Published in final edited form as:

Fertil Steril. 2013 June ; 99(7): 2031–2036. doi:10.1016/j.fertnstert.2013.02.010.

Fertility Drug Use and the Risk of Ovarian Tumors in Infertile Women: A Case-Control Study

Albert Asante, MD, MPH, Phoebe H Leonard, MD, Amy L Weaver, Ellen L Goode, PhD, MPH, Jani R Jensen, MD, Elizabeth A Stewart, MD, and Charles C Coddington, MD
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Mayo Clinic, 200 First St SW, Rochester, MN 55905

Abstract

Objective—To assess the influence of infertility and fertility drugs on risk of ovarian tumors.

Design—Case-control study (Mayo Clinic Ovarian Cancer Study).

Setting—Ongoing academic study of ovarian cancer.

Patient(s)—A total of 1900 women (1028 with ovarian tumors and 872 controls, frequency matched on age and region of residence) who had provided complete information in a self-report questionnaire about history of infertility and fertility drug use.

Intervention(s)—None

Main outcome measure(s)—Effect of infertility history, use of fertility drugs and oral contraception and gravidity on the risk of ovarian tumor development, after controlling for potential confounders.

Result(s)—Among women who had a history of infertility, use of fertility drugs was reported by 24% (44/182) of controls and 17% (38/226) of cases. Infertile women who used fertility drugs were not at increased risk of developing ovarian tumors compared to infertile women who did not use fertility drugs, adjusted odds ratio was 0.64 (95% CI 0.37, 1.11). Findings were similar when stratified by gravidity and when analyzed separately for borderline versus invasive tumors.

Conclusion(s)—We did not find any significant association between fertility drug use and risk of ovarian tumors. Further larger, prospective studies are needed to confirm this observation.

Keywords

Fertility drugs; ovarian tumors; borderline tumors; case-control; primary infertility

INTRODUCTION

Infertility, nulliparity and late-onset of menopause are some of the factors known to be associated with an increased risk for ovarian cancer (1–4). Several studies have been done to assess the association between fertility drug use and risk of ovarian tumors; however, the available data is conflicting. While early studies reported an association between exposure to

Corresponding author: Albert Asante, MD, MPH, Mayo Clinic, Charlton 3A, 200 First St SW, Rochester, MN 55905, Please correspond via asante.albert@mayo.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

fertility drugs and the development of ovarian tumors (5–7), subsequent studies did not find any statistically significant association (8–15). In contrast, other recent studies (16, 17) have reported an increased risk among a subgroup of nulliparous women, especially regarding risk of borderline ovarian tumors.

Fertility drug use has increased markedly in the U.S. and is expected to continue to rise as the percentage of women who postpone attempting pregnancy until after age 35 increases (23). The association, if any, between fertility drug use and risk of ovarian tumors should therefore be an integral part of preconception counseling.

Establishing the relationship between fertility drug use and risk of development of ovarian tumors is complicated by the fact that infertility itself is associated with an increased risk of ovarian tumors (18, 19). Two theories have been proposed to explain the mechanisms by which fertility drug use may increase the risk of ovarian tumor development. 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 tumors (20). The increased risk of ovarian cancer in chickens, a species of incessant ovulators, supports this hypothesis (21). 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 tumors (22). The protective effect of oral contraceptive pills is consistent with this hypothesis. Both of these theories suggest that fertility drugs, which also stimulate ovulation by transiently increasing gonadotropins, may increase the risk of ovarian tumors. Separation of the effects of underlying infertility and other important confounding factors from those of fertility drug use is essential if the true relationship between fertility drug use and ovarian tumor risk can be established. This requires for studies assessing the relationship to have large sample sizes.

Interpreting the available data on fertility drugs and ovarian tumors for the average U.S. woman undergoing fertility treatment is complicated by a number of factors among which is the fact that most of the studies have been conducted outside of the U.S., and the few conducted in the U.S. have used very small sample sizes (5, 6). Our goal was to use a large on-going U.S. case-control study of epithelial ovarian tumors to assess the long-term effects of infertility and use of fertility drugs on the risk of ovarian tumors among U.S. women, incorporating important confounding factors such as use of oral contraceptives, parity, gravidity, and family history of ovarian cancer.

