Pregnancy outcomes and risk of endometrial cancer

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Pregnancy outcomes and risk of endometrial cancer: A pooled analysis of individual participant data in the Epidemiology of Endometrial Cancer Consortium

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Abbreviations: BMI, body mass index; E2C2, Epidemiology of Endometrial Cancer Consortium; MHT, menopausal hormone therapy; OC, oral contraceptive; OR, odds ratios.

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Abstract

A full-term pregnancy is associated with reduced endometrial cancer risk; however, whether the effect of additional pregnancies is independent of age at last pregnancy is unknown. The associations between other pregnancy-related factors and endometrial cancer risk are less clear. We pooled individual participant data from 11 cohort and 19 case-control studies participating in the Epidemiology of Endometrial Cancer Consortium (E2C2) including 16 986 women with endometrial cancer and 39 538 control women. We used one- and two-stage meta-analytic approaches to estimate pooled odds ratios (ORs) for the association between exposures and endometrial cancer risk. Ever having a full-term pregnancy was associated with a 41% reduction in risk of endometrial cancer compared to never having a full-term pregnancy (OR = 0.59, 95% confidence interval [CI] 0.56-0.63). The risk reduction appeared the greatest for the first full-term pregnancy (OR = 0.78, 95% CI 0.72-0.84), with a further ~15%

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reduction per pregnancy up to eight pregnancies (OR = 0.20, 95% CI 0.14-0.28) that was independent of age at last full-term pregnancy. Incomplete pregnancy was also associated with decreased endometrial cancer risk (7%-9% reduction per pregnancy). Twin births appeared to have the same effect as singleton pregnancies. Our pooled analysis shows that, while the magnitude of the risk reduction is greater for a full-term pregnancy than an incomplete pregnancy, each additional pregnancy is associated with further reduction in endometrial cancer risk, independent of age at last full-term pregnancy. These results suggest that the very high progesterone level in the last trimester of pregnancy is not the sole explanation for the protective effect of pregnancy.

KEYWORDS

endometrial cancer, induced abortion, miscarriage, parity, sex of offspring

1 | INTRODUCTION

Full-term pregnancy is associated with reduced endometrial cancer risk,[1] although the mechanism underlying the association is not well understood. It has been suggested that hormonal factors may underpin the relationship,[2] because progestins can potentially reverse premalignant changes in the endometrium[3] and progesterone levels are very high during pregnancy.[4] Alternatively, it has been suggested that the physical shedding of the endometrium at childbirth may remove preneoplastic endometrial cells.[5] Greater understanding of the relationship between other pregnancy-related factors and endometrial cancer risk will increase our understanding of the mechanisms underlying the protective effects of full-term pregnancy.

Although most epidemiological studies indicate that additional full-term pregnancies up to at least four are associated with progressive reductions in endometrial cancer risk, few studies have had sufficient power to investigate whether subsequent pregnancies beyond this further reduce risk and their results have not been consistent. One showed no further risk reduction after six births;[6] one showed that risk continued to decline up to at least 10 births;[7] and another showed smaller, nonsignificant risk reductions for the fifth birth.[8] In addition, studies have shown that older age at last full-term pregnancy is associated with lower risk of endometrial cancer[9]; therefore, the reduced risk associated with increasing numbers of full-term pregnancies may just reflect later age at last full-term pregnancy. However, this has not been adequately explored.

What's new?

Having a full-term pregnancy reduces a woman's risk of endometrial cancer, perhaps due to a protective effect from high levels of progesterone in the third trimester. Here, the authors conducted a pooled analysis of 11 cohort studies and 19 case-control studies to learn more about the effect of multiple pregnancies on endometrial cancer risk. They found that up to eight full-term pregnancies each reduced endometrial cancer risk, independent of maternal age and oral contraceptive use. Interestingly, incomplete pregnancies were associated with a smaller reduction in risk, suggesting that high third trimester progesterone levels are not the only contributing factor.

