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Assisted reproductive techniques after fertility-sparing treatments in gynaecological cancers

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BACKGROUND: The trend toward late childbearing has made fertility preservation a major issue for women who face gynecological cancer. New techniques in assisted reproductive medicine enable conception after primary treatment of these cancers. Here, we aimed to review the efficacy and safety of assisted reproductive techniques (ART) after fertility-preserving treatment of gynaecological cancers.

METHODS: We conducted a systematic literature review of both prospective and retrospective studies in the PubMed, EMBASE, CENTRAL and SciSearch databases. In the retrieved studies, we evaluated live births, clinical pregnancies, overall survival and disease-free survival.

RESULTS: We identified many prospective and retrospective studies on this topic, but no relevant randomized clinical trials. Fertility-sparing treatments with safe oncological outcomes are feasible in endometrial, cervical and ovarian cancer cases. After cancer treatment, ART seem safe and show variable obstetrical outcomes.

CONCLUSIONS: After fertility-preserving treatment for gynaecological cancers, ART can enable pregnancy to be achieved with apparent oncological safety. The success of such procedures should directly impact clinical practice and management of those patients who require fertility-sparing treatment.

Key words: fertility sparing / assisted reproductive techniques / gynaecological cancer / fertility preservation / oncological safety / ovarian cancer / cervical cancer / endometrial cancer

Introduction

Although gynaecological cancers generally affect older women, a significant number of affected women are of childbearing age. The trend toward late childbearing has made fertility preservation a major issue in the treatment of young women with gynaecological cancer. New surgical options enable young patients to achieve pregnancy after cancer treatment, although most will require the use of assisted reproductive techniques (ART).

Young women (<35 years) comprise < 5% of endometrial cancer patients, 2% of cervical cancer patients and 1.5–17% of ovarian cancer patients (Siegel *et al.*, 2013). The surgical management of these malignancies often involves the removal of ovaries and/or the uterus. Thus fertility loss is a concern among patients who have not yet fulfilled their maternity desire. Fertility-sparing treatments have been successfully employed in selected cervical, endometrial and ovarian cancer cases, and gynaecologists should be familiar with fertility-preserving options for women with gynaecological malignancies (Martinez *et al.*, 2012). Techniques in assisted reproductive medicine, such as oocyte vitrification and ovarian tissue cryopreservation, can enable the use of oocytes or embryos after primary cancer treatment, which thus helps retain the possibility of pregnancy without impairing oncological outcomes.

The present study aimed to review the efficacy and safety of ART after fertility-preserving surgical treatments of cervical, endometrial and ovarian cancer cases in both reproductive and oncological outcomes terms.

Methods

In this review, we have attempted to clarify the relationship between ART and gynaecological cancers by synthesizing the results of primary studies, while using strategies to limit bias and random error. These strategies include the comprehensive search of all potentially relevant articles and the use of explicit, reproducible criteria followed by selection of the articles included in the review.

We conducted a computer search of the Pubmed, MEDLINE, EMBASE, CENTRAL and SciSearch databases for all the prospective and retrospective studies with no date limits. We used the following MeSH terms and keywords both alone and combined: fertility-sparing, gynaecological cancer, ovarian cancer, cervical cancer, endometrial cancer, conservative treatment, ART, fertility preservation, perinatal outcomes and obstetric outcomes. Additional cross-references were identified during the review search. Relevant abstracts were identified and full texts were obtained. Only English and Spanish full-text publications were reviewed. The same terms were used to look for ongoing clinical trials in the US NIH database *ClinicalTrials.gov* and among institutional guidelines and protocols.

Safety of pregnancy after gynaecological cancer treatment

Women of reproductive age who survive cancer may wish to reproduce. Cancer survivors who retain their fertility can conceive naturally, while those with impaired reproductive function may seek help from fertility specialists. Apart from the risks posed by fertility treatment, physicians may be concerned about pregnancy-related risks on cancer recurrence.

In 2012, Azim *et al.* (2012) published a meta-analysis of studies that examined whether pregnancy increased the risk of breast cancer recurrence. They reported that women who became pregnant tended to have better overall survival than the control group, which confirmed the safety of pregnancy and inspiring hypotheses to explain a possible protective effect. To address bias, the authors matched each case patient to the control subjects who had been relapse-free for a period roughly equivalent to the time between breast cancer diagnosis and pregnancy of the matched case. However, given the retrospective nature of the study, it was not altogether possible to control for the 'healthy mother effect'; i.e. the idea that women who become pregnant represent an overall healthier group of patients with perhaps an already lower risk of disease relapse than those who do not become pregnant. This type of bias exists for any retrospective study, so the data cannot be considered definitive.

Breast cancer patients who have became pregnant may be at less risk of death than their matched control subjects, regardless of their estrogen-receptor (ER) status (Azim *et al.*, 2013). This finding is in line with epidemiological evidence which has shown that pregnancy is associated with a lower breast cancer risk (Asztalos *et al.*, 2010). Although researchers do not yet fully understand the biological mechanisms that confer these protective effects, it has been suggested that fetal antigens boost a pregnant immune system (Kamper-Jorgensen *et al.*, 2012). Furthermore, although estrogen can fuel tumour growth, treatment with high doses of estradiol may cause cancer cells to undergo apoptosis (Song *et al.*, 2001). It should be noted that pregnancy after breast cancer is different from pregnancy-associated breast cancer (PABC). The latter is defined as breast cancer diagnosed during pregnancy or breastfeeding, typically up to 1 year after pregnancy. This cancer is rare and data on outcomes are scarce, but some evidence suggests that PABC behaves more aggressively (Azim *et al.*, 2012).

It is generally reasonable to conclude that pregnancy is safe in women with a history of breast cancer. Thus counselling against pregnancy in these patients remains unjustified. No concerns have been raised about the safety of pregnancy following cancers other than breast cancer. Neonatal outcomes in women with a prior history of cancer are highly

comparable with those of the general population (De Sanctis *et al.*, 2012; Peccatori *et al.*, 2013).

Providing reproductive medical assistance to cancer survivors may raise ethical issues about the impact on their future children. Such concerns may include whether the resulting offspring is at higher risk of congenital anomalies, chromosomal defects or cancer due to previous cancer treatment or the effects of assisted reproductive treatments. Most studies have shown no increase in major malformations among the offspring of cancer survivors (Practice Committee of American Society for Reproductive Medicine, 2013), although these studies have primarily evaluated women who conceived spontaneously many years after chemotherapy treatment. Notwithstanding, the ASRM Ethics Committee guidelines state that concerns about the welfare of resulting offspring should not be the cause for denying reproductive assistance to cancer patients.

Steroid hormones and oncological safety

In order to understand the possible influence of ART and pregnancy on gynaecological cancer, the effects of estrogen on gynaecological cancers has been reviewed to a point. Estrogens seem to affect breast, endometrial and ovarian cancer metabolism and behaviour. Estrogen receptors are present in 70% of breast cancer cases, and these cases tend to show a higher relapse rate (Schneider *et al.*, 2009; Sparano *et al.*, 2012). The principal mechanism behind this difference seems to be that estrogen-related G0-phase cell stimulation increases cellular proliferation, which thus leads to more genetic mistakes and angiogenesis (Vergote *et al.*, 2000). Estrogen receptors are present in 90% of cases of endometrial cancer type I which can develop from hormone-dependent endometrial hyperplasia. Administration of exogenous estrogen hormones alone carries an increased relative risk (RR) of endometrial cancer (Chlebowski and Anderson, 2014); however, the use of oral contraceptives has shown a significantly reduced RR of 0.76 for endometrial cancer with every 5 years of use (Collaborative Group on Epidemiological Studies on Endometrial Cancer, 2015). The increase in RR for ovarian cancer has been found to be only 2.2–3.2% depending on the years of continuous estrogen use. Estrogen is also described as having a protective effect against ovarian cancer as anovulatory cycles reduce the effects of ovary-surface microtraumatisms due to ovulation. The endometrioid and serous histological types of ovarian cancer are reportedly related to estrogen administration (Trabert *et al.*, 2012). This effect can be caused by the overexpression of basal estrogen receptors in ovarian cancer cells, and also by the activation of vascular endothelial growth factor A in these cancer cells (Ptak and Gregoraszczuk, 2015; Ren *et al.*, 2015).

Cervical cancer does not seem to be influenced by estrogen administration, although recent studies have provided new insights into the influence of estrogen and progesterone receptors in cervical cancer that seem to inhibit cell proliferation (Chung, 2015; Zhang *et al.*, 2015). However, in cervical adenocarcinoma, positive estrogen receptor alpha has been found to be an independent prognostic factor, at least among Stage Ib-IIa (Fan *et al.*, 2014).

Thus, the available data reveal the possible mechanisms and influence of estrogen administration on gynaecological cancer development, and these factors needs to be taken into account when using ART.

Assisted reproductive techniques and gynaecological cancer risks

In the past decade, several studies have investigated risk of cancer following the use of fertility drugs for *in vitro* fertilization cycles, and have concluded that these procedures seem safe (Venn *et al.*, 1995, 1999; Brinton *et al.*, 2004; Lerner-Geva *et al.*, 2006). However, new studies indicate controversy. New research, not from case–control, but from prospective cohort studies, which accurately control for the precise cause of infertility (as infertility alone may be associated with risks of cancer independently of fertility drug use) and weigh against the benefits that pregnancy induces on substantial long-term reduction in the risk of breast cancer, will be needed to fully understand the associations (Brinton *et al.*, 2012; Fei *et al.*, 2012). Regarding ovarian cancer, it seems that ovarian stimulation may increase the risk of borderline ovarian tumours (BOTs), but confounding risk factors, such as subfertility and infertility, an individual risk factor for these malignancies, mean that the relationship remains unclear (Mahdavi *et al.*, 2006; Vlahos *et al.*, 2010; van Leeuwen *et al.*, 2011). There is no evidence that ART influences endometrial cancer (Impicciatore and Tiboni, 2011; Brinton *et al.*, 2012) or cervical cancer.

Regarding the safety of ART in patients with a past history of gynaecological cancer, some reports have provided interesting data and several concerns are currently being discussed. However, ovulation induction does not appear to be associated with increased risk of relapse, and subsequent pregnancies do not lead to worse oncological outcomes (Oktay *et al.*, 2005; Matthews *et al.*, 2012; Ichinose *et al.*, 2013).

