endometrial cancer: a Nordic population-based case-control study

Britton Trabert, Ph.D.[1], Rebecca Troisi, SC.D.[1], Tom Grotmol, MD, Ph.D.[2], Anders Ekbom, MD, Ph.D.[3], Anders Engeland, Ph.D.[4,5], Mika Gissler, Ph.D.[6,7], Ingrid Glimelius, MD, Ph.D.[3,8], Laura Madanat-Harjuoja, MD[9,10], Henrik Toft Sørensen, MD, Ph.D.[11], Steinar Tretli, Ph.D.[2], Anne Gulbech Ording, Ph.D.[11], Tone Bjørge, MD, Ph.D.[2,5]

[1] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, United States of America

[2] Cancer Registry of Norway, Oslo, Norway

[3] Department of Medicine, Division of Clinical Epidemiology, Karolinska Institutet, Stockholm, Sweden

[4] Division of Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway

[5] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[6] Information Services Department, National Institute for Health and Welfare (THL), Helsinki, Finland

[7] Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Stockholm, Sweden

[8] Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

[9] Cancer Society of Finland, Finnish Cancer Registry, Helsinki, Finland.

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[10] Department of Pediatrics, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[11] Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

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Corresponding Author:

Britton Trabert

9609 Medical Center Drive

Bethesda, MD 20892-9774

Phone: 240-276-7331

Fax: 240-276-7838

email: britton.trabert@nih.gov

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Novelty and Impact: While many pregnancy-related factors are associated with reduced endometrial cancer risk, it remains unclear whether pregnancy-related complications (e.g., hypertensive conditions) are associated with risk. In the present study, the reduced endometrial cancer risk associated with higher number of births and later age at birth suggests the important role of hormonal and/or cell clearance mechanisms in endometrial carcinogenesis. Whereas, increased risks associated with

pre-existing and gestational hypertension, as well as preeclampsia suggest that immunologic and/or inflammatory etiologies also may be relevant.

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Abstract

Many pregnancy-related factors are associated with reduced endometrial cancer risk. However, it remains unclear whether pregnancy-related complications (e.g., hypertensive conditions) are associated with risk and whether these associations vary by endometrial cancer subtype. Thus, we evaluated the risk of endometrial cancer, overall and by subtype, in relation to pregnancy-related factors, pregnancy complications, and birth characteristics. Utilizing population-based register data from four Nordic countries we conducted a nested case-control analysis of endometrial cancer risk. We included 10,924 endometrial cancer cases and up to 10 matched controls per case. Odds ratios (ORs) with 95% confidence intervals (CIs) were derived from unconditional logistic regression models. We further evaluated associations by individual histology (i.e., endometrioid, serous, etc.) or, for rare exposures (e.g., pregnancy complications), by dualistic Type (Type I (n=10,343) and Type II (n=581)). Pre-existing and pregnancy-related hypertensive conditions were associated with increased endometrial cancer risk [OR (95% CI): pre-existing hypertension 1.88 (1.39-2.55); gestational hypertension 1.47 (1.33-1.63); preeclampsia 1.43 (1.30-1.58)], with consistent associations across dualistic Type. Increasing number of pregnancies [≥four versus one birth: 0.64 (0.59-0.69)] and shorter time since last birth [<10 versus ≥30 years: 0.34 (0.29-0.40)] were associated with reduced endometrial cancer risk, with consistent associations across most subtypes. Our findings support the role for both hormonal exposures and cell clearance as well as immunologic/inflammatory etiologies for endometrial cancer. This research supports studying endometrial hyperplasia, a precursor condition of endometrial cancer, in the context of pregnancy-related

exposures, as this may provide insight into the mechanisms by which pregnancy affects subsequent cancer risk.

Introduction

The risk of endometrial cancer is dependent on events related to hormonal exposures during a woman's life. Thus, various aspects of reproduction and use of exogenous hormones have been extensively explored.[1] Pregnancy is known to confer long-term protection against endometrial cancer.[1] Conversely, nulliparity is associated with an elevated endometrial cancer risk.[1] The hormonal milieu of pregnancy is characterised by elevated levels of estrogen, progesterone, and intrauterine growth factors, almost exclusively produced by the placenta.[2] The pregnancy history of women with endometrial cancer has been examined with regard to timing of births[3-7], twin births, and sex of offspring.[8] Recent data indicate that the associations between established endometrial cancer risk factors: high BMI and diabetes, and some reproductive factors (*e.g.*, parity) were stronger for Type I tumors compared with Type II tumors, while associations between other reproductive factors (*e.g.*, age at menarche) may be slightly stronger for Type II tumors, albeit based on limited data.[9, 10] Few studies have evaluated associations of pregnancy and birth-related characteristics with endometrial cancer by dualistic Type (I and II) or histologic subtype. Pregnancy complications such as preeclampsia also have been examined in relation to endometrial cancer; however, results have been inconclusive with limited evaluations of associations by subtype.[11, 12] Examination of associations with hypertensive disorders during pregnancy may provide insights into unrecognized biological mechanisms of endometrial carcinogenesis.[13]

Large longitudinal datasets with decades of observations are needed to evaluate endometrial cancer associations with rare pregnancy conditions and/or to explore associations of timing of pregnancy across endometrial cancer subtypes. We therefore

conducted a pooled analysis of population-based register data from four of the Nordic countries. We aimed to evaluate the risk of endometrial cancer, overall and by subtype, in relation to pregnancy-related factors, including pregnancy complications, and birth characteristics.

