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Fertility drugs and endometrial cancer risk: results from an extended follow-up of a large infertility cohort

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STUDY QUESTION: Do fertility drugs influence the subsequent risk of endometrial cancer in a manner that is independent of other risk predictors, such as parity?

SUMMARY ANSWER: In this follow-up of a large cohort of women evaluated for infertility and for whom information was captured on fertility drugs, indications for usage and other risk factors that might influence cancer risk, we found no evidence for a substantial relationship between fertility drug use and endometrial cancer risk.

WHAT IS ALREADY KNOWN: Although the hormonal etiology of endometrial cancer has been well established, it remains unclear whether the use of fertility drugs has an influence on risk. Results regarding the effects of fertility drugs on endometrial cancer risk have been inconsistent, although several studies have shown some evidence for possible increases in risk. The relationship is of particular interest given that clomiphene, a commonly prescribed drug, is a selective estrogen receptor modulator, with chemical properties similar to tamoxifen, another drug linked to an increase in endometrial cancer risk.

STUDY DESIGN, SIZE, DURATION: In a retrospective cohort of 12 193 women evaluated for infertility between 1965 and 1988 at five US sites, follow-up was pursued through 2010 via both passive as well as active (questionnaire) means.

PARTICIPANTS, SETTING, METHODS: Among the 9832 subjects for whom follow-up was allowed and achieved, 259 346 at-risk person-years (i.e. prior to hysterectomy) were accrued, and 118 invasive endometrial cancers identified. Cox regression determined hazard ratios (HRs) and 95% confidence intervals (CIs) for fertility treatments adjusted for endometrial cancer risk factors and causes of infertility.

MAIN RESULTS AND THE ROLE OF CHANCE: Although we observed slight increases in endometrial cancer risk associated with clomiphene (HR = 1.39, 95% CI: 0.96–2.01) and the less commonly prescribed gonadotrophins (1.34, 0.76–2.37), there were no convincing relationships of risk with either cycles of use or cumulative exposures for either drug. A statistically significant risk associated with the use of clomiphene among women who began use at younger ages (<30) (1.93, 1.24–3.00) may have reflected indications for drug usage rather than the effect of the drug itself. Women who received clomiphene followed by gonadotrophins were at a non-significantly elevated risk (1.77, 0.98–3.19).

LIMITATIONS, REASONS FOR CAUTION: Like most studies of endometrial cancer, we were limited by sample sizes, particularly for evaluating subgroup associations. We were also unable to follow all women and were not able to obtain complete risk factor information (including hysterectomy status) for the entire cohort.

WIDER IMPLICATIONS OF THE FINDINGS: Although we found no support for a relationship between fertility drugs and endometrial cancer risk, the association should continue to be monitored given that our study population was still young and had not yet reached the age of peak endometrial cancer incidence.

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Key words: endometrial cancer / risk / infertility / clomiphene citrate / gonadotrophins

Introduction

A number of studies have addressed relationships of fertility drugs with either breast or ovarian cancers, but fewer have evaluated associations with endometrial cancer risk (Brinton *et al.*, 2012). Given that these drugs raise estradiol levels (Sovino *et al.*, 2002), they are clearly of interest with respect to endometrial cancer, which has been shown to be affected by many other hormonal agents and hormonally related risk factors (Cramer, 2012). The relationship is of further interest given that clomiphene citrate, one of the most widely used fertility drugs, is a selective estrogen receptor modulator (SERM) with chemical properties similar to tamoxifen (Sovino *et al.*, 2002), another drug that has been linked with substantial increases in endometrial cancer risk (Varras *et al.*, 2003).

