Reproductive Challenges in Young Female Cancer Patients

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The last three decades have seen a significant improvement and advancement in both the diagnostic and therapeutic modalities with improved surgical technique, chemoradio and supportive therapy in cancer treatment. This has produced a correspondingly increase in the 5-year relative survival rate for many cancers and for all races. However, the chemoradiotherapy which is often gonadotoxic, has a substantial impact on quality of life issues especially that of reproduction in young female patients on account of increasing survival rates and delayed childbearing in the western hemisphere. This case based discussion paper using two real life case scenarios from our department focuses on the negative impact of cancer treatments on fertility and various options available for fertility preservation and / or fertility preservation measures. It is concluded that a lot of variables have to be considered when deciding upon fertility preservation treatments including patient’s age, cancer stage, proposed treatment regime and time before it is initiated, availability of partner sperm and issues of individual patients. The latter include surgical complications, ovarian hyperstimulation syndrome, delay in cancer treatment and reintroduction of cancer cells, cost, low success rates and experimental nature of these treatments and the disposition of gametes in the event that the patient does not survive her cancer. It is very important for physician to advise patients of all these factors so that they can make an informed decision regarding the fertility preservation options and each case is unique and requires a different strategy of fertility preservation.

Key words: fertility preservation; chemotherapy; radiotherapy; in vitro fertilization (IVF); cryopreservation; cancer treatment in young females
The last three decades have seen a significant improvement and advancement in both the diagnostic and therapeutic modalities with improved surgical technique, chemo-radio and supportive therapy in cancer treatment. This resulted in an increase in the 5-year relative survival rate for many cancers. The 5-year survival rates changed from 50% in 1975–1977 to 66% in 1996–2004 for all cancers and for all races\[1\].

Cervical cancer is the most common cancer in women under 35 years old in the UK. Around 6 in 10 of all new cases are diagnosed in women under 50 years. In the last decade, there has been an increase in incidence of nearly 10%, mostly in women in their late 20s\[2\]. Since 1970, cervical cancer mortality rates have decreased by 70% in the UK\[2\] and survival rates for women under 40 years old have reached almost 90%\[2\].

As a result, more survivors have to cope with the consequences of the disease and its treatment. Sterility due to treatment induced ovarian failure is one of most emphasized consequences. Approximately 35% of women who have undergone chemotherapy or pelvic radiation during their reproductive years experienced subsequent infecundity. Fertility is of utmost importance to young patients diagnosed with cancer during their reproductive years. Furthermore, 64% of oncological patients consider the impact of cancer-treatment related infertility as the most concerning issue during their treatment. This means that an increasing number of cancer survivors, particularly younger ones, might still want to have children in the future. Consequently, fertility preservation in cancer patients, infertility treatment among survivors and consequences of reproductive dysfunction have become a current challenge.

There has been a major advancement in fertility preservation techniques with promising results including preservation of fertility such as chemoprotection, ovariopexy and assisted reproductive technology (ART) techniques. Although some of these are already established but there are some which are promising but still highly experimental such as oocyte banking, auto-transplantation, oocyte and ovarian tissue cryopreservation.

This paper employs two case scenarios as basis for case based discussion to evaluate the fertility preservation methods available to young female cancer patients with the principal aim of providing guidance to fertility specialists on how to preserve fertility and to aid patients in reproducing after receiving gonadotoxic treatment from specialists who provide such a treatment including oncologists, rheumatologist and haematologist.

**Case summary**

**Case 1**

A 26-year multiparous lady, presented with abnormal uterine bleeding and severe dyskaryosis on cervical smear. Colposcopy was suggestive of high grade cervical intraepithelial neoplasia (CIN [I]) and punch biopsy confirmed invasive, moderately differentiated,
non-keratinising squamous cell carcinoma of the cervix (at least FIGO IB1). Staging abdomino-pelvic MRI suggested stage IIB disease with a 5 cm cervical tumour, involving the upper vagina and bilateral parametrium but sparing pelvic side walls. Multiple pelvic lymph nodes were noted, including a 12 mm obturator node with no other organ involvement.

Laparoscopic bilateral ovariopexy was performed prior to initiating cancer treatment (Figure 1) to preserve ovarian function by avoiding risk of treatment induced menopause and infertility and also to avoid long-term use of hormone-replacement therapy (HRT).

