Maternal height, pregnancy estriol and birth weight in reference to breast cancer risk in Boston and Shanghai

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Birth weight has been positively associated with breast cancer risk in adult life and is positively associated with the principal pregnancy estrogen estriol. Birth weight is lower among Chinese women than among Caucasian women, but paradoxically, pregnancy estriol levels are higher among the former than the latter. We studied a cohort of 317 Caucasian pregnant women in Boston, MA, and 339 Chinese pregnant women in Shanghai, China. We investigated whether maternal height, which is inversely associated with pregnancy estriol levels, interacts with this hormone in relation to birth weight, thus accommodating the apparently contradictory ecologic and analytic evidence concerning the role of pregnancy estrogens on breast cancer risk in the offspring. In both Boston and Shanghai, there was a positive association of pregnancy estriol with birth weight among taller women, whereas among shorter women the association was essentially null. The relevant interaction terms were highly significant in Boston (p ≈ 0.006), whereas in Shanghai, where pregnant women were generally shorter, the interaction term was suggestive (p ≈ 0.14). We conclude that maternal height should be considered an important risk factor for breast cancer in the offspring since it is a crucial determinant of birth weight, both directly and through positive interaction with the principal pregnancy estrogen estriol.

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Key words: breast cancer; maternal height; birth weight; estrogen; estriol

Over the last 15 years, several studies have examined whether birth weight is positively associated with breast cancer risk in adult life. The results of most of these studies have been interpreted as supportive of an association,1-11 although in a few studies the results have been interpreted as null.12-15 These findings from analytic investigations are compatible with the ecologic contrast in breast cancer incidence between Caucasian women in Western countries and Chinese or Japanese women in their home countries since both birth weight16-18 and breast cancer risk19 are generally lower in China and Japan.

The link that underlies the birth weight–breast cancer risk association is likely to be hormonal. Two categories of hormones have attracted particular attention: estrogens20 and the IGF system.21,22 The dominant pregnancy estrogen, estriol,23,24 as well as IGF-I25,26 are positively associated with birth weight; and both estrogens27 and IGF-I in premenopausal women28 have been positively associated with breast cancer risk in adult life.

No studies have evaluated at the analytic or ecologic level pregnancy IGF-I in relation to breast cancer risk, but the issue has been explored with respect to estrogens. A cohort study comparing women exposed in utero to diethylstilbestrol, an estrogenic substance, with unexposed ones reported a 2-fold increase in breast cancer risk among women aged 40 years or older (among younger women, breast cancer with a genetic basis is likely to be particularly common).29 This coherent overall picture has, however, been challenged by the results of one ecologic study. This study compared pregnancy estrogen levels between Caucasian women in Boston, MA, and Chinese women in Shanghai, China. Contrary to the hypothesis, pregnancy estrogens were higher among the Asian compared to the Caucasian women.30

We postulated that a crucial determinant of birth weight and subsequent breast cancer risk might be maternal body size, which imposes physical constraints on fetal growth,31 and that in small women (more frequently found among the native Chinese) pregnancy growth hormones, including estriol and IGF-I, tend to increase in order to compensate for the physically constrained fetal growth.32 According to this hypothesis, in shorter women, who are known to have smaller babies,33,34 pregnancy growth hormones, including estriol and IGF-I, would tend to increase without concomitant increases in birth weight, thus attenuating the positive associations between the hormones and birth weight. In contrast, among taller women, maternal size does not impose constraints on fetal growth, so pregnancy growth-enhancing hormones, including estriol and IGF-I, would tend to be positively associated with birth weight. We evaluated this hypothesis by studying the association between the dominant pregnancy estrogen estriol and birth weight among women in Boston, MA, and Shanghai, China, stratified by height. Pregnancy IGF-I levels were not determined in these women.

Material and methods

Between March 1994 and October 1995, a total of 402 Caucasian and 424 Asian eligible women were identified, respectively, at the Beth Israel Hospital in Boston, MA, and the Shanghai Medical University in China. All pregnant women coming for their first routine prenatal visit to the collaborating maternity clinic were met by authorized health professionals, who ascertained the woman’s eligibility to participate, explained to her the objectives of the study and obtained informed consent. The study was approved by the institutional review boards of the Beth Israel Hospital, Shanghai Medical University and Harvard School of Public Health.