Ovarian stimulation drugs and cancer risk

Ovarian-stimulation drugs have been widely used in infertility-treatment regimes for nearly 40 years. Limited studies, mainly case reports and retrospective studies, have investigated the safety of these drugs and the associated risks (Whittemore *et al.*, 1992; Rossing *et al.*, 1994; Mahdavi *et al.*, 2006; Vlahos *et al.*, 2010), and have reported that treatments may be associated with the increased risk of some specific cancers. However, most research into the long-term effects of ovarian-stimulation medications on the risk of cancer have had their shortcomings as many cohort studies have short follow-up periods. Thus they cannot detect effects that involve long latency intervals. There are also some problems with the availability of appropriate comparison groups; for example, in order to compare the disease experience of infertile women with that of the general population, standardized incidence ratios (SIRs) are calculated, which compare the number of observed cancers in the cohort of interest to the expected number based on incidence rates in the general population (Kanakas and Mantzavinos, 2006). While the incidence rate in the general population accounts for age, race and calendar time, no data are available on the likely differences in other cancer predictors between infertile women and the general population, which makes the understanding of such comparisons of cancer rates difficult.

Although cervical cancer is not generally viewed as a hormone-related tumour, this disease shows a relationship with parity and contraceptive use, which raises concerns about the effects of other hormonal agents. The most informative data available indicate that IVF is not associated with increased risk of cervical cancer (Siristatidis *et al.*, 2013) either in a summary of studies compared with the general population

(Venn et al., 1995; Dor et al., 2002; Lerner-Geva et al., 2003) or within a study that treats infertile women as the reference group (Venn et al., 1995; Dor et al., 2002; Lerner-Geva et al., 2003; Källèn et al., 2011; Yli-Kuha et al., 2012).

Since ovarian-stimulation drugs raise estradiol levels, they are clearly of interest for endometrial cancer, which is well established as being hormonally sensitive (Cramer, 2012). However, the relationship between fertility drugs and risk of endometrial cancer is inconsistent across trials. Several studies, including good-sized case numbers, have suggested the possibility of increased endometrial cancer rates being linked to clomiphene use (Althuis et al., 2005; Silva Idos et al., 2009) or to fertility drug use in general (Calderon-Margalit et al., 2009; Jensen et al., 2009). The two largest cohort studies in this field both raise some concern as to the effects of ovarian stimulation agents on the endometrium. Modan et al. (1998) reported a significant 2-fold increase in the risk associated with fertility drugs such as clomiphene and hMG, whileAlthuis et al. (2005) observed a non-significant increase in the risk associated with clomiphene use. Several cohort studies have shown no association with clomiphene citrate (Potashnik et al., 1999; Benshushan et al., 2001; Dor et al., 2002; Althuis et al., 2005) or gonadotrophins (Venn et al., 1999; Doyle et al., 2002), but these studies have some limitations such as short follow-up times and include only small numbers of exposed cancer cases. No association was found in a study by Brinton et al. (2013b) with 41 endometrial cancer cases derived from cycles stimulated with clomiphene citrate or gonadotrophins, or in a study by Lerner-Geva et al. (2012) that included 30 cases, also of women treated with clomiphene or hMG. Finally, the most recent follow-up study of a large cohort of women evaluated for infertility, which included information on drug exposures, indications for usage and other risk factors that might influence the risk of cancer, found no evidence of a substantial relationship between fertility drugs (GnRH analogue, clomiphene or progestogen exposure) and risk of endometrial cancer (Brinton et al., 2013a). In summary, our understanding of the association between ovarian-stimulation agents and endometrial cancer is inconclusive given the short follow-up terms and lack of information on important confounders. The most recent results are encouraging compared with previous results, but the association should be further monitored to disentangle the effects of different medications and infertility causes.

Since ovulation is a main factor implicated in ovarian cancer aetiology, it is biologically plausible that ovarian-stimulation drugs can be associated with the risk of ovarian cancer. However, the currently available evidence suggests no conclusive link between these two variables. The first two studies suggested an augmented risk with clomiphene, hCG and hMG (Rossing et al., 1994) or with oral contraceptive use (Whittemore et al., 1992), while more recent studies suggest no association with clomiphene, hCG, hMG or FSH (Modan et al., 1998; Doyle et al., 2002; Brinton et al., 2004; Jensen et al., 2009; Sanner et al., 2009; Silva Idos et al., 2009; Lerner-Geva et al., 2012; Trabert et al., 2013). Concerns persist since ovarian-stimulation drugs have been linked to the risk of ovarian cancer in nulligravid women (Kurta et al., 2012; Trabert et al., 2013) and to BOTs (Mosgaard et al., 1998). As we previously stated, inconsistent results may be due to methodological limitations because large studies with sufficient post-medication follow-up are lacking, thus the hypothetical association is supported mainly by theories of ovarian cancer pathogenesis. Notably, most subfertile women use fertility drugs for a rather limited period compared with their total reproductive lives, and ovarian cancer aetiology is probably multifactorial with genetic, environmental and endocrinological factors that interact on various causal pathways. So it is questionable whether any effects of ovarian stimulation agents on the risk of ovarian cancer would even be detectable.

Very few studies have investigated either fertility drugs, such as gonadotrophins and clomiphene, or oral contraceptives on the risk of ovarian cancer with BOTs as the outcome of interest (Parazzini et al., 1998; Cusido et al., 2007; Sanner et al., 2009; van Leeuwen et al., 2011; Stewart et al., 2013). Among these studies, the majority have found an increased risk. These overall results have been recently summarized in a Cochrane review, which identified a potentially increased risk for BOT, especially after IVF, and indicated the need for future research in this field (Rizzuto et al., 2013). Bjornholt et al. (2015) recently found that fertility drug use (clomiphene citrate, hMG, FSH, GnRH analogues, hCG and progesterone) do not increase the overall risk of BOTs, but progesterone use can increase the risk for serous BOTs. It is not clear what biological mechanisms can explain this association. One of the major and unavoidable shortcomings of the reviewed studies is short follow-up periods and only two studies (van Leeuwen et al., 2011; Bjornholt et al., 2015) have provided longer follow-up periods. So this condition seems indispensable for evaluating the impact of ovarian stimulation drugs on the risk of gynaecological cancer.

Finally, it has been suggested that sex hormones are the most potent carcinogenic hormones, and that hormone therapy regimes with include both progestin and estrogen increase the risk of borderline ovarian cancer (Morch et al., 2012). However, the most recent WHO review was completed before the results from the largest studies were published, and it merely concluded that there was insufficient evidence for any risk of ovarian cancer. Indeed most individual studies are too small to reliably assess any risks associated with use over a few years (De Villiers et al., 2013). In line with this, a meta-analysis has been recently published (Collaborative Group on Epidemiological Studies on Ovarian Cancer et al., 2015), which included almost all the worldwide evidence available for menopausal hormone use and risk of ovarian cancer, It confirmed that risk of ovarian cancer was more likely in current hormone therapy users, and lower when no longer used and can change depending on the tumour type. In relation to the last point, is has also been suggested that combined oral contraceptives may have a protective effect according to tumour aggressiveness in women with increasing parity compared with older women and women who have never used oral contraceptives (Poole et al., 2013). The factors that most strongly and inversely relate to rapidly developing fatal cancer, i.e. oral contraceptive use and fewer lifetime ovulatory cycles, suggest that the effect of ovulation may drive an ovarian tumour towards an aggressive phenotype. Yet it is not clear why increasing parity has been associated with a lower risk of developing less destructive cancers. An explanation could be taken from some studies (Batra et al., 1978; Haning et al., 1985), which have suggested a potential role for progesterone in preventing aggressive ovarian cancers as this hormone increases during pregnancy and remains higher in multiple pregnancies. Additional large epidemiological studies are clearly needed to confirm or reject these findings on progesterone and the risk of serous BOTs.

Risk of transferring malignant cells with ovarian tissue

Ovarian tissue cryopreservation is a rapidly developing strategy for fertility preservation in cancer patients. However, its clinical application is

limited by the possibility of reseeding tumour cells into cured patients. This risk should be evaluated separately for each disease according to the threat of ovarian metastasis and the ability to detect single malignant cells. In situations in which there is any consistent doubt about the possibility of reintroducing malignant cells with cryopreserved-thawed ovarian tissue, other fertility preservation means should be considered.

Ovarian tissue cryopreservation is most commonly indicated in haematological malignancies (Dolmans *et al.*, 2010; Donnez and Dolmans, 2011) given the lack of time for ovarian stimulation and oocyte freezing. However in leukaemias, ovarian tissue cryopreservation is considered a high-risk procedure because cancer cells in the bloodstream can infiltrate the ovary (Oktay and Buyuk, 2004). Three different research groups have demonstrated that >50% of ovarian tissue samples taken from leukaemia patients are positive for malignant cells (Meirow *et al.*, 2008; Dolmans *et al.*, 2010; Greve *et al.*, 2012). Greve *et al.* (2012) further reported that ovaries from leukaemia patients in complete remission do not appear to contain viable malignant cells, unlike ovarian tissue retrieved before chemotherapy. This suggests a low risk of finding viable malignant cells in cryopreserved ovarian tissue from leukaemia patients in complete remission, although it cannot be completely excluded given the possibility of submicroscopic and undetectable infiltration. Another concern is that chemotherapy administered to achieve complete remission may compromise ovarian reserve. In summary, a cryopreservation procedure before chemotherapy makes sense to avoid reduced ovarian reserve; after treatment, damage may have already occurred, although we assume that the risk of finding malignant cells in leukaemia patients in complete remission is very low. Alternative methods, such as *in vitro* maturation and isolated follicle transplantation, should be evaluated for fertility preservation in these patients. However, if not performed before treatment, *in vitro* follicle growth and *in vitro* oocyte maturation can also be compromised by exposure of resting primordial follicles to chemotherapy (Dolmans *et al.*, 2010). Presently available results remain to be confirmed and should be interpreted cautiously (Dolmans, 2012; Donnez and Dolmans, 2013).

The possibility of reintroducing metastatic cells within reimplanted tissue in relation to breast cancer is also a major concern. However, the data suggest that even if clinical and radiological evidence for distant metastasis is lacking, the chance of finding ovarian metastasis in breast cancer patients with early-stage tumours is extremely unlikely (Oktay and Buyuk, 2004).

Regarding cervical cancer, five cases of ovarian tissue auto-transplantation after cervical carcinoma have been published with no signs of relapse from the grafted tissue (Schmidt *et al.*, 2011; Kim, 2012; Donnez *et al.*, 2013).

Since early-stage endometrial carcinoma entails a very low risk of metastasis (Dundar *et al.*, 2002), ovarian tissue auto-trnasplantation in also likely to be safe for these patients.

Fertility-sparing options for gynaecological cancers

In recent years, early detection protocols and advanced treatment strategies have significantly improved the survival outcomes for gynaecological cancer patients. Improved oncological outcomes has meant that increased attention is now being paid to quality of life issues, such as the childbearing potential for young women. The surgical treatment of cervical, endometrial and ovarian cancers has traditionally involved the removal of the uterus, fallopian tubes and/or ovaries, regardless of the patient's desires and of the impact on fertility (Vitobello *et al.*, 2011). However, fertility-sparing procedures can now be offered to young women affected by gynaecological malignancies at a nearly stage.

