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Infertility, fertility drugs, and invasive ovarian cancer: a case-control study*

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

Design: A case-control study.

Setting: Nationwide data based on public registers.

Patient(s): All Danish women (below the age of 60 years) with ovarian cancer during the period from 1989 to 1994 and twice the number of age-matched population controls. Included in the analysis were 684 cases and 1,721 controls.

Main Outcome Measure(s): Influence of parity, infertility, and fertility drugs on the risk of ovarian cancer after multivariate confounder control. Risk measure(s): odds ratios (OR) with 95% confidence intervals.

Result(s): Nulliparous women had an increased risk of ovarian cancer compared with parous women: OR 1.5 to 2.0. Infertile, nontreated nulliparous women had an OR of 2.7 (1.3 to 5.5) compared with noninfertile nulliparous women. The OR of ovarian cancer among treated nulliparous women was 0.8 (0.4 to 2.0) and among treated parous 0.6 (0.2 to 1.3), compared with nontreated nulliparous and parous infertile women, respectively.

Conclusion(s): Nulliparity implies a 1.5- to 2-fold increased risk of ovarian cancer. Infertility without medical treatment among these women increased the risk further. Among parous as well as nulliparous women, treatment with fertility drugs did not increase the ovarian cancer risk compared with nontreated infertile women. (Fertil Steril® 1997;67:1005–12. © 1997 by American Society for Reproductive Medicine.)

Key Words: Case-control study; epidemiology; parity; infertility; fertility drugs

In the industrialized world, 10 new cases of ovarian cancer develop per 100,000 women (all ages) per year corresponding to a lifetime risk of 2.0%.

The etiology of ovarian cancer is multifactorial. The most well-established risk factor is parity with an inverse relationship to the number of births (1–6). Several studies have found that infertility implies an increased risk, although less pronounced than it is for nulliparity (1–4, 6–10).

Recent studies have suggested an association between exposure to fertility drugs and ovarian cancer (6, 9–12). In 1992, Whittemore et al. (6) found an extremely high risk of ovarian cancer among nulliparous women treated with fertility drugs. Three later epidemiological studies have found insignificantly increased risk for invasive ovarian cancer (9, 10, 12), or no risk at all (11). Because of the increasing use

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of fertility drugs (13), it is important to clarify whether this treatment implies an increased risk of ovarian cancer.

The aim of this case-control study was to assess the risk of ovarian cancer according to parity, infertility, and treatment with fertility drugs.

MATERIALS AND METHODS

All Danish inhabitants are registered in The National Person Register by a personal identification number. Since 1977, the diagnoses of all hospitalized patients in Denmark have been recorded in the Danish National Patient Register according to the World Health Organization (WHO) International Classification of Diseases (ICD). As well, all patients with malignancies have, since 1943, been recorded in The Danish Cancer Registry, which, since 1978, has included histological diagnoses according to the WHO ICD for oncology (ICD-O).

This study is a case-control study of prevalent and incident cases and population controls. Information about exposures was obtained by questionnaires. The study was approved by the Regional and Central Scientific Ethical Committees of Denmark, as well as by the Board of Registers and Central Health Board.

Cases

Included were all Danish women 18 to 59 years of age with a first-ever diagnosis of ovarian cancer during the period from 1989 to 1994. During 1989 through 1993, patients were coded in the Danish National Patient Register according to ICD-8 as 183.0 to 183.9; during 1994, coding was according to ICD-10 as C56.0 to C56.9. The total number of identified cases was 1,455. To verify the diagnoses, the patients identified in the Danish National Patient Register were cross checked with the patients in The Danish Cancer Registry. Ten non-Danish inhabitants were excluded.

Written permission to contact the cases was obtained from the head of each of the 48 gynecologic and 39 surgical departments involved. The questionnaires were sent out January 1994 (for those patients diagnosed between 1989 and 1992), in May 1994 (for those diagnosed in 1993), in September 1994 (for a supplemental group diagnosed between 1989 and 1993), in April 1995 (for patients diagnosed in 1994), and in October 1995 (for those identified only in The Danish Cancer Registry).

