

Effects of cancer on ovarian response in controlled ovarian stimulation for fertility preservation

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Objective: To evaluate the effects of cancer on ovarian response in controlled ovarian hyperstimulation (COH).

Design: Retrospective analysis study.

Setting: University-based tertiary medical center.

Patient(s): 81 cancer patients undergoing controlled ovarian stimulation cycles for fertility preservation, and age- and date-matched controls undergoing COH for in vitro fertilization (IVF) for male factor infertility.

Intervention(s): Controlled ovarian hyperstimulation and oocytes retrieval.

Main Outcome Measure(s): Maximal estradiol levels at day of human chorionic gonadotropin administration, duration of stimulation, total amount of gonadotropins administered, number of dominant follicles, number of oocytes retrieved, and rate of metaphase 2 oocytes.

Result(s): The overall number of dominant follicles and the number of oocytes aspirated of the study group and control were comparable (8.8 ± 5.3 vs. 9.7 ± 4.9 , and 11.93 ± 8.3 vs. 12.3 ± 7.9 , respectively). The total dose of gonadotropins used and number of stimulation days of the study group (2,250 IU [1,800–3,000 IU] and 9.5 [8–11]) were also similar to the controls (2,100 IU [1,700–2,900] and 10 [9–13]). Comparison between four subgroups of cancer—breast cancer, soft tissue sarcoma, hematologic malignancies, and gastrointestinal tract cancers—showed no difference in their ovarian response indexes. Regression analysis to assess the effect of cancer on ovarian response showed no effect on the main outcome measured.

Conclusion(s): Cancer does not influence ovarian response in COH for fertility preservation. (Fertil Steril® 2012;98:957–60. ©2012 by American Society for Reproductive Medicine.)

Key Words: Cancer, controlled ovarian hyperstimulation, fertility preservation, in vitro fertilization, ovarian response

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The advancement of treatment protocols and pharmaceuticals for reproductive-age patients with cancer has shifted our attention to issues previously set aside. Cure and survival are the major issues to consider, but preservation of fertility has also become a goal in treatment. Women diagnosed with cancer have

different options for fertility preservation, but embryo freezing after in vitro fertilization (IVF) seems the best option available today. Concerns over ovarian response in cancer patients during IVF treatment are now being brought up in conjunction with studies of men with cancer who demonstrate reductions in sperm count and

quality even before treatment (1, 2). However, the data regarding this subject with women are conflicting.

Recent studies (3–5) have demonstrated no significant change in ovarian reserve or response to gonadotropins in patients with different cancers who are undergoing IVF treatment. By contrast others (6, 7) have found a worse ovarian response in cancer patients who are undergoing IVF treatment protocols. A recent meta-analysis by Friedler et al. (8) found a reduced number of oocytes in patients with malignancies undergoing controlled ovarian hyperstimulation (COH) for fertility preservation. In their analysis, which included seven

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retrospective case control studies, they were able to demonstrate that women with malignancies should expect a lower number of oocytes to be retrieved after COH for fertility preservation compared with healthy, age-matched patients. Our study investigated the effect of cancer on ovarian response in a large cohort of patients undergoing COH for IVF treatment for fertility preservation.

MATERIALS AND METHODS

We examined the medical records of 81 women who underwent IVF treatments between April 2000 and March 2011 for fertility preservation related to cancer. The data recorded included demography, type of cancer involved, gonadotropin-starting dose, maximal estradiol (E_2) levels, duration of stimulation, total amount of gonadotropins administered, number of dominant follicles, and number of oocytes retrieved. Each case of the study group was matched by age and closest date of stimulation cycle to a patient who underwent IVF treatment for male factor infertility.

The IVF treatment was performed as previously described elsewhere (9). Briefly, we used the short flare-up protocol with triptorelin 100 mg/day down-regulation from day 1 onward and recombinant follicle-stimulating hormone (FSH) from day 3. Human chorionic gonadotropin (hCG) was administered when three follicles above 17 mm in diameter were demonstrated. Transvaginal ultrasound guided oocyte retrieval was performed 36 hours after hCG administration.

