TITLE PAGE

Title: Incomplete pregnancy and risk of ovarian cancer: results from two Australian case-control studies and systematic review

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~~Running head~~Abbreviated Title: Incomplete pregnancy and risk of ovarian cancer: 2 case control studies and a systematic review.

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ABSTRACT

Although full-term pregnancies reduce the risk of ovarian cancer, whether incomplete pregnancies also influence risk is not established. We investigated the relationship between a history of incomplete pregnancy and incident epithelial ovarian cancer. Participants in two large Australian population-based case-control studies in 1990 - 1993 and 2002 -2005 (2,300 incident cases and 2,263 controls) provided responses to a range of questions about their reproductive histories. Summary odds ratios (OR) and confidence intervals (CI) were derived from multivariate analysis of each study using the same covariates. Logistic coefficients (log(OR)) for each of the studies were aggregated using inverse variance weights before exponentiation. A systematic review of studies (1966-2007) of incomplete pregnancies and risk of ovarian cancer was also undertaken. The authors' own studies demonstrated no statistically significant associations in relation to incomplete pregnancy (either spontaneous or induced ~~miscarriage~~abortion) and ovarian cancer, irrespective of previous childbirth, consistent with the net findings of 37 studies in the systematic review. Further, there were no clear differences in risk of ovarian cancer between women with a history of spontaneous compared with induced ~~miscarriage~~abortion. It is concluded that a history of incomplete pregnancy does not influence a woman's risk of epithelial ovarian cancer.
(word count 197)

Key words (MeSH): Abortion, Spontaneous, Abortion, Induced, Ovarian Neoplasms, Risk, Carcinoma

INTRODUCTION

In the United States of America,(1)~~(1)~~ the United Kingdom(2)~~(2)~~ and Australia,(3)~~(3)~~ ovarian cancer is the most common cause of death from gynaecological malignancy, and responsible for high burdens of cancer mortality. Unfortunately, effective screening mechanisms for ovarian cancer have yet to be established, and determinants of epithelial ovarian cancer (EOC) – the most common type of ovarian cancer – have to date only partially been identified.

Increasing number of childbirths (parity) is known to reduce risk of EOC,(4)~~(4)~~ and the protection conferred is in keeping with the mechanisms proposed by two major hypotheses to explain the pathogenesis of ovarian cancer. The incessant ovulation theory proposes that disruption to the outer epithelial cells of the ovary at the time of ovulation may lead to malignant transformation,(5)~~(5)~~ while the pituitary ~~hormone~~ gonadotrophin ovarian stimulation theory proposes that the continual monthly stimulation of the ovary by gonadotrophins contributes to the development of malignant change.(6)~~(6)~~ If full-term pregnancies reduce the risk of ovarian cancer by either mechanism, it is reasonable to hypothesise that incomplete pregnancies might also, though perhaps to a lesser extent.

Comment [m1]: Reviewer 2, point 3.

Previous publications have explored the relationship of incomplete pregnancies and risk of ovarian cancer, however reported results vary according to the reference group and definitions used during analysis, and the extent of adjustment for other factors. Also, many of the results have been based on hospital-based studies, with few population-based studies. Some studies have shown a significant reduction in risk of ovarian cancer, some a significant increase in risk, and many others have shown no effect.

This paper analyses data from two large Australian case-control studies of ovarian cancer (hereafter referred to as Studies 1 and 2), and sets the findings in the context of other identifiable published studies in order to determine the association between incomplete pregnancies and EOC as comprehensively as possible.

MATERIALS AND METHODS

Subjects

Study 1.: A detailed description of the study has been published.(7)~~(7)~~ In brief, all incident cases of histologically confirmed primary EOC in women aged 18-79 years treated in the major gynaecologic-oncology treatment centres of three Australian States (and additionally those identified from the cancer registry in Queensland) were included in the study. For New South Wales and Victoria, women diagnosed in 1991 and 1992 were included, ~~whilst~~while in Queensland, incident cases from late 1990 through 1993 were enrolled (7)~~(7)~~. Controls were randomly selected from State and Commonwealth electoral rolls, according to the ages and geographic distributions of cases. Electoral enrolment in Australia is compulsory by law, with coverage estimated to be 97% (8)~~(8)~~.

Study 2. A detailed description of the study methodology has been published (9)~~(9)~~. In brief, women aged 18-79 years with newly diagnosed histologically confirmed EOC were recruited primarily from specialized gynaecologic-oncology units between January 2002 and June 2005. Women missed at treatment centers were identified through state-based cancer registries and invited to participate. Controls were women aged 18-79 years randomly selected from the Australian Electoral Roll, frequency matched to the entire case series by age (in five-year groups) and state of residence.

All women gave their written informed consent prior to their participation. The studies were approved by the Human Research Ethics Committees at all participating hospitals

and cancer registries, and at the Queensland Institute of Medical Research, and also for Study 2, at the Peter MacCallum Cancer Centre and the University of Melbourne..

In Study 1, there were 1,116 cases of incident epithelial ovarian cancer originally identified and 1,527 women whose names were randomly selected from the electoral roll, ~~whilst~~while in Study 2, there were 3,553 women initially identified with suspected ovarian cancer (many women were approached prior to surgery and thus before histological confirmation), and 3,600 women randomly selected from the electoral roll. Following exclusions (due to ineligible age, ineligible tumor histology, inability to be contacted, etc) response rates of eligible participants were 95% (794/835) for cases and 73% (855/1173) for controls in Study 1 and 94% (1580/1685) for cases and 45% (1509/3339) for controls in Study 2. After further excluding women with missing reproductive information in their surveys, a total of 2,300 cases of epithelial ovarian cancer (792 from Study 1 and 1508 from Study 2) and 2,263 controls (853 from Study 1 and 1410 from Study 2) were available for the analysis of incomplete pregnancies in relation to ovarian cancer.

Data Collection

Study 1. All women participated in a face-to-face interview with a trained interviewer and provided responses to a range of questions about reproductive, sociodemographic, medical, lifestyle and environmental factors. In the Pregnancy and Breastfeeding Calendar section of the questionnaire, women were asked to report whether they had had any past pregnancies, and if so, whether the pregnancies had ended as 'miscarriage', 'induced abortion', 'stillbirth', 'live birth' or 'other'. The duration (in months) of any pregnancies was sought, and women also recorded the date (month and year) of each pregnancy outcome in the Pregnancy and Contraceptive Calendar section of the

questionnaire. Information recorded in the two calendars was crosschecked for consistency of responses.

The words ‘miscarriage’ and ‘abortion’ as they apply to incomplete pregnancies are used variably in the medical literature and in the general community. Sometimes these terms are used interchangeably but at other times to distinguish whether the premature ending of a pregnancy occurred naturally (spontaneously) or was induced. Except when citing results from other studies, we use the word ‘~~miscarriage’~~ abortion’ throughout this manuscript to indicate a pregnancy that ended prematurely, and preface the word with “spontaneous” or “induced” when a distinction in meaning between the two methods of premature ending of the pregnancy is required. We use the term ‘incomplete pregnancy’ to refer to either a spontaneous or an induced ~~miscarriage~~abortion, including ectopic pregnancy.

