclampsia. The frequency of the recessive gene for Mendelian inheritance model mother-fetus homozygous (aa/aa), in agreement with the Hardy-Weinberg Law, was 0.41 for the sample.

Keywords Eclampsia, Etiology, Familial history, Genetic factors, Physiopathology, Preeclampsia.

INTRODUCTION

Preeclampsia is a pregnancy-specific multisystem disorder of unknown etiology, usually associated with raised blood pressure (BP) and proteinuria after the 20th week of gestation (1). This hypertensive disorder is present as a complication approximately in 5 to 7% of pregnancies (2). Around the world, high-pressure disorders during gestation are responsible for up to 50,000 deaths concerning the mother and up to 900,000 perinatal deaths annually (3). Both a rapid diagnosis and intervention are of great importance in lowering
mortality rates. The etiology of preeclampsia is still unknown, despite many attempts to identify its possible causes. In its pathogenesis preeclampsia has two stages, we can say. The first one involves abnormal implantation of the placenta; the second one presents an endothelial dysfunction (4).

For many years in preeclampsia studies it has been recognized that it has a familial component, which probably involves multiple genes in several biological pathways (3,5). Retrospective studies suggest some heritable allelic variations, specifically the utero-placental renin-angiotensin complex where defective placental vascular developments are found (6,7). The relation between preeclampsia and the familial predisposition has been demonstrated in some studies that show a 2- to 5-fold increase in risk in women with preeclampsia and their first-degree relatives (8–10).

As a mode of inheritance, mendelism is suggested in some studies, having as possibilities maternal recessive or maternal dominant with partial penetrance type of inheritance (3,11,12). But there are different genetic hypothesis, some suggest a single-gene expression that is pregnancy specific and that alone is responsible for the progression from preeclampsia to eclampsia (13).

An immunological basis was also a possibility, which led to some studies on the human leukocyte antigen (HLA) system, but linkage studies discounted a direct influence of HLA genes (14,15). Apart from the renin complex, some associations with other genetic markers are suggested, such as lipoprotein lipase (16), methylenetetrahydrofolate reductase (17), factor V Leiden (18), and apolipoprotein E (19).

A hypothesis also suggests that the risk for preeclampsia to women is influenced by genes in the mother and in the fetus, whereas paternal genes can act only via the fetus. That study showed an increased risk of preeclampsia presenting before the 34th week of gestation if the father or mother had been born of an affected pregnancy, suggesting that genetic factors are predictive of severe disease (3).

Between ethnic groups, allele frequencies differ at many polymorphisms. Hence, differences in allele frequencies between cases and controls can be wrongly interpreted as indicating genetic susceptibility (3). The majority of gene studies in preeclampsia have investigated white Western European descent women. Very few studies have included mestizo women, which is regrettable in view of the high risk of preeclampsia in Latino women and the high incidence of preeclampsia in Latin America and other developing countries (20).

Genetic studies of preeclampsia and eclampsia should be directed probably towards genes involved in the maternal-fetal interaction as described above. There are available comprehensive reviews of genetic studies in preeclampsia (21,22), and we will not attempt to repeat such excellent and detailed informations here. The goal of this study is to present some of the recent genetic studies in the context of the immunological and genetic contributions predisposing preeclampsia in a sample of mestizo Ecuadorian women.

**SUBJECTS AND METHODS**

This is a retrospective, observational, case-control study to identify immunogenic factors that trigger the onset of the preeclampsia. It analyzed 71 cases
and 71 control individuals of pregnant women. It used a previously validated survey to gather information; it asked the patient directly. It verified the information obtained with a double-checking of the full medical history of each patient and their relatives. It obtained the informed consent to acquire the personal information. We followed the ethical standards of Helsinki.

**Inclusion Criteria**

Pregnant women, primipara, with no history of essential hypertension and no history of chronic degenerative diseases, were selected. All patients came from the outpatient facility of Obstetric and Gynecologic Hospital Isidro Ayora in Quito.

**Methods**

High BP was assessed with a calibrated tensiometer; proteinuria was analyzed by urine test strips (Comburtest; Boehringer-Ingelheim, Germany). Blood type and rhesus factor were typed, and the newborn was weighed after delivery. A genetic pedigree of each woman was performed to determine the inheritance pattern of disease.

**Definitions**

A *case* is defined as any pregnancy with previously diagnosed preeclampsia, by physical examination and laboratory tests. A *control* is defined as any gravid woman with a clinical pregnancy, who is healthy and has comparable characteristics to disease cases in origin, age, and ethnic group who came to our hospital for control and/or termination of the pregnancy.