Subsequently, she received chemo-radiotherapy with weekly cisplatin 40 mg/m² followed by intrauterine brachytherapy and tolerated them well. Abdomino-pelvic MRI after treatment showed good treatment response with no residual tumour detected. The original mass lesions in the cervix and upper vagina had completely resolved and there was no evidence of pelvic lymphadenopathy. Despite ovariopexy, the ovaries were still included in the radiotherapy field as there was elevated follicle stimulating hormone (FSH) and luteinising hormone (LH), consistent with premature ovarian failure. HRT was subsequently commenced.

Case 2

A 32-year-old nulliparous lady was referred to our colposcopy clinic with cervical cytology suggestive of invasive carcinoma. Colposcopic examination confirmed CIN III. Large loop excision of the transformation zone (LLETZ) of cervix revealed invasive, moderately-differentiated squamous cell carcinoma, FIGO stage IB with vascular space invasion.
Abdomino-pelvic MRI confirmed stage IB1 cervical malignancy. On sagittal imaging, an area of abnormal signal was detected within the posterior lip of the cervix (extending over a distance of 1.4 cm from the external os) with prominent thickening of the endocervical tissues, measuring approximately 1.3 cm. There was no parametrial extension or involvement of the upper vagina. The uterus was anteverted with normal endometrium. Ovaries were normal bilaterally. There was no free fluid in the pelvis. None of the pelvic or retroperitoneal lymph nodes were significantly enlarged by size criteria.

Although on MRI there was no residual tumour and the residual cervical length was satisfactory at 2.5 cm but in view of lymphovascular space invasion and residual CIN III, fertility sparing surgery was contraindicated and she was offered a radical Wertheim’s hysterectomy, bilateral pelvic lymphadenectomy and salpingectomies. She made an uneventful recovery with no signs of disease recurrence. She was keen to achieve pregnancy and was referred to the fertility clinic for discussion of surrogacy.

Impact of cervical cancer and its treatment on reproduction

Treatment of cervical cancer depends on staging. Stage I and stage IIA disease is often surgically managed as in case 2 while the primary treatment for stage IIB or above disease is chemo-radiotherapy as in case 1. The disease and its treatments often induce ovarian function loss, which not only puts patients at risk of menopause-related complications at a very young age but also compromises fertility capacity.\textsuperscript{6-8}

It is important to assess a patient’s ovarian reserve before and after cancer treatment in order to counsel patients of fertility preserving options. Several modalities are available for evaluation of ovarian reserve, including early FSH, anti-Müllerian hormone (AMH) and antral follicular count (AFC). AMH is the most appealing tool for ovarian reserve assessment since its level is not affected by other hormone use such as oral contraceptives and can also be tested at any point in the menstrual cycle. Whilst FSH, AMH and AFC were all capable of predicting future ovarian activity in a study of premenopausal women receiving chemotherapy, AMH was the most predictive.\textsuperscript{9} Table 1 compares the efficacy of different markers in evaluating ovarian reserve.\textsuperscript{10}

Each ovary is endowed with a finite non-renewable number of eggs which are chemoradiosensitive.\textsuperscript{11} The ovaries contain an irreplaceable number of follicles and follicles constitute the functional apparatus of the ovary and they are found at different developmental stages in the ovary (Figure 2). The non-growing primordial follicles, the earliest stage of follicular development constitute about 90% of follicles in the human adult ovary. The pool of primordial follicles determines ovarian reserve and hence reproductive life span of women.\textsuperscript{12} They are therefore extremely vulnerable to irreversible damage by cytotoxic drugs.
Table 1 Efficacy of different markers in assessment of ovarian reserve[10]

<table>
<thead>
<tr>
<th>Marker</th>
<th>AMH</th>
<th>AFC</th>
<th>FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference range</td>
<td>0.2–0.7 ng/ml</td>
<td>3–10</td>
<td>10–20 IU/L</td>
</tr>
<tr>
<td>Reliability</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Sensitivity for ovarian response / pregnancy</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Specificity for ovarian response / pregnancy</td>
<td>Intermediate (ovarian response), no data on pregnancy</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Timing of test</td>
<td>Any day of menstrual cycle</td>
<td>Beginning of menstrual cycle</td>
<td>Days 2–4 of menstrual cycle</td>
</tr>
<tr>
<td>Influence by oral contraceptives</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Current use</td>
<td>Seldom</td>
<td>Widespread</td>
<td>Widespread</td>
</tr>
</tbody>
</table>

*: The study was carried out primarily in the general infertility population. Sensitivity and specificity were determined based on evaluation of ovarian response to fertility medications and subsequent pregnancy after treatment with *in vitro* fertilization.