Material and methods

Data sources

The nationwide health registers from Denmark, Finland, Norway, and Sweden, have been described previously.[14-16] In brief, this study combined data across birth and cancer registers in each country. The population-based birth registers contain information on all births, including characteristics of both the mother and the offspring, in Norway since 1967, in Denmark and Sweden since 1973, and in Finland since 1987. Additional information on preeclampsia was identified from the Danish National Patient Registry [17], from the hospital and birth register in Finland, and from the birth register in Norway and Sweden.

Reporting of cancer cases is compulsory in the Nordic countries, and their cancer registries cover the entire population starting in 1943 in Denmark, 1952 in Finland, 1953 in Norway, and 1958 in Sweden. The unique identifiers used in all administrative and medical registers in the Nordic countries ensure accurate record linkage. Completeness and validity of the registers are high.[18-21]

Study design/study population

Using a nested case-control design the study included all first primary invasive uterine cancer cases and up to 10 controls per case (matched on country and birth year) among women registered with a prior pregnancy lasting at least 22 weeks in the birth registers. We sampled 10 controls per case to ensure we could stably represent the prevalence of the rare conditions in the underlying population. The study period was 1973-2011 in Denmark, 1987-2012 in Finland, 1967-2013 in Norway, and 1974-2013 in Sweden. Uterine cancer cases (n=12,413) were identified using International Classification of Disease (ICD) topography codes (C54.0-55.9 from ICD-10 for reference) as follows: Denmark and Finland (ICD-10), Norway (ICD-O-3), and Sweden (ICD-7). The controls were sampled among the women in the birth registers with a prior pregnancy, who were alive and free of cancer at the time of diagnosis of the corresponding case.

We first evaluated associations for endometrial cancers, limited to Type I and Type II cancers (n=10,924), thus excluding uterine carcinosarcoma (n=234), uterine sarcoma (n=737), and cases with missing histology (n=518). Next, we evaluated associations by histologic subtype based on morphology codes: endometrioid tumors (n=4994), adenocarcinoma (n=5271), serous (n=428), and clear cell (n=153) [we did not provide subtype analyses on mucinous (n=78) tumors given sparse data]; and by the dualistic classification of Type I (n=10,343, including endometrioid tumors, adenocarcinomas, and mucinous cancers) and Type II (n=581, including serous and clear cell) tumors for rare exposures (*e.g.*, pre-existing conditions, pregnancy complications).

The analytic dataset included information from the medical birth registers on all births until the date of diagnosis for cases and corresponding index date for controls. We

obtained information on selected conditions (diabetes, chronic hypertension, rheumatoid arthritis, epilepsy, asthma) diagnosed before pregnancy, as well as maternal complications that occurred during any pregnancy (*e.g.*, gestational diabetes, gestational hypertension, preeclampsia, etc).

Data were complete for parity, age at last birth, and time since last birth; 46.2% of cases and 47.1% of controls lacked information on the first birth, primarily due to the relatively recent establishment of the birth registers. Data for pregnancy-related complications were available across all years of data collection and were characterized as being present (exposed) if they occurred in any pregnancy. Data on additional potential confounding factors, including maternal body mass index (BMI) and smoking (during pregnancy), were limited. BMI before or early in the last pregnancy was collected in Sweden starting in 1992, in Denmark and Finland starting in 2004, and in Norway starting in 2007. Information on smoking habits during pregnancy was first recorded in Sweden in 1982, Finland in 1987, Denmark in 1991, and Norway in 1999.

The study was approved by ethics committees in Norway and Sweden and by the Data Protection Agency in Denmark. Permission to use health register data in Finland was granted by the National Institute of Health and Welfare after consultation with the data protection authority. The datasets analyzed as part of the current study are not freely available due to national regulations.

Statistical analysis

Associations, presented as odds ratios (ORs) with 95% confidence intervals (CIs), were estimated using unconditional logistic regression with adjustment for matching factors

(country and categorical birth year [<1940, 1940-49, 1950-1959, 1960+]) and the following potential confounding factors (defined *a priori*): age at index date (continuous), marital status at first birth (unmarried, married/cohabiting, divorced/widowed, unknown/missing), pre- or early-pregnancy BMI at last pregnancy (<25, 25-29.9, ≥30 kg/m^2, unknown/missing). We report associations with and without adjustment for parity as relevant. Associations by dualistic Type or histologic subtype were estimated using multinomial logistic regression with the controls as the reference group and adjusting for matching factors and confounders as described. We utilized unconditional logistic regression for analyses of endometrial cancer risk overall, to ensure comparability with the multinomial models used to evaluate subtype associations. P values for heterogeneity across subgroup associations were estimated from models with the largest subgroup as the reference and excluded non-cases.

In sensitivity analyses we evaluated associations restricted to women with available data on 1) BMI, 2) marital status, and 3) smoking in relation to any pregnancy with additional adjustment for smoking as a potential confounder. We evaluated simultaneous adjustment for chronic hypertension and diabetes prior to pregnancy (correlates (proxies) of increased BMI and risk factors for endometrial cancer in the current analysis) to further explore the possible effects of confounding by BMI. Adjustment for these variables individually or in combination did not change effect estimates substantially, and therefore we did not include them in our adjusted models. Data were analysed using SAS version 9.4 (Cary, North Carolina).

Results

Endometrial cancer cases were on average 57.8 years of age at diagnosis (standard deviation [SD]=8.0, Supplemental Table 1). The average time between a woman's last birth and the index date was 26.7 years (SD=8.2) in cases and 25.5 years (SD=9.0) in controls.

