Title

Fertility preservation for medical reasons in girls and women: British Fertility Society Policy and Practice guideline

Authors: on behalf of BFS

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Abstract

Fertility preservation in the female poses several challenges due to the invasive nature of the techniques available towards that end. The guideline aims to bring together the evidence available for the measures for fertility preservation and their outcome. The guideline address fertility preservation for medical reasons and includes both oncological and non-oncological causes.

The techniques that the guideline scrutinizes are embryo and oocyte cryo-preservation, ovarian tissue cryo-preservation, GnRH agonist suppression and ovarian transposition. Although ovarian tissue cryo-preservation is still considered experimental, the availability of this technique is gaining momentum as more live births from auto-transplanted tissue are reported. The guideline also highlights use of current treatment modalities for benign and malignant conditions that have a better fertility sparing profile.

The guideline recommends multidisciplinary approach in counseling women and girls about the risk to their fertility and available techniques. The role of psychological support in assisting women and girls with decision making is highlighted.

The guideline also highlights the risks associated with these invasive procedures. Patients need to be medically fit to have procedures. Fertility preservation techniques are appropriate when treatment has curative intent.

Fertility preservation is a subject of ongoing research on outcomes of different techniques and at the time of publication, studies are still likely to emerge adding to the available literature.

Introduction

Advances in oncology treatments have led to increased survival rates in cancer patients. Efforts to minimise the long-term morbidity of treatments and improve quality of life among cancer survivors are increasingly a priority. One of the most significant late-effects of cancer treatment is the loss of fertility, which is often rated as the most distressing outcome of therapy by cancer survivors (Bastings et al., 2014; Corney and Swinglehurst, 2014; Mancini, et al., 2008 ; Peate et al., 2009; Ruddy et al., 2014) Given that the average age of first time mothers in the UK is continuing to rise (Office of National Statistics, 2016), it is likely that more women will be nulliparous at the time of diagnosis of cancer, adding greater focus to the need for fertility preservation. Fortunately, techniques used for fertility preservation are becoming more established as evidence grows concerning their efficacy and safety.

A number of guidelines pertaining to fertility preservation exist in the worldwide literature (Table 1). However comprehensive guidance encompassing all aspects of fertility preservation in the female, from counseling to outcome of techniques of fertility preservation, would further assist clinicians in this rapidly progressing field. This guidance is aimed primarily at clinical practice in the United Kingdom, where provision of specific services is subject to regulation by the Human Fertilisation and Embryology Authority (HFEA) or the Human Tissue Authority (HTA).

The growing utilisation of fertility preservation by women and the recognition of the importance of this in their care by the National Institute of Health and Clinical Excellence (NICE), highlights the need for a framework of care for women who are at risk of loss of fertility (NICE, 2016). The British Fertility Society first produced a strategy for developing policy and practice in fertility services for survivors of cancer in 2003 (British Fertility Society). Since then the field of fertility preservation has seen significant progress. In 2007 a Joint Collegiate working party representing relevant professional bodies published 'The effects of cancer treatment on reproductive functions' (Royal College of Physicians, 2007). The Scottish Intercollegiate Guideline Network (SIGN) produced guidance on long-term follow-up of survivors of childhood cancer in 2004 and updated this guidance in 2013 (SIGN, 2013). In 2016, the updated NICE guidance on fertility included recommendations on fertility preservation (NICE, 2016). The guidance recommends that discussion about fertility preservation should occur early, NHS eligibility criteria for infertility should not be used for women seeking fertility preservation, and that no lower age limit should be used.

Aim

This document aims to provide evidence-based guidance to healthcare professionals involved in offering and providing fertility preservation to girls and women.

Scope of the guideline

This guideline evaluates the evidence for the different techniques of fertility preservation in females. The guideline is aimed at oncologists, haematologists, endocrinologists, gynaecologists and all other healthcare professionals such as nurses, psychologists, counsellors and general practitioners who play important roles in the management of women with cancer considering fertility preservation.

The content of this guideline reflects the fact that the evidence regarding fertility preservation is more robust in the post-pubertal age group, but includes current options for pre-pubertal girls. In addition, we consider those at risk of premature ovarian insufficiency from non-cancer related conditions and individuals transitioning from female to male gender. Research recommendations are made to encourage the development of evidence in all relevant cohorts.

Elective ('social') fertility preservation is outside the remit of the guideline, although the technical considerations for oocyte freezing are the same.

Background

There are more than 300,000 new cases of cancer every year in the UK (Cancer Research UK). The most frequently diagnosed malignancies in women of reproductive age are breast cancer, cervical cancer, lymphoma, leukaemia, sarcomas, brain tumours, melanomas and ovarian cancer (Miller et al., 2016).

Chemotherapy, radiotherapy and surgical treatments to the ovary may lead to reduction or loss of ovarian function with consequent subfertility and premature ovarian insufficiency (POI). Novel targeted therapies are increasingly used by oncologists, but their impact on reproductive function is largely unknown. The degree of damage to gonadal function depends on the type and dose of chemotherapy and radiotherapy, the age of the individual and the initial ovarian reserve (Meirow et al., 2010). Apart from oncology treatments, a broad range of medical conditions requiring gonadotoxic therapy may compromise fertility potential: for example, stem cell transplantation for benign haematological diseases such as sickle cell anaemia and thalassaemia. Surgical therapies for benign gynaecological conditions, such as ovarian cystectomy, can also compromise the ovarian reserve. Genetic conditions such as Fragile X premutation, mosaicism or monosomy X (Turner Syndrome), balanced translocation of the X chromosome and autoimmune conditions may also merit consideration for fertility preservation. Fertility preservation in the transgender population of transitioning females to males is another area of increasing interest.

Although many survivors of childhood cancers will subsequently conceive children naturally, higher rates of infertility are reported after some oncology treatments, particularly in those who received radiotherapy to the abdomen and pelvis or high doses of alkylating agents (Barton et al., 2013, Bramswig et a., 2015) The Childhood Cancer Survivor Study cohort shows that the prevalence of subfertility is higher in survivors compared with their siblings, even when ovarian function is maintained (Barton et al., 2013). Increasingly, more precise data are emerging as to which

treatments have significant effects on fertility, and which treatments are associated with a better fertility prognosis (Chow et al., 2016).

Embryo cryopreservation has been established in practice for thirty years. Mature oocyte cryopreservation is an alternative option for fertility preservation and is no longer experimental (The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology (ASRM), 2013a). Ovarian tissue cryopreservation is less widely available, particularly in the UK, and is still considered experimental, as is *in vitro* maturation of immature oocytes (ASRM, 2013a; ASRM, 2013b).

The likelihood of subsequent utilisation of stored oocytes, embryos or ovarian tissue is unknown. Many patients will conceive children naturally, whilst others may not be able to use their stored oocytes or embryos. The longer, more extensive experience with sperm cryopreservation in oncology suggests that future utilisation of stored material is likely to be low (Agarwal et al., 2005 ; Cardozo et al., 2015), and due consideration to the management of storage banks is important.

Methods

A search of online databases (MEDLINE, EMBASE, Cochrane library and Central register of controlled trials) was performed using the keywords: fertility preservation, cancer, oncofertility, oncology, embryo cryopreservation, oocyte cryopreservation, ovarian tissue freezing, ovarian transposition, ovarian suppression, GnRH agonists, gonadotoxity. Searches were carried out for randomised control trials, systematic reviews, existing guidelines, cohorts, case series and case studies until September 2016. Only English language articles were selected, as resources for translations of non-English articles were not available. Peer-reviewed articles, reviews and guidance from professional interdisciplinary bodies were included. Conference abstracts and unpublished studies were excluded. The literature search and decisions regarding study inclusion were undertaken by all authors, whilst the interpretation of final data and quality assessment was undertaken by the co-ordinating author (EY). We identified 20 published guidelines from professional bodies (Table 1).

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Grading of evidence

The Royal College of Obstetricians and Gynaecologists grading of evidence was used (Table 2)

Limitations of available literature

Randomised control trials were lacking for many of the techniques for fertility preservation. Cohort studies, small non-randomised trials and case series formed the main body of evidence for most of the techniques.

Pregnancy outcome in cancer survivors

Naturally conceived pregnancies in healthy cancer survivors who were not exposed to irradiation are probably at no higher risk than in the general population. There may be an increased risk of miscarriage should conception occur within a few months of chemotherapy, but not in the longer term (Signorello et al., 2012; Winther et al., 2012). In particular, there is no evidence of increased risk of congenital anomalies, even after ovarian irradiation or exposure to alkylating agents (Signorello et al., 2012).

