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# Fertility Preservation in Gynecologic Cancers Patients

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## 1. Introduction

Infertility can arise as a consequence of treatment of oncological conditions. (5) The parallel and continued improvement in both, the management of oncology and fertility cases in recent times, has brought to the fore-front the potential for fertility preservation in patients being treated for cancer. (26)(27)

Clearly Oncologists must be aware of situations where their treatment wills affect fertility in patients who are being treated for cancer and they must also be aware of the pathways available for procedures such as cryopreservation of gametes and/or embryos. (6)

This surge in activity is based largely on the improved survival of women and girls from malignant disease. This has been particularly so in paediatric oncology, with a transformation from very low success rates for many conditions to the current situation where 80-90% of children with cancer can expect to survive long term. (1)

The loss of fertility is a common consequence of the use of many therapeutic agents for non-malignant as well as malignant conditions, including systemic lupus erythematosis and other rheumatological diseases. Bone marrow stem cell transplantation with chemotherapy conditioning is now being used in many other conditions.

Some people are at risk for impaired fertility or infertility because of exposure to occupational or environmental hazards and thus might want to take measures to preserve their fertility. For example, some industries, particularly textiles, clinical laboratories, manufacturing, printing, and dry cleaning, frequently involve exposure to chemical hazards. Health-care workers can receive significant exposures to gonadotoxic agents such as estrogenic compounds, anesthetic gases, and chemotherapeutics, or compounds that can exert embryotoxic, teratogenic, or carcinogenic effects on the zygote, embryo, or fetus. Exposure to biologic agents (e.g., cytomegalovirus, hepatitis B virus, human immunodeficiency virus, human parvovirus B19, Listeria monocytogenes, rubella virus, or varicella/herpes zoster virus) also exposes risks to reproductive health. Also military personnel might want to take measures to preserve their fertility due to a risk of exposure to radiation, biologic, or chemical agents that can compromise their fertility. Furthermore, some individuals live in communities that could disproportionately expose them to pesticides, lead, and other toxins.

Female cancer patients between the ages of fifteen and forty-nine years are expected to not only survive their disease but also lead normal lives, mainly because of newer, more effective cancer therapies such as sterilizing chemotherapy and/or radiotherapy. (3) Consequently, fertility preservation has become an important quality-of-life issue. Problems with fertility and obstetric disorders such as early pregnancy loss, premature labor, and low birth weight have all been described after cancer treatment. (1)

There is a range of alternative options to preserve fertility, based on the type and timing of chemotherapy, the type of cancer, the patient's age and the partner status.

Fertility preservation should be an integral part of improving the quality of life in cancer survivors. However it is neither possible nor ethical to recommend the same recipe for every cancer patient.

## 2. The impact of oncology therapy on fertility

### 2.1 Surgical management

Surgery can impact on fertility. It can either render someone infertile by removal of reproductive organs or it can be affected by complications of surgery. There is no doubt, however, that in recent years there has been a tendency towards more conservative treatment for many malignancies affecting the reproductive organs.(16)

In women, there has been tendency towards less radical approaches to **cervical cancer** with the development of loop excision techniques for premalignant cervix lesions or in situ carcinoma and more recently the development of the radical abdominal and vaginal trachelectomy indicated in cervical cancer lesions stage I less than 2 cm (fig. 1), which allows a radical approach to cervix cancer that is treatable surgically, but with preservation of the uterus and thus fertility. (28)(22)

**Endometrial cancer** is usually a disease of the postmenopausal group or at least in those who have had completed their family, and therefore it's unusual for treatment of this disease, which does involve hysterectomy and bilateral oophorectomy, to impact upon fertility. Today exist the possibility to detect early stage well-differentiated tumors that can be treated with resection of the lesion and progestin therapy. (29)

Epithelial **ovarian cancer** continues to be treated radically with loss of reproductive organs. But increasing understanding of germ cell malignancies, borderline tumours of the ovary and epithelial tumors at stage IA grade I, has led to a more conservative approach to these neoplasms and often a single oophorectomy will be performed where in the past, a hysterectomy and/or bilateral oophorectomy would have been the treatment of choice. (10)