MATERIALS AND METHODS

Study Design and Patient Population

We used data from an ongoing case-control study of prevalent and incident epithelial ovarian tumors initiated in December 1999 at Mayo Clinic (Rochester, MN). Written informed consent was obtained from all participants. For this analysis, we included participants enrolled during the period December 14, 1999 through May 10, 2012. The Institutional Review Board at the Mayo Clinic approved the study protocol.

Clinic attendance formed the sampling frame for the cases and controls. Eligible women were at least 19 years old. All cases had histologically confirmed epithelial ovarian tumor (borderline or invasive) and most of them were enrolled in the study within 1 year of date of initial diagnosis. Cases lived in the six-state region that defines the primary service population of Mayo Clinic (Minnesota, Iowa, Wisconsin, Illinois, North Dakota, and South Dakota).

Controls were selected from women without ovarian tumors, and with at least one ovary intact, who had presented to the clinic for general medical examination. These women were frequency matched on age (5-year age categories), and region of residence to cases. A total of 2253 women (1157 cases and 1096 controls) were enrolled as of May 10, 2012. Of these, 1900 women (1028 cases and 872 controls) provided complete information in the self-report questionnaire about history of infertility and fertility medication use and were included in our study.

Risk Factor Data Collection

Information on known and suspected ovarian cancer risk factors and demographic data were collected. These included race/ethnicity, height and weight 1 year before the interview, use of tobacco, education level, medical and surgical history, use of exogenous hormones, and family history of breast or ovarian cancer in first and second-degree relatives.

Detailed menstrual and reproductive history including age at menarche, pregnancies, live births, age at first birth, infertility diagnosis, use and duration of use of oral contraceptives, surgical sterilization, age at menopause, and hormone replacement therapy were self-reported by the patients via a questionnaire. Infertility was defined as the inability to achieve a pregnancy over an interval of at least 12 months in a woman who desired to get pregnant and engaged in regular intercourse without contraception. Information about specific fertility treatment provided by the study participants included type of fertility medication used and duration of treatment.

Statistical Analyses

Unconditional logistic regression models were fit to compare patient characteristics and risk factors between cases and controls. Models were adjusted for potential confounders including age, race, gravidity, parity, oral contraceptive use, and family history of ovarian cancer. Associations were summarized by calculating odds ratios (OR) and 95% confidence intervals (CI) based on the parameter estimates obtained from the univariable and multivariable models. All calculated p-values were two-sided and p-values less than 0.05 were considered statistically significant. Analyses were performed using SAS version 9.2 software package (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline characteristics of the study population are presented in Table 1. Women with ovarian tumors were less likely to have post-high school education compared to controls. Also, women with ovarian tumors were almost twice as likely to be current smokers (vs. never smoked) compared to controls. As summarized in Table 2, women with ovarian tumors were significantly less likely to have used OCs for 60 months or greater and, less likely to have two or more live births or pregnancies compared to controls.

A history of infertility was reported by 182 (21%) of the 872 of controls and 226 (22%) of the 1028 cases. Overall, there was no significant association between infertility and ovarian tumor risk (adjusted OR 0.99; 95% CI 0.78, 1.26). Because risk of ovarian tumor is generally influenced by gravidity, we stratified by gravidity, and noted that among the subgroup of women who had never been pregnant, the adjusted odds ratio (OR) for ovarian tumors among those who reported a history of infertility was 1.65(95% CI 0.80, 3.43) compared to those who did not have a history of infertility, suggesting no statistically significant association between history of infertility and risk of ovarian tumors among nulligravid women (Table 3). Similarly, among women who had been pregnant, there was no statistically significant association between a history of infertility and risk of developing

ovarian tumors (adjusted OR 0.90; 95% CI 0.69, 1.16). Analyses were repeated separately for borderline and invasive ovarian tumors and no significant association was found between infertility and type of tumor histology (data not shown).

Among women who had a history of infertility, use of fertility drugs was reported by 24% (44/182) of controls and 17% (38/226) of cases. Among infertile women, ever use of fertility drugs was not significantly associated with ovarian tumor risk (Table 4) and remained non-significant after additional adjustment for potential confounders (adjusted OR 0.64; 95% CI 0.37, 1.11). When we stratified by tumor histology (data not shown), we had a small number of women with borderline ovarian tumors (32 borderline cases and 194 invasive cases, with a history of infertility), and observed no significant association between fertility drug use and borderline ovarian tumor (adjusted OR 0.61; 95% CI 0.23; 1.61) or with invasive ovarian cancer (adjusted OR 0.66; 95% CI 0.37, 1.16). We also examined the association of ovarian tumor risk and fertility drug use separately among women with a history of infertility who had been pregnant (gravids) versus those who had never been pregnant (nulligravids). We observed that among both nulligravids and gravids who had a history of infertility, there was no statistically significant difference between the odds of exposure to fertility drugs among cases compared to controls.