Several large population-based studies have examined the outcome of pregnancies in survivors of childhood cancer. A British study found that female survivors exposed to abdominal irradiation had a significantly increased risk of preterm delivery and low birth weight (Reulen et al., 2009) An increased risk of miscarriage was associated with abdominal radiotherapy. Live birth amongst survivors were two-thirds lower than expected. Mueller et al., (2009) demonstrated similar findings of preterm birth and low birth weight from the US Childhood Cancer Survivor Study data. Infants born to childhood cancer survivors were more likely to be preterm and have low birth weight. However, reassuringly, no increased risks of malformations or infant death was found, suggesting no increased germ cell mutation. In a Danish study of 472 survivors of childhood and adolescent cancer, no increase in genetic defects was seen in the offspring despite mutagenic chemotherapy and radiotherapy doses to the gonads (Winther et al., 2012).

Pelvic irradiation (including abdomino-pelvic and spinal irradiation in girls) is associated with increased obstetric risks due to poor uterine function, especially when exposure occurs before menarche (Bath et al., 1999; Larsen et al., 2004; Signorello et al., 2012). These risks include early and late miscarriage, prematurity, low birth weight, stillbirth, neonatal haemorrhage, postpartum haemorrhage, and possibly uterine rupture and placental attachment disorders such as placenta accreta and percreta (Wo and Viswanathan, 2009).

It is outside the scope of this document to consider fully assessment of fitness for pregnancy after cancer, the impact of pregnancy on the risk of recurrence, or the impact of a recurrence on pregnancy. However, these issues do need to be addressed prior to embarking on pregnancy. For example, maternal cardiac failure precipitated by pregnancy in cancer survivors has been described associated with exposure to anthracyclines, high dose cyclophosphamide or cardiac irradiation, which may include the scatter from local radiotherapy for breast cancer and not just mediastinal irradiation (Appel et al., 2007; Hudson et al., 2010). Pregnancy has not been shown to increase the risk of cancer recurrence, including breast cancer, but with the exception of trophoblastic disease. In the UK, these issues will need to be considered as part of the statutory Welfare of the Child assessment when a licensed fertility treatment is planned (such as transfer of a frozen-thawed embryo or fertilisation of frozen-warmed oocytes).

Recommendations:

- Women should be informed that risk of congenital anomalies or genetic disease is not increased after cancer treatment. **C**
- Women who received radiotherapy to a field that included the uterus should be informed of the obstetric risks. **C**

- Women should be informed that there is no evidence of increased risk of cancer recurrence as a result of pregnancy, with most cancers. **C**

Carriers of BRCA1 gene mutations may have lower ovarian reserve compared with age-matched non-carriers (Phillips et al., 2016; Titus et al., 2013). BRCA genes play critical roles in the repair of double-stranded DNA breaks. Germline mutations in these genes may lead to accelerated oocyte apoptosis and depletion (Wang et al., 2014). Markers used to assess the ovarian reserve (AMH, AFC) may be reduced in women with cancer, and this may predict a lower response to ovarian stimulation (Phillips et al., 2016).

Evaluation of the risk of loss of fertility

Many studies have used amenorrhoea as a primary outcome of the effect of cancer therapy on fertility. The observed risk of amenorrhoea following various treatments for malignancy is listed in **Table 3.** Amenorrhoea can occur during or shortly after completion of radiotherapy or chemotherapy (Jacobson et al., 2015) and may be temporary or permanent. However, few studies have had the long-term follow-up necessary to diagnose POI with accuracy.

Chemotherapy

The risk of infertility is related to the type of chemotherapeutic agent, dose and drug regimen and age at time of treatment. Depletion of the pool of primordial follicles and compromised vascularity of the gonads are thought to be among the gonadotoxic effects of chemotherapy (Morgan et al., 2012). The size of the pre-treatment ovarian reserve will also impact on the degree of ovarian toxicity (Anderson and Cameron, 2011). The gonadotoxity of many chemotherapeutic agents, especially newer ones, has not been fully evaluated, and their use in combination also complicates assessment of risk. There do not seem to be deleterious long-term effects on the genetic competency of surviving oocytes (Signorello et al., 2012; Winther et al., 2012) and future pregnancies (Signorello et al., 2006)

Recommendation:

- The risk of infertility, diminished ovarian reserve and premature ovarian insufficiency should be assessed based on age, type and dose of chemotherapy. **C**

Radiotherapy

The impact of irradiation on the reproductive organs depends on site, dose and age of the patient, fractionation of treatment and adjuvant therapy. Abdomino-pelvic radiation of 2Gy can cause loss of more than 50% of the primordial pool and radiation doses of 24Gy will usually cause ovarian failure (Anderson et al., 2015). Cranial irradiation causes impairment of hypothalamic–pituitary–gonadal function; radiation doses

exceeding 50Gy will usually cause hypogonadism (Gleeson and Shalat, 2005). Patients who undergo bone marrow transplantation have extremely high rates of ovarian failure, ranging from 72% to 100% after total body irradiation (De Bruin et al., 2008). The dose of radiotherapy depends on the diagnosis and stage of the disease. The typical range of doses of radiotherapy in different conditions is listed in **Table 4**.

Brachytherapy has significant local effects. Vaginal irradiation leads to dryness, and vaginal stenosis. Radiation to the uterus can cause vascular, endometrial and myometrial damage leading to tissue fibrosis and restricted uterine capacity and blood flow. The ESHRE guideline on premature ovarian insufficiency highlights abnormal uterine function and the risk of early and late pregnancy complications in women who have received radiotherapy to the uterus (including total body irradiation) (ESHRE, 2015). The effect on uterine function is dose-dependent and also related to age at the time of exposure. Exposure to radiotherapy before puberty causes significant impairment of the development of the uterus (Bath et al., 1999; Larsen et al., 2004) and reduced responsiveness to exogenous sex steroids (Critchley et al., 1992).) Implications for pregnancy outcome are discussed in the section above on **Pregnancy outcome in cancer survivors**.

Recommendation*:*

- Patients undergoing pelvic, abdomino-pelvic or cranio-spinal irradiation should informed of the risk of infertility, depending on the field of direct and scatter exposure **C**

Hormone therapy

Women with hormone-sensitive tumours who are advised to take endocrine therapy will have an age-related decline in fertility even if they do not have adjuvant chemotherapy and radiotherapy. The recent ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) study indicated that 10 years of treatment with tamoxifen is superior to a 5-year course, and this will likely result in a larger proportion of breast cancer patients needing to further delay childbearing (Davies et al., 2013) . However, some women may choose to take a break from endocrine therapy in order to have a baby, after discussion with their oncologist.

Recommendations:

- The effect of delay in attempting conception due to prolonged endocrine therapy after breast cancer should be borne in mind when advising women about fertility preservation, even if they do not require gonadotoxic therapy **GPP**

Techniques of fertility preservation

This section discusses established and as yet experimental approaches to fertility preservation. It should be recognised that the techniques discussed here do not constitute an exhaustive list. In many clinical situations, the patient may have recourse to treatment options that have a lesser impact on fertility than other available

treatments. This includes, for example, medical treatment with selective progesterone receptor modulators and myomectomy rather than hysterectomy for uterine fibroids. For any technique, evidence of safety and efficacy in the context of fertility preservation is needed before its use for this indication.

Cryopreservation of embryos and oocytes

NICE Guidance recommends embryo and oocyte freezing for fertility preservation where a threat exists from oncological treatments or illnesses that compromise fertility (NICE, 2016).

Cryopreservation of either oocytes or embryos is preceded by controlled ovarian stimulation (COS) and oocyte collection. The possible risks of delay in starting cancer treatment should be included in the discussion of these options with patients, and also the consequences of any complications of the fertility preservation technique. In general, from the start of ovarian stimulation to oocyte retrieval takes approximately 2 weeks, with chemotherapy usually able to start within 48 hours of egg retrieval. A longer recovery period may be required before surgery and radiotherapy to the pelvis.

Recommendations:

Women in the reproductive age range should be offered fertility preservation if:

- there is a material risk of infertility as a result of the intended treatment
- the treatment for the disease has curative intent or there is good prospect for long-term survival
- the woman is fit for ovarian stimulation and oocyte collection
- the time required for ovarian stimulation and oocyte collection does not jeopardise prognosis.