Options to preserve fertility include shielding of the tissue to reduce radiation damage, fertility-sparing surgical procedures, fertility preservation before undergoing cytotoxic treatments and assisted reproduction techniques. Conservative gynaecological surgery is defined as surgery with preservation of at least the uterine corpus and part of one ovary. New developments in assisted reproductive technologies, including cryopreservation of ovarian tissue, oocytes or embryos, have extended available options to young gynaecological cancer patients (Leblanc *et al.*, 2009). Such cases should be managed in a reference centre, which can coordinate surgical management, follow-up and gestation management. Appropriate patient selection is mandatory, as is careful oncological, psychological, reproductive and obstetric counselling.

Cervical cancer

In some situations, young cervical cancer patients who genuinely desire pregnancy and present no evidence of sterility can be treated by fertility-sparing methods (Robova *et al.*, 2008; Rob *et al.*, 2010; Pareja *et al.*, 2013). For cases of micro-invasive carcinoma stage IA1 with no lymph vascular space involvement, conisation or simple trachelectomy is a very common procedure and an efficient fertility-sparing treatment. Other such scenarios include cases of clinical stage IA1 with LVSI to IB1 cervical tumours, with any carcinoma type (except small-cell carcinoma and sarcomas) with the largest dimension of <2 cm and deep stromal invasion of <10 mm, with an upper limit that does not involve the cervical canal, but provides an adequate margin and a negative sentinel node or pelvic node status. In highly selected cases, IB2 cervical carcinomas can also be treated with fertility-sparing methods (Salas *et al.*, 2015). Although the risk of parametrial involvement among different stages varies vastly, general recommendations include radical trachelectomy performed either by laparoscopy or a vaginal approach. For larger tumours, some authors have advocated the use of neoadjuvant chemotherapy to reduce tumour size so that the residual cervical tumour is eligible for radical trachelectomy, or even a simple trachelectomy or cone. This may also be an option for patients who do not meet the standard criteria for fertility-sparing treatments. Unfortunately, data on long-term outcomes is currently lacking, and this procedure remains in its experimental stage (Robova *et al.*, 2015).

Radical vaginal or laparoscopic trachelectomy with laparoscopic lymphadenectomy is an oncologically safe fertility-sparing procedure. It has gained worldwide acceptance as a surgical treatment for small early-stage cervical cancers and presents better perioperative results compared with laparotomic routes (Vieira *et al.*, 2015) with the same oncological outcomes (Rob *et al.*, 2011). Oncological outcomes are similar to those of radical hysterectomy, with a recurrence rate close to 4% (Li *et al.*, 2013; Pareja *et al.*, 2013) (Table I).

Endometrial cancer

In endometrial cancer cases, fertility-sparing can be considered only in stage IA grade 1 endometrioid tumours without myometrial invasion. Contrast-enhanced MRI seems the most accurate imaging technique to detect myometrial involvement, and is thus useful for determining

Table I Representative series reported on the oncological outcomes after fertility preservation in cervical cancer.

Publications	Patients *n*	Median age (years)	FIGO stage *n* (%)	Type of treatment	Histology *n* (%)	Median follow-up (months)	Relapses *n* (%)	Death due to disease *n* (%)
Dargent *et al.* (2000)	47	NRA	IA1 5 (10.6) IA2 13 (27.6) IB1 25 (53) IIA 1 (2) IIB 3 (6.8)	VRT	NRA	52	2 (4.2)	1 (2.1)
Ungár *et al.* (2005)	30	30.5	IA2 10 (33) IB1 15 (50) IB2 5 (17)	LRT	Squamous 26 (86.6) Adeno 2 (6.7) Other 2 (6.7)	47	0	0
Marchiole *et al.* (2007)	118	32	IA1 10 (8.4) IA2 19 (16.1) IB1 83 (70.3) IIA1 6 (5.2)	VRT	Squamous 90 (76.2) Adeno 25 (21.1) Other 3 (2.7)	95	7 (5.2)	5 (4.2)
Chen *et al.* (2008)	16	27.6	IA1 3 (18) IA2 7 (44) IB1 6 (38)	LapRT	Squamous 14 (87.5) Adeno 2 (12.5)	28.2	0	0
Sonoda *et al.* (2008)	43	31	IA1 8 (18) IA2 7 (16) IB1 28 (66)	VRT	Squamous 24 (56) Adeno 16 (37) Other 3 (7)	21	1 (2.3)	0
Shepherd and Milliken (2008)	158	30.6	IA2 3 (2) IB1 152 (96) IIA1 2 (2)	VRT	Squamous 103 (65) Adeno 51 (32) Other 4 (3)	NRA	4 (2.5)	0
Beiner *et al.* (2008)	90	31	IA-IB (NRA)	VRT	Squamous 39 (43) Adeno 44 (49) Other 7 (8)	51	5 (5.5)	3 (3.3)
Nishio *et al.* (2009)	61	33	IA1 4 (6.5) IA2 8 (13) IB1 49 (80.5)	LRT	Squamous 58 (95) Adeno 2 (3.3) Other 1 (1.7)	27	6 (9.8)	0
Li *et al.* (2011)	62	29.5	IA1 16 (26) IA2 7 (11) IB1 36 (63)	LRT	Squamous 50 (80) Adeno 8 (13) Other 4 (7)	22.8	0	0
Plante *et al.* (2011)	125	31	IA1 3 (2.4) IA2 34 (27) IB1 86 (69) IIA1 2 (1.6)	VRT	Squamous 70 (56) Adeno 46 (37) Other 9 (7)	93	6 (4.8)	2 (1.6)
Marchiole *et al.* (2011)	7	28	IB1-IIA1	NACHT	Squamous 4 (57) Adeno 3 (43)	22	0	0
Saso *et al.* (2012)	30	32.2	IA2 2 (6.6) IB1 25 (83) IB2 2 (6.6) IIA1 1 (3.8)	LRT	Squamous 15 (48) Adeno 10 (32) Other 5 (20)	24	3 (10)	2 (6.6)
Wethington *et al.* (2012)	101	31	IA1 3 (3) IA2 8 (8) IB1 88 (87) IB2 1 (1) IIA1 1 (1)	LRT	Squamous 40 (40) Adeno 54 (54) Other 7 (7)	61	4 (4)	0
Persson *et al.* (2012)	13	29	IA1 4 (31) IA2 5 (38) IB1 4 (31)	RRT	NRA	24	0	0
Park *et al.* (2014)	79	31	IA2 2 (3.6) IB1 53 (96.4)	LapRT	Squamous 42 (76.4) Adeno 13 (23.6)	44	9 (11.4)	1 (1.2)
Mangler *et al.* (2014)	320	31.8	IA1 46 (14) IA2 68 (21) IB1 206 (65)	VRT	Squamous 215 (67) Adeno 93 (29) Other 12 (4)	48	10 (3.1)	5 (1.5)
Lanowska *et al.* (2014)	18	32	IB1 18 (100)	NACHT	Squamous 11 (61) Adeno 7 (39)	23	1 (5.5)	0

Continued

Table I *Continued*

Publications	Patients *n*	Median age (years)	FIGO stage *n* (%)	Type of treatment	Histology *n* (%)	Median follow-up (months)	Relapses *n* (%)	Death due to disease *n* (%)
Robova *et al.* (2014)[a]	28	28	IB1 28 (100)	NACHT	Squamous 15 (53.6) Adeno 13 (46.4)	42	4 (14.3)	2 (7.1)
Vieira *et al.* (2015)	100	30	IA1 6 (6) IA2 25 (25) IB1 69 (69)	LRT 50 LapRH RRT	Squamous 49 (49) Adeno 42 (42) Other 9 (9)	51	1 (1)	1 (1)
Pareja *et al.* (2015)	65	NRA	IB1 65 (100)	NACHT	NRA	NRA	5 (7.7)	2 (3.1)
Salihi *et al.* (2015)[b]	11	NRA	IB1 10 (91) IB2 1 (9)	NACHT	NRA	58	1 (9)	0
Total	1522	31	IA1 108 (7.5) IA2 218 (15.3) IB1 1074 (75.3) IB2 9 (0.8) IIA-IIB 16 (1.1)	All types	Squamous 865 (62.4) Adeno 431 (31.1) Other 90 (6.5)	47	69 (4.5)	24 (1.6)

n, number; NRA, not reported/available; VRT, vaginal radical trachelectomy; RRT, robotic radical trachelectomy; LapRT, laparoscopic radical trachelectomy; LRT, laparotomic radical trachelectomy; NACHT, neoadjuvant chemotherapy followed by vaginal radical trachelectomy.
[a]NACHT followed by simple trachelectomy.
[b]NACHT followed by large cone resection.

treatment. Vaginal sonographic scans are also accurate (near 90%) (Jantarasaengaram *et al.*, 2014). Before considering fertility-sparing management of a superficial endometrial carcinoma, it is also necessary to determine the tumour pathological type and grade via a dilatation–curettage of the uterine cavity or hysteroscopy.

The two available options for fertility-sparing management are hormonal treatment and surgical resection, either combined or alone. Endometrial tumours usually express hormone receptors and are sensitive to progesterone therapy, but the treatment schedule is not well defined. The most extended schema involves high-dose progestin treatment (200–400 mg daily) (Ramirez *et al.*, 2004) or a levonorgestrel intrauterine device after hysteroscopic tumour resection (Chiva *et al.*, 2008; Mazzon *et al.*, 2010). The complete response rate after treatment is near 75%, but with a relapse rate of 15–50% (Ramirez *et al.*, 2004; Alonso *et al.*, 2015). Patients should be clearly informed about the risks and benefits of progestin treatment in this context. The hysteroscopic control of maintenance treatment must be conducted every 3 months until pregnancy. Once the woman has fulfilled her maternity, simple hysterectomy and bilateral oophorectomy are required (Niwa *et al.*, 2005) (Table II).

Ovarian cancer

In ovarian cancer, fertility-sparing treatment is considered in cases of selected invasive or BOTs and early germ cell or sex cord tumours. After checking the peritoneal cavity and sampling the peritoneal fluid, a diagnosis must be made by adnexal resection, and by avoiding spillage during tumour manipulation or extraction (in a bag, if a laparoscopy is utilized). The uterus and contralateral ovary may be preserved if they appear normal. In fertility-sparing treatments, dilatation–curettage will replace the hysterectomy, especially for invasive tumours of the endometrioid or granulose subtype (Zapardiel *et al.*, 2014).

In early-stage (FIGO IA–IB stage) Grade 1–2 (G1–G2) ovarian cancer cases (Kajiyama *et al.*, 2011c; Morice *et al.*, 2011), it may be safe to perform unilateral salpingo-oophorectomy, plus surgical staging. However, this procedure is controversial as some authors have reported poor oncological results following the fertility-sparing treatment of high-grade (G3) and stage IC tumours (Park *et al.*, 2008; Fotopoulou *et al.*, 2012; Utrilla-Layna and Zapardiel, 2015). Patients with Stage I mucinous epithelial ovarian carcinomas who undergo fertility-sparing treatment do not necessarily show a poorer prognosis than those who undergo radical surgery (Kajiyama *et al.*, 2011b) (Table III).