Of 1,304 patients registered in both the Danish National Patient Register and the Danish Cancer Registry, 145 had a borderline malignancy and were excluded. These tumors underwent a separate (ongoing) analysis because previous studies have suggested different risks for invasive cancer and borderline tumors.

A letter of discharge and/or the histologic diagnoses of 141 patients not found in The Danish Cancer Registry were retrieved from the relevant surgical, gynecologic, and pathology departments. Histologic diagnoses were available for 116 of these patients. Seven were confirmed, whereas 109 without an ovarian cancer were excluded. Of 25 patients without a histologic diagnosis, 14 patients confirmed their malignant disorder in the questionnaire and were included. The remaining 11 patients were excluded.

Of 395 patients identified in The Danish Cancer Registry but not in the Danish National Patient Register, 27 were excluded because of malignancies other than ovarian cancer and 176 because of benign or borderline ovarian tumors. The remaining 192 with invasive ovarian cancer were included.

Thus, 1,372 cases of ovarian cancer were identified and verified. At the time the questionnaires were sent out, 513 (37%) patients had died and 11 (<1%) were excluded because of nonpermission from the departments, mainly because these patients were considered to be too mentally distressed to be asked to participate.

A total of 848 questionnaires were sent out and 746 (88.0%) responded. Fifty-four patients refused to participate and eight questionnaires were insufficiently filled out, leaving 684 (80.7%) of 848 cases with invasive ovarian cancer valid for analysis.

Controls

For each case registered with ovarian cancer in the Danish National Patient Register during the period from 1989 to 1992 (n = 803), three women were randomly selected 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. Because the distribution of age and residence was the same among the 381 primarily included cases diagnosed during the period from 1989 to 1992 and the 303 included cases diagnosed during the period from 1993 to 1994, no further controls were included. By April 1994, 2,210 control questionnaires had been sent out; 1,866 (84.4%) responses were received, including 100 who refused to participate. Two questionnaires were insufficiently filled out. Thus, 1,764 (79.8%) of 2,210 questionnaires were completed.

An appropriate correction for different exposure times for specific risk factors and time at risk of developing ovarian cancer among women with bilateral oophorectomy was not possible. Therefore, 43 women who previously had undergone bilateral

oophorectomy were excluded, leaving a final control group of 1,721 women.

Data Collection

The questionnaire for cases and controls included questions on menarche, age at menopause, periods of amenorrhea, pregnancies (miscarriages, abortions, and ectopic pregnancies), parity, age at first birth, difficulty in conceiving and length of pregnancy attempt (difficulty for more than 12 months was considered as infertility), hysterosalpingography, treatment with specific fertility drugs, duration of treatment, hyperprolactinemia, hyperandrogenism, duration of use of oral contraceptives and intrauterine device, sterilization, oophorectomy and other previous laparotomies, hormone replacement therapy, family cancer disposition, previous cancer diseases, years of schooling, smoking habits, and height and weight. To obtain information about specific fertility drugs, all women were asked how their medical fertility treatment had been administrated: Treatment with clomiphene citrate is given as tablets only; and treatment with clomiphene citrate and hCG is given as tablets followed by one injection per cycle, whereas treatment regimens with hMG and hCG involves several injections per cycle.

The questionnaire for cases included a verification 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 oophorectomy.

A reminder was sent to nonresponders 3 to 6 months after the first application.

Statistical Analyses

Unconditional logistic regression analysis was used. Because the influence of infertility and ovarian stimulation was expected to be different between nulliparous and parous women, the variables, parity, infertility, and fertility drugs and the interactions between them were included in the modeling first; the other variables were tested in a combination of backward and forward elimination.