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Embryo cryopreservation

The most established technique for fertility preservation is cryopreservation of embryos derived from the patient's oocytes and partner or donor sperm. Embryo cryopreservation is suitable for women in a relationship where both partners consent to creation and storage of embryos; counseling should address the requirement for both partners to consent to the use of embryos in any future fertility treatment. In the case of embryos created with donor sperm, future use requires the consent of the woman alone. UK clinics providing licensed fertility treatment are obliged to consider all factors that may affect the welfare of any child conceived through treatment.

Live birth rates from the transfer of thawed cryopreserved embryos are dependent on the age of the woman at the time of oocyte retrieval (HFEA, 2016). It should be noted that these data are from subfertile couples undergoing assisted conception, rather than couples who have embryos cryopreserved for fertility preservation. The live birth rates in women following transfer of pre-chemo/radiotherapy frozen embryos show comparable results when compared with age-matched controls, however low rates of

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utilisation of stored embryos are also observed (Cardozo et al., 2015). Some of the causes of non-utilisation are death and ill-health, natural conceptions, and relationship breakdown (Barcroft et al., 2013)

Recommendation:

- Women/couples should be advised that embryo cryopreservation is an established technique, with success rates for the transfer of frozen-thawed embryos comparable to those for the transfer of fresh embryos **D**

Oocyte cryopreservation

Women who are not in a relationship, or who do not wish to cryopreserve embryos, are offered oocyte cryopreservation. However, the prospect of relationship breakdown and inability to use embryos in the future must be borne in mind. For this reason, oocyte cryopreservation is an equally important option for women in relationships. The development of vitrification has dramatically changed the success of oocyte cryopreservation, which is no longer experimental (ASRM, 2013a; NICE, 2016). A meta-analysis of the clinical application of oocyte vitrification showed that pregnancy rates did not differ between use of vitrified and fresh oocytes, although the study population was healthy oocyte donors (Cobo et al., 2013). Indeed, the confidence with oocyte cryopreservation derives mainly from experience with cryopreserved donor oocytes in recipient cycles (Cobo and Diaz, 2011). In one study, oocyte survival after vitrification ranged between 90%–97%, fertilization rates were between 71%-79%, clinical pregnancy rates per transfer ranged from 36%-61% and the clinical pregnancy rate per thawed oocyte was 4.5%-12% (Cobo and Diaz, 2011 ; Cobo et al., 2016). Comparable results have been reported for women whose oocytes were vitrified for social fertility preservation, demonstrating that the outcome of oocyte vitrification depends on the number and quality of oocytes cryopreserved, and the age of the woman at cryopreservation (Doyle et al., 2016) with an overall vitrified-warmed oocyte to live-born child efficiency of 6.4% (ASRM, 2013a). Ongoing pregnancy rates in 182 oocyte vitrification/warming cycles were significantly lower in women over 40 years of age compared with younger women (Borini et al., 2006).

Ovarian stimulation and oocyte vitrification can be performed in post-pubertal adolescent girls (Lavery et al., 2016) although such interventions in this age group raise specific practical and ethical issues, and it is unknown whether the pregnancy rate obtained from use of cryopreserved oocytes in this age group is the same as for adult women. In the UK, centres performing oocyte retrieval procedures in patients under the age of 18 years require specific inspection by the Care Quality Commission.

A key benefit of oocyte cryopreservation over embryo cryopreservation is that it obviates the need for partner consent to use the stored oocytes in the future.

Recommendation:

- Women should be advised that oocyte cryopreservation is an effective technique, which may have a similar success rate to that using fresh oocytes **C**

Controlled ovarian stimulation and oocyte retrieval

Controlled ovarian stimulation (COS) involves administration of exogenous gonadotrophins to promote development and maturation of multiple ovarian follicles, thereby increasing the number of oocytes available for cryopreservation or generation of embryos.

Controlled ovarian stimulation regimens

Safe and effective COS and oocyte retrieval for women undergoing fertility preservation should take into account the following considerations:

- Minimal delay to treatment: the COS regimen should be applicable without delay and aim to elicit a good ovarian response within the shortest possible time, thus minimising delay in starting cancer treatment.
- Ovarian Hyperstimulation Syndrome (OHSS): OHSS may require hospital assessment and inpatient care, further delaying the start of cancer treatment. Minimising the risk of developing OHSS is therefore of particular significance in this group of patients. Oncology patients may also be at increased risk of VTE should OHSS occur. The antagonist protocol with agonist trigger is suitable due to the short stimulation to oocyte collection interval and reduced risk of OHSS.
- Procedural risks: increased risk of haematoma due to thrombocytopenia and infection due to neutropenia, secondary to either the underling condition or treatments already commenced, should be discussed with the patient and appropriate antibiotic cover provided.
- Anaesthetic risks: patients should be reviewed by an anaesthetist prior to oocyte harvest if any risk factors for anaesthesia are present, e.g. mediastinal mass in lymphoma patients.
- Women with pelvic malignancies (e.g. of the cervix or ovary) may be at risk of dissemination of malignancy and increased risk of bleeding due to vascularity associated with the tumour. It is not known if women with malignancy are at increased risk of VTE during or after COS due to the associated increased estrogen levels.
- The route of oocyte collection may have to be altered depending on pelvic disease, e.g. abdominal or laparoscopic oocyte collection may be required in women with cervical cancers

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GnRH antagonist regimens exhibit potential advantages over the use of GnRH agonist in fertility preservation, although there have been no comparative trials. Use of GnRH antagonist enables ovarian stimulation to be started flexibly at any point in the menstrual cycle, thereby minimising delay in treatment. Retrospective studies indicate that random-start ovarian stimulation protocols are associated with the collection of similar numbers of oocytes, comparable proportions of mature oocytes and similar fertilisation rates as conventional early follicular start ovarian stimulation (Cakmak et al., 2013). There are no studies comparing live birth rates with these regimens. In addition, the risk of OHSS is lower in treatment cycles using GnRH antagonist compared to GnRH agonist. Meta-analysis of 20 trials involving 5141 women

undergoing IVF shows a lower rate of moderate or severe OHSS in women receiving GnRH antagonist compared with GnRH agonist (Youssef et al., 2011). A further advantage of GnRH antagonist regimens is that the pituitary gonadotrophs of women receiving GnRH antagonist retain their sensitivity to the initial flare effect of GnRH agonist, allowing the use of GnRH agonist to induce final follicular maturation. This avoids the use of human chorionic gonadotropin (hCG), which has a longer half-life, and hence a greater potential to precipitate OHSS, than endogenous luteinizing hormone. Meta-analysis shows that the use of GnRH agonist 'trigger' for final follicular maturation is associated with a significantly reduced risk of OHSS compared with the use of hCG, both in women receiving fresh embryos and in women donating oocytes (Youssef et al., 2011).

Evidence is lacking on the type of gonadotropin preparation (recombinant FSH *vs* purified urinary FSH) and the starting dose of FSH specifically in women requiring fertility preservation. However, evidence from the wider population of women undergoing IVF supports the use of ovarian reserve tests such as serum anti-Mullerian hormone (AMH) or antral follicle count (AFC) to determine the starting dose of FSH (Jayaprakasan et al., 2012; Nelson et al., 2009). There is evidence to suggest that the ovarian response is reduced in women with some cancers (Domingo et al., 2012); hence the use of a moderately high dose of FSH is justified for ovarian stimulation in these patients.

COS regimens designed specifically to mitigate the effect of elevated oestrogen concentrations during ovarian stimulation have been developed for use in women with breast cancer. This can be extrapolated to other oestrogen-sensitive cancers. Letrozole co-treatment during ovarian stimulation is associated with significantly lower oestradiol concentrations compared with conventional gonadotropin stimulation, while resulting in similar numbers of oocytes retrieved and cryopreserved (Oktay et al., 2006). Tamoxifen, a selective oestrogen receptor modulator often used as adjuvant treatment for women with hormone-sensitive breast cancer, has been studied as a means of managing the potential risk posed by elevated oestradiol concentrations during ovarian stimulation in breast cancer. Meirow et al., (2014) reported outcomes of 76 cycles of embryo cryopreservation in women with breast cancer undergoing ovarian stimulation with or without concomitant tamoxifen use (Meirow et al., 2014). A recent prospective controlled, non-randomised study in women with Stage 3 or less invasive breast cancer showed no increased risk of recurrence in 120 women who underwent fertility preservation using letrozole as part of the ovarian stimulation protocol, over a mean duration of follow-up of 5 years (Kim et al., 2016).

