Ovarian response to stimulation for fertility preservation in women with malignant disease: a systematic review and meta-analysis

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Objective: To evaluate the current available data regarding ovarian performance of patients diagnosed with malignant disease undergoing controlled ovarian hyperstimulation (COH) for fertility preservation, before radio/chemotherapy, compared with age-matched, healthy patients undergoing COH for in vitro fertilization/intracytoplasmic sperm injection (IVF-ICSI).
Design: Meta-analysis of the data available from a systematic review of the literature.
Setting: Academic centers of infertility and IVF.
Patient(s): Patients with malignant disease, before radio/chemotherapy, undergoing COH for fertility preservation within comparative studies with healthy, age-matched controls.
Intervention(s): None.
Main Outcome Measure(s): Peak estradiol levels on day of human chorionic gonadotropin administration, number of oocytes retrieved, fertilization rate, incidence of low ovarian response, and cycle cancellation.
Result(s): Only seven retrospective, case-controlled studies were found to match our objective. Overall, the results of the meta-analysis indicate that the number of retrieved oocytes rate was statistically significantly lower compared with age-matched healthy IVF patients. The incidence of poor ovarian performance and risk of cycle cancellation as well as the calculated number of two pronuclei zygotes achieved among patients with cancer were comparable with their age-matched controls.
Conclusion(s): Women with malignant disease should expect a lower number of oocytes retrieved after COH for fertility preservation, compared with healthy, age-matched patients. Presently, there is paucity of evidence to assess the effect of a specific malignant disease on ovarian response to COH before IVF for fertility preservation. Multicentric studies should be conducted to resolve these important issues. (Fertil Steril® 2012;97:125–33. ©2012 by American Society for Reproductive Medicine.)
Key Words: Cancer, fertility preservation, fertilization rate, in vitro fertilization, retrieved oocyte numbers

With the increasing patient survival and high infertility rates associated with chemo/radiotherapy (1–3), public and professional attention to future female fertility preservation has risen (4, 5). Candidates for fertility preservation are a rather heterogeneous group with a variety of underlying malignancies, the most common cancers being breast, melanoma, cervical, non-Hodgkin lymphoma, and leukemia (6, 7). These patients are under considerable stress as well as the threat of potential depletion of their ovarian reserve via chemo/radiotherapy damage, so evidence-based consultation is crucial for them to participate in an effective decision-making process.

Fertility may be preserved by variable methodologies, including in vitro fertilization (IVF) and embryo cryopreservation (8), which represent the best-established method; oocyte freezing, with comparable fertilization and embryo developmental rates compared with fresh mature oocytes (9, 10); and cryopreservation of ovarian tissue for later autotransplantation (11–15). In vitro maturation of immature oocytes followed by IVF and embryo freezing are evolving as new additional, experimental options (16, 17).

The number of oocytes retrieved and their quality are imperative factors predicting the potential efficacy of the fertility preservation procedure. Consequently, information regarding the expected ovarian performance after controlled ovarian hyperstimulation (COH) is crucial when consulting with the patient.

The existence of a malignant disease may have a negative effect on reproductive system. In male patients, the literature suggests that malignancy,

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especially testicular cancer and lymphoma, adversely affects fertility by reducing the quality and quantity of sperm (18–23). In female patients, Pal et al. (24) reported an apparent adverse influence of malignant disease on the quality and performance of oocytes. Agarwal et al. (25) discussed a possible adverse association between the neoplasia with an increased metabolic state and hypothalamic dysfunction, causing infertility. Moreover, recently Oktay et al. (26) stated that women with breast and ovarian cancer, carriers of BRCA1 mutation, may respond poorly to ovarian stimulation.

Our review gathers and analyzes the current available data on ovarian performance in patients with malignant diseases who are undergoing COH for fertility preservation before radio/chemotherapy. We conducted a systematic review and meta-analysis of studies comparing the outcomes of these patients with age-matched, healthy patients who undergoing COH for IVF/ICSI in the same IVF centers.