Among all cases and controls with a history of infertility who reported using fertility drugs ($n=82$), 31 (38%) used them for less than 6 months, 34 (41%) used them for 6 to 12 months, 9 (11%) used them for >12 months, and the duration was unknown for 8 (10%). We did not observe any association between duration of fertility drug use and risk of ovarian cancer (data not shown). Approximately 65% of patients did not provide information on specific types of fertility drugs used; we therefore did not assess the association between specific types of fertility drugs and ovarian cancer risk.

DISCUSSION

The results from our study are consistent with results from previous studies (1–4, 6, 24), which showed that OC use, gravidity, and parity are associated with decreased risk for development of ovarian tumors. We did not find any statistically significant increased risk of ovarian tumors among women with primary infertility (women with infertility who had never been pregnant); this observation is inconsistent with findings from previous studies (1–4, 6, 24). Given our large sample size (1900 women) and the observation that 20.9% of the controls had a history of infertility, the study had 80% power to detect an odds ratio of 1.36 and above. Even though our study was sufficiently powered to detect odds ratios consistent with previous studies, we only observed a slightly higher exposure rate among the ovarian cancer cases yielding an unadjusted odds ratio of 1.07. However, among the subset of 408 women with a history of infertility, given that 24% of the controls used fertility drugs the study was potentially underpowered as there was 80% power to only detect odds ratios of 1.85 and above.

Ever use of fertility drugs was not significantly associated with development of ovarian tumors; this did not change when we stratified by gravidity. We conducted the analyses separately for borderline tumors and invasive cancers, and, similar to previous reports (15, 25); we found no significant association between fertility drug use and borderline ovarian tumors.

Our finding that fertility drug use does not significantly contribute to ovarian tumor risk among infertile women is in line with results from other, recent studies (8–15; 24, 26). However there are also several reports, mostly from studies conducted in the 1990s, which have reported increased risk for ovarian cancer with fertility drug use (5–7). The

contradictory findings may stem from the fact that these earlier studies had small sample sizes, and were unable to adjust for important confounding factors known to impact ovarian tumor risk. Also, fertility drugs have been used in the U.S. since 1967 (23); it is possible that there have been significant changes in the fertility drugs of choice and doses over the past 5 decades, which could account for the differences observed between the earlier studies and most recent ones, however there is no reliable data to support this argument.

The strengths of our study include a large sample size and availability of important reproductive and medical histories of women included in the study. By being able to adjust for important factors linked to ovarian cancer risk, risks of ovarian cancer associated with these factors were separated clearly from risk associated with fertility drug use. By comparing with an unexposed group of infertile women, we were able to better assess the risk of fertility drugs vs. infertility itself and also evaluate the importance of other known confounders. We were therefore able to determine whether fertility drug use is an independent risk factor for ovarian tumors.

A limitation of our study is that we did not review the medical records and therefore could not verify the self-reported reproductive and medical history provided by the study participants. Also, we were unable to assess the effect of specific fertility drugs on ovarian tumor risk, as this information was not provided by approximately 65% of our patients. Another limitation of our study is related to errors in recall of important fertility-related information. However, the associations we observed of ovarian tumors with other factors generally known to influence ovarian tumor risk including OC use, gravidity, and parity are consistent with those previously reported (1, 3, 4), suggesting that the extent of recall or selection bias in our study is not likely to be significantly different from that of previous research.

Overall, our findings do not support the null hypothesis that fertility drug use significantly increases the risk of ovarian tumor development, when known confounding factors are adjusted for (adjusted OR 0.64; 95% CI 0.37, 1.11). We also did not find any statistically significant association between history of infertility and risk of ovarian tumors among nulligravids.

In conclusion, our case-control study provides modest evidence that fertility drugs do not increase risk of ovarian tumor development. Further larger, prospective studies are needed to confirm this observation.