Because infertility was found to be a modifier according to parity, the determinants parity, infertility and fertility drugs were included as three-factor interacting variables. As no other effect modifiers were found, the confounders intrauterine device, menopause, previous cancer of the breast and cervix, familial disposition to cancer of the colon, and body mass index were included as categorized variables and the confounders oral contraceptives and hormone replacement therapy were included as categorized but continuous (ordinal) variables. The variables age and residence were included because of the frequency matching.

To evaluate the influence of the number of births and of infertility, nulliparous women without infertility were used as the reference group. This reference group included women who responded that they had never had any difficulties in conceiving, including a few without pregnancy attempt.

For the analysis of the ovarian cancer risk associated with infertility and use of fertility drugs, three categories of fertility status were applied in order to avoid misclassification: infertile women, noninfertile women, and women with unknown fertility. If women with unknown fertility status had been categorized as being noninfertile women, the risk of ovarian cancer associated with infertility would be underestimated.

Risk estimates were calculated as odds ratios (ORs) with 95% confidence intervals (CIs). In cases of continuous variables, a rank correlation test statistic was applied and the P values are expressed as "P_{trend}."

RESULTS

Epithelial tumors (n = 595) accounted for the majority (87.0%) of the histologic diagnoses. Stromal tumors (n = 24) accounted for 3.5%; germ cell tumors (n = 23) for 3.4%; and unspecified tumors (n = 5), tumors that were histologically unclassifiable (n = 23), and histologically unverified tumors (n = 14) accounted for 6.1%. The distribution of the histologic diagnoses among infertile women treated with fertility drugs and the remaining case group was not significantly different.

Characteristics of the study populations are given in Table 1.

Pregnancy and Parity

Fewer cases than controls had conceived and given birth (Table 1). The average number of births among parous women was 2.2 in both groups.

Parous women had a decreased risk of ovarian cancer as compared with nulliparous women (crude OR = 0.56, CI = 0.45 to 0.70). After adjustment for included confounders (Table 2), the risk decreased by 31% for the first birth and by a further 30% after the second birth. No statistically significant association was found in relation to miscarriages (OR = 0.93, CI = 0.72 to 1.20), induced abortions (OR = 0.85, CI = 0.66 to 1.09), or ectopic pregnancies (OR = 0.94, CI = 0.51 to 1.73) as compared with women without these aborted pregnancies (data not shown). Among infertile nulliparous women, a crude protection of ever pregnant (OR = 0.80) disappeared after confounder control (OR = 1.11).

Table 1 Characteristics of the Study Population

Factor	Cases	Controls
Age (y)*	47.2 (18 to 59)	46.0 (19 to 59)
Menarche (y)*	13.5 (9 to 23)	13.4 (9 to 18)
Pregnancy, ever†	572 (83.6)	1,551 (90.1)
Pregnancies among ever-pregnant*	2.6 (1 to 11)	2.7 (1 to 13)
Parous, ever†	536 (78.4)	1,492 (86.7)
Births among parous*	2.2 (1 to 5)	2.2 (1 to 8)
Age at first birth (y)*	23.9 (15 to 41)	23.2 (14 to 42)
Nulliparous†	148 (21.6)	229 (13.3)
Infertility, ever†‡	135 (22.0)	245 (15.5)
Duration of infertility among infertile women (y)*	6.5 (1 to 28)	5.5 (1 to 21)
Fertility drugs among women with infertility, ever†	28 (20.7)	58 (23.8)
Hyperstimulation syndrome, ever†	1 (3.6)	0 (0)
Hysterosalpingography among infertile, ever†	67 (49.6)	118 (48.0)
Hyperandrogenism, ever†	11 (1.6)	21 (1.2)
Hyperprolactinemia, ever†	9 (1.3)	11 (0.6)
Oral contraceptives, ever use†	426 (62.3)	1,322 (77.1)
Intrauterine device, ever use†	187 (27.7)	646 (37.8)
Hormone replacement therapy, ever†	172 (25.6)	356 (21.1)
Amenorrhea, ever†	72 (10.7)	169 (9.8)
Postmenopausal†	295 (43.7)	658 (40.2)
Age at menopause (y)*	48.4 (21 to 57)	48.3 (23 to 59)
Previous laparotomy, ever†	202 (29.5)	478 (27.8)
Sterilization†	62 (9.1)	201 (11.7)
Age at sterilization*	34.6 (24 to 49)	34.8 (23 to 49)
Previous cancer diseases, any†	40 (5.8)	69 (4.0)
Familial disposition to cancer, any†	254 (37.1)	571 (33.2)
Smoking, ever†	417 (61.3)	993 (59.4)
Body mass index (kg/m^2)*	23.4 (15 to 47)	23.4 (14 to 53)