MATERIALS AND METHODS

Literature Review and Analysis

A systematic MEDLINE (PubMed) search was performed that was restricted to papers published in English, using key words such as "fertility preservation," "cancer," "retrieved oocyte number," "fertilization rate," and "in vitro fertilization." We included studies comparing the ovarian response of healthy, age-matched controls with patients with malignancy who were undergoing COH before any chemo/radiotherapy. No randomized controlled trials were found, so the studies included were observational case-controlled studies.

Only 12 out of 59 publications dealing with fertility preservation in cancer patients included comparisons between the cancer patients and their controls. Studies in which no healthy patients (27–31) or natural IVF treatment cycles (32) served as control groups were not included in our analysis. A total of only seven retrospective, case-controlled studies were identified that matched our inclusion criteria.

Statistical Analysis

Quantitative results are represented using their mean and standard deviation (SD); categorical results are represented with their percentages. To compare the results between the study group (the cancer patients) and their controls, we used the following methods: [1] for quantitative data such as mean length of stimulation or mean gonadotropin dose, the *t*-test for independent groups was used; [2] for the categorical data such as the incidence of poor responders, the relative risk was calculated with its *P* value and 95% confidence interval (CI). These statistical tests served us both for comparing the control with the study group in each of the studies that were used for the meta-analysis and also for comparing the weighted pooled effect size for all the studies together. The weighted pooled effect size, either the overall difference in the mean or the overall relative risk, was calculated by combining the results of all the studies, giving each study its appropriate weight. The statistical analysis was performed with S-PLUS 6.1 for Windows Professional Edition (Lucent Technologies) statistical software.

RESULTS

The seven reviewed studies included 218 patients who underwent 227 COH cycles for fertility preservation before radio/chemotherapy for a malignant disease. Their ovarian performance was compared with that of 1,253 healthy, age-matched patients who underwent 1,258 cycles of COH for IVF/intracytoplasmic sperm injection (IVF-ICSI) for male factor or tubal infertility.

In the study groups, the mean age ranged between 31 ± 2.0 years and 36 ± 3.6 years, and 31 ± 4.6 and 36 ± 3.9 years in the control groups. Comparing the mean age of the patients included in the various studies (Table 1), the difference was highly statistically significant ($P<.001$, analysis of variance [ANOVA]). The patients in the study by Oktay et al. (28) were statistically significantly older compared with the other groups with the exception of Robertson et al. (33), which was statistically significantly different from the groups of Knopman et al. (34), Klock et al. (35), and Quintero et al. (36) ($P<.05$).

The underlying malignancy reported in the study groups is included in Table 1. The patients in the seven studies represent a heterogenous group with various malignancies. Among the total group of 218 patients, 124 (56.9%) were diagnosed with breast cancer (no BRCA mutation status reported), 31 (14.2%) with lymphoma or leukemia, 18 (8.2%) with gynecologic cancer, and the other 45 patients (20.7%) had variable underlying diseases, including adenocarcinoma of colon, and lung, Hodgkin, thymoma, multiple myeloma, lymphoma, acute myeloblastic leukemia, Ewing sarcoma, brain, colorectal cancer, osteosarcoma, mesenchymal chondrosarcoma, pseudomyxoma peritonei, focal proliferative glomerulonephritis, systemic autoimmune disease (including multiple sclerosis, systemic sclerosis, and systemic lupus erythematosus). Criteria for exclusion in the various studies included patients with a single ovary (24), stage IV cancer (28), too ill or with elevated follicle-stimulating hormone (FSH >20 mIU/mL) (35), day-3 FSH level ≥12 IU/mL, age >40 years (36), prior diagnosis of infertility or prior fertility preservation attempt (33), or not mentioned (34, 37).

The indications for assisted reproduction treatment (ART) in the control group are presented in Table 1. In summary, 1,106 of the 1,253 age-matched, healthy controls underwent IVF-ICSI for male factor infertility, 90 for tubal factor, and 57 for either male factor or tubal infertility. Comparing the study groups with the controls, the ratio of the total number of patients (218:1,253) and cycles (227:1,258) was 1:5.7 and 1:5.5. Several parameters characterized the ovarian stimulation given to the patients, as discussed in the following sections.

