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TOPIC HIGHLIGHT

Mona A El-Bahrawy, MBBCh, MSc, PhD, FRCPath, *Series Editor*

Ovulation induction in the gynecological cancer patient

Amr H Wahba, Hesham Al-Inany

Amr H Wahba, Hesham Al-Inany, Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, 11562 Cairo, Egypt
Author contributions: Wahba AH searched the literature and wrote the manuscript; Al-Inany H reviewed and edited the manuscript.
Correspondence to: Dr. Amr H Wahba, Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Kasr Al Ainy St., 11562 Cairo, Egypt. dr.amrwahba@yahoo.com
Telephone: +20-2-1002642285
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Abstract

Malignancy is a serious disease that can lead to serious morbidity and mortality. However, the survival rates for women with cancers have increased significantly during the past decades, reflecting improved diagnosis and treatment. With the increased survival in young women with cancer, more attention is being paid to preservation of fertility, which is potentially jeopardized by chemotherapy and radiation therapy, aiming to limit the devastating sequelae of this serious illness by providing these young women with a hope for motherhood. *In vitro* fertilization with oocyte or embryo cryopreservation has emerged as an astounding method to preserve fertility. It entails induction of ovulation to produce oocytes, the number and quality of which are imperative factors predicting the potential efficacy of the fertility preservation procedure. The aim of this review is to discuss ovarian stimulation for fertility preservation in women with gynecological cancer.

Key words: Ovulation induction; Ovarian stimulation; Gynecological cancer

Core tip: Malignancy is a serious illness that is potentially life threatening. However, the survival rates for women with cancers have increased significantly during the past decade, reflecting improved diagnosis and treatment. The aim of this review is to discuss options for ovarian stimulation for fertility preservation in women with gynecological cancer.

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CANCERS IN REPRODUCTIVE AGE

Over the past two decades, cancer incidence rates have continued to increase[1], with approximately 10% of female cancer cases occurring under the age of 45 years[2]. Owing to the advancement in diagnosis and treatment of certain cancers at an earlier stage, improvement has been observed in the survival rates[2], raising more attention to improving the quality of life, particularly through the preservation of fertility, in these young women.

Candidates for fertility preservation are a rather heterogeneous group with a variety of underlying malignancies, the most common cancers being breast, melanoma, cervical, non Hodgkin's lymphoma and leukemia[3,4]. Gynecological cancers in this context include cancer of the breast and cancers arising from the reproductive organs (ovary, uterus, cervix and vulva). These cancers can affect patients in their reproductive years when their childbearing is not completed yet.

Approximately half of the demand for fertility preservation is from women with breast cancer[5] since it is the most common cancer in women in developed countries. In Europe, the incidence of breast cancer in premenopausal women over the past three decades was 30/100000[6]. Approximately 2% of cases occur in women aged 20-34 years and 11% in women aged 35-44 years[7]. Survival rates for breast cancer have risen in recent years, reaching 81%-87%.

Table 1 Risk of ovarian damage according to chemotherapy treatment used

High risk	Moderate risk	Low risk
Cyclophosphamide	Cisplatinum	Vincristine
Ifosfamide	Adriamycin	Vinblastine
Chlorambucil	Actinomycin	Methotrexate
Melphalan		Bleomycin
Busulfan		
Nitrogen mustard		
Procarbazine		

Endometrial cancer is considered the most common gynecological malignancy in the United States according to the American Cancer Society and the fourth most common cancer among women, behind only breast, lung and colorectal cancer[8]. However, it is rarely encountered for fertility preservation since more than 80% of cases occur in postmenopausal women and only less than 5% develop in patients younger than 40 years[9]. Ovarian cancer is primarily a disease of older women; however, it is estimated that 3% to 17% of ovarian tumors occur in women aged ≤ 40 years[10].

The oncological management of gynecological cancers used to bring the patient's fertility potential to an end due to the surgical removal of the reproductive organs harboring the malignancy. However, recently fertility sparing management of such cancers has been developed to safely remove or treat cancer without extirpating the reproductive organs. These include development of new surgical techniques, *e.g.*, radical trachelectomy for early stage cancer cervix (stage I AII)[11], unilateral adnexectomy with preservation of contralateral ovary and uterus for low malignant potential ovarian tumor[12] and early stage cancer ovary (stage I)[13], as well as novel treatment modalities, *e.g.*, high dose progestin therapy for early stage endometrial cancer (stage I A, grade 1)[14].