Maternal conditions and pregnancy-related complications

Pre-existing diabetes and chronic hypertension were associated with increased endometrial cancer risk [OR (95% CI) diabetes=1.59 (1.22-2.07); hypertension OR=1.88 (1.39-2.55)] (Table 1). Epilepsy during pregnancy was also associated with increased endometrial cancer risk [OR=1.46 (1.06-2.02)]. Other pre-existing conditions, like rheumatoid arthritis and asthma, were not associated with risk.

Gestational diabetes was associated with a modestly elevated endometrial cancer risk, albeit it was not statistically significant [OR=1.27 (0.81-1.99)] (Table 1). Hypertension diagnosed during pregnancy was associated with increased endometrial cancer risk [OR=1.47 (1.33-1.63)], as was preeclampsia [OR=1.43 (1.30-1.58)]. Associations were consistent with and without adjustment for parity. Further, both pre-existing hypertension [OR=1.74 (1.28-2.35)] and gestational hypertension [OR=1.44 (1.30-1.59)] remained associated with increased risk of endometrial cancer in mutually adjusted models (results not tabulated).

(Table 1 here)

Chronic hypertension, gestational hypertension, and preeclampsia were associated with increased risks of both Type I and Type II endometrial tumors [chronic hypertension: Type I=1.88 (1.38-2.56), Type II=1.78 (0.44-7.21); gestational hypertension: Type I=1.45 (1.31-1.61), Type II=1.42 (0.92-2.18); preeclampsia: Type I=1.44 (1.30-1.59), Type II=1.39 (0.91-2.15); P values for heterogeneity>0.05] (Table 1).

Other pregnancy-related characteristics, including hyperemesis gravidarum [OR=0.93 (0.74-1.18)], abruptio placentae [OR=1.07 (0.88-1.29)], or antepartum haemorrhage [OR=1.08 (0.83-1.40)], were not associated with endometrial cancer risk. Women whose most recent infant was born in the highest categories of birthweight were at increased risk [4000-4499 vs. 2500-3999 grams: OR=1.22 (1.16-1.29); ≥4500 vs. 2500-3999 grams: OR=1.39 (1.22-1.47)]. A higher placental weight in the last pregnancy was associated with increased endometrial cancer risk in the mother [≥700 vs. 500-699 grams: OR=1.50 (1.26-1.78)], while lower placental weight was not associated with risk [<500 vs. 500-699 grams: OR=0.99 (0.78-1.26)].

Our data suggest that the birth weight association may be heterogenous by Type I/II subtype (P heterogeneity=0.09); the highest categories of birthweight were associated with increased risk of Type I tumors [4000-4499 vs. 2500-3999 grams: OR=1.21 (1.14-1.27); ≥4500 vs. 2500-3999 grams: OR=1.36 (1.24-1.50)] and a null association for Type II tumors [ORs=1.08 (0.86-1.34); 0.97 (0.63-1.51), respectively]; while the lowest category of birthweight was associated with increased risk of Type II tumors [<1000 vs. 2500-4000 grams: OR=3.52 (1.30-9.56)] but not with Type I tumors [OR=1.11 (0.72-1.70)]. Associations with the other factors evaluated were not strongly heterogeneous across Type I and II tumors.

Parity and timing of pregnancy

Compared with having one recorded birth, increased parity progressively decreased risk of endometrial cancer [*e.g.*, four or more births: OR=0.64 (0.59-0.69)] (Table 2). Older age at and shorter time since first birth were both associated with substantial reductions in endometrial cancer risk [≥40 vs.<20 years old: OR=0.44 (0.29-0.66); <10 vs. ≥30 years since first birth: OR=0.51 (0.39-0.65)] as were older age at and shorter time since last birth [≥45 vs.<25 years old: OR=0.69 (0.53-0.89); <10 vs. ≥30 years since last birth: OR=0.31 (0.26-0.36)]. Simultaneous adjustment for age at and time since birth in the analytic models did not substantially change the interpretation of the results (data not shown).

(Table 2 here)

The risk reductions for age at first and age at last birth were similar among women who had only one birth (uniparous) and those who had more than one birth (Supplemental Table 2). However, the risk reductions for time since first and last birth among multiparous women were greater than among the uniparous women [*e.g.*, time since first birth <10 vs. ≥30 years: uniparous OR=0.43 (0.30-0.61); multiparous OR=0.24 (0.15-0.38)].

Increasing number of births was associated with equivalent reductions in risk for Type I and Type II endometrial cancers (Table 2). When evaluating individual subtypes (Table 3), reductions in risk for four or more births compared with one birth were apparent for endometrioid tumors [OR=0.63 (0.56-0.71)], and adenocarcinomas [OR=0.64 (0.57-

0.72)]. Similar reductions were also suggested for serous [OR=0.72 (0.48-1.10)] and clear cell tumors [OR=0.60 (0.30-1.23); P heterogeneity=0.03].

(Table 3 here)

Older age at first birth and shorter time since first birth were associated with strong risk reductions for Type I tumors, with very weak reductions in risk or no association suggested for Type II tumors [e.g., time since first birth <10 vs. ≥30 years: Type I OR=0.40 (0.31-0.52); Type II OR=0.75 (0.20-2.82); P heterogeneity=0.01]. This pattern was consistent when evaluating individual subtypes. For example, shorter time since first birth was associated with reductions in risk for endometrioid [OR=0.33 (0.22-0.50)] and adenocarcinomas [OR=0.41 (0.29-0.58)], but not for the other subtypes (P heterogeneity<0.001).

