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COMMENTARY

Effect of cancer on ovarian function in patients undergoing *in vitro* fertilization for fertility preservation: a reappraisal

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1. INTRODUCTION

The past decade has witnessed an increase in cancer survival rates[1]. Fertility preservation for young women destined to undergo treatment with chemotherapy or radiotherapy has become a significant issue, with future childbearing being a powerful stimulus to get well[2]. Only half the patients who discussed fertility issues with their doctors believe that their concerns were adequately addressed[3]—a situation that is probably attributable to the fact that, although most physicians are familiar with the toxic gonadal effect of alkylating agents, they are unaware of fertility preservation options and the effect of cancer *per se* on ovarian function.

Recent evidence demonstrated a negative effect of cancer on spermatogenesis, with a decrease in sperm quality and indices in patients diagnosed with hematologic and testicular cancers[4,5]. Likewise, the effect of cancer on baseline ovarian function and ovarian response to stimulation for *in vitro* fertilization (IVF) has been studied with mixed results. Various aspects of ovarian function and response to stimulation have been studied: baseline ovarian function and reserve, the effects of cancer on ovarian stimulation for IVF, and the effects of cancer on oocyte yield and fertilization rates.

Our aim was to review the available literature and to add the data from our large series of patients diagnosed with cancer so that physicians treating young women who desire to preserve fertility will be able to provide advice based on the available current and accumulating data.

2. EFFECT OF CANCER ON BASELINE OVARIAN FUNCTION

Measurements of follicle-stimulating hormone (FSH) on days 2–5, antral follicular count (AFC), and estradiol levels have all been used to compare baseline ovarian characteristics in patients with cancer and in control subjects.

All researchers found that FSH levels were similar in patients with cancer and in control subjects. Moria *et al.*[6] reported lower baseline levels of FSH for patients with hematologic malignancy, but similar levels of FSH in control subjects and in patients with breast cancer and other types of cancer. The younger age of patients with hematologic malignancies (mostly Hodgkin lymphoma) in all probability explains the statistical difference. Quintero *et al.*[3] reported higher baseline levels of FSH in patients with breast cancer. In that study, the higher proportion of significantly older patients in the group with a breast malignancy probably explains the upward shift in FSH levels. In both the foregoing studies, the different baseline levels of FSH were determined by age rather than by background disease.

Das *et al.* and Moria *et al.*[2,6] used the AFC to assess ovarian reserve. Both groups found no significant difference between cancer patients and control subjects.

Pal *et al.*[7] and Knopman *et al.*[8] measured day 2–5 estradiol levels in study patients and in control subjects and found no significant difference between the groups.

To summarize, using levels of FSH, the AFC, and estradiol, previous studies could not demonstrate a significant difference in baseline ovarian characteristics and reserve between cancer patients and healthy women. Levels of FSH tended to be (as expected) related to age rather to baseline condition.

3. EFFECT OF CANCER ON OVARIAN STIMULATION

Ovarian stimulation has been assessed using FSH total dose, duration in days of FSH stimulation, and maximal estradiol levels reached in patients and in control subjects. In most studies, no differences in those parameters were observed between patients with cancer and control subjects.

Robertson *et al.*[9] found that the maximal level of estradiol reached on the day of administration of beta–human chorionic gonadotropin was lower in study

patients than in control subjects. Among the patients in that study, many (16 of 38) had breast cancer, and where the disease was positive for the estrogen receptor, letrozole was used to reduce the risk of estradiol exposure, thereby lowering estradiol levels. The duration of stimulation and total FSH dose were, however, unchanged in Robertson's patient group.

Quintero and colleagues[3] found that higher dosages—and a longer duration—of FSH treatment (estradiol was not measured) were needed in patients with cancer. Those authors also demonstrated a trend toward more frequent poor response among cancer patients than among control subjects. The groups were matched for age, and although no difference was noted in the number of oocytes collected, the differences in dose and duration of FSH were not explained other than by the hypothesis that patients with cancer may have reduced reproductive capacity[3].

At our centre, we recently conducted a study comparing outcomes of IVF stimulation before treatment for patients diagnosed with various types of cancer. In our study, the largest single-centre effort conducted so far (n = 81), we found no significant change in the total gonadotrophin dose and the number of stimulation days between the study group and the control group.

4. EFFECT OF CANCER ON NUMBER AND QUALITY AND QUANTITY OF OOCYTES

The numbers of mature and immature oocytes and rates of fertilization have all been assessed. No researchers found an effect on those parameters in patients with cancer (except for breast cancer, to be discussed shortly) compared with control subjects. Pal *et al.*[7] found that reduced-quality oocytes were significantly increased in patients with cancer than in patients with tubal-factor infertility (control subjects). It is noteworthy, however, that the study group in the latter report included only 5 patients with cancer. Other studies, with significantly larger series of patients, reported no difference in quality or quantity or in the fertilization rates of oocytes for patients with cancers other than breast cancer.

