Fertility preservation for female cancer patients: early clinical experience

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Objective: To characterize the early experience of a clinical program designed to provide strategies for fertility preservation to female cancer patients about to undergo chemotherapy or radiation therapy.
Design: Retrospective chart review; case–control study.
Setting: Academic medical center.
Patient(s): Sixty-five female cancer patients and 57 age-matched infertility patients.
Intervention: Enrollment in a program for fertility preservation.
Main Outcome Measure(s): Choice of active participation, fertility preservation option selection, clinical outcomes of patients undergoing oocyte retrieval, attitudes regarding embryo disposition.
Result(s): Of 65 patients referred to the program, 18 declined to undergo embryo, oocyte, or tissue cryopreservation. Six were found not to be eligible for medical reasons. Of the remaining 41 patients, 35 chose to cryopreserve embryos, four chose to cryopreserve oocytes, and two chose to undergo ovarian tissue freezing. Fewer oocytes were recovered from the embryo cryopreservation group when compared with an age-matched control group, but the mean number of zygotes generated was similar. Attitudes regarding embryo disposition were different between the two groups. No serious clinical sequelae resulted from participation.
Conclusion(s): Fertility preservation techniques employing available technology may provide safe and practical options to female cancer patients facing chemotherapy or radiation therapy. A significant number of otherwise appropriate participants decline active management. Cancer patients display different attitudes regarding embryo disposition when compared with infertility patients without cancer. (Fertil Steril® 2009;■:■–■. ©2009 by American Society for Reproductive Medicine.)

Key Words: Cancer treatment, fertility preservation, embryo disposition

Interest in the provision of fertility preservation options to female cancer patients has increased dramatically in recent years (1). Survival rates for women of reproductive age with cancer are steadily improving (2), and many young women with cancer have reported that fertility issues are an area of major concern to them (3). The Ethics Committee of the American Society for Reproductive Medicine and the American Society of Clinical Oncology have both recently issued position articles on this topic (4, 5).

Several strategies for fertility preservation are available to women with cancer (6). They include cryopreservation of embryos, oocytes, or ovarian tissue, as well as various medical or surgical approaches for reducing the impact of chemotherapy or radiation therapy upon the ovary.

In 2005, our unit initiated a program to systematically provide female cancer patients access to appropriate counseling and a full range of fertility preservation options. An initial consultation with a reproductive endocrinologist was promptly arranged following a referral from the patient's oncologist. This meeting provided an opportunity to assess: [1] the risk to ovarian function posed by the proposed therapy, [2] the patient's social situation and desire for fertility preservation, [3] the patient's overall medical condition, and [4] the time available before the initiation of therapy. Basic ovarian reserve testing and appropriate psychologic counseling were also immediately arranged. At the time of the first visit patients were informed about available strategies for fertility preservation in the context of their specific circumstances. These included embryo cryopreservation, oocyte cryopreservation, or ovarian tissue freezing following an elective laparoscopic unilateral oophorectomy. Tissue freezing is performed under the aegis of an institutional review board (IRB) approved protocol. A minimum of 80% of the tissue is set aside for future use by the patient, whereas no more than 20% is made available for scientific investigation.

Several questions presented themselves during the initial phase of our program: [1] how would the various cancer diagnoses be distributed and how would a patient's particular diagnosis impact her fertility preservation efforts? [2] How much flexibility could we expect from referring physicians with respect to the delay in cancer treatment required to carry out a proposed oocyte retrieval? [3] How would the patients choose among their clinical options? [4] Do patients with cancer respond differently than infertility patients to

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injectable gonadotropins? [5] What differences might we observe between cancer patients and infertility patients employing embryo cryopreservation with respect to clinical outcomes and decision-making bearing on embryo disposition?

Few data are currently available that shed light on these questions, although two recent reports regarding cancer patients' response to gonadotropins are reassuring (7, 8). A third report (8) provided additional evidence that breast cancer patients respond appropriately to controlled ovarian hyperstimulation, but also revealed that many women in this group were reluctant to undergo an oocyte retrieval, presumably because of concerns about the potential impact of the medical therapy upon their disease or because of required delays in treatment. Consequently, we thought it would be of value to explore these issues in a systematic way, and in particular, we thought that this type of information would ultimately enable us to provide cancer patients with more informed and accurate counseling. To this end we collected data on the first 65 patients who participated in our program. The subset of patients who underwent embryo cryopreservation were compared with an appropriate comparison group of healthy first-time in vitro fertilization (IVF) patients to explore possible differences in a number of specific outcome variables.