* Values are means with range in parentheses.
† Values in parentheses are percentages.
‡ Among women who knew their fertility status.

Thus, a decreasing risk of ovarian cancer with increasing number of births was found. Aborted pregnancies did not protect against ovarian cancer.

Infertility

Infertility was more frequent among cases than among controls (Table 1). Among nulliparous women, 43.2% of the cases and 51.5% of the controls did not know their capability of conceiving. The main reason for this was that they were young and had never tried to become pregnant. These women were grouped apart in the analysis of infertility. No differences in frequency of hyperandrogenism or hyperprolactinemia between cases and controls were found.

Among all subjects with known fertility status, infertility implied a crude OR of ovarian cancer of 1.54 (range, 1.22 to 1.95) (data not shown). Infertile nulliparous women without treatment had a crude OR of 3.13 (CI = 1.60 to 6.08) times increased risk of ovarian cancer as compared with nulliparous women without infertility (Table 3). After adjustment for included confounders (Table 3), the ovarian cancer risk was 2.71 (1.33 to 5.52). Exclusion of the nonepithelial tumors did not change the risk significantly (OR = 2.53, CI = 1.19 to 5.37).

Women who had given birth had no increased risk associated with periods of infertility, when compared with parous women without infertility (OR = 1.15, CI = 0.83 to 1.58)) or compared with nulliparous women without infertility (OR = 1.14, CI = 0.60 to 2.17).

Among nulliparous women with unknown fertility status, the OR of ovarian cancer as compared with noninfertile nulliparous was 1.56 (CI = 0.83 to 2.93), indicating a heterogeneity among these women.

After adjustment for age, residence, use of oral contraceptives and intrauterine device, menopausal status, previous cancer, familial cancer, body mass index, hormone replacement therapy, and parity, a crude increased risk of ovarian cancer associated with long-term infertility (≥10 years) was no longer statistically significant (data not shown).

Thus, infertility among nulliparous women implied a 2.7 times increased risk of ovarian cancer, whereas periods of infertility among parous women did not influence the risk. The duration of infertility was not significantly associated with risk of ovarian cancer.

Fertility Drugs

The use of fertility drugs was less frequent among infertile cases (20.7%) than among infertile controls (23.8%) (Table 1). Among infertile nulliparous women, 28.1% of the cases and 32.8% of the controls had been treated versus 14.1% of the cases and 20.9% of the controls among parous women with a history of infertility. For both nulliparous and parous women the risk of ovarian cancer among infertile treated women was lower than the risk among infertile women without treatment. The average age of onset of ovarian cancer was 42.3 years among stimulated, and 46.1 years among nonstimulated, infertile cases. This difference was not statistically significant. After adjustment for included confounders (Table 3), the OR of ovarian cancer was 2.26 (CI = 0.92 to 5.58) among treated nulliparous women and 0.73 (CI = 0.29 to 1.82) among treated parous women as compared with nulliparous women without infertility. For invasive epithelial ovarian cancer, the ORs

Table 2 Ovarian Cancer Risk According to Parity

Births	Cases*	Controls*	Crude OR	Adj OR†	95% CI
0	148 (21.6)	229 (13.3)	1.00	1.00	Reference†
1	124 (18.1)	276 (16.0)	0.70	0.69	0.47 to 1.02
≥2	412 (60.2)	1,216 (70.7)	0.52	0.48	0.33 to 0.69

* $P_{trend} = 0.0001$. Values are sample size with percentage in parentheses.
† Adjusted for age, residence, use of oral contraceptives and intrauterine device, menopausal status, previous cancer, familiar cancer, hormone replacement therapy, body mass index, infertility, and fertility drugs.