With BOTs, conservative surgery is often possible in early stages and for selected advanced-stage tumours (Trope *et al.*, 2012; Park *et al.*, 2015). Among non-epithelial tumours, only dysgerminoma presence precludes fertility-sparing surgery. Young patients may exhibit sex cord tumours, especially granulose cell tumours. Most of these cases are Stage I and can, thus, be also managed conservatively (Zapardiel *et al.*, 2010). Some authors have reported that fertility preservation is possible in Stage IA clear cell ovarian cancer (CCC). Kajiyama *et al.* (2011a) reported no difference in the recurrence rate between patients conservatively treated with CCC (13.2%) or without CCC (10.9%) ($P = 0.614$).

Adjuvant chemotherapy sometimes leads to premature ovarian failure (POF). Gonadotoxicity depends on the type of chemotherapy agent (alkylating), dose, number of cycles, age (POF occurs in 40% of women under the age of 40), previous ovarian reserve base and radiotherapy. No consensus on completion of surgery after pregnancy has yet been reached, and this option must be evaluated individually. Overall survival is not affected after pregnancy, but increased rates of pregnancy loss, preterm delivery, and intrauterine growth restriction have been reported (Blumenfeld, 2003).

Patients should be offered appropriate fertility-sparing techniques during therapeutic planning. Such decisions must be individualized, depending on desire for pregnancy, age, tumour type, tumoural stage, type of surgery and adjuvant treatment. Choices of ART depend on the risk of sterility, age, ovarian reserve, cancer prognosis, delay of

Table II Representative series on the oncological and obstetric outcomes after fertility preservation in endometrial cancer.

Publications	Patients *n*	Age limit for treatment (years)	Type of treatment	Dosage (mg/day)	Complete response *n* (%)/time	Median follow-up (mo)	Relapses *n* (%)	Number pregnancies/ number patients	Live births
Randall and Kurman (1997)	29	40	MPG	200	25 (86)/9 mo	40	0	5/25	5
Kaku *et al.* (2001)	29	42	MPG	200	24 (83)/3 mo	24	2 (6.8)	7/7	5
Ramirez *et al.* (2004)	81	NRA	MPG 36 MGA 28 Other 17	400	62 (76)/3 mo	20	15 (24)	20/20	20
Niwa *et al.* (2005)	12	35	MPG	400–600	12 (100)/10mo	30	8 (66.6)	7/10	5
Yamazawa *et al.* (2007)	9	40	MPG	400	7 (78)/6 mo	39	2 (22.2)	4/4	3
Chiva *et al.* (2008)	130	45	MPG	200–600	99 (76)/6 mo	NRA	44 (34)	53/68	NRA
Mazzon *et al.* (2010)	6	40	HSC + MGA	160	6 (100)/6 mo	50.5	0	5/4	5
Laurelli *et al.* (2011)	14	40	HSC + MGA 6 LNG-IUD 8	160	14 (100)/12 mo	40	1 (7)	1/1	1
Marton *et al.* (2012)	2	40	HSC + MPG 1 LNG-IUD 1	400	2 (100)/3 mo	16.5	1 (50)	2/2	2
Shan *et al.* (2013)	14	40	HSC + MGA	160	11 (78.5)/6 mo	34.7	2 (14)	2/2	2
Simpson *et al.* (2014)	44	45	NRA	NRA	24 (55)/6 mo	NRA	13 (29.5)	5/5	3
Pronim *et al.* (2015)	70	42	LNG-IUD + GRA	3.6	58 (83)/6 mo	17	3 (4)	10/8	8
Ohyagi-Hara *et al.* (2015)	27	43	MPG	400–600	20 (74)/3 mo	39.2	9 (33.3)	5/5	9
De Marzi *et al.* (2015)	23	45	HSC + MGA	160	12 (52.2)/3 mo 9 (31.1)/6 mo 2 (8.7)/9 mo	25	5 (21.7)	7/6	7
Total	490	40–45	MPG/MPG	160–400	387 (78.9)/3–10 mo	25	105 (21.4)	133/167	75

n, number; NRA, not reported/available; HSC, hysteroscopic resection; MGA, megestrol acetate; mo, months; MPG, medroxiprogesterone; LNG-IUD, levonogestrel intrauterine device; GRA, gonadotrophin-releasing hormone agonist (3.6 mg depot).

Table III Series reported on the oncological outcomes after fertility sparing surgery of epithelial ovarian cancer.

Publications	Patients *n*	Median age (years)	FIGO stage *n* (%)	Grade *n* (%)	Histology *n* (%)	Relapses *n* (%)	5-Year survival (%)
Zanetta *et al.* (1997)	56	29	IA 32 (57) IB 2 (4) IC 22 (39)	G1 35 (62) G2 14 (25) G3 7 (12)	muc 23 (41) serous 18 (32) endo 13 (23)	5 (9)	NRA
Schilder *et al.* (2002)	52	26	IA 42 (81) IC 10 (19)	G1 38 (73) G2 9 (17) G3 5 (10)	muc 25 (48) serous 20 (38) clear cell 5 (10) mixed 2 (4)	5 (9.6)	98
Morice *et al.* (2005)	34	27	IA 30 (88) IC 3 (9) II 1 (3)	G1 15 (44) G2 15 (44) G3 4 (12)	muc 21 (62) serous 3 (9) clear cell 2 (5) endo 5 (15) mixed 3 (9)	10 (29)	84
Borgfeldt *et al.* (2007)	11	27.5	IA 10 (90.9) IC 1 (9.1)	G1 9 (81.8) G2 1 (9.1) G3 1 (9.1)	muc 8 (72.7) serous 2 (18.2) endo 1 (9.1)	1 (9.1)	90.9
Park *et al.* (2008)	62	26	IA 36 (58) IB 2 (3.3) IC 21 (33.9) IIA 1 (1.6) IIIA 1 (1.6) IIIC 1 (1.6)	G1 48 (77) G2 5 (8) G3 9 (15)	muc 41 (66) serous 7 (11) clear cell 4 (7) endo 8 (13) mixed 2 (3)	11 (18)	90
Kwon *et al.* (2009)	21	26.7	IA 17 (81) IC 4 (19)	G1 16 (76) G2 3 (14) G3 2 (10)	muc 16 (76.2) serous 1 (4.8) clear cell 2 (9.5) endo 2 (9.5)	1 (4.7)	NRA
Schlaerth *et al.* (2009)	20	27	IA 11 (55) IC 9 (45)	G1 14 (70) G2 5 (25) G3 1 (5)	muc 11 (55) serous 1 (5) clear cell 1 (5) endo 6 (30)	3 (15)	84
Satoh *et al.* (2010)	211	29	IA 126 (60) IC 85 (40)	G1 160 (76) G2 15 (7) G3 36 (17)	muc 126 (60) serous 27 (13) clear cell 30 (14) endo 27 (13)	18 (8.5)	83
Cheng *et al.* (2012)	17	NRA	IA 10 (59) IC 6 (35) IIIC 1 (6)	G1 15 (88) G2 2 (12)	muc 13 (76) serous 2 (12) endo 1 (6) mixed 1 (6)	1 (6)	100
Fruscio *et al.* (2013)	240	32	IA 130 (54) IB 2 (1) IC 105 (44) II 3 (1)	G1 141 (59) G2 70 (29) G3 29 (12)	muc 99 (41) serous 62 (26) clear cell 17 (7) endo 60 (25)	27 (11.3)	99.5
Ditto *et al.* (2014)	18	31.1	IA 12 (66.6) IB 1 (5.5) IC 5 (27.9)	G1 7 (38.8) G2 6 (33.3) G3 5 (27.9)	muc 6 (33.3) serous 1 (5.5) clear cell 1 (5.5) endo 7 (38.8) undif 3 (16.9)	4 (22.2)	NRA
Kajiyama *et al.* (2014)	94	30.5	IA 43 (45.7) IC 51 (54.3)	G1 75 (74.5) G3 5 (10.5) NRA 14 (15)	muc 45 (48) serous 3 (3) clear cell 16 (17) endo 15 (19) NRA 14 (15)	14 (14.8)	84.3
Lee *et al.* (2015)	35	28.6	IA 21 (60) IC 13 (37.1) IIC 1 (2.9)	G1 27 (77.1) G2 5 (14.3) G3 1 (2.9) NRA 2 (5.7)	muc 35 (100)	6 (17.1)	91.3
Total	871	27.3	IA 520 (59.7) IB 7 (0.8) IC 335 (38.4) II 6 (0.7) III 3 (0.4)	G1 600 (68.8) G2 150 (17.2) G3 105 (12) NRA 16 (2)	muc 469 (53.8) serous 147 (16.8) clear cell 78 (8.9) endo 145 (16.6) other 32 (3.9)	106 (12.1)	87

n, number; NRA, not reported/available; muc, mucinous; endo, endometroid; undif, undifferentiated.

chemotherapy treatment, hormonal schedule, and the risk of tumour cell persistence in frozen ovarian tissue (Georgescu et al., 2008; Matthews et al., 2012).

Ovarian transposition

Oophoropexy can be performed to surgically remove ovaries from the direct field of radiation when pelvic radiation is performed as cancer treatment. It is useful to treat gynaecological cancers and haematological cancers, such as Hodgkin's lymphomas (Ajala et al., 2010). The exact transposition location depends on the planned treatment and the patient's anatomy. For example, for midpelvic radiation (e.g. for cervical cancer), the ovary would be transposed to the lateral abdominal wall, and would be more protective than median transposition (Huang et al., 2007). In the event of post-treatment non-transposed ovary failure, ovarian stimulation and oocyte retrieval can be performed from the transposed ovary. Depending on the exact ovary location, this might require abdominal oocyte retrieval. Therefore the accessibility of the transposed ovaries for oocyte collection during an IVF procedure is an important consideration. A transposed ovary located in the paracolic gutter is likely to be inaccessible for safe oocyte retrieval.

Although ovaries may be beyond the field of direct radiation, a scatter dose can still cause significant ovarian damage. A review of the literature has found that women who received pelvic irradiation after oophoropexy still experienced ovarian failure in 50–90% of cases (Wo and Viswanathan, 2009), indicating the need for transposition. However complications to the oophoropexy procedure can include chronic pelvic pain, vascular injury, fallopian tube infarction and ovarian migration. Furthermore oophoropexy should be performed as close to the time of radiation treatment as possible due to the risk of ovary remigration (Loren et al., 2013).

Ovarian suppression/GnRH agonist therapy

An ideal fertility-preservation method does not require surgery and protects ovaries from gonadotoxicity *in situ*. Ovarian suppression to prevent oocyte loss during chemotherapy has been proposed based on the observations that non-cycling cells appear more resistant to cytotoxicity, and that pre-pubertal girls more commonly resume menstruation after cancer treatment than post-pubertal girls (Meistrich and Shetty, 2008). Yet the use of GnRH agonists to prevent chemotherapy-induced gonadotoxicity remains controversial (Blumenfeld, 2007; Oktay et al., 2007).