COH Protocol

In four studies (28, 33, 34, 36) used a gonadotropin-releasing hormone (GnRH) antagonist protocol, comprising 159 patients in 165 cycles (representing 73% of the cycles included). Because of concerns over high estrogen exposure in patients with breast cancer, Oktay et al. (28) added an aromatase inhibitor (letrozole) to ovarian stimulation the protocol. The letrozole was stopped on the day of human chorionic gonadotropin (hCG) administration; letrozole was restarted if the

TABLE 1

Patients' age and malignancies, and indication for in vitro fertilization in the controls.

Study	No. of patients		Age (mean ± SD)		Gynecologic cancer						Indication for IVF/ICSI in controls	
	Study (N = 218)	Control (N = 1,53)	Study	Control	Breast cancer	Lymphoma	Leukemia	Ovarian	Uterine	Cervix	Other malignancies[a]	Male factor	Tubal
Pal et al., 1998 (24)	5	12	31 ± 2	32 ± 1						3	2		12
Oktay et al., 2006 (28)	47	56	36 ± 3.6	36 ± 3.9	47								56
Knopman et al., 2009 (34)	28	135	34 ± 5.1	32 ± 5	10	4	1	4	4	1	4	135	
Klock et al., 2010 (35)	28	57	31 ± 5.3	31 ± 4.6	11	4	3	1			9	57-y	y
Quintero et al., 2010 (36)	50	50	32 ± 5	32 ± 5	28	11-x	x				11	50	
Michaan et al., 2010 (37)	22	22	32 ± 8	34 ± 4.2	12		2				8		22
Robertson et al., 2011 (33)	38	921	34 ± 5	35 ± 4	16	3	3	3	1	1	11	921	

[a] Comprises colon, lung, thymoma, multiple myeloma, colon, Ewing sarcoma, brain, osteosarcoma, pseudomyxoma peritonei, and focal proliferative glomerulonephritis.

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estradiol level was >250 pg/mL 3 days after oocyte retrieval and maintained until the level decreased below 50 pg/mL. Quintero et al. (36) also reported the addition of tamoxifen in patients with breast cancer. Michaan et al. (37), used GnRH-agonist in a short protocol in all but six patients with breast cancer who had tamoxifen in addition to gonadotropins. The long midluteal GnRH-agonist protocol was used only in the smallest study, published 12 years ago by Pal et al. (24), similar to the control group. Klock et al. (35) did not specify the treatment protocol (Table 2).

The patients in the control groups were treated by similar COH protocols as the study groups, except in the Oktay et al. study (27), which used the long GnRH-a protocol. In the study by Robertson et al. (33), the large control group of patients undergoing IVF-ICSI for male factor infertility was treated by variable standard long COH protocols. Several of the parameters expressing the ovarian response to COH are analyzed and presented in Tables 2A and 2B.

Total Gonadotropin Dose

The total gonadotropin dose was compared between study and control groups in six studies. The variable outcomes are presented in Table 2A. The weighted pooled effect size was calculated for the six studies and showed a statistically significantly lower mean dose of gonadotropin in the study group compared with the controls: 3,031 ± 1,726 versus 3,387 ± 1,763, $P=.008$ (95% CI, −619.946; −91.942).

Length of Stimulation

Length of stimulation was compared between the study and the control groups in four studies. The variable outcomes are presented in Table 2A. The weighted pooled effect size was examined, and there was no statistically significant difference in the mean length of stimulation for the control versus the study group: 10.9 ± 2.2 versus 10.9 ± 1.9, respectively, $P=.97$ (95% CI, −0.334; 0.322).

