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Review article

Fertility preservation with ovarian stimulation protocols prior to cancer treatment

Running title: Ovarian stimulation and cancer treatment

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An increasing trend towards later childbearing has been reported recently in many developed countries. Although the incidence of reproductive age women who have delayed pregnancy with cancer is 10%, they may be concerned regarding preservation of ovarian function due to advanced fertile age and with the impact of cancer treatment on later fertility. Among multiple strategies controlled ovarian stimulation for embryo or oocyte cryopreservation is currently the most established method for fertility preservation. It is important to choose the appropriate ovulation induction protocol prior to oncologic treatment, because most of these patients have only the chance of a single cycle to conceive. Current treatment protocols offer a minimal time delay until oncologic treatment is commenced. In urgent settings, random-start ovarian stimulation represents a new technique which provides a significant advantage by decreasing the total time of the treatment, and because it may be started irrespective of the phase of the cycle without compromising oocyte yield and maturity before cancer treatment. However, in patients with oestrogen-sensitive cancers stimulation protocols using letrozole are currently preferred over tamoxifen regimens, and therefore it may be highly advisable to use letrozole with gonadotrophins routinely as a safe, effective and novel protocol of ovulation induction.

Introduction

Many countries of the developed world have experienced an increasing trend towards later childbearing, commonly between 30 to 44 years of age in recent years and for a variety of reasons. In the United States the birth rate for women aged 30-34 years increased from 80.8 births per 1,000 women in 1990 to 96.5 births per 1,000 women in 2011. In addition, the rate for women aged 35-44 years rose 54% from 1990 to 2011, increasing from 37.2 to 57.5 births per 1,000 women [1]. Although about 10% of female cancers occur under the age of 45 years, over the past three decades there has been a remarkable improvement in survival rates due to advances in cancer diagnoses and therapies at an earlier stage. It was found that from 2002 to 2012, 83% of women younger than 45 years who were diagnosed with cancer survived [2].

Because the incidence of premenopausal women with cancer who have delayed pregnancy is increasing, they may have concerns regarding the quality of life and preservation of ovarian function due to advanced fertile age, particularly with the impact of cancer treatment on the outcome of later fertility and pregnancy. Therefore, women of reproductive age should have expert counselling and should be given the opportunity to make active decisions about preserving fertility. Specialized counselling about loss of reproductive function and fertility preservation is associated with more empowered decision-making and increased quality of life for survivors. For patients to receive appropriate counseling, it is important that they understand the potential increased risk of infertility and early menopause beyond that of acute ovarian failure [3,4]. Fertility preservation issues should be addressed within a multidisciplinary environment, including oncologists and fertility specialists [5].

The treatment for most of the cancer types in reproductive age-women includes removal of the reproductive organs or cytotoxic treatment that may partially or definitively affect reproductive function. One of the most devastating consequences of cytotoxic treatment

with chemotherapy and radiation in the young female population is ovarian damage, resulting in diminished fertility potential [6]. The impact of chemotherapy on a woman's fertility depends on her age and the types and doses of the drugs used. Alkylating agents have the biggest negative impact on ovarian function. The effects of external radiation therapy and brachytherapy on the ovaries depend on three factors: the patient's age, the dose delivered to the ovaries, and concurrent use of chemotherapy. Female patients who receive high-dose abdominal and/or pelvic irradiation or chemotherapy based on alkylating agents are at highest risk of developing ovarian failure [7]. In addition, women treated with abdomino-pelvic radiation have an increased rate of uterine dysfunction leading to miscarriage, preterm labour, low birth weight, and placental abnormalities [8].

The field of fertility preservation has been developed in order to overcome the adverse effects of cytotoxic cancer treatments on gonadal function. The strategy of fertility preservation depends on the patient's age, and the time frame before the initiation of gonadotoxic treatments. Multiple strategies have emerged aimed at preserving fertility in women with different types of malignancies including embryo and oocyte cryopreservation, cortical and whole ovary cryopreservation, ovarian transplantation, ovarian transposition, and administration of GnRH agonists during chemotherapy. Embryo or oocyte cryopreservation after controlled ovarian hyperstimulation is currently the most established technique of fertility preservation, but ovarian tissue freezing may also be offered despite the fact that it is still considered experimental. More recently, in vitro maturation of the oocyte has been proposed in the strategy of fertility preservation since it does not require ovarian stimulation and can be performed at any time of the menstrual cycle. Therefore, in vitro maturation represents an attractive approach for urgent fertility preservation and/or in patients suffering from oestrogen-sensitive cancers [9]. Currently, sperm and embryo cryopreservation and oocyte cryopreservation are the only techniques endorsed by the American Society of Clinical

Oncology widely available as standard practice. Other fertility preservation methods should be considered investigational and should be performed by care providers with the necessary expertise [10].