Older age at last birth and shorter time since last birth were associated with strong risk reductions for both Type I and Type II endometrial cancers [e.g., time since last birth <10 vs. ≥30 years: Type I OR=0.36 (0.31-0.43); Type II OR=0.22 (0.08-0.59); P heterogeneity<0.01]. Risk reductions within these same categories of time since last birth were observed for endometrioid tumors [OR=0.31 (0.25-0.40)], adenocarcinoma [OR=0.39 (0.31-0.48)], serous [OR=0.19 (0.05-0.75)], and clear cell [OR=0.25 (0.06-1.15); P heterogeneity<0.001] endometrial cancers.

In sensitivity analyses effect estimates conveyed a similar pattern of risk after: 1) excluding individuals with missing data on BMI (Supplemental Table 3), 2) excluding individuals with missing data on marital status (results not shown), or 3) adjusting for smoking status (results not shown), and 4) excluding individuals with missing smoking

status in models adjusting for smoking status (results not shown). Given that BMI is a very strong, if not the strongest, endometrial cancer risk factor, we were concerned about the potential bias that could have been introduced by not adjusting for BMI in our analysis or using a missing indicator. Although imprecise, the effect estimates limiting the study population to cases and controls with available pre-pregnancy BMI data and adjusted for BMI (complete case analyses) were remarkably consistent with the full study population analysis adjusted for BMI with a missing indicator. For example, risk estimates for exposures most plausibly confounded by BMI were as follows [full study population vs. complete case analysis]: diabetes, 1.59 (1.23-2.07) vs. 1.60 (0.88-2.93); chronic hypertension 1.83 (1.35-2.48) vs. 1.78 (0.93-3.42); gestational hypertension 1.45 (1.32-1.60) vs. 1.49 (0.63-3.52); and preeclampsia 1.41 (1.28-1.56) vs. 1.66 (1.25-2.19) (Supplemental Table 3).

Discussion

In this large analysis of linked registry data in four Nordic countries, hypertensive conditions, whether diagnosed before or during pregnancy, including preeclampsia, were associated with increased risk of endometrial cancer, with consistent associations by dualistic tumor Types (Type I and II). The association between birthweight and endometrial cancer risk appeared heterogenous by subtype, with elevated risks with high birthweights (4000+ grams) for Type I tumors, and with very low birthweights (<1000 grams) for Type II tumors. With respect to number and timing of pregnancies, we observed reductions in endometrial cancer risk across most of the subtypes with increasing number of pregnancies and shorter time since last birth.

Prior studies evaluating preeclampsia and endometrial cancer risk are rare and limited by small numbers given the relatively low prevalence of preeclampsia.[11, 12] A study utilizing linked register data in Denmark reported an increased endometrial cancer risk with early onset preeclampsia (22-33 weeks of gestation, 9 exposed cases) and no association with late onset disease (>33 weeks of gestation, 5 exposed cases),[12] while the Jerusalem Perinatal Study (n=9 exposed cases) showed no association between preeclampsia and uterine cancer.[11] Data on gestational age were not collected in the Jerusalem Perinatal Study, but it is likely that many of the preeclampsia diagnoses are late onset. Further, edema was included in the early definition for preeclampsia utilized in the Jerusalem study and it is not included in contemporary definitions utilized in the Danish study and our current study,[22] thus results may not be directly comparable.

Preeclampsia is characterized by elevated blood pressure and urinary protein excretion, and it is suggested that the protective effects of preeclampsia on breast cancer risk are via altered circulating hormone levels associated with the syndrome. Increased androgen levels in preeclampsia may well be a possible factor since increased serum androgens are associated with increased risk of endometrial cancer in postmenopausal women (reviewed in [23]). This is consistent with an increased risk of endometrial cancer in women with polycystic ovary syndrome (reviewed in [24]). In addition, increased risks associated with hypertension, as well as preeclampsia, suggest that immunologic and/or inflammatory etiologies during and preceding pregnancy may also be relevant factors in endometrial carcinogenesis. Specifically, preeclampsia has been associated with inflammation and immune activation in both maternal circulation and the uteroplacental unit[25], which may be relevant to increased endometrial cancer risk.

Epidemiologic data that support a possible role of inflammation in the development of endometrial cancer are emerging. Inflammation-related exposures such as obese BMI and diabetes, as well as circulating biomarkers of inflammation have been associated with endometrial cancer risk.[10, 26] Further, aspirin and non-aspirin nonsteroidal anti-inflammatory drug use are associated with modest reductions in endometrial cancer risk in some studies.[27]

Pregnancy affects many endogenous systems. Thus the mechanisms by which all births, but specifically births later in life, may reduce endometrial cancer risk in the mother include: 1) exposures to higher levels of progesterone (relative to estrogen) throughout pregnancy which possibly facilitate removal/apoptosis of premalignant lesions (*e.g.*, reduction in endometrial hyperplasia with progesterone treatment in the PEPI trial [28]; 2) mechanical removal/sloughing of premalignant cells during parturition and/or uterine involution; 3) immune-mediation during pregnancy. Other hormones produced in the placenta may also be related to the carcinogenic process[13], but have not been evaluated with respect to endometrial cancer. Finally, it is also possible that women capable of maintaining a pregnancy at a late age may simply have a healthy uterus or have experienced fewer anovulatory cycles.

Our results are consistent with prior studies evaluating overall endometrial cancer risk and number of pregnancies and timing of pregnancy.[3-7, 9, 10] Our study is also consistent with prior research suggesting that parity is associated with similar reductions in risk by dualistic Type and histologic subtype.[9, 10] Our results differ from these prior studies in that we report that older age at first birth and shorter time since first birth were associated with strong risk reductions for Type I tumors compared with Type II tumors,

while shorter time since last birth was associated with stronger risk reductions for Type II tumors.