As with both breast and ovarian cancers, the relationship of fertility drugs to endometrial cancer risk is not entirely consistent across investigations. While several cohort studies have shown no association (Potashnik *et al.*, 1999; Venn *et al.*, 1999; Dor *et al.*, 2002; Doyle *et al.*, 2002), these have involved small numbers of exposed cancer cases (<15 cases) and short follow-up times. One previous case–control study that found no association also involved relatively small numbers (Benshushan *et al.*, 2001). Although two other studies involving between 30 and 41 observed endometrial cancers have also not found any association (Lerner-Geva *et al.*, 2012; Brinton *et al.*, 2013b), several other studies that have involved sizable numbers have shown some consistency with respect to the possibility of increases in endometrial cancer being linked to fertility drug use in general (Calderon-Margalit *et al.*, 2009; Jensen *et al.*, 2009) or specifically to clomiphene (Althuis *et al.*, 2005; dos Santos Silva *et al.*, 2009). In several of these studies, further support for an association derived from dose–response relationships with either follow-up times (Althuis *et al.*, 2005) or cumulative dosages of clomiphene (dos Santos Silva *et al.*, 2009; Jensen *et al.*, 2009).

Interpretation of some of these risk elevations has been hindered by the absence of information on indicators for use (i.e. causes of infertility) or correlates of drug use that could independently affect endometrial cancer risk. We therefore undertook additional follow-up of a previously assembled cohort of US infertility patients in whom prior analyses, based on relatively small numbers and limited follow-up, showed a potential relationship of clomiphene use to increased endometrial cancer risk (Althuis *et al.*, 2005).

Materials and Methods

Study subject eligibility

Study subjects comprised women who had sought advice for infertility between 1965 and 1988 at five reproductive endocrinology practices in Boston, MA; Chicago, IL; Detroit, MI; Palo Alto, CA and New York City, NY. These practices were chosen because they retained all records and had evaluated large numbers of infertility patients, many of whom received high doses of fertility drugs. This study was approved by institutional review boards at the National Cancer Institute and the participating institutions.

A total of 12 193 patients met study eligibility criteria, based on having a US address at the first evaluation and having been seen more than once or having been referred by another physician who provided relevant medical information. Patients with either primary or secondary infertility were eligible, but those evaluated for reversal of a tubal ligation were not.

Trained staff abstracted data regarding the infertility workup (all procedures and tests), medications prescribed, menstrual and reproductive histories, and other factors that might affect health. Information on the clinical workup was used to define causes of infertility, as previously described (Brinton *et al.*, 2005).

Follow-up of patients

An initial attempt at follow-up was pursued during 1998–2001 (Althuis *et al.*, 2005). Because of the relatively young age of the patients at that time, a second follow-up attempt was initiated in 2010. Follow-up procedures included searches for deaths and updated addresses through several publically available and proprietary databases (Social Security Administration Death Master File, SSA DMF; MaxCOA, a change of address service; LexisNexis, a legal database service; US Postal Service National Change of Address and the Center for Disease Control National Death Index). Attempts were made to mail a short questionnaire to located subjects who did not expressly indicate that they wanted no further follow-up. This questionnaire focused on the development of cancers and cancer risk factors that might have changed over time (e.g. reproductive and menopause status).

In addition to information on cancers identified through death records and completed questionnaires, we completed linkages against cancer registries in the 14 states in which the majority of patients resided (Arizona, California, Connecticut, Florida, Illinois, Indiana, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Ohio, Pennsylvania and Texas). For the 12.4% of patients who resided outside these states, outcome information was dependent on completed questionnaires, with attempts to validate any self-reports of cancers by requesting records from the patients' treating physicians. Another SSA DMF search was completed at the end of the study to identify new deaths.

After excluding the 1319 patients who requested no additional follow-up, 8 who were enrolled twice, 6 found to be <18 years of age, 1 who requested removal from the study and 1 with a missing date of birth, we were able to obtain information related to death, development of cancer or date last known alive and free of cancer for 10 018 patients—or all but 840 subjects (7.7%) of the remaining 10 865 study subjects. Outcome information through 2010 was available from completed questionnaires or cancer registry linkages through 2010 for 9404 patients, from earlier follow-up efforts for 469 patients and from information 1 or more years after the first infertility evaluation in their original clinic records for 145 patients.

Analytic approaches

Person-years were accrued beginning 1 year after the date of the first infertility evaluation and continuing through the earliest date of cancer occurrence, death, date last known alive and free of cancer, or if vital status depended on cancer registry linkage, a variable ending date, depending on when each registry had complete information (range of 2008–2010). For those subjects who we identified either through clinic records or a completed questionnaire as having a hysterectomy, we further truncated person-years at the time of the surgery.

