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Intrauterine Factors and Risk of Nonepithelial Ovarian Cancers

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ABSTRACT

Objective: The majority of ovarian tumors in girls and young women are nonepithelial in origin. The etiology of nonepithelial ovarian tumors remains largely unknown, and intrauterine exposures may play an important role. We examined the association of perinatal factors with risk of nonepithelial ovarian tumors in girls and young women.

Methods: National cohort study of 1,536,057 women born in Sweden during 1973-2004 and followed for diagnoses of nonepithelial ovarian tumors through 2009 (attained ages 5-37 years). Perinatal and maternal characteristics, and cancer diagnoses were ascertained using nationwide health registry data.

Results: 147 women were diagnosed with nonepithelial ovarian tumors in 31.6 million person-years of follow-up, including 94 with germ cell tumors and 53 with sex-cord stromal tumors. Women born preterm (<37 weeks of gestation) had significantly increased risk of developing nonepithelial ovarian tumors (adjusted hazard ratio 1.86, 95% CI 1.03-3.37; p=0.04). Histological subgroup analyses showed that preterm birth was associated with increased risk of sex-cord stromal tumors (4.39, 2.12-9.10; p<0.001), but not germ cell tumors (0.68, 0.21-2.15; p=0.51). No significant associations were found with fetal growth, birth order, and maternal age at birth.

Conclusions: This large cohort study provides the first evidence that preterm birth is a risk factor for developing sex cord-stromal tumors. Ovarian hyperstimulation in response to high gonadotropin levels in preterm girls could mediate disease risk through the proliferative and steroidogenic effects of FSH and LH on granulosa and theca cells, from which most sex-cord stromal tumors are derived.

INTRODUCTION

The majority of ovarian tumors in girls and young women are nonepithelial in origin.[1] Nonepithelial ovarian cancers are comprised of sex-cord stromal tumors, believed to arise from the sex cord and stromal components of the embryonic gonad, and germ cell tumors, derived from the primordial germ cells.[2] Together, these tumors account for about 10% of all ovarian cancers.[3] Because of their rarity, nonepithelial ovarian cancers have seldom been studied and their etiology remains largely unknown. Recent genetic studies have shown that somatic missense mutations in the *DICER1* and *FOXL2* genes are common in nonepithelial ovarian tumors.[4-6] However, the risk factors which predispose to the development of these oncogenic mutations in some women are unknown. We hypothesize that the perinatal period constitutes a critical window of susceptibility to exposures because elevated hormone levels and ovarian follicular development and maturation occur during fetal life and early infancy.[7] We conducted a Swedish national cohort study to examine the association of gestational age at birth, fetal growth and other perinatal factors with the risk of developing nonepithelial ovarian cancers in childhood through young adulthood. To our knowledge, this is the first epidemiologic study of gestational age at birth and fetal growth in relation to subsequent risk of nonepithelial ovarian cancers.

METHODS

Study population and procedures

We identified 1,546,771 women in the Swedish Birth Registry who were born during 1973-2004. We excluded women with missing information for gestational age at birth (n=3797) or birth weight (n=4601), and recorded birth weight >4 standard deviations above or below the

mean birth weight for gestational age and sex based on a Swedish reference growth curve[8] because of possible coding errors (n=2316). We included the remaining 1,536,057 women (99.3% of the entire birth cohort). This study was approved by the Regional Ethics Committee of Lund University in Malmö, Sweden.

The study cohort was followed for diagnoses of nonepithelial ovarian tumors from birth through December 31, 2009; the maximum attained ages ranged from 5 to 37 years. The Swedish Cancer Registry includes all primary cancers diagnosed since 1958, with compulsory reporting nationwide. Ovarian tumors were identified by diagnosis code 175 in the *International Classification of Diseases*, version 7 (*ICD*-7); code 183 in *ICD*-8 and *ICD*-9; and code C56 in *ICD*-10. Histologic types were classified using morphology codes in the *International Classification of Diseases for Oncology* according to World Health Organization guidelines.[9] Family history of ovarian or breast cancer in a parent or sibling was determined by Swedish Cancer Registry records for 1958-2009 rather than by self-report, enabling complete and unbiased ascertainment. Breast cancer history was ascertained in both male and female first-degree relatives.

