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SPECIAL ARTICLE

Gynecology

Fertility stimulation protocols in women with cancer

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Abstract

All female oncology patients undergoing controlled ovarian stimulation for fertility cryopreservation should be offered an antagonist protocol. Therapy can begin at the time of the first visit, providing consent is obtained. There is no need to delay until the next period. Stimulated patients should be monitored with ultrasound and estradiol levels as per normal clinic practice. For women with a diagnosis of breast cancer, and with the agreement of the treating oncologist, the stimulation protocol should include an aromatase inhibitor such as letrozole to reduce the circulating estradiol levels. All patients should have a gonadotropin-releasing hormone trigger to eliminate the risk of ovarian hyperstimulation syndrome and facilitate timely return for cancer therapy.

KEYWORDS
cancer treatment, controlled ovarian hyperstimulation, gonadotropin, letrozole

1 | INTRODUCTION

The first group to stimulate the ovary with human menopausal gonadotropin to achieve a live birth was reported by Jones[1] in 1982. Since then, ovarian stimulation has changed significantly and there has been much debate regarding the optimal dose for controlled ovarian hyperstimulation (COH). There was some controversy surrounding whether increasing the gonadotropin dose in COH increased the risk of embryonic aneuploidy. In contrast, others argue that with increased patient age and decreased ovarian reserve, it would be optimal to use higher doses to obtain a higher oocyte number for current and future use.[2]

Today, most stimulation protocols are decided based on age and various markers of ovarian reserve, such as antral follicle count (AFC) and anti-Müllerian hormone (AMH) levels. For women with a poorer ovarian reserve, increasing the gonadotropin dose does not always improve outcomes.[3] There are three basic COH protocols: (1) antagonist, (2) long agonist, and (3) flare.[2] The antagonist protocol is often the preferred protocol for cryopreservation with oncofertility patients. The major benefit is the shorter duration from start to finish, when compared with the long protocol. A more recent approach to fertility preservation is the double stimulation or DuoStim protocol, which aims to maximize the number of oocytes retrieved in a short time interval without delaying cancer treatment.[4]

The objective of individualizing treatment in assisted reproduction is to offer every woman the best possible outcome.[5] Personalization of the patient's treatment protocol is based on the patient's likelihood of responding to COH. The response can be predicted using female age, AFC, AMH level, and previous response with certain medications and female weight. Previous responses to gonadotropins should be considered when prescribing the dose required. The dose prescribed must be aimed at producing the maximum number of eggs with the lowest risk of ovarian hyperstimulation syndrome (OHSS). This is especially important in oncology patients, who may only ever have one attempt at egg collection. It is also important to ensure that the risk of OHSS is minimal, as this can delay the start of oncology treatment. When a dose is decided upon, one must be aware that increasing the dose midcycle may have a detrimental effect on the outcome.[6] However, the duration of stimulation does not affect the outcome in antagonist cycles.[7]

In addition to the dose of the drug and the type of protocol, one must also consider the type of drug for COH. The options include highly purified urinary formulations of follicle stimulating hormone (FSH), human menopausal gonadotropin (hMG), and recombinant FSH.[8] For some patients, including women with hypothalamic

amenorrhea or of advanced maternal age, the addition of recombinant luteinizing hormone (LH) should be used. The options for oocyte maturation trigger are human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH) agonist, or a combination of both (dual trigger). The introduction of the GnRH trigger has revolutionized the management of patients at risk of OHSS during an antagonist cycle. HCG has the same effect as LH with a longer half-life.[9] The GnRH trigger causes the natural release of FSH and LH. The shorter duration of release of LH reduces the risk of OHSS.[10] Maturation and fertilization rates and the number of cryopreserved embryos are higher in cycles where GnRH agonists were used, as opposed to the hCG trigger.[11]

This article is aimed at fertility practitioners who preserve fertility for patients undergoing cytotoxic therapy, as well as oncologists, hematologists, and other healthcare practitioners who refer cancer patients to fertility preservation clinics.

2 | WHEN CAN STIMULATION START?

Once the fertility consultant is satisfied following patient history, review of the investigations, and liaison with the referring consultant that it is safe to proceed with COH for egg collection, a prescription with the advised medication must be given with detailed instructions on dosage, technique, and timing of drug administration.

