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Ovulation induction and risk of endometrial cancer: a pilot study

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Abstract

Objective: To determine whether women with endometrial carcinoma are more likely to have been exposed to fertility drugs, in particular clomiphene, than healthy population controls. *Study design*: A nationwide case-control, pilot study. About 128 living women 35–64 years old, with a histologicaly confirmed diagnosis of endometrial carcinoma that was first diagnosed and reported to The Israel Cancer Registry between 1 January 1989 and 31 December 1992 were enrolled. The controls were 255 women from the same dialing areas selected by random digit dialing. A variety of demographic and clinical parameters were compared between cases and controls. A multivariate logistic model, controlling for age, was used to assess the independent effects of factors found to be significantly associated with endometrial cancer on univariate analysis. *Results*: About 7 women with endometrial carcinoma (5.5%) and 10 healthy controls (3.9%) reported that they had used any fertility drug (crude odds ratio (OR) 1.4; 95% confidence interval (CI) 0.47–4.2). Use of fertility drugs did not meet the criteria for entry into the logistic model. The following parameters were found to be independently associated with endometrial cancer controlling for age, European–American background OR = 2.2, (95% CI 1.3–3.7, $P = 0.004$); nulliparity OR = 2.7 (95% CI 1.1–6.5, $P = 0.03$); history of infertility OR = 1.8 (95% CI 1.0–3.3, $P = 0.05$); BMI $\geq$ 27 OR = 2.3 (95% CI 1.4–3.9, $P = 0.001$). The use of oral contraceptives and IUD were found to be protective, OR = 0.29 and 0.37, respectively, (95% CI 0.14–0.61, $P = 0.001$ and 0.19–0.70, $P = 0.003$, respectively). *Conclusions*: We found no evidence that the use of ovulation induction agents, including clomiphene citrate, are associated with a higher risk of endometrial carcinoma. The association between infertility drugs and endometrial carcinoma should be examined in other, larger studies.

Keywords: Ovulation induction; Clomiphene; Infertility; Endometrial cancer; Case-control study

1. Introduction

Ovulation inducing agents have been widely used since the beginning of the 1960s for all types of infertility. Over the last decade, several series of cases and numerous case reports have discussed the safety of ovulation inducing drugs and the risks associated with their use. Investigators have raised considerable concern about the potential of increased risk of ovarian cancer associated with drugs administered for induction of ovulation [1–4]. One commonly used ovulation inducing agent, clomiphene citrate is pharmacokinetically and structurally very similar to tamoxifen [5], and like tamoxifen it has been shown to stimulate the growth of human endometrial carcinoma (EnCa101) when transplanted into athymic mice [6]. Furthermore, a possible link between tamoxifen treatment and endometrial cancer, ascribed to its estrogenic activity, is well established by many clinical studies [7–11]. However, unlike tamoxifen which is used on a daily basis, for a long period of time in breast cancer patients, clomiphene is prescribed for only a few days during ovulation induction. Nevertheless, in 1987, Ron et al. [12], published a report based on a follow-up of 2575 infertile women, they reported an excess of endometrial but not ovarian cancer. These clinical observations, combined with biological data, such as the increased serum estradiol levels during menstrual cycles of induced ovulation [13] necessitate further exploration of this question. This is especially important in view of the increasing use of modern techniques for assisted reproduction that involve ovulation inducing agents. We performed a preliminary case-control study to determine the extent of exposure of fertility drugs among women with endometrial carcinoma compared to a control group of healthy women. The study methodology

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closely resembles that of a previous case-control study examining the association between ovulation induction and ovarian cancer in Israeli women [1].