Table 3 Ovarian Cancer Risk According to Parity, Infertility, and Fertility Drugs

Parity	Fertility status	Fertility drugs	Cases*	Controls*	Crude OR	Adj OR†	95% CI
Nulliparous	−Infertility		20 (13.5)	53 (23.1)	1.00	1.00	Reference
	+Infertility	− Drugs	46 (31.1)	39 (17.0)	3.13	2.71‡	1.33 to 5.52
		+ Drugs	18 (12.2)	19 (8.3)	2.51	2.26	0.92 to 5.58
	Fertility unknown		64 (43.2)	118 (51.5)	1.44	1.56	0.83 to 2.93
Parous	−Infertility		458 (85.4)	1,286 (86.2)	0.86	0.99	0.56 to 1.75
	+Infertility,	− Drugs	61 (11.4)	148 (9.9)	0.99	1.14	0.60 to 2.17
		+ Drugs	10 (1.9)	39 (2.6)	0.62	0.73	0.29 to 1.82
	Fertility unknown		7 (1.3)	19 (1.3)	1.03	0.84	0.27 to 2.65

* Values are sample size with percentage in parentheses.
† Adjusted for age, residence, use of oral contraceptives and intrauterine device, menopausal status, previous cancer, familial cancer, hormone replacement therapy, and body mass index.
‡ $P = 0.02$.

were 2.03 (CI = 0.78 to 5.23) and 0.49 (CI = 0.17 to 1.37), respectively. The risk of ovarian cancer among treated infertile versus nontreated infertile women was 0.83 (CI = 0.35 to 2.01) for nulliparous and 0.56 (CI = 0.24 to 1.29) for parous women, respectively (Table 4). Exclusion of nonepithelial tumors did not change these odds.

After stratification for type of fertility drug, no statistically significant difference in risk of the different treatment regimens was found, but the figures were small (Table 4).

For the 6-year period from 1989 through 1994, the frequency of ovarian stimulation among cases according to year of diagnosis were 3.7%, 3.6%, 5.1%, 5.0%, 4.6%, and 2.6%, respectively, and thus, on the average, 4.1% (95% CI 2.6% to 5.6%) and without any significant trend.

DISCUSSION

Validity of Data

The involvement of both the Danish National Patient Register and The Danish Cancer Registry ensured a nearly 100% inclusion of prevalent and incident cases during the study period. The validity of the ovarian cancer diagnoses was probably high because of the histologic confirmation and the two independent registers involved.

Recall and Selection Bias

In this study, we believe that recall bias, which might be an important problem in case-control studies, had only a minor influence. Pregnancies, births, and difficulties in conceiving and in particular treatment for infertility are important events in every women's life and therefore are expected to be equally remembered by cases and controls. Furthermore, if the women did not recall the name of any infertility treatment, they indicated how their medical treatment had been administered.

How the selection because of deaths (37%) could have influenced the results is an important issue. If the risk factors among dead patients were different from those among the included cases, this would be reflected in a trend in prevalence according to year

Table 4 Ovarian Cancer Risk According to Use of Fertility Drugs Among Infertile Women*

