Placental Weight and Risk of Invasive Epithelial Ovarian Cancer with an Early Age of Onset

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Abstract

Background: Epithelial ovarian cancer is associated with reproductive factors, but we lack knowledge of hormonal factors during pregnancy influence the mother’s risk. Because pregnancy hormones are primarily produced by the placenta, placental weight may be an indirect marker of hormone exposure during pregnancy.

Methods: In a nationwide Swedish cohort study, we included women with singleton births from 1982 to 1989. Women were followed for occurrence of invasive epithelial ovarian cancer, death, or emigration through 2004. Hazard ratios (HR) with 95% confidence intervals (95% CI) from Cox models were used to estimate associations between pregnancy exposures and epithelial ovarian cancer.

Results: Among 395,171 women with information on placental weight in their first recorded birth, 316 women developed invasive epithelial ovarian cancer. Mean age at diagnosis was 44 years. Compared with women with a placental weight of 500 to 699 g, women with a high (≥700 g) placental weight had an increased risk of developing epithelial ovarian cancer (HR, 1.47; 95% CI, 1.14-1.90). Compared with women with term pregnancies (40-41 weeks), women with post-term (≥42 weeks) pregnancies had an increased risk of developing epithelial ovarian cancer (HR, 1.48; 95% CI, 1.00-2.19). These associations were slightly stronger when we included information about women’s overall first birth, and slightly weaker when we included information about last recorded birth or ever last birth from 1982 to 1989.

Conclusions: Because pregnancy hormone levels increase with placental weight, our study supports the hypothesis that hormone exposures during pregnancy influence the risk of invasive epithelial ovarian cancer among young women.

Introduction

Epithelial ovarian cancers constitute 80% to 90% of all invasive ovarian cancers. Evidence from epidemiologic and experimental studies indicates that ovarian carcinogenesis is in large part influenced by reproductive factors. The risk is reduced with increasing maternal age at first birth and use of oral contraceptives, whereas hormone replacement therapy (including estrogens but not continuous progestins) increases the risk (1, 2). The risk of epithelial ovarian cancer is reduced with increasing parity, whereas a short pregnancy exposure, such as a spontaneous abortion, does not influence risk (1, 3). We have previously reported that women who have an infant of low birth weight adjusted for gestational age (a measure of reduced fetal growth) is at reduced risk of developing epithelial ovarian cancer with an early age of onset (mean age at diagnosis was 43 years; ref. 4). Because fetal growth is closely associated with placental function, these findings support the hypothesis that pregnancy hormones influence the woman’s risk of developing epithelial ovarian cancer.

Pregnancy hormones, including estrogens and progesterones, are primarily produced by the placenta. Other placental hormones, such as human placental lactogen and placental growth hormone, are important regulators of maternal insulin-like growth factor-I (IGF-I), which stimulates fetal growth. Maternal serum levels of these hormones are many times higher in pregnant compared with nonpregnant women (5-8). Placental weight is positively associated with maternal serum values of estrogens, progesterone (6, 8), and IGF-I values (9). Placental weight is also positively associated with women’s subsequent risk of breast cancer (10, 11).

In the present investigation, we linked nationwide Swedish registers to investigate associations between placental weight and subsequent maternal risk of epithelial ovarian cancer with an early age of onset.

Materials and Methods

Data Sources. The Swedish National Board of Health and Welfare and Statistics Sweden provided access of data from four population-based registers. Individual
record linkage across these registers was possible through the individually unique national registration number, assigned to each Swedish resident.

The nationwide Swedish Birth Register includes prospectively collected information on 98% to 99% of all deliveries in Sweden (12). Information about placental weight was included in the Birth Register from 1982 to 1989. The Swedish Cancer Register includes histologically verified cancers. The Swedish law mandates and regulates both physicians and pathologists to report newly diagnosed malignant tumors to the Cancer Register. All case reports are verified for completeness at one of six regional cancer registries in Sweden and are then pooled in the Swedish Cancer Register. Case reporting is essentially 100% complete, and ~99% of the cases are morphologically verified (13). Cancer diagnoses are coded according to the International Classification of Diseases (ICD). To facilitate comparisons over time, all cases in the Cancer Register are also coded according to ICD-7 for all years. The Cancer Register also includes information about histologic classification using pathologic anatomic diagnostic codes.