Acknowledgments

We are indebted to Michaela E McGree at the Biomedical Statistics and Informatics Division (Mayo Clinic, Rochester MN) for data support and analysis and Kimberly R Kalli, PhD, of the Women's Cancer Program at the Mayo Clinic Cancer Center for study outcomes ascertainment and management.

Grant Support: This research was supported by National Institutes of Health grants R01 CA122443, P50 CA136393 and Mayo Foundation

REFERENCES

1. McGowan L, Parent L, Lednar W, Norris HJ. The woman at risk for developing ovarian cancer. *Gynecol Oncol.* 1979; 7:325–344. [PubMed: 447120]
2. Hartge P, Schiffman MH, Hoover R, McGowan L, Leshner L, Norris HJ. A case-control study of epithelial ovarian cancer. *Am J Obstet Gynecol.* 1989; 161:10–16. [PubMed: 2750791]
3. Risch HA, Marrett LD, Howe GR. Parity, contraception, infertility, and the risk of epithelial ovarian cancer. *Am J Epidemiol.* 1994; 140:585–597. [PubMed: 7942759]

4. Adami HO, Hsieh CC, Lambe M, Trichopoulos D, Leon D, Persson I, et al. Parity, age at first childbirth, and risk of ovarian cancer. *Lancet*. 1994; 344:1250–1254. [PubMed: 7967985]
5. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol*. 1992; 136:1184–1203. [PubMed: 1476141]
6. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. *N Engl J Med*. 1994; 331:771–776. [PubMed: 8065405]
7. Shushan A, Paltiel O, Iscovich J, Elchalal U, Peretz T, Schenker JG. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertil Steril*. 1996; 65:13–18. [PubMed: 8557128]
8. Mosgaard BJ, Lidegaard O, Kjaer SK, Schou G, Andersen AN. Infertility, fertility drugs, and invasive ovarian cancer: a case-control study. *Fertil Steril*. 1997; 67:1005–1012. [PubMed: 9176436]
9. Modan B, Ron E, Lerner-Geva L, Blumstein T, Menczer J, Rabinovici J, et al. Cancer incidence in a cohort of infertile women. *Am J Epidemiol*. 1998; 147:1038–1042. [PubMed: 9620047]
10. Doyle P, Maconochie N, Beral V, Swerdlow AJ, Tan SL. Cancer incidence following treatment for infertility at a clinic in the UK. *Hum Reprod*. 2002; 17:2209–2213. [PubMed: 12151460]
11. Rossing MA, Tang MT, Flagg EW, Weiss LK, Wicklund KG. A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol*. 2004; 160:1070–1078. [PubMed: 15561986]
12. Jensen A, Sharif H, Frederiksen K, Kjaer SK. Use of fertility drugs and risk of ovarian cancer: Danish Population Based Cohort Study. *BMJ*. 2009; 338:b249. [PubMed: 19196744]
13. Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, et al. Ovarian cancer risk after the use of ovulation-stimulating drugs. *Obstet Gynecol*. 2004; 103:1194–1203. [PubMed: 15172852]
14. Harris R, Whittemore AS, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. III. Epithelial tumors of low malignant potential in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol*. 1992; 136:1204–1211. [PubMed: 1476142]
15. Mosgaard BJ, Lidegaard O, Kjaer SK, Schou G, Andersen AN. Ovarian stimulation and borderline ovarian tumors: a case-control study. *Fertil Steril*. 1998; 70:1049–1055. [PubMed: 9848294]
16. Sanner K, Conner P, Bergfeldt K, Dickman P, Sundfeldt K, Bergh T, et al. Ovarian epithelial neoplasia after hormonal infertility treatment: long-term follow-up of a historical cohort in Sweden. *Fertil Steril*. 2009; 91:1152–1158. [PubMed: 18371964]
17. Källén B, Finnström O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Malignancies among women who gave birth after in vitro fertilization. *Hum Reprod*. 2011; 26:253–258. [PubMed: 21088017]
18. Mosgaard BJ, Lidegaard O, Andersen AN. The impact of parity, infertility and treatment with fertility drugs on the risk of ovarian cancer. A survey. *Acta Obstet Gynecol Scand*. 1997; 76:89–95. [PubMed: 9049278]
19. Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, et al. Ovarian cancer risk associated with varying causes of infertility. *Fertil Steril*. 2004; 82:405–414. [PubMed: 15302291]
20. Tung KH, Wilkens LR, Wu AH, McDuffie K, Nomura AM, Kolonel LN, et al. Effect of anovulation factors on pre- and postmenopausal ovarian cancer risk: revisiting the incessant ovulation hypothesis. *Am J Epidemiol*. 2005; 161:321–329. [PubMed: 15692075]
21. Giles JR, Elkin RG, Trevino LS, Urick ME, Ramachandran R, Johnson PA. The restricted ovulator chicken: a unique animal model for investigating the etiology of ovarian cancer. *Int J Gynecol Cancer*. 2010; 20:738–744. [PubMed: 20973263]
22. Mohle J, Whittemore A, Pike M, Darby S. Gonadotrophins and ovarian cancer risk. *J Natl Cancer Inst*. 1985; 75:178–180. [PubMed: 3859691]
23. Wysowski DK. Use of fertility drugs in the United States, 1973 through 1991. *Fertil Steril*. 1993; 60:1096–1098. [PubMed: 7902301]