Chemotherapy-associated ovarian damage is drug and dose dependent and also relates to the age of patient at the time of treatment with progressively smaller doses required to induce ovarian failure with increasing age 9[13]. Using cyclophosphamide as an example, 80% of patients aged over 40 years developed permanent amenorrhoea after treatment compared to 20% in those younger than 30 years of age[13].

Common chemotherapy agents used for treatment for cervical malignancy, their mechanism of action and different levels of risk of gonadotoxicity are shown in Table 2[14].

Radiation is a well-recognized cause of ovarian damage and permanent infertility. In
Radiation with a dose of 6 or more Gy (1 Gy = 1 J/kg) directly over the ovary would lead to permanent infertility\textsuperscript{[15]}. If pregnancy is achieved, patients would still have increased risks of complication, including early pregnancy loss, premature labour and low birth weight due to impaired uterine growth and blood flow\textsuperscript{[15]}. 

The fertility preservation options

**Preservation of reproductive organs**

About 45% of fertile cervical cancer patients have stage IB1 or lower disease at diagnosis\textsuperscript{[16]}. These patients are suitable candidates for fertility preservation by trachelectomy with laparoscopic pelvic node dissection\textsuperscript{[17]}. Specifically, these procedures have been offered to patients with a \(\leq 2\) cm-sized tumour and disease stage IA1 with lymphovascular space invasion or stage IA2 or IB1\textsuperscript{[16]}. Unfavourable histology (e.g. clear cell carcinomas or small cell neuroendocrine tumours) and evidence of lymph node or distant metastasis are contraindications given the extremely high risk of locally or regionally advanced cancer.

Radical trachelectomy were traditionally performed via a vaginal or abdominal approach. Since 1994, over 700 cases of radical vaginal trachelectomy have been described which resulted in 250 pregnancies and 100 live births\textsuperscript{[18]}. The conception rate ranged from 41% to 79%. Infertility was likely attributable to cervical stenosis, decreased cervical mucus, surgical

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<table>
<thead>
<tr>
<th>Table 2 Chemotherapy agents used in the treatment of cervical malignancy and their risks of gonadotoxicity\textsuperscript{[14]}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy agents</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Alkylating agents</td>
</tr>
<tr>
<td>· Cisplatin</td>
</tr>
<tr>
<td>· Carboplatin</td>
</tr>
<tr>
<td>· Ifosfamide</td>
</tr>
<tr>
<td>· Fluorouracil</td>
</tr>
<tr>
<td>Antimetabolites</td>
</tr>
<tr>
<td>· Gemcitabine</td>
</tr>
<tr>
<td>Mitotic spindle agent</td>
</tr>
<tr>
<td>· Paclitaxel</td>
</tr>
<tr>
<td>· Doxetaxel</td>
</tr>
<tr>
<td>Topoisomerase inhibitor</td>
</tr>
<tr>
<td>· Topotecan</td>
</tr>
<tr>
<td>· irinotecan</td>
</tr>
<tr>
<td>Combination therapy</td>
</tr>
<tr>
<td>· Paclitaxel + Cisplatin</td>
</tr>
<tr>
<td>· Topotecan + Cisplatin</td>
</tr>
</tbody>
</table>
adhesions and chronic infections. Interestingly, although the first-trimester spontaneous miscarriage rate in patients post-vaginal trachelectomy was similar to that of the general population, the second-trimester spontaneous miscarriage rate was twice that of the general population\[16\]. About 65% of pregnancies were delivered in the third trimester of which 28% and 12% had gestation <36 weeks and <28 weeks, respectively\[16\].

Recently, laparoscopic and robotic techniques were developed with significant improvement in perioperative outcomes (less blood loss and shorter length of stay)\[19,20\]. Robotic assisted radical trachelectomy is accurate and reproducible in the level of resection, length of vaginal cuff and extent of parametrial dissection\[19\].