Some trials have reported reduced post-chemotherapy amenorrhea (Badawy et al., 2009; Del Mastro et al., 2011), while others have not indicated this benefit (Sverrisdottir et al., 2009). Until additional studies investigate pregnancy outcome or surrogate markers, GnRH agonist therapy can be considered to potentially reduce the risk of POF in women who undergo chemotherapy. However, this method should not be considered an established fertility-sparing technique as the evidence indicates that it is extremely weak.

Fertility preservation techniques in women with cancer

Fertility risk assessment and the selection of an individualized strategy to optimize fertility after cancer treatment are significant challenges that require the intense cooperation of fertility preservation specialists, oncologists, other healthcare workers and patients. Guidelines that have been developed are based the scientific literature analyses which recommend that fertility-preserving approaches are chosen according to the age of the patient, the type of cancer and treatment required the presence or not of a male partner or patient preference for using donor sperm, the time available for fertility preservation interventions and the probability of ovarian metastasis (Loren et al., 2013; Practice Committee of American Society for Reproductive Medicine, 2013; De Vos et al., 2014).

There is a lack of published randomized controlled trials on this topic, most probably due to ethical reasons as it is difficult to randomize oncological patients in a group that receives treatment or not. It is also difficult to assess the quality of studies since they have small sample sizes. This is why the studies are checked for clinical heterogeneity to find major differences in study participants, baseline disease severity and intervention.

Many published reports have indicated the weaknesses of individual findings, and have consequently recommended performing further trials to capture larger populations and to include longer follow-ups by relying on more precise data and on the better adjustment for confounding factors. Others have suggested the inclusion of subfertile women who were indicated to undergo treatment, but were not eventually treated (Jensen et al., 2009; Calderon-Margalit et al., 2009).

Embryo cryopreservation

Embryo cryopreservation is an established safe and effective technique in couples who undergo IVF. It is recommended for various clinical reasons, including storage of supernumerary embryos (Bedoschi and Oktay, 2013), risk of ovarian hyperstimulation syndrome (OHSS) (Cakmak et al., 2013), impaired endometrial development and impractical embryo transfer (Devroey et al., 2011). Since this technique was introduced (Trounson and Mohr, 1983), it has become an established fertility preservation technique (Lee et al., 2006).

For decades, embryo cryopreservation was the only fertility preservation method that was not considered investigational by the American Society for Reproductive Medicine (ASRM) (Practice Committee of American Society for Reproductive Medicine, 2013). All centres that now offer ART have ample experience in IVF and embryo cryopreservation, and the pregnancy rates from cryopreserved embryos are generally well known within each program. Ideal candidates have a male partner or are willing to use donor sperm, and can safely delay the start of cancer therapy to allow for ovarian stimulation. For cancer patients with no male partner, oocyte cryopreservation is also a valid option and is no longer considered experimental.

Oocyte cryopreservation

Oocyte cryopreservation is a fertility-preserving option for young/adolescent females, women without a partner, women who wish to maintain maximum reproductive flexibility, and patients with ethical or religious concerns about embryo preservation (McLaren and Bates, 2012). This technique has advanced vastly in recent years. Growing experience and the advances made in cryopreservation have continued to close the gap; indeed some centres have reported IVF outcomes with cryopreserved oocytes that are comparable with fresh IVF/ICSI rates (Cobo et al., 2010; Cobo and Diaz, 2011). Although promising post-vitrification results have been reported in oocyte donation programs, it is unclear whether they can be extrapolated to outcomes after fertility preservation. If chemotherapy can be delayed, oocyte vitrification should be proposed to cancer patients, but further studies are needed to confirm the brilliant results obtained in oocyte donation programmes.

Ovarian stimulation, followed by embryo/oocyte cryopreservation, is a recognized fertility-preserving method for cancer patients. Thus it should be recommended as long as the patient's medical condition and time constraints do not impede safely performing ovarian stimulation and oocyte retrieval. To facilitate the initiation of ovarian stimulation and to avoid unnecessary delays, a prompt consultation with a reproductive specialist and care coordination are essential following cancer diagnosis (Lee *et al.*, 2010). Regardless whether cryopreserving oocytes or embryos, the stimulation protocol selection approach in the cancer population differs from that in the general infertility population because of the limited amount of time for fertility preservation before cancer treatment initiation, and also due to the specificity of some estrogen-sensitive cancers.

Standard ovarian stimulation is often modified to adapt this treatment to best suit the cancer patient. GnRH-antagonist protocols are generally preferred to long protocols thanks to their shorter stimulation duration, fewer exogenous gonadotrophin requirements and lower OHSS incidence (Al-Inany *et al.*, 2011). The need to minimize the OHSS risk is particularly important in cancer patients as OHSS can delay cancer treatment. Under some conditions, GnRH agonists induce final oocyte maturation by promoting the release of endogenous gonadotrophin stores from the hypophysis (Humaidan *et al.*, 2011). Using a GnRH agonist trigger dramatically lowers the OHSS risk, and this strategy is particularly convenient in cancer patients who pursue oocyte or embryo preservation. If a patient is in the early follicular phase of the menstrual cycle, ovarian stimulation can begin immediately by following a GnRH-antagonist protocol, and stimulation and oocyte retrieval can be completed in 10–14 days. Sometimes it is necessary to wait up to 3 weeks for a menstrual cycle to start, which may be an unacceptable delay. For such cases, alternative protocols have been developed to start ovarian stimulation in the luteal phase, which does not appear to significantly alter the number of mature oocytes retrieved (von Wolff *et al.*, 2009; Maman *et al.*, 2011; Nayak and Wakim, 2011). For patients with estrogen-sensitive tumours, stimulation protocols with aromatase inhibitors may reduce estrogen production, which is usually proportional to the number of growing follicles. Letrozole reportedly lowers estrogen levels without compromising oocyte yield or fertilization rates when utilized in breast cancer patients who undergo IVF prior to chemotherapy (Oktay *et al.*, 2006). A prospective study has demonstrated that patients who undergo ovarain stimulation with a combination of letrozole plus gonadotrophins present similar recurrence and survival rates to patients who decided to not undergo an ovarian stimulation cycle (Azim *et al.*, 2008). This limited evidence is supportive of ovarian stimulation not substantially affecting cancer treatment outcomes.

Finally, it has been speculated that female cancer patients may present reduced fertility and ovarian response to gonadotrophins before cancer treatment. A relatively recent study has demonstrated that patients who undergo ovarian stimulation before chemotherapy have fewer oocytes and are at a higher risk of poor ovarian response compared with the control group (Domingo *et al.*, 2012).

Ovarian tissue cryopreservation and transplantation

Ovarian tissue cryopreservation is another fertility preservation strategy, which is indicated for patients at a high risk of ovarian failure after cancer treatment. It is the only option available for pre-pubertal girls, and may be the best option for patients who should start their treatment immediately. Surgical removal of ovarian tissue entails no delay in cancer treatment initiation, and yields an abundance of primordial follicles. In young cancer patients who have recently been exposed to chemotherapy treatments, this method is the only fertility-preserving option because it preserves mainly primordial follicles, which are not subjected to the chemotherapy effects that negatively impact growing and mature follicles (Chung *et al.*, 2013). However, according to ASCO and ASRM, ovarian tissue freezing is still considered experimental.

The primary goal of ovarian tissue storage is to reimplant a few thawed cortical strips into the patient following cancer treatment completion once she is disease-free and desires pregnancy. Pieces of ovarian cortex should be ideally grafted to the remaining ovary. If this is not possible, orthotopic placement in the pelvis is also an effective option. Two orthotopic reimplantation techniques are available, with the choice depending on whether the patient still has an ovary (Donnez and Dolmans, 2013). If an ovary is present, thawed ovarian cortex pieces can be fixed to the medulla after ovary decortications. If no ovary is present, slices can be positioned in a peritoneal window in an area with small visible retroperitoneal vessels (Donnez *et al.*, 2012). It is believed that an orthotopic site is the optimal environment for follicular development, as the temperature, pressure, paracrine factors and blood supply are similar to that in the physiological situation. Despite, the highly invasive nature of orthotopic transplantation, it is a favourite approach thanks to its proven efficacy in restoring ovarian function and fertility, and it does not require ovarian stimulation.

With ovarian tissue cryopreservation followed by avascular transplantation, one main problem is that the graft is completely dependent on neo-vascularisation. A large proportion of follicles are lost during initial post-transplantation ischaemia (Silber *et al.*, 2005; Demeestere *et al.*, 2006), which thus limits the duration of its function. To maintain the follicular reserve and to extend the lifespan and function of the graft, it is essential to cut the ischaemic interval between transplantation and revascularisation. Theoretically, the best way to achieve this objective is by transplanting the intact ovary with vascular anastomosis, which allows immediate revascularization (Donnez *et al.*, 2010).

Oocyte *in vitro* maturation

To substantially reduce the delay before chemotherapy, it is possible to circumvent the need for ovarian stimulation with gonadotrophins before oocyte collection by using *in vitro* maturation of immature oocytes. This technique is an now emerging as an option for women who must begin chemotherapy soon after diagnosis and for pre-pubertal girls who cannot undergo ovarian stimulation given their immature hypothalamic–pituitary axis. Although many pubescent girls present antral follicles in ultrasounds, the true development of any immature oocytes retrieved is unknown (De Vos *et al.*, 2014). The technique involves the surgical removal of immature oocytes, followed by *in vitro* gonadotrophin exposure to mature oocytes outside the body. This is a clinically difficult technique, reinforced by its limited success compared with other techniques. Although small antral follicles are a valuable source of oocytes for fertility preservation, the fertilization potential of *in vitro* matured oocytes may be affected by the cryopreservation process itself. Thus, the vitrification of metaphase II oocytes is now preferred (Brambillasca *et al.*, 2013).

Primordial and pre-antral follicle culture

Much research has focused on developing strategies for culturing follicles *in vitro* to address fundamental questions of follicle development and for fertility preservation applications. Many methods are being developed worldwide. A dynamic multi-step system is needed to support each follicle transitional stage plus the changing requirements of the developing oocyte and its surrounding somatic cells in order to maintain the interactions between them (Telfer and McLaughlin, 2012).