The Cause of Death Register includes information about date and cause of death on all Swedish residents. The completeness has been estimated to exceed 99% (results are available mainly in Swedish) on the Web[6]. The Inpatient Register contains data for individual hospital discharges. The register covered 85% of the population from 1978, and from 1987, complete national coverage was achieved. Every inpatient discharge includes dates of hospital admission and discharge, up to eight discharge diagnoses (coded according to the ICD classifications), and up to 12 operation codes (coded according to the Swedish Classification of Operations and Major Procedures). Correct coding for surgical procedures is achieved in 98% of records (14). The Register of Population and Population Changes includes information about dates of birth, death, emigration, and immigration of all Swedish residents.

**Study Cohort.** The study base included 540,293 women with only singleton births, and at least one birth recorded in the Birth Register from 1982 to 1989, the years when placental weight was recorded. The study was approved by the research ethics committee at Karolinska Institutet (Stockholm, Sweden).

**Exposures and Outcome Data.** The Birth Register includes standardized information from antenatal, obstetric, and neonatal medical records. The following maternal and infant variables were collected from each consecutive singleton delivery: maternal age (years), parity, birth weight (grams), gestational age (in completed weeks), placental weight (grams), birth year, and gender of infant. In Sweden, the placenta is weighed with the membranes and the umbilical cord attached. We included in the analyses only histologically verified invasive epithelial ovarian cancer (ICD-7 code 175, combined with pathologic anatomic diagnostic codes 096 for adenocarcinoma, 196 for undifferentiated carcinoma, and 146 for squamous cell tumor; ref. 15). Data on bilateral oophorectomy were obtained from the nation-wide Inpatient Register, deaths from the Cause of Death Register, and emigrations from the Register of Population and Population Changes.

**Follow-up.** The 540,293 women in the study base were followed through December 31, 2004. We excluded women who had emigrated before start of follow-up [the birth of their last recorded infant (n = 5,768)], women with obvious erroneous data (n = 83), women who died the same day as they gave birth and therefore had no time of follow-up (n = 20), and, to allow at least 1 y of follow-up, women whose last birth was in 2004 (n = 2,244). We only used data where we had complete information on all covariates that would potentially be used in the statistical models, namely, age at first birth, birth year of first infant, attained parity at end of follow-up (using information from the Birth Register through 2004), and, for births from 1982 to 1989, information on birth weight, gestational age, placental weight, and sex of infant. Of the 532,178 eligible women, 2,404 women had nonnumeric placental weights or values outside the range of 200 to 1,499 g, which are likely to be errors in the data base, and these were set to missing. In all, 395,171 (74%) women had complete information on covariates, including information from their first recorded birth between 1982 and 1989. Of these, 350 developed borderline tumors and 404 invasive ovarian cancer (of which 316 (78%) were epithelial tumors, 54 (13%) were stromal, and 34 (8%) were germ-line ovarian cancers). Because of the variation in the risk factor profile for histologic subtypes of ovarian cancer (16), we present analyses limited to women with invasive epithelial ovarian cancer.

**Statistical Analyses.** Risk time (person-years) was accrued from the time of the woman’s overall last birth until a first diagnosis of epithelial ovarian cancer or censored at the date of first emigration from Sweden, death, bilateral oophorectomy, or end of follow-up (December 31, 2004), whichever occurred first. Associations between exposures in first recorded birth and epithelial ovarian cancer risk were assessed by incidence rates (i.e., number of epithelial ovarian cancer cases per 100,000 person-years). Incidence rates were calculated for placental weight (categorized into ≤499 g, 500-699 g, and ≥700 g), birth weight (categorized into ≤2,499 g, 2,500-2,999 g, 3,000-3,499 g, 3,500-3,999 g, and ≥4,000 g), gestational age (in completed weeks, and categorized as ≤36 wk, 37-39 wk, 40-41 wk, and ≥42 wk), offspring sex, highest attained parity during follow-up (categorized as 1, 2, 3, or ≥4), and maternal age at first birth (categorized as ≤24 y, 25-29 y, 30-34 y, and ≥35 y).

