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## Gestational Age and Fetal Growth in Relation to Maternal Ovarian Cancer Risk in a Swedish Cohort

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### Abstract

**Background**—Pregnancy influences subsequent maternal ovarian cancer risk. To date, there is limited evidence whether two characteristics of pregnancy, gestational age and birth weight, could modify risk.

**Materials and Methods**—We studied 1.1 million Swedish women who delivered singleton births between 1973 and 2001. Information on infant gestational age and birth weight was abstracted from the nationwide Swedish Birth Register. Women were followed prospectively through linkage with other population-based registers for occurrence of ovarian cancer, death, or emigration through 2001. Hazard ratios [relative risk (RR), 95% confidence interval (95% CI)] from Cox models were used to estimate associations between gestational age, birth weight, and epithelial ovarian cancer risk.

**Results**—During 12.6 million person-years, 1,017 epithelial ovarian cancers occurred. Mean age at diagnosis was 43 years. Compared with women with term deliveries ( $\geq 40$  weeks), women with moderately (35–36 weeks) or very ( $< 35$  weeks) preterm deliveries had increased risks of epithelial ovarian cancer (RR 1.4, 95% CI 1.0–2.0 and RR 2.3, 95% CI 1.3–3.8, respectively). In contrast, women giving birth to small-for-gestational-age babies had a reduced risk (RR 0.7, 95% CI 0.4–1.0). Stratifying on birth weight and gestational age, there was a strong protective effect of low birth weight on maternal risk of epithelial ovarian cancer among term deliveries, whereas birth weight seemed to have little effect among preterm births ( $P_{\text{interaction}} = 0.022$ ).

**Conclusions**—Our results lend further support that the hormonal milieu of a pregnancy may modify long-term risk of developing ovarian cancer.

## Introduction

The risk of invasive epithelial ovarian cancer decreases with increasing parity (1–4), whereas incomplete pregnancies, such as spontaneous abortions or ectopic pregnancies, seem to confer no protection (5). These lines of evidence suggest that the protective effect of pregnancy on a woman may be modified by specific pregnancy characteristics over the course of childbearing.

The pregnancy hormonal milieu is characterized by elevated levels of estrogens, progesterone, and intrauterine growth factors, which are almost exclusively produced by the placenta. A woman's exposure to these hormones is markedly higher during the latter compared with earlier stages of pregnancy. Moreover, the duration of exposure to pregnancy hormones is greater for women who deliver term births compared with preterm births. Placental hormones and growth factors, such as insulin-like growth factor I (IGF-I), are positively associated with fetal growth (6–10). Thus, birth weight and gestational age can be viewed as potential proxies of maternal exposure to pregnancy hormones.

Two previous studies failed to find an association between infant's birth weight and mother's risk of ovarian cancer (11,12). However, birth weight reflects the influence of both gestational age and fetal growth, and these measures were not accounted for in the published analyses. To this end, we undertook a nationwide cohort study of more than 1.1 million women in the Swedish Birth Register between 1973 and 2001. These women were followed prospectively to study gestational age and fetal growth in relation to maternal risk of invasive epithelial ovarian cancer.

## Materials and Methods

### Swedish Birth Cohort

The study base included all Swedish women with singleton births whose first birth was delivered from January 1, 1973, and whose subsequent births, if any, were recorded before January 1, 2002. Information on births during this time was obtained from the nationwide Swedish Birth Register established in 1973 and collecting information on 98% to 99% of all deliveries in Sweden (13). An individually unique national registration number, assigned to each Swedish resident, facilitated linkage of the birth register data with other nationwide population registers. The study was approved by the research ethics committee at Karolinska Institutet, Stockholm.

### Exposure and Covariate Data

The birth register included 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), birth weight (grams), gestational age (through completed week), birth year, and infant sex. The birth register was recently validated, and the quality of the variables included in the present investigation is considered high (13). Through linkage with the education register, years of formal education completed as of December 31, 1997, were obtained from Statistics Sweden. If this information was missing, we retrieved similar information on completed education as of December 31, 1992. Data on bilateral oophorectomy [isolated bilateral oophorectomy, bilateral salpingoophorectomy, and (vaginal and abdominal) hysterectomy combined with salpingoophorectomy] or other surgical removal of remaining ovarian tissue were obtained from the nationwide in-patient register, which maintained 85% of Sweden from 1978 and a nation-wide coverage from 1987 onwards.

