Familial Risk of Preeclampsia in Newfoundland: A Population-Based Study

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Abstract. This study sought to quantify the familial risk of preeclampsia (proteinuric hypertension) in Newfoundland and to identify characteristics in probands that predict increased familial risk. Reviewed were 5173 obstetric charts from 10 hospitals, representing 99% of deliveries on the island of Newfoundland for a 1-yr period from April 1996 to March 1997; pregnancy-induced hypertension was diagnosed according to strict criteria. Family obstetric histories were obtained from identified probands with preeclampsia, and sisters and mothers of probands were interviewed. In addition, the obstetric charts from sisters and mothers were reviewed to identify preeclampsia. The incidence of preeclampsia in the population was 5.6% (n = 292), and in primiparous women it was 7.9%. Factors independently associated with increased risk of preeclampsia included primiparous delivery, multiple gestation, pregestational and gestational diabetes, maternal age of more than 35 yr, and region of the province. Of 330 sisters identified, 217 had 445 pregnancies, with 331 charts located for review. The incidence of preeclampsia (based on chart review) in 163 primiparous sisters was 20.2%. The relative risk of preeclampsia in primiparous sisters of probands with preeclampsia compared with primiparous women in the population was 2.6 (95% confidence interval, 1.8 to 3.6). Factors in probands independently associated with a higher risk of preeclampsia in sisters included at least 2+ proteinuria and region of the province. This population-based study, which used unbiased ascertainment and strict diagnostic criteria, demonstrated a significantly higher risk of preeclampsia in sisters of probands with preeclampsia, particularly when probands were defined by severity of preeclampsia and by geographic region.

Preeclampsia is an important cause of morbidity and mortality in mothers and newborns. The pathophysiology of the systemic vasospasm, proteinuric hypertension, and multiple end-organ ischemia remains poorly understood. Modest progress in prediction, prophylaxis or treatment has occurred during the past 30 yr. Preeclampsia occurs at higher rates in sisters, daughters, and mothers of affected women (1–7), but genetic study of this disease remains an enormous challenge, requiring not only female gender and reproduction to manifest the phenotype, but consideration of fetal-maternal and fetal-paternal genotype interactions (8–11). To date, the molecular determinants important in the inherited predisposition to preeclampsia remain unknown.

The population of Newfoundland has arisen from Irish and English settlement in the late 18th and early 19th centuries, with little subsequent outmigration or immigration (12). A total of 90% of the island’s current 550,000 residents are descended from approximately 20,000 original settlers. Until recent decades, isolation was enhanced by dependence on outport fisheries, lack of roads, and segregation by religion. This persistent genetic isolation produced a high coefficient of kinship (13,14), which, together with relatively large families, close family ties, and a modern health care system, facilitates investigation of genetic disease. Our objective was to quantify the risk for the development of preeclampsia in the sisters and mother of probands with preeclampsia in the population, to identify predictors of enhanced familial risk in Newfoundland, and to determine whether a search for susceptibility genes should be undertaken. Strict diagnostic criteria (15) were applied by using data derived from the primary documents, and probands were identified from the total provincial population at risk during 1 yr.

Materials and Methods

Identification of preeclamptic probands and sisters at risk of developing preeclampsia is shown in Figure 1. A total of 5173 obstetric charts from 10 hospitals were reviewed, constituting 99% of all third-trimester deliveries on the island of Newfoundland from April 1996 to March 1997. Each record was reviewed by a research nurse or trained research assistant, who summarized relevant information into a detailed data summary sheet. This included demographic and clinical information, data regarding obstetric history, diabetes, renal disease, previous preeclampsia, hypertension, BP during pregnancy, and results of urine tests. ICD-9 hospital codes for hypertension as
used by Canadian Institute for Health Information were collected for comparison with research results. One chart contained too few data to include in the analysis. Consequently, our study population size was 5172. All data sheets were reviewed by a specialist obstetrician (L.D.), who assigned the diagnoses for hypertensive diseases in pregnancy. Strict diagnostic criteria were used in concordance with guidelines from the 1997 Canadian Hypertension Society Consensus Conference (16).