Women’s responses regarding outcomes of past pregnancies were examined, and any responses of ‘other’ to the outcomes question that satisfied the definition of spontaneous or induced ~~miscarriage~~ abortion were re-classified. Scrutiny of responses also demonstrated that some women reported a history of “miscarriage” when they had experienced an ectopic pregnancy, ~~whilst~~while others referred to ectopic pregnancies as “other” pregnancies. Ectopic pregnancies were excluded from the “spontaneous ~~miscarriage~~abortion” class, but included in the “incomplete pregnancy” class (15 women – 7 cases and 8 controls - had at least one ectopic pregnancy). The number of incomplete pregnancies was derived as the sum of the number of spontaneous ~~miscarriages~~abortions, ~~terminations~~ induced abortions and ectopic pregnancies.

Study 2. As for Study 1, all participants were asked to complete a health and lifestyle questionnaire, including demographic characteristics and detailed questions regarding medical, reproductive and contraceptive histories, however Study 2 participants were asked to self-administer the questionnaires. Where possible, missing information and / or inconsistencies were clarified by research nurses in a follow-up telephone interview. Reported ectopic pregnancies were handled as in Study 1. Forty-one women (19 cases and 22 controls) had at least one ectopic pregnancy.

Dates of pregnancies were not always listed in chronological order in completed questionnaires and dates of incomplete pregnancies were frequently not listed. Where there was at least one incomplete pregnancy of unknown date, the variables 'age at first/last miscarriage/abortion/incomplete pregnancy", "first miscarriage/abortion/incomplete pregnancy before/after first full-term pregnancy" and "duration of first miscarriage/abortion/incomplete pregnancy" were derived wherever possible by inspection of the set of responses to the question seeking detailed information regarding each of the pregnancies. Undated terminations listed after a number of live births were also assumed to be in correct order. If dates of birth were not listed in ascending order, no such decision was made. There were in consequence an appreciable number of missing values for these outcome variables in Study 2, whereas in Study 1 almost all data collected in the face-to-face interviews could be assigned to "age at first/last miscarriage/abortion/incomplete pregnancy" categories.

Statistical Analysis

Our major aims were to determine the associations between incomplete pregnancy (either spontaneous ~~miscarriage~~abortion, induced ~~miscarriage~~abortion, or both) and epithelial ovarian cancer overall, and separate ~~amongst~~among women without children (i.e. nulliparous women) and also ~~amongst~~among women who had given birth (i.e.

parous women). For each of Studies 1 and 2, conditional logistic regression, conditioning on strata of age in years, was used to calculate the odds ratios (OR) (estimated relative risks) and 95% confidence intervals (CI) for ovarian cancer associated with aspects of incomplete pregnancy, and spontaneous and induced ~~miscarriage~~abortion. The specific variables examined were: number of incomplete pregnancies (0, 1, 2, 3+), spontaneous ~~miscarriages~~ abortions (0, 1, 2, 3+) and induced ~~miscarriages~~ abortions (0, 1, 2+); age at first and last incomplete pregnancy or ~~miscarriage~~ abortion (<20, 20-29, 30+); timing of first incomplete pregnancy or ~~miscarriage~~ abortion relative to first full-time birth; and gestational length of first incomplete pregnancy / ~~miscarriage~~ abortion (≤ 2, > 2 months). Where data were too sparse, categories were combined.

The following factors were associated to some degree with the number of incomplete pregnancies in parous or nulliparous cases or controls in either / both data sets and were controlled for in the conditional logistic analyses: duration of oral contraceptive (OC) use in years; history of tubal ligation; history of hysterectomy; smoking status (current, past, never); average daily alcohol consumption (none, 0.1-2.5g, or > 2.5g); menopausal status, and for parous women: age at last birth (less than 30 years, or 30 or more years) and number of births (1, 2, 3, 4, 5 or more). Preliminary inclusion of the covariables for education and State of residence made no material difference to the results/odds ratios and so was not included in the final conditional logistic analyses.

Summary ORs and CIs were derived from the separate multivariate analyses on the two data sets, using identical sets of covariates. Logistic coefficients (log(OR)) for each of the case control studies were aggregated using inverse variance weights before exponentiation.

Systematic Review

PubMed software was used to search Medline (U.S. National Library of Medicine, Bethesda, MD) (1966 – September 2007) to identify published articles exploring the association of incomplete pregnancies / miscarriage / abortion with ovarian cancer. Reference lists in relevant publications were also reviewed to identify any further articles. Where multiple reports from one study were found, we included the report that was incorporated into a pooled analysis (if available), or alternatively the report containing data for the greatest number of ovarian cancer cases. Where more than one risk estimate was given, those adjusted for the greatest number of potential confounding variables were included.

RESULTS

Baseline demographic data for cases and controls from both studies have been reported elsewhere (7, 9)~~(7, 9)~~.

A total of 1,490 women (33%) - 762 (33%) cases and 728 (32%) controls - reported having ever had an incomplete pregnancy (i.e. one or more spontaneous and/or induced ~~miscarriage~~abortion) (Table 1). A total of 1105 women (24%) - 570 (25%) cases and 535 (24%) controls - reported at least one spontaneous ~~miscarriage~~abortion, ~~whilst~~while 476 women (11%) - 246 cases (11%) and 230 controls (10%) - reported at least one induced ~~miscarriage~~ abortion (Tables 2 and 3).

Overall no statistically significant associations were seen in relation to incomplete pregnancy (and either spontaneous or induced ~~miscarriage~~abortion) and ovarian cancer risk, in either parous or nulliparous women. Additionally, no statistically significant associations were identified in relation to gestational length of first incomplete pregnancy (or spontaneous or induced abortion~~miscarriage~~), timing of first incomplete pregnancy (or spontaneous or induced abortion~~miscarriage~~) relative to first full-term birth, or age at last incomplete pregnancy (or spontaneous or induced abortion~~miscarriage~~). The median duration of incomplete pregnancy was 2 months.

The only findings approaching statistical significance were an increased risk of ovarian cancer in parous women whose age at first spontaneous abortion ~~miscarriage~~ or last spontaneous abortion ~~miscarriage~~ was less than 20 years (OR = 1.66, CI: 1.00, 2.8 and OR = 2.0, CI: 0.99, 4.1 respectively) (Table 3). This pattern was also seen in nulliparous women whose age at first or last spontaneous abortion ~~miscarriage~~ was less than 29, but was not significant (OR = 1.52, CI:0.59, 3.9 and OR = 1.71, CI: 0.60, 4.9) These trends were not seen in parous women with induced abortion~~miscarriage~~, and a non-significant reduction in risk was seen for nulliparous women with induced abortion ~~miscarriage~~ (Table 3).