### Outcome Assessment

Information on incident ovarian cancer was derived from the Swedish Cancer Register established by the National Board of Health and Welfare in 1958. Swedish law mandates and

regulates physicians and pathologists to report every newly diagnosed malignant tumor to the register, and case reporting is essentially 100% complete (14). All case reports are verified for completeness at one of six regional registries in Sweden, computerized, and then pooled in the Swedish Cancer Register. Cancer diagnoses are classified according to the International Classification of Diseases. To facilitate comparison over time, the cancer register includes information about the seventh version of the International Classification of Diseases classification (ICD-7) for all years. Invasive ovarian cancer was defined by ICD-7 code 175; borderline tumors were excluded from the analysis. The cancer register also includes histologic classification (PAD codes).

Information on deaths was available from the National Cause of Death Register, which includes dates of death from specific causes obtained from death certificates. Established in 1953 with complete coverage since 1961, this database maintains date and cause of death for >99% of deaths among residents (15). From the register of total population changes, we collected data on emigration from Sweden.

We excluded from the cohort women who were <15 years of age at their first birth or who were diagnosed with cancer before the index birth. Of the 1,176,784 million women identified, 2,432 have missing data on gestational age or birth weight and were excluded, so that the final sample size for analysis was 1,174,352. Through 2001, 1,173 cases of ovarian cancer occurred in the birth cohort, of which 1,017 (87%) were epithelial tumors, 61 (5%) were stromal, and 56 (5%) were germ-line ovarian cancers. Because of the variation in the risk factor profile for histologic subtypes of ovarian cancer (16), we focused on women with epithelial ovarian cancer.

### Statistical Analysis

Person-years were accrued from time of the index birth (i.e., latest birth) until a diagnosis of epithelial ovarian cancer or censored at the date of other subtypes of ovarian cancers, emigration from Sweden, death, bilateral oophorectomy, or end of the study period (December 31, 2001), whichever came first. Incidence rates of epithelial ovarian cancer were calculated by dividing the number of incident cancers by person-years in each category. To estimate the total effect of pregnancy on a woman's risk of cancer, we calculated the mean gestational age and birth weight across each pregnancy, evaluating these variables as continuous, ordinal, and categorical variables to examine potentially nonlinear risk effects.

We used Cox proportional hazard models to evaluate the relation between birth characteristics and maternal risk of epithelial ovarian cancer, calculating hazard ratios [relative risk (RR)] and 95% confidence intervals (95% CI) as effect measures. The following factors were included in models as potential confounders: age at birth (continuously), birth year (ordinally), parity (categorically), infant sex, and maternal education (categorically). Additionally, we simultaneously adjusted for birth weight (categorically) and gestational age (ordinally) in the same model. Birth weight adjusted for gestational age provides an estimate of fetal growth. Tests for trend were estimated by modeling each exposure category ordinally in multivariable regression. To examine the joint effects of birth weight and gestational age, we cross-classified women according to both factors and compared the  $-2$  log-likelihood from this model compared with a model with only the main effects. We further assessed the relation between birth characteristics and pregnancy stratifying by parity, comparing estimates among uniparous, biparous, and triparous women.

### Results

The cohort included 1,174,352 Swedish women who gave birth between 1973 and 2001 and contributed 12.6 million person-years to the study base. The cohort was relatively young, with a mean age at study entry of 28.8 years and a mean follow-up of 10.3 years. The mean age at

cancer diagnosis in this young cohort was 43 years; age-specific incidence rates of ovarian cancer peak in most populations between the ages of 65 and 79 years (5). The distribution and incidence of cancer overall and stratified by parity is presented in Table 1. As expected, the age-adjusted incidence of epithelial ovarian cancer decreased with increasing parity. The gestational age of pregnancies was similar across parity, whereas mean birth weight increased with increasing parity (Table 1). Because only 32 cancer cases occurred among women who had four or more births, these women were excluded from analyses stratified by parity.