Strategies for ovarian stimulation

Controlled ovarian stimulation for mature oocyte and embryo cryopreservation is the preferred method for fertility preservation in cancer patients due to its higher success rates compared with other, more experimental techniques. The reports about the response of cancer patients to ovarian stimulation protocols widely vary, from some reporting no significant change and others demonstrating worse ovarian response compared with age-matched healthy women. It appears that in women with malignancy undergoing in vitro fertilization (IVF) before chemotherapy or radiotherapy, ovarian reserve, response to gonadotrophins, oocytes retrieved, and oocyte maturity remain unaltered by the neoplastic process [11]. However, the results of a recent meta-analysis indicate that the number of retrieved oocytes was statistically significantly lower compared with age-matched healthy IVF patients [12]. Moreover, ovarian reserve assessed with anti-mullerian hormone (AMH) and antral follicle count (AFC) were found to be significantly lower in patients with malignancy before gonadotoxic therapy, which may be explained by either accelerated follicle loss or a defect in recruitment of antral follicles due to disease state [13, 14]. Therefore, maximizing the number of embryos and oocytes during a fertility preservation cycle without causing ovarian hyperstimulation syndrome is extremely important, because most women have only the opportunity to undergo a single cycle of IVF owing to time constraints before starting oncologic treatment. Determination of the ovarian stimulation protocol and gonadotrophin dose for oocyte/embryo cryopreservation requires an individualised assessment. The choice of

the specific ovarian stimulation strategy is usually determined by the time available until the initiation of chemotherapy or radiotherapy [15].

Traditional ovarian stimulation protocols for IVF required awaiting spontaneous menses before 9–14 days of ovarian stimulation with exogenous gonadotrophins preceded by ovarian suppression with gonadotrophin releasing hormone (GnRH) agonists to prevent premature ovulation for approximately 2 weeks. Therefore, preserving oocytes or embryos has required a delay in cancer treatment of more than a month to complete the IVF cycle [15].

Conventional-start stimulation protocols that include the introduction of GnRH antagonists have significantly decreased the interval from patient presentation to oocyte or embryo cryopreservation. Currently, the majority of patients are treated with a GnRH antagonist-based regimen, which usually enables the shortest time to initiation of chemotherapy or radiotherapy. In contrast to GnRH agonists, GnRH antagonists immediately suppress pituitary release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) and do not require the 10–14 days of administration prior to gonadotrophin initiation. Conventional-start ovarian stimulation can be started following spontaneous menses with gonadotrophins and GnRH antagonists initiated in the early follicular phase or with menses following luteolysis induced by GnRH antagonist during the preceding luteal phase. In the first approach GnRH antagonists are initiated usually at day six of the cycle when the size of the lead follicle reaches 12-13 mm during gonadotrophin stimulation, which begins on day 2-3 of the cycle. Although this approach still requires awaiting spontaneous menses prior to initiating gonadotrophins, it decreases the interval to oocyte retrieval compared to traditional IVF stimulation protocols. However, if the use of a GnRH antagonist (e.g. single dose of 3 mg cetorelix subcutaneously) is initiated during the midluteal phase, menses usually ensues a few days later following corpus luteum breakdown. Administration of GnRH antagonists in the luteal phase results in the quicker initiation of ovarian stimulation and restart of GnRH

antagonist in a standard fashion, reducing delays for cancer treatment and improving clinical outcome in poor responders. Nevertheless, despite these effects adhering to the conventional-start antagonist protocols may result in either significant delay of cancer treatments or forgoing of fertility preservation due to time constraints [15,16].