Parity	Drug use	Drug type	Cases†	Controls†	Crude OR	Adj OR‡	95% CI
Nulliparous	No		46 (71.9)	39 (67.2)	1.00	1.00	Reference
	Yes	Total	18 (28.1)	19 (32.8)	0.80	0.83	0.35 to 2.01
		Clomiphene	9 (14.1)	11 (19.0)	0.69	0.67	0.23 to 1.96
		Clomiphene and hCG	7 (10.9)	3 (5.2)	1.99	1.12	0.32 to 3.96
		hMG and hCG	5 (7.8)	4 (6.9)	1.06	0.82	0.18 to 3.71
		Unknown	0 (0.0)	3 (5.2)	—	—	—
Parous	No		61 (85.9)	148 (79.1)	1.00	1.00	Reference
	Yes	Total	10 (14.1)	39 (20.9)	0.62	0.56	0.24 to 1.29
		Clomiphene	6 (8.4)	16 (8.6)	0.91	1.11	0.40 to 3.06
		Clomiphene and hCG	1 (1.4)	10 (5.3)	0.24	0.56	0.12 to 2.70
		hMG and hCG	2 (2.8)	9 (4.8)	0.54	0.50	0.10 to 2.47
		Uknown	2 (2.8)	5 (2.7)	—	—	—

* Only women with known fertility status were included.
† Values are sample size with percentages in parentheses. Some had more than one treatment regimen, and for two cases and eight controls, the specific drug type was unknown.
‡ Adjusted for age, residence, use of oral contraceptives and intrauterine device, menopausal status, previous cancer, familial cancer, hormone replacement therapy, and body mass index.

of diagnosis because the proportion of dead patients per year diminishes through the study period. We did not find any such trends, indicating that selection bias according to death has hardly influenced the risk estimates of ovarian cancer.

How the secularly increasing use of fertility drugs has influenced the results is another important issue. Because of the method of matching, the controls have lived on average 2.5 to 3 years later (calendertime) than the cases. The time of stimulation was not available, but the difference in the average age among treated cases (42.3 years) and among treated controls (46.6) suggests that if the mean age at time of stimulation was alike in the two groups, they had been treated in almost the same years. Furthermore, the mean ages among stimulated women indicate that they were treated in the late seventies and early eighties where the use of fertility drugs was stable (13). Therefore, the risk estimates were hardly biased by the short secular time difference between cases and controls.

Parity

The decreasing risk of ovarian cancer with increasing number of births is in accordance with several other reports (1–5, 14–19). For example, Adami et al. (5) found that each birth reduced the risk of ovarian cancer by 20% ($p_{trend} = 0.0001$).

Infertility

The increased ovarian cancer risk among infertile women has also been demonstrated in several previous epidemiologic studies (1–4, 6–10, 12, 17, 20), with odds ratios ranging from 1.5 to 2.5. Only the case-control study of Franceschi et al. (11) found an insignificantly decreased risk of ovarian cancer among infertile women (OR = 0.8, CI = 0.3 to 2.3).

Because the frequency of nulliparity is higher among infertile than among fertile women, it is important to stratify according to, or adjust for, parity. Otherwise, as a consequence of the increased risk among nulliparous, the risk among infertile women will be overestimated. In accordance with other authors stratifying for parity (2, 3, 6, 20), we found no risk among parous women who temporarily had difficulties in conceiving.

The minor variation in the published risks of ovarian cancer among infertile women may partly be attributed to differences in the definition of infertility. Some authors apply "difficulties in conceiving," whereas other restrict the analysis to physician-diagnosed infertility. In this study, women who did not know whether they had ever had difficulties in conceiving were included as a separate group in the analyses of infertility. This corresponds to studies restricting the analysis to "ever-married" in order to assure a known fertility status (6).

From cohort studies, information about the influence of different types of infertility is available. Rossing et al. (9) found the highest risk among women with ovulatory abnormalities (relative risk [RR] = 3.7) and the lowest risk when the infertility was attributable to male factors, but the figures were small and the differences not significant. Brinton et al. (7) found that hormonal disturbances and male factor infertility was associated with the highest risks (RR of 1.6 and 2.0, respectively) and that secondary infertility implied a higher risk than primary infertility. Ron et al. (8) also demonstrated the highest risk among women with infertility because of a male factor (RR = 6.7), whereas Venn et al. (10) found the highest risk among women with unexplained infertility (RR = 19.2 CI = 2.2 to 165.0). Thus, no consistency exists concerning the risk of ovarian cancer according to different types of infertility.