We excluded from analysis 15 patients with missing information on a cancer diagnosis date, 111 with <1 year of follow-up and 60 with a hysterectomy during the first year of follow-up, leaving 9832 analytic study subjects and 259 346 person-years of follow-up. Person-years reflected the truncation of follow-up for 1362 patients with a hysterectomy 1 or more years after initial follow-up, with 8.4% having a hysterectomy 1–5 years, 13.1% 6–10 years, 17.8% 11–15 years, 22.7% 16–20 years and 38.0% 21 or more years after study entry.

Information on clomiphene and gonadotrophins included age at first use, treatment cycles and total cumulative dosage. Race, gravidity and/or parity at study entry, causes of infertility and BMI at study entry were also defined through clinic records. Other potential confounding factors were obtained

through questionnaire data, supplemented, as appropriate, by information in clinic records. The 1998–2001 questionnaire obtained extensive information on menstrual and reproductive history; use of exogenous hormones; anthropometric factors; cigarette smoking; alcohol consumption and screening for breast and ovarian diseases. The 2010 questionnaire obtained updated information on reproductive behavior, body size, gynecologic operations, use of menopausal hormones and mammographic screening history. Questionnaires were obtained from 6696 patients (68.1% of the analysis subjects); 5462 completed the 1998–2001 questionnaire and 4781 the 2010 questionnaire (3547 completed both).

Statistical analyses

Hazard ratios (HRs) and 95% confidence intervals (CIs) for endometrial cancer associated with fertility treatments, with adjustment for potential confounding factors, were obtained using Cox proportional hazards regression (Cox, 1972) with age as the time metric. Tests for linear trends across cycle and dose categories were calculated using an ordinal variable. We also tested the assumption of proportional hazards for fertility treatments using the Wald test of interaction with the time-scale (continuous).

Results

Among the analytic cohort of 9832 women, the mean age at first evaluation for infertility was 30.1 years. During an average of 26.4 years of follow-up, 118 invasive endometrial cancers were identified among study participants, with a mean age at diagnosis of 51.6 years.

A comparison of demographic information for the 9832 patients who were traced for cancer outcomes versus the remaining eligible patients for whom follow-up information was not available showed similarities with respect to calendar year and age at first clinic visit. A larger proportion of subjects from New York and Boston were excluded from the analysis, largely due to the incompleteness of social security numbers for these patients—which hindered efforts to locate them. Patients excluded from analyses also more often had missing information on race.

A total of 38.2% of the patients had been exposed to clomiphene and 9.7% to gonadotrophins. Users of clomiphene were more likely than non-users to have been evaluated in New York, Boston or Detroit, be white, be gravid (at either entry or follow-up), be users of exogenous hormones and have been diagnosed with either endometriosis or anovulation (Table I). Characteristics of women who had used gonadotrophins were generally similar to those who had used clomiphene, although, when compared with non-users, women who had been prescribed gonadotrophins were also more likely to have been evaluated at older ages, have remained nulliparous through follow-up and to be thinner at age 40.

The identified risk factors for endometrial cancer in this study population (Table II) generally reflected those found in other populations, with high risks noted for Caucasians, those who were nulligravid at either the first clinic visit or at follow-up or remained nulliparous through follow-up, individuals with early ages at menarche and subjects who were obese at either initial clinic visit or at age 40. Users of oral contraceptives were at a somewhat reduced risk. Male factor infertility, unadjusted for other factors (such as parity) and without considering factors associated with partners being evaluated, was a significant risk factor, but other causes of infertility were unrelated to risk.

After adjustment for study site, calendar year and gravidity at the first clinic visit, ever use of clomiphene was related to a non-significantly elevated risk (HR = 1.39, 95% CI: 0.96–2.01) (Table III). Additional adjustment for other endometrial cancer risk factors, including number of births, age at menarche, BMI at age 40 and causes of infertility did not alter this or other fertility drug-related risks. There were no convincing trends of risk with either cumulative dosage or the number of cycles of clomiphene prescribed, but subjects who first received clomiphene prior to the age of 30 years were at a significantly increased risk (HR = 1.93, 95% CI: 1.24–3.00). Among these early users, there was no difference in risk according to the number of cycles of clomiphene prescribed, although those who had received the highest cumulative dosages (≥2251 mg) were at highest risk (2.24, 1.22–4.13).

