

Ovarian stimulation and borderline ovarian tumors: a case-control study

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Objective: To assess the risk of borderline ovarian cancer among infertile women treated with fertility drugs.

Design: Case-control study.

Setting: Nationwide data obtained from public registers and postal questionnaires.

Patient(s): All Danish women <60 years old with borderline ovarian cancer during the period 1989–1994 and randomly selected population controls. The analysis included 231 cases and 1,721 controls.

Intervention(s): None.

Main Outcome Measure(s): Influence of parity, infertility, and fertility drugs on the risk of borderline ovarian cancer after multivariate confounder control.

Result(s): The odds ratio (OR) for borderline ovarian cancer among infertile untreated nulliparous women compared with fertile nulliparous women was 1.9. The OR for borderline ovarian cancer among treated nulliparous women compared with untreated infertile nulliparous women was 1.5, and the OR among treated parous women compared with untreated infertile parous women was 1.5.

Conclusion(s): Among fertile women, the difference in the risk of borderline ovarian cancer between nulliparous women and parous women was not statistically significant. Nulliparous women who were infertile and who did not receive medical treatment had a twofold higher risk of borderline ovarian cancer than fertile nulliparous women. There was no statistically significant increase in the risk of borderline ovarian cancer among nulliparous women who were treated with fertility drugs compared with nulliparous untreated infertile women or among parous women who were treated with fertility drugs compared with parous untreated infertile women. (Fertil Steril® 1998;70:1049–55. ©1998 by American Society for Reproductive Medicine.)

Key Words: Case-control study, epidemiology, ovarian cancer, borderline, parity, infertility, fertility drugs

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Several case reports have suggested an association between exposure to fertility drugs and the development of ovarian cancer. No convincing evidence of an increased risk of invasive ovarian cancer after treatment with fertility drugs has emerged. The risk of borderline ovarian cancer, however, may be increased (1–7). The empiric data on the risk of borderline ovarian cancer after ovarian stimulation are sparse (2, 6). If borderline tumors precede invasive ovarian cancer, borderline tumors could be a more sensitive marker for an increased cancer risk than ovarian cancer in general. The aim of this study was to assess the influence of parity, infertility, and treatment with fertility drugs on the risk of borderline ovarian cancer.

MATERIALS AND METHODS

All patients with malignancies since 1943 have been recorded in The Danish Cancer Registry, which since 1978 has included histologic diagnoses according to the World Health Organization's International Classification of Diseases for Oncology (ICD-O). Tumors classified as borderline have an atypical proliferation without destructive invasion of the stromal component.

This study is a case-control study of prevalent cases and population controls. Information about exposures was obtained through questionnaires that included questions on relevant confounders. Information about treatment with fertility drugs was obtained through informa-

TABLE 1

Characteristics of 231 patients with borderline ovarian cancer and 1,721 controls.

Variable	Cases (n = 231)	Controls (n = 1,721)
Mean age in y (range)	43.6 (22–59)	46.0 (19–59)
Mean age of menarche in y (range)	13.4 (10–18)	13.4 (9–18)
No. (%) of women who had ever been pregnant	201 (87.0)	1,551 (90.1)
Mean no. of pregnancies among women who had ever been pregnant (range)	2.5 (1–9)	2.7 (1–13)
No. (%) of parous women	181 (78.4)	1,492 (86.7)
Mean no. of births among parous women (range)	2.2 (1–7)	2.2 (1–8)
Mean age at first birth in y (range)	23.4 (16–36)	23.2 (14–42)
No. (%) of women who had ever been infertile	53 (22.9)	245 (14.2)
Mean duration of infertility in y (range)	6.5 (1–16)	5.5 (1–21)
No. (%) of women who had ever used fertility drugs	17 (32.1)	58 (23.7)
No. (%) of women who had ever used oral contraceptives	164 (71.0)	1,322 (76.8)
No. (%) of women who had ever used an intrauterine device	80 (34.6)	646 (37.5)
No. (%) of women who had ever received hormone replacement therapy	51 (22.1)	356 (20.7)
No. (%) of women who had ever experienced amenorrhea	31 (13.4)	169 (9.8)
No. (%) of postmenopausal women	78 (33.8)	658 (38.2)
Mean age at menopause in y (range)	48.2 (26–58)	48.3 (23–59)
No. (%) of women who had undergone laparotomy	84 (36.4)	478 (27.8)
No. (%) of women who had undergone sterilization	18 (7.8)	201 (11.7)
Mean age at sterilization in y (range)	36.2 (22–45)	34.8 (23–49)
No. (%) of women with a history of cancer	10 (4.3)	69 (4.0)
No. (%) of women with a family disposition to cancer	86 (37.2)	571 (33.2)
No. (%) of women who had ever smoked	156 (67.5)	993 (57.7)
Mean body mass index (kg/m ²) (range)	23.8 (17–42)	23.4 (14–53)