Random-start ovarian stimulation protocol is emerging as a new technique for the purpose of fertility preservation for cases in which waiting for the next menstrual period to start with ovulation induction is advisable due to the urgency of the cancer treatment. Controlled ovarian stimulation has been proposed to be initiated in the late follicular phase or luteal phase following spontaneous LH surge or after ovulation induction with human chorionic gonadotrophin (hCG) or a GnRH agonist [15]. If the cancer patient presented in the late follicular phase, ovarian stimulation may be started without a GnRH antagonist if the follicle cohort following the lead follicle is < 12 mm and continues to be < 12 mm before spontaneous LH surge. After the LH surge, a GnRH antagonist may be started later in the cycle after the secondary follicle cohort reaches 12 mm to prevent premature secondary LH surge. Alternatively, ovulation may be induced with hCG or a GnRH agonist and ovarian stimulation can start in 2-3 days in the luteal phase. However, if the cancer patient is in the luteal phase, GnRH antagonists may be initiated similarly to conventional ovarian stimulation later in the cycle to down-regulate LH with proceeding luteolysis, and follicular stimulation with recombinant FSH may be started simultaneously. Both of the random-start ovarian stimulation protocols are as effective as conventional-start regimens in the early follicular phase. In addition, random-start ovarian hyperstimulation provides a significant advantage by decreasing the total time for the IVF cycle, and because it may be started irrespective of the phase of the cycle for the purpose of fertility preservation without compromising oocyte yield and maturity before cancer treatment [17, 18].

Oestrogen-sensitive cancers

The supraphysiologic levels of oestrogens associated with ovarian stimulation with gonadotrophins may promote the growth of oestrogen-sensitive tumours and therefore in the past elevated oestrogen levels have precluded the use of assisted reproductive technologies in the presence of breast cancer [19]. Currently, potentially safer and alternative stimulation protocols have been used for fertility preservation for oestrogen-sensitive cancer patients, including natural cycle IVF, tamoxifen and aromatase inhibitors to induce lower levels of estradiol [20].

Natural cycle IVF has been offered traditionally for women with breast cancer in order to avoid the possible risks of ovarian stimulation, but it resulted in an extremely low gamete yield. Because the technique of natural cycle IVF is accompanied with a high rate of cancellation and gives the smallest number of oocytes or embryos per cycle, it is not recommended when a gonadotoxic therapy is approaching and when the patient is without another chance of IVF treatment [15].

Tamoxifen, a nonsteroidal compound related to clomiphene, expresses its action by competitive antagonism at its receptor site. In some organs such as the uterus and bones tamoxifen has agonist actions on oestrogen receptors, and antagonist effects on breast cancer cells, thus inhibiting the proliferative effect of oestrogens. Tamoxifen has been accepted as the first-line drug in hormonal prevention and treatment of receptor-positive breast cancer tissue. In addition to its negative effects in the breast it also has an antagonist action in the oestrogen receptors in the central nervous system which interferes with the negative feedback of the oestrogen, leading to an increase of GnRH and gonadotrophins. Tamoxifen can be used for ovulation induction alone starting on day 2-5 of the menstrual cycle in doses 20-60 mg/d, or in combination with gonadotrophins similar to the use of clomiphene [20]. Although oestrogen levels during ovarian stimulation with tamoxifen are not altered, its use in

oestrogen receptor-positive breast cancer patients is desirable, due to its antioestrogenic effect on breast tissue. Ovulation induction with tamoxifen for fertility preservation in cancer patients has been shown to increase mature oocyte and embryo yield compared with natural cycle IVF (1.6 vs.0.7 and 1.6 vs. 0.6 respectively), reducing cycle cancellations. Whereas all patients had at least one embryo in the tamoxifen group, 40% of cycles did not result in embryo development in the natural cycle IVF group [21]. Moreover, the combination of low-dose FSH with tamoxifen (60 mg/d) further increased the number of cryopreserved oocytes and embryos compared with ovulation induction with tamoxifen alone (5.1 vs.1.5 and 3.8 vs.1.3 respectively) [22].