Ever use of gonadotrophins was also associated with a non-significant elevation in endometrial cancer risk (1.34, 0.76–2.37), without evidence of further increases among those with the most extensive exposures. In contrast to relationships observed for clomiphene, the highest risk was seen among subjects first exposed at older ages (≥35 years), but this risk was not significantly elevated (1.92, 0.82–4.50). All of the women who received gonadotrophins also received clomiphene (presumably as the first-line treatment), and the highest risk was observed for the small group of women who received both clomiphene and gonadotrophins (HR = 1.77, 0.98–3.19 for those receiving both drugs compared with 1.24, 0.83–1.86 for those receiving clomiphene alone).

We were able to obtain medical verification for 97 of the 118 reported invasive endometrial cancers (82.2%), either through cancer registry or medical records. When we restricted analyses to these validated cancers, we saw little change in risk parameters compared with those derived for the total series of patients.

We assessed whether the associations of fertility drugs with endometrial cancer risk were modified by risk predictors and causes of infertility (Table IV). Somewhat higher drug-related risks were observed for the subjects <50 years of age at follow-up as well as those gravid at either initial clinic visit or follow-up, but interactions with these factors were not statistically significant. Drug usage relationships did not appear to be modified by BMI. Although somewhat higher risks associated with use of both clomiphene and gonadotrophins were seen among subjects who were identified as having been diagnosed with either endometriosis or uterine factors, or for clomiphene among those with male factor, these risks were based on small numbers of exposed subjects and none were statistically significant.

Discussion

In this follow-up study of a large cohort of women evaluated for infertility and for whom information was captured on drug exposures, indications for usage and other risk factors that might influence cancer risk, we found no evidence for a substantial relationship between fertility drugs and endometrial cancer risk. This is in contrast to our previous follow-up efforts within this same cohort study, as well as several other investigations, that suggested a potential link between clomiphene exposures and increases in endometrial cancer risk. Although such an association has seemed biologically feasible given that clomiphene is an SERM with chemical properties similar to tamoxifen, another drug extensively linked with increases in endometrial cancer risk, our results suggest that a cautious interpretation of any relationship may be warranted.

In assessing reasons for the discrepancy between our latest findings and those of earlier studies, including our own from a previous follow-up of this cohort (Althuis *et al.*, 2005), the most probable explanation relates to imprecision of prior estimates. Endometrial cancer is a relatively rare

Table I. Comparison of selected demographic and risk factors by use of clomiphene and gonadotrophins.