As in the case of the stimulation protocol, Moria *et al.* found that significantly fewer oocytes were retrieved in breast cancer patients[6]. Their work used *in vitro* maturation, and so no stimulation protocol was given. Oktay *et al.*[10] published similar findings in a large series of patients with breast cancer. Those authors demonstrated a reduced number of oocytes in *BRCA1*- but not *BRCA2*-positive patients. An association between *BRCA* mutations and diminished oocyte reserve or occult primary ovarian insufficiency is biologically plausible on the basis of previous laboratory and clinical data. A comparative analysis of the results from Oktay *et al.* and the studies already mentioned is difficult, because Oktay and colleagues used a stimulation protocol combining letrozole and gonadotrophin, and because the patients were grouped based on *BRCA* status rather than being compared with a group having mechanical or male-factor infertility[10].

In our group of patients, the number of retrieved oocytes and the number of mature M2 oocytes were comparable in the study and control groups despite a lower maximal estradiol level having been achieved in the study group compared with the control group [1442 pg/mL (range: 1042–2375 pg/mL) vs. 2274 pg/mL (range: 1204–3372 pg/mL); $p = 0.005$; 95% confidence interval: 180–956 pg/mL).

5. DISCUSSION

Interest in the effect of cancer on ovarian function has probably been fueled by reports of decreased sperm quality and count in patients with cancer[4,5]. Those observations sparked an interest in reports describing baseline ovarian function and outcomes of ovarian stimulation in patients needing fertility preservation because of background malignancies.

With some minor exceptions to be outlined shortly, it is possible to say that, in the few hundred cases examined, cancer has had no effect on ovarian reserve as measured by AFC, day 2–5 FSH, or day 2–5 estradiol. A deleterious effect of cancer was also not observed during stimulation (length and dosage of FSH stimulation) or at stimulation outcome (number of oocytes retrieved, oocyte quality, or fertilization rates).

In general, breast cancer patients tended to need higher doses and longer administration of FSH[3], to show reduced maximal levels of estradiol on beta–human chorionic gonadotropin administration day, and to have a reduced number of oocytes[6,9]. Those observations might be explained by the relatively older age of patients diagnosed with breast cancer (Quintero *et al.* found a higher degree of poor response among breast cancer patients). The lower yield of oocytes might also be attributed to different stimulation protocols, as mentioned earlier (use of a combination of letrozole and FSH in an effort to minimize the effect of estradiol on breast cancer tissue).

Sperm cells proliferate and divide continuously, and it is common knowledge that a multitude of factors can hamper that process, lowering sperm counts and quality. Unlike sperm cells, oocytes are mature cells arrested in the first meiotic division until ovulation; the ways in which external or internal factors affect that process is unknown. Nakamura *et al.* suggested that there is biologic evidence of an immune–endocrine disruption that can lead to reproductive failure because of psychological stress[11]. Various explanations about an impaired hypothalamic–pituitary axis in catabolic patients with cancer and suppression of gonadotrophin levels because of an elevation in prolactin under stress conditions have also been suggested[12]. Oktay *et al.*[10] introduced a hypothetical explanation of reduced oocyte counts

in patients with *BRCA1* mutations. Patients with that mutation have a reduced DNA repair ability, and hypothetically, oocytes that reside in the ovary for years before final maturation may have acquired lethal unrepairable DNA damage.

Notably, in a recent meta-analysis of seven retrospective studies, Friedler *et al.* demonstrated reduced number of oocytes in patients with malignancies undergoing controlled ovarian hyperstimulation for fertility preservation[13]. Those authors concluded that, compared with control subjects, patients with cancer have significantly lower peak estradiol levels and lower numbers of retrieved and mature oocytes. The retrospective studies included in the meta-analysis were of patients with various types of cancer, but breast cancer patients dominated (n = 124, 56.9%). As outlined earlier, this specific group of patients included those treated with various low-estradiol protocols such as letrozole and tamoxifen, and lower peak estradiol levels were inevitably found. Those lower levels may be a contributing factor in the lower oocyte yields found. Also, the combined number of patients in the meta-analysis was 218, with two studies having 50 patients each, and five others having smaller samples.

Our own experience as outlined earlier—and that in most of the studies already described—demonstrates no significant change in baseline ovarian function parameters or in ovarian response to stimulation in terms of oocyte yield in patients diagnosed with various types of cancer compared with control subjects. This information, which is based on accumulating evidence, should be used by physicians dealing with cancer patients to reassure them about the good outcomes of ovarian stimulation for fertility preservation.

6. CONFLICT OF INTEREST DISCLOSURES

Both authors have no financial, ethical, professional, or other conflicts of interest to disclose.

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