Perinatal and familial characteristics potentially related to the risk of nonepithelial ovarian tumors were identified from the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number.[10,11] Gestational age at birth was based predominantly on the mother's reported last menstrual period in the 1970s, when ultrasound estimation was introduced gradually, and was based exclusively on ultrasound starting in the 1990s. Fetal growth was defined as the number of standard deviations (SD) from the mean birth weight for gestational age and sex based on a Swedish reference growth curve.[8] We focused on fetal growth rather than birth weight because birth weight is the outcome of

gestational age and fetal growth and a separate examination of each component yields more informative and interpretable results.

Statistical analysis

We estimated hazard ratios (HRs) for nonepithelial ovarian tumors overall, and germ-cell and sex-cord-stromal tumors separately, using Cox regression with age as the analysis time. Women were censored at: death (n=12,322; 0.8%), emigration determined by the absence of a Swedish residential address in census data (n=53,246; 3.4%), or diagnosis with epithelial ovarian cancer (n=281; 0.02%). We categorized gestational age at birth as <37, 37-41, and ≥42 weeks; fetal growth as <-1, -1 to <1, and ≥1 SD; birth order as 1, 2, 3, and ≥4; and mother's age at birth as <25, 25-29, 30-34, and ≥35 years, in order to allow for non-linear effects. Mother's education level was categorized as: compulsory high school or less (<10 years), practical high school or some theoretical high school (10-11 years), theoretical high school and/or some college (12-14 years), college and/or post-graduate study (≥15 years), or unknown. Father's education level was also examined, but not retained in the final model because it was highly correlated with mother's education level and did not significantly predict or confound associations with disease risk. Parity (0 vs. ≥1 live births) was modeled as a time-dependent variable to account for changes in a woman's childbearing status over time. Age at first birth was modeled as a continuous variable among 267,958 parous women by left truncation of the data up to the time of the woman's first birth. We assessed the proportional hazards assumption using the method of Grambsch and Therneau[12] and found no evidence that this assumption was violated. All statistical tests were 2-sided and performed using Stata (version 13.0).

RESULTS

Among 1,536,057 women in this study cohort, 147 were diagnosed with nonepithelial ovarian tumors, including 94 with germ cell tumors and 53 with sex-cord stromal tumors in 31.6 million person-years of follow-up (Table 1). The median age at diagnosis was 19.1 years (range 5.5-33.9) for germ cell tumors, and 21.2 years (range 3.0-34.0) for sex-cord stromal tumors. The 94 germ cell tumors comprised: 48 (51.1%) teratomas, 30 (31.9%) dysgerminomas, 11 (11.7%) yolk sac tumors, 2 (2.1%) polyembryomas, 1 (1.1%) embryonal carcinoma, 1 (1.1%) gonadoblastoma, and 1 (1.1%) mixed germ cell tumor. The 53 sex-cord stromal tumors comprised: 32 (60.4%) granulosa-stromal cell tumors, 14 (26.4%) Sertoli-stromal cell tumors, 1 (1.9%) steroid cell tumor, and 6 (11.3%) unclassified sex-cord stromal tumors. Of the 94 germ cell tumors, 86 (91.5%) were malignant, and 8 (8.5%) had uncertain tumor behavior. Of the 53 sex-cord stromal tumors, 27 (50.9%) were malignant, 10 (18.9%) were benign, and 16 (30.2%) had uncertain tumor behavior.