24. Ness RB, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol.* 2002; 155:217–224. [PubMed: 11821246]
25. Cusido M, Fabregas R, Pere BS, Escayola C, Barri PN. Ovulation induction treatment and risk of borderline ovarian tumors. *Gynecol Endocrinol.* 2007; 23:373–376. [PubMed: 17701767]
26. Kurta ML, Moysich KB, Weissfeld JL, Youk AO, Bunker CH, Edwards RP, Modugno F, Ness RB, Diergaarde B. Use of fertility drugs and risk of ovarian cancer: results from a u.s.-Based case-control study. *Cancer Epidemiol Biomarkers Prev.* 2012; 21:1282–1292. [PubMed: 22707710]

Table 1

Characteristics of the study population

Characteristic	Controls (N=872)	Cases (N=1028)	Unadjusted OR (95% CI)	P-value
Age (years) *, mean (SD)	60.5 (13.2)	61.3 (12.8)	1.05 (0.98, 1.13) [‡]	0.17
Marital status, N (%)				<0.001
Missing/unknown	7	29	-	
Married	698 (80.7)	736 (73.7)	Reference	
Not married	167 (19.3)	263 (26.3)	1.49 (1.20, 1.86)	
Race, N (%)				0.05
Missing/unknown	35	120	-	
White	825 (98.6)	882 (97.1)	Reference	
Other	12 (1.4)	26 (2.9)	2.03 (1.02, 4.04)	
Education, N (%)				<0.001
Missing	4	83	-	
No high school	25 (2.9)	71 (7.5)	1.95 (1.21, 3.16)	
High school	270 (31.1)	393 (41.6)	Reference	
Some college	256 (29.5)	272 (28.8)	0.73 (0.58, 0.92)	
College graduate	189 (21.8)	109 (11.5)	0.40 (0.30, 0.53)	
Graduate school	128 (14.7)	100 (10.6)	0.54 (0.40, 0.73)	
Smoking status, N (%)				<0.001
Missing/unknown	9	84	-	
Never smoked	552 (64.0)	583 (61.8)	Reference	
Former smoker	269 (31.2)	269 (28.5)	0.95 (0.77, 1.16)	
Current smoker	42 (4.9)	92 (9.7)	2.07 (1.41, 3.04)	
Age at menarche (years), mean (SD)	13.0 (1.6)	12.8 (1.6)	0.47 (0.26, 0.86) [‡]	0.01
Age at first live birth (years), mean (SD)	24.1 (4.5)	23.0 (4.4)	0.57 (0.46, 0.71) [‡]	<0.001
Family history of OVCA, N (%)				0.01
No	801 (91.9)	906 (88.1)	Reference	
Yes	71 (8.1)	122 (11.9)	1.52 (1.12, 2.07)	

Abbreviations: OR, odds ratio; CI, confidence interval

* Age for controls is age at study consent and age for cases is age at ovarian tumor diagnosis