Participating women had to be less than 40 years old and to have a maximum parity of 2. Regarding the age limit, our rationale was that women who have a pregnancy after 40, particularly a first pregnancy after that age, may be a select group that could generate some sort of unidentifiable bias. The limitation of parity to a maximum of 2 aimed at improving comparability between the 2 groups of women and was dictated by the fact that Shanghai women were under the “one-child policy” of the Chinese government. Women were not eligible if they had a prior diagnosis of diabetes mellitus or thyroid disease, if they had taken any hormonal medication during the index pregnancy or if the fetus had a known major anomaly. Of the 402 eligible women in Boston, 64 refused to participate in one or more aspects of the study or had crucial missing values, 9 were subsequently excluded because of a spontaneous or induced abortion in the index pregnancy, 2 were excluded because of twin birth and only

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10 were lost to follow-up after the initial meeting. Of the 424 eligible women in Shanghai, 74 refused to participate in one or more aspects of the study or had crucial missing values, 2 were subsequently excluded due to induced abortion in the index pregnancy, another 2 were excluded because of twin birth and 7 were lost to follow-up. For 6 Shanghai women, gestational age was indirectly estimated, blindly as to estriol levels or birth weight; but to assess the robustness of the results, the analyses were repeated after the exclusion of these 6 women.

Thus, 317 Caucasian and 339 Chinese pregnant women who delivered live single births were eventually included in the analysis. Women who refused to participate in the study were not different from those who participated with respect to age and parity.

Baseline demographic information as well as information about medical conditions was abstracted from the medical records and recorded in interviews at the 16th and the 27th gestational week visits of the women to the clinic. At delivery, additional information concerning the newborn, notably birth weight, was ascertained from medical records and pediatric charts. Information concerning questionnaire administration and medical record review was given in earlier publications.

From every woman, 10 ml of venous blood were drawn at the 16th and 27th completed weeks of gestation. Blood was collected in sterile tubes and stored at −4°C without preservative. Samples were centrifuged, and the serum was aliquoted and stored for hormonal assay at −80°C. Serum levels of several pregnancy hormones, including unconjugated estriol, at both samplings were measured.

In an earlier analysis focusing only on U.S. women, without stratification by maternal height or assessment of possible interaction of maternal height with pregnancy hormone levels in relation to birth size, only estriol at the 27th gestational week was substancially, consistently and significantly associated with birth weight. Based on the results of this study and because estriol represents the principal pregnancy estrogen and has been associated with birth weight in other investigations, we a priori decided to examine only estriol at the 27th gestational week as possibly interacting with maternal height in relation to birth weight. Unconjugated estriol in 50 μl serum was measured with a time-resolved competitive solid-phase fluorimmunoassay method (AutoDELFIA unconjugated estriol kit; Wallac Oy, Turku, Finland). The coefficient of variation was 8.0 ± 1.8%. Statistical analyses were conducted using the SPSS statistical package (v. 11.5; Chicago, IL). After presentation of descriptive data, birth weight was regressed on maternal height and pregnancy estriol, adjusting also for duration of gestation until birth. Height increments were set at 5 cm, whereas estriol increments were set at 1 SD in the respective population (Caucasian or Chinese). Use of SD increments has several advantages, including comparability of results among different settings and hormones and control of the unavoidable variability between various hormone determination methods used in different studies. An interaction term of maternal height and pregnancy estriol (both as continuous variables) was then introduced. To facilitate pictorial representation, these analyses were repeated, categorizing maternal height into low (lower quartile), medium (2 intermediate quartiles) and high (upper quartile), all categorizations being population-specific. Analyses were done separately for the Caucasian women in Boston and the Asian women in Shanghai.

### Results

Distributions and mean values of height, estriol levels around the 27th gestational week, gestational age at birth and birth weight, by study center, are presented in Table I. With respect to height, the lower end of the distribution was not very different between the women in the 2 centers, but the upper end was significantly far higher among the Caucasian women; the height of 99% of the Chinese women fell below the median height of Caucasian women. Pregnancy estriol levels were substantially higher among the Chinese women. There was no difference with respect to gestational age at birth, whereas mean birth weight of Chinese offspring was significantly lower compared to that of Caucasian offspring. Height was weakly inversely associated with pregnancy estriol at the 27th week among both Chinese and Caucasian women, with correlation coefficients around −0.11 (p < 0.05). Aspects of these results in different forms and parameterizations have been previously reported in different contexts.