Advancement in fertility preservation techniques and infertility treatment provide patients with more advanced-stage disease, the option of future pregnancies when preservation of the reproductive organs is not possible. Some of the surgical and assisted-reproduction innovations include embryo/oocyte/ovarian tissue cryopreservation, ovarian transposition, ovarian suppression, apoptotic inhibitor and the construction of artificial gametes\[8,9,15,17,21\]. The American Society for Reproductive Medicine and the American Society of Clinical Oncology classify these treatments into established and experimental procedures\[22\]. Figure 3 summarises the approach to identify suitable fertility preservation strategies for cervical cancer patients.

There is no evidence to show that fertility preservation leads to suboptimal treatment and hence lower cure rates for female cancer. Specifically for stage IA2–IB cervical cancers, it appears that the recurrence rates of radical trachelectomy (95%) were not significantly higher than that of radical hysterectomy (100% for matched controls and 97% for unmatched controls)\[23\]. Zanetta et al.\[24\] studied 169 women with malignant germ cell ovarian tumors in which fertility-sparing surgery was performed in 138 (81%) women. Of these women who were treated conservatively, the survival rate was 98%, 90%, 100% and 100%, for dysgerminomas, endodermal sinus tumors, mixed tumors, and immature teratoma respectively (compared with 94% for dysgerminoma, 89% for endodermal sinus tumors, 100% for mixed types, and 98% for immature teratoma in the whole population). They concluded that conservative surgery will not significantly affect the survival or risk of recurrence and compared with controls. Therefore, irrespective of subtype and stage, conservative surgery should become the standard approach to treating most patients with malignant ovarian germ cell tumors\[24\]. However, fertility-sparing surgery has still not received wide acceptance as these trials are often limited in size and lack randomized controls.

**Pharmacological treatment**

*Ovarian suppression*

Evidence regarding ovarian suppression as a fertility preservation method is controversial. Blumenfeld et al.\[25\] demonstrated that chemotherapy induced gonadal damage could be
Figure 3 The algorithm of fertility preservation strategies in young cervical cancer patients

ER=estrogen receptor
AI=aromatase inhibitor
IVM=in vitro maturation

ER+ tumor
Addition of AI

ER- tumor
Conventional ovarian stimulation
minimized by suppressing ovarian function with gonadotrophin-releasing hormone (GnRH) agonist which inhibits gonadotropin (FSH/LH) secretion from the pituitary. This prevents further recruitment and destruction of additional primary follicles after initial FSH elevation associated with gonadotoxic therapy\textsuperscript{[22]}. Treatment should commence 1 month before starting chemotherapy and continue throughout treatment\textsuperscript{[26]}. On the other hand, 2 studies showed that GnRH treatment was not associated with any protective effect\textsuperscript{[27,28]}. Oktay et al.\textsuperscript{[29]} reviewed all evidences in 2007 and concluded that there is no evidence to support the safety and efficacy of GnRH agonist treatment. Up to date, there was no large, randomised controlled trial to establish the efficacy of GnRH agonist therapy and subsequent pregnancy rates. The data on the use of GnRH for ovarian suppression have been conflicting. Until definitive proof of efficacy is established, other fertility preservation options should be offered in addition to GnRH treatment.

A retrospective study in young women undergoing gonadotoxic chemotherapy found a possible protective effect of oral contraceptives\textsuperscript{[30]}. It was hypothesized that oral contraceptives suppress pituitary gonadotropin secretion, thereby inhibit follicular growth\textsuperscript{[26]}. This is a more appealing choice than ovarian hormones, due to its low cost and lack of significant side-effects.

**Apoptotic inhibitors**

Chemotherapy agents cause oocyte depletion and premature ovarian failure by activating apoptotic pathways. Sphinosine-1-phosphate (S1P) is an apoptotic inhibitor that is able to protect oocytes from undergoing apoptosis when exposed to apoptotic triggers, e.g. doxorubicin, and preserve fertility of irradiated female mice \textit{in vitro}\textsuperscript{[31,32]}. Since chemotherapy mostly work via apoptosis of malignant cells, further studies are needed to show that cure rates will not be compromised before apoptotic inhibitors could be developed into a pharmacological tool for fertility preservation. Recently, a study showed that when cultured without serum, S1P may decrease germ cell apoptosis \textit{in vitro} in human ovaries\textsuperscript{[33]}.