**Preeclampsia** is a complication of pregnancy, characterized by a combination of symptoms, including maternal hypertension and proteinuria with or without pathological edema. Preeclampsia usually occurs after the 20th week of gestation, but may develop before this time in the presence of trophoblastic disease. **Mild preeclampsia** was defined with a BP above >140/90, proteinuria 1+ (300 mg/24 hours), and edema +/-; **Severe eclampsia** was established with a BP above >160/110, proteinuria 2+ (1000 mg/24 hours), and edema +; plus the subsequent symptoms of increased reflexes, upper abdominal pain, headache, visual disturbances, decreased urine output, elevation of liver enzymes, decreased platelets, increased bilirubin, and elevated creatinine.

**Statistical Analysis**

The epidemiological software Epi Info Version 6.04 (Centers for Disease Control and Prevention, USA) was used. It performed descriptive and inferential error alpha of 5%. Genetic analysis was performed by calculating the gene frequency of susceptibility gene under the Hardy-Weinberg Law, considering as like recessive gene (q) and as a dominant gene (p).

**RESULTS**

**Mother’s age and Ethnic Group and Gestational Age**

The average age of the mother was 21.3 ± 3.5 years, with a range between 16 to 35 years, and for the controls was 21.8 ± 4.1 years, with a similar range.
There was no significant difference between the two groups \((p = 0.476)\). The most prevalent ethnic group present was mestizo, in 91.5% of cases, as shown in Table 1. The average of gestational age was 37.7 ± 2.6 weeks, with a range between 30 and 43 weeks, and for the control group it was 38.8 ± 1.9 weeks \((p = 0.016)\).

**Blood Type**

Table 2 shows the frequency of each blood type between the cases and the control group. There were no significant differences between the two groups. Of the cases, 73.24% did not receive immunizations or vaccinations during the pregnancy and in the control group, 57.75% \((p = 0.0521)\).

**Obstetric and Gynecological History**

Of the cases, 91.55% are first pregnancy; 15.49% used contraceptive methods before; pills was the preferred method with 55.6% and the condom with 54.5%. In 8.44% of the cases, the mothers had an abortion previously; 50% of them were spontaneous, 16.7% provoked, 16.7% traumatic, and 16.7% were by unknown cause. In the control group, we found 80% of abortions by unknown cause and 20% were spontaneous. Table 3 shows these results.

**Family History**

Nineteen cases (26.8%) showed a family history of preeclampsia, 52.6% the mother, 36.8% the sister, 5.3% the sister-in-law, and 5.3% the mother-in-law.

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**Table 1:** Distribution by ethnic group of origin.

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Case</th>
<th>%</th>
<th>Control</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mestizos</td>
<td>65</td>
<td>91.5</td>
<td>67</td>
<td>94.4</td>
</tr>
<tr>
<td>Native Amerindian (mostly Kichwa)</td>
<td>4</td>
<td>5.6</td>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td>Afroecuadorian blacks</td>
<td>2</td>
<td>2.8</td>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>100</td>
<td>71</td>
<td>100</td>
</tr>
</tbody>
</table>

Note: \(\chi^2 = 1.027; \text{*} p = 0.07057\) (non-significant).

**Table 2:** Blood type and rhesus factor.

<table>
<thead>
<tr>
<th>Blood type</th>
<th>Case</th>
<th>%</th>
<th>Control</th>
<th>%</th>
<th>p-Value</th>
<th>Blood type</th>
<th>Case</th>
<th>%</th>
<th>Control</th>
<th>%</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+</td>
<td>11</td>
<td>15.5</td>
<td>7</td>
<td>9.9</td>
<td>0.313</td>
<td>A+</td>
<td>11</td>
<td>15.5</td>
<td>7</td>
<td>9.9</td>
<td>0.313</td>
</tr>
<tr>
<td>A-</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>1.4</td>
<td>NA</td>
<td>A-</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AB+</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>1.4</td>
<td>NA</td>
<td>AB+</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>1.4</td>
<td>NA</td>
</tr>
<tr>
<td>B+</td>
<td>2</td>
<td>2.8</td>
<td>3</td>
<td>4.2</td>
<td>0.932</td>
<td>B+</td>
<td>4</td>
<td>5.6</td>
<td>4</td>
<td>5.6</td>
<td>0.236</td>
</tr>
<tr>
<td>O+</td>
<td>57</td>
<td>80.3</td>
<td>55</td>
<td>77.5</td>
<td>0.681</td>
<td>O+</td>
<td>54</td>
<td>76.0</td>
<td>59</td>
<td>83.0</td>
<td>0.298</td>
</tr>
<tr>
<td>O-</td>
<td>1</td>
<td>1.4</td>
<td>4</td>
<td>5.6</td>
<td>0.0352</td>
<td>O-</td>
<td>2</td>
<td>2.8</td>
<td>—</td>
<td>—</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, Not available/calculable.
When the history is direct with the mother, we assess the severity of preeclampsia. In 30% preeclampsia was severe and in 70% of cases, mere mild or moderate. Only 10% developed eclampsia. When the sister was affected, the severity was 14% severe preeclampsia and 86% mild.