A meta-analysis by Friedler et al., (2012) indicates that the number of retrieved oocytes in women with a cancer diagnosis was significantly lower than in age-matched healthy IVF patients (Friedler et al., 2012). Other authors show conflicting data. Quinn et al., (2017) demonstrated that response to ovarian stimulation is not impacted by breast cancer. In situations where time permits, consecutive cycles of ovarian stimulation and oocyte retrieval have been reported with the aim of increasing the number of oocytes cryopreserved (Kuang et al., 2014; Turan et al., 2013). This approach may be helpful in women who exhibit a poor response to ovarian stimulation and in whom the initiation of oncological treatment can be delayed without significant adverse effect on prognosis.

Recommendations:

- Antagonist protocols should usually be employed as they shorten the duration of treatment and reduce the risk of OHSS. **A**
- An agonist trigger in an antagonist cycle should be considered as this minimises the risk of OHSS, unless contraindicated **A**
- Consider using an anti-oestrogen [letrozole, clomifene or tamoxifen] during ovarian stimulation in women with oestrogen-sensitive tumours **D**

Duration of Storage

Data on embryo and sperm storage demonstrate prolonged survival without detriment (Di Santo et al., 2012). No differences in survival, fertilisation, cleavage, embryo quality, implantation, and live-birth rates were observed in slow-frozen oocytes thawed after up to 48 months compared to earlier thaws (Parmegiano et al., 2009). While it would seem to be appropriate for the duration of storage to be based on the age of the women at the time of treatment, relevant legislation must of necessity be taken into account. In situations where there is actual or anticipated 'premature infertility', the HF&E Act allows storage of gametes or embryos for a maximum period of 55 years. Initial storage is for a maximum period of 10 years, and can be extended by further 10 year periods (up to the maximum of 55 years) if it is shown at any time within each extended storage period that the criterion of premature infertility continues to be met. The relevant HFEA consent form is required to be completed by the patient at each extension, along with a medical practitioner's certificate.

When assisted conception with use of the stored oocytes/embryos is planned, the welfare of the child assessment will need to be made according to HFEA guidance. Patients need to be made aware that subsequent NHS-funding for use of oocytes/embryos may depend on meeting criteria for fertility treatment at the time.

Recommendations

- Women/couples should be advised of the length of time their oocytes/embryos can be stored and that this limit is statutory. **GPP**
- Women/couples should be advised that there is no evidence to indicate that the duration of storage influences the success rate of using of thawed oocytes/embryos **D**
- Welfare of the child assessment should be made at the time of use of oocytes/embryos for assisted conception. **GPP**

Pregnancy outcome using cryopreserved embryos and oocytes

No particular risk has been identified for children born following frozen-thawed embryo replacement (Williams et al., 2013). In a large systematic review of pregnancy outcome after replacement of frozen-thawed embryos and oocytes, the outcome using slow frozen embryos was comparable to that using fresh embryos (Wennerholm et al., 2009) with no increase in congenital abnormalities. Higher birth weights and lower rates of preterm and low birth weights were observed following use of slow frozen

embryos compared with children born after fresh IVF/ICS, and no increased risk of congenital abnormalities was observed in the analysis of the HFEA data carried out by Maheshwari et al., (2016). However, these large population-based studies were based on the subfertile population and there is no information specific to the use of frozen embryos from cancer patients prior to gonadotoxic treatment.

Recommendation:
Women/couples can be advised that

- pregnancy outcome using cryopreserved oocytes/embryos reveals no increase in congenital anomalies **D**
- current data do not suggest that pregnancy outcomes from oocyte/embryos from oncology patients differ from other patients **GPP**

Ovarian tissue cryopreservation and transplantation

Ovarian tissue cryopreservation (OTC) is the only option for pre-pubertal girls (Anderson et al., 2015) and is an option for post-pubertal adolescents and adult women particularly when there is a narrow time window for fertility preservation. It has the disadvantage of being more invasive, requiring laparoscopy, but successful tissue replacement subsequently can restore the endocrine function of the ovary as well as fertility (Jensen et al., 2015). Although ovarian tissue cryopreservation is still considered experimental, a number of successful pregnancies have been reported after orthotopic ovarian tissue transplant with a live birth rate of approximately 25% in these series (Donnez et al., 2013, Meirow et al., 2016, Jensen et al., 2015; Van der Ven et al., 2016) approximately half of which were natural conceptions and others after IVF. Live birth has also been reported after heterotopic replacement (Stern et al., 2013) although this is generally regarded as much less successful. Almost all births have resulted from tissue that was slow frozen, but births have also been reported after ovarian tissue vitrification (Donnez, et al., 2015). There is limited experience in application of this technique for restoring fertility when ovarian tissue is cryopreserved in adolescence or childhood (Demeestere et al., 2015).

Primordial follicles are located in the ovarian cortex; therefore, obtaining cortical tissue potentially enables cryopreservation of significant number of oocytes. Ovarian tissue is procured laparoscopically, either by removal of ovarian cortex or unilateral oophorectomy. Orthotopic transplantation of ovarian tissue involves transplantation of thin, <1.0–1.5 mm thick strips of thawed ovarian tissue into either the medullary portion of the remaining ovary or a nearby peritoneal pocket.

Advantages of this technique include the possibility of natural conception as the ovarian tissue is in close proximity to the fallopian tube, and importantly the possibility of long-term hormone production avoiding the need for hormone replacement therapy. Disadvantages include the need for general anaesthesia and laparoscopic surgery, and concern about risk of tissue contamination with micrometastatic disease especially in haematological malignancies (Dolmans et al., 2013; Jensen et al., 2015). To date, there are no case reports of relapse related to re-implanted tissue; however, recurrences may occur many years after original disease and it may be difficult to establish whether a recurrence was provoked by transplanted tissue.

Resumption of normal ovulatory menstrual cycles has been reported in over 90% of patients within 4–9 months after transplantation, which is consistent with the time necessary to initiate follicular growth and final maturation (Meirow et al., 2015). Grafts have been reported to continue functioning for up to 10 years (Jensen et al., 2015; Donnez et al., 2015) although this is exceptional, with some grafts showing only very short duration of function.

Whilst ovarian tissue cryopreservation techniques are available, in adult patients there is no consensus on selection criteria. Most OTC programs have been carried out on a research basis, with the use of research criteria. The Edinburgh group published their selection criteria (Wallace et al., 2014) based on age (younger than 35 years), no previous chemotherapy or radiotherapy (mild or non-gonadotoxic chemotherapy acceptable), a realistic chance of surviving for 5 years and a high risk of premature ovarian insufficiency (>50%). To date, these are the only validated criteria but there is a need to update the criteria based on more recent evidence, for instance the availability of accurate measures of ovarian reserve. Where ovarian reserve is reduced, for example with previous chemotherapy, the success from later replacement of ovarian tissue may be diminished. Criteria for offering OTC should logically be aligned with those for oocyte or embryo cryopreservation.

OTC is still not an established treatment and as such, should only be offered by units with relevant clinical and laboratory expertise, protocols and HTA licensing or associated with an established unit using a third party arrangement. NHS Trusts also require local governance requirements to be satisfied before a new surgical technique is introduced.

Recommendations:

- Ovarian Tissue Cryopreservation can be considered for post-pubertal patients, particularly where there is insufficient time for ovarian stimulation and oocyte cryopreservation. **C**
- Increasing numbers of live births from transplantation of frozen ovarian tissue suggests that OTC should be considered for pre-pubertal patients **GPP**
- These procedures should only be performed at centres with relevant expertise, facilities and HTA licensing. **GPP**

In vitro Maturation

In vitro maturation (IVM) and vitrification of oocytes retrieved from unstimulated ovaries is currently considered an experimental technique that can be offered to those women who cannot delay their cancer treatment. In oncological patients, oocyte maturation rates of 79% and clinical pregnancy rates of 18-30% per embryo transfer have been reported with IVM (Hourvitz et al., 2015). Implantation rates are lower following transfer of embryos derived from *in vitro* matured oocytes compared with fresh oocytes. It may be possible to combine IVM with ovarian tissue cryobanking (Abir et al., 2016).

Recommendation:

- IVM should be offered only in specialised units with relevant expertise, facilities and HFEA licensing **GPP**

Ovarian suppression

Suppression of ovarian function by administration of GnRH agonists (GnRHa) immediately before and during chemotherapy has been proposed for the preservation of ovarian function. One rationale is that destruction of follicles by chemotherapeutic agents causes a fall in local anti-Mullerian hormone (AMH) levels; this, with a rise in FSH, stimulates more follicles to enter the maturation pathway, rendering them more susceptible to the toxic effects of chemotherapy. The rise in FSH is prevented by GnRHa. Suppression of follicle growth and reduced ovarian blood flow may also contribute, and there is a possibility of direct effects of GnRHa on the ovary.