Note: Risk factors that differed significantly between cases and controls are described in detail in Table 2.

tion provided on the administration form. Further detailed information was retrieved from the relevant fertility clinics with the patient's permission. The study was approved by the Regional and Central Scientific Ethical Committees in Denmark as well as by the Board of Registers and Central Health Board.

Cases

Cases were all Danish women <60 years old with borderline ovarian cancer coded in the Danish Cancer Registry according to the ICD-O as 8380, 8381, 8441, 8450, 8460, 8470, 8471, and 9014 during the period 1989–1994.

The number of identified cases was 277, of which 11 (4%) had died. Written permission to contact the cases was obtained from the head of each of the 35 gynecologic and 3 surgical departments involved. Three (1%) patients were excluded because permission was not granted by the departments, mainly because these patients were considered to be too mentally distressed to be asked to participate. Thus, a total of 263 questionnaires were sent out in the spring of 1996. Two hundred forty-six (93.5%) women responded and 15 refused to participate, leaving 231 (87.8%) of 263 cases with borderline ovarian cancer that were valid for analysis.

Controls

The control group was established previously in a case-control study on risk factors for invasive ovarian cancer (7).

For each case registered with invasive ovarian cancer in The National Patient Register during the period 1989–1992 (n = 803), three women were selected randomly from The National Person Register, matched for area of residence and for day and month of birth, but with a current age corresponding to the age of the case at the time of the ovarian cancer diagnosis. By April 1994, 2,210 control questionnaires had been sent out: 1,866 (84.4%) women responded and 1,764 (79.8%) questionnaires were completed. Forty-three women were excluded because of previous bilateral oophorectomy, leaving a final control group of 1,721 women.

Data Collection

The questionnaires for cases and controls included questions on menarche, age at menopause, periods of amenorrhea, pregnancies (including miscarriages, abortions, and ectopic pregnancies), parity, age at first birth, difficulty in conceiving, length of pregnancy attempt, hysterosalpingography, treatment with fertility drugs, duration of this treatment, hyperprolactinemia, hyperandrogenism, duration of use of oral contraceptives (OCs) and intrauterine devices (IUDs), sterilization, oophorectomy and other previous laparotomies, hormone replacement therapy (HRT), family cancer disposition, previous cancerous diseases, years of schooling, smoking habits, height, and weight. Information about the different fertility drugs used was retrieved by asking how the medical fertility treatment had been administered: treat-

TABLE 2

Risk of borderline ovarian cancer according to selected variables.