Aromatase inhibitors significantly reduce plasma oestrogen levels by competitively suppressing the activity of the aromatase enzyme. Because greater proliferative capacity of endocrine-responsive breast cancer is often due to increased local aromatase activity and oestrogen production, letrozol, a third-generation aromatase inhibitor, is important in adjuvant treatment reducing the risk of recurrent disease. In contrast to tamoxifen, which inhibits the activity of oestrogen by competitively binding to the oestrogen receptor, aromatase inhibitors block the conversion of androgens to estrogens and reduce oestrogen levels in tissue and plasma [23]. Oestrogen receptor-positive breast cancer patients undergoing controlled ovarian hyperstimulation for embryo or oocyte cryopreservation should be induced by the method that leads to the least increase in estradiol levels. In addition to local inhibitory effects on aromatase activity, aromatase inhibitors release the hypothalamic-pituitary axis from estrogenic negative feedback, increase the secretion of gonadotrophins, stimulate follicle growth, and thereby can be used in ovulation induction. In patients with oestrogen-sensitive cancers the main advantage of adding daily letrozol to gonadotrophins in ovarian stimulation protocols is decreasing plasma estradiol levels and bringing them closer to those observed in natural cycles, or about 50% of the results with clomifene. Comparing the efficacy of the

letrozol with gonadotrophin protocol in breast cancer patients before chemotherapy and standard IVF in noncancer women, the former started to receive letrozole (5 mg/d) from day 2 or 3 of the cycle and FSH (150 – 300 IU) two days later. All medications were discontinued on the day of the hCG trigger, and letrozole was reinitiated after oocyte retrieval and continued until oestrogen levels fell to < 50 pg/ml. Whereas letrozole and FSH stimulation resulted in significantly lower peak estradiol levels (483.4 +/- 278.9 vs. 1464.6 +/- 644.9 pg/ml) and a 44% reduction in gonadotrophin requirement, in comparison with controls, the length of stimulation, number of embryos obtained, and fertilization rates were similar. Therefore, ovarian stimulation with letrozole and FSH appears to be a cost-effective alternative with reduced oestrogen exposure for fertility preservation in breast cancer patients, compared with standard IVF. In addition, patients should be referred promptly so that they may undergo embryo or oocyte cryopreservation without a delay in chemotherapy [24]. However, these findings have not been confirmed recently because patients who received letrozole required higher gonadotrophin doses and produced more immature oocytes, suggesting that the response to ovarian stimulation may be impaired in patients with hormone-sensitive cancers receiving letrozole [25]. Stimulation protocols using letrozole are currently preferred over tamoxifen protocols because treatment with tamoxifen alone and tamoxifen 60 mg/d or letrozole 5 mg in combination with FSH results in a greater number of follicles (2 +/- 0.3 vs. 6 +/- 1 and 7.8 +/- 0.9 respectively), mature oocytes (1.5 +/- 0.3 vs. 5.1 +/- 1.1 and 8.5 +/- 1.6 respectively), and embryos (1.3 +/- 0.2 vs. 3.8 +/- 0.8 and 5.3 +/- 0.8, respectively). In addition, peak estradiol levels were lower with letrozole in combination with FSH and tamoxifen compared with tamoxifen and FSH [22]. Moreover, it appears that the safety of fertility preservation by ovarian stimulation with letrozole and gonadotrophins in patients with breast cancer is not compromised because it is unlikely to cause a substantially increased risk of recurrence [26]. In addition, the use of letrozole and gonadotrophins is also

associated with beneficial effects showing lower estradiol levels compared with standard stimulation cycles in young women with endometrial carcinoma [27]. Although letrozole has been shown to be teratogenic in rodents when exposure occurs during organogenesis, there is no clinical evidence that letrozole use is associated with increased birth defects, nor is this biologically plausible in the setting of ovulation induction. [28]. Therefore, in an effort to mitigate the potential effects of elevated oestrogen levels during ovarian stimulation for fertility preservation prior to gonadotoxic treatment of oestrogen-sensitive cancer patients, it may be highly advisable to use letrozole routinely as a safe, effective and novel protocol for ovulation induction [15, 19]. However, anastrozole another third-generation aromatase inhibitor has a minimal suppressive effect on rising estradiol levels during ovarian stimulation, even at five times the comparable dose of letrozole. As a result, breast cancer patients who underwent ovarian stimulation with anastrozole, despite an increased dose of the drug to 10 mg, had a significantly higher exposure to estradiol than those who were stimulated with letrozole [29]. Therefore, the use of anastrozole is not recommended in fertility preservation cycles of oestrogen-sensitive cancer patients prior to chemotherapy [15].