In the control group, we found preeclampsia related with the family history in 9.9% of the cases. Among them, 42.9% showed affection in the mother and 14.3% in the sister. We found a \( p \)-value of 0.0169 between both groups. The familial incidence in this study was 26.8% for cases and 9.9% for controls. Table 4 shows these results.

### Table 3: Obstetric and gynecological history.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case</th>
<th></th>
<th>Control</th>
<th></th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Gravida 1</td>
<td>65</td>
<td>91.55</td>
<td>66</td>
<td>92.96</td>
<td>0.7535</td>
</tr>
<tr>
<td>Gravida 2</td>
<td>4</td>
<td>5.63</td>
<td>5</td>
<td>7.04</td>
<td>0.9309</td>
</tr>
<tr>
<td>Gravida 3</td>
<td>2</td>
<td>2.81</td>
<td>—</td>
<td>—</td>
<td>NA</td>
</tr>
<tr>
<td>Abortion 1</td>
<td>4</td>
<td>5.63</td>
<td>5</td>
<td>7.04</td>
<td>0.9309</td>
</tr>
<tr>
<td>Abortion 2</td>
<td>2</td>
<td>2.81</td>
<td>—</td>
<td>—</td>
<td>NA</td>
</tr>
<tr>
<td>Contraception</td>
<td>11</td>
<td>15.49</td>
<td>9</td>
<td>12.68</td>
<td>0.6294</td>
</tr>
</tbody>
</table>

NA, Not available/calculeable.

### Table 4: Family history of preeclampsia.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>19</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>Negative</td>
<td>52</td>
<td>64</td>
<td>116</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>71</td>
<td>142</td>
</tr>
</tbody>
</table>

Note: OR = 3.34; \( \chi^2 \) Yates = 5.7; \( p = 0.0169 \).

Mothers’ Physical Exam

The average systolic blood pressure (SBP) was 150.9 ± 13.1 mmHg, with a range between 140 and 190 mmHg. The control group showed an average of 112.5 ± 8.8 mmHg, with a range between 90 and 120 (\( p = 0.0014 \)). The average diastolic blood pressure (DBP) was 99.9 ± 8.3 mmHg, with a range between 90 and 125; the control group showed an average of 72.5 ± 7.8 mmHg, with a range from 60 to 80 (\( p = 0.001 \)). Proteinuria of 300 mg was found in 42.3% of cases, 500 mg in 22.5%, 1500 mg in 33.8%, and 3000 mg in 1.4%. Edema was found in 4.2% of pregnant women with eclampsia; in 7.04% of severe cases of preeclampsia and in 88.7% of mild cases.

Newborns’ Physical Exam

Most of newborns of preeclamptic women were males, with 69.01%, and 87.32% in control group (\( p = 0.0082 \)). See Table 5. The newborn of preeclamptic mothers had lower weight, 2759 ± 459.4 g in comparison with the control group, 2966 ± 365.9 g (\( p = 0.035 \)).
Penetrance and Gene Expression

Calculation of the penetrance of allele-q showed a value of 23.9%. The expressivity for eclampsia was 11.7%, severe preeclampsia of 23.5% and mild preeclampsia 64.7%. The frequency of allele-q for the hypothesis of the shared gene recessive (mother and product) is 0.41. The expected proportion of affected mothers is 41% and the observed proportion was 14.08%. In sisters, the expected frequency of diseases was 20% and the observed was only 9.8%. Table 6 shows the genotypic frequencies of allele-q and Table 7 shows the frequencies in cases of dominant homozygotes, and recessive homozygotes and heterozygotes in the progeny, when they cross randomly, according to the Hardy-Weinberg equilibrium.

DISCUSSION

In reference to age, we found that the two groups analyzed are similar ($p = 0.476$). Previous reports point to age as predisposing to preeclampsia because teenage mothers has higher tendency to develop the disease: a biolog-
Genetic Risk in Preeclamptic Ecuadorian Women

It has been argued that there is a predisposition to the development of the disease in primigravidae; our results support these findings because we found that in the case group, 91.55% were primigravid. Although the 8.44% of the preeclamptic were multigravida, whose first pregnancy had ended in abortion and only 16.7% knew the cause. There is a close relationship between repeated abortions and the development of the disease, because there is a common genetic region determined by HLA genes that code for both process; however, our research has not established that there is a statistical relationship between abortions and development of preeclampsia (p = 0.9309). It has further been suggested that the application of barrier methods predisposes to the development of the pathology by avoiding maternal iso-immunization with paternal antigens, but our results failed to confirm this, probably owing to the small size of the sample. A 54.5% of cases had a history of family planning with this method.