Each woman in the study group was compared with her own control in terms of baseline and cycle parameters (age, starting dose of gonadotropins, total amount of gonadotropins administered, and number of stimulation days) and also by ovarian response (maximal E_2 levels on hCG day, number of maximal dominant follicles, and number of oocytes retrieved). The dominant follicle was defined as a follicle sized ≥ 17 mm. Additionally we compared the ovarian response—maximal E_2 levels on the day of human chorionic gonadotropin administration, number of maximal dominant follicles, and number of oocytes retrieved—in four main subgroups of cancers: breast cancer, hematologic cancer, soft tissue sarcoma, and gastrointestinal tract cancer.

A multivariate regression analysis was performed to investigate the association of any type of cancer, breast cancer alone, and age on the ovarian response. Institutional review board approval was not required because of the retrospective nature of our study.

Statistical Analysis

We used a Shapiro-Wilks test to evaluate the distribution of the data. Because the data were not normally distributed, we used a Mann-Whitney U test and Wilcoxon's signed ranks test for bivariate comparison (none paired and paired, respectively) and Kruskal-Wallis for multiple comparisons as appropriate. $P < .05$ was considered statistically significant. Multivariate regression analysis was performed to evaluate the effect of age and type of cancer (breast cancer vs. hematologic cancer vs. soft tissue sarcoma vs. gastrointestinal tract cancer) on ovarian response (total oocyte retrieved).

RESULTS

The mean age of the patients in the study group and the controls were matched (31.8 ± 4.8 vs. 31.7 ± 4.8 years, respectively). The starting gonadotropin dose, total dosage of gonadotropin administered, and number of stimulation days were comparable (Table 1). The number of dominant follicles and number of oocytes retrieved were equal, as was the rate of metaphase 2 (M2) matured oocytes. However, the maximal E_2 levels for the study group ($1,442$ pg/mL [$1,042$ – $2,375$]) were lower than for the control group ($2,274$ pg/mL [$1,204$ – $3,372$], $P = .005$, 95% confidence interval [CI], 180 – 956).

We further subdivided the study group into four subgroups: breast cancer ($n = 42$), soft tissue sarcoma ($n = 11$), hematologic malignancies ($n = 12$), and gastrointestinal tract cancers ($n = 9$) (seven cases of miscellaneous tumor types were excluded) to investigate possible different effects on ovarian response by the various types of cancers. Comparisons among the four subgroups showed no differences in all of the following variables (Table 2): starting daily dose of gonadotropins, total dose of gonadotropins used, number of stimulation days, maximal E_2 levels, number of dominant follicles, and number of oocytes aspirated. Patients with breast and gastrointestinal tract cancers were older (33.1 ± 3.6 and 33.28 ± 4.58) than the patients with hematologic malignancies or soft tissue sarcoma (29.9 ± 5.3 and 27.17 ± 5.9) ($P = .001$), but no statistically significant effect on ovarian response was observed. Multivariate regression analysis to evaluate the effect of age, starting gonadotropin dose, any cancer, and only breast cancer on the ovarian response demonstrated that only age was statistically significantly associated with the number of oocytes retrieved ($P < .0001$) (Table 3).

DISCUSSION

Our aim was to investigate the effect of cancer on ovarian response in COH for fertility preservation patients. We found no difference in starting or total dose of gonadotropins used, number of stimulation days, number of dominant follicles, number of oocytes retrieved, or rate of M2 oocytes obtained between the study group and the healthy matched controls. Additionally, the ovarian response of four subgroups of cancers was comparable.