Risk factor	Odds ratio (95% CI)		
	Crude	Adjusted for age and residence	Multivariate analysis*
Parity (nulliparous versus parous)	1.79 (1.28–2.56)	1.64 (1.11–2.38)	ND†
Infertility among all subjects			
Never	1.00	1.00	ND†
Ever	1.78 (1.27–2.50)	1.70 (1.20–2.39)	ND†
Unknown	1.06 (0.61–1.82)	0.83 (0.46–1.49)	ND†
Infertility among nulliparous subjects (ever versus never)	1.90 (0.87–4.16)	2.05 (0.84–5.00)	ND†
Infertility among parous subjects (ever versus never)	1.28 (0.83–1.96)	1.24 (0.80–1.92)	ND†
Use of fertility drugs among all subjects	2.27 (1.30–3.96)	2.19 (1.24–3.85)	ND†
Use of oral contraceptives			
Never	1.00	1.00	1.00
Ever	0.73 (0.54–0.99)	0.59 (0.43–0.82)	0.54 (0.37–0.77)
<1 y	0.90 (0.60–1.36)	0.79 (0.52–1.20)	0.67 (0.42–1.07)
1–5 y	0.63 (0.43–0.93)	0.51 (0.34–0.76)	0.45 (0.29–0.71)
>5 y	0.72 (0.50–1.03)	0.56 (0.38–0.81)	0.52 (0.34–0.80)
Menopause (yes versus no)	0.74 (0.55–0.98)	1.16 (0.74–1.83)	0.90 (0.53–1.50)
Use of hormone replacement therapy			
Never	1.00	1.00	1.00
Ever	1.12 (0.80–1.56)	1.47 (1.01–2.12)	1.54 (1.04–2.28)
<1 y	0.77 (0.42–1.42)	0.98 (0.52–1.84)	0.99 (0.51–1.91)
1–5 y	1.29 (0.80–2.09)	1.68 (1.01–2.77)	1.80 (1.06–3.05)
>5 y	1.32 (0.77–2.25)	1.86 (1.04–3.32)	1.93 (1.05–3.57)
Smoking (ever versus never)	1.50 (1.12–2.02)	1.45 (1.08–1.96)	1.54 (1.11–2.15)

Note: CI = confidence interval; ND = no data.

* Included the following variables: age, residence, parity, infertility, use of fertility drugs, use of oral contraceptives, use of hormone replacement therapy, and smoking.

† Because of effect modification between the three variables (parity, infertility, and use of fertility drugs), a stratification according to each of these three axes was necessary; see Table 3.

ment with tablets only, with tablets followed by one injection per cycle, or with several injections per cycle.

The questionnaire for cases included a confirmation of the ovarian cancer diagnosis as well as a written permission to retrieve further information from hospitals, specialists, and general practitioners. The controls were asked about previous bilateral oophorectomy.

Statistical Analysis

Primarily, an analysis with adjustment for age and residence was performed. Subsequently, a multivariate analysis with unconditional logistic regression was used (8). Because the influence of infertility and ovarian stimulation was expected to be different among nulliparous and parous women, the variables of parity, infertility, and use of fertility drugs, and the interactions between them, were investigated in the model first, and the other variables were tested thereafter in a combined backward and forward elimination and included as categorized confounding variables in the analysis. Risk estimates were calculated as odds ratios (ORs) with 95% confidence intervals (CIs).

Three categories of fertility status were used: infertile

women, fertile women, and women with unknown fertility. Twelve women who had not answered the question about infertility and/or use of fertility drugs were excluded.

RESULTS

Mucinous cystadenoma of borderline malignancy (n = 100) accounted for most (43.3%) of the histologic diagnoses. Serous cystadenoma of borderline malignancy (n = 75) accounted for 32.5%. Papillary serous cystadenoma of borderline malignancy (n = 33), papillary mucinous cystadenoma of borderline malignancy (n = 10), and unspecified papillary cystadenoma of borderline malignancy (n = 7) accounted for 21.6%, and endometrioid adenoma of borderline malignancy (n = 2) accounted for 0.9%. The remaining 1.7% was serous adenofibroma of borderline malignancy (n = 3) and endometrioid adenofibroma of borderline malignancy (n = 1). Characteristics of the study population are given in Table 1.

Menarche, age at menopause, previous laparotomy, previous cancer, familial disposition to cancer, use of an IUD,

TABLE 3

Risk of borderline ovarian cancer according to parity, infertility, and use of fertility drugs.