Table II presents the regression of birth weight on maternal height and estriol at the 27th week of pregnancy in women in Boston. Maternal height was introduced alternatively as a continuous

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**Table I – Descriptive Data of the Variables Studied in Women and Their Offspring in Boston, MA, and Shanghai, China**

<table>
<thead>
<tr>
<th>Category means</th>
<th>Lower quartile</th>
<th>Intermediate quartile</th>
<th>Upper quartile</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Caucasian women (n = 317)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.55</td>
<td>1.64</td>
<td>1.73</td>
<td>1.64 (0.07)</td>
</tr>
<tr>
<td>Estriol around 27th week (nmol/l)</td>
<td>9.1</td>
<td>13.5</td>
<td>20.0</td>
<td>14.0 (4.4)</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>37.7</td>
<td>40.0</td>
<td>41.7</td>
<td>39.9 (1.8)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2,821.2</td>
<td>3,507.0</td>
<td>4,160.4</td>
<td>3,501.1 (538.4)</td>
</tr>
<tr>
<td>Chinese women (n = 339)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.54</td>
<td>1.60</td>
<td>1.66</td>
<td>1.60 (0.05)</td>
</tr>
<tr>
<td>Estriol around the 27th week (nmol/l)</td>
<td>13.6</td>
<td>20.5</td>
<td>33.2</td>
<td>21.9 (9.5)</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>37.5</td>
<td>39.9</td>
<td>41.6</td>
<td>39.7 (1.9)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2,846.1</td>
<td>3,390.5</td>
<td>3,934.3</td>
<td>3,396.8 (456.5)</td>
</tr>
</tbody>
</table>

**Table II – Regression of Birth Weight (g) on Maternal Height and Estriol at the 27th Week of Pregnancy in Women in Boston, MA**

<table>
<thead>
<tr>
<th>b coefficient</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (per 5 cm)</td>
<td>64.8</td>
<td>24.7 – 104.8</td>
</tr>
<tr>
<td>Estriol (per 4.4 nmol/l)</td>
<td>105.6</td>
<td>53.7 – 157.5</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>163.4</td>
<td>133.4 – 193.3</td>
</tr>
<tr>
<td>Medium stature</td>
<td>95.5</td>
<td>–37.6 – 228.7</td>
</tr>
<tr>
<td>Relatively tall</td>
<td>228.6</td>
<td>73.8 – 383.3</td>
</tr>
<tr>
<td>Estriol (per 4.4 nmol/l)</td>
<td>106.6</td>
<td>54.4 – 158.8</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>164.6</td>
<td>134.6 – 194.6</td>
</tr>
</tbody>
</table>
variable, for an unbiased evaluation of possible interaction, or in 3 categories to facilitate the subsequent pictorial representation. Categories of height are defined using the 25th and 75th percentile cut-off points among these Caucasian women. Hence, women with height < 160 cm are classified as relatively short, those with height 160–168 cm as having intermediate stature and those with height > 168 cm as relatively tall.

Both height and estriol were strongly positively and significantly associated with birth weight, after adjustment for gestational age at birth. Moreover, there was statistically significant positive interaction, shown in Figure 1, indicating that the positive association between pregnancy estriol and birth weight which is present among taller women may be absent (or even change sign) among shorter women. Controlling for additional variables, like maternal age, parity and gender of newborn, had essentially no effect on the indicated patterns.

Similar to Table II, Table III presents the regression of birth weight on maternal height and estriol at the 27th week of pregnancy in women in Shanghai. Categories of height are defined using the 25th and 75th percentile cut-off points among these Chinese women. Hence, women with height < 157 cm are classified as relatively short, those with height 157–163 cm as having intermediate stature and those with height > 163 cm as relatively tall.

