Clinical Medicine Insights: Reproductive Health

REVIEW

Fertility Preservation in Gynecological Cancers

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Abstract: For cancers of reproductive system in women, fertility preservation is complex. Fertility is also affected by therapies, however prevention is possible. Radiotherapy affects gonads, uterus, and subsequent pregnancy outcomes in all ages. However, degree and damage depend on dose, irradiation field, and age at the time of exposure. Ovarian transposition is considered if ovarian involvement is unlikely. Gonadotoxic effects of chemotherapy are related to agent's type, cumulative doses, age, and ovarian reserve. Some agents are highly toxic. Rendering follicular development quiescent by suppression of gonadotropins does reduce the ovarian damage. Simple or radical trachelectomy can be used in early cervical cancer. Fertility saving surgery is possible only in early stage low grade epithelial cancers of the ovary, however, in germ cell tumors even in advanced stages it may be possible to preserve fertility. There are no standard recommendations for endometrial cancer. Embryo, oocyte, and ovarian tissue cryopreservation are possible. The human embryo is very resistant to damage. In view of these possibilities, it is advocated that attention to long term health and quality of life in gonadotoxic therapy must be incorporated into plans as early as possible.

Keywords: fertility, preservation, cancers, gynecological

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Background

Some years back, it was predicted that in 2010, every 250th adult will be a survivor of childhood cancer.[1] As cancer survivors are increasing and assisted reproductive technologies (ART) are developing, fertility preservation of the reproductive-age women with cancer is emerging as a challenging, but rewarding, application of ART. When faced with the diagnosis of any cancer, reproductive-age women have to face the possibility of never conceiving a child with their own eggs. Preservation of fertility in men may be easier with the banking of sperms before treatment but for the women, storage of the gametes is technically very complex with limited success.

While cancer anywhere in the body affects reproductive system because of the effects of therapies, when cancer is of reproductive organs, it is a complex and possibly devastating situation. All the therapies which are used in genital cancers affect fertility however preventive modalities are also being discovered. Fertility preservation is being considered in various clinical situations, like cervical cancer, low grade endometrial adenocarcinoma, and certain ovarian tumors (border-line tumors, epithelial cancers, germ cell tumors).[2–4]

Treatments and Therapies

Radiotherapy

Ovarian effects

Ovarian damage can occur due to radiotherapy. While damage occurrence is irrespective of age, the degree and persistence of the damage is dependant on the dose, the irradiation field, and the patient's age, older women are at greater risk of damage.[5] Wallace et al[6] have reported that the effective sterilizing dose (ESD, dose of fractionated radiotherapy [Gy] at which premature ovarian failure occurs immediately after treatment in 97.5% of patients) decreases with increasing age. ESD at birth is 20.3 Gy, 18.4 Gy at 10 years, 16.5 Gy at 20 years, and 14.3 Gy at 30 years. Authors have calculated 95% confidence limits for age of premature ovarian failure with estimated radiation doses from birth to 50 years.

It was reported by Lushbaugh and Casarett[7] that women under 40 years of age are less sensitive to radiation-induced ovarian damage, with an estimated dose of 20 Gy required to produce permanent ovarian failure in comparison to 6 Gy in older women. The lethal dose of radiation required to kill half of the primordial follicles in the ovaries is estimated to be less than 2 Gy.[8] Stroud et al[9] report that younger patients have more follicles and therefore require higher doses of radiation to ablate ovarian function.

Uterine effects

Radiation effect on the uterus and subsequent pregnancy outcome is known. Direct effects on the uterus include irreversible changes in the uterine musculature and blood flow, as well as hormone resistant endometrial insufficiency. Uterine irradiation is associated with infertility, miscarriage and intrauterine growth retardation, and higher rates of obstetric complications in comparison with the general population. These higher rates occur for complications such as spontaneous abortions (38% vs. 12%), preterm labor (62% vs. 9%), and low-birth weight (LBW) infants (62% vs. 6%).[8] Fenig et al[10] have also reported increase in LBW infants and spontaneous abortions, especially when conception occurred within a year of radiation exposure. Wallace et al[6] report that uterine radiotherapy in childhood or adolescence is associated with an increased incidence of spontaneous miscarriage and intrauterine growth retardation in subsequent pregnancies. Earlier, Hawkings and Smith[11] had reported no risk of subsequent teratogenicity if radiation was not administered during pregnancy; however this needs to be researched. It is also reported that doses of radiation of 14–30 Gy administered in childhood to the whole body or abdomen compromise growth and development of the uterus.[12–16] Several small series published in the 1980s demonstrated an increased risk of adverse pregnancy outcome among women who had received abdominopelvic irradiation.[11,17–19] Additionally, the likelihood of perinatal, infant mortality and LBW were significantly related to radiation dose[20] and these findings were attributed to radiation-induced uterine damage.

