Use of Aromatase Inhibitors in IVF for Fertility Preservation of Non-Breast Cancer Patients: A Case Series

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ABSTRACT: **Background:** Controlled ovarian hyperstimulation (COH) followed by oocyte retrieval is a leading option for fertility preservation before chemotherapy, yet this procedure causes excessive serum levels of estradiol (E2), which are often detrimental for cancer patients. Aromatase inhibitors are often used in breast cancer patients during COH to prevent elevated levels of E2.

Objectives: To describe our experience with COH for oocyte cryopreservation in non-breast cancer patients using aromatase inhibitors.

Methods: Of the five patients treated, two had an aggressive abdominal desmoid tumor, one had endometrial carcinoma, one had uterine sarcoma, and one patient had a brain oligodendroglioma. In all cases the treating oncologist suggested an association between estrogen and possible tumor progression. All patients were treated with a standard in vitro fertilization antagonist protocol combined with aromatase inhibitors, similar to the protocol used for breast cancer patients.

Results: The average duration of treatment was 10.5 days, mean peak E2 was 2348 pmol/L, mean number of oocytes aspirated was 17.3, and a mean of 14.6 embryos/oocytes were cryopreserved.

Conclusions: COH with aromatase inhibitors is apparently effective in non-breast cancer patients and spares exposure to high E2 levels.

IMAJ 2018; 20: 145–146

KEY WORDS: aromatase inhibitors, fertility preservation, non-breast cancer patients

Controlled ovarian hyperstimulation (COH) followed by oocyte retrieval and freezing of embryos or oocytes is a leading option for fertility preservation in cancer patients before they begin chemotherapy treatment [1]. However, COH is accompanied with high serum levels of estradiol (E2), at times reaching > 15000 pmol/L [2]. The use of aromatase inhibitors during COH for fertility preservation of breast cancer patients has been previously reported to prevent excessively elevated E2 levels [3].

Oktay and colleagues [3] were the first to describe the use of letrozole (an aromatase inhibitor) during ovarian stimulation of the gonadotropin-releasing hormone antagonist protocol in a study of 29 patients with breast cancer. Their analysis included ovarian stimulation cycles with tamoxifen 60 mg/day alone, tamoxifen 60 mg/day in combination with low-dose follicle-stimulating hormone (FSH) or letrozole 5 mg/day in combination with low-dose FSH (150 U/day). They found that the patients given letrozole and FSH had more follicles, more mature oocytes (8.5 ± 1.6), and more embryos (5.3 ± 0.8) than the other groups. As expected, peak E2 levels were lower with letrozole (1370 ± 205 pmol/L).

In a previous study [4], we reported the use of aromatase inhibitors in 24 breast cancer patients, using higher doses of FSH (150–450 U/day, mean 270 U/day). This dosage resulted in a higher number of retrieved oocytes (12.0 ± 8.8) and frozen embryos (8.2 ± 6.4) than the lower-dose schedule [3], and similarly low levels of peak E2 were recorded (1248 ± 1138 pmol/L).

Our objective in this study was to describe our experiences with the addition of aromatase inhibitors to COH protocols for oocyte cryopreservation in non-breast cancer patients.

RESULTS

We report a case series of five patients treated in our in vitro fertilization (IVF) unit before chemotherapy for various indications. The various indications included one patient with endometrial carcinoma, one with uterine sarcoma, two sisters with familial adenomatous polyposis (FAP) and an aggressive intra-abdominal desmoid tumor (2 cycles for each), and one patient with brain oligodendroglioma. Desmoid tumors are locally aggressive fibroblastic proliferation of deep soft tissue caused by monclonal proliferation of fibroblast like cells [5-9].

A standard IVF antagonist protocol combined with aromatase inhibitors was used in the current group of non-breast cancer patients. Average duration of treatment was 10.5 days, and mean peak E2 levels were 2438 pmol/L (range 229–3829), yielding a mean number of 17.3 aspirated oocytes (range 10–22), and a mean number of 14.6 embryos/oocytes cryopreserved (range 6–21). Oocyte or embryo freezing was performed using vitrification or slow freezing.

DISCUSSION

In a recent study [10], the use of letrozole in cryopreservation cycles for breast cancer patients resulted in lower peak estradiol levels (1705 pmol/L, range 1160–2474) and a higher number of oocytes retrieved 12.3 ± 3.99 compared to the standard cryopreservation protocols without letrozole (6226 pmol/L, range 3877–8785, $P < 0.01$) and 10.9 ± 3.86 oocytes ($P < 0.01$). The high number of oocytes attained and the low E2 levels in our case series of non-breast cancer patients were similar to those found in breast cancer patients treated with letrozole.

Elevated estrogen levels are clearly detrimental to endometrial carcinoma [11], yet a significant percentage of uterine leiomyosarcomas also express estrogen receptors, and estrogen may be correlated with disease progression [12]. Estrogen receptors have been described in brain glial tumors [13,14] and nearly all desmoid tumors express estrogen receptors [15]. In all five cases reported, the treating oncologists suggested an association between estrogen and possible growth of the tumor and recommended that estrogen levels be kept at a minimum level.

It should be noted that use of letrozole in Israel for premenopausal women is currently unapproved (since 2005) due to a manufacturer warning released following an abstract presentation suggesting that the use of letrozole for infertility treatment might be associated with a higher risk of congenital cardiac malformations in newborns [16]. However, subsequently Tulandi et al. [17] evaluated the incidence and type of congenital malformations among 911 newborns from mothers who had conceived with letrozole compared with a control group of infertile women who had conceived with clomiphene citrate. Their study demonstrated no difference in the overall rates of malformations or chromosomal abnormalities among the newborns from mothers who had conceived after letrozole or after clomiphene citrate treatments. Congenital cardiac anomalies in their study were statistically significantly less frequent in the letrozole group than in the clomiphene citrate group. Based on their data, there is no concern that letrozole use for ovulation induction is teratogenic [18].

CONCLUSIONS

Ovarian stimulation with letrozole and high-dose FSH is apparently successful in non-breast cancer patients, achieving a similar number of oocytes cryopreserved, and spares them exposure to high E2 levels that may be detrimental to underlying malignancy.

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"Perhaps travel cannot prevent bigotry, but by demonstrating that all peoples cry, laugh, eat, worry, and die, it can introduce the idea that if we try and understand each other, we may even become friends"

Maya Angelou, (1928–2014), American poet, memoirist, and civil rights activist