However, conservative surgery might entail the use of adjuvant chemotherapy or radiation therapy, both of which can still adversely affect the fertility potential. Ginsburg *et al*[15] reported decreased response in patients with cancer who had received chemotherapeutic agents before oocyte retrieval. The effect will depend on the patient's age as well as the type and dose of chemotherapeutic agent. According to their effect on ovarian reserve, chemotherapeutics are divided into three groups (high, moderate and low risk) (Table 1[16]). Alkylating agents seem to present the greatest risk of ovarian failure due to the profound loss of primordial follicles[17]. The effect of radiation therapy depends on the patient's age, site, type and dose of radiation[18].

Following fertility preserving management of gynecological cancer, the patient might conceive spontaneously. However, ovarian stimulation may be considered to cryopreserve oocytes and embryos before the adverse impact of chemotherapy/radiation therapy on ovarian reserve (as in breast cancer and cervical cancer). It might also be considered to increase the likelihood of pregnancy and decrease time interval to conception (as in endometrial cancer)[19] and in cases of associated infertility.

INDUCTION OF OVULATION IN GYNECOLOGICAL CANCER PATIENTS: THE CHALLENGES

Inducing ovulation in women with cancer should be considered cautiously and approached differently than inducing ovulation in women without cancer. Since these patients usually undergo only a single *in vitro* fertilisation (IVF) attempt before commencing chemotherapy or radiation therapy, it is crucial that as many cryopreserved embryos or oocytes as possible be obtained in this cycle for future use. Meanwhile, this should be attained with the absolute avoidance of ovarian hyperstimulation syndrome (OHSS), which can result in delay of chemotherapy and radiotherapy[20]. Unlike non-gynecological malignancies (*e.g.*, colon, hematological), gynecological cancers can be hormone responsive with resultant aggravation of the tumor due to the supraphysiological levels of estrogen released with ovarian stimulation. Thus, the fertility specialist encounters many challenges to attain this critical mission. Among these challenges are the following:

Decreased ovarian response

There are controversial reports on how cancer patients would respond to ovarian stimulation in IVF. Although some studies observed no significant change[21,22], the reproductive capacity of patients with cancers seems to be diminished and subjects with cancers are more likely to be poor responders[23]. Pal *et al*[24] reported an apparent adverse influence of malignant disease on the quality and performance of oocytes. Many explanations have been suggested. Among them, that cancer is associated with an increased catabolic state and malnutrition, resulting in weight loss which may affect the hypothalamic pituitary axis, resulting in hypothalamic dysfunction and a decrease in gonadotropin levels, thereby impairing the reproductive capacity[25]. Cancer is also associated with an increase in stress hormones which can lead to an increase in prolactin and endogenous opiate production, suppressing gonadotropin levels and further reducing fertility[26]. Moreover, recently Oktay *et al*[27] reported that women with breast and ovarian cancer, carriers of BRCA1 mutation, may respond poorly to ovarian stimulation. This may indicate a possible role of BRCA1 as an important factor responsible for the impairment in double stranded DNA break repair and a woman's infertility.

Time factor

Induction of ovulation has to be initiated before chemotherapy or radiation therapy since both therapies have deleterious effects on the ovarian reserve, resulting in premature ovarian failure and subsequent infertility[28]. Meanwhile, it is important to avoid prolonged deferral of chemotherapy or radiation therapy which can be det-

rimental to the success of cancer therapy. Typically, there is a gap of 4 to 6 wk between women undergoing breast cancer surgery and the commencement of chemotherapy, which is often sufficient to undergo ovarian stimulation. However, delayed referral of the patient to the fertility specialist results in time pressure. In this case, the best protocol that allows the quickest initiation of ovarian stimulation should be selected to shorten the deferral of chemotherapy/radiotherapy and allow early commencement of therapy. This can be ideally achieved with the use of the GnRH antagonist protocol[29]. In the conventional stimulation protocol, depending on the timing of the patient presentation, it takes up to 3 wk to reach the luteal phase when downregulation with a GnRH agonist can be started and continued for about 2 wk to prevent premature ovulation. Then, 9-14 more days are needed for ovarian stimulation with gonadotropins. On the contrary, GnRH antagonists immediately suppress the release of FSH and LH, preventing a premature LH surge. Administration is started when the size of the lead follicle reaches 12-14 mm at approximately day 6 of gonadotropin stimulation which begins on day 2, 3 of a menstrual cycle. Thus, GnRH antagonists significantly decrease the interval from patient presentation to oocyte retrieval compared to the conventional GnRH agonist protocol[30].