Prevention

Ovariopexy and ovarian transposition should be considered in each case of planned pelvic or whole body irradiation where ovarian involvement is unlikely and chemotherapy is not necessary. In order to displace the ovaries away from the radiation field, several techniques have been advocated.[21–23] In the case of

craniospinal irradiation, the ovaries are fixed as laterally as possible, away from the spine; in the case of pelvic irradiation, the ovaries are moved outside the pelvis and anchored as high as possible, to the anterior abdominal wall or laterally in the paracolic gutter. This may require section of the utero-ovarian ligaments. Titanium clips are placed on the two opposite borders of the ovaries for radiological identification.

Chemotherapy

Chemotherapy induced ovarian damage, the gonadotoxic effect of chemotherapy on female gonadal function, is dependant on the age of the patient, type of agent, cumulative doses, and the patient's ovarian reserve.[5,24] The prepubertal ovary is least susceptible to the gonadotoxicity. Older women have a higher incidence of complete ovarian failure and permanent infertility in comparison with younger women.[25,26] In everyday practice, single chemotherapeutic agents are less commonly used, except in some situations such as methotrexate in Gestational Trophoblastic Neoplasm. The effects of single agent, therefore, are not well known.[26] Chemotherapeutic agents are mostly used in combination because of better efficacy due to synergistic effects. This also leads, however, to an increase in their adverse effects. All chemotherapeutic drugs act by interrupting vital cell processes and arresting the normal cellular proliferation cycle. Alternative chemotherapy protocols can reduce long-term gonadotoxicity.

Bokemeyer et al[27] reported that alkylating agents are the most gonadotoxic.[28] The work of Oktem[29] and Familiari[30] has provided histologic confirmation of ovarian impact of alkylating agents on follicular, oocyte depletion, and ovarian fibrosis[25,31] and should be avoided whenever possible. Since pregnancies occur long after treatment is ceased, it can be assumed that there are corrective mechanisms within the oocyte or that there are undetected miscarriages at a very early stage due to dominant lethal mutations.[25]

It has been suggested that gonadotoxic treatments induce a vicious pathophysiological cycle of follicular destruction. Depletion of follicles reduce the secretion of estradiol and inhibin, which causes serum FSH concentration to rise, and may lead to enhanced recruitment of other follicles, which are further destroyed by chemotherapy.[32] Taxanes may also contribute to germ cell damage.[33]

Prevention

Rendering the ovarian follicular development quiescent by suppression of gonadotropins has been proposed to protect women from damage by cytotoxic therapy. Concomitant treatment with gonadotropin-releasing hormone agonists (GnRH-a) is likely to prevent ovarian failure induced by cancer therapy,[32] though the effectiveness of this intervention is controversial.[34] Waxman[35] reported use of GnRH-a as chemoprotective agent with reports of no improvement in outcome compared to placebo. However, multiple small studies have evaluated the utility of GnRH-a treatment in order to preserve ovarian function during cytotoxic therapy.[36–40] Treatment with GnRH-a should begin at least 1 week before the beginning of chemotherapy as the initial flare-up effect causes undesirable ovarian stimulation. The application should continue when chemotherapy is given in the form of depot-injections, so that the down-regulating effect remains for at least two weeks after the chemotherapy. In the case of estrogen sensitive tumors, tamoxifen therapy can be initiated after the GnRH-a treatment. Maltaris et al[41] report that the available information is limited due to small sample size, lack of randomized controls, and lack of definitive information regarding actual fertility outcomes. Del Mastro et al[42] report that the use of triptorelin-induced temporary ovarian suppression during chemotherapy in premenopausal patients with early-stage breast cancer reduced the occurrence of chemotherapy induced early menopause. In some studies, the results of gonadoprotective hormonal therapy have been disappointing and contradictory and with possible hazards. Not only is GnRH-a treatment expensive and causes severe menopausal symptoms, but the direct effects of GnRH-a on human cancer cells are not sufficiently understood; a variety of cells including those of the breast, ovary and endometrium express GnRH receptors. These receptors mediate several effects, such as inhibition of proliferation, induction of cell-cycle arrest, and inhibition of apoptosis, induced by cytotoxic drugs. Emons[43] reported that GnRH-a therapy concomitant with cytotoxic chemotherapy might reduce the efficacy of chemotherapy.