We used Cox proportional hazard regression models to evaluate associations of placental weight and gestational age with maternal risk of epithelial ovarian cancer by estimating hazard ratios (HR) with 95% confidence intervals (95% CI). In our first model, we only adjusted for attained age. In the second model, we also adjusted for birth year, child’s gender, highest attained parity, and maternal age at first birth. In the third model, we also mutually adjusted for placental weight and gestational age. Birth year was analyzed as a continuous variable, whereas other variables were categorized as presented above. Because differences between these models were minor, we limit the presentation to the fully adjusted (third) model.

Birth weight was highly correlated with placental weight and may also be considered to be in the causal pathway between placental weight and epithelial ovarian cancer. Because our prime exposure of interest was placental weight, birth weight was therefore not included in the Cox analyses. Likelihood ratio tests were used to evaluate the overall effect of each factor by testing all categories jointly against the reference group. The proportional hazards assumption was assessed graphically on each variable separately and also formally by conducting model-specific tests based on the Schoenfeld residuals (17). We found no evidence that our model specifications violated the proportional hazards assumption.

Our measurement of exposures was restricted to births from 1982 to 1989, when information about placental weight was recorded in the Birth Registry. However, because too few women had all their deliveries within the period 1982 to 1989, our possibilities to study the importance of exposures by pregnancy order were limited. We therefore investigated associations between placental weight and gestational age in overlapping cohorts of women with births from 1982 to 1989. First, we restricted the analyses to birth characteristics from women’s overall first birth (i.e., primiparous women) from 1982 to 1989 (n = 233,615). Second, we analyzed birth characteristics from women’s first recorded birth from 1982 to 1989 (n = 395,171). Third, we analyzed birth characteristics from last recorded birth from 1982 to 1989 (n = 399,745). Finally, we only included birth characteristics from women’s overall last birth (i.e., parous women) from 1982 to 1989 (n = 247,161). Descriptive statistics of women’s first recorded birth in Sweden 1982 to 1989 are presented in Table 1.

Due to the limited number of cases, we had insufficient statistical power to assess interactions between parity, placental weight, and gestational age with respect to risk of epithelial ovarian cancer. In addition, because information on exposures from two successive pregnancies was only available for 74 women who later developed epithelial ovarian cancer, it was not meaningful to study associations between placental weight in two successive pregnancies and risk of epithelial ovarian cancer.

### Results

The number of invasive epithelial ovarian cancers ranged from 129, when we only included women with information from their overall first birth, to 316, when we included information from the first recorded birth from 1982 to 1989. In these analyses, mean age at diagnosis varied from 40.5 to 44.2 years. Mean age at entry (i.e., age at overall last birth) was ~31 years, and mean years of follow-up varied from 13.7 to 18.3 years (Table 1).

Table 2 shows the distribution of pregnancy and maternal characteristics in the first recorded birth from 1982 to 1989 in relation to epithelial ovarian cancer. The crude incidence rates were higher among women with high (≥700 g) placental weight, women with low birth weight (<2,500 g) infants, and women with post-term (≥42 weeks) pregnancies. There was a U-shaped relationship between highest attained parity (i.e., parity number at end of follow-up) and incidence rates of epithelial ovarian cancer. The increasing incidence rates with maternal age at first birth were expected because age at first birth was positively associated with age at end of follow-up. Because the follow-up is on average 15 years, the majority of women with low age at first birth never reach ages above 40 when the majority of

### Table 1. Descriptive birth and ovarian cancer characteristics among women with single births, by different births in Sweden 1982 to 1989