Peak Estradiol Level Attained (Day of hCG)

The peak estradiol level on hCG administration day was compared between the study and the control groups in six studies. The variable outcomes are presented in Table 2A. The weighted pooled effect size was calculated for the six studies and showed a statistically significantly lower mean peak estradiol level on the day of hCG administration in the study group compared with the control group: 1,205 ± 960 versus 1,980 ± 1,021, $P=.0001$ (95% CI, −935.26; −615.14). However, Klock et al. (35) intentionally gave a lower starting dose of gonadotropins in the study group, and Oktay et al. (27) used additional letrozole to reduce estradiol levels.

Mean Number of Oocytes Retrieved

The mean number of oocytes retrieved was compared between the study and control groups in all seven studies. The variable outcomes are presented in Table 2B. The weighted pooled effect size calculated for the seven studies showed a statistically significantly lower mean number of oocytes retrieved in the

TABLE 2A

Parameters of patients' ovarian response to controlled ovarian hyperstimulation.

Study	No. of cycles		Total gonadotropin dose (IU) (mean ± SD)		*P* value two-sided 95% CI (LL to UL)	Length of stimulation (d)		*P* value two-sided 95% CI (LL to UL)	E_2 at hCG day (pg/mL)		*P* value two-sided 95% CI (LL to UL)
	Study (N = 227)	Control (N = 1,258)	Study	Control		Study	Control		Study	Control	
Pal et al., 1998 (24)	8	17	2,250 ± 225	2,932 ± 438	.000414 −339.79, −1,024.20				1,491 ± 300	2,101 ± 154	.000000 −424.19, −795.81
Oktay et al., 2006 (28)	53	56	1,317 ± 578	2,382 ± 1,062	.000000 −737.73, −1,392.26	11.7 ± 2.3	12.2 ± 1.5	.179414 0.23, −1.23	483 ± 278	1,464 ± 644	.000000 −790.77, −1,171.23
Knopman et al., 2009 (34)	28	135	3,507 ± 1,012	3,306 ± 1,164	.397072 668.46, −266.46				1,515 ± 712	1,393 ± 769	.440479 433.56, −189.56
Klock et al., 2010 (35)	28	57				10. ± 1.4	9.9 ± 1.0	.706202 0.62, −0.42	1,245 ± 724	2,053 ± 1186	.001386 −322.33, −1,293.67
Quintero et al., 2010 (36)	50	50	4,174 ± 1,276	3,416 ± 1,209	.002950 1,251.32, 264.68	10.5 ± 2.4	9 ± 1.4	.000236 2.28, 0.72			
Michaan et al., 2010 (37)	22	22	2,250 ± 1,541	2,544 ± 921	.446708 478.41, −1,066.41	10.4 ± 4.8			1,963 ± 1,371	1,695 ± 757	.426697 941.83, −405.83
Robertson et al., 2011 (33)	38	921	4,184 ± 1,791	3,487 ± 1,897	.026361 1,311.95, 82.05	11 ± 2	11 ± 2	1.000000 0.65, −0.65	1,456 ± 1,093	2,098 ± 1,037	.000201 −304.41, −979.59
Total			3,031 ± 1,726	3,387 ± 1,763	.008264 −619.95, −91.94	10.9 ± 2.2	10.9 ± 2.0	.971479 −0.33, 0.32	1,205 ± 960	1,980 ± 1,021	.000000 −935.25, −615.14

Note: LL = lower limit; UL = upper limit.

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TABLE 2B

Parameters of patients' ovarian response to controlled ovarian hyperstimulation.