Previous studies had showed conflicting results (3–7) and were conducted on small series of patients (4–6): $n = 28$ (4), $n = 38$ (5), and $n = 5$ (6). A larger scale study ($n = 41$) recently published substantiated previous reports of no effect on ovarian response in such patients (3). Recently, Friedler et al. (8) demonstrated in a meta-analysis conducted on seven retrospective studies the reduced number of oocytes in patients with malignancies undergoing COH for fertility preservation. In this study, which included seven retrospective case control studies, the investigators were able to demonstrate that women with malignancies should expect a lower number of oocytes retrieved after COH for fertility preservation compared with healthy, age-matched patients. This study is limited by the low total number of cases included ($n = 227$), by including several small studies ($n < 55$ in all seven studies), and by the low quality of the original data (all seven studies

TABLE 1

Comparison of baseline cycle parameters: maximal estradiol (E₂) levels, days of stimulation, mean and total gonadotropins administered, number of dominant follicles, and oocytes collected among the study group and controls.

	Study	Control	P value ^a	95% CI
Age (y) ^b	31.8 ± 4.8	31.7 ± 4.7	.78	NR
Starting daily dose of gonadotropins (IU) ^c	225 (225–300)	225 (200–225)	.13 ^d	NR
Total dose of gonadotropins used (IU) ^c	2,250 (1,800–3,000)	2,100 (1,700–2,900)	.46 ^d	NR
No. of stimulation days ^c	9.5 (8–11)	10 (9–13)	.12 ^d	NR
Maximal E ₂ levels (pg/mL) ^c	1,442 (1,042–2,375)	2,274 (1,204–3,372)	.005	180–956
No. of dominant follicles ^b	8.8 ± 5.3	9.7 ± 4.9	.13	NR
No. of oocytes aspirated ^b	11.93 ± 8.3	12.3 ± 7.9	.74	NR
Rate of M2 oocytes (%) ^b	80.1 ± 0.16	79.8 ± 0.18	.89	NR
Fertilization rate (%)	72.2 ± 27.5	72.0 ± 21.8	.82	NR

Note: CI = confidence interval; E₂ = estradiol; M2 = metaphase 2; NR = not relevant.

^a Mann-Whitney U test.

^b Mean ± standard deviation.

^c Median (lower quartile–upper quartile).

^d Wilcoxon's signed ranks test.

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were retrospective case-control studies). In addition, the known disadvantages of meta-analyses such as publication bias and skewed data may have significantly affected its results.

Of interest is the finding of lower maximal E₂ levels in the study group versus the controls, as described previously elsewhere (5), which also was demonstrated by our study. This finding was attributed to the use of letrozole for ovarian stimulation in the study group (5). However, in our series letrozole was not administered. In view of the similar number of dominant follicles, retrieved oocytes, and mature oocytes as main parameters of the ovarian response, the significance of this finding is interesting. Because the granulosa cells are the main source of E₂, reduced E₂ production may represent an early sign of the possible negative effect of cancer state on granulosa-cell performance. Oktay et al. (10) demonstrated a reduced number of oocytes in patients diagnosed with breast cancer and undergoing fertility preservation. They were able to demonstrate this in patients with the BRCA1 mutation but not BRCA2. The investigators postulated that because DNA repair is defective in BRCA1 mutations, oocyte

DNA lack of repair is the probable cause of the reduced number of oocytes when these patients are stimulated. We unfortunately did not test for the BRCA mutation in our patients. Our results are consistent with those of Das et al. (3) and Knopman et al. (4), who found no effect of cancer on ovarian response measured by similar variables.

Although not statistically different, the upper quartile of FSH dose in the study group (300 IU) was higher than the upper quartile dose of the controls (225 IU). A possible reason for this observation may be the clinical tendency of practicing physicians to achieve a maximal number of oocytes in patients destined to undergo chemotherapy. Additionally, because we froze all embryos in the study group, the concern of ovarian hyperstimulation syndrome was reduced. Due to the retrospective nature of our study, the conclusions may have been biased due to the limited sample and the large individual variations; a possibility of type 2 error must be acknowledged.

Recently, a large multicenter study was published by Domingo et al. (11) found that patients with hormone-

TABLE 2

Comparison of baseline cycle parameters: maximal estradiol (E₂) levels, days of stimulation, mean and total gonadotropins administered, number of dominant follicles, and oocytes collected among the different subgroup of cancers.