MATERIALS AND METHODS

Subjects

The initial study population was comprised of 65 women with cancer who were referred to the fertility preservation program. We then compared the subset of these patients who subsequently elected to cryopreserve embryos and did not have a history of prior chemotherapy (n = 28) with an age-matched sample of women undergoing their first cycle of IVF with a diagnosis of either tubal factor or male factor infertility (n = 57).

Procedures

Subjects in the initial study population were identified by chart review. An age-matched comparison group was subsequently selected from our IVF patient database. The following information was retrieved from the patients' medical records: medical history, infertility diagnosis (control subjects only), cancer diagnosis and previous cancer treatment (if any), ovulation induction medication dosage, and duration and the following IVF outcome measures: peak serum estradiol (E_2) concentration, number of mature oocytes retrieved, and the number of zygotes created for cryopreservation. The study was approved by the IRB of Northwestern University.

Analyses

The data were entered into an SPSS data file and *t* tests and chi-square analyses were employed to compare variables between the two groups. A value of $P<.05$ was considered to be significant.

RESULTS

A total of 65 women were referred to our program between January 2005 and April 2008 (Fig. 1). Of these, 26 had been diagnosed with breast cancer, 13 with lymphoma, 7 with leukemia, 2 with ovarian cancer, and 17 with other types of cancer including brain, endometrial, and colorectal cancer. Both of the patients with ovarian cancer had epithelial tumors. One patient with thalessemia was also referred to us. Six women (9.2%) were considered not to be candidates for oocyte retrieval either because of an elevated FSH (>20 mIU/mL) level or because they were too ill. Three of these women had breast cancer, one had brain cancer, and two had lymphoma; their mean age was 34 years; four were single, two were married, and all were nulliparous. Four (6.2%) patients ultimately underwent oocyte retrieval but choose to freeze oocytes instead of embryos. Three of these women had breast cancer and one had thalessemia; their mean age was 27 years; all were single and nulliparous. Two (3.1%) women elected to have ovarian tissue frozen. Both of these women had breast cancer with a mean age of 34 years. One was married, one was single, and both were nulliparous. Fertility preservation choices as a function of cancer diagnosis are summarized in Table 1.

Of the remainder, 53 (81.5%) were judged to be appropriate candidates for embryo cryopreservation. Thirty-five proceeded with this option, but 18 (30.5%) women declined because of concerns about delaying cancer treatment, logistic constraints, psychologic stress, or concerns about long-term risks. Of these, 10 had breast cancer, 4 lymphoma, 1 leukemia, 1 ovarian, and 2 other types of cancer. Their mean age was 34 years (range = 26–43), 8 (44%) were married or engaged, 10 (55%) were single, and 17 (94%) were nulliparous.

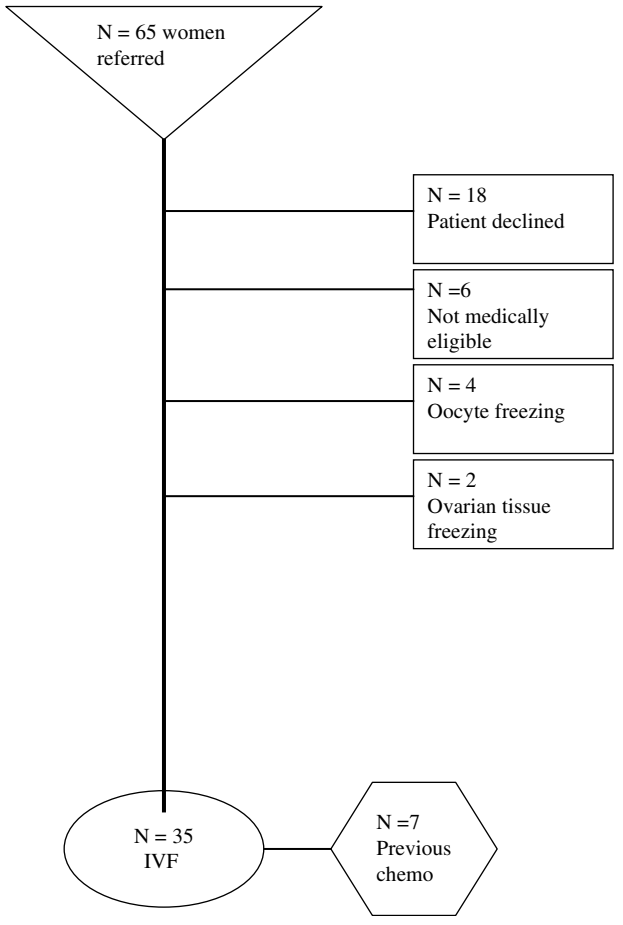
Of the 35 women who opted for embryo cryopreservation, 12 had breast cancer, 7 had lymphoma, and 5 had leukemia, 1 had ovarian cancer, and 10 were diagnosed with other types of cancer. Within the same group of 35, 7 (19.4%) had previous chemotherapy (1 breast cancer, 2 leukemia, 3 lymphoma, and 1 other cancer), and 13 (37.1%) had had previous surgery but none had had previous radiation therapy. The demographic characteristics of the 35 cancer patients and the 57 comparison subjects are displayed in Table 2.