Among the strengths of our study are the very large study size, inclusion of histologically verified cancer cases among women with at least one registered pregnancy in four Nordic countries, and linkages among comprehensive and mandatorily established databases with reliable information. The study design using standardized data from registers also minimizes bias due to participant self-selection or recall of information. Residual confounding by BMI is possible. However, we compared our full analysis adjusted for BMI with a complete case analysis—limiting the study population to cases and controls with complete BMI data and adjusting for BMI—and the effect estimates, and thus interpretation of the associations, across these two analyses were remarkably consistent. Additional limitations include the lack of details on possible confounders, such as use of exogenous hormones. Menopausal hormone therapy is unlikely to be a confounder as it does not precede exposure and is not associated with the exposures evaluated. The use of oral contraceptives, a known protective factor for endometrial cancer, may be correlated with maternal characteristics like age at first/last pregnancy. However, we could not adjust for this factor in our analysis due to lack of information in the birth/cancer registers. As information on hysterectomy status was not available across all registers, we did not limit control selection to women with no history of hysterectomy. However, the prevalence of hysterectomy in the Nordic countries is low, reducing the potential impact of this bias.[29-32]

In conclusion, our data support an important role for hormonal exposures during pregnancy and/or cell clearance in the etiology of endometrial cancer. Our data also suggest that pregnancy-related immunologic and/or inflammatory exposures may be relevant to endometrial carcinogenesis, given the increased risks we observed for gestational hypertension and preeclampsia. Future research should consider evaluations of endometrial hyperplasia, an endometrial cancer precursor condition, in the context of pregnancy related exposures. This may help provide insight into the mechanisms by which pregnancy protects against subsequent endometrial cancer risk, although some pregnancy related exposures (*i.e.*, hypertension and preeclampsia) increase risk.

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Table 1. Maternal conditions and pregnancy-related complications and subsequent endometrial cancer risk, overall and by dualistic subtype; Nordic countries, 1967-2013.

	Controls (N=123 749)	Endometrial Cancer Cases (N=10 924)					Type I (N=10 343)			Type II (N=581)			
	n (%)	n (%)	OR[a]	(95% CI)	OR[b]	(95% CI)	n (%)	OR[b]	(95% CI)	n (%)	OR[b]	(95% CI)	*P*
Pre-existing conditions (recorded at any pregnancy)													
Diabetes	444 (0.4)	65 (0.6)	1.59	(1.23-2.07)	1.59	(1.22-2.07)	65 (0.6)	1.66	(1.27-2.15)	0 (0.0)	--	--	--
Chronic hypertension	299 (0.2)	49 (0.5)	1.83	(1.35-2.48)	1.88	(1.39-2.55)	47 (0.5)	1.88	(1.38-2.56)	2 (0.3)	1.78	(0.44-7.21)	0.96
Rheumatoid Arthritis[c]	157 (0.2)	12 (0.2)	0.90	(0.50-1.62)	0.91	(0.50-1.63)	12 (0.2)	0.95	(0.53-1.71)	0 (0.0)	--	--	--
Epilepsy[c]	334 (0.3)	42 (0.4)	1.46	(1.06-2.01)	1.46	(1.06-2.02)	41 (0.4)	1.50	(1.08-2.08)	1 (0.2)	--	--	--
Asthma	941 (0.8)	80 (0.7)	0.99	(0.78-1.24)	1.01	(0.80-1.27)	76 (0.7)	1.00	(0.79-1.27)	4 (0.7)	1.18	(0.44-3.18)	0.51
Gestational Complications (diagnosed in any pregnancy)													
Gestational diabetes[c]	216 (0.4)	21 (0.4)	1.23	(0.78-1.93)	1.27	(0.81-1.99)	20 (0.4)	1.20	(0.76-1.91)	1 (0.4)	--	--	--
Gestational hypertension[c]	3961 (6.5)	476 (9.2)	1.45	(1.32-1.60)	1.47	(1.33-1.63)	453 (9.3)	1.45	(1.31-1.61)	23 (8.2)	1.42	(0.92-2.18)	0.77
Preeclampsia	3795 (3.1)	470 (4.3)	1.41	(1.28-1.56)	1.43	(1.30-1.58)	448 (4.3)	1.44	(1.30-1.59)	22 (3.8)	1.39	(0.91-2.15)	0.82
Hyperemesis gravidarum	978 (0.8)	78 (0.7)	0.91	(0.72-1.15)	0.93	(0.74-1.18)	76 (0.7)	0.97	(0.76-1.22)	2 (0.3)	0.45	(0.11-1.80)	0.30
Abruptio placentae	1231 (1.0)	113 (1.0)	1.02	(0.84-1.24)	1.07	(0.88-1.29)	109 (1.1)	1.08	(0.89-1.32)	4 (0.7)	0.76	(0.28-2.04)	0.66
Antepartum hemorrhage[c]	642 (0.9)	62 (1.0)	1.04	(0.80-1.36)	1.08	(0.83-1.40)	60 (0.6)	1.06	(0.81-1.39)	2 (0.3)	0.71	(0.18-2.85)	0.69
Birth characteristics (most recent birth)													
Birth weight, grams													
<1000	258 (0.2)	27 (0.3)	1.23	(0.83-1.83)	1.23	(0.82-1.83)	23 (0.2)	1.11	(0.72-1.70)	4 (0.7)	3.52	(1.30-9.56)	0.12
1000-1499	506 (0.4)	52 (0.5)	1.21	(0.91-1.61)	1.20	(0.90-1.60)	49 (0.5)	1.20	(0.89-1.61)	3 (0.5)	1.25	(0.40-3.91)	
1500-2499	4384 (3.6)	353 (3.2)	0.95	(0.85-1.07)	0.94	(0.84-1.05)	336 (3.3)	0.95	(0.85-1.06)	17 (2.9)	0.84	(0.52-1.37)	
2500-3999	94613 (76.7)	8003 (73.5)	1.00	reference	1.00	reference	9902 (96.0)	1.00	reference	554 (95.9)	1.00	reference	
4000-4499	19034 (15.4)	1927 (17.7)	1.20	(1.14-1.26)	1.22	(1.16-1.29)	1832 (17.8)	1.21	(1.14-1.27)	95 (16.4)	1.08	(0.86-1.34)	
>4500	4630 (3.8)	526 (4.8)	1.34	(1.22-1.47)	1.39	(1.27-1.53)	505 (4.9)	1.36	(1.24-1.50)	21 (3.6)	0.97	(0.63-1.51)	
Low birth weight in last birth (<2500 grams)	5148 (4.2)	432 (4.0)	0.95	(0.86-1.05)	0.94	(0.85-1.04)	408 (4.0)	0.93	(0.84-1.04)	24 (4.2)	1.00	(0.66-1.51)	0.59
Preterm delivery	6891 (5.6)	675 (6.2)	1.11	(1.03-1.21)	1.11	(1.02-1.20)	646 (6.3)	1.12	(1.03-1.22)	29 (5.1)	0.88	(0.60-1.28)	0.22
Placental weight, grams													