Advocates of GnRH-a hypothesize that chemotherapy simulates a prepubertal hormonal milieu, and through this mechanism, and/or possibly others, might minimize the gonadotoxic effect of chemotherapy

and increase the chances of spontaneous ovulations and successful conceptions and deliveries.[44–46]

Meta-analysis by Clowse et al[47] reveals that co-treatment with a GnRH-a during chemotherapy is associated with an increased odds of a woman maintaining ovarian function and having a pregnancy following chemotherapy by 68%. Meta-analysis also revealed that on average, 40% of women who undergo chemotherapy will develop ovarian failure.[47]

The other researchers also suggest that GnRH analogues are effective in protecting ovaries during chemotherapy and should be given before or during treatment, although no significant difference in pregnancy rates was seen.[48]

Wong et al,[49] in a very recent study, report that the GnRH agonist, Goserelin, given with chemotherapy for early breast cancer is associated with a low risk of long term chemotherapy induced amenorrhea and a high chance of pregnancy.

A review by Critchley and Wallace[15] reveals that physiological sex steroid replacement therapy improves uterine characteristics in some patients after irradiation at a young age.

Patients who recover from ovarian failure after high-dose chemotherapy or radiotherapy should not delay childbearing for too many years and should try to conceive after a few years of a disease-free interval, not for a year after the treatment, due to the possible toxic effects of the treatment on growing oocytes.[50]

Surgical therapy

For all three common gynecological cancers, fertility protecting surgeries have been advocated, some with proven efficacy, others are to be tested. Vulvar, vaginal and fallopian tubes' cancers are uncommon. For vulvar cancer, conservative therapies have been advocated.

Cervical Cancer

Cervical cancer, the most common cancer in women of Africa, Central and South America, and Asia, constitutes 20% to 30% of all cancers among women, however invasive cancer before 35 years of age is relatively uncommon.[51,52] In Spain, where the prevalence of cervical cancer is one of the lowest in Europe, 10% to 15% of cases are diagnosed in reproductive age.[53]

Standard treatments of invasive cancer in early stages are radical hysterectomy and pelvic radiotherapy, both of which are almost incompatible with normal fertility. The incidences of cervical cancer is increasing in young women and women are delaying their childbearing.[54,55] These two phenomena have led to an increased recognition that the pressure of fertility preservation needs to be looked into.[56] The idea is not new. In fact the idea of preserving the uterine corpus and the adnexae during radical hysterectomy was first published by Aburel in 1932, cited by Chiricuta[57] and Dursun[58] and many others. However, no follow up data or successful pregnancies have been reported.

Simple trachelectomy (cervicectomy) and radical trachelectomy (resection of parametrial tissue with cervix) are being used in women with early stage disease. Cervical conization used in preinvasive cancer as investigative biopsy could also become a therapy. Radical trachelectomy has been proposed by Dargent as a conservative treatment for cervical cancer in stage 1A or 1B tumors (less than 2 cm) and without evidence of pelvic metastasis combined with pelvic lymphadenectomy, open or laparoscopic.[59] The radical vaginal trachelectomy was developed for treatment of stages IA to IIA cancers in 1987, allowing preservation of the uterine fundus, removal of the cervix, part of the parametrium, and the upper one-third of the vagina.[59] The similarity of abdominal radical trachelectomy to a traditional radical hysterectomy lends itself to its use. Pregnancies following the abdominal radical trachelectomy procedure have been reported.[60–65] There have been no recurrences of tumors in patients treated with abdominal radical trachelectomy in the study by Ungar.[55] Dargent et al[59] suggest that the vaginal approach limits the parametrial resection to tissue in the medial half of the broad ligament, restricting radical vaginal trachelectomy to those women with tumors less than 2 cm and with invasion of less than 10 mm. Because the abdominal radical trachelectomy procedure appears to be equivalent to the traditional radical procedure, this limitation may not be applicable to abdominal trachelectomies. Complication rates for radical abdominal trachelectomy appear to be similar to those of radical hysterectomy. Ureteric injury was the only intra-operative injury in the series by Ungar.[66] Subsequent fertility of women who undergo the abdominal approach is probably similar to that of the vaginal approach. In a study of 236 women reported to have undergone radical vaginal trachelectomy,[67] 63 live born babies have been reported. Successful pregnancies have been reported