The associations between other pregnancy-related factors, such as incomplete pregnancy (spontaneous or induced abortion), multiple birth (eg, twins) and sex of offspring and endometrial cancer have also been infrequently investigated and results were mixed. Some[8,10-12] but not all[2,13-15] studies suggest incomplete pregnancies are associated with reduced risk, but most included small numbers of exposed case women. Differences have also been observed for spontaneous vs induced pregnancy loss.[8,16,17] In particular, a recent Danish data linkage study found that induced abortion was associated with an ~50% reduction in endometrial cancer risk, whereas the risk reduction associated with a miscarriage was much smaller and not statistically significant.[8] However, they were unable to adjust for important potential confounders including contraceptive use and smoking status.

To assess the association between pregnancy outcomes and endometrial cancer risk in detail, we pooled data from 30 observational studies (cohort and case-control; 16 986 women with endometrial cancer and 39 538 controls) participating in the Epidemiology of Endometrial Cancer Consortium (E2C2). We hypothesized that if progesterone is responsible for the previously observed inverse associations, endometrial cancer risk would decrease with each subsequent full-term pregnancy; risk would also decrease for incomplete pregnancies, but to a lesser extent. Risk reduction with twin birth might be greater because of higher progesterone levels, and risk might differ by offspring sex because of differences in maternal hormone levels.[18,19] However, if shedding of the endometrium is the underlying mechanism, we hypothesized the risk reduction would be similar for all types of pregnancy.

2 | MATERIALS AND METHODS

2.1 | Participants and data collection

We included 11 cohort and 19 case-control studies with individual participant data on pregnancy outcomes including numbers of full-term pregnancies, incomplete pregnancies (miscarriages and induced abortions), twin/multiple births and sex of babies. All studies had institutional review board approval and participants provided informed consent. The E2C2 data harmonization process has been described elsewhere.[20] In brief, studies provided information on demographic, anthropometric, and lifestyle factors (eg, height, weight 1-5 years before diagnosis, oral contraceptive (OC) and menopausal hormone therapy (MHT) use and smoking) according to specified definitions.

For the current analyses, cohort studies were analyzed as nested case-control studies with up to four controls per case, matched on year of birth, cohort entry date and other study-specific criteria as appropriate, randomly selected from cohort members without a hysterectomy or endometrial cancer by the case diagnosis date. We excluded cases (and, for cohort studies, their matched controls) with nonepithelial tumors or tumors of unknown histology (179 cases/418 controls), and women missing data for all pregnancy outcomes (549 cases/438 controls, including controls individually matched to cases with missing data). The remaining eligible participants included 16 986 women with endometrial cancer and 39 538 controls.

2.2 | Exposures

Data on full-term pregnancies (defined by E2C2 as at least 7 months duration) including both livebirths and stillbirths were provided by 22 of the 30 studies (Supplementary Table 1 for full study names). Eight studies (ALBERTA, BCDDP, CNBSS, MEC, NHS, NLCS, ORDET and TURIN) provided information on livebirths but not stillbirths, hence livebirths was used as a proxy for full-term pregnancies; a sensitivity analysis excluding these studies gave essentially the same results. The total number of incomplete pregnancies (miscarriages + induced abortions) was provided by 16 studies (ANECS, BWHS, CONN, EDGE, FHCRC, IMS, IWHS, ML1, ML2, NYU, PEDS, POL, SECS, TURIN, VAUD and WNYDS) or estimated as total number of pregnancies minus number of full-term pregnancies/livebirths. Five studies provided the number of daughters and sons (ANECS, CONN, EDGE, FHCRC and TURIN,). Another five (IWHS, PEDS, POL, SECS and USC) provided the number of daughters; therefore, the number of sons was estimated as the number of livebirths minus the number of daughters. Seven studies provided data on twin/multiple births (ANECS, BWHS, CONN, EDGE, FHCRC, TURIN and WNYDS). All pregnancy data were self-reported.