Parity	Fertility status	Use of fertility drugs	No. of cases (%)	No. of controls (%)	Crude OR	Adjusted OR* (95% CI)
Nulliparous	Fertile		12 (24.0)	53 (23.1)	1.00	1.00
	Infertile	No	15 (30.0)	39 (17.0)	1.70	1.92 (0.76–4.89)
		Yes	10 (20.0)	19 (8.3)	2.32	2.88 (0.95–8.74)
Parous	Fertile		150 (82.9)	1,286 (86.2)	0.52	0.69 (0.34–1.41)
	Infertile	No	21 (11.6)	148 (9.9)	0.63	0.76 (0.33–1.76)
		Yes	7 (3.9)	39 (2.6)	0.79	1.11 (0.37–3.30)

Note: CI = confidence interval; OR = odds ratio.

* Adjusted for age, residence, use of oral contraceptives, use of hormone replacement therapy, and smoking.

sterilization, and body mass index all had no statistically significant association with the risk of borderline ovarian cancer.

More controls than cases had ever used OCs (crude OR = 0.73; CI = 0.54–0.99), and in the multivariate analysis, a decreasing risk with increasing duration of use was found (Table 2). Postmenopausal women had a crude decreased risk of borderline ovarian cancer, but after adjustment, the risk was no longer significantly decreased (OR = 0.90; CI = 0.53–1.50) (Table 2). Hormone replacement therapy was associated with an increased risk of borderline ovarian cancer, and the analyses showed an increasing risk with increasing duration of use (Table 2). Significantly more cases than controls had ever smoked (OR = 1.54; CI = 1.11–2.15) (Table 2).

Pregnancy and Parity

Adjusted for age only, nulliparous women as a whole had an increased risk of borderline ovarian cancer compared with parous women (OR = 1.64; CI = 1.11–2.38) (Table 2). In the multivariate analysis, nulliparity without infertility did not significantly increase the risk (OR = 1.46; CI = 0.71–3.00) (data not shown). Pregnancies that did not reach term, age at first birth, and number of births among parous women were not significantly associated with the risk of borderline ovarian cancer.

Infertility

Adjusted for age and residence, there was an overall increased risk of borderline ovarian cancer among infertile women (OR = 1.70; CI = 1.20–2.39) (Table 2). Among nulliparous women, 26% of the cases and 51.5% of the controls did not know their capability of conceiving. The main reason for that was that they were young and never had tried to become pregnant. These women formed a separate group and had no increased risk (OR = 0.83; CI = 0.46–1.49) (Table 2). The duration of infertility had no statistically significant influence (data not shown).

There was no statistically significant increased risk of

borderline ovarian cancer in the multivariate analysis among infertile untreated nulliparous women compared with fertile nulliparous women (OR = 1.92; CI = 0.76–4.89) (Table 3). Among parous women, infertility without treatment did not increase the risk compared with nulliparous women without infertility (OR = 0.76; CI = 0.33–1.76) (Table 3) or compared with parous women without infertility (OR = 1.13; CI = 0.68–1.88) (data not shown).

Fertility Drugs

Among infertile women, 32% of the cases and 24% of the controls had used fertility drugs, corresponding to an OR of 2.19 (CI = 1.24–3.85) after adjustment for age and residence (Table 2). In the multivariate analysis, infertile nulliparous women who were treated with fertility drugs did not have a significantly increased risk of borderline ovarian cancer compared with untreated women (OR = 1.50; CI = 0.51–4.39) (Table 4). The OR for borderline ovarian cancer was 3.01 (CI = 0.73–12.33) for women who received clomiphene citrate (cc) and hCG and was 0.91 (CI = 0.14–6.13) for women who were treated with hMG and hCG.

Among infertile parous women, ovarian stimulation in general and each of the three specified treatment regimens (clomiphene, clomiphene and hCG, and hMG and hCG) were similarly not associated with a significantly increased risk of borderline ovarian cancer (OR = 1.4–1.9) (Table 4). An association between the duration of stimulation and the risk of borderline ovarian cancer could not be demonstrated, either for the treatment as a whole or for the specific treatment regimen, but the sample size was small.