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>First overall birth (n = 233,615)</th>
<th>First recorded birth (n = 395,171)</th>
<th>Last recorded birth (n = 399,745)</th>
<th>Last overall birth (n = 247,161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry (y)</td>
<td>Mean 30.1 (13-52)</td>
<td>Mean 31.1 (13-54)</td>
<td>Mean 31.1 (13-54)</td>
<td>Mean 30.6 (13-54)</td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>Mean 40.5 (24-59)</td>
<td>Mean 43.6 (21-61)</td>
<td>Mean 43.5 (21-61)</td>
<td>Mean 44.2 (21-61)</td>
</tr>
<tr>
<td>Mean follow-up (y)</td>
<td>Mean 13.7 (4.5-23)</td>
<td>Mean 15.5 (0-23)</td>
<td>Mean 15.5 (0-23)</td>
<td>Mean 18.3 (0-23)</td>
</tr>
<tr>
<td>Placental weight (g)</td>
<td>Mean 71,545</td>
<td>Mean 238,310</td>
<td>Mean 133,526</td>
<td>Mean 63,346</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>Mean 16,588</td>
<td>Mean 47,366</td>
<td>Mean 134,345</td>
<td>Mean 133,526</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>Mean 23,864</td>
<td>Mean 47,366</td>
<td>Mean 134,345</td>
<td>Mean 133,526</td>
</tr>
<tr>
<td>Sex</td>
<td>Female 191,675</td>
<td>Female 176,039</td>
<td>Female 134,345</td>
<td>Female 63,346</td>
</tr>
</tbody>
</table>

### Table 2. Birth characteristics and maternal characteristics of women’s first recorded birth in Sweden 1982 to 1989 in relation to incidence rates of maternal epithelial ovarian cancer (n = 395,171)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. (%)</th>
<th>Crude incidence rates*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental weight (g)</td>
<td>&lt;500</td>
<td>71,545 (18.1)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>&lt;2,500</td>
<td>16,588 (4.2)</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>&lt;37</td>
<td>23,864 (6.0)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 203,496 (51.5)</td>
<td>157</td>
</tr>
<tr>
<td>Highest attained parity</td>
<td>1</td>
<td>168,096 (42.5)</td>
</tr>
<tr>
<td>Age at first birth (y)</td>
<td>&lt;24</td>
<td>217,648 (55.1)</td>
</tr>
</tbody>
</table>

*Number of cases per 100,000 person-years.
cancers occur. Thus, it is not possible to provide robust estimates of age-standardized rates of ovarian cancer for the variable ‘age at first birth.’

Table 3 presents the HRs of maternal epithelial ovarian cancer in relation to placental weight and gestational age following (a) women’s overall first birth (i.e., primiparous women), (b) women’s first recorded birth, (c) women’s last recorded birth, and (d) women’s overall last birth from 1982 to 1989. In primiparous women, the HR related to a high (>700 g) placental weight was 1.69 (95% CI, 1.12-2.56). When similar analyses were done by including information from first recorded birth, last recorded birth, and overall last birth, the risk related to a high placental weight risk successively decreased. Gestational age was not significantly associated with risk of epithelial ovarian cancer in any model. However, similar to placental weight, the point estimate of the risk related to a post-term pregnancy (>42 weeks) was highest in primiparous women (HR, 1.60; 95% CI, 0.91-2.80) and successively decreased to 1.22 when information of women’s overall last birth was included.

**Discussion**

In the present population-based cohort study, we found that a high placental weight increased mother’s risk of developing invasive epithelial ovarian cancer with an early age of onset. We also found that the risk may be increased among mothers with post-term pregnancies. These findings support the hypothesis that pregnancy hormone levels influence women’s risk of early-onset epithelial ovarian cancer. However, given our previous finding that a low birth weight in term pregnancies is associated with a reduced risk of epithelial ovarian cancer among young women (4), we would also have expected a protective role of low placental weight.