2.3 | Statistical analysis

We initially used two-stage individual-participant meta-analysis to estimate risk per full-term or incomplete pregnancy. We estimated study-specific odds ratios (OR) and 95% confidence intervals (CI) using multivariable logistic regression (conditional logistic regression for matched studies). Models were adjusted for age at diagnosis (cases) or interview (controls) (<40, 40-49, 50-59, 60-69, 70+ years), BMI (kg/m^2, continuous), education (≤high school, technical college, university), smoking (never, former, current) and OC use (never, ever; further adjustment for duration in studies with this information made little difference). Analyses of the relation between incomplete pregnancies and endometrial cancer risk were further adjusted for a number of full-term pregnancies (continuous). The proportion of missing data on confounders ranged from 0.6% for education to 3% for BMI with a total of 6% of women missing data on ≥1 variable. These women were excluded from study-specific analyses. Study-specific estimates were pooled using random-effects models to calculate summary ORs. Heterogeneity was assessed using I^2 and Q statistics.[21] If substantial heterogeneity was identified, we performed a sensitivity analysis removing one study at a time to investigate the influence of individual studies.

We examined the effects of other potential confounders including age at menarche, early adult BMI, race, age at last full-term pregnancy and breastfeeding, but these did not materially alter the magnitude of the associations (Supplementary Table 2).

Given the limited heterogeneity between studies, we conducted all other analyses in one-stage model using generalized linear mixed regression models to allow the exposure effect to vary by study. One- and two-stage approaches produce similar estimates, but the

one-stage approach provides greater flexibility to evaluate interactions and undertake subgroup analyses.[22] This approach was used to assess the associations between endometrial cancer risk and each additional full-term or incomplete pregnancy after the first, offspring sex and twin/multiple births. We also used one-stage meta-analysis for stratified analyses to assess whether the magnitude of the association per full-term or incomplete pregnancy varied by age at diagnosis/interview, race, BMI, smoking, OC use, menopausal status and use of MHT (among postmenopausal women), age at last full-term pregnancy and histological subtype (type 1 vs type 2).[20] For incomplete pregnancies, we also stratified by number of full-term pregnancies.

In our main analyses, the reference group was women who never had a full-term pregnancy (for analyses of full-term pregnancy) or women who never had an incomplete pregnancy (for analyses of incomplete pregnancy). We conducted sensitivity analyses using women who had never been pregnant (nulligravid) as the reference. We also assessed the impact of subsequent pregnancies after the first by excluding nulliparous women from the full-term pregnancies analyses and examined endometrial cancer risk per incomplete pregnancy separately in nulliparous and parous women. As the results were similar, we have presented results based on the entire study population (including nulliparous and nulligravid women) unless otherwise specified.

We calculated statistics for linear trend across ordinal categorical variables and assessed interactions between full-term and incomplete pregnancies using log-likelihood test statistics, where models with and without interaction terms were compared. We calculated Woolf's statistic for homogeneity of ORs to assess differences in estimates between case subgroups. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina) and Stata version 15 (StataCorp LP, College Station, Texas).

3 | RESULTS

The characteristics of the included studies and the prevalence of pregnancy outcomes in controls are presented in Supplementary Table 1. The proportion of controls who reported at least one full-term pregnancy ranged from 67% to 96%, and the proportion who reported an incomplete pregnancy ranged from 28% to 68%. Among parous control women, the prevalence of twin births was 2% to 4%.