Embryo Cryopreservation Outcomes

We examined the outcomes of the IVF cycles of the 35 cancer patients choosing to cryopreserve embryos compared with those of an age-matched sample of 57 women who were undergoing their first IVF cycle. Seven of the 35 cancer patients had undergone prior chemotherapy and were assessed separately, leaving a final cohort of 28 women with cancer undergoing a cycle of IVF for embryo creation and freezing. Of these 28 patients, 11 had breast cancer, 4 had lymphoma, 3 had leukemia, 1 had ovarian cancer, and 9 had other types of cancer. Women with breast cancer frequently expressed their concerns about additional exposure to reproductive hormones during IVF but were not significantly more likely to

FIGURE 1

Patient flow-through program.



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decline IVF treatment than patients with other cancer diagnoses.

All the women and their husbands/partners underwent the program's routine IVF registration process, which included a 2-hour nursing education session, a 1-hour consultation with a psychologist, and a 40-minute consultation with their physician. Women without male partners were counseled regarding the option of employing sperm from an anonymous donor. Women with partners to whom they were not married were required to have a legal consultation and contracts written specifying the role of the sperm provider and the status of the embryos in the event of an end of the relationship, death, or unforeseen circumstances.

Patients in our IVF program are assigned initial dosages of injectable gonadotropins based on their anticipated responses. Patients who are viewed as likely to be sensitive to the medication ("high" responders) were started on 150 IU of FSH/day. Patients expected to be "low" responders were started on a minimum of 225 IU of FSH twice daily. "Normal" responders were begun on 225 IU/day. Women with cancer were more likely than control women to be assigned the "high responder" protocol, and therefore had lower initial dosages of hormonal stimulation (low = 1 cancer, 12 comparison; normal = 17 cancer, 44 comparison, high = 14 cancer, 1 comparison; $\chi^2 = 3.06$, $P<.001$). This largely reflected our desire, particularly in the early days of our program, to minimize the chances of ovarian hyperstimulation syndrome (OHSS) in the cancer patients, given the likelihood that this would result in a delay in the initiation of their cancer treatment. With respect to IVF outcome, the cancer group had significantly more women whose cycles were cancelled compared with the noncancer group, 7.1% (2/28) versus 0 ($\chi^2 = 8.54$, $P<.01$). Finally, 2 of the women with cancer who had initially expressed their intention to undergo embryo cryopreservation and had completed the registration process never began treatment. No information was subsequently obtained regarding why.

The results of the IVF cycles are provided in Table 3. As can be seen from the data, the only two significant differences between groups were peak E_2 ($X_{CANCER} = 1245$, $X_{COMP} = 2053$, $P<.002$) and number of oocytes retrieved ($X_{CANCER} = 10.0$, $X_{COMP} = 13.9$, $P<.02$). The total number of normal appearing (2pn) zygotes created did not significantly differ between groups, with an average of 6.62 for the cancer patients and 8.25 for the comparison women. Fifty-seven percent of the

TABLE 1

Cancer patients' (n = 65) choices regarding fertility preservation.

	Declined	Not eligible	Embryo cryo	Oocyte cryo	Ovarian tissue cryo
Type of cancer					
Breast (n = 26)	10 (38%)	2 (8%)	12 (46%)	2 (8%)	0
Lymphoma (n = 13)	4 (31%)	1 (8%)	7 (54%)	0	1 (8%)
Leukemia (n = 7)	1 (14%)	1 (14%)	5 (71%)	0	0
Ovarian (n = 2)	1 (50%)	0	1 (50%)	0	0
Other (n = 17)	2 (12%)	2 (12%)	10 (58%)	2 (12%)	1 (5%)
Total	18 (27%)	6 (9%)	35 (54%)	4 (6%)	2 (3%)

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TABLE 2

Demographic characteristics of the cancer and comparison groups.