In recent years, large RCTs have been performed to assess this approach in women with early breast cancer. The most recent meta-analysis, including 12 trials (n= 1231 women) indicated a significant reduction in the risk of 'premature ovarian failure' (variably defined in the various studies) with OR 0.36, 95%CI 0.23-0.57, although with significant heterogeneity. Eight trials reported rates of amenorrhea at 1 year after chemotherapy, with OR 0.55, 95%CI 0.41-0.73, without significant heterogeneity (Lambertini et al., 2015). None of the studies have assessed the degree of ovarian function 'saved' by GnRHa treatment, for example by use of AMH measurements.

The possible clinical benefits from ovarian protection may be increased fertility, or reduced impact of estrogen deficiency from delayed POI, although both are likely to also be influenced by post-chemotherapy hormone treatments (tamoxifen, ongoing ovarian suppression with GnRHa) that may be indicated in these patients. No studies have been designed to assess these later outcomes, but the meta-analysis indicates that there were more pregnancies in women treated with GnRHa than in those not treated. As this was not a primary outcome for any studies, this result should be treated with caution.

The majority of studies assessing this approach have been in women with breast cancer, although there have been smaller RCTs in women with lymphoma and ovarian cancer which did not show a benefit. These studies were included in an earlier meta-analysis (Del Mastro et al., 2014), which highlighted the lack of power of studies in diseases other than breast cancer. It remains possible that GnRHa treatment might have a beneficial effect in other malignancies (or indeed in other conditions involving cytotoxic therapy) and larger RCTs are required to assess this. The most recent trial to report in Hodgkin lymphoma found no benefit in terms of POI with GnRHa administration although power was low (Demeestere et al., 2016). Whether GnRHa administration during treatment impacts survival has been addressed in 3 studies in women with breast cancer, and showed no effect (Lambertini et al., 2015). These RCTs have used monthly administration of goserelin or triptorelin. GnRH antagonists have not been used in RCTs.

An additional benefit of GnRHa administration is suppression of menstruation during chemotherapy and the avoidance of heavy menstrual bleeding, which is often due to

thrombocytopenia during chemotherapy. The risk is highest at the nadir of thrombocytopenia. Menstrual suppression can also be achieved with progestagen. GnRHa carries the side-effects of oestrogen-deficiency vasomotor symptoms (hot flushes and night sweats) and a risk of osteoporosis. It would seem inappropriate in women with hormone sensitive breast cancer to use add-back therapy with low-dose estrogen patch or oral tibolone to reduce symptom severity. The initial flare effect of GnRHa should be borne in mind when used for menstrual suppression.

Recommendations:

- In premenopausal women with early breast cancer consider temporary ovarian suppression with GnRHa started immediately before and continued during chemotherapy as this may partially preserve ovarian function. **A**
- Women should be advised that it is possible there is a benefit of using GnRHa when other cancers are treated with gonadotoxic chemotherapy. **GPP**

Ovarian transposition

The ovaries can be protected from radiation injury by moving them out of the radiation field. This technique is called ovarian transposition, ovarian suspension, oophoropexy, or ovariopexy and was introduced more than 50 years ago (McCall et al., 1958) The procedure is now performed laparoscopically unless laparotomy is necessary for the primary treatment of the tumour (Al-Asari and Abduljabbar, 2012). Techniques for ovarian transposition vary according to the radiation field shape, size, and location and there are several sites that the ovaries can be moved to (Gershenson, 2005). Instances when this may be performed include cervical, rectal and colon cancer, pelvic Hodgkin lymphoma and Ewing's sarcoma (Gershenson, 2005).

Morice et al., reported a series of 24 patients who underwent ovarian transposition to the paracolic gutters, before radiation for gynecologic malignancies (Morice et al., 1998). The authors concluded that this procedure was a safe and effective method of preserving ovarian function. Complications are rare in the reported literature. The technique involves transposing the ovaries above the pelvic brim and as lateral as possible, aiming to minimize the ovarian dose of radiation (Gubbala et al., 2014). The ovarian ligament is transected and the ovary mobilised. Blood supply is maintained through the infundibulo-pelvic ligament. Attention should be paid to avoid torsion and extension of the ovarian vessels which may reduce blood supply to the ovaries, with a subsequent effect on ovarian reserve. The ovaries can be marked with metallic clips for radiologic identification (Al-Badawi et al., 2010).

Ovarian function after ovarian transposition has been measured by gonadotrophins, anti-Mullerian hormone (AMH) and fertility outcomes. Retention of ovarian function has been found to be 60-89% after ovarian transposition (Gubbala et al., 2014; Falcone et al., 2014), although as all reports are non-randomised the size of the effect is unclear. The results may also depend on the type of radiotherapy used (Shou et al., 2015).

Natural pregnancies are possible if tubal function is preserved as part of the ovarian transposition. Morice et al. (1998) reported 16 natural pregnancies after ovarian

transposition. In one report of medial ovarian transposition by positioning the ovaries behind the uterus in 11 girls with Hodgkin lymphoma, the authors reported 14 pregnancies over a 15 years follow-up period (Terenziani et al., 2009).

IVF can be carried out following ovarian transposition using abdominal oocyte collection. No difference in fertilization and pregnancy rates have been observed with trans-vaginally and trans-abdominally collected oocytes (Barton et al., 2011). Scattered radiation and reduction in ovarian blood supply after transposition appear to be the main factors causing failure of the technique (Crawshaw, 2009). There is a small risk of pelvic pain due to the potential for ovarian torsion and fallopian tube infarction (Gubbala et al., 2014).

The potential effect of radiation upon the uterus should be borne in mind when considering ovarian transposition. Uterine damage from doses in the range of 8500 cGy or intra-cavitary brachytherapy essentially precludes successful pregnancy, either naturally or with *in vitro* fertilization (Agorastos et al., 2009). Where significant uterine damage has occurred, ovarian transposition may allow the patient to retain the potential to have biological children with host surrogacy (Agorastos et al., 2009)

Recommendation:

- Consider ovarian transposition to move ovaries away from the field of irradiation. **D**
- Fallopian tubes should not be transected in order to retain the possibility of natural conception. **GPP**

Shielding of ovaries during radiotherapy

Aside from surgical approaches to protect the ovaries from irradiation, modification of radiation techniques to achieve the same end have been explored. External shielding is used in an attempt to minimize radiation exposure to ovaries. The entire pelvis cannot be blocked from radiation without the potential for also shielding tumour cells as well. Such blocks have been shown to offer poor ovarian protection owing to the mobility of the pelvic anatomy (Fawcett et al., 2012).

The use of more complex X-ray planning techniques, such as intensity-modulated radiation therapy (IMRT), has also been examined. Although IMRT reduces doses to many organs, its capacity to reduce the dose meaningfully for a tissue as radiosensitive as the oocyte is quite limited, and ovarian exposure during craniospinal irradiation is likely to exceed 3–5 Gy(RBE) even when IMRT is utilized (Pérez-Andújar et al., 2013).

Proton therapy is being used for the delivery of craniospinal irradiation in certain centres and has been shown to allow reduction in the radiation dose delivered to visceral organs anterior to the spinal cord (Yoon, 2012); it may be used for targeted pelvic radiotherapy (Fukushima et al., 2015). Proton beam therapy will be available in the UK soon with 2 centres being set up in the country.

Recommendation

- Ovarian shielding is of limited use to prevent damage from irradiation and generally should not be offered **D**

Fertility-sparing surgery

Fertility-sparing surgery is used in gynaecological cancers with the aim of retaining fertility whilst achieving outcomes that are not inferior to more extensive conventional surgery. A well-established fertility-sparing surgical procedure in young women with early-stage cervical cancer is radical trachelectomy. This may be offered in cases of early-stage invasive cervical cancer instead of hysterectomy. A meta-analysis by Willows et al., (2016) found that among 1238 patients who underwent fertility-sparing surgery for early cervical cancer, 469 pregnancies occurred with a 67 % live birth rate. Outcomes after simple trachelectomy or cervical conization were similar. Cervical stenosis and subfertility are common after trachelectomy. The risk of recurrence has not been found to be higher after these procedures (Okugawa et al., 2016).