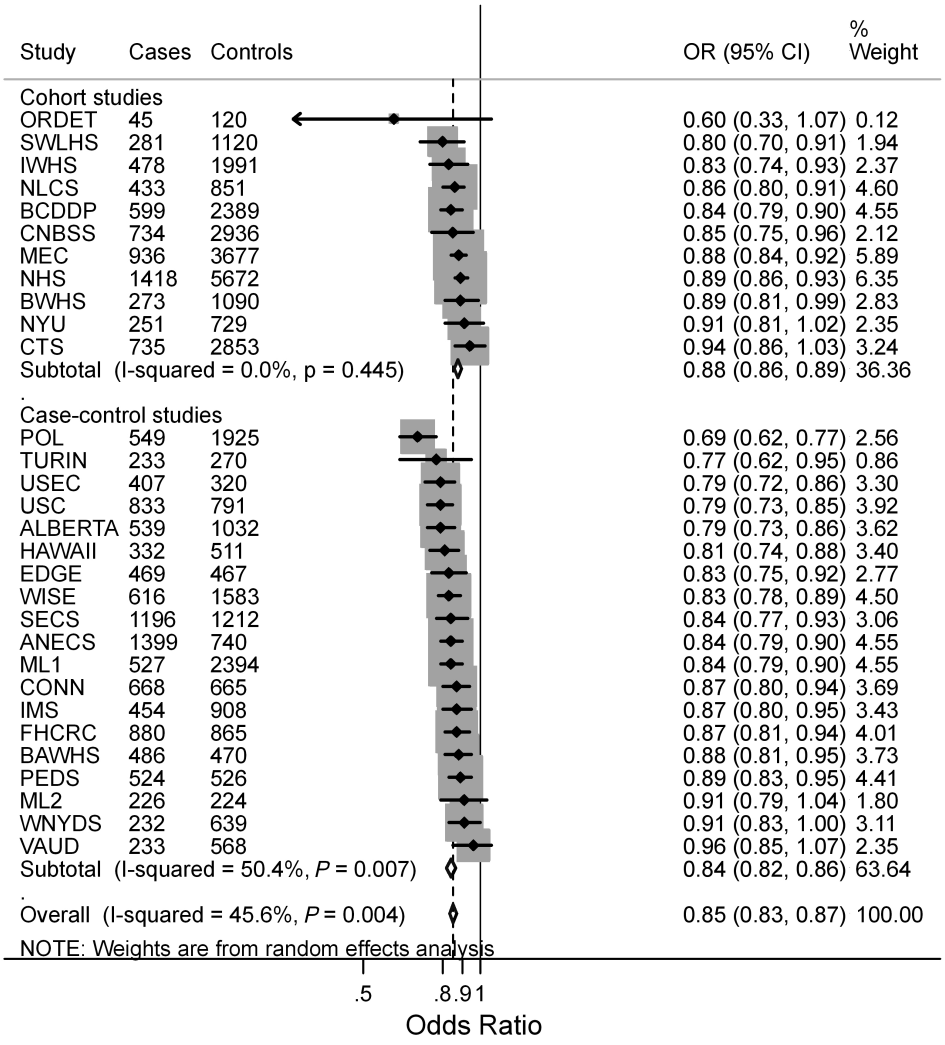

FIGURE 1 Forest plot showing adjusted estimates and 95% confidence intervals for the risk of endometrial cancer per full-term pregnancy

TABLE 1 Associations between number of full-term pregnancies and risk of endometrial cancer

Variable	Full-term pregnancy Controls n (%)	Cases n (%)	OR[a]	95% CI
Any vs none				
No full-term pregnancies	4955 (13)	3121 (18)	1.00	—
At least one full-term pregnancy	34 468 (87)	13 819 (82)	0.59	(0.56 to 0.63)
Number of full-term pregnancies vs none				
1	5522 (14)	2777 (16)	0.78	(0.72 to 0.84)
2	11 866 (30)	4910 (29)	0.65	(0.61 to 0.69)
3	8370 (21)	3260 (19)	0.55	(0.52 to 0.59)
4	4548 (12)	1634 (9.6)	0.49	(0.45 to 0.53)
5	2078 (5.3)	689 (4.1)	0.43	(0.39 to 0.48)
6	950 (2.4)	313 (1.8)	0.39	(0.34 to 0.46)
7	675 (1.7)	133 (0.8)	0.25	(0.20 to 0.30)
8	253 (0.6)	50 (0.3)	0.20	(0.14 to 0.28)
9+	206 (0.5)	53 (0.3)	0.27	(0.20 to 0.37)
P trend				<.001
Per full-term pregnancy—all women	39 423	16 940	0.84	(0.83 to 0.85)
Per full-term pregnancy—excluding nulliparous women	34 468	13 819	0.85	(0.84 to 0.87)

Abbreviations: CI, confidence interval; OR: odds ratio.

[a]One-stage models adjusted for age at diagnosis or interview (<40, 40-49, 50-59, 60-69, 70+), BMI at diagnosis or interview (kg/m^2, continuous), education (≤high school, technical college, university), smoking (never, former, current) and OC use (never, ever). Includes all studies; for ALBERTA, BCDDP, CNBSS, MEC, NHS, NLCS, ORDET and TURIN, livebirth was used as a proxy for full-term pregnancies.