In the cohort, 4% of women had a mean gestational age across pregnancies of <37 weeks gestation (preterm birth) whereas, in 3%, mean birth weight was <2,500 g (low birth weight). Table 2 presents the RR of maternal epithelial ovarian cancer in relation to gestational age and birth weight among the women. Overall, the data suggest an inverse relation between pregnancy gestational age and cancer risk. Adjusting for maternal characteristics, women who deliver at 35 weeks gestation or earlier have a 60% higher risk compared with term women, although the RR was more than doubled when mutually adjusting for birth weight. For birth weight, the cancer incidence rates were similar for women whose infants had low, normal, and high birth weights and, adjusting for maternal characteristics, did not change this pattern. However, when we simultaneously adjusted for gestational age in the model, low birth weight was associated with a lower risk of maternal epithelial ovarian cancer compared with normal for gestational age infants.

The effect of gestational age seemed to be most evident among uniparous women, wherein women who delivered at <35 weeks had, compared with women who delivered term infants, a tripled risk of ovarian cancer (RR 3.0, 95% CI 1.6–5.6), after adjusting for maternal characteristics and birth weight. For biparous women, the corresponding RR was 1.9 (95% CI 0.7–5.0), whereas no risk estimate could be obtained among triparous women given small numbers in that category ( $P_{\text{interaction by parity}} = 0.12$ ). As with gestational age, the protective effect of low birth weight adjusted for gestational age was somewhat stronger among uniparous women (adjusted RR 0.6, 95% CI 0.3–1.0) compared with biparous (adjusted RR 0.8, 95% CI 0.4–1.7) and triparous women (adjusted RR 0.8, 95% CI 0.1–6.9;  $P_{\text{interaction by parity}} = 0.01$ ). For all analyses, excluding cancers that occur during the first 5 years of follow-up did not change the findings.

The apparent dual effect of birth weight and gestational age on a mother's cancer risk is further shown by simultaneously stratifying on gestational age and birth weight (Table 3). We see a protective effect of low birth weight on maternal cancer risk among term deliveries, whereas birth weight seems to have little effect among preterm births. Among all women who had low birth weight babies (<2,500 g), women who delivered a preterm birth were at greater risk of developing ovarian cancer compared with term births (contrast RR 3.3, 95% CI 1.3–8.6). Preterm birth among higher birth weight infants remained a positive predictor, albeit weaker, of maternal ovarian cancer risk.

## Discussion

In the present population-based cohort study, we found that the risk of epithelial ovarian cancer was higher for pregnancies with a shorter gestation but lower if the mother delivered a small-for-gestational-age infant. The effects of gestational age and fetal growth seemed stronger among uniparous women. Given the young age of the cohort, these findings have implications, particularly for premenopausal ovarian cancer risk. The results from this study lend further support that the hormonal milieu of a pregnancy may impart long-term effects in the development of ovarian cancer and also highlight the complexity of ovarian cancer etiology.

The finding that gestational age influences risk of epithelial ovarian cancer among parous women lends support to the “progesterone deficiency hypothesis,” whereby progesterone deficiency may increase the risk of ovarian cancer (17). Progesterone may be effective in suppressing epithelial proliferation, promoting cell differentiation and apoptosis, or removing premalignant cells from ovaries (18). During pregnancy, progesterone levels increase with gestational age (10), and thus, women with preterm births would have a pregnancy characterized by a relative deficit compared with term births. The progesterone deficiency hypothesis is further supported by evidence of lack of effect of hormone replacement therapy on ovarian cancer risk when progestins are continuously added (19). Moreover, twinning is associated with a reduced risk of maternal ovarian cancer (20–23), and pregnancy levels of progesterone are elevated among mothers who give birth to dizygotic twins (24).

In the present study, low birth weight was associated with a reduced risk of epithelial ovarian cancer after adjustment for gestational age. This unexpected finding, which was prominent in term pregnancies, needs to be confirmed, and we can only speculate about possible mechanisms. Although pregnancy levels of progesterone are positively associated with birth weight (25), fetal growth measures are likely to have a weak discriminatory ability as indicator of progesterone exposure (8). Exposure to IGF-I may be a more plausible possibility. Although IGF-I levels increase with gestational age, they are reported to decrease after 37 weeks of gestation and severely growth-restricted pregnancies have reduced IGF-I levels (26–29). A role of IGF-I on ovarian cancer is emerging, with higher levels associated with an almost 5-fold increased risk of developing ovarian cancer before 55 years in one prospective study (30).