<500	1296 (14.1)	90 (13.0)	1.02	(0.80-1.29)	0.99	(0.78-1.26)	84 (12.6)	0.95	(0.74-1.22)	6 (20.7)	1.93	(0.72-5.20)	0.66
500-699	5149 (56.0)	348 (50.1)	1.00	reference	1.00	reference	336 (50.5)	1.00	reference	12 (41.4)	1.00	reference	
≥700	2758 (30.0)	256 (36.9)	1.47	(1.24-1.75)	1.50	(1.26-1.78)	245 (36.8)	1.49	(1.25-1.78)	11 (37.9)	1.77	(0.77-4.08)	

[a] Unconditional logistic regression models adjusted for matching factors (country, birth year), index age, body mass index, and marital status at first pregnancy.
[b] Unconditional logistic regression models adjusted for matching factors (country, birth year), index age, body mass index, marital status at first pregnancy, and parity. Index age was defined as the age at endometrial cancer diagnosis among cases and age at endometrial cancer of the matched case among controls.
P for heterogeneity
[c] Due to complete/near complete (>99%) missing data models exclude the following: data from Sweden for Rheumatoid Arthritis, data from Finland for Epilepsy, data from Norway for Antepartum hemorrhage, data from Sweden before 1997 and data from Denmark before 1995 for gestational diabetes and gestational hypertension.

Table 2. Number and timing of births and endometrial cancer risk; Nordic countries, 1967-2013.

