Short Communication

Pregnancy Hormones, Pre-eclampsia, and Implications for Breast Cancer Risk in the Offspring

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Abstract

The aim of this study is to prospectively assess pregnancy hormone levels as correlates of subsequent development of pre-eclampsia, a condition that has been shown to be inversely associated with breast cancer risk in the offspring. A cohort of 260 Caucasian women in Boston, Massachusetts, was followed through pregnancy. Maternal blood was collected at the 16th and 27th weeks of gestation, and 18 women were diagnosed with pre-eclampsia after blood collection. Information on sociodemographic variables and risk factors of pre-eclampsia was collected through an interviewer-administered questionnaire and review of medical records. At the 16th week, there was a nonsignificant positive association between progesterone levels and pre-eclampsia [relative risk (RR) = 1.63, 95% confidence interval (CI), 0.97–2.74, per 1 SD increase]. By the 27th week, the association between progesterone and pre-eclampsia was strengthened (RR = 2.65, 95% CI, 1.46–4.81, per SD), and sex hormone-binding globulin levels were somewhat inversely related to pre-eclampsia (RR = 0.61, 95% CI, 0.31–1.20, per SD). No difference was found with respect to prolactin, estradiol, and estril levels. Our findings indicate that progesterone may have a role in the late manifestation of pre-eclampsia pathology but are also compatible with the hypothesis that increases in progesterone represent an early compensatory mechanism.

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Introduction

There is evidence that hormone-related cancers such as those of the breast, testes, and prostate may be influenced by in utero exposures (1, 2). Pre-eclampsia has been associated with a reduced risk of these cancers in the offspring (2). This condition is characterized by impaired placental function, and some studies indicate that pregnancy estrogens are reduced, whereas pregnancy androgens are increased (3). Most of the earlier studies correlating hormone levels with pre-eclampsia (3–7) were cross-sectional, and some of them were done when biochemical assays were suboptimal. Thus, it cannot be confidently stated whether altered hormone levels in pre-eclampsia are determinants or consequences of the condition. Only prospective studies can effectively address this issue.

We have followed 260 pregnant women throughout pregnancy and examined maternal hormone levels measured around the 16th and 27th week of gestation in relation to subsequent pre-eclampsia.

Materials and Methods

The data for this study are derived from an international investigation focusing on pregnancy hormones and undertaken with an identical protocol in the United States and China (8). This study, however, relies only on the United States data because no Chinese woman with pre-eclampsia was recorded.

Between March 1994 and October 1995, 402 eligible women coming for their first prenatal visit were identified at the Beth Israel Hospital in Boston. The procedures followed complied to the ethical standards of the Institutional Review Boards of the Harvard School of Public Health and Beth Israel Hospital. Women had to be Caucasian, <40 years old, and have a parity of one or two. Of the 402 eligible women, 77 refused to participate, 11 were subsequently excluded because of abortion or twin birth, 10 were lost to follow-up, and 44 had missing values; thus, 260 pregnant women were eventually included.

At the 16th week visit, demographic information was abstracted from the medical records, and the first blood sample was drawn. At the 27th week visit, a health professional interviewed the study participant and drew the second blood sample. At both visits, the exact gestational age was recorded as the time since the first day of the last menstrual period.

The operational definition for pre-eclampsia was the assignment of this diagnosis by the attending physicians.

At both visits, 10 ml of venous blood were drawn from each woman. Coded serum aliquots were sent to Uppsala, Sweden, for analyses concerning estradiol-17b (E2), unconjugated estriol (E3), SHBG3, progesterone, and prolactin (8–10). RR for pre-eclampsia associated with an increment of ~1 SD of each of the studied hormones, at the corresponding sampling.

The abbreviations used are: SHBG, sex hormone-binding globulin; RR, relative risk; CI, confidence interval.
were estimated through multiple logistic regressions, controlling for exact gestational age at blood sampling, age (<30, ≥30 years), parity (1, 2), prepregnancy body mass index (<25, 25–29, ≥30 kg/m²), smoking during pregnancy (yes, no), offspring gender, and mutually among the studied hormones. The results were essentially identical when age and body mass index were treated as continuous variables.

## Results

Of the 260 women, 18 were diagnosed with pre-eclampsia (3 before or at the 34th gestational week, 3 between the 35th and 37th weeks inclusive, 2 at the 38th week, 3 at the 39th week, and 7 at the 40th or 41st week). For 9 women, all classical manifestations of pre-eclampsia (i.e., pregnancy-related hypertension, edema, and proteinuria) were present, whereas for the other 9, diagnosis was based on two of these manifestations and additional signs, including liver dysfunction and thrombocytopenia.

