Fertility drug use and the risk of ovarian tumors in infertile women: a case-control study

Albert Asante, M.D., M.P.H., Phoebe H. Leonard, M.D., Amy L. Weaver, Ellen L. Goode, Ph.D., M.P.H., Jani R. Jensen, M.D., Elizabeth A. Stewart, M.D., and Charles C. Coddington, M.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota

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 1,900 women (1,028 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 44 (24%) of 182 controls and 38 (17%) of 226 cases. Infertile women who used fertility drugs were not at increased risk of developing ovarian tumors compared with infertile women who did not use fertility drugs; the adjusted odds ratio was 0.64 (95% CI, 0.37, 1.11). The findings were similar when stratified by gravidity and when analyzed separately for borderline versus invasive tumors.
Conclusion(s): We found no statistically significant association between fertility drug use and risk of ovarian tumors. Further larger, prospective studies are needed to confirm this observation. (Fertil Steril® 2013;99:2031–6. ©2013 by American Society for Reproductive Medicine.)
Key Words: Borderline tumors, case control, fertility drugs, ovarian tumors, primary infertility
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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 are conflicting. Although early studies reported an association between exposure to 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 the risk of borderline ovarian tumors.

Fertility drug use has increased markedly in the United States and is expected to continue to rise as the percentage of women who postpone attempting pregnancy until after age 35 increases (18). 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 (19, 20). 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

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Reprint requests: Albert Asante, M.D., M.P.H., Mayo Clinic, Charlton 3A, 200 First Street SW, Rochester, Minnesota 55905 (E-mail: asante.albert@mayo.edu).

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occur during ovulation on the epithelial surface of the ovary contributes to DNA damage and increases the risk of developing ovarian tumors (21). The increased risk of ovarian cancer in chickens, a species of incessant ovulators, supports this hypothesis (22). The "gonadotropin hypothesis" postulates that exposure to high levels of circulating pituitary gonadotropins, which stimulate the ovarian surface epithelium, plays a role in the development of ovarian tumors (23). 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 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 the United States, and the few conducted in the United States 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 of 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 the 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 with the cases. A total of 2,253 women (1,157 cases and 1,096 controls) were enrolled as of May 10,

TABLE 1

Characteristics of the study population.

Characteristic	Controls (N = 872)	Cases (N = 1028)	Unadjusted OR (95% CI)	*P* value
Age (y), mean (SD)[a]	60.5 (13.2)	61.3 (12.8)	1.05 (0.98, 1.13)[b]	.17
Marital status, n (%)				< .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 (%)				.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 (%)				< .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 (%)				< .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 (y), mean (SD)	13.0 (1.6)	12.8 (1.6)	0.47 (0.26, 0.86)[b]	.01
Age at first live birth (y), mean (SD)	24.1 (4.5)	23.0 (4.4)	0.57 (0.46, 0.71)[b]	< .001
Family history of OVCA, n (%)				.01
No	801 (91.9)	906 (88.1)	Reference	
Yes	71 (8.1)	122 (11.9)	1.52 (1.12, 2.07)	

Note: CI = confidence interval; OR = odds ratio; OVCA = ovarian cancer; SD = standard deviation.
[a] Age for controls is age at study consent and age for cases is age at ovarian tumor diagnosis.
[b] Odds ratio is per 10-year increment.

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