	Controls (N=123 749)	Endometrial cancer cases (N=10 924)					Type I (N=10 343)			Type II (N=581)			
Parity	n (%)	n (%)	OR[a]	(95% CI)	OR[b]	(95% CI)	n (%)	OR[a]	(95% CI)	n (%)	OR[a]	(95% CI)	*P*
1 birth	14669 (11.9)	1607 (14.7)	1.00	reference			1545 (14.9)	1.00	reference	62 (10.7)	1.00	reference	
2 births	49314 (39.9)	4596 (42.1)	0.83	(0.78-0.88)			4350 (42.1)	0.81	(0.76-0.87)	246 (42.3)	1.08	(0.80-1.45)	0.19
3 births	35948 (29.1)	2946 (27.0)	0.71	(0.67-0.77)			2774 (26.8)	0.70	(0.66-0.76)	172 (29.6)	0.91	(0.66-1.25)	
4+ births	23818 (19.3)	1775 (16.3)	0.64	(0.59-0.69)			1674 (16.2)	0.63	(0.58-0.69)	101 (17.4)	0.69	(0.48-0.99)	
Age first birth													
<20	11454 (9.3)	1238 (11.3)	1.00	reference	1.00	reference	1179 (11.4)	1.00	reference	59 (10.2)	1.00	reference	
20-24	35783 (28.9)	3500 (32.0)	0.88	(0.82-0.94)	0.92	(0.86-0.99)	3335 (32.2)	0.93	(0.87-1.00)	165 (28.4)	0.77	(0.56-1.04)	0.01
25-29	43126 (34.9)	3704 (33.9)	0.74	(0.69-0.80)	0.80	(0.75-0.86)	3515 (34.0)	0.82	(0.76-0.88)	189 (32.5)	0.68	(0.49-0.93)	
30-34	25723 (20.8)	1929 (17.7)	0.62	(0.57-0.67)	0.67	(0.62-0.73)	1814 (17.5)	0.68	(0.62-0.74)	115 (19.8)	0.64	(0.45-0.92)	
35-39	7232 (5.8)	528 (4.8)	0.58	(0.51-0.65)	0.63	(0.56-0.71)	480 (4.6)	0.62	(0.55-0.70)	48 (8.3)	0.85	(0.55-1.33)	
≥40	431 (0.4)	25 (0.2)	0.44	(0.29-0.66)	0.48	(0.32-0.72)	20 (0.2)	0.42	(0.27-0.67)	5 (0.9)	1.34	(0.52-3.47)	
Time since first birth, years													
<10	1958 (3.0)	90 (1.5)	0.51	(0.39-0.65)	0.37	(0.29-0.48)	86 (1.5)	0.40	(0.31-0.52)	4 (1.6)	0.75	(0.20-2.82)	0.01
10-19	9375 (14.3)	708 (12.1)	0.82	(0.72-0.92)	0.69	(0.61-0.78)	689 (12.3)	0.73	(0.64-0.82)	19 (7.7)	0.72	(0.37-1.39)	
20-29	23395 (35.8)	2190 (37.4)	1.01	(0.94-1.09)	0.93	(0.87-1.00)	2143 (38.2)	0.96	(0.90-1.03)	47 (19.1)	0.56	(0.39-0.83)	
≥30	30702 (46.9)	2866 (49.0)	1.00	reference	1.00	reference	2690 (48.0)	1.00	reference	176 (71.5)	1.00	reference	
Age last birth													
<25	4940 (7.6)	485 (8.3)	1.00	reference	1.00	reference	460 (8.2)	1.00	reference	25 (10.2)	1.00	reference	
25-29	22577 (34.5)	2140 (36.6)	0.94	(0.85-1.05)	0.92	(0.83-1.02)	2065 (36.8)	0.94	(0.85-1.05)	75 (30.5)	0.52	(0.33-0.84)	0.12
30-34	22423 (34.3)	1894 (32.4)	0.82	(0.73-0.91)	0.76	(0.68-0.85)	1810 (32.3)	0.78	(0.70-0.88)	84 (34.2)	0.49	(0.30-0.80)	
35-39	10359 (15.8)	890 (15.2)	0.80	(0.71-0.91)	0.69	(0.61-0.79)	847 (15.1)	0.71	(0.62-0.81)	43 (17.5)	0.46	(0.26-0.81)	
40-44	4133 (6.3)	364 (6.2)	0.78	(0.67-0.92)	0.62	(0.52-0.72)	351 (6.3)	0.64	(0.55-0.76)	13 (5.3)	0.29	(0.13-0.62)	
≥45	998 (1.5)	81 (1.4)	0.69	(0.53-0.89)	0.50	(0.39-0.65)	75 (1.3)	0.51	(0.39-0.67)	6 (2.4)	0.47	(0.17-1.31)	
Time since last birth, years													
<10	6998 (5.7)	281 (2.6)	0.31	(0.26-0.36)	0.34	(0.29-0.40)	274 (2.7)	0.36	(0.31-0.43)	7 (1.2)	0.22	(0.08-0.59)	0.001
10-19	26380 (21.3)	2037 (18.7)	0.67	(0.62-0.73)	0.73	(0.67-0.79)	1995 (19.3)	0.78	(0.72-0.84)	42 (7.2)	0.38	(0.24-0.59)	
20-29	48467 (39.2)	4596 (42.1)	0.91	(0.86-0.96)	0.95	(0.90-1.01)	4425 (42.8)	0.99	(0.93-1.05)	171 (29.4)	0.66	(0.53-0.83)	
≥30	41904 (33.9)	4010 (36.7)	1.00	reference	1.00	reference	3649 (35.3)	1.00	reference	361 (62.1)	1.00	reference	

[a] Unconditional logistic regression models adjusted for matching factors (country, birth year), index age, body mass index, and marital status at first pregnancy.
[b] Unconditional logistic regression models adjusted for matching factors (country, birth year), index age, body mass index, marital status at first pregnancy, and parity.
Index age was defined as the age at endometrial cancer diagnosis among cases and age at endometrial cancer of the matched case among controls.
P heterogeneity

Table 3. Number and timing of births and endometrial cancer risk by histologic subtype; Nordic countries, 1967-2013.

	Endometrioid (n=4994)			Adenocarcinoma (n=5271)			Mucinous[b] (n=78)
Parity	n (%)	OR[a]	(95% CI)	n (%)	OR[a]	(95% CI)	n (%)
1 birth	689 (13.8)	1.00	reference	850 (16.1)	1.00	reference	6 (7.7)
2 births	2031 (40.7)	0.84	(0.76-0.92)	2279 (43.2)	0.78	(0.72-0.85)	40 (51.3)
3 births	1391 (27.9)	0.74	(0.67-0.82)	1363 (25.9)	0.66	(0.60-0.73)	20 (25.6)
4+ births	883 (17.7)	0.63	(0.56-0.71)	779 (14.8)	0.64	(0.57-0.72)	12 (15.4)
Age first birth							
<20	679 (13.6)	1.00	reference	496 (9.4)	1.00	reference	4 (5.1)
20-24	1691 (33.9)	0.95	(0.86-1.04)	1617 (30.7)	0.90	(0.81-1.00)	27 (34.6)
25-29	1621 (32.5)	0.85	(0.77-0.94)	1864 (35.4)	0.77	(0.69-0.87)	30 (38.5)
30-34	784 (15.7)	0.69	(0.62-0.78)	1016 (19.3)	0.62	(0.55-0.71)	14 (18.0)
35-39	213 (4.3)	0.65	(0.55-0.77)	264 (5.0)	0.56	(0.47-0.66)	3 (3.9)
≥40	6 (0.1)	0.28	(0.13-0.64)	14 (0.3)	0.48	(0.28-0.84)	0 (0.0)
Time since first birth, years							
<10	33 (1.1)	0.33	(0.22-0.50)	53 (2.0)	0.41	(0.29-0.58)	0 (0.0)
10-19	286 (9.9)	0.63	(0.52-0.75)	400 (15.0)	0.74	(0.63-0.87)	3 (7.7)
20-29	969 (33.4)	0.93	(0.84-1.02)	1154 (43.3)	0.98	(0.88-1.09)	20 (51.3)
≥30	1614 (55.6)	1.00	reference	1060 (39.8)	1.00	reference	16 (41.0)
Age last birth							
<25	319 (11.0)	1.00	reference	138 (5.2)	1.00	reference	3 (7.7)
25-29	1215 (41.9)	0.91	(0.79-1.03)	839 (31.5)	1.09	(0.90-1.31)	11 (28.2)
30-34	861 (29.7)	0.75	(0.65-0.86)	929 (34.8)	0.88	(0.72-1.07)	20 (51.3)
35-39	339 (11.7)	0.71	(0.59-0.84)	503 (18.9)	0.78	(0.63-0.96)	5 (12.8)
40-44	135 (4.7)	0.67	(0.53-0.84)	216 (8.1)	0.64	(0.49-0.82)	0 (0.0)
≥45	33 (1.1)	0.60	(0.41-0.89)	42 (1.6)	0.44	(0.30-0.65)	0 (0.0)
Time since last birth, years							
<10	118 (2.4)	0.31	(0.25-0.40)	155 (2.9)	0.39	(0.31-0.48)	1 (1.3)
10-19	814 (16.3)	0.62	(0.55-0.70)	1170 (22.2)	0.87	(0.78-0.98)	11 (14.1)
20-29	1995 (40.0)	0.92	(0.85-1.00)	2387 (45.3)	1.04	(0.96-1.13)	43 (55.1)
≥30	2067 (41.4)	1.00	reference	1559 (29.6)	1.00	reference	23 (29.5)