The Medline search identified 37 studies that reported risk of ovarian cancer associated with incomplete pregnancy : 16 population-based studies (2 cohort studies (10, 11)~~(10, 11)~~ and 14 case-control studies (12-25)~~(12-25)~~); 20 hospital-based case-control studies (26-45)~~(26-45)~~; and one case-control study with equal numbers of population and hospital-based controls (46)~~(46)~~. The results of 6 USA population-based case-control studies (12, 15, 18, 22, 24, 25)~~(12, 15, 18, 22, 24, 25)~~ and 5 USA hospital-based studies (28, 32, 33, 35, 42)~~(28, 32, 33, 35, 42)~~ were pooled in a review by Whittemore et al. 1992 (4)~~(4)~~. The results of 3 hospital-based case control studies based in Italy (37)~~(37)~~,

the United Kingdom (27)~~(27)~~ and Greece (40)~~(40)~~ were pooled in a review by Negri et al. 1991(47)~~(47)~~. These pooled results are included in the systematic review rather than individual study results. Key results from the population-based studies and hospital-based studies are presented in Tables 4 and 5 respectively, together with the results of the present study (Table 4). Four studies did not report odds ratios, (34, 41, 43, 46)~~(34, 41, 43, 46)~~ however estimated odds ratios and confidence intervals were able to be calculated for three of these studies from data provided in their manuscripts (34, 43, 46)~~(34, 43, 46)~~.

The studies varied substantially according to several factors: whether they reported data relating to incomplete pregnancies, and/or spontaneous abortions~~miscarriages~~, and/ or induced ~~miscarriages (or~~ abortions~~)~~; the reference groups against which these outcomes were compared; the histological types of ovarian cancer; whether they were stratified by parity; and also with respect to the variables adjusted for in their analyses. Thus they were not all directly comparable. Despite this however, it is possible to summarise the data by stating that there is no convincing reproducible evidence that incomplete pregnancies or spontaneous or induced abortions~~miscarriages~~, materially increase or decrease risk of ovarian cancer.

~~Whilst~~While a number of studies showed some non significant trends in ovarian cancer risk (in both directions), only one of the population based studies(19)~~(19)~~, 5 of the hospital-based studies and the pooled analysis of 3 hospital-based studies demonstrated associations with statistical significance. Neither of the 2 cohort studies demonstrated any association between incomplete abortion ~~miscarriage~~ and ovarian cancer risk. (Tables 4 and 5)

The population-based case-control study described by Riman et al. (2002) (19)~~(19)~~ reported a 24% reduction in risk of invasive epithelial ovarian cancer for women with a

history of one 'incomplete pregnancy' (OR = 0.76, CI 0.59-0.98); the risk reduced further for women having had 2 or more "incomplete pregnancies", but this did not reach statistical significance (OR = 0.70, CI: 0.44, 1.12) (Table 4).

With respect to the case-control studies, El-Khwsky et al, 2006 (30)~~(30)~~ showed an increase in risk of ovarian cancer with one or more "fetal losses" (OR = 1.7, CI: 1.16, 2.59 for one to three "fetal losses" and OR = 3.7, CI: 1.02, 13.45 for four or more losses), Bernal et al., 1995 (26)~~(26)~~ reported an 82% increase in risk for women having had one or more "abortions", and calculations from data published by Wynder et al., 1969 (43)~~(43)~~ gave an estimated increase in risk of 69% for women having one or more spontaneous abortions (OR = 1.69, CI: 1.03, 2.76). Conversely, Mori et al. 1988 (36)~~(36)~~ reported a 40% reduction in risk of ovarian cancer for women having had an "induced abortion" (OR = 0.6, p = 0.04) (36)~~(36)~~, and Zhang et al., 2004 reported a 44% reduction in risk for women with two or more incomplete pregnancies (OR = 0.56, CI: 0.39, 0.82). Negri et al. 1991(47)~~(47)~~ in their pooled analysis of three studies (27, 37, 40)~~(27, 37, 40)~~, reported a 30% reduction in risk for women with a history of 2 or more "abortions" (OR = 0.7, CI: 0.6, 0.9) (Table 5).

In addition to our own study, several studies explored associations between incomplete pregnancies and ovarian cancer specifically for nulliparous women (4, 13, 16, 47)~~(4, 13, 16, 47)~~, and no statistically significant associations were identified. For parous women, Negri et al. (1991) (47)~~(47)~~ reported a 30% reduction in risk for ovarian cancer in women who had had two or more "abortions" (OR = 0.7, CI: 0.0.5, 0.9), ~~whilst~~while Bernal et al. (1995) (26)~~(26)~~ reported a 100% increase in risk of ovarian cancer with one to three "abortions" (OR = 2.05, CI: 1.33, 3.16) and an even greater risk with four "abortions" (OR = 5.44, CI: 1.43, 22.28). Chen et al. 1996 (13)~~(13)~~, Risch et al. 1994 (20)~~(20)~~ and Shu et al. 1989 (21)~~(21)~~ did not find any significant associations.

Discussion

~~The~~ Our results ~~of our case control studies~~ are based on 2,300 cases of epithelial ovarian cancer from two of the largest ovarian case control studies ever undertaken that explore the association of incomplete miscarriage and ovarian cancer risk. No statistically significant association was found between either spontaneous or induced abortion~~miscarriage~~, and ovarian cancer. This absence of association persisted after considering such factors as timing of first incomplete pregnancy / abortion ~~miscarriage~~ in relation to first full-term birth, gestational length of first incomplete pregnancy / abortion ~~miscarriage~~ and parity.

Comment [m2]: Response to Reviewer 1, point 1

We do not have a biological explanation for our study's isolated finding of an increased risk of ovarian cancer in parous women whose age at first spontaneous abortion ~~miscarriage~~ or last spontaneous abortion ~~miscarriage~~ was less than 20 years (Table 2 – based on 33 cases and 38 controls), and indeed it is possibly a chance finding given the large number of statistical tests performed. Chen et al., 1996 report a statistically significant increased risk of ovarian cancer in every-pregnant women whose age at first spontaneous abortion was less than 20 years (OR = 3.1, CI: 1.3, 7.8). (13) These findings are based on 14 cases and 9 controls. Gierach et al. 2004 however report a non significant reduction in risk of ovarian cancer among gravid women with a history of incomplete pregnancy with a first incomplete pregnancy at age less than 25 years. (16)

Comment [m3]: Additions here in response to Reviewer 1, point 3.

The systematic review identified 37 relevant epidemiological studies. ~~Whilst~~While the studies are not all directly comparable due to their variability with respect to such factors as their outcome measures, the reference groups against which their outcomes were compared, and the variables adjusted for in their analyses, the absence of a significant

association between incomplete pregnancies (including spontaneous and/or induced abortions~~miscarriages~~) and ovarian cancer was demonstrated for the large majority of studies identified in the systematic review. Of the small number of studies reporting a statistically significant association, some reported a reduced risk of ovarian cancer, ~~whilst~~while others reported an increase in risk. The pooled analysis of 3 hospital-based studies by Negri et al. 1991 (47)~~(47)~~, the hospital-based studies by Mori et al. 1988 (36)~~(36)~~, and Zhang et al. 2004(45)~~(45)~~ and the population-based study by Riman et al. 2002 (19)~~(19)~~ showed a reduction in risk of ovarian cancer in all women (or ever married women for Mori et al.) with "abortion", "induced abortion", "incomplete pregnancies" and "abortions – spontaneous or induced" respectively, ~~whilst~~while the hospital-based case-control studies by El-Khwsky et al. 2006 (30)~~(30)~~ and Bernal et al. 1995 (26)~~(26)~~ reported an increase in risk of ovarian cancer in women with one or more "fetal losses" or "abortions" respectively.(Tables 4 and 5). Furthermore, our study and the systematic review did not identify any substantial differences in risk of ovarian cancer between women with a history of spontaneous abortion ~~miscarriage~~ and women with a history of induced abortion~~miscarriage~~, nor between parous and nulliparous women.

The predominant absence of any significant risk of ovarian cancer with incomplete pregnancy does not lend support to the hypothesis that incomplete pregnancies may confer (albeit to a lesser extent) a protective effect similar to that noted with full-term pregnancies. Nor does it lend support to a proposed mechanism that the recovery of equilibrium in the reproductive organs following pregnancy interruption could be a risk for ovarian cancer. (26) It may be that any true risk due to incomplete pregnancies (the vast majority of which are less than 3 months in duration) is of insufficient magnitude compared with associations with live births to be detectable at a level of statistical significance in case-control studies.

Comment [m4]: An attempt to briefly respond to Reviewer 2, point 7.

While it is a limitation that Study 2 had a lower response rate for controls and less accurate information on incomplete pregnancies than Study 1, it is of note that there were no major differences in findings between the two studies.

Comment [m5]: Not sure what to put here in response to Reviewer 2, point 8 as I'm not sure whether or not there were any statistically significant differences in results for Study 1 and Study 2. Do you know Vic? I've made a suggestion, but am not sure if it is technically correct. Suggestions please!

We consider it unlikely that poor recall explains the lack of association since previous studies have shown that menstrual and reproductive events can be recalled with reasonable accuracy (48, 49)~~(48, 49)~~, and the value of calendars as used in our studies to assist recall (for example by first recalling significant "landmark events"(50)~~(50)~~) has been supported by a strong body of evidence (51)~~(51)~~. Missing dates for some of the incomplete pregnancies in Study 2, and the subsequent decisions made by the research team in determining the chronological order of pregnancies based on inspection of participant responses to other reproductive questions in the questionnaire, could result in misclassification error. ~~Whilst~~While any such error might influence variables exploring the timing of the incomplete pregnancy, it should not impact upon the total numbers of incomplete pregnancies reported.

Induced abortion ~~miscarriage~~ is a sensitive issue for women, and it is possible that women may under-report their experience of induced miscarriage due to social stigma and legality issues.(52-54)~~(52-54)~~ Such under-reporting may occur among both cases and controls. ~~Whilst~~While recent research suggests that under-reporting does not differ between cases and controls,(55)~~(55)~~ others suggest controls are more likely to under-report, with cases being more prepared to report details about any factors which may have contributed to the development of their disease (rumination bias).(56)~~(56)~~ Our results showed no significant differences in reporting of induced abortion ~~miscarriage~~ between cases and controls. Differential under-reporting by controls would if anything, move our estimated effect of incomplete pregnancies on ovarian cancer risk in the direction of being more protective. Non-differential under-reporting of induced abortion

~~miscarriage~~ however, would result in a weakening of any true effect, and our observed results might then be masking a very small association of abortion ~~miscarriage~~ with ovarian cancer, the direction of which is impossible to determine. Ideally this issue could be overcome if a prospective study were conducted in regions where all ~~miscarriages and terminations~~spontaneous and induced abortions were recorded in a register as they occurred. Unfortunately there is no accurate national data on the prevalence of past abortions with which to compare our study results.

Comment [m6]: Reviewer 1, point 2.

The potential association of ovarian cancer with occult miscarriages / abortions (i.e. those miscarriages that occur so early in the course of the pregnancy that they go unnoticed by women, and are often considered to be their own natural or slightly late menstrual cycle) is not possible to measure. If ovarian cancer risk were linked with suppression of ovulations, then any reduction in risk attributable to occult miscarriages is unlikely to be of sufficient size in case-control studies to contribute substantially to any observed association, since occult miscarriages are of less than 2 months duration.

In summary, the results of our own large studies and those results of 37 other relevant population and hospital-based studies provide reasonably consistent evidence of the absence of an effect of incomplete pregnancy (either spontaneous or induced abortion or both) on ovarian cancer risk. These results may be reassuring to women with a history of incomplete pregnancy that they are at no greater risk of ovarian cancer than other women as a result of this history.

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Table 1. Estimated Relative Risk of Ovarian Cancer Associated With Incomplete Pregnancy (One or More Spontaneous and/or Induced ~~Miscarriage~~Abortion), by Parity Status, Australia, 1990 - 1993 and 2002 -2005

		Case Control Study 1				Case Control Study 2				Both Studies[a,b]	
		Cases		Controls		Cases		Controls			
Parity Status	**Variable**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**OR**	**95% CI**
Parous	**Number of incomplete pregnancies**										
	0[c]	416	67.1	469	64.9	842	63.4	730	63.6	1.0	
	1	140	22.6	167	23.1	301	22.7	257	22.4	1.02	0.86, 1.20
	2	32	5.2	49	6.8	123	9.3	100	8.7	0.90	0.70, 1.17
	3+	32	5.2	38	5.2	61	4.6	61	5.3	0.93	0.68, 1.28
	~~Quantiative~~[d] **Trend in risk**[d]									0.99	0.93, 1.06
	Age at first incomplete pregnancy										
	< 20	23	11.4	23	9.1	54	12.4	58	16.2	1.38	0.98, 1.95
	20-29	113	55.9	166	65.4	252	57.8	192	53.8	0.87	0.73, 1.03
	30+	66	32.7	65	25.6	130	29.8	107	30.0	1.06	0.84, 1.35
	Age at last incomplete pregnancy										
	< 20	11	5.5	12	4.7	24	5.5	31	8.6	1.66	1.03, 2.7
	20-29	106	52.7	140	55.1	233	53.4	185	51.5	0.96	0.80, 1.15
	30+	84	41.8	102	40.2	179	41.1	143	39.8	0.93	0.76, 1.15
	Timing of first incomplete pregnancy relative to first full-term birth										
	Before	70	34.3	93	32.7	163	37.8	129	37.0	0.97	0.78, 1.21
	After	134	65.7	161	67.3	268	62.2	220	63.0	0.97	0.81, 1.15
	Gestational length of first incomplete pregnancy										
	≤ 2 months	132	66.3	162	65.3	229	59.5	167	51.7	0.94	0.78, 1.12
	> 2 months	67	33.7	86	34.7	156	40.5	156	48.3	1.16	0.93, 1.43
Nulliparous	**Number of incomplete pregnancies**										
	0[c]	144	83.7	118	90.8	136	75.1	218	83.2	1.0	
	1	16	9.3	9	6.9	26	14.4	20	7.6	0.72	0.40, 1.29
	2	12	7.0	3	2.3	19	10.5	24	9.2	1.14	0.60, 2.2
	Trend in risk~~Quantiative~~[d]									1.05	0.85, 1.28
	Age at first incomplete pregnancy										
	< 20	4	14.3	0	0.0	8	19.5	9	24.3		
	20-29	16	57.1	10	83.3	27	65.9	22	58.5	0.98	0.59, 1.63
	30+	8	28.6	2	16.7	6	14.6	6	16.2	0.76	0.28, 2.1
	Age at last incomplete pregnancy										
	< 20	3	10.7	0	0.0	4	9.5	6	15.8		
	20-29	13	46.4	8	66.7	25	59.5	17	44.7	0.81	0.44, 1.49
	30+	12	42.9	4	33.3	13	31.0	15	39.5	0.90	0.45, 1.82
	Gestational length of first incomplete pregnancy										
	≤ 2 months	20	71.4	8	66.7	24	61.5	24	68.6	1.07	0.60, 1.91
	> 2 months	8	28.6	4	33.3	15	38.5	11	31.4	0.74	0.35, 1.58

CI=95% Confidence Interval; OR=Odds Ratio..

[a] No deviance differences, with degrees of freedom, approached significance.

[b] Conditional logistic analysis controlled for duration of OC use in years, tubal ligation, hysterectomy, smoking, alcohol use, parity (1,2,3,4,5+), menopausal status, age at last birth >/= 30 years.

[c] Reference category for all odds ratios

[d] Per incomplete pregnancy

Table 2. Estimated Relative Risk of Ovarian Cancer Associated With Spontaneous ~~Miscarriage~~ Abortion by Parity Status, Australia, 1990 - 1993 and 2002 -2005.

		Case Control Study 1				Case Control Study 2				Both Studies[a,b]	
		Cases		Controls		Cases		Controls			
Parity Status	**Variable**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**OR**	**95% CI**
Parous	**Number of spontaneous ~~miscarriages~~abortions**										
	0[c]	443	71.5	514	71.1	958	72.2	844	73.5	1.0	
	1	134	21.6	148	20.5	255	19.2	202	17.6	0.97	0.80, 1.17
	2	22	3.6	33	4.6	74	5.6	62	5.4	0.93	0.75, 1.15
	3+	21	3.3	28	3.9	40	3.0	40	3.5	0.94	0.61, 1.46
	Trend in risk~~Quantitative~~[d]									0.97	0.90, 1.04
	Age at first spontaneous ~~miscarriage~~abortion										
	< 20	15	8.5	11	5.3	18	5.4	27	10.4	1.66	1.00, 2.8
	20-29	100	56.5	146	69.9	199	60.0	151	58.1	0.86	0.71, 1.04
	30+	62	35.0	52	24.9	115	42.6	82	31.5	1.04	0.80, 1.35
	Age at last spontaneous ~~miscarriage~~abortion										
	< 20	10	5.6	9	4.3	6	1.8	14	5.4	2.0	0.99, 4.1
	20-29	97	54.8	124	59.3	185	55.6	147	56.5	0.95	0.78, 1.15
	30+	70	39.5	76	33.4	142	42.6	99	38.1	0.89	0.70, 1.12
	Timing of first spontaneous ~~miscarriage~~ abortion relative to first full-term birth										
	Before	56	31.6	75	35.9	102	30.7	80	22.3	0.91	0.71, 1.17
	After	121	68.4	134	64.1	230	69.3	180	77.7	1.02	0.81, 1.27
	Gestational length of first spontaneous ~~miscarriage~~abortion										
	≤ 2 months	107	60.5	131	62.1	148	50.5	102	43.0	0.89	0.72, 1.09
	> 2 months	70	39.5	80	37.9	155	49.5	135	57.0	1.08	0.87, 1.34
Nulliparous	**Number of spontaneous ~~miscarriages~~abortions**										
	0[c]	160	93.0	124	95.4	169	93.3	246	93.9	1.0	
	1	10	5.8	4	3.1	7	3.9	7	2.7	0.89	0.35, 2.3
	2	2	1.2	2	1.5	5	2.8	9	3.4	1.05	0.36, 3.1
	Trend in risk~~Quantitative~~[d]									1.11	0.76, 1.61
	Age at first spontaneous ~~miscarriage~~abortion										
	< 20	2	16.7	0	0.0	0		3	21.4		
	20-29	6	50.0	4	66.7	6	60.0	7	50.0	1.52	0.59, 3.9
	30+	4	33.3	2	33.3	4	40.0	4	28.6	0.72	0.22, 2.4
	Age at last spontaneous ~~miscarriage~~abortion										
	< 20	2	16.7	0		0		1	7.1		
	20-29	6	50.0	3	50.0	5	50.0	6	42.9	1.71	0.60, 4.9
	30+	4	33.3	3	50.0	5	50.0	7	50.0	0.77	0.27, 2.2
	Gestational length of first spontaneous ~~miscarriage~~abortion										
	≤ 2 months	9	75.0	4	66.7	5	50.0	10	71.4	1.78	0.70, 4.6
	> 2 months	3	25.0	2	33.3	5	50.0	4	28.6	0.49	0.14, 1.67

CI=95% Confidence Interval; OR=Odds Ratio..

[a] No deviance differences, with degrees of freedom, approached significance.

[b] Conditional logistic analysis controlled for duration of OC use in years, tubal ligation, hysterectomy, smoking, alcohol use, parity (1,2,3,4,5+), menopausal status, age at last birth >/= 30 years.

[c] Reference category for all odds ratios

[d] Per spontaneous ~~miscarriage~~ abortion

Table 3. Estimated Relative Risk of Ovarian Cancer Associated With Induced ~~Miscarriage~~ Abortion by Parity Status, Australia, 1990 - 1993 and 2002 -2005.

		Case Control Study 1				Case Control Study 2				Both Studies[a,b]	
		Cases		Controls		Cases		Controls			
Parity Status	Variable	n	%	n	%	n	%	n	%	OR	95% CI
Parous	Number of induced ~~miscarriages~~abortions										
	0[c]	580	93.5	670	92.7	1173	88.4	1007	87.7	1.0	
	1	22	3.6	38	5.3	114	8.6	98	8.5	1.08	0.82, 1.41
	2	18	2.9	15	2.1	40	3.0	43	3.7	1.22	0.80, 1.84
	Trend in risk~~Quantiative~~[d]									1.08	0.94, 1.24
	Age at first induced ~~miscarriage~~abortion										
	< 20	9	22.5	13	24.5	38	27.8	31	27.0	1.15	0.74, 1.81
	20-29	18	45.0	24	45.3	68	49.6	46	40.0	0.94	0.66, 1.33
	30+	13	32.5	16	30.2	31	22.6	38	33.0	1.38	0.90, 2.1
	Age at last induced ~~miscarriage~~abortion										
	< 20	5	12.5	10	18.9	28	20.4	22	19.1	1.10	0.65, 1.87
	20-29	15	37.5	20	37.7	62	45.3	46	40.0	1.05	0.72, 1.54
	30+	20	50.0	23	43.4	47	34.3	47	40.9	1.19	0.85, 1.67
	Timing of first induced ~~miscarriage~~ abortion relative to first full-term birth										
	Before	16	40.0	22	41.5	70	51.1	55	47.8	1.13	0.80, 1.60
	After	24	60.0	31	58.5	67	48.9	60	52.2	1.09	0.79, 1.49
	Gestational length of first induced ~~miscarriage~~abortion										
	≤ 2 months	31	81.6	44	83.0	97	78.2	73	72.3	1.01	0.76, 1.34
	> 2 months	7	18.4	9	17.0	27	21.8	28	27.7	1.28	0.78, 2.1
Nulliparous	Number of induced ~~miscarriages~~abortions										
	0[c]	156	90.6	123	94.6	145	80.1	233	88.9	1.0	
	1	16	9.4	7	5.4	36	19.9	29	11.1	0.80	0.47, 1.38
	Trend in risk~~Quantiative~~[d]									1.05	081, 1.36
	Age at first induced ~~miscarriage~~abortion										
	< 20	2	12.5	0	0.0	8	24.2	6	26.1	0.60[e]	0.18, 2.0
	20-29	10	62.5	7	100.0	22	66.7	14	60.9	0.54[e]	0.24, 1.19
	30+	4	25.0	0	0.0	3	9.1	3	13.0	0.65[e]	0.11, 3.7
	Age at last induced ~~miscarriage~~abortion										
	< 20	1	6.2	0	0.0	5	15.2	5	21.7		
	20-29	7	43.8	6	83.3	21	63.6	9	39.1	0.58	0.29, 1.14
	30+	8	50.0	1	16.7	7	21.2	9	39.1	1.29	0.48, 3.5
	Gestational length of first induced ~~miscarriage~~abortion										
	≤ 2 months	11	68.8	4	57.1	22	71.0	14	66.7	0.73	0.36, 1.47
	> 2 months	5	31.2	3	42.9	9	29.0	7	33.3	1.33	0.75, 2.3

CI=95% Confidence Interval; OR=Odds Ratio..

[a] No deviance differences, with degrees of freedom, approached significance.

[b] Conditional logistic analysis controlled for duration of OC use in years, tubal ligation, hysterectomy, smoking, alcohol use, parity (1,2,3,4,5+), menopausal status, age at last birth >/= 30 years.

[c] Reference category for all odds ratios

[d] Per induced ~~miscarriage~~ abortion

[e] ORs here only from case control study 2.

Table 4. Summary of Published Population-Based Studies Exploring the Risk of Incomplete Pregnancies and OvarianCancer (Medline Search 1966 – September 2007)

			All women (or [a] ever gravid women)				Parous women				Nulliparous women				
First author, year, (ref) study place.	**Reference Years (Age Range)**	**Total no. cases / non-cases**	**Outcome**	**Freq (no. of cases where specified)**	**OR / RR**	**95% CI**	**Outcome**	**Freq (no. of cases where specified)**	**OR / RR**	**95% CI**	**Outcome**	**Freq (no. of cases where specified)**	**OR / RR**	**95% CI**	**Adjustment**
Cohort Studies															
Rosenblatt, 2006,(11)~~(11)~~ China	1989 – 2000 (~31-75)	Cases: 285 OC Cohort: 267,400	Induced abortions	0 (140) ≥1 (145)	1.0 0.97	 0.76, 1.24									Age and parity. Restricted to women with ≥1 pregnancy and without prior bilateral oophorectomy.
Kvale, 1988,(10)~~(10)~~ Norway	1961-1980 (27-69 on 1 Jan 1956)	Cases: 445 OC all types Cohort: 60,565	Abortion	0 ≥1	1.0 0.89	 0.69, 1.16									Demographic variables and parity.
Population-Based Case-Control Studies															
xxxxx, 2008, , Australia	1990-1993 and 2002-2005 (18-79)	Cases: 2300 EOC Controls: 2263					Incomplete pregnancies	0 (1258) 1 (441) 2 (155) 3+ (93) ~~quantitative~~Trend in risk	1.0 1.02 0.90 0.93 0.99	 0.86, 1.20 0.70, 1.17 0.68, 1.28 0.93, 1.06	Incomplete pregnancies	0 (280) 1 (42) 2 (31) Trend in risk~~Quantitative~~	1.0 0.72 1.14 1.05	 0.40, 1.29 0.60, 2.20 0.85, 1.28	Duration of OC use in years, tubal ligation, hysterectomy, smoking, alcohol use, parity (1,2,3,4,5+), menopausal status, age at last birth >/= 30 years
							Spontaneous ~~miscarriages~~abortions	0 (1401) 1 (389) 2 (96) 3+ (61) Trend in risk~~quantitative~~	1.0 0.97 0.93 0.94 0.97	 0.80, 1.17 0.75, 1.15 0.61, 1.46 0.90, 1.04	Spontaneous abortions~~miscarriages~~	0 (329) 1 (17) 2 (7) Trend in risk~~Quantitative~~	1.0 0.89 1.05 1.11	 0.35, 2.30 0.36, 3.10 0.76, 1.61	
							Induced abortions~~miscarriages~~	0 (1753) 1 (136) 2 (58) Trend in risk~~quantitative~~	1.0 1.08 1.22 1.08	 0.82, 1.41 0.80, 1.84 0.94, 1.24	Induced abortions~~miscarriages~~	0 (389) 1 (45) Trend in risk~~Quantitative~~	1.0 0.8 1.05	 0.47, 1.38 0.81, 1.36	
Gierach, 2005,(16)~~(16)~~ USA (Delaware Valley)	1994-1998 (20-69)	Cases: 739 EOC Controls: 1313	Incomplete pregnancy [a] (Excluded women with history of both spontaneous and induced abortions)	0 (366) 1 (140) 2 (43) ≥3 (14) ever (197)	1.0 0.94 1.09 0.69 0.95	 0.74, 1.21 0.73, 1.64 0.36, 1.32 0.76, 1.18					Incomplete pregnancy	0 (176) ≥1 (47)	1.0 1.12	 0.66, 1.89	Age, number of livebirths/ stillbirths, duration of OCP use, race, tubal ligation, family history of ovarian cancer, educational level.
			Spontaneous abortion [a]	0 (366) 1 (88) ≥2 (37) ever (125)	1.0 0.83 0.87 0.84	 0.62, 1.11 0.57, 1.32 0.65, 1.09					Spontaneous abortion	0 (176) ≥1 (14)	1.0 1.77	 0.60, 5.20	
			Induced abortion [a]	0 (366) 1 (52)	1.0 1.30	 0.87, 1.94					Induced abortion	0 (176) ≥1 (33)	1.0 0.98	 0.55, 1.75	

				≥2 (20)	1.32	0.73, 2.38								
				ever (72)	1.31	0.91, 1.86								
Riman, 2002(19)(19) and 2001(57)(57) Sweden	1993-1995 (50-74)	Cases: 655 INV OC Controls: 3899	Abortions (spontaneous or induced)	0 (547)	1.0									Age, parity, BMI, age at menopause, duration of OCP use and ever use of HRT.
				1 (86)	0.76	0.59, 0.98								
				≥2 (22)	0.70	0.44, 1.12								
		Cases: 193 BL Controls: 3899	Abortions (spontaneous or induced)	0 (157)	1.0									Age, parity, BMI, age at menopause, + ever use of OCPs, unopposed oestrogens with cyclic progestins, or oestrogens with continuous progestins.
				1 (28)	0.84	0.54, 1.29								
				≥2 (8)	0.78	0.35, 1.71								
Titus-Ernstoff., 2001,(23)(23) USA (Massachesetts and New Hampshire)	1992-1997 (20-74)	Cases: 563 EOC including BL Controls: 523	Miscarriage	0 (427)	1.0									Age, state, and full term live-singleton births.
				≥1 (136)	1.0	0.70, 1.30								
			Abortion	0 (499)	1.0									
				≥1 (64)	1.1	0.70, 1.60								
Chen , 1996,(13)(13) USA (Washington State)	1986-1988 (20-79)	Cases: 322 INV or BL EOC Controls: 426	Induced abortion [a]	0 (230)	1.0		Incomplete pregnancy (n = 583)	0	1.0		Incomplete pregnancy (n = 164)	0	1.0	Induced abortion and incomplete pregnancy data adjusted for age, OC use, number of pregnancies / births (as applicable). Spontaneous abortion data also adjusted for marital status, and BMI.
				1 (23)	1.0	0.50, 1.70		1	1.4	0.90, 2.10		1	0.9	0.40, 2.00
				≥2 (12)	1.2	0.50, 2.50		≥2	0.8	0.50, 1.40		≥2	0.8	0.30, 2.10
				ever (35)	1.0	0.60, 1.70		ever	1.1	0.80, 1.60		ever	0.8	0.40, 1.70
			Spontaneous abortion [a]	0 (187)	1.0									
				1 (55)	1.6	1.00, 2.50								
				≥2 (23)	0.8	0.40, 1.40								
				ever (78)	1.3	0.80, 1.90								
Risch, 1994,(20)(20) Canada	1989-1992 (35-79)	Cases: 450 EOC Controls: 564	Miscarriage	Trend in risk for each	1.04	0.88, 1.24	Miscarriage	Trend in risk for each	1.04	0.88, 1.24				Age group, age as a continuous variable, total duration of OCP use, number of full-term pregnancies.
			Induced abortion	Trend in risk for each	1.00	0.77, 1.30	Induced abortion	Trend in risk for each	0.98	0.75, 1.29				
Chen, 1992(14)(14) China (Beijing)	1984-1986 (mean ~ 49)	Cases: 112 EOC Controls: 224	Miscarriage	0 (97)	1.0									Education and parity
				1 (11)	0.4	0.20, 1.10								
				≥2 (4)	0.9	0.20, 3.60								
				Trend test	p=0.64									
			Induced abortion	0 (71)	1.0									
				1 (24)	0.8	0.40, 1.50								
				2 (12)	0.8	0.40, 1.90								
				≥3 (5)	0.5	0.20, 1.60								
				Trend test	p=0.39									
Whittemore, 1992,(4)(4) USA Pooled analysis of 12 USA studies, 6 being population-based (12, 15,	1973-1985 (18-79)	Cases: 1400 INV EOC Controls: 5600	Failed pregnancies (abortions, miscarriage, ectopic pregnancies and stillbirth)	0 (1011)	1.0						Failed pregnancies	0 (271)	1.0	Age, study, parity and OCP use (and marital status for nulliparous women)
				1-2 (307)	0.88	0.75, 1.00						Ever (51)	1.4	0.91, 2.10
				≥3 (52)	0.83	0.59, 1.20								
				Any (359)	0.87	0.75, 1.00								
				Trend /failed pregnancy	0.94 (*P* = 0.09)									

18, 22, 24, 25)~~(12, 15, 18, 22, 24, 25)~~											
Shu, 1989,(21)~~(21)~~ China (Shanghai)	1984-1986 (18-70)	Cases: 172 EOC Controls: 172					Miscarriages and stillbirths	0 (144) 1 (20) ≥2 (8) Trend test	1.0 1.3 1.0 *P* = 0.77	0.60, 2.90 0.30, 3.40	Education, ovarian cyst, age at menarche, number of livebirths.
							Induced abortions	0 (122) 1 (35) ≥2 (15) Trend test	1.0 0.7 0.6 *P* = 0.14	0.40, 1.40 0.20, 1.30	
Harlow, 1988,(17)~~(17)~~ USA (Washington)	1980-1985 (20-79)	Cases: 116 BL only Controls: 158	Induced abortions [a]	0 (76) 1 (12) ≥2 (5)	1.0 1.2 0.9	 0.50, 3.10 0.20, 3.70					Age and gravidity.
			Miscarriages [a]	0 (61) 1 (22) ≥2 (10)	1.0 2.2 3.0	 1.00, 5.10 0.90, 11.2					
Newhouse, 1977,(46)~~(46)~~ United Kingdom	NS (<45 – 65+)	Cases: 300 OC Controls: 300	Miscarriages	0 (ca 240) ≥1 (ca 60)	1.0 1.41[b]	 0.85, 2.33[b]					Nil specified.

BL = borderline; CI = confidence intervals; EOC = epithelial ovarian cancer; INV = invasive; LMP = low malignant potential; NS = not specified; OC = ovarian cancer; OCP = oral contraceptive pill; OR = odds ratio; RR = relative risk

[a] in ever gravid women

[b] Result/s calculated from published study data

Table 5. Summary of Published Hospital-Based Case Control Studies Exploring the Risk of Incomplete Pregnancies and Ovarian Cancer (Medline Search 1966 – September 2007)

