**Short Communication**

**Pregnancy Hormones, Pre-eclampsia, and Implications for Breast Cancer Risk in the Offspring**¹

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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 estriol 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.

**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), SHBG¹, 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,
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 primiparous 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 multiple logistic regression-derived RRs and 95% CIs for the association between pre-eclampsia and pregnancy hormones by an increment of one standard deviation.

<table>
<thead>
<tr>
<th>Pregnancy hormone</th>
<th>16th gestational week</th>
<th>27th 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&lt;/sup&gt;)</td>
<td>16.3 (10.4)</td>
<td>14.4 (6.7)</td>
</tr>
<tr>
<td>Estriol (nmol/l&lt;sup&gt;-1&lt;/sup&gt;) 4.2 (1.7)</td>
<td>3.9 (1.8)</td>
<td>1.28</td>
</tr>
<tr>
<td>SHBG (nmol/l&lt;sup&gt;-1&lt;/sup&gt;) 347.2 (101.4)</td>
<td>367.7 (90.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>Testosterone (nmol/l&lt;sup&gt;-1&lt;/sup&gt;) 156.5 (122.0)</td>
<td>133.3 (116.1)</td>
<td>1.50</td>
</tr>
<tr>
<td>Prolactin (µg/l&lt;sup&gt;-1&lt;/sup&gt;) 51.6 (20.6)</td>
<td>44.4 (24.5)</td>
<td>1.48</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 progestrone, 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 primiparae and biparae 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 predictive of later development of pre-eclampsia. Although estrogen levels were slightly lower in pre-eclampsia cases before diagnosis than in other women, the differences were marginal. SHBG was somewhat lower among women who subsequently developed pre-eclampsia, whereas prolactin was clearly unrelated 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 progesterone 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 generally relied on cross-sectional investigations (4, 7, 11–13), but two recent prospective studies also suggested that estriol tends to be reduced before the clinical manifestations of pre-eclampsia (14, 15). We could identify only one investigation examining prolactin in relation to pre-eclampsia, and 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 association 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, indicates 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 consequence 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 prospective 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 etiology 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 suggests 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 prediagnostic levels of progesterone and, perhaps, a decrease in prediagnostic 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 increase 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.

Acknowledgments
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References
Breast Cancer Risk in the Offspring

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