Instead of awaiting menses, further shortening of the interval to oocyte retrieval has been suggested by administering a GnRH antagonist during the preceding luteal phase to induce corpus luteum breakdown and synchronize the development of the next wave of follicles[31]. Menses will ensue a few days later with the ovarian stimulation initiated more quickly and the GnRH antagonist would then be restarted in the standard fashion[31]. Random-start stimulation protocol has been recently proposed as another alternative to avoid time wastage while awaiting the menses[32,33]. In this protocol, cancer patients in the luteal phase were started on GnRH antagonists to downregulate LH and initiate luteolysis. Simultaneously, follicular stimulation was initiated with recombinant FSH only to avoid exogenous LH activity which might prevent luteolysis. When this protocol was compared in a prospective multicenter trial with cancer patients stimulated during the follicular phase with either a short "flare up" protocol or an antagonist protocol, random start stimulation protocol yielded a similar number of aspirated oocytes, mature oocytes and fertilization rate[33]. However, more clinical studies are needed to assess the efficacy of this protocol, especially regarding the rates of clinical pregnancy and live-born infants originating from the use of cryopreserved embryos and oocytes[34]. It is important to stress that once a cancer diagnosis is established, early referral to a fertility specialist is highly encouraged to avoid unnecessary delay and facilitate prompt initiation of ovarian stimulation[35].

The associated increase in estradiol levels in hormonal dependent cancers

Induction of ovulation is typically associated with increased levels of estradiol. This can be serious in women with estrogen sensitive cancers, such as breast and endometrial cancer. Many strategies have been applied to minimize these estradiol peak levels. Among them are the following: (1) Tamoxifen. Tamoxifen can be used for controlled ovarian stimulation alone, starting on day 2-5 of the menstrual cycle in doses of 20-60 mg/d or in combination with gonadotropins**.** Not only does tamoxifen lower the peak estradiol levels compared to standard stimulation protocols[36], but also it has an antiestrogenic effect on breast tissue and is thus desirable to be used in estrogen receptor-positive breast cancer patients[37]; (2) Aromatase inhibitors. Aromatase inhibitors (including anastrozole and letrozole) are drugs of choice for the treatment of breast cancer in women with receptor-positive metastatic breast cancer. Their use has also been introduced as a new treatment option for ovulation induction[38]. It was reported that the peak estradiol level is lower in protocols that use aromatase inhibitors for ovarian stimulation[36]. Oktay *et al*[36] were the first to describe the use of letrozole in the GnRH-antagonist protocol in a study of 29 patients with breast cancer. The study included 33 ovarian stimulation cycles. In their study, letrozole in combination with FSH (letrozole-IVF) was compared to tamoxifen alone (Tam-IVF) and to tamoxifen in combination with FSH (TamFSH-IVF). They concluded that letrozole-IVF and TamFSH-IVF yielded more follicles, more mature oocytes and more embryos than Tam-IVF. Peak estradiol levels were lower with letrozole-IVF and Tam-IVF compared with TamFSH-IVF. Azim *et al*[39] described the use of letrozole in combination with gonadotropins in four patients with endometrial cancer. The estradiol levels in their study were lower compared with standard stimulation cycles. Data on the use of anastrozole for ovarian stimulation in anovulatory women, however, is more limited and studies so far do not support its use due to higher peak estradiol levels compared to letrozole[40]; (3) Using low doses of gonadotropins. The use of low dose gonadotropins (FSH 150 U/d) in the GnRH antagonist protocol in combination with letrozole was found to result in acceptable oocyte yield while maintaining low estradiol levels[36]. However, the use of higher doses of gonadotropins (FSH 150-375 U/d) in a GnRH antagonist protocol in combination with letrozole was recently studied by Ben-Haroush *et al*[41]. They reported a higher number of retrieved oocytes and frozen embryos than the lower dose schedule used in the study by Oktay *et al*[36], while similarly resulting in low levels of peak estradiol; (4) Using a GnRH antagonist protocol allows quick initiation of ovarian stimulation and pituitary suppression with a GnRH antagonist reduces the concentration of estradiol in patients with hormone dependent tumors[42]. Ben-Haroush *et al*[41] compared the use of high doses of FSH (150-375 U/d) in combination with letrozole in GnRH antagonist *vs* the long GnRH agonist protocol. Although the number of retrieved oocytes was higher in women in the long GnRH agonist protocol than the GnRH-antagonist protocol, the difference was not statistically significant; and (5) GnRH agonist trigger in the GnRH antagonist protocol has been shown to yield lower

estradiol concentrations compared to hCG trigger which potentiates the endogenous production of estrogen during the luteal phase owing to its longer half-life[43].