	No. of cycles		Mean no. of retrieved oocytes (mean ± SD)			Mean no. of mature oocytes			Fertilization rate (%)		
Study	Study (N = 227)	Control (N = 1,258)	Study	Control	*P* value two-sided 95% CI (LL to UL)	Study	Control	*P* value two-sided 95% CI (LL to UL)	Study	Control	*P* value two-sided 95% CI (LL to UL)
Pal et al., 1998 (24)	8	17	13 ± 3	13 ± 1	1.000000 1.64, −1.64	8.7	10.5	.003674 −0.65, −2.95	6.6 ± 1.53	10.66 ± 0.82	.000000 −3.09, −5.02
Oktay et al., 2006 (28)	53	56	12.4 ± 7	11.1 ± 5.5	.282020 3.68, −1.08	8.7 ± 4.8	9.7 ± 5.1	.294804 0.88, −2.88	9.17 ± 5.18	8.1 ± 4.05	.230875 2.83, −0.69
Knopman et al., 2009 (34)	28	135	14 ± 9	12 ± 7	.193340 5.02, −1.02				8.8 ± 5.6	13.06 ± 7.1	.006796 −1.21, −7.31
Klock et al., 2010 (35)	28	57	10 ± 6.4	13.9 ± 7.6	.021853 −0.58, −7.22						
Quintero et al., 2010 (36)	50	50	11.5 ± 8.3	13 ± 5.7	.294740 1.32, −4.32	9.6 ± 8.8	9.7 ± 5.4	.945537 2.79, −2.99	8.05 ± 5.81	9.88 ± 4.33	.077222 0.20, −3.86
Michaan et al., 2010 (37)	22	22	8.8 ± 6	8.8 ± 6.6	1.000000 3.84, −3.84				5.4 ± 4.5	5 ± 3.6	.746370 2.88, −2.08
Robertson et al., 2011 (33)	38	921	12 ± 8	14 ± 9	.177998 0.91, −4.91	9 ± 6	11 ± 7	.083074 0.26, −4.26	7.44 ± 4.96	7.7 ± 4.95	.751098 1.35, −1.87
Total			11.7 ± 7.5	13.5 ± 8.4	.002766 −2.97, −0.62	9.0 ± 6.5	10.8 ± 6.7	.002691 −2.94, −0.62	7.98 ± 5.2	8.08 ± 5.1	.810703 −0.87, 0.68

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TABLE 3

Incidence of low responders to controlled ovarian hyperstimulation.

	Study population		Controls	
Study	**Low responders**	**Patients**	**Low responders**	**Patients**
Pal et al., 1998 (24)	0	5	2	12
Oktay et al., 2006 (28)	4	47	1	56
Knopman et al., 2009 (34)	0	28	0	135
Klock et al., 2010 (35)	2	28	0	57
Quintero et al., 2010 (36)	9	50	2	50
Michaan et al., 2010 (37)	2	22	0	22
Robertson et al., 2011 (33)	0	38	71	921
Total	17 (7.79%)	218	74 (5.88%)	1,258
Relative risk	RR = 1.32			
P value	.3000			
95% Confidence interval	0.7873; 2.1772			

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study group compared with the control group: 11.7 ± 7.5 versus 13.5 ± 8.4, *P*=.002 (95% CI, −2.976; −0.621).

Number of Mature Oocytes Retrieved

The outcome of four studies that reported the number of mature oocytes retrieves is presented in Table 2B. The calculated weighted pooled effect size for the four studies shows a statistically significantly lower mean number of mature oocytes were retrieved in the study group compared with the control group: 9.0 ± 6.5 versus 10.8 ± 6.8, *P*=.002 (95% CI, −2.943; −0.619).

Fertilization Rate and the Mean Number of 2PN Zygotes

The outcome of the six studies that reported fertilization rate is presented in Table 2B. The number of two pronuclei (2PN) zygotes out of the number of fertilized oocytes was not reported in the studies, so we calculated this number using the number of oocytes retrieved and the reported fertilization rate. There was no statistically significant difference between the study and the control groups when comparing the weighted pooled effect size of the six studies: 7.9860 ± 5.2775 versus 8.0809 ± 5.1275, *P*=.81 (95% CI, −0.872; 0.682). In the study by Quintero et al. (36), all the outcome parameters we compared were between patients with breast cancer (n = 28) or other malignant diseases (n = 22).