Figure 1 shows that each full-term pregnancy was associated with a 15% reduction in endometrial cancer risk. This association was slightly stronger for case-control (OR = 0.84, 95% CI 0.82-0.86) than cohort studies (OR = 0.88, 95% CI 0.86-0.89). There was significant heterogeneity in results from case-control studies (I^2 = 50%, *p* heterogeneity = 0.007) due to the POL study. After excluding POL, the overall pattern remained (OR = 0.85, 95% CI 0.83-0.87) and the heterogeneity was no longer significant (I^2 = 25%, *P* = .1).

Table 1 shows that each additional full-term pregnancy was associated with progressively reduced risk up to eight full-term pregnancies (OR = 0.20, 95% CI 0.14-0.28) although the risk reduction appeared the greatest for the first birth (OR = 0.78, 95% CI 0.72-0.84) compared to an average 15% reduction in risk (OR = 0.85, 95% CI 0.84-0.87) for each birth after the first (ie, excluding nulliparous women).

Supplementary Figure 1 shows the association per full-term pregnancy stratified by participant and tumor characteristics. Notably, the inverse association seen overall was present across all categories of age at last full-term pregnancy. The inverse associations were also seen for all strata of age, race, BMI, smoking, OC use, menopausal status, MHT use and tumor type but the association attenuated with increasing age; appeared stronger in white women than black women; and for Type 1 vs Type 2 endometrial cancer.

Meta-analysis of study-specific results in Figure 2 shows that each incomplete pregnancy was associated with a 9% reduction in endometrial cancer risk (OR = 0.91, 95% CI 0.88-0.95). Estimates did not vary by study design (case-control studies OR = 0.92, 95% CI [0.88-0.95]; cohort studies OR = 0.90, 95% CI [0.79-1.03]). Excluding POL removed the heterogeneity (I^2 = 18%, *P* = .2) and did not change the estimate.

Table 2 shows the estimates for each additional incomplete pregnancy. The estimate per pregnancy was slightly closer to the null in the one-stage vs the two-stage model (7% vs 9% risk reduction) although the confidence intervals were overlapping. Estimates were similar for parous and nulliparous women (*p* for heterogeneity = 0.7). Inverse associations were seen for both spontaneous (OR = 0.83, 95% CI 0.76-0.90 for ever vs never) and induced abortions (OR = 0.89, 95% CI 0.79-1.01 for ever vs never). Neither the association with spontaneous abortions nor the association with induced abortions differed appreciably by study design.

Supplementary Figure 2 shows the association between incomplete pregnancy and risk of endometrial cancer stratified by participant and tumor characteristics. The inverse association did not vary by age group, race, BMI, smoking status, OC use, menopausal status or type of endometrial cancer.

With respect to other pregnancy variables, we found that the risk reduction per full-term pregnancy was similar irrespective of the sex of the child (OR = 0.85, 95% CI 0.82-0.89 for girls; OR = 0.83, 95% CI 0.79-0.86 for boys); however, women who had only boys or a mix of boys and girls had a lower risk of endometrial cancer compared with women with only girls (Table 3). This pattern remained when we restricted to women with only two children. The association did not