Avoidance of OHSS

OHSS is the most serious complication of ovarian stimulation since it is associated with significant morbidity which might necessitate hospitalization and intensive care. In cancer patients, the occurrence of this complication is critical since it may result in delaying or complicating planned life-saving cancer therapy. The risk of OHSS can be significantly lowered with the use of a GnRH antagonist protocol since it allows the use of a GnRH agonist trigger instead of the traditional hCG trigger if there is suspicion of overresponse to stimulation. Triggering the final oocyte maturation with hCG carries the risk of inducing OHSS[43], while using a GnRH agonist trigger in GnRH antagonist-based protocols dramatically reduces the risk of OHSS owing to the short half-life of GnRH agonist-induced endogenous LH surge which lasts for approximately 24-36 h compared to the longer half life of hCG which lasts for 7-10 d[44]. A recent Cochrane review comparing hCG to GnRH agonist trigger in antagonist cycles confirmed a 90% reduction in moderate to severe OHSS in the GnRH agonist group (OR = 0.10; 95%CI: 0.01-0.82 5 RCTs, 504 women)[45]. Meanwhile, the use of a GnRH agonist trigger was found to result in at least similar numbers of mature oocytes and cryopreserved embryos compared with hCG[46].

Therefore, in cases of estrogen sensitive cancers, the most recommendable protocol for induction of ovulation is the use of a GnRH antagonist in combination with letrozole (5 mg/d from the second day of menstrual cycle for 5-7 d) plus low dose gonadotropins[36]. This regimen allows an acceptable oocyte yield and keeps the circulating estradiol levels rather low compared with the standard ovarian stimulation protocols[47].

SAFETY OF OVARIAN STIMULATION IN CANCER PATIENTS

Safety is a major concern when considering induction of ovulation in cancer patients for the aim of fertility preservation, which may potentially decrease the chance of successful cancer treatment, increase the risk of maternal or perinatal complications, or compromise the health of offspring.

Risk of recurrence after ovarian stimulation

The risk of recurrence and the adverse impact on survival are real concerns for gynecological cancer survivors who desire to conceive after cancer therapy. Many studies have shown that pregnancy after breast cancer treatment does not appear to adversely affect recurrence or survival[48,49]. Oktay *et al*[36] followed their patients for a mean duration of 554 ± 31 d and they found that the cancer recurrence rate was similar in the IVF and control groups (3/29 *vs* 3/31 patients, respectively; HR = 1.5, 95%CI: 0.29-7.4). They noticed that the risk was not affected by cancer stage. In a larger follow-up report by Azim *et al*[50], the rate of cancer recurrence was compared among 79 women who elected to undergo ovarian stimulation with letrozole and gonadotropins for embryo or oocyte cryopreservation and 136 control patients (whom did not undergo fertility preservation procedures). The median follow-up after chemotherapy was 23.4 mo in the study group and 33.05 mo in the control group. They concluded that the recurrence and survival rates were similar in the two groups[50]. Thus, based on the above studies, induction of ovulation does not seem to increase the risk of recurrence compared to controls; however, more studies and longer follow up are needed.

Women who had undergone fertility sparing management for endometrial cancer did not have a higher incidence of cancer recurrence with the use of fertility drugs[51].

Several rare cases of ovarian stimulation have been reported in the literature after conservative treatment for borderline or invasive ovarian tumors[52-54]. Several pregnancies were achieved but in one case a uterine recurrence was observed and, most importantly, one woman died 7 mo after ovarian stimulation following extensive recurrence of an invasive lesion[52-54].

Newborn safety

Concerns about the safety of letrozole have been raised by the American Society for Reproductive Medicine through an abstract claiming possible teratogenic effects of letrozole[55], for which the use of letrozole for the purpose of induction of ovulation was discouraged. However, this concern was not supported by a large trial published in 2006 comparing newborn safety of letrozole with that of clomiphene citrate showing that congenital malformations were less frequent in the letrozole group[56]. It has been shown that the half-life of letrozole (approximately 30-60 h) is shorter than that of clomiphene citrate (5-7 d) and, thus, should be effectively cleared from the body by the time of embryo implantation, likely preventing a teratogenic effect when used in ovulation induction[57]. Another concern of cancer patients is whether offspring exposed to cytotoxic agents have an increased risk of birth defects. Several large studies that included more than 4000 offspring of cancer survivors showed no statistically significant increase in childhood malignancies or genetic malformations[58].

CONCLUSION

Fertility preservation through IVF technology is an evolving discipline that can minimize the devastating sequelae of cancer. Induction of ovulation is the critical step that determines the success of the fertility preservation. Gynecological cancers represent a real challenge to the fertility specialist due to possible hormonal responsiveness of the cancer, making induction of ovulation potentially detrimental. The use of GnRH antagonists, aromatase

inhibitors and triggering with GnRH agonists may provide reliable methods to minimize the unfavorable rise in estradiol levels. So far, reports on the safety of ovulation induction in these patients are reassuring and young women with cancer should be counseled about the option of fertility preservation as soon as the diagnosis of cancer is established.

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