DISCUSSION

Validity of Data

The validity of the borderline ovarian cancer diagnoses probably was high due to the histologic confirmation in The Danish Cancer Registry. The information on exposure was obtained by asking how the fertility treatment was administered. Treatment with cc is given as tablets only, treatment

TABLE 4

Risk of borderline ovarian cancer according to use of fertility drugs among infertile women.

Parity	Use of fertility drugs	Type of fertility drugs	No. of cases* (%)	No. of controls (%)	Crude OR	Adjusted OR† (95% CI)
Nulliparous	No		15 (60.0)	39 (67.2)	1.00	1.00
	Yes	Total	10 (40.0)	19 (32.8)	1.37	1.50 (0.51–4.39)
		cc	3 (12.0)	11 (19.0)	0.71	0.80 (0.19–3.38)
		cc and hCG	6 (24.0)	3 (5.2)	5.20	3.01 (0.73–12.33)
		hMG and hCG	3 (12.0)	4 (6.9)	1.95	0.91 (0.14–6.13)
	Unknown	0	3 (5.2)			
Parous	No		21 (75.0)	148 (79.1)	1.00	1.00
	Yes	Total	7 (25.0)	39 (20.9)	1.26	1.46 (0.56–3.81)
		cc	4 (14.3)	16 (8.6)	1.76	1.93 (0.56–6.59)
		cc and hCG	2 (7.1)	10 (5.3)	1.41	1.54 (0.30–7.81)
		hMG and hCG	2 (7.1)	9 (4.8)	1.57	1.43 (0.28–7.19)
	Unknown	0	5 (2.7)			

Note: cc = clomiphene citrate; CI = confidence interval; OR = odds ratio. Only women with a known fertility status were included.

* Some cases and controls had more than one treatment regimen, and for eight controls, the specific type of drug was unknown.

† Adjusted for age, residence, use of oral contraceptives, use of hormone replacement therapy, and smoking.

with cc and hCG is given as tablets followed by one injection per cycle, and treatment with hMG and hCG involves several injections per cycle. The reverse relation (e.g., that the use of tablets means the drug given was cc) might not necessarily be true.

Because of a lack of information about the duration of the fertility treatment on some questionnaires, various fertility clinics were contacted. For all infertile treated women for whom further detailed information was retrieved (12% in this study; 13% in a previous study [7]), it was confirmed that the fertility treatment included only cc, hCG, and/or hMG. Considering the information from the fertility clinics as a test sample, the validity of the exposure data seems to be good.

The control group was matched for age and residence but otherwise randomly selected. The control group seems to be representative of the Danish population of women. For example, the prevalence of infertility (ever) in the control group of 14.2% corresponds with that in other Danish references (9).

Recall and Selection Biases

Pregnancies, births, difficulties in conceiving, and particularly treatment of infertility are important events in every woman's life and probably are equally well remembered by the cases and the controls. Therefore, recall bias, which might be an important problem in case-control studies, did not significantly influence the results.

On the other hand, the increased risk of borderline ovarian cancer could have been influenced by surveillance bias because women who are undergoing fertility treatment are examined more often than other infertile women. The time of stimulation in relation to the time of cancer diagnosis was

not available, but all 10 nulliparous cases and 14 (82%) of 17 (10 nulliparous and 7 parous) cases who underwent ovarian stimulation were ≤ 40 years old at the time of cancer diagnosis, indicating that they still could have been attending a fertility clinic at the time of diagnosis and therefore may have been under more intensive surveillance. Among infertile cases who did not undergo ovarian stimulation, only 12 (33%) of 36 were < 40 years old when their cancer was diagnosed.