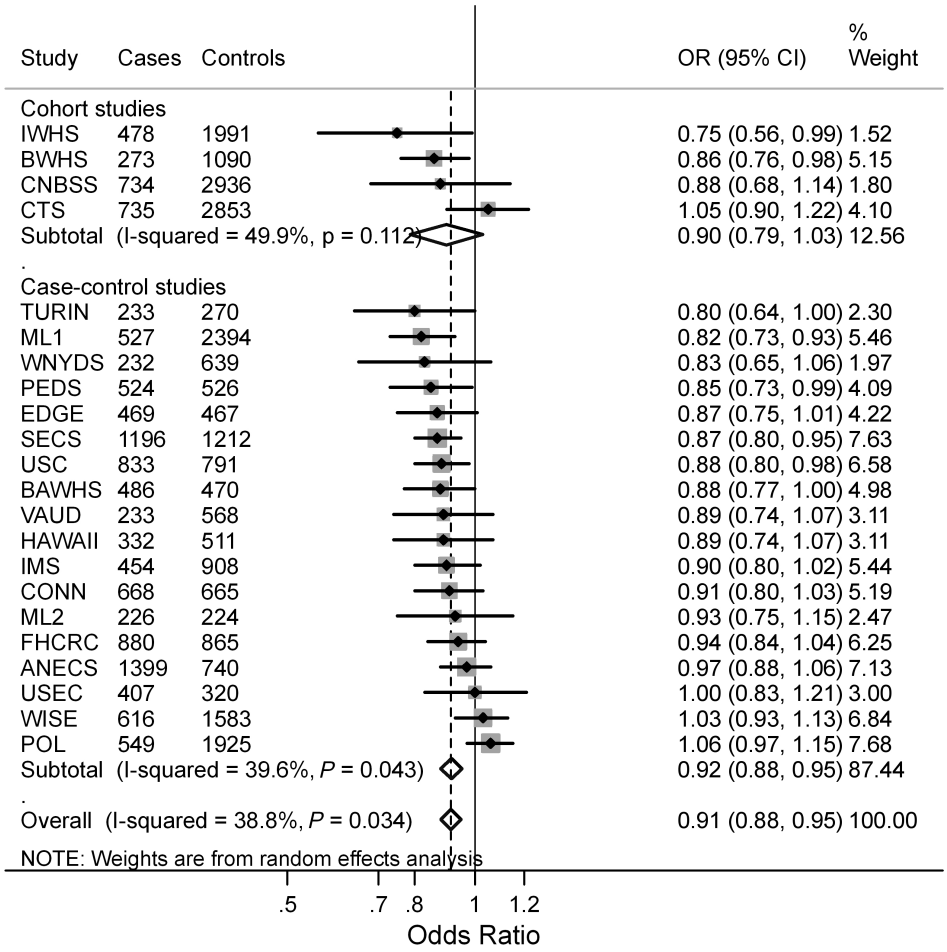

FIGURE 2 Forest plot showing adjusted estimates and 95% confidence intervals for the risk of endometrial cancer per incomplete pregnancy

TABLE 2 Associations between number of incomplete pregnancies and risk of endometrial cancer

Variables	Controls[a]	Cases[a]	OR[b]	95% CI
Any vs none				
No incomplete pregnancies	15 233 (64)	8370 (67)	1.00	—
At least one incomplete pregnancy	8493 (36)	4042 (33)	0.87	(0.82 to 0.92)
Number of incomplete pregnancies vs none				
1	5110 (21)	2516 (20)	0.89	(0.84 to 0.95)
2	2078 (9)	981 (8)	0.86	(0.78 to 0.94)
3	787 (3.3)	339 (2.7)	0.82	(0.71 to 0.95)
4	287 (1.2)	105 (0.9)	0.75	(0.58 to 0.96)
5	108 (0.4)	55 (0.4)	0.79	(0.55 to 1.14)
6	123 (0.5)	46 (0.4)	0.69	(0.47 to 1.02)
P trend				<.001
Per incomplete pregnancy—all women	23 726	12 412	0.93	(0.90 to 0.95)
Per incomplete pregnancy—parous	20 494	10 051	0.93	(0.91 to 0.96)
Per incomplete pregnancy—nulliparous	3228	2352	0.95	(0.87 to 1.02)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Numbers may not sum to total because of missing data.

[b]One-stage models adjusted for age at diagnosis or interview (<40, 40-49, 50-59, 60-69, 70+), BMI at diagnosis or interview (kg/m^2, continuous), education (≤high school, technical college, university), smoking (never, former, current), OC use (never, ever) and number of full-term pregnancies (continuous). Includes data from ANECS, BAWHS, BWHS*, CNBSS*, CONN, CTS*, EDGE, FHCRC, HAWAII, IMS, IWHS*, ML1, ML2, PEDS, POL, SECS, TURIN, USC, USEC, VAUD, WISE and WNYDS. Note: Asterisk (*) indicates cohort study.