It is unusual for **vulvar carcinoma** to be seen in the reproductive age group, and although it may have major psychosexual impact is unusual that surgical treatment impact upon fertility. In the case of early-stage vulvar cancer, the radical excision of the lesion and removing and examining one or two sentinel nodes in the groin and upper leg is an effective way to detect whether cancer has spread, but also results in fewer adverse side effects with great results and without being a posible cause of infertility. (10)
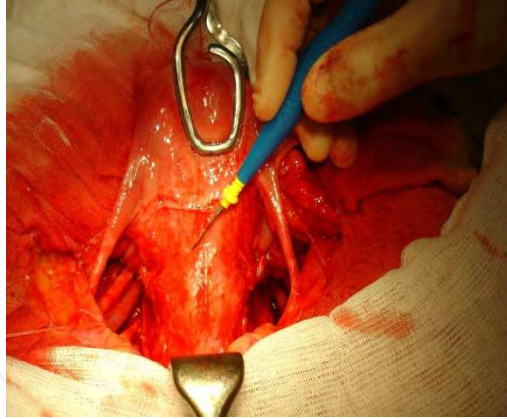
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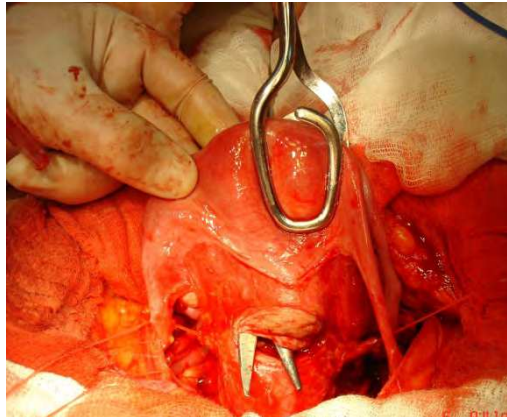


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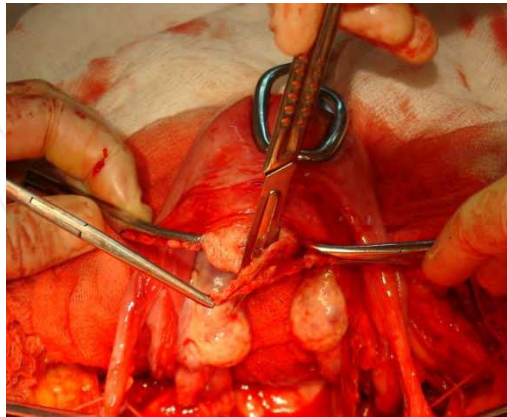


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Fig. 1. Radical Abdominal Trachelectomy for cancer of the cervix. A-B-C-D surgery stages.

## 2.2 Effects of chemotherapy and radiotherapy

With the improved survival rate of childhood and young adult cancer patients, the long-term sequelae of the treatments used are increasingly important. Current knowledge of the gonadotoxicity of commonly employed chemotherapeutic agents and radiotherapy regimens is needed to differenciate  between the effect of "high-risk" and "low-risk" agents tailoring treatment to suit the individual and counseling patients regarding reduced fertility have resulted in the best practice.

### 2.2.1 Chemotherapy

Chemotherapy can produce significant effects upon patient fertility. (27)(26) These effects are dependent on a number of factors:

- Radical versus adjuvant chemotherapy. Radical chemotherapy generally has more profound effects on fertility than adjuvant chemotherapy,
- Single agent versus combination chemotherapy. Increasing complexities of regimes are more likely to have impacts upon fertility than single agent,
- Dose-dependent effects. Increasing doses are likely to have more profound effects on fertility than lower doses,
- Drug-dependent effects. Different agents have a markedly different impact upon fertility with some chemo-therapeutic agents sparing fertility while others are extremely toxic in this regard,
- Age-dependent effects. In the female in particular, age has a profound effect on chemotherapy toxicity.

Chemotherapy regimens administered to women under the age of 40 have a much higher chance of regaining the normal ovarian function whilst the majority of women over 40, administered toxic chemotherapy will be rendered menopausal by their treatment.

Presumably part of the reason for this is the fact that the natural attrition rate of oocyte sees a large drop in oocyte numbers over age 40 (decreased ovarian reserve) and this corresponds with decreased live birth rates in fertility patients over the age of 40.

Detailed information regarding fertility effects of many chemotherapy regimes is lacking, but specific examples where chemotherapy affects fertility is documented include the following.

**Toxic effects of commonly used chemotherapeutic agents**

A fixed number of primordial follicles present at birth form the ovarian reserve into puberty. Postpuberty these primordial follicles contain single oocytes arrested in the prophase of the first meiotic division and are highly sensitive to cytotoxic drugs leading to cellular death.

Follicular depletion has been shown to be physiologically age dependent, the maximum rate of depletion occurring around the age of 38 years when the reserve is just about 10% the number present at menarche. The gonadal toxic effect is thus not just dependent on type(s) and dosage of the cytotoxic drug(s) employed but also on the age of the woman.

Cell cycle nonspecific agents such as cyclophosphamide (alkylating agent) are very gonadotoxic because they destroy resting primordial cells as opposed to cell cycle specific agents such as methotrexate (antimetabolite) and Antibiotics which spare the rest primordial cells and, as such, are less gonadotoxic.