Uterus transplantation

Patients with uterine-factor infertility (UFI) are unable to conceive a child because their uterus is absent or non-functional. In this situation, uterine transplantation is an important potential option for women with UFI (Brannstrom and Wranning, 2008; Grynberg *et al.*, 2011). The first human clinical trial was performed by Fageeh *et al.* (2002) in 2000 using a uterus from a live donor. Although they had experienced no problems with immunosuppression, the obstruction of vessels, resulting from the surgical technique, led to the uterus having to be removed on day 99. The second case involved a uterus from a deceased donor being transplanted into a patient with Rokitansky syndrome (Ozkan *et al.*, 2013); the patient underwent embryo transfer 18 months after transplantation and two pregnancies that miscarried before gestational week 6 have been reported. Finally, the first live birth after uterus transplantation has been described (Brannstrom *et al.*, 2015). In this case, *in vitro* fertilization was performed during the period from 18 to 6 months before transplantation. A single embryo transfer was done around 12 months after transplantation during the natural menstrual cycle according to their local frozen embryo transfer routine. The main reason to do *in vitro* fertilization before transplantation is that it is good to ascertain that fertility, in terms of fertilization and initial embryo development, exists in the couple. The ART procedure after transplantation might be more difficult than one before the surgery because of abnormal uterine vascular pedicles and anastomosis sites, which increase the risk of bleeding at oocyte pick-up, and also because the immunosuppressed patient may be at increased risk of pelvic infection after oocyte recruitment.

Recent developments in assisted reproductive treatment have provided new therapies, but the application of this technology in humans requires fully discussion of the medical, ethical, social and legal issues.

Use of ART after gynaecological cancers

Surgical gynaecological cancer management has been traditionally considered a 'sterilizing' procedure given the frequency of adnexa and uterus removal. Consequently, younger patients faced with this diagnosis often worry about their fertility, particularly those who have not yet completed childbearing. Among affected women, 15–21% are under the age of 40 years when diagnosed. This population is likely to have an early-stage disease that may be cured with fertility preservation being a priority (Wright *et al.*, 2009). The continuous trend of delayed childbearing in developed countries will further result in more women being diagnosed with gynaecological cancer before their first pregnancy (Martin *et al.*, 2006). Unfortunately, fertility-sparing options may not be appropriately offered for various reasons, including lack of knowledge or concern about compromised cancer outcome. Moreover, patients who face a cancer diagnosis may not be emotionally ready to discuss the complex risks and benefits that surround this decision.

Cervical cancer

Many women are diagnosed with cervical cancer during their reproductive years. A cervical cancer patient who wishes to preserve her fertility may feel that she must choose between her best chances of saving her own life and preserving her fertility. Such decisions must be individualized according to the woman's specific situation. Advice on fertility-preserving and fertility-sparing options is available from experts in reproductive medicine and gynaecological oncologists.

Until quite recently, women who required surgery to treat cervical carcinoma were faced with a bleak reproductive outlook. Patients who underwent radical hysterectomy were left with the options of surrogacy or adoption. Radical trachelectomy (RT) has been pioneered to treat early-stage cervical carcinoma, while conserving the body of the uterus, and thus retaining reproductive potential. While subsequent pregnancies have been reported, the operation can be followed by subfertility and a need for assisted reproduction (Aust *et al.*, 2007). After RT, fertility may be impaired by anatomical and physiological changes, such as adhesions, cervical stenosis and/or loss of cervical function. As surgery itself seems to create a degree of subfertility, patients with infertility problems when diagnosed with cervical carcinoma should be advised about their realistic chances of pregnancy.

There are very few reports on ART use after radical trachelectomy, but these patients show good results with intrauterine insemination (IUI) and *in vitro* fertilization/embryo transfer (IVF/embryo transfer) (Bernardini *et al.*, 2003; Plante *et al.*, 2011). Managing tight cervical stenosis with a nearly invisible cervical opening can be a challenge. Nevertheless, reasonable results have been achieved by dilating the cervix under general anaesthesia using tiny lachrymal probes, and by progressively dilating the cervical ostium enough to temporarily suture a Smit sleeve in place to keep the cervical ostium open while the patient prepares for either intrauterine insemination or embryo transfer following IVF. Alternatively, the Malecot catheter can be used as a stent to hold the isthmo-vaginal opening patent (Aust *et al.*, 2005). The problem of cannulating a tight cervical ostium is very common in this context. So a dummy embryo transfer may be advisable before initiating treatment.

Many spontaneous conceptions have been reported after RT (Shepherd *et al.*, 2006; Jolley *et al.*, 2007; Plante, 2008; Plante *et al.*, 2011). However, the absent cervix presents a number of problems because, compared with the general population, RT patients present comparable first-trimester miscarriage rates, but increased second-trimester losses. First-trimester complete miscarriages can be conservatively managed without cerclage removal or curettage, while second-trimester miscarriages or incomplete abortions may require the use of prostaglandins, cervical laminaria insertion or cerclage removal, sometimes followed by additional procedures (Schneider *et al.*, 2012). Preterm labour seems to appear more frequently in RT patients (Shepherd *et al.*, 2001; Dargent, 2002; Jolley *et al.*, 2007; Plante *et al.*, 2011) due to mechanical effects and possibly to subclinical chorioamnionitis related to lack of the protective mucus plug. In RT patients with a cervix, prophylactic antibiotics and procedures to cover the cervical canal in the second trimester have shown some degree of success (Saling, 1984), but entail some drawbacks (e.g. infection and membrane rupture). Finally, their optimal timing and whether they should be routinely used remain unclear.

Available data on reproductive and obstetric outcomes largely derive from vaginal radical trachelectomy (VRT) results and reports of obstetric outcomes following abdominal radical trachelectomy (ABRT) are limited. A retrospective study has reported lower pregnancy rates and a higher proportion of patients who need assisted reproduction after ABRT compared with VRT (Nishio *et al.*, 2013). Although uterus body preservation did not differ between these two procedures, the abdominal approach may affect the reproductive function to a greater extent. Post-VRT pregnancies imply a higher risk of prematurity and complications and these women should be followed-up by a maternal-fetal medicine specialist (Alexopoulos *et al.*, 2002). Very few data and no definitive guiding principles on post-VRT pregnancy management are available. The only recommendations found are extrapolated from the classical obstetrical literature on premature labour and premature rupture of membranes secondary to an incompetent cervix. Some authors recommend following up cervical length with serial ultrasounds (Petignat *et al.*, 2004; Plante *et al.*, 2005; Jolley *et al.*, 2007), while others favour more strict management (Ishioka *et al.*, 2007). The short-scarred cervix and the proximity of uterine vessels may make a vaginal delivery dangerous, so a planned low-transverse Caesarean section at around 37–38 weeks is recommended.

Endometrial cancer

Young women with endometrial carcinoma generally have a more favourable prognosis upon diagnosis due to the early stage and good differentiation (Rackow and Arici, 2006). Avoiding undertreatment and cancer recurrence requires appropriate patient selection for fertility-sparing endometrial cancer treatment. Conservative management typically requires early-stage disease with well-differentiated adenocarcinoma, with no myometrial invasion and extra-uterine spread upon pelvic imaging (Yarali *et al.*, 2004).

In patients who desire fertility preservation with detailed counselling, conservative management with high-dose progestin treatment may be considered to allow a disease-free window in which to attempt pregnancy (Eftekhar *et al.*, 2009; Hahn *et al.*, 2009). This approach has been evaluated, and recent meta-analyses have shown good complete resolution rates for both endometrial cancer and complex atypical hyperplasia. These results suggest the relative safety and efficacy of such progestin treatment (Baker *et al.*, 2012; Gunderson *et al.*, 2012; Penner *et al.*, 2012). In a retrospective study, Kudesia *et al.* (2014) reported a live birth rate in the IVF group of over 30%. This finding mitigates concern about permanent pathological effects on the endometrium. Nevertheless, women must be informed that hysterectomy remains the standard care option for atypical endometrial hyperplasia and endometrial cancer. Women who opt for hormonal treatment should be extensively counselled as to the risks, including the lack of response or disease progression while on hormonal therapy.

For younger patients, with a shorter duration of infertility and reassuring ovarian reserve without anovulation or severe male factor, spontaneous conception may be attempted for a limited time period. However, spontaneous conception may take several months, which can lead to anxiety about the risk of recurrent disease during the preconception period and the delay of complementary surgery following childbearing (Gurgan *et al.*, 2007). Thus assisted reproduction treatments may be performed for earlier pregnancy attainment. Efficient ART therapies have helped successful pregnancies to be increasingly reported (Lowe *et al.*, 2003; Demirol *et al.*, 2005; Elizur *et al.*, 2007; Gurgan *et al.*, 2007; Bozdag *et al.*, 2009; Sodano *et al.*, 2009; Chao *et al.*, 2011). The data that derive from these cases do not seem to show worse prognoses as ART probably increases the chances of gestation and cuts the interval to conception.

During ovarian stimulation with high-dose gonadotrophin, the impact of a high serum estradiol concentration on endometrial carcinoma is unclear, although some data suggest the disadvantage of ovarian stimulation. Apparently there is no clearly optimal duration, protocol or number of attempts for ovarian stimulation in patients with early-stage endometrial carcinoma. In early trials of cases with existing endometrial cancer, the endometrium has usually been regularized with high-dose progestin treatment before attempting IVF with conventional stimulation protocols. Letrozole is used in stimulation protocols in breast cancer patients. Similarly, tests in endometrial cancer show that the use of letrozole with gonadotrophins can provide further protection (Azim and Oktay, 2007).

Finally, the progesterone-releasing intrauterine device (IUD) is a newly available delivery system to treat estrogen-dependent endometrial cancer. The rationale for using this device instead of oral progesterone is that it provides very high doses of the hormone at the specific pathology site, which avoids the adverse effects produced by systemic administration. If we bear these arguments in mind, it has been shown that the uterus-sparing treatment of atypical endometrial hyperplasia and endometrial cancer with a combination of an injected GnRH analogue and a progestin-impregnated IUD can be effective in some patients (Minig *et al.*, 2011)

Many premenopausal endometrial cancer patients are affected by infertility, generally due to chronic anovulation and/or obesity. Following remission, the treatment aims to address the causes of infertility and to achieve pregnancy in a timely fashion by thereby minimizing the risk of recurrence. Once childbearing is completed, patients with high and persistent endogenous estrogen levels may be encouraged to undergo hysterectomy due to the high risk of recurrence. No large prospective or retrospective studies have evaluated the safety and efficacy of ART in this patient population. While ART use does not appear to increase endometrial cancer recurrence, available data must be interpreted cautiously as very few cases have been reported.

Ovarian cancer

In recent decades, the incidence of ovarian tumour diagnosis has increased significantly, both for invasive epithelial and borderline tumours, in patients aged under 40 years (Ayhan *et al.*, 2003). This increased diagnosis rate in women of reproductive age may be attributed to the advances made in health provision and to the development of sensitive diagnostic methods, including ultrasonography. However, media attention has focused on the potential associations between infertility, ovarian-stimulation drugs and ovarian tumours.