We also found that the influence of gestational age and fetal growth of ovarian cancer may be more pronounced among uniparous women versus biparous or triparous women. Chance is an unlikely explanation, as we included more than 328,000 uniparous, 561,000 biparous, and 219,000 triparous women, of whom 401, 447, and 137 developed epithelial ovarian cancer, respectively. Selection bias is not an issue because we did a nationwide population-based study and found, consistent with literature (5,20,31), that the risk of ovarian cancer was higher among uniparous than multiparous women. The explanation for our finding of a differential effect may be related to inherent differences between uniparous women and women with higher parity. For example, uniparous women may, in part, represent women with a history of subfecundity. Infertile women may be predisposed to preterm delivery (32), and women with single pregnancies after *in vitro* fertilization have a doubled risk of preterm birth (33). There is also growing concern that fertility treatments that induce ovulation may influence ovarian cancer risk (20,31).

A related possibility is the polycystic ovarian syndrome (PCO). Highly related to subfertility and infertility (28), PCO is thus likely to be more common among uniparous compared with biparous women. PCO is associated with increased risks of ovarian cancer (34,35) and preterm birth (36,37) and reduced risk of small-for-gestational-age birth (38). PCO is also associated with hyperandrogenism and increased IGF-I levels (34), which may also impart effects in the risk of ovarian cancer (17,28). PCO is notoriously underreported, and it is estimated that between 5% and 20% of all premenopausal women suffer from this syndrome (39). In the present data set, information about PCO was not available. Thus, we may only speculate whether the observed associations between gestational age, fetal growth, and risk of epithelial ovarian cancer among uniparous women may be explained, at least in part, by a high prevalence of PCO in this group of women.

The availability of population-based data from nation-wide health registers in Sweden allows for a valid and efficient design to study birth characteristics and maternal ovarian cancer risk. The birth register and cancer register have virtually complete coverage of the population in



Sweden, and linkages to the cause of death and population registers ensure minimal loss to follow-up. The large study base provided information on more than a thousand cases of incident epithelial ovarian cancers diagnosed primarily among premenopausal women over follow-up, affording substantial statistical power to evaluate the research question. Women in the cohort under study were young at entry, and the majority of cases were diagnosed before menopause. As such, these effects are generalizable to ovarian cancer occurring among premenopausal women. It will, of course, be important to examine the longer term influence of pregnancy during menopause.

For multiparous women, we modeled the mean gestational age and birth weight across pregnancies, thereby accounting for the average pregnancy experience of the women on her future cancer risk. We also examined the effect of the first pregnancy alone, the last pregnancy alone, as well as the joint effects across pregnancies. Qualitatively, the findings were similar.

Based on histopathologic review at the reporting medical center, we restricted the study to women diagnosed with invasive epithelial ovarian cancer, whereas borderline tumors were excluded. Histologic classification of ovarian cancer based on cell types in the ovary can be complex, given the cellular diversity of the ovary, and classification of tumors as borderline is somewhat controversial (40). The extent to which, the association of birth weight and gestational age differs for borderline and invasive tumors could introduce a bias. However, the number of borderline tumors, incorrectly classified as invasive, is likely to represent only a small proportion of the total overall and unlikely to impart significant influence on our risk estimates.

The reporting of birth weight and gestational age is standardized from the antenatal records and has been shown to be of high quality (41). Any misclassification would be minimal and nondifferential and would not account for the differential effect among uniparous and biparous women. Finally, we cannot exclude the possibility that residual confounding could explain the study findings. For example, the registries do not contain information on oral contraceptive use, a factor associated with a lower risk of ovarian cancer (5). Although use of oral contraceptives may be correlated with birth weight and pregnancy hormones (42), it seems unlikely that use of oral contraceptives could impart substantial confounding to explain the findings among uniparous women, nor it would have a differential effect among the uniparous and biparous women.