Complications of ovarian stimulation

Ovarian hyperstimulation syndrome the most serious complication of ovulation induction, may appear during a fertility preservation cycle in cancer patients after obtaining a sufficient number of oocytes and embryos to maximize the chance of a successful pregnancy due to time constraints before oncologic treatment. Therefore, it is important to choose the appropriate ovulation induction protocol in patients with malignancy because most of these patients have only the opportunity of a single cycle to conceive. Otherwise, the risk of ovarian hyperstimulation syndrome may result in a delay or interference of the programmed cancer treatment [15]. It is that known that hCG induces the final oocyte maturation and contributes

as the main trigger to ovarian hyperstimulation syndrome. In women at risk for the syndrome GnRH agonists can be used as an alternative to hCG in GnRH antagonist-based regimens, which reduce the risk owing to the short half-life of agonist-induced endogenous LH surge. Accordingly, a significantly lower rate of moderate/severe ovarian hyperstimulation syndrome in the GnRH agonist group has been found compared with patients receiving hCG (3.7 vs. 21.3%) [30]. However, trigger failures that have been observed with GnRH agonists at doses 1 mg to 4 mg may be explained by partial binding to its receptors due to competition with GnRH antagonists, resulting in a limited LH surge. It appears that with hCG supplementation (< 1500 IU) at the time of trigger there will be fewer failures. However, in women at risk for the syndrome in the case of a GnRH trigger failure determined on the next morning by low post-trigger LH (< 12 IU), an hCG (2,500-5,000 IU) trigger can be used on the same day. In the case that oocyte aspiration does not result in a retrieval of a couple of mature-sized follicles, the oocyte retrieval should be stopped and oocyte maturation should be again triggered by the same dose of hCG [15].

Patients with cancer undergoing ovarian stimulation with the exogenous administration of high dose gonadotrophin for ovulation induction are at risk of thromboembolic disease due to a hypercoagulable state associated with haemostasis and thrombophilias induced by their malignancy and hyperestrogenism. Therefore, the safety and efficacy of anticoagulation by dose-adjusted heparinisation is recommended as the first-line treatment of choice [31]. In addition, during induction of ovulation in patients at risk for thrombosis, the introduction of low molecular weight heparin as a cycle protective treatment was not associated with any medical complication [32]. Although there are no guidelines for anticoagulation during ovulation induction prophylactic low molecular weight heparin may be stopped 24 hours before the oocyte retrieval and reinitiated 12 hours after the retrieval continuously until oestrogen returns to its baseline level. An alternative strategy of

anticoagulant therapy is the use of letrozole at 2.5 or 5 mg/d during ovarian stimulation to decrease oestrogen concentrations similar to those in natural cycles [15].

Conclusions

It is important to choose the appropriate controlled ovarian stimulation protocol for oocyte/embryo cryopreservation in patients with malignancy because most of these patients have only the chance of single cycle chance to conceive prior to cancer treatment. The influence of ovarian hyperstimulation syndrome may be a serious complication in cancer patients because it may result in a delay and interference of planned cancer treatment. Current treatment protocols offer a minimal time delay until malignancy treatment is commenced. Emergency IVF is a promising approach for preserving fertility in cancer patients, because random-start ovarian stimulation protocol represents a new technique which provides a significant advantage by decreasing the total time of the IVF cycle. In addition, it may be started irrespective of the phase of the cycle for the purpose of fertility preservation without compromising oocyte yield and maturity before cancer treatment. However, in patients with oestrogen-sensitive cancers stimulation protocols using letrozole are currently preferred over tamoxifen regimens, because treatment with letrozole in combination with gonadotrophins results in a greater number of follicles, oocytes and embryos. Therefore, it may be highly recommended to use letrozole with gonadotrophins routinely as a safe, effective and novel protocol of ovulation induction for oocyte/embryo cryopreservation in cancer patients prior to oncologic treatment. Despite the efficacy of these newly developed ovarian stimulation protocols in order to obtain the maximal number of oocytes and embryos for fertility preservation, future studies are required to estimate their final implantation and conception success rates.

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