**Surgical ovarian transposition**

Women treated with whole abdominal and/or pelvic irradiation are at high risk of acute ovarian failure. Surgically transposing the ovaries above the pelvic brim before radiotherapy decreases ovarian radiation exposure to only 5%–10% of non-transposed ovaries\textsuperscript{[34]}. The success rate of fertility preservation by ovarian transposition ranges from 16% to 90%, depending on the age of patient, dose of radiation, vascular compromise, degree of scatter radiation, type of irradiation (vaginal brachytherapy or pelvic external beam irradiation), whether the ovaries were shielded and whether concomitant chemotherapy was used\textsuperscript{[22,35]}. Studies showed that 88.6% of women under 40 who have had ovariopexy retained ovarian function and 89% of pregnancies were spontaneous, with 75% occurring without repositioning the
There was no increase in stillbirth rates, low birth weight, congenital malformations, abnormal karyotypes or cancer in the offspring\cite{36,37}. In addition, intensity-modulated radiotherapy, a new conformal radiotherapy that precisely delivers radiation to tumour while sparing surrounding tissues, facilitates treatment success by reducing the dose of scattered radiation to the ovaries\cite{38}.

Ovarian transposition is often performed laparoscopically by dividing the utero-ovarian ligaments and mesovarium to separate the ovary from the uterus and fallopian tubes as in case 1. The complications of fallopian tube dysfunction, chronic ovarian pain, ovarian cyst formation and migration of ovaries back to their original position have been reported. Additionally, when ovaries are transposed to the abdomen, spontaneous pregnancy may not be possible unless a second procedure is performed to relocate the ovaries back to the pelvis. To minimize the risk of single treatment failure, it is recommended that only one ovary should be transposed while the other one should be removed for cryopreservation\cite{39}.

**Cryopreservation (embryo, oocyte and ovarian tissue)**

Cryopreservation is the maintenance of the viability of excised tissue or organs by storing them at very low temperatures (Table 3). It can be used in combination with ovariopexy and/or IVF.

Embryo cryopreservation is the most established method of fertility preservation in patients who have a male partner or elect to use donor sperm and are diagnosed with cancer at relatively early stages and can therefore afford to defer treatment for some time. Embryo cryopreservation itself is not a challenging procedure and it also allows multiple attempt of embryo transfer following a single ovarian stimulation cycle. Thawed embryo survival rates

<table>
<thead>
<tr>
<th>Type of cryopreservation</th>
<th>Embryo</th>
<th>Oocyte</th>
<th>Ovarian tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of development</td>
<td>Established</td>
<td>Experimental</td>
<td>Experimental</td>
</tr>
<tr>
<td>Live birth in humans</td>
<td>✓ ✓</td>
<td>✓</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Success rates</td>
<td>19%–60%\cite{36,37}</td>
<td>36%–61%\cite{42}</td>
<td>No RCT data\cite{48}</td>
</tr>
<tr>
<td>Delay in initiation of treatment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Suitability for prepubertal patients</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risk of ovarian hyperstimulation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risk of cryodamage</td>
<td>Low (Mature oocyte &gt; Immature oocyte)</td>
<td>Intermediate - high</td>
<td>Low (Xenograft &lt; autograft)</td>
</tr>
<tr>
<td>Risk of cancer seeding</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Requires surgery</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Requires male partner</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Avoidance of hormonal replacement</td>
<td>✓</td>
<td>✓</td>
<td>✓ (possible)</td>
</tr>
</tbody>
</table>

RCT = randomised controlled trial

\(\times\) = no

\(✓\) = yes, to a small extent

\(✓ ✓\) = yes, to a moderate extent

\(✓ ✓ ✓\) = yes, to a large extent

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range from 35% to 90% while implantation rates range from 8% to 30% and cumulative pregnancy rates range from 19% to 60%, depending on the age of patients and the stage of embryo development during transfer[40-42].

The biggest limitation is time constraint. Controlled ovarian hyperstimulation (COH) and oocyte retrieval for IVF have to occur prior to start of treatment and usually takes 2–3 weeks. This leads to a delay in commencing treatment. On top of that, ovarian hyperstimulation would result in supra-physiologic oestрадiо levels which have a significant effect in patients with concurrent oestrogen-dependent tumours, e.g. breast cancer. Interestingly, oestrogen has also been shown to promote tumour growth even in oestrogen receptor-negative breast cancer[43].