In women with borderline ovarian tumours (BOT) concern exists about the effect of ovarian stimulation and the risk of microscopic seeding at oocyte collection after ovarian cystectomy. Most pregnancies after conservative treatment of BOT are natural conceptions. Although BOT are associated with good prognosis, caution needs to be exercised because these tumours can relapse and malignant transformation can also occur. Nevertheless, the patient should be informed that stimulation treatment may be associated with an increased risk of relapse. Cryopreservation of ovarian tissue is recommended by certain teams (Fain-Kahn et al., 2009). However, when autologous transplant is carried out at a later date for fertility, re-transplantation of borderline tissue or the de novo development of a borderline tumour cannot be excluded.

In principle, a pregnancy occurring spontaneously after fertility preservation surgery or ovarian stimulation is preferable to cryopreservation of ovarian tissue so that the ovarian reserve is not further reduced by the removal of ovarian tissue. Unfortunately, evidence about fertility preservation in women with BOT is limited. The patient is usually advised to try to conceive spontaneously after fertility sparing surgery. Ovarian stimulation and oocyte recovery may be considered after ovarian cystectomy if bilateral oophorectomy is planned as a subsequent step and no significant risk has been reported (Darai et al, 2013). According to a review of the studies the risk of relapse of a borderline tumour after ovarian stimulation treatment was 19.4% without resulting in mortality (Denschlag et al., 2010). Letrozole during COH may be considered to reduce circulating oestradiol levels. Oocyte retrieval from affected ovaries at the time of oophorectomy can be considered with a view to in-vitro maturation of oocytes (Mangili et al., 2016). Ovarian tissue cryopreservation is also possible although the tissue will only be usable if *in vitro* culture of oocytes becomes available.

Recommendations:

- Where feasible, fertility-preserving surgery should be considered in selected women with gynaecological malignancies **B**

- Fertility preservation for women with borderline ovarian tumours may be associated with additional risks and should be discussed with the patient and her oncology team. **D**

Discussion of oocyte donation, surrogacy, adoption

In discussing the effect of cancer and treatment of fertility, alternatives to oocyte, embryo and ovarian tissue cryopreservation should be explained. These options include oocyte donation and surrogacy, especially where significant radiation damage to the uterus is involved, adoption, and life without children.

Recommendation:
Alternatives to fertility preservation should be discussed **GPP**

Fertility preservation in special conditions

Women at risk of non-iatrogenic premature ovarian insufficiency

A small number of women are at risk of POI due to chromosomal, genetic, or metabolic conditions (such as Turner mosaicism, fragile X syndrome (FMR1) carrier status, or galactosaemia).

At present, strategies for fertility preservation in post-pubertal girls who are at risk of premature ovarian insufficiency (POI) are limited to ovarian tissue cryopreservation alone or in combination with immature oocyte collection from the tissue followed by *in vitro* maturation and vitrification of mature oocytes. In addition, patients with Turner syndrome, FMR1 carrier status and translocation of X chromosome are candidates for Preimplantation Genetic Diagnosis (PGD) (which requires IVF), because of the increased risk of fetal chromosomal or genetic abnormalities.

As the majority of women with Turner syndrome have POI, fertility preservation with oocyte or ovarian tissue cryopreservation may only be an option for those who have spontaneous puberty such as Turner mosaicism (Oktay and Bedoschi, 2014). Almost every woman with classic galactosaemia develops POI, although spontaneous conception has been described in this condition Gubbels et al., 2009; (van Erven et al., 2013). Fertility preservation is only likely to be successful in very young prepubertal patients by cryopreservation of ovarian tissue.

B**enign conditions treated with chemotherapy**

Some non-malignant diseases may require treatments that can impact reproductive function. In patients with systemic lupus erythematosus (SLE), the predominant mechanism of infertility is related to medication rather than disease. The incidence of amenorrhea following cyclophosphamide treatment for SLE ranges from 27% to 60% (Katsifis & Tzioufas, 2004).

A variety of disorders may be treated with bone marrow transplantation or haematopoietic stem cell transplant with preconditioning alkylating chemotherapy with or without radiation, including thalassemia major, sickle cell anaemia, aplastic anaemia, Fanconi anaemia, and myeloproliferative diseases (Gidoni et al., 2008; Tan et al., 2006). The combination of radiation and high-dose chemotherapy required before bone marrow transplant makes recovery of ovarian function in this patient population unlikely, and spontaneous recovery of ovarian function, as defined by a return of menstrual cycles, has been found to occur in only 6% of patients (Griessahmmer et al., 1998). Some of these conditions (eg sickle cell disease) will themselves affect ovarian reserve and may reduce the number of oocytes collected, should FP be undertaken. In children and young adults, ovarian tissue cryopreservation should also be considered for this group of patients (Lavery et al., 2016).

Commented [LT6]: Consider adding multiple sclerosis?

Pelvic surgery

Surgery for endometriomas, large ovarian dermoid cysts, and recurrent benign ovarian cysts is also likely to reduce ovarian reserve. Therefore women at risk of recurrent ovarian cystectomies should have a discussion about the effect of repeated surgery and the option of oocyte and embryo cryopreservation should be discussed.

Recommendations

- Discuss fertility preservation options with girls and women at risk of premature ovarian insufficiency from non-malignant conditions **GPP**
- Advise women and girls that the evidence for the success of fertility preservation for these indications is limited. **GPP**

Individuals transitioning from female to male gender

The implications for fertility should be discussed with individuals transitioning from female to male gender. The treatment pathway may include administration of GnRHa to suppress the hypothalamic-pituitary ovarian axis in young people and testosterone to induce virilisation, with finally oophorectomy with or without hysterectomy. To retain the possibility of becoming a genetic or biological parent, individuals may wish to store gametes, and may decide to postpone sterilising surgery. Duration of storage will be the same as for other medical indications.

Fertility preservation should be discussed and, if appropriate, carried out as early as possible in this pathway. Oocyte freezing is likely to be the appropriate mode of fertility preservation. The practicalities of regrafting make it unlikely that OTC would be a viable option in these cases.

There is no report of fertility preservation after testosterone has been given to induce virilisation. Although low doses of androgens have been described as an adjunct to ovarian stimulation (Nagels et al., 2015), it is not known whether ovarian stimulation

and collection of competent oocytes is possible after high doses of androgens prescribed for virilisation.

Counselling is strongly recommended in this complex situation; it should also cover the potential use of stored material following transition, i.e. whether the individual would be prepared to carry a pregnancy in the future, or whether surrogacy would be required.

Recommendations

- Discuss fertility preservation with people transitioning from female to male gender **GPP**
- If appropriate, fertility preservation should be performed as early as possible in the treatment pathway **GPP**
- Offer counselling, both prior to fertility preservation and prior to use of stored material **GPP**

Timing of discussion on fertility preservation

It is generally agreed that women with cancer should be given detailed information about the threat that cancer treatment poses to fertility as early as possible in the cancer treatment pathway (De Vos et al., 2014). The optimal time for FP information appears to be shortly after cancer diagnosis and during the cancer treatment planning stage, specifically before the FP consultation appointment (Balthazar et al., 2011; Garvelink et al., 2015). Information should be provided by both the referring oncologist and fertility team.

Counselling and psychological support in fertility preservation

There is ample evidence that women of reproductive age with cancer have significant concerns about the effect of cancer treatment on their fertility and the means by which they can preserve it (Peate et al., 2012; Tschudin and Bitzer, 2009). The potential to have biological children appears to be high on their list of priorities (Peate et al., 2012). Women find themselves in a situation where they have to come to terms with their diagnosis and make decisions about their cancer and fertility preservation treatments in a very short period of time. This can be a source of distress and anxiety. However, the provision of guidance for psychological support is difficult because the decision-making process is often complex and hindered by a number of factors with little evidence of psychological interventions that may help support women through the fertility preservation process.

Supporting patients to make decisions about their future fertility depends on a multidisciplinary approach involving clinical, nursing and surgical teams, psychologists and counsellors. Women often express many fears and anxieties, for example, over the implications of pursuing fertility preservation alongside cancer diagnosis/cancer recurrence and the potential health of a future child (Wilkes et al., 2010). A discussion about fertility preservation with a trained counsellor is advocated in existing clinical guidelines (Loren et al., 2013) although many patients do not appear to get access to

this type of service (Letourneau et al., 2011; Niemasik et al, 2012). Evidence suggests that many women feel that they do not have access to information that would support them with their decision-making and feel 'too rushed' in consultations to initiate or have the fertility discussion (Jones et at., 2016a; Jones et al., 2017; Woodruff et al., 2014). It is therefore important that women are given high quality information and the time needed to absorb this information.