Study design was approved by the hospital ethics committee. Once probands with preeclampsia had been identified, each was sent an initial explanatory contact letter from the delivering physician or their family physician. Each proband was then contacted by telephone, and after consent had been provided, detailed pregnancy history and family history were obtained. Contact information for female first-degree relatives was obtained. Mothers and sisters were then interviewed in the same manner as for probands. Written consent for obstetric chart review was obtained, regardless of history of hypertensive pregnancy. Consent forms were forwarded to delivering hospitals. Charts on the island of Newfoundland were reviewed by research staff in person. For deliveries occurring elsewhere, charts were forwarded to the research team for analysis. Multiple attempts were made in every case to locate older records or those in other provinces or countries. We reviewed all available charts from deliveries in sisters and mothers by using the same procedure and criteria as for the provincial population. The same research staff and clinician reviewed both population and relative data. Each record was allocated to one diagnostic category on the bases of defined clinical criteria, in concordance with guidelines from the 1997 Canadian Hypertension Society Consensus Conference (16) (Table 1).

Of 292 probands who developed preeclampsia in this population, 15 probands were excluded from the family study because they had a factor predisposing to preeclampsia—9 had twin pregnancies, and 6 had insulin-dependent diabetes mellitus. Of 277 eligible probands, 210 (76%) were interviewed. The population under study did not reflect the important contribution of donated gametes to the incidence of preeclampsia (17). Women were not interviewed for the following reasons: 6 refused, 55 had inaccurate contact information, and 6 had no physician contact available. The 67 probands not included in the family study differed from the 210 included, in that 76 versus 67% were primiparous and 12 versus 4% were aged <19 yr. There were no differences for regions of domicile.

Of the 330 sisters of probands identified from these 210 interviews, 95 were nulliparous. Of 235 parous sisters, 217 (92%) were interviewed, and 445 pregnancies with third-trimester births were con-

Table 1. Definitions for diagnostic categories of pregnancy-induced hypertension

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normotensive pregnancy</td>
<td>No evidence of hypertension. Proteinuria may be present.</td>
</tr>
<tr>
<td>2. Preeclampsia (proteinuric hypertension)</td>
<td>(a) Diastolic BP ≥90 mmHg on 2 measurements, 6 hours apart, outside of labor or immediate postpartum period (b) No diastolic BP &gt;85 mmHg before 20 weeks’ gestation (c) Proteinuria ≥0.3 g/d on 24-hour urine or ≥1+ protein on urine dipstick analysis within 72 hours of first or last hypertension (d) No urinary tract infection</td>
</tr>
<tr>
<td>3. Nonproteinuric hypertension</td>
<td>As for 2 (a) and (b) No proteinuria as defined in 2 (c)</td>
</tr>
<tr>
<td>4. Intrapartum hypertension</td>
<td>High BP only during labor or immediate postpartum period ± proteinuria</td>
</tr>
<tr>
<td>5. Unassignable hypertension</td>
<td>(a) Proteinuria occurred more than 72 hours from first or last high BP measurement (b) No urine analysis record (c) Insufficient information on BP record to diagnose pregnancy induced hypertension or preexisting hypertension.</td>
</tr>
<tr>
<td>6. Preexisting hypertension</td>
<td>(a) High BP before pregnancy or diastolic BP &gt;85 mmHg before 20 weeks’ gestation (b) High BP &gt;42 days postpartum (when available)</td>
</tr>
</tbody>
</table>

*From Helewa et al. ((15)).
firmed. Seventy-four percent (n = 331) of pregnancies were reviewed by using the hospital chart as the source document (Figure 1).

Two hundred eight mothers of probands were located for interview and consented for chart review of their 821 deliveries. Of those, 446 charts (54%) were located for analysis. Of 375 pregnancies without charts available, 269 occurred before 1965 or had no available delivery date. Forty-one were home deliveries.

Univariate comparison of continuous variables was undertaken by $t$ tests and of ordinal variables by $\chi^2$ tests. Incidence rates (with 95% confidence intervals [CI]) for all types of hypertension in pregnancy were calculated in the population. Relative risk (with 95% CI) for each risk factor potentially contributing to development of preeclampsia was calculated. Predictors for the development of preeclampsia in probands and in primiparous sisters of probands were sought by multiple logistic regression, the forward stepwise method, and SPSS software version 10.0 (SPSS Inc., Chicago, IL).