With regard to immunization with tetanus toxoid during pregnancy as a predisposing factor for the occurrence of the disease, we found that although there was not a demonstrable statistical difference (p = 0.0521), 73.24% of cases that referred history of immunization during pregnancy developed the pathology. Pregnant women diagnosed with preeclampsia had a greater predisposition to preterm birth, our study corroborated this; the set of cases filed gestational age at less than 37 weeks was 25.35%, in the control group it was 7.04% (p < 0.05). We do not understand if the preterm birth in the preeclampsia woman is an immune response to the rejection of the progeny or simply owing to the therapeutic necessity of saving the life of the mother and fetus.

It was found that SBP was 150.9 ± 13.1 mmHg and DBP 99.9 ± 8.3 mmHg, and proteinuria were also evident, like edema, in all cases, but there is a tendency to examine the connection between hypertension and proteinuria for the diagnosis. An association between maternal blood type AB and the occurrence of preeclampsia was reported. That was not apparent in this work because in Ecuador the predominant blood type is O. Analyzing the results of blood type and Rh factor of mothers and their children allowed us to hypothesize that a greater burden on the part of the immune parent is inherited by the progeny, because in some situations, blood type and Rh factor of the newborn presents even more than 50% of the expression, which shows the mother, and must be inherited from the father’s burden immunogenetics.

It is noticed that there is a direct association between affectation of preeclampsia and male progeny. Our research found statistical difference (p = 0.0082) consistent with previous studies, but coincidentally in the control group the identical relationship existed because of a high percentage of male offspring. It is worth noting that for the years 2000–2003 in the Hospital Isidro Ayora most births were female. A 33.80% of the preeclampsia progeny are small for
gestational age, whereas for the controls, this was only 9.85% of overall. This is due to various causes without regard to hypertensive disorders. It has been shown by separate studies there is a straight link between preeclampsia and the weight of the product due mainly to widespread vasoconstriction that decreases placental blood flow and alters the fetal nutrition, as a response to an initial immune process. There is a close relationship between the forecast model of recessive inheritance and the observed data at the hospital, where the incidence of preeclampsia/eclampsia for Obstetric-Gynecologic Hospital Isidro Ayora is 7.01% for a population of 10,133 patients. Other studies had shown lower impact on the overall population.

This research demonstrates the association between family history of preeclampsia and the risk of developing it, odds ratio = 3.34, \( p = 0.016 \), relative risk = 1.7. The frequency of the gene for the shared recessive gene model was 0.41; other studies show a lower frequency. We found the higher frequency of the gene is probably due to the higher incidence (7.01%), also occurs for the proportion of observed and expected frequencies. The fraction of mothers living with preeclampsia of the propositus was 14.8% and 41% of the expected frequencies. In sisters, first-degree relatives, this proportion was 10% for the expected frequency and 20% for the observed frequency. This deviation is explained, first by the modest size of the samples, second by a lack of statistical computing that would allow us to validate the information being referred to, and third the likely genetic action of genetics events, such as the probabilistic meiotic production of gametes and the random union of the latter during fertilization.

We suggest that the pattern of inheritance of the recessive gene shared by mother and fetus, homozygous (aa/aa), as the most reasonable explanation for the development of preeclampsia. Other authors have questioned the model of single fetal recessive inheritance, because the relative prevalence among daughters and daughters-in-law would be the same, and the model of recessive maternal inheritance, only because the degrees of severity would always remain dependent on the penetrance of the gene. We have to accept with caution that a single gene is responsible for the onset of preeclampsia, as an autosomal recessive trait must have a penetrance in homozygotes of close to 100%. The shared recessive gene hypothesis cannot explain by itself the appearance of preeclampsia under unusual conditions, such as maternal diabetes, hydatidiform mole, fetal hydrops, and twin pregnancy. Our value of penetrance was 26.8%.

**CONCLUSION**

The results prompt us to conclude that there is a genetic susceptibility for the development of preeclampsia but it is not the exclusive cause. The disease is perhaps the greatest predisposing factor. Therefore, there are nongenetic switches, which include previous pregnancy and contraceptive use, in correspondence with previous studies. Despite the multitude of theories, the role of genetics in the pathogenesis of preeclampsia remains in doubt even. Many studies have found a collection of clusters of polymorphism, for that it is unlikely that a particular gene cause susceptibility for preeclampsia. This is a
multifactorial disease that possibly in conjunction with environmental factors predisposing to the development of this condition. It is likely that there is a fetal genetic contribution, which can be considered only after birth.

Declaration of Interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES