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Use of fertility drugs and risk of ovarian cancer: results from a US-based case-control study

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Abstract

Background—Previous studies examining associations between use of fertility drugs and ovarian cancer risk have provided conflicting results. We used data from a large case-control study to determine whether fertility drug use significantly impacts ovarian cancer risk when taking into account parity, gravidity, and cause of infertility.

Methods—Data from the Hormones and Ovarian Cancer Prediction (HOPE) study were used (902 cases, 1802 controls). Medical and reproductive histories were collected via in-person interviews. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Models were adjusted for age, race, education, age at menarche, parity, oral contraceptive use, breastfeeding, talc use, tubal ligation, and family history of breast/ovarian cancer.

Results—Ever use of fertility drugs was not significantly associated with ovarian cancer within the total HOPE population (OR: 0.93, 95%CI: 0.65–1.35) or among women who reported seeking medical attention for infertility (OR: 0.87, 95%CI 0.54–1.40). We did observe a statistically significant increased risk of ovarian cancer for ever use of fertility drugs among women who, despite seeking medical attention for problems getting pregnant, remained nulligravid (OR: 3.13, 95%CI 1.01–9.67).

Conclusions—These results provide further evidence that fertility drug use does not significantly contribute to ovarian cancer risk among the majority of women; however, women

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who despite infertility evaluation and fertility drug use remain nulligravid, may have an elevated risk for ovarian cancer.

Impact—Our results suggest that fertility drug use does not significantly contribute to overall risk of ovarian cancer when adjusting for known confounding factors.

Keywords

ovarian cancer; fertility drugs; infertility; case-control

Introduction

Ovarian cancer is multifactorial and complex in etiology. Lifestyle factors shown to increase the risk of ovarian cancer include low parity (1–4), late onset of menopause (5, 6) and perineal talc use (7–9). Oral contraceptive (OC) use (10–13), breastfeeding (14–16) and tubal ligation (17–19) have been shown to have a protective effect on ovarian cancer risk. Several theories have been proposed to explain the mechanisms by which these factors affect risk of ovarian cancer. The incessant ovulation hypothesis theorizes that the repeated damage and subsequent repair cycles that occur during ovulation on the epithelial surface of the ovary contributes to DNA damage and increases the risk of developing ovarian cancer (20–23). The gonadotropin hypothesis postulates that exposure to high levels of circulating pituitary gonadotropins, which stimulates the ovarian surface epithelium, plays a role in the development of ovarian cancer (24, 25). Both of these theories suggest that the use of fertility drugs, which often contain gonadotropins and stimulate ovulation, may increase the risk of ovarian cancer.

Fertility drug use has increased markedly in the U.S. (26). Based on data from the 2002 National Survey of Family Growth, 12% of the 61.6 million U.S. women between the ages of 16 and 44 sought infertility services. The use of infertility services was more common among older women, women with higher incomes, and women who were childless (27). The utilization of fertility drugs and other infertility services is expected to continue to rise as the percentage of women who postpone attempts to become pregnant until after the age of 35 increases. Stephen *et al.* projected that the number of infertile women will increase to between 5.4–7.7 million in 2025 (28). Despite the growing number of women seeking fertility treatment, the effects of fertility drug use on ovarian cancer risk remain uncertain. Several early studies reported an association between exposure to fertility drugs and the development of ovarian cancer, which spurred concern regarding the safety of these drugs (29–31). Subsequent studies did not provide evidence of an increased risk of ovarian cancer with the use of fertility drugs (32–37). However, concern regarding fertility drug use remains after other studies reported that women who were exposed to fertility drugs for more than 12 cycles were at an increased risk of ovarian cancer (38, 39). Nulliparous women who failed to conceive after treatment have also been reported to have an increased risk of ovarian cancer (29, 35). Finally, several studies have shown that fertility drug use may increase the risk of borderline ovarian tumors (30, 31, 40–43).

The conflicting results from previous studies might be due to the generally small sample sizes and/or inability to control for important reproductive factors known to influence ovarian cancer risk. Establishing the relationship between fertility drug use and ovarian cancer risk is complicated by the fact that infertility itself increases the risk of ovarian cancer (10, 44–46). It is also of particular importance to account for parity because the frequency of nulliparity is high among infertile women and nulliparity has been established as an important ovarian cancer risk factor (24, 47, 48). The increasing use of fertility drugs necessitates the separation of the effects of underlying infertility and other confounding factors from those of fertility drug use. Ours is one of the largest case-control studies of

ovarian cancer conducted to date. Our objective was to contribute to the debate regarding whether fertility drug use significantly impacts ovarian cancer risk when taking into account parity, gravidity, and cause of infertility.

Material and Methods

Study Population and Data Collection

We used data from the Hormones and Ovarian Cancer Prediction (HOPE) study, a population-based case-control study of ovarian cancer described in detail elsewhere (13, 49). Briefly, subjects were residents of a contiguous region comprising Western Pennsylvania, Eastern Ohio, and Western New York State. All cases were histologically confirmed to have primary epithelial ovarian, peritoneal, or fallopian tube cancers diagnosed between 2003 and 2008. Eligible women were at least 25 years old and were within 9 months of initial diagnosis at the time of recruitment. A total of 902 cases were enrolled. Controls, N=1802, were frequency matched to cases (~2:1) by 5-year age group and telephone area code through random-digit dialing. Women who had undergone a bilateral oophorectomy were ineligible. All study participants provided informed consent. The study was approved by the University of Pittsburgh Institutional Review Board and by the human subject committees at each hospital where cases were identified.

Trained interviewers collected questionnaire data that included detailed reproductive, gynecological, and medical histories as well as information regarding lifestyle and family medical history; a reference date of 9 months before the interview date was used for all participants.

Infertility and Fertility Drug Use

All study participants were asked if they had ever sought medical attention for problems becoming pregnant. Women who responded with “yes” to this question were asked whether their partner was tested, they were personally tested, they were both tested, or if neither of them were tested for infertility. They were also presented with a list of infertility causes and asked whether each was found to be a probable cause for their problems becoming pregnant. Women were able to respond “yes,” “no,” or “don’t know” to whether they were diagnosed with a problem involving: partner’s sperm, their ovaries, ovulation, their fallopian tubes, their cervix, cervical mucous, their uterus, scarring of the uterus, menstruation, endometriosis, or some other problem. For the current analyses, we collapsed the cervix and cervical mucous variables into one cervical problem variable. Similarly, we combined the variables for uterus problems and scarring of the uterus. We chose to collapse these variables because the mechanism affecting infertility is similar for both cervical variables as well as both uterine variables. Combining similar causes of infertility resulted in a greater number of exposed women and increased our power to determine whether uterine or cervical causes of infertility were significantly associated with ovarian cancer risk.

All study participants were asked if they had ever used fertility drugs. Women who responded with “yes” to this question were asked the name of the fertility drugs used. The majority of women used clomiphene citrate, which we defined as one group of fertility drugs (“clomiphene”). We pooled follicle stimulating hormone (FSH), human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH), urofollitropin, and human menopausal gonadotropin (hMG) drugs into one group of fertility drugs, “gonadotropins”, because they utilize the same method of stimulating ovulation. We also created a group for women who had used a combination of gonadotropins and clomiphene citrate (“clomiphene + gonadotropins”). Finally, we grouped together any other fertility drugs, such as progesterone and unknown hormone pills, into an “other” fertility drug group (“other

fertility drug"). Women who reported taking fertility drugs were also asked how many months they took each fertility drug. This information was collected for the first four periods of fertility drug use. We do not have information regarding type of fertility drug or the duration of use for fertility drugs used after the first four time periods of fertility drug use; however, only 9 women reported using fertility drugs for more than four time periods.

Covariates

Based on anthropometric data provided by the participants, we calculated body mass index (BMI) as weight (kg) at reference date divided by height (m) at reference date squared. Family history of ovarian and breast cancers was defined as having at least one reported diagnosis of, respectively, ovarian or breast cancer among a first-degree relative. Hormone replacement therapy (HRT) use was defined as the use of hormones for menopause, to treat osteoporosis, or after hysterectomy/removal of ovaries; any use of estrogen or estrogen plus progesterone among postmenopausal women was also classified as HRT use. Women were classified as postmenopausal if they were 55 years or older, reported natural menopause, had used HRT, or reported no menstrual periods in the 6 months prior to the reference date. Women were considered to be premenopausal if they had never taken HRT and reported having menstrual periods in the 6 months prior to the reference date, and were younger than 55 years old (50). All participants were asked if they had ever been pregnant. Women reporting at least 1 pregnancy were subsequently asked to provide information regarding the outcome of the pregnancy and the duration they breastfed. This information was repeated for up to four pregnancies. Duration of breastfeeding was calculated as the sum of the number of months they breastfed after each of their first four pregnancies. Information regarding pregnancy outcomes, and breastfeeding was not available for later pregnancies; however, women did report their total number of pregnancies and live births. Among women who reported more than four pregnancies, we calculated their average length of breastfeeding for their first four pregnancies, multiplied this average by the number of additional pregnancies resulting in live births, and added this to the total months of reported breastfeeding. Perineal talc use was defined as ever using dusting powder or deodorizing spray on: the genital or rectal areas, on sanitary napkins, on underwear, or on diaphragms or cervical caps.

Statistical Analysis

Associations between ovarian cancer risk and demographic and reproductive factors were evaluated using logistic regression models. These models were used to calculate odds ratios (OR) and corresponding 95% confidence intervals (95% CI), as well as p-trend values for continuous factors.

Backward stepwise regression was used to determine which demographic and reproductive variables should be included as covariates in the regression models used to evaluate the effect of exposure to fertility drugs on ovarian cancer risk. Age was locked into the stepwise model as a continuous variable; a p-value criterion of 0.10 was used to identify additional covariates. The following variables were evaluated for inclusion: race (white, black, other), education (less than high school graduate, high school graduate, post-high school education), site (Pittsburgh, Cleveland, Buffalo), BMI (<25, 25–29.99, ≥30), family history (none, first-degree breast, first-degree ovarian, first-degree ovary and breast), tubal ligation (yes, no, missing), OC use (continuous), number of live births (0, 1, 2, 3, 4, ≥5), breastfeeding (never, < 6, 6 < 12, ≥12 months), age at menarche (continuous), menopausal status (premenopausal, postmenopausal), perineal talc use (ever, never), and HRT use (ever, never). All models are adjusted for the covariates identified through this process with the exception of models in which collinearity occurred between these covariates and the variables of interest (indicated with the results).

Associations between ovarian cancer risk and ever versus never use of fertility drugs and also duration of use, which was evaluated as a continuous variable and as a categorical variable (never, < 6 months, ≥6 months), were evaluated among the total HOPE population and separately among women who reported seeking medical attention for infertility. We chose 6 months as the cutoff for duration of use because this was the median duration of fertility drug use among all women who had taken fertility drugs and using this grouping provided adequate sample size for each group when stratifying for parity and gravidity. Among women who reported seeking medical attention for infertility, we additionally evaluated associations between ovarian cancer risk and year medical attention was sought, who was tested, and underlying cause of infertility using unconditional logistic regression. We also determined whether the relationship between fertility drug use and ovarian cancer risk was modified by year medical attention was sought, age at which medical attention for infertility was sought, cause of infertility, and person tested for infertility problems by creating interaction terms between fertility drug use and these variables and including them in the adjusted model. Finally, we evaluated whether use of specific types of fertility drugs (clomiphene, gonadotropins, clomiphene + gonadotropins, other fertility drugs) was associated with ovarian cancer risk. These analyses were repeated separately for invasive and borderline ovarian tumors; analyses were also repeated using all cases and controls within the HOPE study population.

To examine the impact of parity and gravidity on the association between fertility drug use and ovarian cancer risk, we evaluated ever compared to never use of fertility drugs while stratifying by the following groups of women: parous, nulliparous-gravid, and nulligravid. These analyses were conducted among women who reported seeking medical attention for infertility and repeated using the total HOPE study population.

All significance tests were two-sided; *P* values <0.05 were considered statistically significant. All analyses were conducted using Stata version 12.1 (StataCorp, College Station, TX).

Results

Demographic and reproductive characteristics of the HOPE study population are presented in Table 1. Compared to Caucasians, African Americans had a significantly increased risk of ovarian cancer. High-school graduates and women with post-high school education had a significantly decreased risk of ovarian cancer compared to women with less than a high school education. The following variables were also significantly associated with ovarian cancer risk: age at menarche, OC use, parity, gravidity, duration of breastfeeding, perineal talc use, and tubal ligation. Seeking medical attention for infertility was not significantly associated with ovarian cancer risk (Table 1). Backward stepwise regression yielded a model that included age, race, education, age at menarche, OC use, parity, duration of breastfeeding, perineal talc use, and tubal ligation. First-degree family history of breast/ovarian cancers was associated with a p-value of 0.14 using this method but was nevertheless included in the model because of its known association with ovarian cancer risk.

Table 2 provides medical information for the 445 women who reported seeking medical attention for infertility. No statistically significant association with ovarian cancer was observed for age at which women sought medical attention, year medical attention was initially sought or with person tested for infertility problems. None of the causes of infertility were significantly associated with ovarian cancer risk; however, borderline significant associations were observed for ovulation problems and menstrual problems.

Among the 47 women who reported ovulation problems, 11 had also reported an issue with their menstrual cycles.

Use of fertility drugs was reported by 148 (33%) of the women seeking medical attention for infertility (Table 2). The majority used fertility drugs for less than 12 months (66.7%); mean duration was 11.4 months (range: 1–134 months). Ever use of fertility drugs was not significantly associated with ovarian cancer risk (Table 2) and remained non-significant after additional adjustment for cause of infertility (OR: 0.66, 95%CI: 0.36–1.22), age medical attention was sought (OR: 0.86, 95%CI: 0.53–1.40), year attention was sought (OR: 0.90, 95%CI: 0.58–1.38), and who was tested for infertility problems (no one tested or partner-only tested compared to self tested or partner and self tested, OR: 0.90, 95%CI: 0.54–1.49) (not in table). No significant interactions between fertility drug use and these variables were observed (data not shown). Similar results were observed for duration of fertility drug use (Table 2 and data not shown). Regarding specific types of fertility drugs, the majority of women who ever used fertility drugs reported using only clomiphene citrate (56.1%). None of the drugs evaluated were significantly associated with ovarian cancer risk when looking at ever compared to never use (Table 2) or duration of use (data not shown). Analyses were repeated excluding the 12 cases and controls that reported using unknown or other fertility drugs and the results were unchanged. Additionally, no significant associations between ever use of fertility drugs and ovarian cancer risk were observed when separately assessing borderline (OR: 0.96, 95%CI: 0.31–2.94; adjusted for age, duration of OC use, talc, and age at menarche) and invasive tumors (OR: 0.85, 95%CI: 0.52–1.39; adjusted for all covariates identified by stepwise regression).

Among all 2704 HOPE participants, 152 (5.6%) women reported ever using fertility drugs, this included the 148 women who reported seeking medical attention for infertility and 4 women who had used fertility drugs but had never sought medical attention for fertility issues. All 4 of these latter women were controls; 2 reported taking clomiphene only and 2 reported taking gonadotropins only. Data regarding why these four women reported taking fertility drugs without ever seeking medical attention for infertility were not collected. Ever use of fertility drugs was not significantly associated with ovarian cancer risk in the total HOPE population (OR: 0.93, 95%CI: 0.65–1.35), nor was duration of use (never compared to <6 months of use, OR: 1.05, 95%CI: 0.61–1.80; never compared to ≥6 months of use, OR: 0.82, 95%CI: 0.50–1.34), adjusting for age, race, education, tubal ligation, age of menarche, duration of OC use, number of live births, duration of breastfeeding, perineal talc use, and family history. Adjusting for the same covariates, no significant associations between ovarian cancer risk and ever use of fertility drugs were observed when separately evaluating borderline (OR: 0.64, 95%CI: 0.26–1.55) and invasive tumors (OR: 1.02, 95%CI: 0.69–1.50).

Table 3 presents results of the evaluation of associations between fertility drug use and ovarian cancer risk stratified by parity and gravidity. Among those seeking medical attention for infertility, nulligravid women who used fertility drugs were significantly more likely to develop ovarian cancer than nulligravid women who had never used fertility drugs. However, fertility drug use among parous and nulliparous-gravid women was not significantly associated with ovarian cancer risk among this group of women. Within the total HOPE study population, the association between ovarian cancer risk and ever use of fertility drugs was non-significant among parous and nulliparous-gravid women. Ovarian cancer risk was elevated among nulligravid fertility drug users; however, this was not significant (Table 3).

Discussion

In this large case-control study, we evaluated whether fertility drug use significantly affects ovarian cancer risk when taking into account, parity, gravidity, and cause of infertility. Consistent with results from previous studies, OC use, breastfeeding, and tubal ligation significantly decreased ovarian cancer risk in our study population while nulliparity, and perineal talc use increased risk (19, 24, 36, 40, 51). Ever use of fertility drugs was not significantly associated with ovarian cancer risk within the total HOPE population or among women who reported seeking medical attention for infertility. Risk did not differ significantly according to duration of use or type of fertility drug. However, we did observe a statistically significant increased risk of ovarian cancer for ever use of fertility drugs among women who, despite seeking medical attention for problems getting pregnant, remained nulligravid.