During pregnancy, maternal concentrations of hormone levels possibly involved in ovarian cancer development generally increase with gestational age, placental weight, and fetal growth (18). Progesterone has been suggested to have a protective role in ovarian cancer development by suppressing epithelial proliferation, promoting cell differentiation and apoptosis, or removing premalignant cells from ovaries (19). Because progesterone levels increase with placental weight (7), our findings that a high placental weight increases the risk of epithelial ovarian cancer do not support a protective role of progesterone during pregnancy in ovarian cancer development. Alternately, a protective role of progesterone may be outweighed by the influence of other hormonal factors during pregnancy. One plausible explanation is exposure to IGF-I because serum levels of IGF-I are strongly positively associated with risk of premenopausal ovarian cancer (20). IGF-I values increase with placental weight (21) and are increased in late pregnancy (22), and growth-restricted pregnancies have reduced IGF-I values (23).

The positive association between placental weight and risk of epithelial ovarian cancer may also be explained by other hormonal exposures. Maternal serum levels of estrogens increase with placental weight (6), and long-term use of postmenopausal estrogens may increase the risk of epithelial ovarian cancer (2). However, serum levels of estrogens have not been associated with risk of ovarian cancer (24, 25). Circulating levels of androgens may also play a role because androstenedione has been positively associated with premenopausal ovarian cancer (24). Because of the active metabolism of androgens in the placenta, androgen metabolites are present in much higher concentrations in pregnant compared with non-pregnant women (18).

Our results also unexpectedly indicate an increased risk of epithelial ovarian cancer among women with post-term pregnancies. Dehydroepiandrosterone sulfate is considered to be a biologically inactive precursor, which is first converted to androgens and thereafter to estrogens. If dehydroepiandrosterone sulfate is provided i.v. to post-term and term pregnancies, the half-life of estrogens is increased compared with non-pregnant women (18). Progesterone is considered to be a biologically inactive precursor, which is first converted to androgens and thereafter to estrogens. If androstenedione has been positively associated with premenopausal ovarian cancer (24). Because of the active metabolism of androgens in the placenta, androgen metabolites are present in much higher concentrations in pregnant compared with non-pregnant women (18).

Our results also unexpectedly indicate an increased risk of epithelial ovarian cancer among women with post-term pregnancies. Dehydroepiandrosterone sulfate is considered to be a biologically inactive precursor, which is first converted to androgens and thereafter to estrogens. If dehydroepiandrosterone sulfate is provided i.v. to post-term and term pregnancies, the half-life of dehydroepiandrosterone sulfate is longer in post-term than term pregnancies, whereas the increases in estrogens are less pronounced (26). The endocrinology of post-term pregnancies is not well studied, and we do not know androgen levels in post-term pregnancies. If the

### Table 3. Placental weight and gestational age in relation to maternal epithelial ovarian cancer

<table>
<thead>
<tr>
<th>No. epithelial ovarian cancers</th>
<th>First overall birth (n = 233,615)</th>
<th>First recorded birth (n = 399,171)</th>
<th>Last recorded birth (n = 399,745)</th>
<th>Last overall last birth (n = 247,161)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)*</td>
<td>HR (95% CI)*</td>
<td>HR (95% CI)*</td>
<td>HR (95% CI)*</td>
</tr>
<tr>
<td>Placental weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>1.38 (0.89-2.15)</td>
<td>1.13 (0.83-1.54)</td>
<td>1.06 (0.76-1.47)</td>
<td>1.06 (0.75-1.50)</td>
</tr>
<tr>
<td>500-699</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>700+</td>
<td>1.69 (1.12-2.56)</td>
<td>1.47 (1.14-1.90)</td>
<td>1.35 (1.05-1.74)</td>
<td>1.29 (0.98-1.69)</td>
</tr>
<tr>
<td>Likelihood ratio test</td>
<td>0.039</td>
<td>0.014</td>
<td>0.075</td>
<td>0.198</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37</td>
<td>1.00 (0.48-2.07)</td>
<td>1.01 (0.61-1.66)</td>
<td>0.85 (0.49-1.49)</td>
<td>0.90 (0.50-1.61)</td>
</tr>
<tr>
<td>37-39</td>
<td>0.98 (0.67-1.45)</td>
<td>1.08 (0.85-1.38)</td>
<td>1.14 (0.90-1.45)</td>
<td>1.19 (0.92-1.54)</td>
</tr>
<tr>
<td>40-41</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>42+</td>
<td>1.60 (0.91-2.80)</td>
<td>1.48 (1.00-2.19)</td>
<td>1.40 (0.92-2.14)</td>
<td>1.22 (0.75-1.99)</td>
</tr>
<tr>
<td>Likelihood ratio test</td>
<td>0.423</td>
<td>0.312</td>
<td>0.297</td>
<td>0.469</td>
</tr>
</tbody>
</table>