Borderline ovarian tumours account for 10–15% of all epithelial tumours, and share some histological features with malignant epithelial ovarian tumours, but are characterized by the absence of identifiable destructive stromal invasion (Gershenson, 2002). Patients with borderline tumours are typically younger when diagnosed, or show an earlier stage at presentation, longer survival and later recurrences. Combined with the increasing trend of late childbearing women in developed countries, these data mean that more women diagnosed with BOT wish to

preserve their childbearing potential. Thus conservative management and fertility-preserving and sparing therapeutic options are becoming increasingly important.

Pregnancies in patients with conservatively treated BOT have been reported (Gotlieb *et al.*, 1998; Zanetta *et al.*, 2001; Camatte *et al.*, 2002; Donnez *et al.*, 2003, 2013; Boran *et al.*, 2005; Fauvet *et al.*, 2005). Reported rates of spontaneous pregnancy range between 30 and 80%, and are likely to be influenced by conservative treatment type, patient age (Darai *et al.*, 2013) and the histological tumour subtype (Darai *et al.*, 2013). Despite conservative BOT management, some patients experience infertility due to post-operative ovarian adhesions and to altered ovarian function and reserve. Although ART is an option for women with BOT-associated infertility, it remains unclear whether ovarian stimulation or IVF is recommended for this population given the possible involvement of ovarain stimulation in BOT and ovarian cancer onset. However, *in vitro* data have suggested that gonadotrophins and/or high-dose estrogens do not induce proliferation in BOT cell cultures (Basille *et al.*, 2006).

Very few clinical data are available on fertility results after conservative surgery within the reproductive medicine context (Hoffman *et al.*, 1999; Beiner *et al.*, 2001; Fasouliotis *et al.*, 2004; Marcickiewicz and Brannstrom, 2006; Fortin *et al.*, 2007; Park *et al.*, 2007; Palomba *et al.*, 2010; Koskas *et al.*, 2011). The results that have derived from these trials suggest the possibility of proposing ovarian stimulation for patients with Stage I BOT without affecting prognosis. However, it is believed that the number of stimulation cycles should be limited to avoid potentially increasing the recurrence risk. Presently available data suggest that IVF may be considered for patients who select conservative fertility-sparing management for borderline tumours as there is no evidence for any adverse effects of pregnancy on the course of BOT. However, patients should receive detailed counselling on potential risks, as well as a close follow-up during and after IVF therapy.

Invasion of the ovarian stroma is the differential criterion between epithelial ovarian cancer (EOC) and BOT. The standard surgical procedure for EOC is radical hysterectomy with bilateral salpingo-oophorectomy. It is difficult to analyse data on the conservative management of EOC since many published trials have described conservative treatment in both epithelial and non-EOC, or have included both invasive and borderline tumours (considering both to be epithelial lesions). Very few studies (Colombo *et al.*, 1994; Zanetta *et al.*, 1997; Schilder *et al.*, 2002; Morice *et al.*, 2005; Park *et al.*, 2008) have focused on conservative treatment exclusively in EOC, and the results have indicated the safety of conservative surgery in patients with Stage IA Grade 1.

Patients with ovarian cancers and their treating physicians face a therapeutic dilemma because systemic and operative oncological treatments consistently compromise ovarian function, which often results in infertility and premature menopause (Partridge *et al.*, 2010). Regarding fertility outcomes after conservative treatment, the successful conception rate among women with childbearing desire has been reported to be >60%, with an acceptable 17% miscarriage rate (Fotopoulou *et al.*, 2012; Zapardiel *et al.*, 2014), but have indicated no relevant reproductive impairment after fertility-sparing surgery. Available reports have shown that only a minority of patients require ART for successful conception and pregnancy (Zanetta *et al.*, 1997; Schilder *et al.*, 2002; Morice *et al.*, 2005; Park *et al.*, 2008; Kwon *et al.*, 2009; Satoh *et al.*, 2010).

After considering the encouraging fertility results for both borderline and epithelial ovarian tumours, conservative surgery is an appealing solution for young women with low-stage disease who wish to preserve their childbearing potential. A careful selection of candidates for such treatment is necessary, and they need to be closely followed up.

Obstetric and perinatal outcomes after fertility preservation treatments

In addition to the fertility preservation options discussed above, oocyte vitrification is another means for a female cancer patient to achieve a pregnancy with her own gametes after overcoming disease (Jeruss and Woodruff, 2009). Scarce information is available on outcomes in cancer patients who have preserved their fertility through oocyte vitrification, mainly because their gametes have not yet been used given the novelty of this option and the patients focusing on complete healing before attempting pregnancy.

The first reported European case of pregnancy after oocyte vitrification involved a patient whose ovarian cortex was first cryopreserved. After grafting, four ovarian stimulation cycles were performed to accumulate and vitrify mature oocytes. Finally, an IVF cycle ended in a twin pregnancy (Sanchez-Serrano *et al.*, 2010). This case highlights the methods that increase IVF success to maximize productivity in the short lifespan of transplanted ovarian tissues. Later, Kim *et al.* (2011) reported the first birth of a baby after oocyte vitrification in a patient with chronic myeloid leukaemia. Garcia-Velasco *et al.* (2013) reported clinical outcomes from a fertility preservation programme for oncological patients who desired oocyte vitrification. Of the four patients who returned to use their cryopreserved oocytes, two patients achieved pregnancy. Finally, Martinez *et al.* (2014) reported the first series of live births after fertility preservation in women with cancer, and obtained similar success rates to women with vitrified oocytes for other indications.

Although very limited evidence is available for oocyte vitrification outcomes for fertility preservation (Yang *et al.*, 2007; Porcu *et al.*, 2008; Sanchez-Serrano *et al.*, 2010; Kim *et al.*, 2011), the experience reported in infertile patients may be useful for counselling purposes. There is an emerging collection of clinical outcome data from IVF cycles that have used vitrified oocytes from women with or without cancer. A long-term follow-up of the babies born is required to definitively consolidate this strategy (Cobo *et al.*, 2013).

Following ovarian tissue transplantation, pregnancies and live births by natural conception have been reported (Donnez *et al.*, 2012) and after IVF (Meirow *et al.*, 2005). No reports have suggested adverse pregnancy outcomes or congenital abnormalities after performing this technique. Pregnancy and live birth rates cannot be extrapolated from case reports as the number of reimplantations performed worldwide is unknown. To date, 37 live births after orthotopic reimplantation of cryopreserved ovarian tissue have been described (Donnez *et al.*, 2015). Combining the available results has yielded 80 cases (Donnez and Dolmans, 2013; Macklon *et al.*, 2014; Dittrich *et al.*, 2015). Among these series, the pregnancy rate was 25% and 16 women gave birth, which confirmed the results of a previous review (Donnez *et al.*, 2013). However, not all women who underwent ovarian transplantation became pregnant, which could be due to a high empty follicle rate during IVF when this procedure was needed after transplantation (Dolmans *et al.*, 2009).

Table IV Main series on obstetrical outcomes after fertility preservation surgery for cervical cancer.

Publications	Patients *n*	Type of treatment	Childbearing wish *n* (%)	Successful conception patients *n* (%)	Live births *n*	Abortions *n*	Deliveries <32 weeks *n*	IVF patients *n* (%)
Dargent *et al.* (2000)	47	VRT	NRA	25 (NRA)	13	11	0	NRA
Bernardini *et al.* (2003)	80	VRT	39 (48.7)	22 (56.4)	18	4	3	3 (13.6)
Ungár *et al.* (2005)	30	LRT	5 (17)	3 (60)	2	1	0	1 (33.3)
Chen *et al.* (2008)	16	LapRT	16 (100)	5 (31.2)	0	2	4	1 (20)
Sonoda *et al.* (2008)	43	VRT	14 (32.5)	11 (78.5)	10	1	0	3 (27.2)
Shepherd and Milliken (2008)	158	VRT	NRA	31 (NRA)	44	31	10	7 (22.5)
Li *et al.* (2011)	62	LRT	10 (16)	2 (20)	1	1	0	NRA
Marchiole *et al.* (2011)	7	NACHT	1 (14.2)	1 (100)	1	0	0	NRA
Plante *et al.* (2011)	125	VRT	NRA	58 (NRA)	77	29	19	12 (20.6)
Speiser *et al.* (2011)	212	VRT	76 (35.8)	60 (65.7)	31	11	18	NRA
Persson *et al.* (2012)	13	RRT	5 (38)	4 (80)	2	0	0	0
Saso *et al.* (2012)	30	LRT	10 (33)	3 (30)	2	1	1	1 (33.3)
Wethington *et al.* (2012)	101	LRT	38 (38)	28 (74)	25	3	6	NRA
Nishio *et al.* (2013)	114	LRT	69 (60.5)	25 (36)	26	5	4	17 (68)
Lanowska *et al.* (2014)	18	NACHT	7 (38.8)	5 (71.4)	4	2	2	0
Park *et al.* (2014)	55	LapRT	18 (33)	14 (78)	10	4	6	2 (14.2)
Robova *et al.* (2014)[a]	28	NACHT	13 (46.4)	10 (76.9)	8	3	3	NRA
Pareja *et al.* (2015)	65	NACHT	65 (100)	20 (30.7)	16	4	NRA	NRA
Vieira *et al.* (2015)	100	LRT 50 (50%) MIS 50 (50%)	34 (41)	16 (47)	11	4	9	NRA
Salihi *et al.* (2015)[b]	11	NACHT	9 (81.8)	6 (66.6)	7	2	2	NRA
Total	1315	All types	429 (43.5)	349 (NRA)	308	119	87	NRA

n, number; NRA, not reported/available; VRT, vaginal radical trachelectomy; RRT, robotic radical trachelectomy; LapRT, laparoscopic radical trachelectomy; LRT, laparotomic radical trachelectomy; MIS, minimally invasive surgery including LapRT and RRT.
[a]NACHT followed by simple trachelectomy.
[b]NACHT followed by large cone resection.

It is difficult to estimate the effectiveness of this procedure because reports come from different centres, patients were evaluated by different groups, and several techniques were used for ovarian tissue collection, freezing and transplantation. Insufficient data on failed transplantations precludes the estimation of overall success rates or the evaluation of the effectiveness of the techniques and factors used to improve transplantation outcomes. These results are important because they contribute to the evidence that suggests the success of this strategy.

Cryopreservation of ovarian tissues preserves only primordial and primary follicles. An additional fertility-preservation strategy is the retrieval of immature oocytes from visible antral follicles after ovarian resection, with subsequent *in vitro* maturation and vitrification, which can be offered as an adjunct to ovarian tissue cryobanking (Huang *et al.*, 2007). Prasath *et al.* (2014) recently reported the first live birth to result from a cryopreserved embryo obtained from this combination.

Many young women with cancer present unique challenges and concerns; thus the approach to fertility preservation must be individualized. In many cases, embryo cryopreservation is not ideal because the patient has no partner or due to the ethical compromise of freezing embryos for a patient who may not survive her disease. In such cases, oocyte vitrification is often an effective fertility-preservation method. Ovarian tissue cryopreservation is also a promising method and, in many cases, it is the only possible option. The results of the reported series on obstetrical outcomes after fertility sparing treatment in cervical, endometrial and ovarian cancers are found in Tables II, IV and V, respectively.