Variable	Cancer (n = 35)	Comparison (n = 57)	*P*
	Mean (SD)	Mean (SD)	
Age	31.0 y (5.3 y)	31.2 y (4.6 y)	ns
Gravidity	0.5 (0.7)	0.5 (0.8)	ns
	n (%)	n (%)	
Parity			
No children	29 (83%)	54 (95%)	ns
1 child	5 (14%)	3 (5%)	
2 children	1 (3 %)	0	
Ethnicity			ns
Caucasian	30 (86%)	47 (82%)	
African American	1 (3%)	5 (9%)	
Asian	2 (6%)	4 (7%)	
Hispanic	2 (6%)	1 (2%)	
Marital status			<.000
Single	13 (37%)	0	
Married	16 (46%)	57 (100%)	
Partnered	6 (17%)	0	
Tobacco use			ns
Current smoker	3 (9%)	13 (23%)	
Nonsmoker	26 (74%)	41 (72%)	
No information	6 (17%)	3 (5%)	
History of depression			<.02
Yes	6 (17%)	4 (7%)	
No	26 (74%)	53 (93%)	
No information	3 (9%)	0	
Antidepressant use			<.006
Yes	5 (14%)	2 (4%)	
No	27 (77%)	55 (96%)	
No information	3 (9%)	0	

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cancer patients' eggs underwent intracytoplasmic sperm injection compared with 63% of the comparison group (NS).

We were also interested in the women's stated preference for the disposition of any unused embryos. As is routine in most IVF programs, couples are asked what their preferences are for the disposition of unused embryos, with options of disposal, donation to research, donation to an infertile couple, or decision left to surviving partner. In this study, women and couples were asked two questions on the consent form pertaining to their unused frozen embryos. The first question was in reference to the patient's wishes in the event she had died, the second if for unforeseen circumstances she could not be contacted. Embryo disposition preferences are given in Tables 4A and 4B. As can be seen from the data, many fewer women with cancer designated their embryos for disposal compared with the comparison group women.

Finally, two patients who underwent embryo cryopreservation have returned for embryo transfer and both have ongoing pregnancies. One had been treated for breast cancer and one had undergone a bone marrow transplant for the treatment of myelofibrosis.

DISCUSSION

Most of the patients (60%) referred to our program had either breast cancer or lymphoma. Seven patients (11%) had leukemia. The other sites of disease were varied with no more than two in any category. Although to some extent this distribution reflects the incidence of these diseases in women of reproductive age, other factors may also play a role. For example, no patients with lung cancer or melanoma were referred to us. It may be that patients with either disease who were advised to undergo chemotherapy had prognoses that disinclined their physicians to refer them for fertility preservation. At our center physicians referring patients with either breast cancer, lymphoma, or gastrointestinal cancers were uniformly comfortable with the 2- to 3-week delay in

TABLE 3

Selected IVF outcome measures between groups.

	Group	n	Mean	SD
Day 3 FSH (mIU/ml)	Cancer	8	4.71	2.06
	Comparison	19	5.79	1.70
Days stim	Cancer	26	10.17	1.46
	Comparison	56	9.95	1.08
Peak E_2[a] (pg/ml)	Cancer	26	1245.84	724.17
	Comparison	57	2053.58	1186.25
Oocytes ret[b]	Cancer	26	10.00	6.43
	Comparison	57	13.93	7.62
Zygotes	Cancer	26	6.62	4.10
	Comparison	57	8.25	5.29
Cancellation rate[c]	Cancer	7.1%		
	Comparison	0%		

[a] $P<.002$.
[b] $P<.02$.
[c] $P<.01$.

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initiating chemotherapy required to allow for an oocyte harvest. Furthermore, these patients were generally in otherwise good health, making them good candidates for such an approach.