Ovarian stimulation with letrozole, an aromatase inhibitor combined with gonadotropins (FSH) has been shown to be a cost-effective alternative method of fertility preservation by reducing the oestradiol levels in oestrogen-dependent breast cancer patients[44].

Almost 25% of children born after assisted reproduction techniques are born following cryopreservation of mostly cleavage-stage embryos and less commonly, blastocysts and oocytes. For patients without a partner and who doesn’t want to use donor sperm for IVF, cryopreservation of unfertilized oocytes may be an option. In 2012, the American Society for Reproductive Medicine released a statement proclaiming oocyte cryopreservation is no longer an experimental procedure[45]. It has a success rate of 36%–61%[46]. It used to be a major challenge since oocytes are extremely sensitive to cryoinjury. The live-birth rates of IVF with conventional slow-freezing protocols were significantly lower than that with fresh oocytes (15.4% vs 38.4%)[47]. Although cryopreservation using vitrification, an ultra-rapid freezing protocol, prevents ice crystal formation in the cytoplasm, this method results in similar live birth rates as the use of fresh oocytes[43].

Mature oocytes have the highest chance of achieving pregnancy, however, they have several characteristics which make them vulnerable for cryodamage. Mature oocytes are larger in size and have higher water content, predisposing to ice crystal formation and rupture. Their lower surface area to volume ratio also limits cryoprotectant penetration. Moreover, since they are arrested in metaphase II, the spindle apparatus is fully extended and hence is susceptible to disassembly at lower temperature, resulting in chromosome dispersion and aneuploidy[48]. Mature oocyte cryopreservation also puts patients at risk of ovarian hyperstimulation syndrome.

When embryo or oocyte cryopreservation is not feasible, ovarian tissue cryopreservation would be the next option. Ovarian tissue can be harvested at laparoscopy or laparotomy by performing several ovarian biopsies or uni-/ bi-lateral oophorectomy and cryopreserved for later transfer to the patient or a surrogate mother. Ovarian tissue may be sutured onto the natural ovary, transplanted within the peritoneum or even within the rectus sheath or placed subcutaneously. The advantage of this method is that tissue can be obtained without delay
since there is no need for ovarian stimulation. This method is especially useful for fertility preservation in prepubertal girls or adolescents and adults who have no time or are contraindicated to undergo oocyte or embryo cryopreservation. Also, no partner is required for male gamete donation at the time of tissue harvesting. Thirdly, there is a chance that the transplanted tissues could resume the production of endogenous hormones, therefore avoiding long-term HRT\(^{[49]}\). Additionally, a large number of oocytes can be harvested to allow for spontaneous pregnancy in the future without IVF or ovarian stimulation. 

**Transplantation**

There are two methods for transplanting thawed ovarian tissue: xenograft and autotransplantation. The optimal method remains to be determined.

Xenografting has the advantages of avoiding further surgery to transplant the tissue back to the patient and hence eliminate the potential risk of re-introducing cancer cells. However, no clinical pregnancies were reported with xenografting.

Autotransplantation of ovarian tissues back to the patient can be done either by orthotopic or heterotopic transplantation. Orthotopic transplantation involves transplanting strips of ovarian tissues near the infundibulopelvic ligaments or on a non-functional ovary. There have been several healthy children born after this procedure\(^{[50-53]}\). However, there were a lot of controversies about the source of fertilized oocytes as the retained ovaries may still be functional.

In heterotopic transplantation, ovarian tissues are grafted subcutaneously at various location including the forearm and abdominal wall. This method is preferred when there is concern for growth of metastatic cells from or malignant transformation of the transplanted tissue.

The success of ovarian cryopreservation and transplantation depends largely on the age of patients. The functional life span of the transplanted tissue is only about 3 years as only a small amount of tissue is transferred and up to 60% of primordial follicles are lost after transplantation from ischaemic injury until a collateral blood supply is developed as evidenced in sheep autograft\(^{[54]}\) and human xenograft\(^{[12]}\) studies.