**NOTE:** Risks are presented for characteristics of women’s overall first birth, first recorded birth, last recorded birth, and women’s overall last birth from 1982 to 1989 in Sweden.

*HRs and 95% CIs derived from Cox proportional hazard models, adjusted for attained age, birth year of first child, child’s gender, highest attained parity, and maternal age at first birth, and mutually adjusted for placental weight and gestational age.

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reduced estrogen levels in post-term pregnancies are caused by reduced conversion of androgens to estrogens, then androgen levels may be increased. Alternatively, if the capacity to convert dehydroepiandrosterone sulfate to androgens is reduced, both androgen and estrogen levels are decreased in post-term pregnancies. Thus, the reasons for a possible increased risk of epithelial ovarian cancer related to post-term pregnancies remain to be determined.

The population-based Swedish Birth Register enabled us to establish a study population of women with prospectively recorded information on maternal and birth characteristics. In addition, the availability of unique national registration numbers and information retrieved from other population-based registers made it possible to do an almost complete follow-up. Because mean age at diagnosis of epithelial ovarian cancer was 44 years, conclusions must be restricted to epithelial ovarian cancer with an early age of onset.

Our novel findings must be interpreted cautiously, given several possible limitations. Although the study population included 400,000 women, mean time of follow-up was limited to 15 years. Because the present study included only ~300 epithelial ovarian cancer cases, it was not possible to study the joint effect of birth weight and gestational age on risk of epithelial ovarian cancer. Thus, we were, possibly due to limited statistical power, unable to confirm our previous finding of a protective effect of restricted fetal growth from a study based on >1,000 epithelial ovarian cancers (4).

The limited number of cases did not allow us to study the “cumulative exposure” related to placental weight by examining the effect of placental weight across several pregnancies, nor was it possible to do interaction analysis between parity number and placental weight. We therefore did separate analyses of birth characteristics from primiparous women, women’s first and last recorded birth during the interval, and women’s overall last birth in largely overlapping cohorts. Risks of epithelial ovarian cancer related to a high placental weight and a post-term pregnancy were highest when we included information from pregnancies to primiparous women and lowest when similar information from women’s overall last birth was included. We have little knowledge how placental weight and gestational age relate to hormonal mechanisms during pregnancy and epithelial cancer etiology in primiparous and multiparous women, respectively. Still, given the previously obtained finding of an inverse association between age at first birth and risk of epithelial ovarian cancer (15), these findings further support the hypothesis that exposures related to the first pregnancy may be of special importance in ovarian carcinogenesis.

Our data permitted adjustments for highest attained parity and age at first birth, factors that influence epithelial ovarian cancer risk (1, 2, 15). However, we cannot exclude the possibility of residual confounding. For example, we do not have information on family history of ovarian cancer, and we also lack information of oral contraceptive use, which reduced risk of ovarian cancer (1, 2). However, we see no compelling mechanisms by which oral contraceptive use or family history of ovarian cancer should be associated with placental weight or post-term birth, and thus act as confounders.

In fact, there has been a report that pregravid oral contraceptive use is positively associated with fetal growth (27), which may introduce negative confounding, partially obscuring the association we report.

Epithelial ovarian cancer is dependent on events related to hormonal exposures throughout a woman’s life. Our findings that a high placental weight increases the risk of epithelial ovarian cancer, combined with the previous finding of a protective effect of reduced fetal growth, agree with the hypothesis that risk of ovarian cancer is also influenced by hormonal exposures in the relatively short time window defined by a pregnancy. Underlying biological mechanisms may also include maternal or genetic characteristics influencing placental and fetal growth.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgments
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References