When examining specific causes of infertility among those seeking medical attention for infertility, none of the evaluated causes were significantly associated with ovarian cancer risk. Specifically, we observed no significant association between ovarian cancer and endometriosis even though previous studies have reported an increased risk (40, 52–54). Endometriosis was also not significantly associated with ovarian cancer risk in the total HOPE population (data not shown). The mechanism by which endometriosis may affect ovarian cancer risk is poorly understood; however, several studies have shown that endometriosis-associated tumors are most commonly linked to clear cell and endometrioid tumors (55–58). The small number of women who reported being diagnosed with endometriosis among those who sought medical attention for infertility in addition to the homogeneity of tumor histologic subtypes among these women may have contributed to the null relationship we observed here. Interestingly, we observed a decreased risk of ovarian cancer among women who reported an ovulation problem as their cause of infertility. Although this observation was of borderline significance, it suggests that women who ovulate less frequently throughout their lifetime may have a decreased risk of ovarian cancer and provides further evidence for the incessant ovulation theory.

In a 2004 case-control study, Rossing et al. observed that women whose infertility manifested past the age of 30 were at increased risk of ovarian cancer (36). We found no significant association between ovarian cancer risk and the age at which women sought medical attention for infertility in our population; however, women who sought help between the ages of 35 and 45 did exhibit a non-significant increased risk compared to women who sought help before they were 25. Women who seek treatment for infertility past the age of 30 have a lower likelihood of success compared to women who seek infertility treatments at younger ages (59) and ovarian cancer risk associated with infertility among older women may reflect additional risk associated with low parity among these women.

Although we did not observe any significant associations between fertility drug use and ovarian cancer risk within the total HOPE study population or among the subset of women who reported seeking medical attention for infertility, we did observe, similar to previous reports, a statistically significant increased risk of ovarian cancer associated with ever fertility drug use among nulligravid women who had infertility problems (29, 35, 40). This suggests that women who never became pregnant despite efforts to conceive are at uniquely increased risk of ovarian cancer. This is further supported by the fact that we found no significant association between fertility drug use and ovarian cancer risk among nulliparous women who had at least one pregnancy. Although our results are in line with those from previous studies, it should be noted that the number of nulligravid women who sought medical attention for infertility was relatively small (N=74). Therefore, confirmation of our results by other studies is necessary.

Our finding that fertility drug use does not significantly contribute to ovarian cancer risk among the majority of women is in line with results from other, recent studies (34, 36, 40, 52). Early studies that reported an increased risk of ovarian cancer among fertility drug users included small numbers of ovarian cancer patients exposed to fertility drugs and were unable to adjust for risk factors known to impact ovarian cancer risk (29, 30). We observed no risk difference between borderline and invasive tumors; these results are in agreement with a recent case-control study (60) but disagree with several previous studies (30, 31, 40–43).

The strengths of this study include a large sample size and availability of detailed reproductive and medical histories of women included in the study. The ability to stratify and adjust for factors linked to ovarian cancer risk allowed us to disentangle risk associated with these factors from risk associated with fertility drug use. A limitation of our study is that we were unable to identify women who were infertile but never sought medical attention. This differential misclassification may have attenuated the associations between infertility and ovarian cancer risk. However, our ability to analyze associations between fertility drug use and ovarian cancer risk in a relatively large subset of women who had sought medical attention for infertility greatly improved the comparability of fertility drug users to non-users. Being able to reduce the study population to only these women also limited biases associated with comparing fertility drug users with infertility issues to non-fertility drug users with no history of infertility issues. Our study is also limited by its reliance on self-reported use of fertility drugs; however, the use of a life calendar during interviews may have improved the accuracy of recalling details about fertility drug use. This study includes a greater number of ovarian cancer cases exposed to fertility drugs than previous studies. Despite this, our study had limited power when completing stratified analyses for fertility drug use and ovarian cancer risk, which resulted in small subgroups and subsequently wide confidence intervals.

Our results build upon previous research and provide further evidence that fertility drug use does not significantly contribute to overall risk of ovarian cancer when adjusting for known confounding factors. Our observation that fertility drug use was only significantly associated with increased ovarian cancer risk among nulligravid women who had ever sought medical attention for infertility suggests that a biological mechanism associated with the inability to conceive may impact ovarian cancer risk to a greater extent than fertility medications do.

To conclude, these results are reassuring for women and clinicians embarking on fertility drug usage in the setting of infertility treatment.

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Abbreviations used

CI	confidence intervals
FSH	follicle stimulating hormone
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
hMG	human menopausal gonadotropin
LH	luteinizing hormone

OC	oral contraceptive
OR	odds ratio

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Table 1

Demographic and reproductive characteristics of the total HOPE population.