The toxicity of chemotherapy on the ovary depends on the type of drug, the mechanism of action and the age of the patient. Alkylating agents are among the most gonadotoxic, and cyclophosphamide remain the most important since it is widely used in therapeutic regimens, especially for breast cancer. The dose of cyclophosphamide that leads to ovarian failure is age dependent, since for example requires 20.4 g for a patient aged 20 to 29 years to start with amenorrhea while for a patient over 40 years only takes 5.5 grams of cumulative dose to a total ovarian failure. Moreover, there are drugs with minimal gonadotoxic effects as antimetabolites (methotrexate and fluorouracil), alkaloids (vincristine or etopocide) and antibiotics (actinomycin-D, doxorubicin and bleomycin). The patients treated for gestational throfoblastic disease and ovarian tumors of germ line, that use this type of drugs have low gonatotoxic effect preserving the possibility of future fertility.

So we can conclude based on what we observed that:

i. Adriamycin and cyclophosphamide have a 38% ovarian failure rate in women aged over 40 years at 2 years post chemotherapy.
ii. Cyclophosphamide, Hydroxydaunorubicin (Adriamycin) Oncovin (vincristine), and Prednisolone do not usually lead to permanent amenorrhoea in women under 40 years of age, but may lead to early menopause in older women.
iii. ABVD (Doxorubicin, Bleomycin, Vinblastin, and Dacarbazine) used in the treatment of Hodgkin's disease is significantly less toxic in terms of fertility than the older MOPP (Mechlorethamine, Vincristine, Procarbazine and Prednisolone).
iv. Bleomycin and doxorubicin have minimal effects on fertility.
v. Vinca alkaloids and antimetabolites have very mild effects on fertility (Methotrexate very mild at 6 gm total dose).

vi.  Taxanes are not clearly defined in terms of their impact on fertility.
vii. Cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) a classical breast cancer regime will render 71% of women over 40 years of age amenorrhoeic at 2 years.(25)(24)

### 2.2.2 Radiotherapy

The principle of radiotherapy is based on the ionisation of cellular atoms and molecules leading to the destruction of double and single DNA structures within the cell structure.

A chain of events is set up, disrupting the cell-cycle leading to apoptosis of the cells. Radiotherapy has its use in oncology because unlike malignant cells, most normal cells have the inert ability to recover from the effects of radiotherapy.

Clearly radiotherapy can be administered as external beam therapy (teletherapy), or as intracavity (brachytherapy) treatments. In addition to this, radiotherapy can be given with radical curative intent or as adjuvant therapy often postoperatively.

The direct effects of radiotherapy are dose dependent and are also dependent on the field applied to the individual. It is important to consider the effect of scattered radiation as well as direct irradiation when assessing likely effects on fertility. (25)

The application of 14.3 Gray to an ovary in a woman over 30 years of age will usually render her irreversibly infertile and menopausal. A dose of 6 Gray to the ovary of a woman less than 30 years of age is usually reversible, but ultimately, will bring the menopause forwards.

Thus the female is not only concerned with issues regarding fertility but also with hormone production, as both seem to be equally affected by radiotherapy.

Although the uterus is relatively resistant to radiotherapy there is no doubt that uterine irradiation is harmful and even if fertility is conserved, uterine irradiation will result in poor implantation. This appears to be due to a number of factors including reduced uterine volume and blood flow which have been demonstrated to result in increased mid-trimester losses, preterm labour and intrauterine growth retardation. (1)

The vagina is relatively radio-resistant however; irradiation of this organ carries with it the risk of loss of lubrication and stenosis which may result in physical impairments to fertility as well as major psychosexual issues. (1)

## 3. Options for fertility preservation

As illustrated in Figure 2, there is a range of clinical scenarios in which different fertility preservation techniques are appropriate. These can be discussed with the patient or, in the case of a child, with the patient and her parents. (8)

The American Society of Clinical Oncology (ASCO), the American Society for Reproductive Medicine and the NICE guidance recommend that all such patients of childbearing age be informed about fertility preservation treatment options. Despite these recommendations and the expanding availability of fertility preservation services, surveys of oncologists have revealed that only a small minority of eligible patients are referred to reproductive endocrinologist for fertility preservation counselling. (17)(18)

Current fertility preservation treatment options include emergency embryo an oocyte cryopreservation and ovarian tissue freezing.

The most successful alternative for female survivors is embryo cryopreservation, which is available in all IVF units ( In Vitro Fertilization), an approach not suitable for many single women or even possible for prepuberal girls.