Thirty-five of 41 (85%) patients who selected an active strategy for fertility preservation chose to cryopreserve embryos. This clearly reflected the fact that: [1] most of them had partners, [2] most of them did not have short term treatment-related time constraints, and [3] embryo cryopreservation is a mature technology with well-defined, and encouraging, pregnancy rates. We expect that as the techniques for oocyte preservation mature and are better characterized, more patients will choose this approach or choose a combination of embryo and oocyte cryopreservation. Only four of the patients we saw elected to cryopreserve ovarian tissue. In three cases time constraints played a role, and in the fourth case the patient chose this option only after an unsuccessful attempt at embryo cryopreservation. Several other aspects of the tissue cryopreservation approach offered by our program may dissuade patients from selecting it. Notwithstanding the fact that this option is only offered to patients thought to have a very high likelihood of losing all ovarian function in the short term, the prospect of having ovarian tissue surgically removed may be viewed negatively by some, particularly given that a portion of the tissue is earmarked for scientific study. Furthermore, as suggested by Meirow (10), unilateral oophorectomy may, in turn, be viewed more negatively than approaches that entail limited tissue removal. The high cost to the patient for the procedure in our program is certainly another significant factor.

Despite the fact that the cancer patients undergoing oocyte retrieval were generally started on lower doses of injectable gonadotropins to minimize the risk of OHSS, the number of zygotes available for cryopreservation on day 1 after fertilization were similar to that of age-matched controls, although the women in the control group were more likely to have recently smoked cigarettes. Seven patients who had undergone prior chemotherapy, but were noted to have normal day 3 FSH levels, had variable outcomes. Two of the patients did not respond well to the medication and their cycles were

TABLE 4A

Women's preferences regarding embryo disposition in the event of their death.[a]

	Disposition choice				
Group	Partner's choice	Research	Dispose	Donate couple	No info
Cancer	16 (57%)	5 (18%)	0	2 (7%)	5 (18%)
Comparison	34 (59%)	5 (9%)	8 (14%)	7 (12%)	3 (5%)

[a] $P<.06$.

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TABLE 4B

Women's preferences regarding embryo disposition in the event of unforeseen circumstances.[a]

Group	Disposition choice			
	Research	Dispose	Donate couple	No info
Cancer	11 (39%)	1 (3%)	12 (43%)	4 (14%)
Comparison	10 (17%)	18 (31%)	26 (46%)	3 (5%)

[a] $P<.007$.

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cancelled. The other five stored between 3 and 11 zygotes (mean 6.4). On the other hand, two of the 28 cancer patients in the final study group were cancelled because of inadequate response to gonadotropins, despite not having had prior chemotherapy. This cancellation rate was significantly higher than that of the control group. Finally, the cancer patients had a significantly lower number of recovered oocytes than the control group. It is not clear whether these differences reflect a true biologic difference between the groups, a consequence of the difference in average gonadotropin dosage, or both. None of the cancer patients who underwent oocyte retrieval developed OHSS. The only patient who had a significant complication was a leukemia patient who had an episode of intraabdominal bleeding after her procedure. Her platelet count was normal before the procedure, and our impression was that her bleeding was unrelated to her underlying disease. She was admitted to the hospital for observation but did not require operative intervention.

One of the main constraints facing cancer patients considering active strategies for fertility preservation is cost. Roughly half of the cancer patients had insurance coverage for infertility treatment. In each case we requested authorization for the proposed procedures with full disclosure of the fact that they were to be performed for fertility preservation. Thus far, essentially all of our requests have been approved. During the first 18 months of our program all of the procedures were offered free of charge to patients who lacked insurance coverage. Currently, patients undergoing oocyte retrievals anticipating either embryo or oocyte cryopreservation are charged a flat flee of $5000 excluding medication, with liberal provisions for paying their balances over time. Patients undergoing tissue freezing are charged a package price of about $9000. Clearly, financial constraints will continue to play an important role in patients' decision making for the foreseeable future.

Roughly a third of the women referred to our program declined any fertility preservation treatment. During the psychologic consultation, many reasons were given for this decision. Many women commented to the effect that they were in a state of shock upon learning of their cancer diagnosis, and they could only focus on treating their cancer. Other women identified being emotionally overwhelmed and unable to gather the emotional stamina to undergo fertility preservation treatment. An additional concern voiced by some women was their fear of exacerbating their disease or increasing the likelihood of a recurrence if they underwent ovarian stimulation. Although not statistically significant when compared with the other cancer diagnoses, we were struck by the fact that 38% of the women with breast cancer elected not to pursue any form of fertility preservation. Further studies will be required to determine if women with this diagnosis are indeed less likely to choose one of these options. Our experience was similar to that reported by Azim (9), in that concern about the potential impact of gonadotropin treatment on long-term outcome was commonly expressed.