A random start in the menstrual cycle is the advised practice. Waiting for a menstrual period prior to beginning an ovarian stimulation cycle could result in further delay to commencing cancer treatment. This may potentially result in patients forgoing their fertility preservation.[12] When ovarian stimulation is started randomly using FSH, the total number of mature oocytes retrieved and fertilization rates are similar to conventional ovarian stimulation. Starting ovarian stimulation in the luteal phase does not alter the follicular development due to the presence of a corpus luteum.[13]

3 | MEDICATION PROTOCOLS

The antagonist protocol is the most commonly used for oocyte retrieval in patients with malignancies owing to its simplicity, shorter duration, and lower risk of OHSS with the GnRH agonist trigger. The antagonist protocol involves administering daily recombinant or purified urinary FSH injections initiated on presentation on any day of the menstrual cycle. A fixed dose of FSH is used for the first 6–7 days, after which the dose is adjusted depending on the ovarian response on transvaginal ultrasonography and the serum estradiol level.[12] A daily dose of a GnRH antagonist is then introduced at a dose of 0.25 mg (subcutaneous administration) until the day of ovulation induction. An ovulation induction trigger is advised when at least three follicles are 18 mm in size. If the woman has a low ovarian reserve, the decision to trigger can be made when only one or two follicles reach 18 mm in size. Oocytes must then be collected with a lag time from ovulation induction of 35–38 h.[14]

The dual stimulation (DuoStim protocol) has been shown to maximize oocyte retrieval without an impact on fertility treatment. A fixed or random start in the follicular phase can be used. GnRH antagonist is administered daily after identifying a leading follicle with a diameter of at least 13–14 mm in the follicular phase until the day of ovulation trigger. The final maturation of oocytes is triggered by a subcutaneous bolus of a GnRH agonist. Five days after the initial retrieval, which is the time needed to complete luteolysis using the same COH protocol regardless of the number of antral follicles visible if ultrasound is performed, luteal phase support is commenced following the same antagonist protocol outlined.[15] Of note, whereas COH can be started any time during either the follicular or the luteal phase, there are specific cases (e.g. women in the periovulatory phase) that would benefit from an induced luteolysis (GnRH antagonists before COH).

4 | CONTROLLED OVARIAN HYPERSTIMULATION IN ESTROGEN-POSITIVE BREAST CANCERS

An increasing number of women under the age of 45 delay childbearing for various reasons. As a result, there is a growing population of women with breast cancer who have not completed their family.[15] Most hereditary breast cancers are associated with the BRCA1 and BRCA2 genes. In addition to the increased risk of malignancies, women carrying BRCA1 are also at risk of low ovarian reserve.[14] There are also concerns surrounding what effect raised estrogen levels have on estrogen receptor-positive tumors during COH. Therefore, conventional stimulation protocols are best avoided in estrogen-sensitive breast cancers.

Aromatase inhibitors (e.g. letrozole) reduce the circulating estrogen levels and stimulate endogenous FSH secretion through negative feedback on the hypothalamic pituitary axis. When letrozole is used in conjunction with FSH in COH, lower estrogen levels can be achieved. In such cases, a lower dose of FSH can be used, and comparable outcomes from COH can be found without a substantially increased risk of tumor recurrence.[16]

Ovarian stimulation begins with an initial dose of 5 mg letrozole, followed by the introduction of FSH injections 2 days later. Both drugs are continued until Days 6–7 of the protocol when a transvaginal scan is performed and the serum estradiol level checked. The FSH dose may be altered in line with the ovarian response. A GnRH antagonist is added. The letrozole, FSH, and GnRH antagonists are continued daily until the ovulation induction trigger. Transvaginal oocyte collection is then performed between 35 and 38 h after (on average after 36 h).

5 | CONCLUSION

Fertility preservation in cancer patients is a rapidly developing field. Embryo and oocyte preservation are important modalities of

fertility preservation prior to chemotherapy and radiotherapy. This requires controlled ovarian stimulation. The antagonist protocol allows for this to be performed in a timely manner, usually between 2 and 3 weeks. A GnRH agonist trigger significantly reduces the risk of OHSS, which can prevent delays to the start of cancer treatments. Furthermore, newer COH protocols including DuoStim can be used to maximize oocyte yield, with no delays to commencing oncology treatment. The addition of aromatase inhibitors is important to reduce estrogen levels in breast cancer patients undergoing COH.

AUTHOR CONTRIBUTIONS

All authors contributed to conceptualizing, writing, and reviewing the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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