Preserving fertility through the cryopreservation of ovarian tissues or oocytes (although still in experimental stages) would increase the chances that children or single women could someday become parents even after exposure to chemotherapy or other agents that can cause infertility. (9)(11)

When there is ovarian involvement, or when potential for occult metastasis is high, however, ovarian tissue should not be cryopreserved for the purpose of autotransplantation. In theory, normal appearing ovarian tissue can be cryopreserved with the idea of future in vitro maturation of primordial follicles and xenografting. (12)

Preventing reproductive failure would be an ideal approach. Research is under way to evaluate treatment with gonadotropin-realising hormones (GnRh) in conjunction with chemotherapy, inducing a transient prepubertal state that might reduce the damage to reproductive organs and thereby prevent oocyte death during cancer treatment.
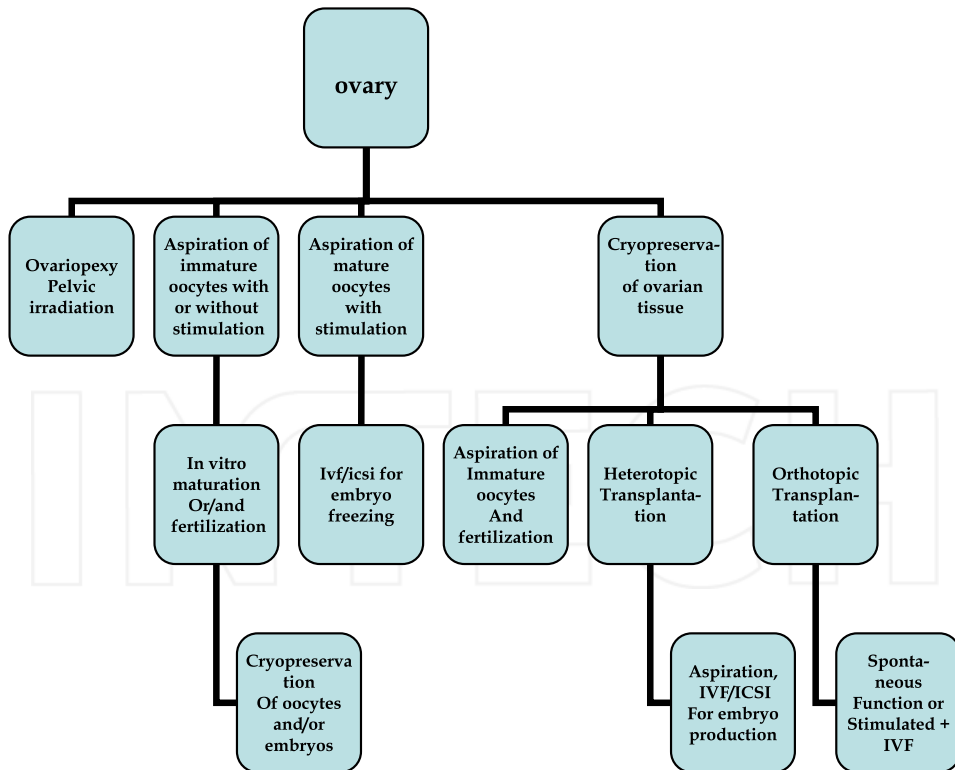


Fig. 2. Fertility Preservation options.

However, fertility preservation using ovarian suppression with GnRh agonists should still be considered experimental. In fact, members of ASCO Panel recommend that interested patients enrol onto clinical trials specifically designed to evaluate the effectiveness of fertility preservation by ovarian suppression methods, rather than receive off-study treatment.

Other strategies under development include producing oocytes from stem cells and regenerating oocytes by inducing natural mechanisms.

It is a central dogma of female reproductive biology that oogenesis ceases around the time of birth in mammalian species. In 2004, one study published by Johnson et al. (30), in which they claimed that in the adult mouse ovary, neo-oogenesis takes place and originates from female germline stem cells that are present in either the ovarian surface epithelium or bone marrow. Following these publications, experiments showed that non-germinal stem cells could generate oocytes. So at this moment there is a lot scientist trying to find the way to achieve oogenesis in adult mammals, but they are all experimental.

### 3.1 Chemoprotection

Preventing reproductive failure would be an ideal approach. Research is under way to evaluate treatment with gonadotropin-realising hormones (GnRh) in conjunction with chemotherapy, inducing a transient prepubertal state that might reduce the damage to reproductive organs and thereby prevent oocyte death during cancer treatment.

However, fertility preservation using ovarian suppression with GnRh agonists should still be considered experimental. In fact, members of ASCO Panel recommend that interested patients enrol onto clinical trials specifically designed to evaluate the effectiveness of fertility preservation by ovarian suppression methods, rather than receive off-study treatment.