Results

Of the 5172 deliveries, 2500 were primiparous. Multiple gestation occurred in 1.3% (n = 67) pregnancies. Mean age was 27 ± 5 yr. There were 0.7% (n = 8) pregnancies in which delivery occurred at less than 30 wk, and 7.0% (n = 364) less than 37 wk. Gestational diabetes mellitus was noted in 3.7% (n = 192). Twenty-eight patients (0.5%) had pregestational diabetes.

The incidence of preeclampsia and hypertension, assessed by the predefined criteria, in all deliveries and in primiparous deliveries in the province is listed in Table 2. A total of 292 (5.6%) women were classified as having preeclampsia and 283 (5.5%) as having nonproteinuric hypertension. There were no cases of eclampsia. Of the 2500 primiparous patients, 198 (7.9%) developed preeclampsia and 6.7% nonproteinuric hypertension (Table 2). Of 3479 normotensive mothers who had urine tests performed, 527 (15.1%, 95% CI, 14.0 to 16.3) had ≥1+ proteinuria. Of 1529 primiparous pregnancies with a urine test available, 248 (16.2%, 95% CI, 14.4 to 18.1) had ≥1+ proteinuria.

The incidence of preeclampsia with at least 2+ proteinuria was 2.3% (n = 119), and of preeclampsia with diastolic BP at least 110 mmHg, it was 1.0% (n = 50). Evidence of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) was observed in 38 (0.7%) patients, of whom 9 patients had increases in serum aspartate transaminase only and 3 more had thrombocytopenia without documentation of liver disease.

Geographic variations in the rates of preeclampsia were observed, with rates varying from 11 to 4% (Figure 2), with significantly higher risk observed in the Peninsulas and Western regions. Multiple logistic regression was undertaken to identify independent risk factors for preeclampsia. For this analysis, only women who did not develop pregnancy-induced hypertension (n = 3767) and those who developed preeclampsia were included (n = 292). It excluded those who developed nonproteinuric hypertension, intrapartum hypertension, those whose hypertension could not be classified, and those who had preexisting hypertension. All predictors included in the model are listed in Table 3. Independent risk factors include primi-

Table 2. Incidence of pregnancy-induced and preexisting hypertension in primiparous (n = 2500) and in all deliveries (n = 5172) in Newfoundland during 1996 to 1997

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>All Pregnancies</th>
<th></th>
<th>Primiparous</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>95% CI</td>
<td>n</td>
</tr>
<tr>
<td>Normotensive pregnancy</td>
<td>3767</td>
<td>72.8</td>
<td>71.6–74.0</td>
<td>1631</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preeclampsia</td>
<td>292</td>
<td>5.6</td>
<td>5.0–6.3</td>
<td>198</td>
</tr>
<tr>
<td>nonproteinuric</td>
<td>283</td>
<td>5.5</td>
<td>4.9–6.1</td>
<td>167</td>
</tr>
<tr>
<td>intrapartum</td>
<td>514</td>
<td>9.9</td>
<td>9.1–10.8</td>
<td>331</td>
</tr>
<tr>
<td>Preexisting hypertension</td>
<td>141</td>
<td>2.7</td>
<td>2.3–3.2</td>
<td>77</td>
</tr>
</tbody>
</table>

a CI, confidence interval.

b Excludes 88 pregnancies, 49 of which were primiparous, with hypertension impossible to define.
Incidence and relative risk of preeclampsia in primiparous sisters of probands with preeclampsia, the latter defined

Table 4.