Women diagnosed with nonepithelial ovarian tumors (Table 1) were more likely to have been born before 37 weeks of gestational age (8.2%), especially among women with sex-cord stromal tumors (17.0%) compared to germ cell tumors (3.2%) or no ovarian tumors (5.4%). Women diagnosed with nonepithelial ovarian tumors were born earlier in the study period, and had greater opportunity to bear children by the end of follow-up in 2009 compared with the rest of the 1973-2004 birth cohort (Table 1). The study cohort included 36,145 (2.4%) women who were twins or higher-order multiple births, among whom 2 women from different twin pairs were diagnosed with 1 germ cell tumor and 1 sex-cord stromal tumor, respectively.

Women who were born preterm (<37 weeks of gestational age) rather than at term (37-41 weeks) had an increased risk of developing nonepithelial ovarian tumors (HR 1.86, 95% CI 1.03-

3.37; p=0.04) independent of fetal growth, birth order, maternal age at birth, maternal education, family history of ovarian or breast cancer, and personal parity (Table 2). Histological subgroup analysis showed that preterm birth was associated with significantly increased risk of sex-cord stromal tumors (HR 4.39, 95% CI 2.12-9.10; p<0.001), but not germ cell tumors (HR 0.68, 95% CI 0.21-2.15; p=0.51). There was also a significant trend of increasing risk of sex-cord stromal tumors (p_{trend} <0.001), but not germ cell tumors (p_{trend}=0.99), with younger gestational age at birth modeled as a continuous variable. Exploratory analyses yielded similar associations of preterm birth with increased risk of invasive sex-cord stromal tumors (HR 2.90, 95% CI 0.86-9.74; p=0.09), but not invasive germ cell tumors (HR 0.74, 95% CI 0.23-2.37; p=0.62). However, only 27 and 86 women, respectively, developed invasive sex-cord stromal and germ cell tumors, which limited statistical power. We found no significant associations with post-term birth (≥42 weeks of gestational age), fetal growth, or birth order (Table 2).

Parity modeled as a time-dependent variable was not associated with risk of nonepithelial ovarian tumors overall, or with risk of germ cell and sex-cord stromal tumors considered separately (Table 2). In exploratory analyses of 267,958 parous women, older age at first birth appeared to be associated with increased risk of subsequent nonepithelial ovarian tumors (p_{trend} <0.001), adjusted for gestational age at birth, fetal growth, birth order, maternal age at birth, maternal education, family history of ovarian and breast cancer, and parity (1 or ≥2 live births, modeled as a time-dependent variable). Similar trends of increased risk with older age at first birth were found for germ cell and sex-cord stromal tumors (data not shown). However, only 40 parous women in this cohort were diagnosed with nonepithelial ovarian tumors, including 23 with germ cell tumors and 17 with sex-cord stromal tumors, precluding robust histological subgroup analyses and inferences.

Mother's age at birth and educational level were not associated with risk of nonepithelial ovarian tumors (Table 2). A positive family history of ovarian or breast cancer was not associated with increased risk of nonepithelial ovarian tumors, although only 6 women with a positive family history developed nonepithelial ovarian tumors, limiting statistical power.

DISCUSSION

Few epidemiologic studies have investigated risk factors for nonepithelial ovarian cancers and, to our knowledge, none have examined gestational age at birth, fetal growth, and birth order. This large cohort study showed that girls and young women who were born preterm have an increased risk of developing sex-cord stromal tumors, independent of other perinatal and maternal characteristics. In contrast, preterm birth was not associated with increased risk of developing germ cell tumors. We found no associations of fetal growth and birth order with risk of nonepithelial ovarian tumors.