Incidence of Poor Responders

No exact definition of low responder patient was given in the various studies. In the studies by Pal et al. (24) and Knopman et al. (34), no cancellations due to low response were mentioned in either group. In the study by Oktay et al. (27), 4 (8.5%) of 47 cycles initiated in the study group were canceled due to low response compared with 1 (1.8%) of 56 cycles in the control group. In the study by Klock et al. (35), two of 28 study cycles were canceled due to low response compared with none of 57 cycles in the control group (*P*<.01). In the study by Quintero et al. (36), 9 of 50 were poor responders compared with 2 of 50 in the control group (*P*=.05). Cancer was found to be independently associated with poor response (odds ratio = 5.4; 95% CI, 1.02–28.2). In the study by Michaan et al. (37), out of the 22 cycles in the study group, in one patient no oocytes were retrieved, and in one patient only immature oocytes were retrieved. In the study by Robertson et al. (33), none of the 38 patients in the study group were canceled, compared with 71 canceled out of 921 in the control group. This difference was not found to be statistically significant in a multiple regression analysis model.

Examining the data from all seven studies (Table 3), 17 (7.69%) of the total of 221 cycles in the study group were reported as poor responders or canceled, compared with 74 (5.88%) of 1,258 in the control groups. Although the relative risk for all the seven studies, which is the weighted pooled effect size, was 1.32, the difference between the groups was not statistically significant (*P*=.3000; 95% CI, 0.787; 2.172).

Clinical Outcome

The number of cryopreserved oocytes or embryos was not stated systematically by the studies included in this review except in the case reports by Pal et al. (24). Among the 20 patients who underwent thawed embryo transfer—three in Oktay et al. (28), one in Knopman et al. (34), two in Klock et al. (35), three in Michaan et al. (37), and 10 in Robertson et al. (33)—10 deliveries, two ongoing pregnancies, one ectopic pregnancy, and one chemical pregnancy were reported, but the implantation rate was not stated.

DISCUSSION

In consideration of cases of poor ovarian response in young patients treated for fertility preservation, we decided to review the current literature regarding the expected ovarian response to COH in patients with cancer. Both the specific disease of the patient and her multisystemic condition may have a great impact on her response to ovarian stimulation. The increased catabolic state, malnutrition, and increased stress hormone levels associated with malignant disease may effect the hypothalamic-gonadal axis and decrease fertility (38, 39). Our literature review found repeated expression of concern regarding a possible adverse association between the

existence of a neoplastic process and ovarian reserve and oocyte quality (24–26). Nevertheless, because of the limited number of IVF treatments available for cancer patients, the effect of cancer on the ovarian response to COH before IVF for fertility preservation has lacked consensus. Recently, Oktay et al. (26) reported an association between BRCA1 mutations and poor ovarian response to COH in cancer patients, which indicates a possible role of BRCA1 as an important factor responsible for the impairment in double-strand DNA break repair and women's infertility.

We noted that the patients included in the seven studies represent a heterogeneous group with various malignancies, of which breast cancer was the most prevalent (56.9%). However, their BRCA mutation carrier state was not reported. Most reports also included patients with malignancies or systemic diseases other than breast cancer (e.g., lymphoma and leukemia). This might reflect the incidence of these diseases among women of reproductive age, but also may represent the practice of the referring oncologists who deferred oncologic treatment to allow fertility preservation. Robertson et al. (33) did not find difference in the ovarian response of patients with local disease (n = 23) compared with those with systemic disease (n = 15). However, as the ovarian response of the patients in the various study groups was not stratified according to their specific disease or their clinical state, no conclusions can be drawn regarding this issue.

The current database does not allow a systematic analysis according the Cochrane guidelines due to the great variability between the studies available. The mean age of the patients included was statistically significantly different among the various studies, although their ovarian response to COH was compared with age-matched controls. The importance of the issue led us to perform a meta-analysis on the basis of these age-controlled comparative studies.

Regarding parameters of the ovarian stimulation given the patients, the choice of the specific COH protocol was probably determined based upon the policy of preferences in each IVF center, influenced by the time available until the initiation of chemotherapy. Although variable COH protocols were used, with various gonadotropins, 73% of the cycles included were treated with a GnRH-antagonist based protocol (the shortest term), which likely allowed the shortest deferral of the initiation of radio/chemotherapy. We found no studies comparing agonist and antagonist protocols in women with cancer.