**Donor oocytes**

IVF with donor oocytes is a standard treatment with very high success rates of up to 52.3%\(^{[55]}\). This method is particularly useful for older women with poorer prognosis; those who do not have a male partner or the risk of reintroducing cancer cells is unacceptable and also those unwilling to utilize experimental treatments. Nevertheless, this method is very expensive and may lead to legal, ethical and emotional problems\(^{[56]}\).

**Artificial gametes**

Advancement in reproductive technologies enables infertile patients to conceive their own genetic child using alternative sources of gametes and embryos\(^{[57]}\) an idea which is still
in experimental phase. The production of an artificial oocyte starting with the karyoplast of an immature donor oocyte has been described by Nagy and Chang.\textsuperscript{[58]}

**Surrogacy**

Surrogacy is a situation where another woman carries and gives birth to a baby for an infertile couple who wants to achieve pregnancy. The Human Fertilisation and Embryology Authority only regulates IVF but not surrogacy, therefore, it is important to offer legal advice for patients considering surrogacy. There are 2 types of surrogacy, full or host surrogacy and partial or traditional surrogacy.\textsuperscript{[59]} Surrogacy is described as traditional (also known as ‘straight’) when the surrogate mother provides the egg (and is therefore the genetic mother of the child) and sperm is donated by the female patient’s partner. In full surrogacy (also known as ‘gestational’ or ‘host’) the surrogate mother carries an embryo from the commissioning couple. Occasionally the embryo may be derived from egg or sperm donation.

Surrogacy is legal in the UK, but infrequently used and it is not legal in other countries. Laws differ widely from one jurisdiction to another as shown in Table 4.\textsuperscript{[60,61]}

**Adoption**

In the UK very few babies are available for adoption. Patients cured of cancer are not excluded from consideration by adoption agencies, but careful consideration will be given to the needs of the child and waiting lists are likely to be long. Parents considering adoption of older children or children with special needs may be considered more readily.

International adoption is a possibility but there may be considerable difficulties.\textsuperscript{[62]} It can be a complex and expensive process although some countries have reciprocal arrangements with the UK. Applications to adopt a child must be approved by the Home Office and local adoption agencies, usually social services.

**Conclusion**

Physicians providing cancer treatment for young female patients should be aware of the adverse effects of treatment on fertility and of ways to minimise these effects. Modern chemotherapy and radiation therapy regimens have enabled women to survive their cancers but at the cost of rendering them sterile due to ovarian failure. Currently, only ovarian transposition, conventional IVF with embryo cryopreservation and IVF with donor oocytes are considered standard treatment options for fertility preservation with reasonable success rates.

Pharmacological treatment has conflicting results, while apoptosis inhibitors have shown promise in animal studies while vitrification techniques improve success rates of IVF after oocyte cryopreservation. Ovarian tissue cryopreservation suffers from the need for surgery to harvest and transplant the tissue, very low success rates and the risk of re-introducing malignant cells. Xenografting may eliminate some of these problems but is yet unproven.
Whole ovary cryopreservation with vascular anastomosis is a challenging procedure but if successful, would not only restore fertility but also long-term endogenous ovarian hormone production.