with radical trachelectomy procedure[68] with a 72% to 73% chance of full term birth.[61,69] However, concerns about long term adverse events limit the possibility of recommendation of this technique for general use.[70] Radical trachelectomy does not appear to increase recurrence rates compared with radical hysterectomy, though some have reported this.[59,71,72]

Adverse effects of the treatment include cervical stenosis, dysmenorrhoea, infertility, hematometra, hematosalpinx, or endometriosis. First trimester miscarriage rate comparable to the rate in the general population has been reported, however the rate of second trimester miscarriage is higher (9.5% vs. 4%).[73,74] The rates of preterm births vary among the different studies (22/6 cases, 56/6 cases and 3/1 cases), depending on the surgical expertise of the teams performing the intervention.[74,75] Therefore, a more conservative treatment, the simple trachelectomy, has been proposed.[76]

Endometrial Adenocarcinoma

Hysterectomy with bilateral salpingo-oophorectomy is the procedure of choice for endometrial adenocarcinoma treatment as it facilitates complete staging.[53] The prognosis of a well differentiated endometrial carcinoma without myometrial invasion is excellent and the 5 year survival rate exceeds 95%.[70] However, 3% to 5% of endometrial cancers occur in women younger than 45 years.[70] Conservative options are justified only in highly selected cases of young women who wish to preserve fertility with stage 1A endometrial cancer or endometrial atypical hyperplasia with well differentiated endometrioid pattern (G1) with absence of concurrent ovarian cancer. Conservative options include treatment with hormones with different routes of administration based on hormone sensitivity of these tumors. Hormones include progestogens, antiestrogens, GnRh agonists, and aromatase inhibitors,[77] while the most widely used are progestogens. Primary treatment with progestins is a safe and effective therapy for women with well-differentiated endometrial adenocarcinoma who wish to preserve fertility. Response of endometrial cancer to progestogens varies between 50% to 75%.[78] Medroxyprogesterone acetate (MPA) is the progestogen most commonly used and has a response rate of 75%.[70,79,80] Approximately 24% of the patients who respond to hormone treatment have recurrence.[80] Although pregnancies have been documented in women treated for endometrial cancer with hormone therapy, it is premature to establish treatment guidelines and suitability criteria.[81–83] However, conservative management of well-differentiated endometrial carcinoma in young patients, combined with assisted reproductive technologies, (ART) if needed, does not seem to worsen the prognosis. All the patients presented in the series by Gotlieb[81] responded to treatment, although longer treatment periods were needed in some cases. Responses were durable, and recurrences responded well to high-dose oral progestins. There are no standard recommendations for selection of appropriate women, treatment protocols, or long-term surveillance for conservative management of clinical stage 1 endometrial adenocarcinoma, and larger prospective clinical studies are warranted.[84]

Ovarian Cancer

Usually, patients with ovarian carcinoma have locally advanced disease with extension to other reproductive organs (uterus, fallopian tube and other ovary).[85] In invasive ovarian cancer, fertility saving surgery is confined to early-stage and low-grade disease.[86] Candidates for these procedures need to be selected according to the FIGO stage, grade, ploidy state, histological subtypes, and patient's desire. The rates of recurrence following conservative and radical surgical procedures in low-stage and low-grade tumors are 9% and 11.6% respectively, and disease-free and overall survival rates do not differ significantly, with 5 and 20-year survival rates of 95% and 80% respectively.