Calculating the length of deferral of the chemo/radiotherapy needed to allow fertility preservation, one should take into consideration the number of days needed until menstruation followed by 9 to 14 days required for COH (especially using the GnRH antagonist protocol), followed by a few days of convalescence after oocyte pickup. This should range approximately between 11 and 40 days. In some patients, the need for immediate intervention precludes routine COH. In these cases, the new methodology of oocyte in vitro maturation offers the possibility of oocyte retrieval during the early follicular or luteal phase, with preservation of the embryos achieved using ICSI (40). However, presently the oocyte yield of such interventions is substantially inferior to that of routine COH.

The length of stimulation was comparable between the study and control groups, but the patients with malignancy received a statistically significantly lower gonadotropin dose. In most cases this apparently was done intentionally to limit the estradiol levels by using an estrogen antagonist (tamoxifen) or aromatase inhibitor (letrozole) as adjuvant agents for COH (27, 35). Indeed, the mean peak estradiol levels on the hCG administration day in the study groups were lower compared with the controls. It is notable that no cases of ovarian hyperstimulation syndrome were reported among the COH cycles performed for fertility preservation.

Regarding the main outcome parameter of this study, the mean number of oocytes and mature oocytes was statistically significantly lower in the study group compared with the control group. This may be explained by the background disease or the milder stimulation protocol administered to patients with malignancy. The relative risk of poor response leading to cycle cancellation was higher in the study than the control group although the observed difference did not reach statistical significance, possibly due to the size of the groups.

The patients referred for fertility preservation due to a malignant disease do not represent the typical population of subfertile patients treated in the IVF units. They undergo usually one single COH cycle before starting their oncologic treatment. Regarding the future fertility potential of these patients, the exact number of two-pronuclei zygotes cryopreserved was not systematically reported in all studies. As most of the cases are included in publications from the last 2 years, only a minority of the patients underwent thawing and embryo transfer, and there is not enough reported consistent data to evaluate the implantation rate of these embryos after thawing. These issues should be appropriately addressed in the future to enable prediction of the number of oocytes/embryos needed to be preserved to offer a realistic chance for later reproduction in these patients.

In addition, the evolving technology of cryopreservation has a dominant effect upon the survival rate of the cryopreserved oocytes, embryos, or ovarian tissue. Oocyte cryopreservation methodology has improved greatly due to the introduction of vitrification (41).

In conclusion, candidates for fertility preservation due malignancy should be informed that the expected number of oocytes retrieved after COH is lower compared with healthy patients of similar age. It is interesting that a recent study comparing the outcome of in vitro maturation in women with malignancy to age-matched controls (42) found that women with breast cancer have fewer numbers of retrieved oocytes than infertile controls. Ovarian reserve and oocyte maturity in other types of malignancy were similar to those in the control group. After completion of that meta-analysis, another report from the same McGill University group (43) compared the pretreatment ovarian reserve and ovarian response to COH of 39 patients with variable malignancies with 48 age-matched controls. Their report was in line with our recommendations; the patients' pretreatment ovarian reserve was assessed, a similar COH protocol was used for the controls, and the outcomes were reported according to groups of malignancies (including hematologic, gynecologic, gastrointestinal, brain, and bone cancer, each group

including a small number of patients). However, lacking the individual data and with the results given according to the variable groups, we could not incorporate their results in our study. They found no evidence that ovarian reserve or response to COH was affected by the underlying malignancy in these small groups of patients. Breast cancer patients were not represented in their study.

Presently, there is a paucity of information regarding the total number and quality of retrieved oocytes in patients with a malignant disease after COH, before chemo/radiotherapy, stratified for the various malignancies and COH protocols used. To overcome the limitations of the small number of patients, we suggest that multicentric studies should be conducted to define the expected number, quality, and fertilization rates of oocytes in patients with a specific malignant disease; this would enable a realistic, more accurate consultation for these patients who wish to preserve their fertility potential.

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