2. Material and methods

Cases of endometrial cancer were identified from the Israel Cancer Registry. Since 1982 notification of malignant diseases to this center by physicians and hospitals has been compulsory by law. The Cancer Registry was established in 1960 and maintains data on all malignancies (excluding non-melanoma skin cancer) and some benign tumors (primarily central nervous system) in the country. The Registry receives notification of all malignancies (including carcinoma in situ) from hospital discharge reports, as well as oncology and pathology departments throughout the country. Depending on the cancer site, cancer ascertainment was found to be approximately 95% complete. Cases were eligible for this study if they had a histologically confirmed diagnosis of endometrial carcinoma that was first diagnosed and reported between 1 January 1989 and 31 December 1992, if they were born between 1 January 1929 and 31 December 1957 (fertility drugs were first used in Israel in 1960, therefore, this age group would have had an opportunity for exposure) and if they were alive at the time of interview. Only living cases were used, such that ascertainment of exposure was based on personal interviews exclusively. Controls were obtained by telephoning randomly selected numbers within the same area codes as those of the cases, a method closely resembling that reported by Hartge et al. [14], and were interviewed during the same period as the cases. Thus, cases and controls were matched for geographic area by the sampling procedure. Eligibility for the control group was based on date of birth in the identical range to that of the cases. Once a household was reached, the interviewer asked if a woman born between 1 January 1929 and 31 December 1957 resided there. Women who had undergone hysterectomy were excluded as controls.

2.1. Statistical analysis

The data were analyzed using SPSS for Windows (SPSS Inc., Chicago, IL). The association between case and control status and demographic and clinical parameters was assessed using Chi square for categorical variables and *t*-test for continuos variables. Variables found to have a statistically significant association with endometrial cancer on univariate analysis were entered into a stepwise logistic regression model which controlled for age. The criterion for entry for the model was $P = 0.05$ and for removal from the model was $P = 0.10$. About 95% confidence interval for adjusted odds ratios for the logistic model were calculated using computer Programs for Epidemiological Analysis PEPI version 2.06 (Galinger PM and Abramson JV. Copyright 1993–97, USD Inc., Stone Mountain, Georgia). A sample size of 130 cases and 260 controls had 90% power to detect an odds ratio of 3.0 fertility drug use comparing cases and controls, and 80% power to detect an odds ratio of at least 2.6 based on a presumed rate of exposure of 7% (1) among the control group.

The study protocol was submitted and approved by the institutional review board of Hadassah Medical Organization and the Ministry of Health. For legal reasons, women located via the Cancer Registry could not be contacted directly. Rather, their physicians were contacted and consent to interview the patient was obtained through them. Verbal consent was obtained from both cases and controls.

3. Results

Before or during the study period, 21.6% of women with endometrial cancer reported to the Cancer Registry between the above dates had died. Of the 325 living women who satisfied our case definition, we interviewed 128 (39.1%). The others were not interviewed because of inability to locate the patient or physician (69.3%), illness (5.0%), refusal by the physician (4.0%) or refusal by the patient (21.6%). Cases alive at the time of interview but who were not interviewed for reasons noted above were compared with cases who participated in the study. There were no significant differences in age, area of residence, or histology. The distribution of histologic diagnosis in the study group is as follows: 91 cases (71.0%) had adenocarcinoma, 16 (12.5%) papillary adenocarcinoma, 7 (5.5%) endometrioid carcinoma, 4 (3.1%) had adenosquamous carcinoma, and 8 (6.3%) had uterine sarcoma, one case (0.8%) was carcinoma in situ and one was defined as ''superficial spread''. The mean age of cases was 53.53 ± 6.37 years at diagnosis, as compared to the controls who were 50.49 ± 7.82 years old, at the time of interview. More cases were from a European–American background (45.3 versus 24.7% $P < 0.0001$), and a larger proportion were widowed (20.3 versus 5.9%, $P = 0.0001$) (Table 1). Cases tended to have a history of hypertension (24.8 versus 13.7%), and to be more obese (BMI greater or equal to 27), the study group had a mean BMI of 29.01 whereas the mean BMI was 25.93 in controls ($P = 0.0001$). Family history of endometrial cancer, a history of diabetes, and smoking were not different between the two groups (Table 2). Obstetric and gynecologic characteristics which were significantly different between controls and cases were, a history of infertility (25.8% versus 16.5, $P = 0.05$), nulliparity (14.8 versus 5.1%, $P = 0.005$), with no significant difference found for months of breastfeeding. We found a significant negative association between oral contraceptive use and endometrial carcinoma. A similar negative association was demonstrated for IUD use ($P = 0.00001$ for both). Seven women with endometrial cancer (5.5%) and 10 healthy controls (3.9%) reported that they had used any infertility drug. On univariate analyses the use of any infertility drug was not associated with an