	Clomiphene				Gonadotrophins			
	Ever (n = 3756)		Never (n = 6076)		Ever (n = 954)		Never (n = 8878)	
	n	Percentage	n	Percentage	n	Percentage	n	Percentage
Study site								
New York and Boston	1376	36.6	1818	29.9	344	36.1	3850	32.1
Chicago	1136	30.2	1731	28.5	404	42.4	2463	27.7
Detroit	901	24.0	1251	20.6	129	13.5	2023	22.8
Palo Alto	343	9.1	1276	21.0	77	8.1	1542	17.4
Race								
White	3076	81.9	4391	72.3	790	82.8	6677	75.2
African–American	97	2.6	348	5.7	10	1.1	435	4.9
Other	171	4.6	361	5.9	65	6.8	467	5.3
Unknown	412	11.0	976	16.1	89	9.3	1299	14.6
Calendar year at the first clinic visit								
<1975	830	22.1	1702	28.0	235	24.6	2297	25.9
1975–1979	1304	34.7	2109	34.7	249	26.1	3164	35.6
1980–1984	1214	32.3	1709	28.1	303	31.8	2620	29.5
1985–1988	408	10.9	556	9.2	167	17.5	797	9.0
Age at the first clinic visit								
<25 years	306	8.2	572	9.4	66	6.9	812	9.2
25–29 years	1502	40.0	2357	38.8	330	34.5	3529	39.8
30–34 years	1383	36.8	2132	35.1	349	36.6	3166	35.7
35–39 years	465	12.4	846	13.9	164	17.2	1147	12.9
≥40 years	100	2.7	169	2.8	45	4.7	224	2.5
Reproductive status at the first clinic visit								
Nulligravid	1501	40.0	2682	44.1	386	40.5	3797	42.8
Gravid	2255	60.0	3394	55.9	568	59.5	5081	57.2
Reproductive status at follow-up								
Nulligravid	521	13.9	859	14.1	159	16.7	1221	13.8
Gravid	2748	73.2	4228	69.6	674	70.6	6302	71.0
Unknown	487	13.0	989	16.3	121	12.7	1355	15.3
Number of births at follow-up								
≥3	418	11.1	589	9.7	103	10.8	904	10.2
2	743	19.8	991	16.3	174	18.2	1560	17.6
1	595	15.8	893	14.7	153	16.0	1335	15.0
0	807	21.5	1265	20.8	252	26.4	1820	20.5
Unknown	1193	31.8	2338	38.5	272	28.5	3259	36.7
Age at menarche								
<12	728	19.4	1193	19.6	166	17.4	1755	19.8
12	1004	26.7	1673	27.5	259	27.2	2418	27.2
13	1143	30.4	1789	29.4	292	30.6	2640	29.7
≥14	797	21.2	1219	20.1	209	21.9	1807	20.4
Unknown	84	2.2	202	3.3	28	2.9	258	2.9
Ever use of oral contraceptives								
No	368	9.8	561	9.2	132	13.8	797	9.0
Yes	2376	63.3	3553	58.5	585	61.3	5344	60.2
Unknown	1012	26.9	1962	32.3	237	24.8	2737	30.8

Continued

Table I. *Continued*

	Clomiphene				Gonadotrophins			
	Ever (n = 3756)		Never (n = 6076)		Ever (n = 954)		Never (n = 8878)	
	n	Percentage	n	Percentage	n	Percentage	n	Percentage
Ever use of menopausal hormones								
No	937	25.0	1134	18.7	250	26.2	1821	20.5
Yes	1091	29.0	1550	25.5	300	31.4	2341	26.4
Unknown	1728	46.0	3392	55.8	404	42.4	4716	53.1
BMI at the first clinic visit (kg/m^2)								
<23.0	1911	50.9	2990	49.2	482	50.5	4419	49.8
23.0–24.9	397	10.6	691	11.4	110	11.5	978	11.0
25.0–29.9	409	10.9	612	10.1	89	9.3	932	10.5
≥30.0	206	5.5	266	4.4	39	4.1	433	4.9
Unknown	833	22.2	1517	25.0	234	24.5	2116	23.8
BMI at age 40 (kg/m^2)								
<23	935	24.9	1293	21.3	271	28.4	1957	22.0
23.0–24.9	446	11.9	646	10.6	129	13.5	963	10.8
25.0–29.9	426	11.3	507	8.3	107	11.2	826	9.3
≥30.0	212	5.7	219	3.6	47	4.9	386	4.4
Unknown	1735	46.2	3411	56.1	400	41.9	4746	53.5
Cause of infertility[a]								
Endometriosis	985	26.2	1218	20.0	270	28.3	1933	21.8
Anovulation	1475	39.3	1283	21.1	402	42.1	2356	26.5
Tubal disease/pelvic adhesions	1236	32.9	2260	37.2	327	34.3	3169	35.7
Male factor	817	21.8	1398	23.0	198	20.8	2017	22.7
Cervical disorder	327	8.7	285	4.7	133	13.9	479	5.4
Uterine disorder	394	10.5	652	10.7	116	12.2	930	10.5

[a]Conditions are not mutually exclusive, i.e. women could be classified as having more than one cause of infertility.

cancer, particularly among younger women, who have been the focus of most prior investigations. In the current analysis, we had 118 study subjects who developed invasive endometrial cancer, compared with much smaller numbers in most previous positive studies—notably 39 in our previous follow-up (Althuis *et al.*, 2005), 44 in a Swedish study that focused only on parous women (Calderon-Margalit *et al.*, 2009), 30 in studies from both the UK (dos Santos Silva *et al.*, 2009) and Israel (Lerner-Geva *et al.*, 2012) and 83 in the largest study, which was undertaken in Denmark (Jensen *et al.*, 2009). In fact, in only one of these studies (Calderon-Margalit *et al.*, 2009) was the overall risk associated with clomiphene usage significantly elevated, with interpretation of these results hindered by the self-reported nature of exposure to fertility drugs and inclusion of only parous women in the investigation.