	Breast CA	Hematologic malignancies	Soft tissue sarcoma	GI tract malignancies	P value ^a
No. of cases	42	12	11	9	NR
Age (y) ^b	33.1 ± 3.6	29.9 ± 5.3	27.17 ± 5.9	33.28 ± 4.6	.001
Starting daily dose of gonadotropins (IU) ^c	225 (150–300)	225 (150–225)	225 (200–300)	225 (150–300)	.63
Total dose of gonadotropins used (IU) ^c	2,250 (1,800–3,000)	1,800 (1,575–3,150)	2,400 (1,300–3,675)	2,700 (2,025–2,700)	.28
No. of stimulation days (d) ^c	9.5 (8–11)	8 (8–13)	9 (8–11.5)	10.5 (9–12.3)	.58
Maximal E ₂ levels (pg/mL) ^c	1,341 (975–2,175)	1,290 (1,054–2,000)	2,778 (856–3,173)	1,827 (1,178–2,450)	.34
No. of dominant follicles ^b	7.5 ± 3.5	10.72 ± 7.1	11.81 ± 8.4	8.42 ± 4.6	.38
No. of oocytes aspirated ^b	9.8 ± 5.9	12.9 ± 6.5	18.1 ± 13.4	12.42 ± 9.4	.16
Rate of M2 oocytes	0.74 ± 0.22	0.80 ± 0.16	0.80 ± 0.20	0.79 ± 0.11	.96

Note: CA = cancer; E₂ = estradiol; GI = gastrointestinal; M2 = metaphase 2; NR = not relevant.

^a Kruskal-Wallis test.

^b Mean ± standard deviation.

^c Median (lower quartile–upper quartile).

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TABLE 3

Multivariate regression analysis to evaluate the effect of cancer, breast cancer alone, type of cancer, age, and starting gonadotropins dose on total number of oocytes collected.

	Slope	t	P value
Cancer vs. control	3.06	1.09	.28
Breast cancer vs. other cancers vs. controls	2.41	−1.44	.15
Age	−0.54	−3.89	<.0001
Starting gonadotropin dose	0.01	0.51	.61

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dependent tumors had a weaker response compared with control. However, the investigators combined letrozole in all breast cancer patients, which may account for the lower E₂ levels. In their other group of cancer patients without the letrozole addition to the stimulation protocol, the number of oocytes retrieved was similar compared with controls (12.2 ± 6.5 vs. 12.4 ± 5.4 for the study and controls, respectively), as was the total dose of gonadotropins used and number of stimulation days.

When we examined the specific type of cancer and the effect on ovarian function, we found no statistically significant change in the study group and controls. Even patients with hematologic cancers had similar outcomes as controls in terms of ovarian function. This is similar to the conclusions of Das et al. (3), who had a relatively large number of patients with such cancers. Moreover, patients with breast cancer and gastrointestinal tract cancers who were older than the other subgroups still had a comparable ovarian response. The multivariate regression analysis strengthened our results, demonstrating age as the sole statistically significant independent factor effecting the number of oocytes collected.

It is important, however, to mention that although the number of aspirated oocytes was not statistically significantly different among our four groups of cancer patients, clinically the difference could be important. Whereas patients with soft tissue sarcomas had 18.1 ± 13.4 oocytes aspirated, patients with breast cancer had only 9.8 ± 5.9 oocytes aspirated ($P=.16$). This clinically apparent change was statistically insignificant, probably due to the small sample size. However, as previously mentioned, there was a statistically significant difference between the patients' ages in the four subgroups

of cancer. This may have had a major effect on the clinically apparent difference in the number of oocytes retrieved.

We were able to demonstrate, in the largest series of patients treated in the same center for fertility preservation for cancer, that the ovarian response in such patients is similar to that of controls undergoing treatment for male factor infertility. This substantiates the mounting evidence we have presented of no effect of cancer on ovarian response. This is true for all types of cancer (including hematologic cancer), and this information should be reassuring both for the patients and for their treating physicians.

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