	Cases (902)		Controls (1802)		OR (95% CI) [a]	p-trend [b]
	N	%	N	%		
Site						
Buffalo	251	27.8	476	26.4	1.0 (ref.)	---
Cleveland	294	32.6	628	34.9	0.89 (0.72, 1.09) [c]	
Pittsburgh	357	39.6	698	38.7	0.97 (0.79, 1.18) [c]	
Age (in years)						
< 30	13	1.4	24	1.3	1.0 (ref.)	0.01
30 < 40	47	5.2	108	6.0	0.80 (0.38, 1.71) [c]	
40 < 50	164	18.2	393	21.8	0.77 (0.38, 1.55) [c]	
50 < 60	276	30.6	569	31.6	0.90 (0.45, 1.79) [c]	
60 < 70	211	23.4	403	22.4	0.97 (0.48, 1.94) [c]	
≥70	191	21.2	305	16.9	1.16 (0.57, 2.33) [c]	
Race						
White	856	94.9	1,758	97.6	1.0 (ref.)	---
Black	35	3.9	29	1.6	2.48 (1.51, 4.08) [c]	
Other	11	1.2	15	0.8	1.51 (0.69, 3.29) [c]	
Education						
Non-high school graduate	83	9.2	82	4.5	1.0 (ref.)	---
High school graduate	303	33.6	535	29.7	0.59 (0.42, 0.83) [d]	
Post-high school	516	57.2	1,185	65.8	0.46 (0.33, 0.64) [d]	
Smoking Status						
Never Smoker	458	50.8	913	50.7	1.0 (ref.)	---
Former Smoker	286	31.7	545	30.2	1.02 (0.84, 1.22)	
Current Smoker	158	17.5	344	19.1	0.86 (0.69, 1.08)	
Body Mass Index (in kg/m^2) [e]						
< 25	300	33.3	671	37.2	1.0 (ref.)	0.08

	Cases (902)		Controls (1802)		OR (95% CI) [a]	p-trend [b]
	N	%	N	%		
25 – 29.99	267	29.6	528	29.3	1.09 (0.89, 1.33)	
≥30	334	37.0	602	33.4	1.18 (0.97, 1.43)	
Family History (1st degree)						
No	715	79.3	1,491	82.7	1.0 (ref.)	---
Breast Cancer Only	147	16.3	255	14.2	1.21 (0.96, 1.51)	
Ovarian Cancer Only	32	3.5	44	2.4	1.51 (0.95, 2.42)	
Breast and Ovarian Cancers	8	0.9	12	0.7	1.21 (0.48, 3.00)	
Age at Menarche (in years)						
<12	182	20.2	444	24.6	1.0 (ref.)	0.22
12	257	28.5	463	25.7	1.38 (1.09, 1.74)	
13	243	26.9	484	26.9	1.26 (0.99, 1.59)	
≥14	220	24.4	411	22.8	1.27 (1.00, 1.62)	
Menopausal Status						
Premenopausal	234	25.9	482	26.8	1.0 (ref.)	---
Postmenopausal	668	74.1	1,320	73.2	0.80 (0.63, 1.03)	
Oral Contraceptive Use (in months) [f]						
Never	367	40.7	531	29.5	1.0 (ref.)	< 0.01
< 6	96	10.6	161	8.9	0.88 (0.65, 1.18)	
6 < 24	135	15.0	282	15.6	0.69 (0.53, 0.89)	
24 < 60	122	13.5	297	16.5	0.61 (0.47, 0.79)	
60 < 120	123	13.6	299	16.6	0.63 (0.48, 0.82)	
≥ 120	58	6.4	232	12.9	0.37 (0.27, 0.52)	
Hormone Replacement Therapy Use						
Never	543	60.2	1039	57.7	1.0 (ref.)	---
Ever	359	39.8	763	42.3	0.87 (0.73, 1.03)	
Number of Pregnancies						
0	167	18.5	167	9.3	1.0 (ref.)	< 0.01
1	114	12.6	188	10.4	0.57 (0.41, 0.78)	
2	216	24.0	458	25.4	0.44 (0.33, 0.58)	
3	167	18.5	426	23.6	0.36 (0.27, 0.47)	