<table>
<thead>
<tr>
<th>Country</th>
<th>Legality of surrogacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Altruistic surrogacy is recently been legalised. Commercial surrogacy is a criminal offense.</td>
</tr>
<tr>
<td>Canada</td>
<td>The assisted human reproduction act permits only altruistic surrogacy (surrogate mothers may be reimbursed for approved expenses but payment of any other consideration or fee is illegal)</td>
</tr>
<tr>
<td>China</td>
<td>Illegal in the mainland of China, commercial surrogacy is criminal under the Human Reproductive Technology Ordinance 2000 in the Hong Kong Special Administrative Region</td>
</tr>
<tr>
<td>Finland</td>
<td>Both commercial and altruistic surrogacy have been illegal since 2007</td>
</tr>
<tr>
<td>France</td>
<td>Since 1994, any surrogacy arrangement that is commercial or altruistic, is illegal or unlawful and is not sanctioned by the law (art 16-7 of the Code Civil)</td>
</tr>
<tr>
<td>Hungary</td>
<td>Commercial surrogacy is illegal in Hungary</td>
</tr>
<tr>
<td>Iceland</td>
<td>All surrogacy arrangements (both commercial and altruistic) are illegal</td>
</tr>
<tr>
<td>India</td>
<td>Commercial surrogacy is legal in India</td>
</tr>
<tr>
<td>Ireland</td>
<td>There is no law in Ireland governing surrogacy</td>
</tr>
<tr>
<td>Israel</td>
<td>In March 1996, the Israeli government legalized gestational surrogacy under the “Embryo Carrying Agreements Law”</td>
</tr>
<tr>
<td>Italy</td>
<td>All surrogacy arrangements (both commercial and altruistic) are illegal</td>
</tr>
<tr>
<td>Japan</td>
<td>In March 2008, the Science Council of Japan proposed a ban on surrogacy and said that doctors, agents and their clients should be punished for commercial surrogacy arrangements</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Altruistic surrogacy is legal</td>
</tr>
<tr>
<td>Pakistan</td>
<td>Surrogacy is illegal in Pakistan</td>
</tr>
<tr>
<td>Portugal</td>
<td>Commercial surrogacy is not allowed by law</td>
</tr>
<tr>
<td>Russia</td>
<td>Gestational surrogacy, even commercial (is legal in Russia) and is available for practically all adults willing to be parents</td>
</tr>
<tr>
<td>Spain</td>
<td>Whereas surrogacy is not legal in Spain (the biological mother’s renouncement contract is not legally valid), it is legal to perform the surrogacy in a country where it is legal, having the mother the nationality from that same country</td>
</tr>
<tr>
<td>South Africa</td>
<td>The South Africa Children’s Act of 2005 (which came fully into force in 2010) enabled the “commissioning parents” and the surrogate to have their surrogacy agreement validated by the High Court even before fertilization. This allows the commissioning parents to be recognized as legal parents from the outset of the process</td>
</tr>
<tr>
<td>Thailand</td>
<td>Surrogacy is not allowed in Thailand</td>
</tr>
<tr>
<td>Ukraine</td>
<td>Since 2002, surrogacy and surrogacy in combination with egg/sperm donation has been legal in Ukraine</td>
</tr>
<tr>
<td>UK</td>
<td>Commercial surrogacy arrangements are not legal in the UK. Such arrangements were prohibited by the Surrogacy Arrangements Act 1985</td>
</tr>
<tr>
<td>US</td>
<td>Surrogacy and its attendant legal issues fall under state jurisdiction and the legal situation for surrogacy varies greatly from state to state</td>
</tr>
</tbody>
</table>
References


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Conference Information

12th International Workshop of Lower Genital Tract Pathology
March 5th to 7th Italy / Rome Obstetrics / Gynecology
Contact: Organizing Secretariat, Triumph C&C Srl
Phone: 011-39-6-3553-0382
Fax: 011-39-6-3553-0362
E-mail: hpv2015rome@thetriumph.com
Website: http://www.hpv2015rome.com/

10th International Symposium on Advanced Ovarian Cancer
March 6th Spain / Valencia Obstetrics / Gynecology, Oncology
Contact: Symposium Secretariat, Doctaforum
Phone: 011-34-91-372-0203
E-mail: aocsymp2015@doctaforum.com
Website: http://www.esmo.org/Conferences/Advanced-Ovarian-Cancer-2015

2015 Sol Shnider, MD, Obstetric Anesthesia Meeting
March 11th to 15th California / San Francisco Anesthesiology, Obstetrics / Gynecology
Contact: Society for Obstetric Anesthesia & Perinatology
Phone: 414-389-8611
Fax: 414-276-7704
E-mail: soap@soap.org
Website: http://soap.org/sol-shnider-meeting.php

Neonatal Cranial Ultrasound-The Basics
March 11th United Kingdom / London Obstetrics / Gynecology, Pediatrics, Radiology / Imaging
Contact: The Symposium Office, Imperial College London
Phone: 011-44-20-7594-2150
Fax: 011-44-20-7594-2155
E-mail: sympreg@imperial.ac.uk
Website: http://www.symposia.org.uk/main/eventprog.asp?evcd=15.02

5th International Neonatology Conference
March 12th to 14th United Arab Emirates / Abu Dhabi Obstetrics / Gynecology, Pediatrics
Contact: Afsal, Ahmad, Mena Conference
Phone: 011-971-2-491-9888
E-mail: afsal@menaconf.com
Website: http://atnd.it/17540-0