Although several of the other studies that interpreted their risks as indicative of a positive relationship were based on elevated risks associated with either extended follow-up (Althuis *et al.*, 2005), higher cumulative dosages (dos Santos Silva *et al.*, 2009) or greater number of cycles (Jensen *et al.*, 2009), these risks were based on relatively small numbers of exposed cases, supporting the possibility of chance relationships. Although our overall risk of 39% associated with use of clomiphene was similar to some of the estimates observed elsewhere, we found no evidence of further increases in risk with more extensive exposures, as measured by either number of cycles or cumulative dosage.

The only significant elevation in risk that we observed in our study was for women who began use prior to the age of 30 years, with somewhat higher risks for those who also received high cumulative exposures of clomiphene. Such a subgroup association could reflect the influence of other risk factors that could place such subjects at elevated risks (e.g. higher frequency of severe anovulation), but we could not immediately identify which, if any, factors would underlie the association. Dissimilar to two previous investigations (Althuis *et al.*, 2005; Jensen *et al.*, 2009), we did not find enhanced drug-associated risks among women who were nulligravid at study entry or follow-up. We also did not observe substantial variations according to BMI, a major endometrial cancer risk factor, which has been shown to modify the effects of fertility drugs (Althuis *et al.*, 2005), as well as other hormonal agents (Beral *et al.*, 2005; Trabert *et al.*, 2013). Although we observed some variation in clomiphene risks by different causes of infertility, including endometriosis, uterine diseases and male factor, it became difficult, given the small numbers, to further evaluate interactive effects according to the age at first use. Further monitoring of risks among women being prescribed fertility drugs early in life, however, thus appears warranted.

Table II Relationship of selected demographic and other factors to endometrial cancer risk.

	Endometrial cancer (n = 118)	Non-cases (n = 9714)	HR[a]	95% CI
Race				
White	91	7376	1.00	Referent
African–American	4	441	0.65	0.24–1.81
Other	7	525	1.04	0.48–2.25
Unknown	16	1372	0.83	0.49–1.42
Reproductive status at the first clinic visit				
Gravid	60	5589	1.00	Referent
Nulligravid	58	4125	1.31	0.91–1.88
Reproductive status at follow-up				
Gravid	79	6897	1.00	Referent
Nulligravid	23	1357	1.54	0.53–1.55
Unknown	16	1460	0.90	0.96–2.44
Number of births at follow-up				
≥3	9	998	1.00	Referent
2	16	1718	1.09	0.48–2.48
1	23	1465	1.77	0.82–3.84
0	35	2037	2.08	1.00–4.33
Unknown	35	3496	1.09	0.52–2.26
Age at menarche				
<12	30	1891	1.00	Referent
12	34	2643	0.82	0.50–1.33
13	30	2902	0.66	0.40–1.09
≥14	17	1999	0.51	0.28–0.93
Unknown	7	279	1.68	0.73–3.89
Ever use of oral contraceptives				
No	14	915	1.00	Referent
Yes	67	5862	0.77	0.43–1.37
Unknown	37	2937	0.82	0.44–1.52
Ever use of menopausal hormones				
No	25	2046	1.00	Referent
Yes	36	2605	1.19	0.71–1.99
Unknown	57	5063	0.95	0.59–1.53
BMI at the first clinic visit (quartiles, kg/m^2)				
<23.0	47	4854	1.00	Referent
23.0–24.9	10	1078	0.99	0.50–1.97
25.0–29.9	11	1010	1.15	0.59–2.23
≥30.0	21	451	5.18	3.06–8.75
Unknown	29	2321	1.55	0.92–2.62
BMI at age 40 (quartiles, kg/m^2)				
<23.0	21	2207	1.00	Referent
23.0–24.9	12	1080	1.20	0.59–2.44
25.0–29.9	17	916	2.00	1.05–3.81
≥30.0	11	422	2.90	1.39–6.04
Unknown	57	5089	1.20	0.72–2.00
Cause of infertility[b]				
Endometriosis	22	2181	0.90	0.54–1.49
Anovulation	35	2723	1.15	0.77–1.72
Tubal disease/pelvic adhesions	39	3457	0.98	0.65–1.47