A subset of our patients were involved in a relationship but were not married. During consultation with this group, we discussed extensively the long-term implications of inseminating all of the oocytes with the partner's sperm versus splitting the oocytes and inseminating half with the partner's sperm and half with donor sperm. This discussion was predicated on our concerns that if the relationship ended, the woman would not be able to use the embryos when she desired if the partner objected. All partnered but unmarried patients were referred to outside legal counsel with expertise in reproductive law who could arrange to see the couple quickly and create contracts that reflected their wishes regarding embryo use and disposition.

We were interested to see that fewer women with cancer designated their unused embryos for disposal than routine IVF patients. Patients most often stated their belief that others could benefit from research that could be conducted with their embryos. Others deferred to their partners regarding embryo disposition, but frequently the patient discussed a scenario in which a friend or family member might be interested in using the embryos for the creation of a pregnancy. As with other IVF couples, some cancer patients chose to donate their embryos to another couple. If this option were ever realized, careful counseling with the recipient couple would be needed to discuss the donor's medical history.

Providing fertility preservation options requiring gonadotropin therapy to women with breast cancer remains controversial, and this concern is reviewed in detail with these patients. To our knowledge, there is no direct evidence that this is unwise, and from the standpoint of biologic

plausibility our view is that a short interval of elevated serum estradiol concentrations is unlikely to bear negatively upon prognosis. In this context the available data regarding the impact of pregnancy on breast cancer progression or recurrence risk are reassuring (11, 12), and referring physicians in our system have been uniformly supportive of our approach. A case can be made, however, that the approach pioneered by Oktay using the coadministration of letrozole in women with estrogen-sensitive tumors may ultimately prove to be the better choice. Serum estradiol concentrations are generally in the range of 400 to 500 pg/mL, less than half of the levels seen in our subjects, and the oocyte yields are similar to ours (8, 9) The impact of letrozole administration before chemotherapy for breast cancer is unknown. Additional studies will be required to clearly determine whether this strategy in particular, and gonadotropin stimulation in general, results in different long-term outcomes for these patients.

Patients with leukemia present particular challenges because of heightened concerns regarding the impact of their disease on the risks associated with an oocyte harvest. Two of the five patients who cryopreserved embryos had already undergone an initial round of induction chemotherapy. As a group, they had an average of 8.4 oocytes retrieved and 4.6 embryos cryopreserved, somewhat lower than was seen in the cancer group as a whole. Our impression is that patients with leukemia, if appropriately screened and counseled, may still be appropriate candidates for oocyte harvests.

Finally, with respect to the option of treating patients with analogs of gonadotropin-releasing hormone before chemotherapy, we do counsel patients regarding this option but do not enthusiastically endorse it given the continuing lack of agreement regarding its efficacy (13). We look forward to the clearer identification of specific subgroups of patients who might expect to benefit from such an approach. Significant emotional side effects from these agents are not unusual, and must be considered in any deliberation regarding the wisdom of their use.

In conclusion, our early experience with providing a comprehensive program for fertility preservation to cancer patients suggests that such an approach may be both safe and worthwhile. Nevertheless, patients considering fertility preservation strategies still face significant obstacles. The time interval over which patients must make decisions is very short, and coincides with the enormous stress of a recent cancer diagnosis, and cost will likely comprise an insurmountable barrier for some patients. Furthermore, key questions regarding these new strategies remain to be answered. First, it has not yet been established that cancer patients can generally be expected to have outcomes comparable to healthy, age-matched controls. Although cancer patients who cryopreserved embryos had similar yields when compared with an appropriate control group, concerns remain regarding the fraction of cancer patients who had cancelled cycles, and difference between the groups with respect to recovered oocytes also may be relevant for patients wishing to cryopreserve oocytes. Nevertheless, when viewed in conjunction with previously published data regarding fertility preservation outcomes (7, 8), our data suggest that, at the very least, these options should be offered to patients seeking fertility preservation strategies. The extent to which a cancer diagnosis per se or heightened concerns about the development of OHSS result in poorer reproductive outcomes for these patients remains to be determined.

Finally, a relatively high number of patients we saw declined to actively participate, and further study is required to further elucidate how we might best counsel these patients. In particular, the proper counseling of patients with breast cancer or other hormone-sensitive tumors will continue to be challenging in light of the continuing uncertainty regarding long-term safety.

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