TABLE 3 Associations between sex of babies, twin births and endometrial cancer among parous women

Variables	Controls N (%)	Cases N (%)	OR	95% CI
Sex of babies[a]				
Per daughter	7273	4952	0.85	(0.82 to 0.89)
Per son	7273	4952	0.83	(0.79 to 0.86)
Sex of babies[b]				
Daughter(s) only	1809 (24)	1361 (26)	1.00	—
Son(s) only	1402 (19)	1001 (19)	0.88	(0.78 to 0.99)
Son(s) and daughter(s)	4318 (57)	2796 (54)	0.89	(0.80 to 0.99)
Restricting to women with two children				
Two daughters	639 (24)	463 (25)	1.00	—
Two sons	553 (20)	387 (20)	0.88	(0.72-1.08)
One son and one daughter	1520 (56)	1040 (55)	0.89	(0.76-1.05)
Multiple births[a]				
No multiple birth	2691 (97)	2663 (96)	1.00	—
At least one multiple birth	83 (3)	99 (4)	1.10	(0.79 to 1.53)
Girl-girl	23 (0.8)	30 (1)	0.98	(0.52 to 1.82)
Boy-boy	18 (0.7)	24 (0.9)	1.23	(0.61 to 2.48)
Boy-girl	22 (0.8)	24 (0.9)	1.11	(0.57 to 2.16)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for age at diagnosis or interview (<40, 40-49, 50-59, 60-69, 70+), BMI at diagnosis or interview (kg/m^2, continuous), education (≤high school, technical college and university), smoking (never, former and current), OC use (ever, never).

[b]Further adjusted for number of full-term pregnancies (continuous). Includes data from ANECS, CONN, EDGE, FHCRC, IWHS*, PEDS, POL, SECS, TURIN and USC; multiple births analysis included data from ANECS, CONN, EDGE, FHCRC, TURIN and WNY. Note: Asterisk (*) indicates cohort study.

differ between women who had a twin/multiple birth and those who had only singleton births.

4 | DISCUSSION

In this large pooled analysis, we observed a reduction in endometrial cancer risk associated with full-term pregnancy that was the greatest for the first full-term pregnancy but also evident for each subsequent full-term pregnancy up to eight. The inverse association was independent of age at last full-term pregnancy and was consistent across strata of BMI, smoking, OC use, menopausal status and MHT use, but stronger among younger women and white women. The association also appeared stronger for Type 1 than for Type 2 cancers. Incomplete pregnancy was also associated with reduced risk although the reduction per additional pregnancy was smaller than for full-term pregnancies (7% vs 15%). We found no evidence that twin births conferred additional protection compared to singleton births, but our results suggested having boys might confer somewhat greater risk reduction than having only girls.

Strengths of our study include the large sample size, which allowed us to assess associations with higher numbers of full-term and incomplete pregnancies and to compare across the different endometrial cancer subtypes. Our pooled design allowed us to define exposures and confounders consistently across studies and to include previously published[12,13,16,17,23,24] and unpublished studies (ALBERTA, ANECS, BAWHS, BCDDP, BWHS, CNBSS, CONN, CTS, EDGE, FHCRC, HAWAII, IMS, MEC, NLCS, NHS, NYU, ORDET, PEDS, SWLHS, TURIN, USC, VAUD and WNYDS) from diverse populations. We also included data from both cohort and case-control studies; the patterns of results and estimates were consistent by study design, providing additional reassurance about the validity of our findings. A limitation is that for most studies we did not have information on length of gestation so could not investigate the possibility that the magnitude of the association is a function of pregnancy duration. Also, all studies relied on participant recall of exposures. Although this is likely to be very accurate for full-term pregnancies, self-report of incomplete pregnancies is less reliable. However, the similarity in pooled estimates between the case-control and cohort studies makes appreciable recall bias unlikely. If anything, misclassification may have biased our results toward the null, meaning that we may have underestimated the magnitude of the risk reduction associated with incomplete pregnancy. We also did not have information on how women with incomplete pregnancy were managed and whether they had any associated procedures. Finally, despite our very large sample, few women reported twin births, so we had limited ability to draw conclusions about any association between these and endometrial cancer.