Table 1 shows the distribution of women with or without pre-eclampsia by maternal characteristics. In these data, pre-eclampsia is more common among younger mothers and among primiparae and overweight women, whereas smoking in pregnancy is inversely associated with this condition. Mean (and SD) birth weight was 3116 g (662 g) among pre-eclamptic and 3529 g (521 g) among nonpre-eclamptic women. The corresponding values for gestational age at birth were 38.5 (2.7) and 40.0 (1.8) weeks.

Table 2 shows mean and SD of pregnancy hormones at the 16th and 27th weeks of gestation in women who developed pre-eclampsia and those that did not. This table also shows additional signs, including liver dysfunction and thrombocytopenia.

### Table 1  Crude and adjusted ORs of maternal characteristics and gender of offspring and risk of pre-eclampsia among Caucasian women in Boston, Massachusetts, 1994–1995

<table>
<thead>
<tr>
<th>Maternal characteristic</th>
<th>Pre-eclampsia</th>
<th>No pre-eclampsia</th>
<th>Crude OR</th>
<th>Adjusted OR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>9 (50.0)</td>
<td>73 (30.2)</td>
<td>1</td>
<td>1</td>
<td>1.00–1.79</td>
</tr>
<tr>
<td>30+</td>
<td>9 (50.0)</td>
<td>169 (69.8)</td>
<td>0.43</td>
<td>0.57</td>
<td>0.18–1.79</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13 (72.2)</td>
<td>148 (61.2)</td>
<td>1</td>
<td>1</td>
<td>1.00–1.79</td>
</tr>
<tr>
<td>2</td>
<td>5 (27.8)</td>
<td>94 (38.8)</td>
<td>0.61</td>
<td>0.48</td>
<td>0.14–1.65</td>
</tr>
<tr>
<td>Prepregnancy BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>10 (55.6)</td>
<td>207 (85.5)</td>
<td>1</td>
<td>1</td>
<td>1.00–1.79</td>
</tr>
<tr>
<td>25–29</td>
<td>6 (33.3)</td>
<td>29 (12.0)</td>
<td>4.28</td>
<td>6.19</td>
<td>1.83–20.89</td>
</tr>
<tr>
<td>30+</td>
<td>2 (11.1)</td>
<td>6 (2.5)</td>
<td>6.90</td>
<td>15.23</td>
<td>2.20–106.25</td>
</tr>
<tr>
<td>Smoking in pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18 (100)</td>
<td>228 (94.2)</td>
<td>1</td>
<td>1</td>
<td>1.00–1.79</td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0)</td>
<td>14 (5.8)</td>
<td>0.00</td>
<td>1 (b)</td>
<td>1.00–1.79</td>
</tr>
<tr>
<td>Gender of offspring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (50.0)</td>
<td>126 (52.1)</td>
<td>1</td>
<td>1</td>
<td>1.00–1.79</td>
</tr>
<tr>
<td>Female</td>
<td>9 (50.0)</td>
<td>116 (47.9)</td>
<td>1.09</td>
<td>0.84</td>
<td>0.29–2.45</td>
</tr>
</tbody>
</table>

<sup>a</sup> With mutual adjustment for the variables in the table and for gestational age at delivery.

<sup>b</sup> No woman with pre-eclampsia was a smoker.

### Table 2  Logistic regression-derived odds ratios (OR) and 95% confidence intervals (CI) for the association between pregnancy hormones and risk of pre-eclampsia by an increment of one standard deviation

<table>
<thead>
<tr>
<th>Pregnancy hormone</th>
<th>16&lt;sup&gt;th&lt;/sup&gt; gestational week</th>
<th>27&lt;sup&gt;th&lt;/sup&gt; gestational week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-eclamptic Mean (SD)</td>
<td>Non-pre-eclamptic Mean (SD)</td>
</tr>
<tr>
<td>Estradiol (nmol/l&lt;sup&gt;1–1&lt;/sup&gt;)</td>
<td>16.3 (10.4)</td>
<td>14.4 (6.7)</td>
</tr>
<tr>
<td>Estradiol (nmol/l&lt;sup&gt;1–1&lt;/sup&gt;)</td>
<td>4.2 (1.7)</td>
<td>3.9 (1.8)</td>
</tr>
<tr>
<td>SHBG (nmol/l&lt;sup&gt;1–1&lt;/sup&gt;)</td>
<td>90.5 (20.6)</td>
<td>44.4 (24.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Controlling for exact gestational age at blood collection and for the maternal variables indicated in Table 1.