Criticism of this approach is also derived from the fact that if the mechanism of action is primarily through hypothalamic pituitary suppression, this should not protect early follicle damage that is gonadotropin independent. However a direct gonadal effect is possible.

At present, the data are unconvincing, with most findings derived from non-randomly controlled studies. There are, however, large studies under way which may yield definitive answers.

Therapy with a variety of suppressive agents such as oral contraceptives or progestins has not been shown to be effective in preventing damage from chemotherapy or radiation therapy.

### 3.2 Ovariopexy

Moving the ovaries out of the field of irradiation can help maintain ovarian function in patients scheduled to undergo gonadotoxic radiotherapy. This significantly reduces ovarian radiation exposure in patients who receive pelvic irradiation such as those with Hodkin's disease or genitourinary or low intestinal malignancies. For instance, the ovarian dose following transposition is reduced to approximately 5-10 percent of the in situ ovaries. Lateral transposition appears to be more effective than suturing the ovaries to the posterior face of the uterus.

The transposition is typically performed by laparotomy. This approach is used at the time of radical hysterectomy for cervical cancer. If there is no need of laparotomy for cancer excision, ovarian transposition should be performed laparoscopically just prior initiation of radiation therapy.

## 3.3 Assisted reproductive technologies

Assisted reproductive technology is probably the most used modality in patients that wish to proceed to fertility preservation. The American Society of Reproductive Medicine recognizes that there is sufficient evidence to recommend embryo cryopreservation as a routine clinical care compared with other therapeutic strategies.

### 3.3.1 Oocyte cryopreservation

Oocyte cryopreservation is an alternative to embryo storage and is ideal for women who do not have a partner and do not want to use donor sperm. For this procedure, the patient has to undergo ovarian stimulation and egg retrieval, the same process required for embryo cryopreservation. Oocyte cryopreservation does not require IVF or ICSI (IntraCitomasplatic Sperm Inyection), and creation of unnecessary embryos can be prevented.

Although oocyte cryopreservation is still considered experimental in the United States, this technology has proven successful. Indeed, current live-birth rates from series of frozen-thawed oocytes are comparable to those in frozen-thawed embryo cycles, and there was no apparent increase in the rate of congenital anomalies as compared with U.S. national statistics for natural conceptions as reported by the Centres for Disease Control.

Actually there are two kind of techniques used for cryopreservation of oocytes: Vitrification and slow freezing.

To date, there is no standard protocol for vitrification of oocytes, which makes an analysis of published data difficult.

Since 2005, the pregnancy rates and live-birth rates have been significantly increased in both slow freezing and vitrification groups. (19).

When the data from 1998–2008 is analyzed, oocyte survival rate was higher in the vitrified group (81%) compared with in the slow frozen group (68%). The live-birth rate per ET was 14%and 34%in the slow frozen and vitrified group, respectively.

Cryopreservation of immature oocytes at the stage of germinal vesicle (GV) can be an attractive alternative to cryopreservation of mature oocytes, especially in breast cancer patients (Figure 3). In theory, there are several advantages of GV stage oocyte cryopreservation. First of all, it does not require full ovarian stimulation, which can be a significant benefit for breast cancer patients who cannot delay cancer treatment or who have ERþ (estrogen-progestin receptors) tumor. It wills also benefit women who are at high risk for ovarian hyperstimulation syndrome such as patients with polycystic ovarian syndrome. (4)

To date, cryopreservation of immature oocytes at the GV stage has not been very successful. Nevertheless, immature oocyte cryopreservation followed by in vitro maturation can be a powerful tool for fertility preservation in breast cancer patients.
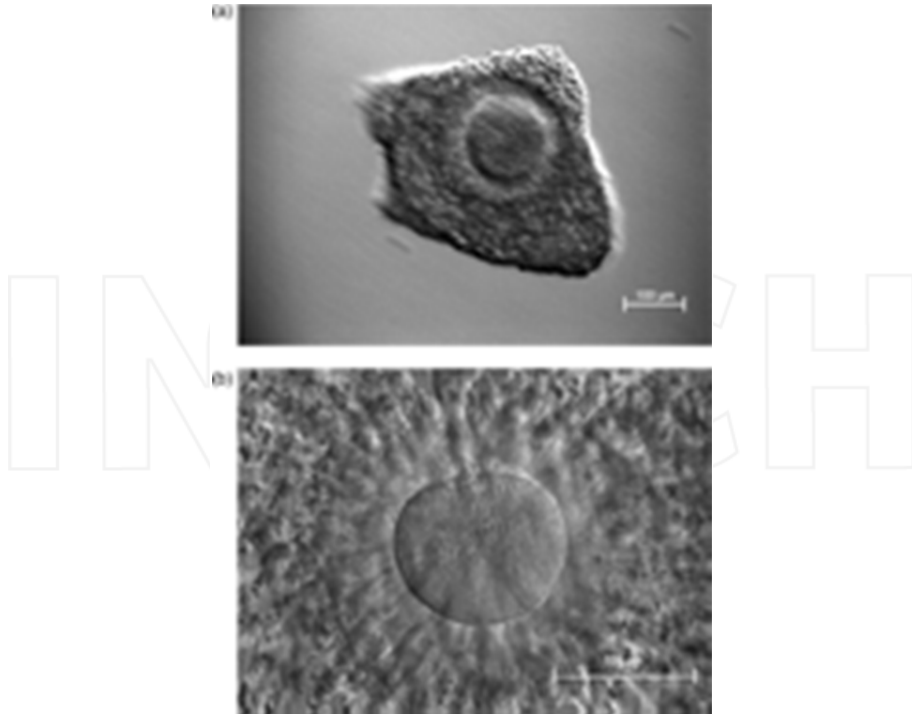
Fig. 3. Examples of GV state above and mature oocyte below.