Preterm birth could increase the risk of sex-cord stromal tumors through altered hormonal exposures during the perinatal period. The latter part of gestation and time around birth are critical periods for ovarian folliculogenesis and development,[7] when potential precursor cells may be particularly susceptible to genetic mutations as a consequence of rapid cell division or the mutagenic effects of sex steroids.[13,14] During the first 10 postnatal weeks, premature girls born before 33 weeks of gestation have serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) that are, respectively, 10-20 and 3-4 times higher than levels in full-term girls.[15] A significantly stronger and prolonged postnatal FSH surge has also been observed in girls born before 37 weeks, indicating that preterm birth disrupts *in utero* maturation of the pituitary-ovarian axis.[7] The extremely high FSH levels in preterm girls is believed to

stimulate the postnatal proliferation of granulosa cells and activation of follicular development, which is delayed compared to full-term girls.[7]

We hypothesize that ovarian hyperstimulation in response to high gonadotropin levels in preterm girls specifically increases the risk of sex-cord stromal tumors through the proliferative and steroidogenic effects of FSH and LH on granulosa and theca cells, from which most sex-cord stromal tumors are derived. In contrast to granulosa and theca cells, oocytes express very low levels of FSH receptors and no LH receptors,[16] which mitigates the direct effects of high gonadotropin levels on these germ cells and may explain the absence of an association between preterm birth and risk of germ cell tumors. Ovarian hyperstimulation has also been postulated to increase estrogen levels[14] which could increase cancer risk through its activity as both a mitogen and mutagen on hormone-responsive cells.[13] A recent study showed that high circulating levels of androgens during pregnancy were associated with increased risk of maternal sex-cord stromal but not germ cell tumors, suggesting that elevated androgens may also play a role in the pathogenesis of sex-cord stromal tumors;[17] to our knowledge, no previous study has examined the risk in daughters. Additionally, androgens have been shown to induce and promote ovarian sex-cord stromal tumors in rodent models.[18,19] LH stimulates ovarian theca cells to produce androgens, and FSH induces granulosa cells to express aromatase which converts androgens to estradiol.[20] Thus, high gonadotropin levels in premature girls plausibly could increase the risk of sex-cord stromal tumors through the carcinogenic effects of elevated androgens as well as estrogens in the ovary.

Reduced fetal growth has been postulated to indicate a lower number of cells at risk for later carcinogenesis and may be associated with reduced risk of epithelial ovarian cancer.[21] However, a recent study found similar serum levels of anti-Müllerian hormone in young women

who were born small versus appropriate for gestational age, indicating that the ovarian follicle pool size is unlikely to be reduced in women born small for gestational age.[22] Our finding that fetal growth is not associated with risk of nonepithelial ovarian cancers is consistent with the lack of association between fetal growth and the ovarian follicle pool size in young women.[22] Lower birth order and older maternal age have been associated with higher estrogen levels during pregnancy, which could increase cancer risk.[23] However, our null findings suggest that alterations to the intrauterine environment due to birth order and maternal age may not be associated with the development of non-epithelial ovarian tumors in daughters. In this cohort of young women in their childbearing years, we found no association of parity with risk of nonepithelial tumors, and suggestive evidence that older age at first birth may increase risk, which was consistent with some[24,25] but not all previous studies[26-28] among mostly older women.

The main strengths of this study were the population-based cohort design, and complete ascertainment of exposures and outcomes using nationwide health registry data. Detailed information on perinatal characteristics was available from birth registries, which minimized potential biases from nondifferential misclassification or differential recall that can impair case-control studies. Cancer diagnoses were prospectively determined using cancer registry data that are nearly 100% complete, minimizing selection bias. Despite the large size of this national cohort, the numbers of women with nonepithelial ovarian tumors was limited as in all previous epidemiologic studies of this rare disease. Thus, we were unable to examine the association of preterm birth with specific subtypes of sex-cord stromal or germ cell tumors.

Our findings indicate that preterm birth may be a risk factor for developing ovarian sex-cord stromal tumors, and demonstrate the importance of early-life exposures on later cancer risk.

Large-scale international collaborative studies are needed to confirm these findings and to delineate the effects of preterm birth on the risk of distinct subtypes of nonepithelial ovarian cancers. Our findings suggest that ovarian hyperstimulation in response to elevated postnatal gonadotropin levels in preterm girls may increase cancer risk by stimulating proliferation and steroidogenesis of granulosa and theca cells, and increasing sex hormone levels in the ovary. Future studies can improve our understanding of the long-term biological consequences of preterm birth, and identify other early-life risk factors for non-epithelial ovarian cancers as well as windows of susceptibility when preventive interventions may be most effective.