[‡]Odds ratio is per 10-year increment

Table 2

Gravidity, parity, OCP use and risk of ovarian tumors

Variable	Controls (N=872)	Cases (N=1028)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
	N (%) [†]	N (%) [†]		
Ever pregnant				
No	49 (5.7)	105 (10.2)	Reference	Reference
Yes	817 (94.3)	923 (89.8)	0.53 (0.37, 0.75)	0.58 (0.39, 0.88)
Number of pregnancies				
0	49 (5.7)	105 (10.2)	Reference	Reference
1	62 (7.2)	90 (8.8)	0.68 (0.42, 1.08)	0.69 (0.42, 1.13)
2	232 (26.8)	262 (25.5)	0.53 (0.36, 0.77)	0.49 (0.32, 0.77)
3	228 (26.3)	252 (24.5)	0.52 (0.35, 0.76)	0.46 (0.28, 0.74)
4	295 (34.1)	319 (31.0)	0.51 (0.35, 0.73)	0.35 (0.20, 0.62)
Ever delivered a live birth				
No	64 (7.4)	126 (12.3)	Reference	Reference
Yes	800 (92.6)	902 (87.7)	0.57 (0.42, 0.79)	0.68 (0.47, 0.98)
Number of live births				
0	64 (7.4)	126 (12.3)	Reference	Reference
1	86 (9.9)	109 (10.6)	0.64 (0.43, 0.97)	0.73 (0.47, 1.13)
2	279 (32.3)	314 (30.5)	0.57 (0.41, 0.80)	0.66 (0.45, 0.96)
3	435 (50.4)	479 (46.6)	0.56 (0.40, 0.78)	0.61 (0.38, 0.95)
Use of OCPs (months)				
Never	254 (30.1)	414 (41.5)	Reference	Reference
<6	10 (1.2)	19 (1.9)	1.17 (0.53, 2.55)	1.23 (0.55, 2.72)
6–59	194 (23.0)	265 (26.5)	0.84 (0.66, 1.07)	0.83 (0.63, 1.08)
60	387 (45.8)	300 (30.1)	0.48 (0.38, 0.59)	0.47 (0.37, 0.60)

Abbreviations: OR, odds ratio; CI, confidence interval

* Each of the variables in this table was evaluated in a separate logistic regression model adjusted for age, race, duration of OCP use, number of pregnancies, number of live births, and family history of ovarian cancer (OVCA) when not the factor of interest

[†] Percentage of the women with non-missing data.

Table 3

Association between history of infertility and ovarian tumor, stratified by gravidity

Subgroups defined by gravidity [†]	History of infertility	Controls N (%)	Cases N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
All women	No	690 (79.1)	802 (78.0)	Reference	Reference
	Yes	182 (20.9)	226 (22.0)	1.07 (0.86, 1.33)	0.99 (0.78, 1.26) [*]
Nulligravid women	No	29 (59.2)	49 (46.7)	Reference	Reference
	Yes	20 (40.8)	56 (53.3)	1.66 (0.83, 3.29)	1.65 (0.80, 3.43) ^{**}
Gravid women	No	656 (80.3)	753 (81.6)	Reference	Reference
	Yes	161 (19.7)	170 (18.4)	0.92 (0.72, 1.17)	0.90 (0.69, 1.16) [*]

Abbreviations: OR, odds ratio; CI, confidence interval

^{*} Adjusted for age, race, duration of OCP use, number of pregnancies, number of live births, and family history of OVCA^{**} Adjusted for age, race, duration of OCP use, and family history of OVCA[†] Information on gravidity was not provided by 6 controls

Table 4

Odds ratios for ovarian tumor associated with use of fertility drugs among women with a history of infertility, stratified by gravidity

Subgroups defined by gravidity [†]	Fertility drug use	Controls N (%)	Cases N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
All	No	138 (75.8)	188 (83.2)	Reference	Reference
	Yes	44 (24.2)	38 (16.8)	0.63 (0.39, 1.03)	0.64 (0.37, 1.11) *
Nulligravid women	No	16 (80.0)	49 (87.5)	Reference	Reference
	Yes	4 (20.0)	7 (12.5)	0.57 (0.15, 2.21)	0.59 (0.14, 2.52) **h
Gravid women	No	122 (75.8)	139 (81.8)	Reference	Reference
	Yes	39 (24.2)	31 (18.2)	0.70 (0.41, 1.19)	0.69 (0.37, 1.26) *

Abbreviations: OR, odds ratio; CI, confidence interval

* Adjusted for age, race, duration of OCP use, number of pregnancies, number of live births, and family history of OVCA

** Adjusted for age, race, duration of OCP use, and family history of OVCA

[†] Information on gravidity was not provided by 1 control