In Chinese women, height was also significantly strongly positively associated with birth weight. Among these generally shorter women, however, estriol was only weakly and nonsignificantly associated with birth weight. The interaction between height and estriol with respect to birth weight among the Chinese women, who tend to be shorter, was not statistically significant. Nevertheless, among taller Chinese women, pregnancy estriol was positively associated with birth weight, whereas among both relatively short and medium-stature Chinese women (who might be thought of as relatively short under U.S. Caucasian standards), there was no evidence for an association between pregnancy estriol and birth weight (Fig. 2). Indeed, the latter 2 slopes were not different from the slope of the regression line among shorter U.S. women. Again, controlling for additional variables, like maternal age, parity and gender of newborn, had essentially no effect on the indicated patterns.

As indicated in the Material and methods section, we repeated the analyses after excluding the 6 Shanghai women for whom gestational age was not recorded, and the results were essentially identical; the largest difference was with respect to the regression coefficient of birth weight on estriol in models with categoric expression of height, which changed from 17.6 (95% confidence interval: 36.3 to 71.5, p = 0.521) to 17.2 (95% confidence interval: 37.6 to 72.0, p = 0.538).

Discussion

Among relatively short women, who are known to have smaller babies, it is possible that the principal pregnancy estrogen estriol, which has both mammotropin and growth-enhancing properties, tend to be higher. We have found that among taller women, who do not impose anthropometric constraints on fetal growth, estriol is strongly positively associated with birth weight, whereas among shorter women the association between estriol and birth weight is essentially null. In this context, it may be of interest that...
the association of birth size with breast cancer risk in the offspring has been reported to be stronger among daughters of taller rather than shorter mothers and that, among Chinese women, who are generally shorter than Caucasian women, birth weight has not been associated with adult breast cancer risk.

If confirmed, this interaction of pregnancy estriol levels and maternal height with respect to birth weight can have a number of implications. Firstly, it explains why among Chinese women (many of whom are of generally shorter stature) the growth-enhancing estriol is not significantly or strongly associated with birth weight (Table III, upper panel). Secondly, it provides an explanation why estriol levels among Chinese women are higher compared to those among Caucasian women, even though birth weight is generally higher among the latter.

Thirdly, it accommodates the previous observation in the context of the early life roots of breast cancer hypothesis by highlighting birth weight and, presumably, the pool of mammary-specific stem cells as the crucial determinants of breast cancer risk. As indicated, we a priori decided to examine the interaction of maternal height only with estriol for the 27th gestational week since this is the only hormone in addition to IGF-I, which was not measured in this study, that has been positively associated with birth weight. Evaluation of the interaction of maternal height with other hormones or estriol earlier during pregnancy would have no biomedical justification in the absence of main effects of these hormones on birth weight, and it would generate multiple comparisons that would compromise the interpretability of the principal findings.

In the context we have presented, specific mammotropic and growth-enhancing hormones during pregnancy are delegated to the role of one among several perinatal determinants of adult breast cancer risk. It is not surprising that the interaction of estriol levels and maternal height with respect to birth weight was statistically significant among Caucasian women in Boston but not among Chinese women in Shanghai: the range of variation of maternal anthropometry and, accordingly, birth weight is more limited in the Chinese women, 89% of whom fall below the median height of Caucasian women in Boston. Overall, our data suggest that maternal anthropometric restrictions may trigger the operation of a feedback mechanism linking fetal size and pregnancy estriol levels.

A strength of this analysis is the specificity of the working hypothesis because physical constraint has been previously suggested as an important factor in fetal growth and estriol levels at the 27th gestational week have been found to be the most important endocrine factor for birth weight among the hormones measured in this project. Other strengths of the study are its prospective nature and its implementation according to a strict protocol at both centers. A limitation of our study is that a hormone which is likely to be as important as estriol for birth weight and perhaps future cancer risk, i.e., IGF-I, has not as yet been measured, nor have there been hormone determinations in cord blood. It would be of considerable importance to assess whether similar patterns to those presented here for maternal estriol also exist with respect to maternal IGF-I and to cord blood levels of these hormones.

In conclusion, we have found evidence that maternal height and, inferentially, physical constraints on fetal growth not only are important determinants of birth weight but also modify the positive association between birth weight and estriol (and conceivably other growth-enhancing mammotropic hormones). The interaction between maternal height and growth-enhancing mammotropic hormones may be crucial in the early life origins of breast cancer and reconciles the relevant analytic and ecologic epidemiologic evidence.

References