CONFLICTS OF INTEREST STATEMENT

The authors declare that there are no conflicts of interests.

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Table 1. Characteristics of women born in Sweden during 1973-2004, by ovarian tumor status.

	None N=1,535,629 n (%)	Nonepithelial N=147 n (%)	Germ cell N=94 n (%)	Sex-cord stromal N=53 n (%)
Birth year				
1973-1979	336,461 (21.9)	57 (38.8)	31 (33.0)	26 (49.1)
1980-1989	474,219 (30.9)	68 (46.3)	51 (54.3)	17 (32.1)
1990-1999	501,274 (32.6)	20 (13.6)	12 (12.8)	8 (15.1)
2000-2004	223,675 (14.6)	2 (1.4)	0 (0.0)	2 (3.8)
Gestational age at birth, weeks				
<37	83,400 (5.4)	12 (8.2)	3 (3.2)	9 (17.0)
37-41	1,325,589 (86.3)	119 (81.0)	80 (85.1)	39 (73.6)
≥42	126,640 (8.2)	16 (10.9)	11 (11.7)	5 (9.4)
Birth weight, g				
<2500	68,495 (4.5)	6 (4.1)	3 (3.2)	3 (5.7)
2500-3999	1,251,896 (81.5)	120 (81.6)	76 (80.8)	44 (83.0)
≥4000	215,238 (14.0)	21 (14.3)	15 (16.0)	6 (11.3)
Fetal growth, SD				
<-1	232,920 (16.5)	33 (22.5)	23 (24.5)	10 (18.9)
-1 to <1	1,026,105 (66.8)	89 (60.5)	57 (60.6)	32 (60.4)
≥1	256,604 (16.7)	25 (17.0)	14 (14.9)	11 (20.7)
Birth order				
1	643,014 (41.9)	60 (40.8)	43 (45.7)	17 (32.1)
2	557,859 (36.3)	46 (31.3)	28 (29.8)	18 (34.0)
3	235,102 (15.3)	31 (21.1)	18 (19.2)	13 (24.5)
≥4	99,654 (6.5)	10 (6.8)	5 (5.3)	5 (9.4)
Mother's age at birth, years				
<25	345,175 (22.5)	36 (24.5)	25 (26.6)	11 (20.8)
25-29	553,271 (36.0)	53 (36.0)	33 (35.1)	20 (37.7)
30-34	429,936 (28.0)	41 (27.9)	24 (25.5)	17 (32.1)
≥35	207,247 (13.5)	17 (11.6)	12 (12.8)	5 (9.4)
Mother's education, years				
<10	306,327 (19.9)	32 (21.8)	20 (21.3)	12 (22.6)
10-11	536,630 (34.9)	60 (40.8)	39 (41.5)	21 (39.6)
12-14	425,937 (27.7)	37 (25.2)	24 (25.5)	13 (24.5)
≥15	202,690 (13.2)	15 (10.2)	9 (9.6)	6 (11.3)
Unknown	64,045 (4.2)	3 (2.0)	2 (2.1)	1 (1.9)
Father's education, years				
<10	350,277 (22.8)	49 (33.3)	29 (30.8)	20 (37.7)
10-11	509,046 (33.1)	44 (29.9)	28 (29.8)	16 (30.2)
12-14	385,288 (25.1)	29 (19.7)	17 (18.1)	12 (22.6)
≥15	214,893 (14.0)	18 (12.2)	15 (16.0)	3 (5.7)
Unknown	76,125 (5.0)	7 (4.8)	5 (15.3)	2 (3.8)
Family history of ovarian or breast cancer*				
No	1,495,521 (97.4)	141 (95.9)	90 (95.7)	51 (96.2)
Yes	40,108 (2.6)	6 (4.1)	4 (4.3)	2 (3.8)
Parity of proband*				
0	1,267,831 (82.6)	107 (72.8)	71 (75.5)	36 (67.9)
≥1	267,798 (17.4)	40 (27.2)	23 (24.5)	17 (32.1)

* Ascertained through 2009.