			All women ([a] or ever gravid women)				Parous women				Nulliparous women				
First author year, (ref) study place.	**Reference Years (Age Range)**	**Total no. cases / non-cases**	**Outcome**	**Freq (no. of cases)**	**OR/RR**	**95% CI**	**Outcome**	**Freq (no. of cases)**	**OR / RR**	**95% CI**	**Outcome**	**Freq (no. of cases)**	**OR/ RR**	**95% CI**	**Adjustment**
El-Khwsky, 2006,(30)(30) Egypt	2000 – 2003 (20-79)	Cases: 172 EOC Controls: 441	Fetal losses (abortion)	0 (103) 1-3 (62) 4+ (7) $X^{2\ trend}$	1.0 1.7 3.7 12.2 ($P<$ 0.001)	 1.16, 2.59 1.02, 13.45									Nil specifically noted, but paper states univariate and multivariate analyses were performed.
Zhang, 2004,(45)(45) China	1999-2000 (< 70)	Cases: 254 EOC Controls: 652 (51 population-based)	Incomplete pregnancies	0 (98) 1 (79) ≥2 (77)	1.0 0.69 0.56	 0.47, 1.00 0.39, 0.82									Age, locality, education, family income, BMI, total energy intake, tobacco smoking, alcohol consumption, ovarian cancer in first degree relatives.
Yen, 2003,(44)(44) Taiwan	1993-1998 (20-75)	Cases: 86 INV EOC Controls: 369	Incomplete pregnancies	0 (46) ≥1 (40) Any	1.0 1.42	 0.86, 2.32									Age, income during marriage, education, number of live births.
Chiaffarino, 2001,(29)(29) Italy	1992-1999 (17-79)	Cases: 1031 EOC Controls: 2411	Spontaneous abortions	0 (795) 1 (167) ≥2 (69)	1.0 1.0 0.9	 0.80, 1.30 0.70, 1.20									Age, centre, education, parity, OC use, family history of ovarian and breast cancer in first degree relatives.
			Induced abortions	0 (916) 1 (66) ≥2 (49)	1.0 1.1 1.1	 0.80, 1.60 0.70, 1.60									
Greggi, 2000,(31)(31) Italy (Rome)	1988-1998 (13-80)	Cases: 440 EOC Controls:868	Spontaneous abortions	0 (349) 1 (65) ≥2 (26)	1.0 1.0 0.9	 0.70, 1.50 0.50, 1.50									Age, education, parity, OC use and duration, family history of ovarian cancer, age at first birth, breast feeding, spontaneous / induced abortions.
Salazar-Martinez, 1999,(39)(39) Mexico	1995-1997 (mean ~53)	Cases: 84 EOC Controls: 668	Miscarriages (not defined)	0 (62) 1 (10) ≥2 (12) $X^{2\ trend}$	1.0 0.61 0.90 P=0.21	 0.30, 1.20 0.44, 1.8									Age, hormonal use, breastfeeding, smoking, diabetes mellitus, hypertension, physical activity, menopausal status, body build index.
Bernal, 1995,(26)(26) Mexico City	1989 – 1992 (18-79)	Cases: 172 EOC Controls: 441	Abortions	0 ≥1	1.0 1.82 P=0.008	 1.17, 2.82	Abortions	0 (68) 1-3 (59) 4 (7) $X^{2\ trend}$	1 2.05 5.44 17.70 (P<0.001)	 1.33, 3.16 1.43, 22.28					Nil listed for parous women. Logistic regression undertaken for all women, but actual variables adjusted for not specified.

Polychronopoulou, 1993,(38)~~(38)~~ Greece	1989-91 (< 75)	Cases: 189 EOC Controls: 200	Miscarriages	0 (124) 1 (42) ≥2 (23)	1.0 1.61 1.30	0.92, 2.81 0.66, 2.53								Age
			Induced abortions	0 (126) 1 (20) 2 (21) ≥3 (22)	1.0 0.87 1.05 0.90	0.44, 1.71 0.53, 2.08 0.46, 1.79								Age
Whittemore, 1992,(4)~~(4)~~ USA Pooled analysis of 12 studies, 5 of which were hospital-based and contributed incomplete pregnancy data.(28, 32, 33, 35, 42)~~(28, 32, 33, 35, 42)~~	1956-1986 (18-85)	Cases: 705 INV EOC Controls: 2783	Failed pregnancies (abortions, miscarriages, ectopic pregnancies, and stillbirths)	0 (482) 1-2 (191) ≥3 (3.2) Any (223) Trend / failed pregnancy	1.0 0.86 0.80 0.86 0.93 *P*=0.19	0.68, 1.10 0.50, 1.30 0.68, 1.1					Failed pregnancies (excluding {McGowan, 1979)	0 (159) ≥1 (29)	1.0 0.82	0.46, 1.50	Age, study, parity, OCP use (and marital status for nulliparous women)
Negri, 1991,(47)~~(47)~~ Italy, UK and Greece. Pooled analysis of 3 studies.(27, 37, 40)~~(27, 37, 40)~~	1978-1989 (~ <75)	Cases: 1140 EOC Controls: 2724	Abortions	0 (805) 1 (184) ≥2 (100) $X^{2\ trend}$	1 0.9 0.7 7.93 (*P*<0.01)	0.80, 1.10 0.60, 0.90	Abortions	0 1 ≥2 $X^{2\ trend}$	1 0.9 0.7 7.39 *P*<0.01	0.70, 1.10 0.50, 0.90	Abortions	0 1 ≥2	1 1.1 0.7	0.60, 2.00 0.30, 1.50	Age, study centre, sociocultural indicators, age at menopause, OCP use for all shown analyses (and parity, number of abortions, age of first birth for all women and parous women).
Mori, 1988,(36)~~(36)~~ Japan (Hokkaido)	1980-1981, 1985-1986 (mean ~51)	Cases: 110 EOC Controls: 220	Miscarriage (98 case/control sets of ever married women)	0 (69) ≥1 (29)	1.0 0.8	0.50, 1.40								Nil
			Induced abortion	0 (60) 1 (38)	1.0 0.6 *P*=0.04									Marital status, number of live births, experience of tubal ligation.
Newhouse, 1977,(46)~~(46)~~ United Kingdom	NS (<45 – 65+)	Cases: 300 OC Controls: 300	Miscarriages	0 (ca 240) ≥1 (ca 60)	1.0 1.22 [b]	0.73, 2.04 [b]								Nil specified.
Joly, 1974,(34)~~(34)~~ USA (Buffalo, New York)	1957-1965 (mean ~ 53)	Cases:276 OC Controls: 273	Miscarriages (in ever-pregnant women)	0 (237) ≥1 (39)	1.00 1.30 [b,c,]	0.86, 1.95 [b, c]								Nil specified.

Wynder, 1969,(43)(43) USA (New York)	NS (3 year span) (<29 – 70+)	Cases: 150 EOC Controls: 300	Spontaneous abortion	0 (78) ≥1 (39)	1.0 1.69 [b]	1.03, 2.76 [b]	Nil specified
			Induced abortion Married, ever pregnant women	0 (103) ≥1 (14)	1.0 1.18[b]	0.58, 2.39	
West, 1966,(41)(41) USA (Boston)	1959-1960 (<76)	Cases: 97 OC Controls: 97	Abortions and miscarriage		*P*>0.3		Nil specified.

BL = borderline; CI = confidence intervals; EOC = epithelial ovarian cancer; INV = invasive; LMP = low malignant potential; NS = not specified; OC = ovarian cancer; OCP = oral contraceptive pill; OR = odds ratio; RR = relative risk

[a] in ever gravid women

[b] Result/s calculated from published study data

[c] Based on data presented for cancer of the ovary class II

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