Infertility Treatment

Studies concerning the risk of ovarian cancer after ovulation induction are sparse and conflicting. Biological studies do not convincingly support the hypothesis that hypergonadotropinemia is a plausible explanation of ovarian cancer and in epidemiologic studies, premature menopause, menopause caused by radiation, and use of exogenous estrogens, which are all associated with alterations in serum gonadotropin, do not influence the risk of ovarian cancer (2, 6, 19, 21–23).

Several circumstances may explain the inconsistency in risk measures concerning the ovarian cancer risk associated with infertility treatment. Use of different reference groups is one explanation. Ideally, the reference group should be infertile women without stimulation, stratified according to parity. Otherwise, adjustment for parity and infertility must be integrated in the statistical analyses.

Whittemore et al. (6) found that infertile women who had been treated with "fertility drugs" had a 2.8 times increased risk of ovarian cancer as compared with women without infertility ($P < 0.01$). The risk was higher among women who did not become pregnant (OR = 27.0, CI 2.3 to 315.6) than among parous women (OR = 1.4, CI = 0.52 to 3.6). The study of Whittemore, however, has been criticized for methodological problems (24) and a low validity of the specific drug exposures (25).

In the study of Franceschi et al. (11) the stimulation implied a nonsignificantly decreased risk of ovarian cancer (OR = 0.73, CI = 0.16 to 3.30). The frequency of infertility was remarkable low both for cases (2.1%) and for controls (2.5%).

Venn et al. (10) found no influence from ovulation induction on the risk of ovarian cancer (RR = 1.45, CI = 0.28 to 7.55).

Rossing et al. (9) found a nonsignificant increased risk of ovarian cancer among women treated with fertility drugs (primarily clomiphene citrate) as compared with infertile without treatment (OR = 2.3, 0.5 to 11.4). Treatment with clomiphene citrate for more than 12 months increased the risk of ovarian cancer 7.2 times (CI = 1.2 to 43.9). If additionally corrected for pregnancies at enrollment, the relative risk increased to 11.1 (CI = 1.5 to 82.3). Stimulation with hCG did not imply any increased risk.

Shushan et al. (12) found in a case-control study no increased risk of invasive ovarian cancer among treated women. However, the odds ratio of borderline tumors among users of fertility drugs was 3.52 (1.23 to 10.09) as compared with nonusers, and in particular treatment with hMG was associated with increased risk (OR = 9.38, CI = 1.66 to 52.08). Use of clomiphene citrate did not influence the risk of ovarian tumors. No stratification according to parity was performed, and adjustment was not made for infertility, which was found not to be significantly associated with the ovarian cancer risk. Because of these circumstances, the figures of Shushan et al. may be overestimated.

The conflicting results between Rossing et al. (9) who found an increased risk of ovarian tumors only after prolonged clomiphene citrate stimulation, and the increased risk after hMG, but not after clomiphene citrate treatment in the study of Shushan et al. (12), could be in concordance, if the length of treatment with ovulation induction agents, rather than the drug per se, constituted the risk. The association between specific treatment regimens and ovarian cancer could also be influenced by the duration of infertility, which has been found to be correlated to the risk of ovarian cancer in some studies (17, 20). We found no significantly increased risk of ovarian cancer with increasing duration of infertility. Because the duration of infertility was equal among treated cases and treated controls, the duration of infertility did not influence the ovarian cancer risk associated with fertility drugs in the present study.

So far, the available epidemiological studies consistently demonstrate that treatment with clomiphene citrate for less than 12 months does not increase the risk of ovarian cancer (treatment with clomiphene citrate for more than 12 months is an unusual regimen today), that treatment with hCG does not influence the risk, and that stimulation with hMG does not imply an increased risk of invasive ovarian cancer. Despite this consistency, new studies have to clarify the impact of the regimens for which no consistent results are available today, for example the risk of borderline tumors after hMG stimulation.

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