Our findings are consistent with results from a data linkage study from Sweden, which indicated that endometrial cancer risk continues to decrease with each additional full-term pregnancy in women with

more than five births.[7] However, an earlier study from Finland[6] suggested that risk did not decrease further after the sixth full-term pregnancy once age at last full-term pregnancy was considered. They also found that in women <50 years, risk of endometrial cancer was *increased* in those with seven or more full-term pregnancies, but this was based on small numbers of women and was not statistically significant. We found a similar risk reduction per full-term pregnancy irrespective of age at last full-term pregnancy and found that the inverse association per full-term pregnancy was strongest (~42% reduction in risk per pregnancy) among the youngest women. Our findings were based on a larger sample size with adjustment for a wider range of potentially important confounders. Some previous studies have reported that incomplete pregnancy was associated with reduced risk of endometrial cancer[8,10-12] but others have not,[2,13-15] although most of these included small numbers of exposed case women (mostly <250 vs >4000 in our study). One large data linkage study from Denmark (n = 872 cases with an induced abortion) found that the risk reduction associated with a first induced abortion (RR = 0.53) was of greater magnitude than for a first-term pregnancy (RR = 0.66)[8] and that while the first miscarriage was also associated with reduced endometrial cancer risk, the magnitude of the reduction was smaller than for induced abortion. Possible explanations for the differences between their findings and ours might include differences in the methods of ascertainment of induced abortions (through data linkage rather than recall); inability to adjust for potentially important confounders such as OC use and smoking; or differences in management of incomplete pregnancy across different settings.

The mechanism responsible for the risk-reducing association with pregnancy is not clear, with some it is due to the effects of reproductive hormones during and subsequent to pregnancy, and others hypothesizing that shedding of the endometrium at the end of pregnancy removes premalignant or malignant cells.[5] Parous women may have lower estradiol levels than nulliparous women,[25] an effect that may persist into postmenopausal years and become more pronounced with increasing numbers of births.[26] As estrogen unopposed by a progestin increases endometrial cell mitoses,[27] the substantial reduction in endometrial cancer that we have observed with multiparity might reflect pervasively lower estradiol levels in these women compared to women with fewer pregnancies. Progesterone reduces estrogen-induced mitotic activity in endometrial cells and promotes cell differentiation,[5,27] and, as serum progesterone levels increase throughout pregnancy to very high levels in the third trimester,[4] the protective effects of multiparity may also reflect recurrent exposure to high serum progesterone levels. However, we also observed risk reductions with increasing numbers of incomplete pregnancies. In the first trimester of pregnancy (when most miscarriages and terminations occur), progesterone is elevated to levels that suppress mitoses[4,27,28] but is consistently lower in pregnancies that end in miscarriage than those that continue to term.[29] We found the association did not appear to differ between miscarriages and induced abortions. Furthermore, the risk reduction we observed with an incomplete pregnancy (encompassing perhaps 4-8 weeks of progesterone at levels that would suppress mitoses) was similar in magnitude to the reduction that has been reported for a year of combined oral contraceptive pill use (~8% reduction per year of use[2]). Notwithstanding our lack of information about gestation duration, these findings suggest that mechanical clearance (eg, via curettage) of endometrial cells may play a role in reducing risk of endometrial cancer.

The reason for the association we observed with off-spring sex and endometrial cancer risk is unclear. Although some studies have indicated that maternal hormone levels vary by offspring sex (eg, higher estradiol[19] and lower progesterone[18] in women carrying female fetuses), others have not[4] and two previous studies showed no difference in endometrial cancer risk according to offspring sex.[30,31] Ours may therefore be a chance finding; hence additional large studies are required to assess this.

5 | CONCLUSIONS

In summary, our large analysis, including individual participant data from 30 studies, provides comprehensive evidence that each additional pregnancy is associated with further reductions in endometrial cancer risk, even among grand multiparous women, and that this risk reduction is independent of age at last full-term pregnancy. Furthermore, incomplete pregnancies are also associated with reduced endometrial cancer risk, providing some reassurance to women who experience pregnancy loss that, at least with respect to cancer, their long-term endometrial health is unlikely to be adversely affected.

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CONFLICT OF INTEREST

Dr. Wise serves as a fibroid consultant for AbbVie, Inc. The other authors declare no conflicts of interests.

DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

DATA AVAILABILITY STATEMENT

For privacy and ethical reasons the data are only available through the Epidemiology of Endometrial Cancer Consortium. Consult the corresponding author (penny.webb@qimrberghofer.edu.au) to discuss the access to the Epidemiology of Endometrial Cancer Consortium.

ETHICS STATEMENT

All studies were approved by the relevant institutional review boards and participants provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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