Table 2. Association of perinatal and familial characteristics with the risks of all nonepithelial, germ cell, and sex-cord stromal ovarian tumors.

Covariates	Nonepithelial N=147		Germ cell N=94		Sex-cord stromal N=53	
	HR[a] (95% CI)	P	HR[a] (95% CI)	P	HR[a] (95% CI)	P
Gestational age at birth, weeks						
<37	1.86 (1.03, 3.37)	0.04	0.68 (0.21, 2.15)	0.51	4.39 (2.12, 9.10)	<0.001
37-41	Reference		Reference		Reference	
≥42	0.97 (0.57, 1.64)	0.91	0.97 (0.51, 1.83)	0.92	0.97 (0.38, 2.48)	0.95
Fetal growth, SD						
<-1	1.23 (0.82, 1.84)	0.32	1.31 (0.81, 2.15)	0.27	1.06 (0.52, 2.18)	0.87
-1 to <1	Reference		Reference		Reference	
≥1	1.26 (0.81, 1.97)	0.31	1.12 (0.62, 2.01)	0.71	1.51 (0.76, 3.02)	0.24
Birth order						
1	Reference		Reference		Reference	
2	0.85 (0.57, 1.27)	0.42	0.72 (0.44, 1.19)	0.20	1.17 (0.58, 2.34)	0.66
3	1.38 (0.85, 2.24)	0.20	1.10 (0.59, 2.03)	0.77	2.07 (0.92, 4.64)	0.08
≥4	1.18 (0.56, 2.47)	0.67	0.78 (0.28, 2.16)	0.64	2.19 (0.71, 6.74)	0.17
Mother's age at birth, years						
<25	Reference		Reference		Reference	
25-29	1.10 (0.70, 1.72)	0.69	1.04 (0.60, 1.81)	0.88	1.20 (0.55, 2.61)	0.65
30-34	1.36 (0.82, 2.28)	0.23	1.31 (0.69, 2.47)	0.41	1.47 (0.62, 3.51)	0.38
≥35	1.43 (0.74, 2.77)	0.29	1.77 (0.80, 3.92)	0.16	0.98 (0.30, 3.24)	0.98
Mother's education, years						
<10	Reference		Reference		Reference	
10-11	1.53 (0.99, 2.37)	0.05	1.55 (0.90, 2.66)	0.12	1.51 (0.74, 3.10)	0.26
12-14	1.72 (1.05, 2.80)	0.03	1.69 (0.92, 3.11)	0.09	1.78 (0.79, 4.00)	0.17
≥15	1.18 (0.63, 2.23)	0.61	1.06 (0.47, 2.38)	0.89	1.42 (0.52, 3.93)	0.50
Unknown	0.65 (0.20, 2.12)	0.47	0.66 (0.15, 2.84)	0.58	0.62 (0.08, 4.81)	0.65
Family history of ovarian or breast cancer						
No	Reference		Reference		Reference	
Yes	1.02 (0.45, 2.32)	0.96	1.08 (0.39, 2.95)	0.88	0.93 (0.22, 3.83)	0.92
Parity						
0	Reference		Reference		Reference	
≥1	0.93 (0.59, 1.47)	0.77	0.84 (0.47, 1.50)	0.56	1.11 (0.53, 2.35)	0.78

[a]Hazard ratios and 95% confidence intervals in Cox regression models including gestational age at birth, fetal growth, birth order, mother's age at birth, mother's education, family history of ovarian or breast cancer (modeled as a time-dependent covariate), and parity (modeled as a time-dependent covariate).