### 3.3.2 Embryo cryopreservation

Embryo storage is ideal for an adult woman in a stable relationship as it is an established technique which has been available since the mid 1980s.

IVF and ICSI offer a success rate of approximately 30% per cycle (dependent on age) and this is similar to the natural conception rate that is achievable by healthy couples without assisted reproductive techniques. It involves stimulating the ovaries using gonadotrophins which results in high oestrogen levels, and certainly this raises concerns for some tumours such as breast cancers with oestrogen receptor positivity. It is still unclear what are the risks of such techniques in terms of tumour progression or relapse in a hormone dependent cancer. Some groups have attempted to address this by using tamoxifen or letrozole alone or in combination with standard IVF stimulation for women with breast cancer or endometrial cancer.

Patient numbers are small and long-term studies are currently not available. There are also no data on the pregnancy outcome from embryos generated from these protocols. However, many women and their physicians will choose not to expose an estrogen-responsive cancer to more estrogenic stimulation than is strictly necessary. (4)

IVF protocols are well defined, although it may be helpful under some circumstances to induce luteolysis with a GnRH antagonist to allow FSH injections to start sooner. GnRH antagonists also allow for a shorter duration of treatment.

IVF stimulation takes a minimum of two to three weeks depending on a patient's menstrual cycle and could be anything up to five weeks. After stimulation of follicles to maturation an egg collection procedure is undertaken usually as a day case under sedation or a general anaesthetic where vaginal ultrasound probe is used to guide transvaginal collection of eggs. IVF is then undertaken to fertilise the patient's eggs with the partner's sperm before freezing the embryo. At present there is limited availability donor sperm for adult women trying to preserve reproductive potential whilst undertaking chemotherapy (Figure 4).
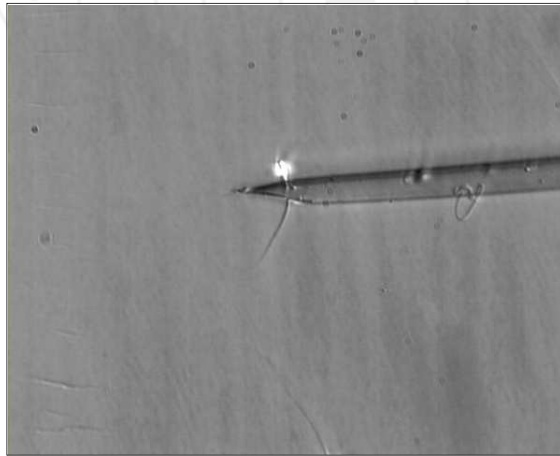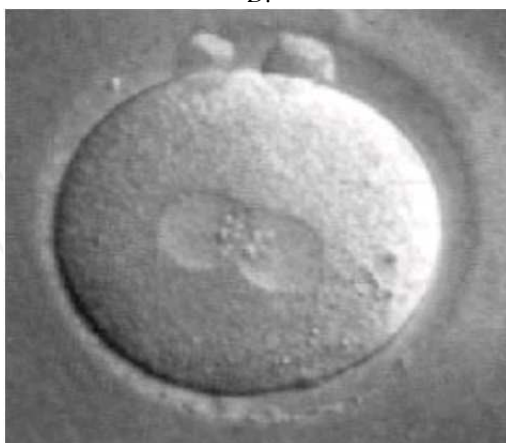


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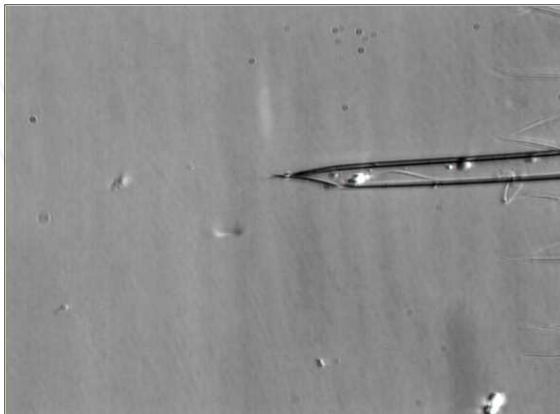


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E.