<table>
<thead>
<tr>
<th>Characteristic of Proband with Preeclampsia</th>
<th>Preeclampsia in Primiparous Sisters of Probands</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE defined by Canadian Hypertension Society</td>
<td>33</td>
<td>163</td>
<td>20.2</td>
</tr>
<tr>
<td>≥2+ proteinuria</td>
<td>19</td>
<td>65</td>
<td>29.2</td>
</tr>
<tr>
<td>DBP ≥110 mmHg</td>
<td>7</td>
<td>27</td>
<td>25.9</td>
</tr>
<tr>
<td>HELLP syndrome (increased LFT)</td>
<td>6</td>
<td>19</td>
<td>31.6</td>
</tr>
<tr>
<td>Delivery on Peninsulas region</td>
<td>10</td>
<td>26</td>
<td>38.5</td>
</tr>
</tbody>
</table>

* The risk of preeclampsia in sisters relative to the risk in primiparous women in the general population (7.9%).

* CI, confidence interval; PE, preeclampsia; DBP, diastolic BP; LFT, liver function tests; HELLP, hemolysis, elevated liver enzymes, low platelets.

Preeclampsia occurred in 33 (20.2%) of first pregnancies. The risk of preeclampsia in primiparous sisters was 2.6-fold more than in primiparous deliveries in the provincial population (95% CI, 1.8 to 3.6).

Predictors of Increased Family Risk

The incidence of preeclampsia in sisters of probands with preeclampsia increased when preeclampsia probands were characterized as having at least 2+ proteinuria, at least one diastolic BP of more than 110 mmHg, HELLP syndrome, or delivery in hospital in the Peninsulas region (Table 4). Preeclampsia occurred in 29.2% of primiparous sisters of probands who had preeclampsia and at least 2+ proteinuria. The relative risk of preeclampsia in the sisters of these probands was 3.7 (95% CI, 2.5 to 5.5), relative to that in primiparous deliveries in the provincial population.

A multiple logistic analysis was performed to identify independent risk factors for preeclampsia in sisters of probands. Included in the model were the presence or absence of the following characteristics in the proband of each sister: 2+ proteinuria, diastolic BP at least 110 mmHg, HELLP syndrome, and living in Peninsulas region. Excluded from analysis were sisters who had gestational diabetes or who had multiple gestation (n = 11). Table 5 reveals that independent risk factors for preeclampsia in sisters were the presence of at least 2+ proteinuria in probands and the region in which the proband was living.

In mothers of probands with preeclampsia and at least 2+ proteinuria, 9 (22.5%) of 40 first pregnancies in mothers were associated with preeclampsia (relative risk, 2.8; 95% CI, 1.6 to 5.1), and in mothers of probands with HELLP, 6 (42.9%) of 14 first pregnancies were associated with preeclampsia (relative risk, 4.5, 95% CI, 2.2 to 9.2).

Families with Preeclampsia

Fourteen families with 3 or 4 members with preeclampsia and 36 families with 2 members with preeclampsia (including proband) have been identified. Two sets of sisters were also probands delivering in the study period, leading to a total of 51 families with 2 or more affected members.

parity, multiple gestation, pregestational diabetes, gestational diabetes, maternal age of more than 35 yr, and two regions of the island (Peninsulas and Western) (overall \( \chi^2 = 167, P < 0.001 \)) (Table 3).

Preeclampsia in Mothers

Mean age at first delivery was 20 ± 4 yr. At interview, 46 (22%) of 208 mothers reported current hypertension. Eighty-seven first pregnancy records were classified, with preeclampsia occurring in 11 (12.6%). The risk of preeclampsia in primiparous mothers was 1.6 more than in primiparous deliveries in the provincial population (95% CI, 0.9 to 3.2).

Preeclampsia in Sisters

Among sisters of probands with preeclampsia, 163 primiparous deliveries were reviewed. The mean age of delivery was 24 ± 5 yr. The rate of pregestational diabetes was unchanged from the population rates. Gestational diabetes occurred more frequently at 6.3%. There were two sets of twins (0.6%).
versus study we report here stressed a population-based recruitment (16) using primary records as sources of data. The design of the eclampsia (18). We have rigorously applied strict definitions a challenge in the genetic studies of the pathogenesis of pre-

### Table 5. Independent predictors of preeclampsia in 152 sisters of probands with preeclampsia, defined by characteristic of proband

<table>
<thead>
<tr>
<th>Characteristic of Proband with Preeclampsia</th>
<th>Sisters (n)</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 + proteinuria</td>
<td>61</td>
<td>3.7</td>
<td>1.5–8.4</td>
</tr>
<tr>
<td>In Peninsula region</td>
<td>22</td>
<td>3.2</td>
<td>1.1–9.1</td>
</tr>
</tbody>
</table>

*CI, confidence interval; HELLP, hemolysis, elevated liver enzymes, low platelets. Sisters with gestational diabetes or multiple births were excluded from analysis (n = 11). Also included in the model were diastolic BP ≥110 mmHg (n = 27) or HELLP (n = 19) in proband.