	Cases (902)		Controls (1802)		OR (95% CI) [a]	p-trend [b]
	N	%	N	%		
4	112	12.4	284	15.8	0.34 (0.25, 0.46)	
≥5	126	14.0	279	15.5	0.34 (0.25, 0.47)	
Number of Live Births						
0	213	23.6	230	12.8	1.0 (ref.)	< 0.01
1	117	13.0	228	12.7	0.51 (0.38, 0.68)	
2	263	29.2	593	32.9	0.45 (0.35, 0.57)	
3	170	18.8	418	23.2	0.39 (0.30, 0.51)	
4	73	8.1	190	10.5	0.32 (0.23, 0.45)	
≥5	66	7.3	143	7.9	0.32 (0.22, 0.47)	
Duration of Breastfeeding (in months)						
Never	610	67.6	928	51.5	1.0 (ref.)	< 0.01
< 6	117	13.0	296	16.4	0.60 (0.47, 0.76)	
6 < 12	66	7.3	199	11.0	0.54 (0.40, 0.72)	
≥ 12	109	12.1	379	21.0	0.46 (0.36, 0.59)	
Perineal Talc Use						
No	653	72.4	1426	79.1	1.0 (ref.)	---
Yes	249	27.6	376	20.9	1.40 (1.16, 1.69)	
Tubal Ligation						
No	666	73.8	1162	64.5	1.0 (ref.)	---
Yes	201	22.3	616	34.2	0.55 (0.46, 0.67)	
Unknown	35	3.9	24	1.3	2.66 (1.57, 4.53)	
Sought Medical Attention for Infertility						
Never	747	82.8	1512	83.9	1.0 (ref.)	---
Ever	155	17.2	290	16.1	1.15 (0.93, 1.43)	

[a] Odds ratios and corresponding confidence intervals are adjusted for age (continuous), race (white, black, other), and education (non-high school graduate, high school graduate, post high-school), unless otherwise noted.

[b] P-trend values were obtained from logistic regression models by using continuous versions of these factors; all models were adjusted for age, race, and education with the exception of age, which was unadjusted.

[c] Unadjusted.

[d] Adjusted for age and race.

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[e] 1 case and 1 control were missing weight information.

[f] 1 case was missing oral contraceptive use information.

Table 2

Medical information, infertility causes, and ovarian cancer risk among HOPE participants seeking medical attention for infertility (N=445).

	Cases (155)		Controls (290)		OR (95% CI) [a]
	N	%	N	%	
Year Medical Attention was Sought					
≤1970	55	35.5	97	33.5	1.0 (ref.)
1970≤1980	39	25.2	76	26.2	1.13 (0.55, 2.31) [b]
1980≤1990	31	20.0	74	25.5	0.77 (0.31, 1.91) [b]
After 1990	30	19.3	43	14.8	1.09 (0.34, 3.47) [b]
Age at Which Medical Attention was Sought (in years)					
< 25	47	30.3	86	29.7	1.0 (ref.)
25 < 30	52	33.5	110	37.9	0.94 (0.55, 1.61) [b]
30 < 35	35	22.6	68	23.4	0.89 (0.48, 1.66) [b]
35 < 40	17	11.0	18	6.2	2.00 (0.84, 4.75) [b]
≥40	4	2.6	8	2.8	0.84 (0.21, 3.37) [b]
Fertility Testing Done					
None	20	12.9	50	17.2	1.0 (ref.)
Partner	12	7.7	17	5.9	1.41 (0.53, 3.75)
Self	55	35.5	84	29.0	1.32 (0.66, 2.67)
Both	68	43.9	139	47.9	0.92 (0.47, 1.81)
Fertility Drug Use					
Never	105	67.7	192	66.2	1.0 (ref.)
Ever	50	32.3	98	33.8	0.87 (0.54, 1.40)
Type of Fertility Drug					
Never	105	67.7	192	66.2	1.0 (ref.)
Clomiphene Only	28	18.1	55	19.0	0.87 (0.49, 1.56) [b]
Gonadotropin Only	7	4.5	20	6.9	0.51 (0.20, 1.32) [b]
Gonadotropin + Clomiphene Only	9	5.8	17	5.8	0.94 (0.37, 2.42) [b]
Other Only [c]	6	3.9	6	2.1	1.87 (0.53, 6.65) [b]