Table 1
Sociodemographic characteristics of cases and controls[a]

	Cases ($n = 128$)	Controls ($n = 255$)	P-value
Mean age (y)[b]	53.53 ± 6.37	50.49 ± 7.82	0.0002
Place of birth			
Israel	35 (27.3)	128 (50.2)	
Asia–Africa	35 (27.3)	64 (25.1)	
Europe–America	58 (45.3)	63 (24.7)	<0.0001
Marital status			
Married	88 (68.8)	205 (80.4)	
Single	8 (6.3)	10 (3.9)	
Widowed	26 (20.3)	15 (5.9)	0.0001
Divorced	6	(4.7)	25 (9.8)
Education (y)			
0–8	37 (28.9)	40 (15.7)	
9–11	20 (15.6)	31 (12.2)	0.01
12	23 (18.0)	61 (23.9)	
>13	48 (37.5)	123 (48.2)	

[a] Values in parentheses are percentages.
[b] At interview for controls at diagnosis for cases.

Table 2
Clinical characteristics of cases and controls[a]

	Cases ($n = 128$)	Controls ($n = 255$)	P-value
Diabetes mellitus			
Yes	9 (7.2)	22 (8.6)	
No	116 (92.8)	233 (91.4)	0.8
History of hypertension			
Yes	31 (24.8)	35 (13.7)	
No	94 (75.2)	220 (86.3)	0.01
Family history of endometrial cancer			
Yes	3 (2.3)	2 (0.8)	
No	125 (97.7)	253 (99.2)	0.34
BMI			
>27	79 (61.7)	91 (36)	0.00001
<27	49 (38.3)	162 (64)	0.0001
BMI (mean)	29.01 ± 6.83	25.93 ± 5.09	
Smoking			
Ever	33 (25.8)	93 (36.5)	
Never	95 (74.2)	162 (63.5)	0.05

[a] Values in parentheses are percentages.

increased risk for endometrial carcinoma (Table 3).Variables found to have statistically significant association with endometrial cancer on univariate analysis were entered into a stepwise logistic regression model which controlled for age. According to the model a European–American background was associated with an increased risk for endometrial cancer (OR = 2.2). Other factors found to be significantly more prevalent in cases were, Obesity (BMI > 27) with an adjusted OR = 2.47; infertility OR = 1.82; and nulliparity OR = 2.58. Use of oral contraceptives and IUD were found

Table 3
Obstetric and gynecologic characteristics of cases and controls[a]

	Cases ($n = 128$)	Controls ($n = 255$)	P-value
Mean age of menarche (y)	13.22 ± 1.46	12.99 ± 1.5	0.17
Parity			
Nulliparous	19 (14.8)	13 (5.1)	0.005
1–3	71 (55.5)	158 (62)	
>4	38 (29.7)	84 (32.9)	
Breast feeding, months[b]	14.68 ± 23.03	11.07 ± 15.66	0.07
Oral contraceptive use			
Yes	14 (10.9)	89 (34.9)	0.00001
No	114 (89.1)	166 (65.1)	
IUD use			
Yes	19 (14.8)	121 (47.5)	0.00001
No	109 (85.2)	134 (52.5)	
Infertility[c]			
Yes	33 (25.8)	42 (16.5)	0.05
No	95 (74.2)	213 (83.5)	
Use of infertility hormones			
Yes	7 (5.5)	10 (3.9)	
No	121 (94.1)	245 (96.1)	0.5
Use of clomiphene citrate			
Yes	4 (3.1)	8 (3.1)	
No	124 (96.9)	247 (96.9)	1.0

[a] Values in parentheses are percentages.
[b] Mean ± S.D.
[c] History of infertility > 12 months of unprotected intercourse.