Table 3. Cont'd

	Serous (n=428)			Clear Cell (n=153)			
Parity	n (%)	OR[a]	(95% CI)	n (%)	OR[a]	(95% CI)	*P* heterogeneity
1 birth	46 (10.8)	1.00	reference	16 (10.5)	1.00	reference	0.03
2 births	178 (41.6)	1.07	(0.76-1.51)	68 (44.4)	1.12	(0.63-1.99)	
3 births	126 (29.4)	0.91	(0.62-1.33)	46 (30.1)	0.90	(0.48-1.69)	
4+ births	78 (18.2)	0.72	(0.48-1.10)	23 (15.0)	0.60	(0.30-1.23)	
Age first birth							
<20	41 (9.6)	1.00	reference	18 (11.8)	1.00	reference	0.005
20-24	118 (27.6)	0.78	(0.54-1.13)	47 (30.7)	0.73	(0.41-1.28)	
25-29	143 (33.4)	0.74	(0.50-1.08)	46 (30.1)	0.54	(0.30-0.98)	
30-34	86 (20.1)	0.70	(0.45-1.07)	29 (19.0)	0.51	(0.26-1.01)	
35-39	36 (8.4)	0.94	(0.56-1.57)	12 (7.8)	0.66	(0.28-1.54)	
≥40	4 (0.9)	1.55	(0.53-4.54)	1 (0.7)	0.83	(0.10-6.64)	
Time since first birth, years							<0.001
<10	2 (1.1)	0.79	(0.14-4.51)	2 (3.0)	0.74	(0.10-5.66)	
10-19	11 (6.1)	0.62	(0.27-1.44)	8 (12.1)	0.87	(0.29-2.61)	
20-29	28 (15.6)	0.48	(0.30-0.77)	19 (28.8)	0.78	(0.40-1.52)	
≥30	139 (77.2)	1.00	reference	37 (56.1)	1.00	reference	
Age last birth							
<25	19 (10.6)	1.00	reference	6 (9.1)	1.00	reference	<0.001
25-29	55 (30.6)	0.49	(0.28-0.84)	20 (30.3)	0.62	(0.24-1.58)	
30-34	61 (33.9)	0.45	(0.25-0.80)	23 (34.9)	0.59	(0.22-1.56)	
35-39	32 (17.8)	0.44	(0.23-0.84)	11 (16.7)	0.51	(0.17-1.56)	
40-44	10 (5.6)	0.28	(0.11-0.69)	3 (4.6)	0.29	(0.06-1.41)	
≥45	3 (1.7)	0.29	(0.08-1.13)	3 (4.6)	1.10	(0.21-5.84)	
Time since last birth, years							<0.001
<10	3 (0.7)	0.19	(0.05-0.75)	4 (2.6)	0.25	(0.06-1.15)	
10-19	28 (6.5)	0.38	(0.23-0.65)	14 (9.2)	0.36	(0.16-0.80)	
20-29	116 (27.1)	0.62	(0.48-0.81)	55 (36.0)	0.76	(0.49-1.19)	
≥30	281 (65.7)	1.00	reference	80 (52.3)	1.00	reference	

[a] Multinomial logistic regression model adjusted for matching factors (country, birth year), index age, body mass index, and marital status at first pregnancy. Index age was defined as the age at endometrial cancer diagnosis among cases and age at endometrial cancer of the matched case among controls.
[b] Given sparse data for mucinous tumors we provide case counts and percent for comparison but do not report effect estimates.

Novelty and Impact:
Many pregnancy-related factors are associated with reduced endometrial-cancer risk. Are pregnancy-related complications also associated with altered risk? In study, the authors found that pre-existing and gestational hypertension, as well as preeclampsia, were associated with an increased risk of endometrial cancer, suggesting that immunologic and/or inflammatory etiologies may be relevant in endometrial carcinogenesis. They also conclude that the reduced risk associated with higher parity and later age also suggest an important role for hormonal and cell-clearance mechanisms. These results support further study of how endometrial hyperplasia in the context of pregnancy-related exposures influences cancer risk.

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