Consideration should be paid to the woman's religious or cultural beliefs and individual values. When dealing with adolescent or pre-pubertal girls, identifying these separately from the wishes of family members can be challenging but the patient's autonomy should be preserved where possible (Tschudin et al., 2010).

Many women will experience cancer after having children. The decisional issues for women starting or completing their family are different.

Decision support interventions help patients think about the choices they face in ways which will help inform decision-making (Elwyn et al, 2012). Patient decision aids are one such example of a decision support intervention. Their aim is to support people to make decisions between healthcare options. Several patient decision aids exist to support the fertility preservation process for women (Peate et al., 2012). Two are specifically for women of reproductive age with a breast cancer diagnosis (Peate et al., 2012; Garvelink et al, 2013). They have undergone more extensive evaluation and have been found to reduce decisional conflict and regret about the decision made and increase FP knowledge. Recently, a new tool to support teenage and adult women with any cancer to make fertility preservation decisions has become available, although it is still in the early stages of evaluation (Jones et al., 2017b).

Decisional conflict appears to be lower when fertility preservation is funded compared with when it is not (Mersereau et al., 2013). Surveys of oncologists have found that many express the need for more fertility preservation information to enable them to support women more effectively (Adams et al., 2013), The implementation of other decision support interventions such as more education and training packages may therefore prove beneficial. In particular, those targeted at improving the communication skills needed to improve collaborative decision-making between patient and provider to deliver care that is patient-centred.

The role of psychology and counseling extends beyond decision-making. Ongoing support needs to be available when patients experience the late effects of cancer treatment and deal with infertility.

Recommendations

- Discuss fertility preservation as early as possible in the cancer treatment pathway **C**
- Refer women to a trained counsellor, both prior to fertility preservation and prior to use of stored material **GPP**
- Decision making aids should be provided to support women's fertility preservation decision-making, ideally at cancer diagnosis/treatment planning. **GPP**

Summary of recommendations

The fertility preservation techniques are summarized in table 5

- Women should be informed that risk of congenital anomalies or genetic disease is not increased after cancer treatment. **C**
- Women who received radiotherapy to a field that included the uterus should be informed of the obstetric risks. **C**
- Women should be informed that there is no evidence of increased risk of cancer recurrence as a result of pregnancy, with most cancers. **C**
- The risk of infertility, diminished ovarian reserve and premature ovarian insufficiency should be assessed based on age, type and dose of chemotherapy. **C**
- Patients undergoing pelvic, abdomino-pelvic or cranio-spinal irradiation should informed of the risk of infertility, depending on the field of direct and scatter exposure **C**
- The effect of delay in attempting conception due to prolonged endocrine therapy after breast cancer should be borne in mind when advising women about fertility preservation, even if they do not require gonadotoxic therapy **GPP**

Women in the reproductive age range should be offered fertility preservation if:

- there is a material risk of infertility as a result of the intended treatment
- the treatment for the disease has curative intent or there is good prospect for long-term survival
- the woman is fit for ovarian stimulation and oocyte collection
- the time required for ovarian stimulation and oocyte collection does not jeopardise prognosis. **GPP**

- Women/couples should be advised that embryo cryopreservation is an established technique, with success rates for the transfer of frozen-thawed embryos comparable to those for the transfer of fresh embryos **D**

- Women should be advised that oocyte cryopreservation is an effective technique, which may have a similar success rate to that using fresh oocytes **C**
- Antagonist protocols should usually be employed as they shorten the duration of treatment and reduce the risk of OHSS. **A**
- An agonist trigger in an antagonist cycle should be considered as this minimises the risk of OHSS, unless contraindicated **A**
- Consider using an anti-oestrogen [letrozole, clomifene or tamoxifen] during ovarian stimulation in women with oestrogen-sensitive tumours **D**
- Women/couples should be advised of the length of time their oocytes/embryos can be stored and that this limit is statutory. **GPP**

- Women/couples should be advised that there is no evidence to indicate that the duration of storage influences the success rate of using cryopreserved and warmed oocytes/embryos **D**
- Welfare of the child assessment should be made at the time of use of oocytes/embryos for assisted conception. **GPP**

Women/couples can be advised that

- pregnancy outcome using cryopreserved oocytes/embryos reveals no increase in congenital anomalies **D**
- current data do not suggest that pregnancy outcomes from oocyte/embryos from oncology patients differ from other patients **GPP**

- Ovarian tissue cryopreservation (OTC) can be considered for post-pubertal patients, particularly where there is insufficient time for ovarian stimulation and oocyte cryopreservation. **C**
- Increasing numbers of live births from transplantation of frozen ovarian tissue suggests that OTC should be considered for pre-pubertal patients **GPP**

- These procedures should only be performed at centres with relevant expertise, facilities and HTA licensing. **GPP**
- IVM should be offered only in specialised units with relevant expertise, facilities and HFEA licensing **GPP**
- In premenopausal women with early breast cancer consider temporary ovarian suppression with GnRHa started immediately before and continued during chemotherapy as this may partially preserve ovarian function. **A**
- Women should be advised that it is possible there is a benefit of using GnRHa when other cancers are treated with gonadotoxic chemotherapy. **GPP**
- Consider ovarian transposition to move ovaries away from the field of irradiation. **D**
- Fallopian tubes should not be transected during ovarian transposition in order to retain the possibility of natural conception. **GPP**
- Ovarian shielding is of limited use to prevent damage from irradiation and generally should not be offered **D**
- Where feasible, fertility-preserving surgery should be considered in selected women with gynaecological malignancies **B**
- Fertility preservation for women with borderline ovarian tumours may be associated with additional risks and should be discussed with the patient and her oncology team. **D**
- Alternatives to fertility preservation should be discussed **GPP**
- Discuss fertility preservation options with girls and women at risk of premature ovarian insufficiency from non-malignant conditions **GPP**
- Advise women and girls that the evidence for the success of fertility preservation for these indications is limited. **GPP**

- Discuss fertility preservation with people transitioning from female to male gender **GPP**
- If appropriate, fertility preservation should be performed as early as possible in the treatment pathway **GPP**

- Offer counselling, both prior to fertility preservation and prior to use of stored material **GPP**
- Discuss fertility preservation as early as possible in the cancer treatment pathway **C**
- Offer counselling, both prior to fertility preservation and prior to use of stored material **D**
- Resources embedded within a decision support intervention framework (such as a patient decision aid) should be provided to support women's fertility preservation decision-making, ideally at cancer diagnosis/treatment planning. **GPP**

Service organisation

Fertility Preservation services should be organised around efficient pathways enabling patients to access the appropriate expertise and treatment in a timely and supportive manner. Local needs and resources should dictate the specific pathways agreed, but close co-operation between relevant disciplines and a patient-centred approach is key. Pathway development requires liaison between the likely sources of referral (such as Oncology and Haematology) and the centres where fertility preservation treatment is carried out. Owing to the time-critical nature of cases, service commissioners should be involved to obtain agreement on funding mechanisms. Patients should be offered follow up in the fertility clinic to advise them of the late effects, provide management and discuss options for fertility.

Embryo and gamete cryopreservation facilities are available in most assisted conception units, which are regulated in the UK by the Human Fertilisation and Embryology Authority (HFEA). Gonadal tissue cryopreservation requires access to Human Tissue Authority (HTA)-licensed storage facilities. Any centre providing care to individuals under the age of 18 must meet specific Care Quality Commission or HFEA requirements.

Recommendations for audit

Audit is essential to monitor and improve the quality of care provided to patients who may require fertility preservation. The paucity of agreed standards is a difficulty that needs to be addressed. There is a role for deriving standards from research. Professional organisations such as the Fertility Preservation Network, a Special Interest Group within the British Fertility Society, may have a role in developing standards based on surveys of practice and the opinions of clinicians and service users.

Useful areas for audit may include the following:

- the proportion of cancer sufferers offered fertility preservation advice in the relevant age group

- proportion of cancer sufferers in whom ovarian reserve is measured before and after cancer treatment
- the uptake of fertility preservation treatment in the relevant age group and among patients offered this option
- proportion of patients offered access to evidence-based patient decision aids
- time from cancer diagnosis to fertility preservation procedure.

The creation of a central registry in the UK for fertility preservation would be a powerful tool to guide future audit and research. At present, licensed treatments for fertility preservation (embryo and oocyte storage) are regulated by and reported to the HFEA, but the data available are limited. Distinguishing between fertility preservation by indication (cancer diagnosis versus infertility or 'social') would be an important first step to collecting usable data.