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	Cases (155)		Controls (290)		OR (95% CI) [a]
	N	%	N	%	
Duration of Fertility Drug Use (in months) [d]					
Never	105	67.7	192	66.2	1.0 (ref.)
< 6	22	14.2	41	14.1	0.92 (0.48, 1.74) [b]
≥6	27	17.4	57	19.7	0.75 (0.42, 1.34) b
Low Sperm Count [e]					
No	130	83.9	229	79.0	1.0 (ref.)
Yes	25	16.1	55	19.0	0.68 (0.39, 1.18) [b]
Problems with ovaries (cysts) [e]					
No	141	91.0	264	91.0	1.0 (ref.)
Yes	14	9.0	21	7.2	1.32 (0.61, 2.84) [b]
Ovulation Problems [e]					
No	144	92.9	248	85.5	1.0 (ref.)
Yes	11	7.1	36	12.4	0.51 (0.24, 1.09) [b]
Tubal Problems [e]					
No	137	88.4	245	83.5	1.0 (ref.)
Yes	18	11.6	40	13.8	0.62 (0.33, 1.18) [b]
Uterine Problems [e]					
No	147	94.8	274	94.5	1.0 (ref.)
Yes	8	5.2	11	3.8	1.04 (0.38, 2.83) [b]
Menstrual Problems [e]					
No	146	94.2	254	87.6	1.0 (ref.)
Yes	9	5.8	30	10.3	0.48 (0.20, 1.11) [b]
Endometriosis [e]					
No	141	91.0	259	89.3	1.0 (ref.)
Yes	13	8.4	25	8.6	0.75 (0.35, 1.59) [b]
Cervical Problems [e]					
No	152	98.1	277	95.5	1.0 (ref.)

	Cases (155)		Controls (290)		OR (95% CI) [a]
	N	%	N	%	
Yes	3	1.9	8	2.8	0.53 (0.11, 2.59) [b]
Other Diagnosis [e]					
No	126	81.3	240	82.8	1.0 (ref.)
Yes	29	18.7	46	15.9	1.56 (0.87, 2.79) [b]

[a] ORs and corresponding 95% CIs are adjusted for age, race, education, tubal ligation, age of menarche, duration of oral contraceptive use, number of live births, duration of breastfeeding, perineal talc use, and family history of breast/ovary cancers.

[b] Due to collinearity, family history of breast/ovarian cancer was omitted from the adjusted logistic regression model. These ORs and corresponding 95% CIs are adjusted for all other variables listed in [a].

[c] Includes the following fertility drugs: roloxifene, danazol, unknown hormone pills, bromocriptine, progesterone, and metformin.

[d] Duration of fertility drug use was missing for one case and was therefore not included in the logistic regression model; percentages correspond to the entire population of women who sought medical attention for problems getting pregnant.

[e] These variables exclude women who responded “don’t know” when asked if they were diagnosed with a particular infertility problem and these women were also not included in logistic regression models. Percentages correspond to the entire population of women who sought medical attention for problems getting pregnant.

Table 3

Ovarian cancer risk according to parity, gravidity, and fertility drug use in total HOPE population and separately among HOPE participants that sought medical attention for infertility.

Parity	Gravidity	Women Who Sought Medical Attention for Infertility				Total HOPE Population			
		Fertility Drug Use	Cases (N=155) N(%)	Controls (N=290)	OR (95% CI)	Fertility Drug Use	Cases (N=902)	Controls (N=1802)	OR (95% CI)
Parous		No	80 (51.6)	156 (53.8)	1.0 (ref.)	No	666 (73.8)	1493 (82.8)	1.0 (ref.)
		Yes	23 (14.8)	75 (25.9)	0.57 (0.31, 1.05) [a]	Yes	23 (2.6)	79 (4.4)	0.72 (0.44, 1.19) [a]
Nulliparous	Ever Pregnant	No	8 (5.2)	9 (3.1)	1.0 (ref.)	No	37 (4.1)	52 (2.9)	1.0 (ref.)
		Yes	9 (5.8)	11 (3.8)	0.47 (0.09, 2.53) [b]	Yes	9 (1.0)	11 (0.6)	0.77 (0.26, 2.25) [d]
Nulliparous	Never Pregnant	No	17 (11.0)	27 (9.3)	1.0 (ref.)	No	149 (16.5)	155 (8.6)	1.0 (ref.)
		Yes	18(11.6)	12 (4.1)	3.13 (1.01, 9.67) [c]	Yes	18 (2.0)	12 (0.7)	1.52 (0.68, 3.41) [e]

[a] Adjusted for: age, age of menarche, duration of OC use, perineal talc use, education, family history of breast/ovarian cancers, tubal ligation, race, duration of breastfeeding, and number of live births.

[b] Adjusted for: age, age of menarche, duration of OC use, and perineal talc use.

[c] Adjusted for: age, age of menarche, duration of OC use, perineal talc use, education, and family history of breast/ovarian cancers.

[d] Adjusted for: age, age of menarche, duration of OC use, perineal talc use, education, family history of breast/ovarian cancers, and tubal ligation.

[e] Adjusted for: age, age at menarche, duration of OC use, perineal talc use, education, and tubal ligation.