Border-line ovarian tumors

Borderline ovarian tumors, neoplasms of controversial biologic potential and clinical significance, appear to share a risk profile similar to that of malignant ovarian tumors, but tend to occur at younger ages and are associated with a much better prognosis.[87–89] In young women who wish to preserve fertility, surgical staging followed by conservative surgery may be considered in borderline cases. Occult metastasis are not common, with a frequency lower than 5%.[90,91] Approximately half of such diagnoses are made in women younger than 40.[85,91–96] About 20% of cases occur in premenopausal women, for whom maintaining fertility can be a significant concern, as many may not have started or completed their expected family.

Conservative surgical techniques are ovarian cystectomy, ovariectomy, and salpingo-ovariectomy; unilateral or bilateral cystectomy is associated with a higher recurrence rate.[97,98] According to a review of various studies, the risk of relapse of a borderline tumor after ovarian stimulation treatment is 19.4% (n = 12/62) however, none of these relapses resulted in death. Nevertheless, the patient should be informed that stimulation treatments may be associated with an increased risk of relapse.[99]

Although the rate of new lesion/recurrence is relatively high, especially in those treated with ovarian cystectomy, mortality remains low. Many patients who desire pregnancy are able to conceive and deliver healthy offspring after conservative surgery.[100] However the post treatment reproductive performance of women who undergo conservative surgery for borderline ovarian tumors has not been adequately studied.

Invasive epithelial tumors

Between 3% to 17% of patients with ovarian cancer are younger than 40 years; 7% to 8% of younger than 35 years of age[101] and most women with ovarian cancer are diagnosed when the cancer is already at an advanced stage.[102,103]

Young women who desire to preserve their fertility and have stage 1A or 1B well differentiated (G1) disease can be considered for conservative treatment.[104] Unilateral salpingo-oophorectomy is considered an appropriate therapy, however 15% of apparently stage 1 ovarian carcinoma have lymph node involvement.[70] The results of unilateral salpingo-oophorectomies have been compared with hysterectomies and bilateral salpingo-oophorectomies, with the five year survival rate similar in both groups. In another study, the recurrence rate of both treatments was 9% and 11.6% respectively.[90] Schilder et al[105] found survival rates of 98% at five years and 93% at 10 years with stage 1A to 1C epithelial ovarian carcinoma treated conservatively. Other authors report similar recurrence rates in different stages treated with conservative surgery.[106]

Germ cell tumors

Germ cell tumors are the most common ovarian cancers found in children and adolescents. Eighty percent of malignant germ cell tumors are diagnosed at less than 30 years of age, and 70%–75% of patients have Stage I disease.[86] Conservative surgery is generally used in malignant germ cell tumors, even in advanced stages. The relation between ovulation induction and tumor recurrence is not consistent in the literature. Spontaneous pregnancy rates following fertility saving surgery have been reported as 60%–88% and menstrual irregularities caused by chemotherapy are transient.[86] The congenital malformation rate of ovarian cancer patients is slightly higher than that of the normal population, but no significant difference has been observed between patients who receive or do not receive chemotherapy.[86]

Other Fertility Preservation Strategies

Increasing survival rates in patients affected by oncological disease and advances in reproductive medicine have led to the development and increasing use of various fertility preservation techniques.[107] For children, adolescents, women without partners, or women wishing to retain their ability for paternity selection at the time of fertilization, oocyte cryopreservation is the only fertility-sparing option as ovarian stimulation and oocyte collection have ethical issues with regards to time needed. Many adult cancer patients will not have sufficient time to undergo ovarian stimulation for oocyte or embryo freezing, however ovarian tissue freezing can be done at any time during the cycle and does not require any delay in the chemotherapy. Any patient who must receive chemotherapy or radiotherapy can thus be considered a candidate for ovarian transplantation if her cancer has a low risk of ovarian metastasis.

The human embryo is resistant to damage caused by cryopreservation, which is a widely used method of fertility preservation and has been available to cancer patients for years. The only prerequisite for providing such a service is the ability to cryopreserve cleavage-stage embryos, a standard technique employed by in vitro fertilization (IVF) clinics for the banking of spare embryos and for situations in which the transfer of fresh embryos is contraindicated.