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A. Sperm selection for insemination into oocyte (ICSI technique)
B. Sperm aspiration.
C. Oocyte punction.
D. Introducing the sperm into the oocyte cytoplasm.
E. Fertilize oocyte at 2 pronuclear stage.
F. Embryo at 72 hs after fertilization at 8 cells stage.

Fig. 4. ICSI technique.

### 3.3.3 Ovarian tissue cryopreservation

An alternative option therefore is to store ovarian tissue, which may contain many more oocytes. Advantages include the fact that no other treatment is required and it can be carried out at short notice. It requires no male involvement, but does require a surgical procedure both to recover the tissue and replace it at a later date.

Replacement provides the option of spontaneous rather than assisted conception as well as the chance of more than one pregnancy; this has now been demonstrated.(11)(13)

Importantly, ovarian tissue cryopreservation also offers a potential option for children and adolescents for whom ovarian stimulation is inappropriate. This, however, may be better described as a theoretical option; as yet no adolescent girl has gone on to have a child following this procedure.

One important consideration is that a significant amount of ovarian tissue must be removed from the patient and will not therefore be available for spontaneous fertility should she not be sterilised by her cancer treatment.

At present there is debate over whether unilateral oophorectomy or ovarian biopsy is the more appropriate surgical technique.

All human trials of cryopreserved autotransplanted tissue have been with cortical strips. This concept was developed from previous work in animal models that have used cryopreserved thawed ovarian cortical strips and reported follicular survival and endocrine

function as well as restoration of fertility after transplantation of cryopreserved-thawed ovarian cortical strips. Using present techniques, ovarian tissue strips are removed from the patient prior to chemotherapy. They are frozen in small strips  (Figure 5). When the patient is ready for pregnancy, they are transplanted back into the patient in a heterotopic or orthotopic site. Since this is an avascular graft, up to two-thirds of follicles are lost after transplantation. Given this limitation it has been recommended that ovarian tissue freezing should be restricted to patients younger than thirty five years.

At present a total of 14 children have been born to women who have had ovarian tissue cryopreserved and reimplanted. Both spontaneous and assisted conceptions have been demonstrated, but interestingly no successful pregnancies have yet been described following heterotopic transplantation of the ovary. Sites where follicular growth has been observed include the anterior abdominal wall and the arm, although successful non-human primate pregnancies have been reported following fresh transplantation to a subcutaneous site. These approaches do, however, offer the opportunity for our improved understanding of the extra-ovarian requirements for normal follicular and oocyte development.
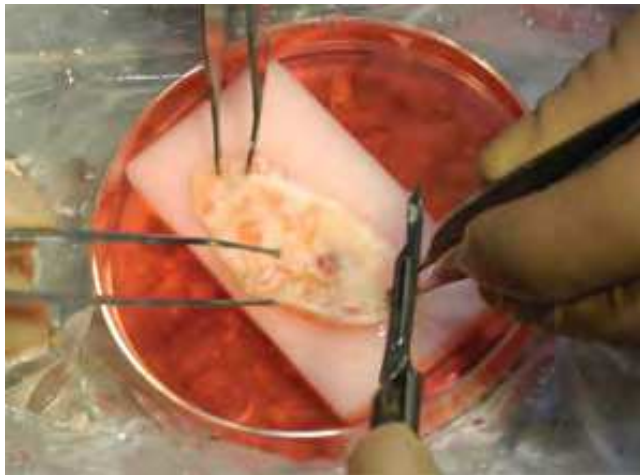


Fig. 5. Ovarian tissue preparation for cryopreservation.

The malignant contamination of the ovarian tissue must also be considered. So far, a total of some 30 women have received transplantation of ovarian tissue without any reports of relapse caused by the transplantation. Two large series of ovarian biopsies in breast cancer patients have recently revealed no evidence of malignant cell contamination, but the availability of specific molecular tumour markers in some conditions has revealed the potential for contamination. This is a particular issue for haematological malignancies; importantly, chemotherapy prior to ovarian cryopreservation did not preclude contamination. (12)

There are several potential uses of cryopreserved ovarian tissue: transplantation back into the host, in vitro maduration of primordial follicles, and xenografting into a host animal. The tissue can be transplanted back into patient.