Table 4
Logistic regression model of variables associated with endometrial cancer[a]

	N	Adjusted OR	95% CI
Region of birth			
Israel; Asia–Africa	183	1	
Europe–America	193	2.2	1.29–3.83
BMI			
Normal (<27)	211	1	
Obese (>27)	165	2.47	1.51–4.06
Diabetes			
No	345	1	
Yes	31	0.48	0.20–1.16
Infertility[b]			
No	301	1	
Yes	75	1.82	0.99–3.32
IUD use			
No	236	1	
Yes	140	0.35	0.19–0.67
Oral contraceptive use			
No	274	1	
Yes	102	0.29	0.14–0.60
Parity			
0	32	2.58	1.08–6.15
1–3	224	1.37	0.77–2.44
4–12	120	1	
Age (years-continuous)		1.01	0.97–1.05

[a] Total number of cases 383; number rejected because of missing data 7 (5 cases, 2 controls); number included in the analysis 376.
[b] History of infertility > 12 months of unprotected intercourse.

to be protective (adjusted OR 0.29 and 0.35, respectively, Table 4).

3.1. Comment

Our study is the first to examine a possible association between infertility treatment, especially clomiphene citrate, and endometrial cancer. A Medline search, revealed only one study which was based on similar assumptions as ours. Rossing et al. [15] performed a case cohort study among 3837 women in their infertility clinic. Their results showed that women who had used clomiphene were less likely than infertile women who had not used this drug to develop breast cancer. The authors have attributed the results to the ''close structural and functional similarity of clomiphene to tamoxifen''.

Our results show no association of any infertility treatment and endometrial carcinoma. However, the interpretation of the results of this study is limited by the small number of women who underwent infertility treatment. Cases exhibited most of the established risk factors for carcinoma of the endometrium including low parity, increased BMI, and a history of infertility [16]. In addition, we have found a protective influence of the use of oral contraceptives and IUD. The effect of combination OC's which reduce risk for subsequent endometrial cancer and ovarian cancer is a well established data [17,18]. The protective effect of IUD use, may be confounded by the fact that in Israel, women are offered IUD only after two deliveries of liveborn, because of the small incidence of PID and subsequent infertility that is associated with IUD insertion.

A history of diabetes mellitus and breastfeeding were not found to be statistically significant in both groups.

Our study had a number of limitations. Firstly, mainly for technical reasons, we were not able to interview the majority of cases who were still alive. This may have introduced considerable bias since non interviewed case, as well as those who had died prior to interview may have differed substantially from interview cases. We had no access to the medical records of subjects, thus we could not verify the information about exposure to fertility drugs that was obtained from the study participants, and under reporting cannot be excluded. Non-response bias is large, 60%, which raises doubts for whether the study group is representative. However, a comparison between cases and those who did not participate in the study shows that the age, area of residency and histology in the two groups were not different. Exclusion of women who had died may limit the reliability of our findings in that a positive association may be relevant only for more severe cases of endometrial cancer, who may have died prior to the interview. Cases are at least 3 years and up to 7 years older than controls at time of interview, which might explain difference in contraceptive history, as well as recall of other exposures.

In conclusion, we did not demonstrate a link between infertility treatments including clomiphene and the risk of endometrial cancer, possibly due to the small number of cases included in this pilot study. Nevertheless, theoretical considerations and clinical observation suggest that this association might exist. Additional, larger studies are needed to further explore this association.

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