Ovarian cortex cryopreservation is initiated either for future reimplantation or follicular isolation and in vitro maturation (IVM).[108] IVM of follicles isolated from cryopreserved ovarian cortex has not yet resulted in pregnancy, but the reimplantation

technique has yielded pregnancies and live births. At present, cryopreservation of ovarian tissue appears to be a very promising way of providing the cancer patient with a realistic chance of fertility preservation, a prospect that is also extremely important for psychological reasons.[4] Cryopreservation and transplantation of ovarian tissue seems to be the most promising way of future fertility. However, the process of germ cell harvest itself might be mutagenic. The risks of ovarian tissue cryopreservation include reimplantation of the primary tumor, malignant transformation, as well as risks related to the invasiveness of the procedure.[109] Some report that in vitro fertilization and embryo cryopreservation is the only established method for fertility prevention in female cancer patients.[111]

IVM during the luteal phase can be offered to patients as an optional treatment for urgent fertility preservation when there is insufficient time for conventional follicular phase oocyte retrieval before chemotherapy is initiated.

Oocyte banking is more problematic than cryopreservation of sperms or embryos. The first obstacle is the sensitivity of oocytes to chilling, probably because of the sensitivity of the spindle apparatus and the higher lipid content of the cells. Cooling and exposure to cryoprotecting agents (CPAs) affect the cytoskeleton and may aggravate the already high incidence of aneuploidy in human oocytes.[111] Cryopreservation of oocytes has been described in prepubertal girls in association with ovarian cortex cryopreservation.[112] At the time of surgical biopsy, antral follicles observed on the ovarian surface are aspirated and the retrieved immature oocytes are then matured in vitro and cryopreserved. Cryopreservation of mature and immature oocytes (necessitating in vitro maturation) is still assumed not to be safe for the offspring. With the introduction of intracytoplasmic sperm injection (ICSI) technique and the publication of reassuring data,[113] efforts to cryopreserve oocytes have resumed in recent years, with conventional slow cooling—rapid thawing protocols followed by vitrification.

Brydoy[114] suggests that patients at risk for hypogonadism and infertility should be defined prior to treatment, and available methods for gonadal protection should maximally be utilized. During follow-up, oncologists should routinely address these issues.[115]

Conclusions

The radical trachelectomy procedure in cervical cancer, hormonal treatment of early endometrial cancer, conservative surgical management of early-stage epithelial ovarian cancer, and novel assisted reproductive technologies for women with impaired ovarian function after cancer treatment are the options for fertility preservation in young women suffering from gynecological cancers.

Options available for fertility preservation that also prevent premature ovarian failure (POF) including the use of GnRH-a during cyclophosphamide (CYC) therapy are increasingly advocated.[43,115,116] GnRH-a has a clear advantage over vastly more expensive, invasive, and inconvenient therapies such as cryopreservation of embryos or ovarian tissue. The extensive comorbidities associated with POF, compounded by poor compliance with hormonal therapy (HT), as well as contraindications for HT among patients with hypercoagulability, make prevention of POF the most attractive strategy. If ovarian protection can be achieved with simple, adjunctive GnRH-a therapy and prevention of POF related comorbidities, it would be clearly cost-effective in comparison to assisted reproductive technologies, which are costly, labor intensive, and focus solely on fertility, without addressing gonadal protection and long-term health issues associated with hypoestrogenism. GnRH-a has the best likelihood among currently available options of preventing POF in women receiving CYC. Increased awareness of the health risks associated with POF is needed.

Canavarro and Pires[117] advocate that the psychological implications of the interface between gynecological cancers and reproduction need to be taken into account in women's health care for which it is necessary to consider the complexity of this interface in three main areas: infertility, decision-making about childbirth, and cancer diagnosis during pregnancy.

With survival after many malignancies improving,[118–120] attention to long-term health and quality of life for patients facing gonadotoxic therapy during their reproductive years must be incorporated into their health care plan as early as possible. A broad focus on ovarian protection and related women's health issues, rather than focus on fertility preservation, is required as the singular goal.

Author Contributions

Conceived and designed the experiments: SC. Analyzed the data: SC. Wrote the first draft of the manuscript: SC. Contributed to the writing of the manuscript: IK. Agree with manuscript results and conclusions: SC, IK. Jointly developed the structure and arguments for the paper: SC, IK. Made critical revisions and approved final version: SC. All authors reviewed and approved of the final manuscript.

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