Research should focus on refining the cryopreservation protocols, cryoprotectants, and transplantation techniques that decrease ischemia, particularly the use of vascularised grafts.

## 4. Facilitating fertility preservation consultation

Treating physicians should initiate the discussion of the possible treatment-related effects to fertility and indicate that there are options to safeguard their future fertility potential. (20)

Women of reproductive potential and interested in learning about options for fertility preservation should be referred real time to a reproductive endocrinologist. Preferably, a fertility preservation consultation should be arranged at the time of the initial diagnosis to expedite necessary options including COS and oocyte retrieval for embryo cryopreservation or alternative fertility preservation techniques. Using these referral mechanisms can eliminate time delays for appointments, initiate education on the process to the patient, and provide documentation such as pathology reports or treatment plans to the referring clinician. Without the development of such a streamlined process, patients and providers will experience frustration and unnecessary time delays. Nevertheless, many patients fail to pursue fertility preservation options owing to two main barriers, time and cost. Of note, most procedures for fertility preservation are not covered by insurance in many countries.(6)

## 5. Conclusion

So it's fair to say that there have been substantial advances in fertility preservation in the last decade, but there still remain very significant gaps in our knowledge as to how best to proceed.

Patient selection remains a challenge, to be confident in offering treatment to those who need it and reassuring to those who do not. In this respect we have recently shown that serum AMH (anti müllerian hormone) predicts long-term ovarian function following chemotherapy in women with breast cancer. Indeed, in a multivariate analysis only AMH, but not age or FSH, remained a significant predictor.

This result, if confirmed, may allow a more individualised risk assessment based on the proposed treatment regime and a measure of the patient's ovarian reserve.

Improved cancer care associated with increased cure rates and long-term survival, coupled with advances in fertility treatment means that it is now imperative that fertility preservation is considered as part of the care offered to these patients. This can only be approached within a multidisciplinary setting. There are obvious challenges that still remain to be resolved, especially in the area of fertility preservation in prepubertal patients. These include ethical issues, such as valid consent and research in the area of tissue retrieval, cryopreservation and transplantation.

Long-term survival is expected in most women with cancer as a result of advances in cancer treatment. For young cancer survivors who have not completed their family, fertility is a crucial issue. Informed decision making regarding future fertility can lead to decreased patient regret and improved quality of life.

Use of less gonadotoxic regimens for adjuvant or neoadjuvant chemotherapy may be considered in young cancer patients with favourable tumors who are in their reproductive years. When there is a high risk of losing fertility with aggressive cancer treatment, currently available options for fertility preservation should be discussed. Embryo cryopreservation is a well-established technology and suitable for women who have a partner. Oocyte cryopreservation is an alternative option that can avoid ethical and legal issues (unlike embryo cryopreservation). However, neither embryo nor oocyte cryopreservation is a practical option for women who cannot delay cancer treatment. In addition, COS (Control Ovarian Stimulation) is required for both embryo and oocyte cryopreservation, and an increase in peak E2 levels with COS may accelerate tumour growth in some types of breast cancer with ERþ (estrogen-progestin receptors). The alternative COS strategy using tamoxifen or letrozole in conjunction with gonadotropin can suppress the elevation of E2 levels and may be considered for women with ERþ tumour in breast cancer.

Where embryo or oocyte cryopreservation is not indicated, cryopreservation of ovarian tissue can be a reasonable alternative, without the worry of delaying cancer treatment or increasing E2 levels. Fertility specialists should work closely with breast cancer treatment teams to provide options for fertility preservation before the initiation of cancer treatment in young women with breast cancer. A multidisciplinary program such as a breast cancer survivorship program will facilitate timely communications between oncologists and fertility specialists as well as effective transmission of information to health care providers and patients.(4)

In addition to developing techniques for preserving or restoring fertility, researchers should consider the long-term effects of such technologies, such as egg quality, healthy pregnancies and, most important, healthy babies.

The advisory panel also acknowledged the need to consider behavioural, cultural, religious, health disparities, ethical, legal and financial aspects of fertility preservation research.

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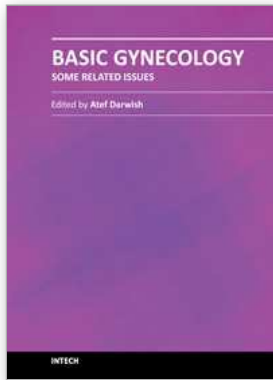
**Basic Gynecology - Some Related Issues**
Edited by Prof. Atef Darwish

ISBN 978-953-51-0166-6
Hard cover, 156 pages
**Publisher** InTech
**Published online** 29, February, 2012
**Published in print edition** February, 2012

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