Continued

Table II *Continued*

	Endometrial cancer (n = 118)	Non-cases (n = 9714)	HR[a]	95% CI
Male factor	39	2176	1.63	1.07–2.50
Cervical disorder	7	605	0.87	0.39–1.93
Uterine disorder	10	1036	0.84	0.43–1.65

[a]HRs adjusted for study site and calendar year of the first infertility evaluation.
[b]Risks are relative to women with no evidence of the condition, taking into account the adequacy of the evaluation. Conditions are not mutually exclusive, i.e. women could be classified as having more than one cause of infertility.

Table III Relationship of clomiphene and gonadotrophin use to endometrial cancer risk.

	Endometrial cancer (n = 118)	Non-cases (n = 9714)	HR[a]	95% CI
Never use of clomiphene	66	6010	1.00	Referent
Ever use	52	3704	1.39	0.96–2.01
Dosage (mg)				
1–900	18	1256	1.39	0.82–2.36
901–2250	15	1201	1.26	0.72–2.22
≥2251	19	1247	1.50	0.89–2.52
Cycles				
<6	32	2423	1.31	0.85–2.01
6–11	14	889	1.57	0.88–2.82
≥12	6	392	1.46	0.63–3.39
Age at first use				
<30	30	1599	1.93	1.24–3.00
30–34	10	1316	0.74	0.38–1.45
≥35	11	543	1.72	0.88–3.35
Unknown	1	246	0.44	0.06–3.20
Never use of gonadotrophins	104	8774	1.00	Referent
Ever use	14	940	1.34	0.76–2.37
Dosage (ampoules)[b]				
1–24	4	317	1.19	0.44–3.26
25–64	5	309	1.37	0.55–3.37
≥65	5	314	1.46	0.59–3.62
Cycles				
<6	12	775	1.37	0.75–2.52
≥6	2	165	1.17	0.29–4.79
Age at first use				
<30	3	255	1.09	0.34–3.50
30–34	5	389	1.13	0.46–2.79
≥35	6	283	1.92	0.82–4.50
Unknown	0	13	0.00	0.00–
Combination of clomiphene and gonadotrophins				
Neither	66	5833	1.00	Referent
Clomiphene only	38	2941	1.24	0.83–1.86
Gonadotrophins only	0	177	NC[c]	NC[c]
Both	14	763	1.77	0.98–3.19

[a]HRs adjusted for study site, calendar year of the first clinic visit and reproductive status at the first clinic visit.
[b]One ampoule = 75 IU of gonadotrophins.
[c]NC = not calculable.

Table IV Relationship of clomiphene and gonadotrophin use to endometrial cancer risk according to selected endometrial cancer risk factors.

	Clomiphene (ever versus never)			Gonadotrophins (ever versus never)		
	Exposed cases	HR[a]	95% CI	Exposed cases	HR[a]	95% CI
Age at follow-up						
<50 years	19	1.56	0.82–2.95	5	1.68	0.63–4.44
50–59 years	25	1.36	0.79–2.33	7	1.55	0.69–3.49
≥60 years	8	0.98	0.41–2.34	2	0.94	0.22–4.11
Reproductive status at the first clinic visit						
Nulligravid	23	1.21	0.71–2.07	6	1.24	0.52–2.93
Gravid	29	1.59	0.95–2.67	8	1.47	0.69–3.15
Reproductive status at follow-up						
Nulligravid	8	0.84	0.35–2.01	3	0.89	0.26–3.13
Gravid	38	1.56	0.99–2.45	10	1.43	0.73–2.81
Unknown	6	1.62	0.57–4.58	1	1.45	0.18–11.44
BMI at age 40						
<25	15	1.13	0.57–2.25	3	0.66	0.20–2.18
≥25	14	1.22	0.57–2.63	5	1.64	0.60–4.44
Unknown	23	1.58	0.92–2.72	6	1.70	0.71–4.05
Causes of infertility						
Endometriosis	13	1.79	0.76–4.23	5	2.74	0.96–7.85
Anovulation	17	0.85	0.43–1.69	8	2.00	0.88–4.55
Tubal disease/pelvic adhesions	15	1.14	0.59–2.21	4	0.94	0.32–2.70
Male factor	18	1.55	0.82–2.96	3	0.74	0.22–2.43
Cervical disorder	7	NC[b]	NC[b]	4	3.55	0.75–16.72
Uterine disease	7	3.11	0.79–12.19	2	1.67	0.34–8.09