Areas for research

This guideline identifies several areas in fertility preservation that require data and information. Some such areas are**-**

Prediction of ovarian damage, risk stratification, accurate identification of risk

Cohort studies with documentation of pre-treatment parameters (e.g., age and AMH) and treatment given

Research in ovarian tissue technologies – risk of re-grafting, micro-metastases and new methods of identifying contaminated tissue

Decision-making in fertility preservation

Conclusions:

Challenges in fertility preservation for women with cancer and other conditions include the distress and vulnerability, the paucity of time, limited quality of evidence for some techniques, and the variation in access to fertility preservation techniques and funding. In some situations, the risk of treatment-related infertility can be difficult to estimate due to the use of new therapies for which there are limited data only. Where the overall risk of infertility is low, patients should be counselled appropriately so that there is no delay to cancer treatment. It is important to emphasise that although some treatments are non-sterilising, they have the potential to reduce fertility and the reproductive lifespan. Moreover, patients may also require gonadotoxic therapy due to relapse of disease after previous treatment with a regimen with low gonadotoxic therapy.

The field of fertility preservation is evolving rapidly and practice will change as the evidence base worldwide develops.

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Table 1. List of currently available guidance

1	American Society of Clinical Oncology (ASCO)	P. Loren	Fertility preservation for patients with cancer: American	Journal of Clinical Oncology	2013	United States

			Society of Clinical Oncology Clinical Practice Guideline Update			
2.	American Society for Reproductive Medicine (ASRM)	Practice committee of the ASRM	Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion	Fertil Steril	2013	United States
3	American Society for Reproductive Medicine (ASRM)	Practice committee of the ASRM	Mature oocyte cryopreservation: a guideline	Fertil Steril	2013	United States
4	American Society for Reproductive Medicine (ASRM)	Practice committee of the ASRM	Ovarian tissue cryopreservation: a committee opinion	Fertil Steril	2014	United States
5	Barcelona-meeting	F. Martinez, M. Devesa	Cancer and fertility preservation: Barcelona consensus meeting	Gynaecological Endocrinology	2013	Spain
6	British Committee for standards in Haematology	Follows G.	Guidelines for the first line management of classical Hodgkin lymphoma	British Journal of Haematology	2014	United Kingdom
7	Canadian fertility and Andrology Society (CFAS)	CFAS	Fertility Preservation In Reproductive Age Woman Facing Gonadotoxic Treatments	CFAS	2014	Canada
8	Canadian Fertility and Andrology Society	CFAS	Assisted Human Reproduction	CFAS	2009	Canada

	Counselling Special Interest Group (CSIG)		Counselling Practice Guidelines			
9.	Center for International Blood and Marrow Transplant Research: Late Effects Working Committee	S. Joshi, B. Savani	Clinical guide to fertility preservation in hematopoietic cell transplant recipients	Bone Marrow Transplant	2014	International
10	Clinical Oncology Society of Australia (COSA)	COSA	Fertility preservation for AYAs diagnosed with cancer. Guidance for health professionals	COS	2014	Australia
11	European Society for Medical Oncology (ESMO)	F. Peccatori	Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Ann Oncol	2013	Europe
12	European Society of Breast Cancer Specialists (EUSOMA)	F. Cardoso	The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer	European Journal of Cancer	2012	Europe
13	FertiPROTEKT	M. von Wolff	Fertility preservation in women- a practical guide to preservation techniques and therapeutic strategies in	Arch Gynaecol Obstet	2011	Austria, Germany

			breast cancer,			
14	International Society of Fertility Preservation (ISFP)	P Jardoul	Fertility preservation in young women with haematological malignancies	J Assist Reprod genet	2012	Internation
15	ISFP	S. Kim	Recommendations for fertility preservation in patients with lymphoma, leukemia and breast cancer	J Assist Reprod genet	2012	International
16	ISFP	J. Klemp	Fertility preservation in young women with breast cancer	J Assist Reprod genet	2012	International
17	ISFP	K. Schmidt	Recommendations for fertility preservation in patients with Lymphoma	J Assist Reprod genet	2012	International
18	National child cancer cancer network	NCCN	Fertility preservation for people with Cancer: A New Zealand Guideline	NCCN		New Zealand
19	National Institute for Health and Care Excellence	NICE	Fertility assessment and treatment for people with fertility problems. Clinical guideline 156	NICE	2013	UK
20	Scottish Intercollegiate Guidelines Network	SIGN	Long term follow up of survivors of childhood cancer	SIGN	2013	UK

Table 2. The Royal College of Obstetricians and Gynaecologists Grading of evidence

Classification of evidence levels	Grades of recommendations
1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias **1+** Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias **1−** Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias	**A**. At least one meta-analysis, systematic reviews or randomised controlled trial rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal **2+** Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal **2−** Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	**B**. A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
3 Non-analytical studies, e.g. case reports, case series	**C**. A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
4 Expert opinion	**D**. Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+"

Table 3. Risk of amenorrhoea after oncology therapy *adapted from ASCO guidelines 2013* (http://ascopubs.org/doi/abs/10.1200/JCO.2013.49.2678)

Degree of risk	Treatment protocol	Dose	Conditions

High risk (>70% risk of amenorrhoea)	Stem cell transplant with total body irradiation		leukemia lymphoma haemoglobinopathies brain tumours in children
	Whole abdominal or pelvic radiation doses	> 6 Gy in adult women > 10 Gy in post-pubertal girls > 15 Gy in pre-pubertal girls	Wilms' tumour, neuroblastoma, sarcoma, Hodgkin's lymphoma
	alkylating agents: • busulphan • chlorambucil • chlormethamine • cyclophosphamide • ifosfamide • Lomustin • melphalan • procarbazine Total cyclophosphamide	 $5\ g/m^2$ in women age > 40 $7.5\ g/m^2$ in women and girls age <20	Breast cancer NHL Conditioning for HSCT
	Protocols containing procarbazine MOPP BEACOPP	 > 3 cycles > 6 cycles	Hodgkin's lymphoma
Intermediate risk (30-70%)	Total cyclophosphamide	5g/m in women 30-40yrs	Breast

	AC for breast cancer	X4+paclitaxel or doxacetal in women >40yrs	Breast
	Monoclonal antibodies		Colon Non-small cell lung Head and neck breast
	Cisplatin		cervical
	Abdominal/pelvic irradiation	10-15Gy in pre-pubertal girls 5-10 Gy in post pubertal girls	Wilms' Tumour Neuroblastoma Spinal tumours Brain tumours Relapsed ALL, NHL
Lower risk (<30%)	Protocols containing non-alkylating agents or lower doses of alkylating agents ABVD CHOP COP		Hodgkin Non-Hodgkin Leukaemia
	Anthracycline and cytarabine		AML
Very low/no risk	Radioactive iodine		Thyroid
	Multi-agent therapies with vincristine		Leukaemia Lymphoma Breast lung
	Methotrexate		GTD
Unknown	Monoclonal antibodies- Cetuximab Trastuzamab		Colon Lung Head and neck breast
	Taxanes		
	Tyrosine kinase inhibitors		CML, GIST
	PARP inhibitors		breast

AC- Adriamycin and Cyclophosphamide

ABVD-
A – doxorubicin (Adriamycin ®)
B – bleomycin
V – vinblastine (Velbe ®)
D – dacarbazine (DTIC)

BEACOP
B – Bleomycin
E – Etoposide
A – Doxorubicin (Adriamycin)
C – Cyclophosphamide
O – Vincristine (Oncovin)
P – Procarbazine
P – Prednisolone

CHOP
C = Cyclophosphamide
H = Doxorubicin Hydrochloride (Adriamycin)
O = Vincristine (Oncovin)
P = Prednisolone

COP
Cyclophosphamide
Vincristine
Prednisolone

HSCT- Haemopoetic stem cell transplant
1. GIST-gastro-intestinal stromal tumour0.1245/s10434-010-0935-1

Table 4. Doses of irradiation in common cancers

Type of cancer	**Dose**
Hodgkin's lymphoma	20-40 Gy
Non-Hodgkin's lymphoma	30 Gy
NK/T Cell lymphoma	50Gy
Soft tissue sarcoma	50 – 66Gy
Skin cancers	18-60Gy

Table 5. Fertility preservation strategies in females

Cryopreservation	**Surgical**	**Medical**	**Delivery of radiation**
Embryo cryopreservation	Ovarian transposition	GnRH agonist suppression	Shielding of ovaries
Oocyte cryopreservation	Fertility-sparing surgery		Intensity modulated radiotherapy
Ovarian tissue cryopreservation (OTC)			Proton beam therapy
OTC with *in vitro* maturation of oocytes (IVM)			