<sup>b</sup> Controlling for exact gestational age at blood collection for the maternal variables indicated in Table 1 and mutually among the evaluated pregnancy hormones.
els of estradiol and estriol during the 27th gestational week were also nonsignificantly lower among pre-eclamptic women. Third, results are more evident during the 27th gestational week, although some trends, particularly with respect to proges-
terone, are already apparent during the 16th week. Fourth, there is no evidence in these data that prolactin plays an important role in pre-eclampsia. We have explored whether patterns were different among primiparous and biparous women or with respect to earlier versus later manifestation of pre-
eclampsia, but data were too sparse to allow inferences.

Discussion
In this study, high maternal serum levels of progesterone measured at around the 27th week of gestation were highly predic-
tive of later development of pre-eclampsia. Although estrogen levels were slightly lower in pre-eclamptic cases before diag-
nosis than in other women, the differences were marginal. SHBG was somewhat lower among women who subsequently developed pre-eclampsia, whereas prolactin was clearly unre-
lated to risk of pre-eclampsia.

Very few investigations have studied progesterone in relation to pre-eclampsia. An early prospective study reported no association (5). In a cross-sectional study, again no association was identified (7). A third study, however, found that proges-
terone production was much higher in pre-eclamptic placentas (11). With respect to pregnancy estrogens, it is widely assumed
that they are reduced in pre-eclampsia (3). Earlier data gener-
alization to pre-eclampsia. An early prospective study reported no
association (5). In a cross-sectional study, again no association
was reported (6). Two earlier cross-sectional studies of pre-
eclampsia in relation to SHBG have reported no association
(12, 13).

Earlier investigations have suggested an inverse associa-
tion of pregnancy estrogens with pre-eclampsia (3, 14). Our
findings are not incompatible with such an association but do
not provide strong support for it. The increase of progesterone
(and perhaps a reduction of SHBG) around the 27th week, that
is at a time proximal to the occurrence of pre-eclampsia, indi-
cates that these hormones may have a role in the pathogenesis
of this condition, but we cannot exclude the possibility that
these changes represent compensatory mechanisms for the
maintenance of the threatened pregnancy. The functional con-
sequence of SHBG reduction, if this actually occurs, could be
associated with an increase of bioavailable estrogens, but the
intriguing observation that lower SHBG levels are associated
with increased insulin resistance should also be considered (16).

The strengths of the present investigation are its prospec-
tive nature, its implementation on a well-defined cohort, its
reliance on modern analytical procedures, and its control for
exact gestational age at blood sampling. It is also reassuring
that the incidence and the risk profile of pre-eclampsia in this
study was compatible with what is currently known about this
condition in Caucasian women (17, 18). A weakness of the
study is the small number of pre-eclamptic cases, although this
is expected when a relatively rare phenomenon has to be
studied among pregnant women with repeated measurements
of several hormones. Another weakness is the lack of androgen
measurements, particularly in view of the emerging evidence
indicating that these hormones may be implicated in the etiol-
ogy of pre-eclampsia (13).

Epidemiological studies have demonstrated that pre-
eclampsia reduces breast cancer risk in both the mother (19)
and the offspring (2). It has been suggested that this is because
of reduced levels of pregnancy estrogens (2). Our study sug-
gests that increasing progesterone levels are associated with an
increased risk of pre-eclampsia. The effect of progesterone
levels on mammary tissue in utero has not been adequately
studied, but it may be relevant that women with high levels of
progesterone during pregnancy appear to be themselves at
lower future risk for breast cancer (20).

In conclusion, in this prospective study, we have found that
pre-eclampsia is associated with an increase in predi-
agnostic levels of progesterone and, perhaps, a decrease in pre-
diagnostic levels of SHBG, whereas estradiol and estriol were
only marginally decreased. These findings may indicate that
progesterone has a role in the development of pre-eclampsia,
but they are also compatible with the hypothesis that an in-
crease in progesterone and a decrease of SHBG represent
compensatory mechanisms. Previous studies have suggested
that the protective effect of pre-eclampsia in hormone-mediated
cancers is related to differences in estrogen levels (2). These
data suggest that progesterone levels may play an integral role
in the development of pre-eclampsia and by extension future
cancer risk of the offspring.

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in his laboratory in the context of the original international study.

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Androgen levels of preeclamptic patients in the third trimester of pregnancy and

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