The way in which the increasing use of fertility drugs may have affected the results is another important issue. Despite age adjustment in the analysis, the trend might have had an influence. Patient age at the time of ovarian stimulation was not available, but the average age among treated cases at the time of cancer diagnosis was 36.7 years and that among treated controls was 46.6 years, suggesting that the cases underwent ovarian stimulation in the late 1980s and early 1990s, when stimulation with fertility drugs was three times more frequent than in the previous decade (10).

Both these potential biases tend to overestimate the risk of borderline ovarian cancer associated with treatment with fertility drugs.

Risk Factors

Several studies have found epidemiologic similarities between borderline ovarian cancer and invasive ovarian cancer with respect to patients' reproductive and personal characteristics (2, 11–13). In their case-control studies, Harlow et al. (12) and Parazzini et al. (13) found, as we did, that the reduced risk of borderline ovarian cancer among parous compared with nulliparous women was not significant. In the collaborative analysis of 12 U.S. case-control studies performed by Harris et al. (2), the risk among parous versus

nulliparous women was significantly decreased. In several case-control studies, consistent results have emerged concerning a protective influence of OCs (2, 11–13). Other risk factors, such as familial ovarian and/or breast cancer, tubal ligation, hysterectomy, use of an IUD, menopausal status, and body mass index, which are established risk factors for invasive ovarian cancer (1, 7, 14–21), have not been found to be associated with borderline ovarian cancer in our study or others (2, 11–13).

An association between smoking and borderline ovarian cancer could not be demonstrated in the study by Harlow et al. (12), and in the two other studies (11, 13), smoking was not evaluated.

Infertility

Only a few other studies that specifically explored the impact of infertility and treatment with fertility drugs on the risk of borderline ovarian cancer are available. In a cohort study, Rossing et al. (4) found that 5 of 11 women with ovarian cancer had a borderline tumor, and these were found to be significantly associated with infertility (age-standardized incidence ratio = 3.3; CI = 1.1–7.8). In their collaborative study, Harris et al. (2) found a significantly increased risk of borderline ovarian cancer among women with a history of infertility (OR = 1.9; CI = 1.3–2.7), and the increase was greater among nulliparous women (OR = 3.8; CI = 1.3–10.8) than among parous women (OR = 1.4; CI = 0.9–2.2).

In the case-control study by Harlow et al. (12), difficulties in conceiving implied an insignificantly increased risk of borderline ovarian cancer among nulliparous women who had ever been married (OR = 6.0; CI = 0.6–57.1), but no increased risk among parous women. Thus, our results are in accordance with the results of these three studies. Risch et al. (11) could not demonstrate any association between infertility and borderline ovarian cancer, but the sample size in their study was small.

Infertility Treatment

Harris et al. (2) found a significantly increased risk of borderline ovarian cancer among women who were treated with fertility drugs compared with fertile women (OR = 4.0; CI = 1.1–13.9). This risk may be overestimated, however, because of the increased risk associated with infertility itself. In addition, this part of the study is based on data from three case-control studies that included a total of 622 patients and 1,101 controls (22–24), in which the validity of the exposure data has been criticized (25).

In a case-control study that included 200 patients with ovarian cancer and 408 controls, Shushan et al. (6) found an increased risk of borderline cancer among users of fertility drugs (OR = 3.5; CI = 1.2–10.1) compared with nonusers; treatment with hMG in particular was associated with an increased risk (OR = 9.4; CI = 1.7–52.1). However, because they did not stratify according to parity and did not

control for infertility, which was not found to be significantly associated with the risk of ovarian cancer, the figures of Shushan et al. also may be overestimated.

In a nested case-control analysis in the cohort study performed by Rossing et al. (4), the investigators did not discriminate between borderline ovarian cancer and invasive cancer.

In conclusion, our study and other studies demonstrate that infertility might be associated with an increased risk of borderline cancer, particularly among nulliparous women. On the other hand, we found no significant increase in the risk of borderline tumors after treatment with fertility drugs. The increase in the risk of borderline cancer after treatment with fertility drugs found in other studies may be explained by a confounding influence from the infertility itself.

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