In summary, novel findings from this large, prospective study suggest specific effects of pregnancy characteristics on maternal ovarian cancer risk. These effects highlight a potential role of fetal growth and gestational age during pregnancy in predicting a woman's future risk.

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Table 1  
 Descriptive birth and ovarian cancer characteristics among 1,174,352 women in the Swedish Birth Cohort 1973–2001, by parity

	Overall	Uniparous	Biparous	Triparous	Multiparous (4+ births)
Cohort	N = 1,174,352	n = 326,251	n = 561,846	n = 219,915	n = 66,340
Mean gestational age across pregnancies, wk	39.8	39.8	39.9	39.9	39.8
Mean birth weight across pregnancies, g	3,496	3,409	3,520	3,552	3,538
Male births, %	51.3%	51.3%	51.3%	51.2%	51.3%
Mean age at index birth, y	28.8	27.7	28.6	30.4	31.5
Epithelial ovarian cancers, <i>n</i>	1,017	401	447	137	32
Mean age at diagnosis, y	43.6	44.4	43.5	43.1	42.4
Incidence rate per 100,000 person-years	8.11	12.06	6.97	6.10	5.06
Age-adjusted RR (95% CI)	—	Reference	0.75 (0.65–0.86)	0.73 (0.60–0.90)	0.63 (0.44–0.91)

**Table 2**

Gestational age and birth weight in relation to maternal epithelial ovarian cancer risk among 1,174,352 women, Swedish Birth Cohort 1973–2001

	Maternal risk of epithelial ovarian cancer			
	Cohort, %	No. cases cancer	RR (95% CI) <sup>*</sup>	RR (95% CI) <sup>†</sup>
Gestational age, wk				
<35	1.4	26	1.6 (1.1–2.4)	2.3 (1.3–3.8)
35	1.0	17	1.6 (1.0–2.6)	1.9 (1.2–3.3)
36	2.0	22	1.0 (0.7–1.6)	1.2 (0.8–1.9)
37	4.5	44	1.0 (0.7–1.3)	1.1 (0.8–1.5)
38	12.0	127	1.1 (0.9–1.3)	1.1 (0.9–1.4)
39	25.3	233	1.0 (0.9–1.2)	1.0 (0.9–1.2)
40+	53.9	548	Reference	Reference
<i>P</i> <sub>trend</sub>			0.028	0.0097
Birth weight, g <sup>†</sup>				
<2,500	2.8	38	1.0 (0.7–1.5)	0.7 (0.4–1.0)
2,500–2,999	10.4	121	1.0 (0.8–1.2)	0.9 (0.7–1.2)
3,000–3,499	35.3	364	Reference	Reference
3,500–3,999	37.6	372	1.0 (0.9–1.2)	1.1 (0.9–1.2)
4,000+	13.9	122	1.0 (0.8–1.2)	1.0 (0.8–1.2)
<i>P</i> <sub>trend</sub>			0.99	0.19

\* Hazard ratios and 95% CIs derived from Cox proportional hazard models and adjusted for maternal age at index birth (continuous), birth year of index birth (continuous), education (categorical), baby's gender, and parity (categorical).

<sup>†</sup> Also mutually adjusted for gestational age and birth weight; birth weight adjusted for gestational age is a measure of fetal growth.

**Table 3**

The dual effect of gestational age and birth weight on epithelial ovarian cancer risk among parous women who gave birth during 1973 to 2001, Swedish Birth Cohort 1973–2001

Birth weight	Gestational age, RR (95% CI) *	
	Preterm (<37 wk)	Term (≥37 wk)
<2,500	1.4 (1.0–2.1)	0.4 (0.2–1.0)
2,500–2,999	1.3 (0.8–2.0)	1.0 (0.8–1.2)
3,000–3,499	1.5 (0.8–2.8)	Reference
3,500+ <sup>†</sup>		1.0 (0.9–1.2)
$P_{\text{interaction}} = 0.023$		

\* Hazard ratios and 95% CIs derived from Cox proportional hazard models and adjusted for maternal age at index birth, birth year of index birth, education, baby's gender, and parity.

<sup>†</sup> Less than 0.2% of women had preterm babies who weighed 3,500+ g, and there were no ovarian cancers in the group.