[a]HRs adjusted for study site, calendar year of the first clinic visit, reproductive status at the first clinic visit.
[b]NC = not calculable.

Given the focus of our investigation on women who had been prescribed fertility drugs mainly in the 1970s and 1980s, the majority of the drug exposure was to clomiphene. We did have a smaller subset of women prescribed gonadotrophins, but all of the cases of endometrial cancer that developed were among women who had been prescribed both clomiphene and gonadotrophins. We therefore could not confirm the increased risk associated with gonadotrophin exposure noted in one previous study, a relationship for which the authors had no ready explanation (Jensen *et al.*, 2009). Given that combination exposure to clomiphene and gonadotrophins is most likely seen among women with resistant infertility, with clomiphene used as an unsuccessful first-line approach, it is probable that any increased risks that we observed were more a reflection of the causes of infertility rather than of the drugs themselves. Further, although the risk among women who sequentially received clomiphene and gonadotrophins was somewhat higher than that among those who received clomiphene alone (1.77 versus 1.24), neither risk was significant and the difference could have reflected the play of chance. However, given that gonadotrophins are increasingly being used in conjunction with IVF and that they have been shown to be associated with greater increases in estradiol levels than clomiphene (Derman and Adashi, 1995), this exposure should continue to be monitored in additional studies. Although a few IVF studies have attempted to evaluate effects on endometrial cancer risk (Venn *et al.*, 1999; Dor *et al.*, 2002; Brinton *et al.*, 2013b), the number of accrued patients was still quite small, reflecting that this is a relatively new procedure and that endometrial cancers generally develop among women later in life.

Our study had a number of strengths, including its large size, documented information on drug exposures and causes of infertility, and reasonably complete information on most endometrial cancer risk factors obtained directly from patients. However, like most studies of endometrial cancer, we were limited by the sample size, particularly for evaluating subgroup associations. Further, given the observational nature of the study, there may have been selection and diagnostic biases affecting our results. We were not able to follow all women, primarily given that we had constraints on contacting some women who did not wish continued study participation. Nonetheless, our loss to follow-up of 7.7% was quite low given the observation time. We also did not have complete information on hysterectomy status for all women as this was derived from completed questionnaires, which were unavailable for 31.9% of our study population. This could have affected our results if there had been substantial differences in exposure prevalences between those for whom we did and did not have access to hysterectomy status, an issue that we unfortunately could not assess. Finally, we were unable to

evaluate associations according to detailed clinical parameters of the tumors, including histology, which has recently been shown to affect other risk factor relationships (Brinton *et al.*, 2013a; Setiawan *et al.*, 2013).

In conclusion, in this follow-up study of women evaluated and treated for infertility, we found no evidence for a substantial relationship of fertility drugs to endometrial cancer risk. Although our results were reassuring in comparison with a few previous studies that have suggested a plausible relationship, further monitoring of this association should be pursued, given that most women in our study were still quite young for developing endometrial cancer.

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Authors' roles

L.A.B., C.L.W., B.S., E.J.L. and K.S.M. were the principal investigators and designed the protocol and oversaw the data collection. S.N. oversaw follow-up activities and data management. B.T. developed the statistical approaches for the data. All authors were involved in the interpretation of the results of the data analyses. L.A.B. wrote the initial draft and all authors took part in the further preparation and finalization of the paper.

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Conflict of interest

None declared.

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