### Discussion

Accurate phenotypic identification of preeclampsia remains a challenge in the genetic studies of the pathogenesis of pre-eclampsia (18). We have rigorously applied strict definitions (16) using primary records as sources of data. The design of the study we report here stressed a population-based recruitment versus a center-based cohort recruitment, thus eliminating ascertainment bias in the identification of probands. Ascertainment of sisters of probands was good because of the excellent participation rate of probands identified from the population and the high response rate from sisters. Ascertainment in mothers was poor because of practical difficulties in locating records, because of home deliveries, or because of remote time frames. In our study, location of pregnancy information was successful in 77% of hospital deliveries occurring after 1965. HELLP syndrome was not well defined as a clinical entity before 1980, and therefore information on liver function or platelet count was not located in charts before this period.

The population rate of preeclampsia in primiparous Newfoundland women (7.9%) is similar to that in the American Calcium to Prevent Preeclampsia trial (7.1%) (15). Previous epidemiologic study of preeclampsia has described factors linked with higher incidence of disease, particularly primiparity, multiple gestation, older maternal age, and pregestational diabetes (19–21). Observations in the Newfoundland population further confirm these risk factors.

The regional differences observed for incidence rates of preeclampsia in the population and for incidence rates in sisters of probands (defined by the proband’s region) suggest multiple genetic isolates may be present in Newfoundland. After the major migrations to Newfoundland before 1840, natural increase became the dominant mechanism of population growth (12). Community expansion occurred predominantly by partition of ancestral lands among heirs or by movement to other nearby uninhabited lands near the settlement core, close to fishing grounds. This kept related families together. Even in 1982, 50% of the population lived in communities of fewer than 2500 people, and 41% lived in communities of fewer than 1000 people (13,14). Thus, the presence of multiple genetically simplified isolates, with strong founder effects and a high coefficient of kinship, may explain the higher sibling risk for preeclampsia observed in certain regions of the province.

However, environmental factors specific to the Western and Peninsulas regions could also be at work here, particularly because there are substantial socioeconomic differences between these regions and the Eastern region, the latter being more prosperous, with less dependence on fishing and with higher employment rates. Our data further confirm that sisters of probands with preeclampsia have an elevated risk of pre-eclampsia, and this is so even with the use of more precise definitions of preeclampsia than in other studies (4,6). Characterization of probands by the severity of preeclampsia (presence of at least 2+ proteinuria, HELLP syndrome) is associated with higher risk in sisters of probands, an observation not previously reported. This increased risk suggests the inheritance of molecular determinants that contribute to development of the disease.

In most populations, a sibling risk of 2 to 4, as seen in this study, would be considered too low for a linkage analysis approach. However, genetically simplified isolates are the optimal choice of study population when mapping genes in complex diseases (22). It has been argued that genetic studies in very young founder populations, such as for Newfoundland, Quebec, and Costa Rica, may be able to exploit less dense marker maps for linkage disequilibrium mapping (23) and that inbreeding may increase the power to detect the role of a disease susceptibility factor by comparison of genotypic distributions among case patients and controls (24). In Newfoundland, the presence of potential founder effects, as identified in other inherited disorders (25–27), may be associated with higher allele frequency of particular genotypes associated with preeclampsia, thereby facilitating successful gene mapping. This study suggests that in Newfoundland, families at high risk for preeclampsia can be identified, and that a search for susceptibility genes for preeclampsia could be undertaken.

We conclude that the incidence of preeclampsia in primiparous Newfoundland women is 7.9%, that the incidence varies by region, and that primiparous sisters of probands with preeclampsia are at increased risk of developing preeclampsia, particularly when probands are defined by the severity of preeclampsia and by region of domicile.

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