Patient counselling and decision-making

As survival rates increase for young cancer patients, growing emphasis is placed on post-treatment quality of life. Fertility preservation is considered a major issue for these patients as the ability to have biological children is often a central element to their quality of life (Howard-Anderson *et al.*, 2012). Despite, proven clinical and psychological benefits (Letourneau *et al.*, 2012; Yee *et al.*, 2012), and recommendations that cancer patients should be routinely asked about their interest in fertility preservation before starting cancer treatment, very few female young adult patients undergo fertility preservation counselling and treatment.

Decisions about fertility preservation counselling and treatment are complex, and occur during a time of turmoil which closely follows a recent cancer diagnosis. People reportedly make higher quality decisions if they well comprehend issues, and have a support system and self-awareness of their own values relating to the decision (O'Connor

Table V Reported series on obstetrical outcome fertility sparing surgery for epithelial ovarian cancer.

Publication	Patients *n*	Median age years	FIGO stage *n* (%)	Childbearing wish *n* (%)	Successful conception	Abortions *n* (%)	IVF *n* (%)
Raspagliesi *et al.* (1997)	10	22.7	IA 2 (20) IC 2 (20) IIIA 2 (20) IIIC 4 (40)	5 (50)	3 (60)	1 (33)	0
Zanetta *et al.* (1997)	56	29	IA 32 (57) IB 2 (4) IC 22 (39)	NRA	20 (69)	4 (20)	0
Morice *et al.* (2001)	25	24	IA 19 (76) IC 6 (24)	4 (16)	4 (100)	1 (25)	NRA
Schilder *et al.* (2002)	52	26	IA 42 (81) IC 10 (19)	24 (46.1)	17 (71)	5 (29)	0
Morice *et al.* (2005)	34	27	IA 30 (88) IC 3 (9) II 1 (3)	NRA	9 (33.3)	1 (11)	0
Borgfeldt *et al.* (2007)	11	27.5	IA 10 (90.9) IC 1 (9.1)	7 (63.6)	7 (100)	0	NRA
Schlaerth *et al.* (2009)	20	27	IA 11 (55) IC 9 (45)	6 (30)	6 (100)	NRA	NRA
Kwon *et al.* (2009)	21	26.7	IA 17 (81) IC 4 (19)	5 (23.8)	5 (100)	0	0
Satoh *et al.* (2010)	211	29	IA 126 (60) IC 85 (40)	84 (40)	55 (66)	10 (18)	5 (2.4)
Cheng *et al.* (2012)	17	NRA	IA 10 (59) IC 6 (35) IIIC 1 (6)	8 (47)	5 (63)	0	NRA
Fruscio *et al.* (2013)	240	32	IA 130 (54) IB 2 (1) IC 105 (44) II 3 (1)	105 (45)	84 (80)	16 (19)	NRA
Ditto *et al.* (2014)	18	31.1	IA 12 (66.6) IB 1 (5.5) IC 5 (27.9)	13 (72)	5 (38)	0	0
Total	715	27	IA 441 (61.6) IB 5 (0.7) IC 258 (36.1) II 4 (0.6) IIIA 2 (0.3) IIIC 5 (0.7)	261 (41.7)	220 (84.2)	38 (17.2)	NRA

n, number; NRA, not reported/available.

et al., 2009). By applying this framework to decision-making on fertility preservation, such comprehension would involve understanding the procedure, safety, time constraints and financial considerations. A woman's support system includes her partner, her family and her healthcare providers, all of whom may have opinions about fertility preservation. Many cancer patients may have never seriously contemplated their own ideas and values about reproductive options. Therefore consultation with a fertility specialist plays a key role in the decision-making process as it is the main source of information for patients, and it supports their desires to investigate and seek treatment (Kim *et al.*, 2013; Kim and Oktay, 2013).

Decisional conflict is a state of uncertainty as to the course of action to take. The decisional conflict scale (DCS) is used to approach the degree of vacillation that individuals encounter when challenging medical decisions are required. In various medical fields, high DCS scores are usually associated with greater emotional distress, delayed decision-making, indecisiveness, future regret and blaming providers (Brehaut *et al.*, 2003). Particularly in fertility preservation, delayed decision-making is extremely important given the time-sensitive nature of cancer treatment.

Studies of patients' attitudes and fertility preservation choices are underway worldwide. Notably, these reports vary in sample size and methodology, and the response rate is often <50% of eligible participants, which possibly means that only patients concerned about fertility choose to respond. Sample sizes are often too small to make valid generalisations for all cancer patients. Nonetheless, these studies reveal

some important aspects of fertility preservation practices, such as the majority of cancer patients (regardless of their final decision) find fertility consultation is an important part of treatment planning, and many patients have not participated in any fertility preservation consultation (Linkeviciute *et al.*, 2014).

Mersereau *et al.* (2013) reported high DCS scores in survivors of a variety of common cancers, and highlighted the challenges faced by young female adult cancer patients regarding fertility preservation decisions when diagnosed with cancer. This analysis found that three factors were associated with increased decisional conflict: lack of referral to fertility preservation consultation; concerns about procedure costs; not undergoing fertility preservation treatment. These data are consistent with other reports (Kim, 2012; Kim *et al.*, 2014), and reinforce the need for early referral to fertility specialists as most patients found that these consultations were very useful for their decision-making progress.

Counselling may facilitate educated decisions, and could provide opportunities for patients to cope with potential treatment-related infertility and for providers to manage expectations (Carter *et al.*, 2005). Decisional conflict is lower when patients feel quite strongly that they can ask questions during consultations. Patients who participate more actively in their consultation generally report more satisfaction with their care, and have improved psychosocial outcomes compared with those who play a more passive role (Peate *et al.*, 2011). Overall, information about fertility preservation options may decrease decisional conflict, but effective educational strategies are needed to adequately address the needs of diverse populations.

A comprehensive fertility preservation programme requires a strong connection between the oncology team and the fertility specialist. Oncologists' support is important in several aspects; for example, strong links between oncologists and fertility specialists might contribute to higher referral rates. The primary physician's support and opinion substantially influence patients' decision-making (Legare *et al.*, 2006), and open communication between these two teams is crucial when having to amend treatment plans. The early identification of key medical contacts facilitates patients' navigation across specialties within the tight timelines required for fertility preservation in cancer patients. These services and practices must be clearly identified to facilitate referrals of newly diagnosed patients by oncology team members (Kim *et al.*, 2014). Finally, the use of a decision aid during fertility preservation consultations may help patients to better understand complex topics (Garvelink *et al.*, 2013). Decision aids help patients get involved in decision-making by explaining the required decision, providing information about options and outcomes, and clarifying personal values (Kim *et al.*, 2013).

Overall, more attention must be paid to design decisional support services for cancer patients. High quality cancer care should include multiple steps in a limited time, which requires close and efficient collaboration

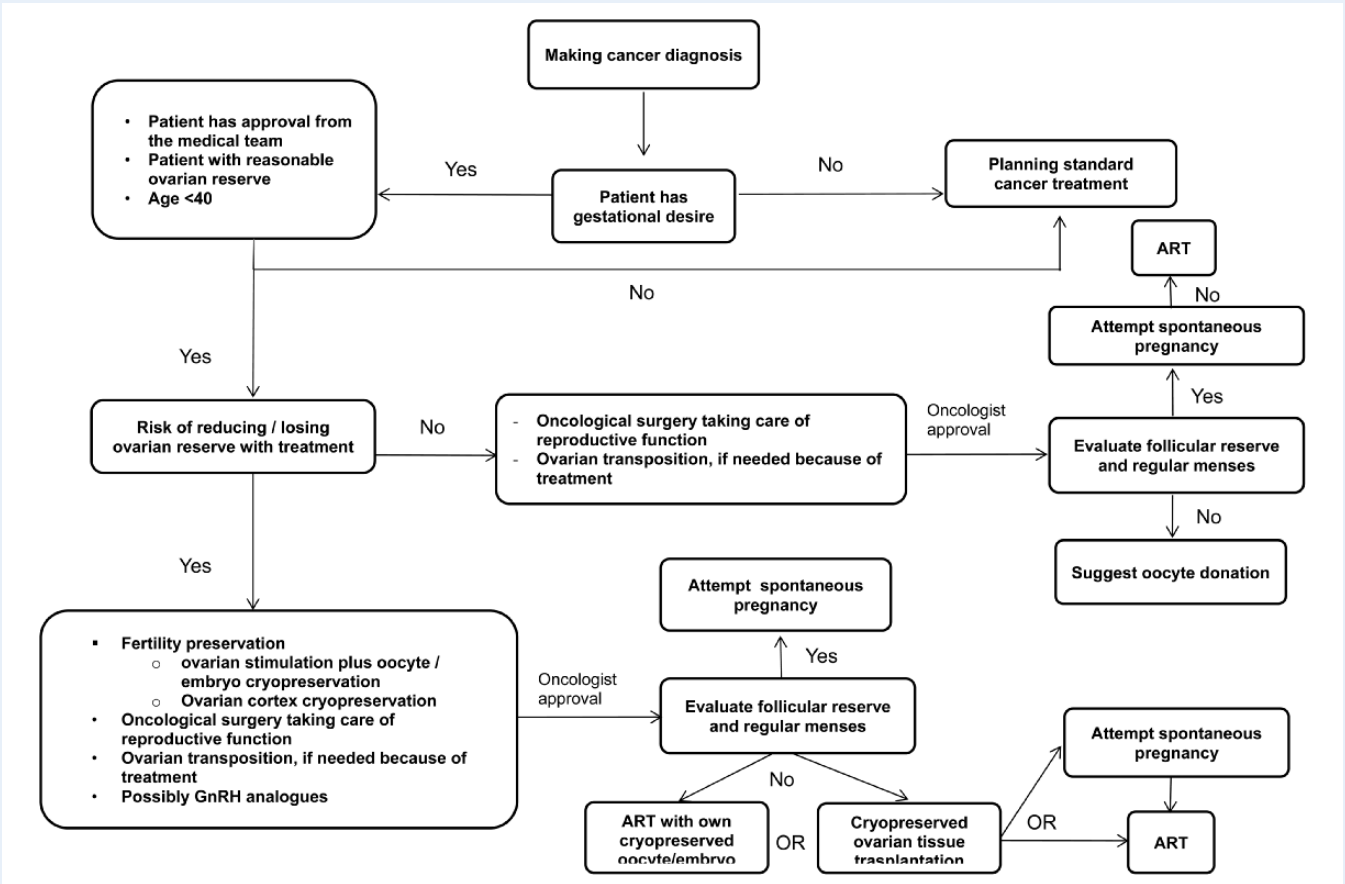

Figure 1 Flux diagram on decision-making after cancer diagnosis.

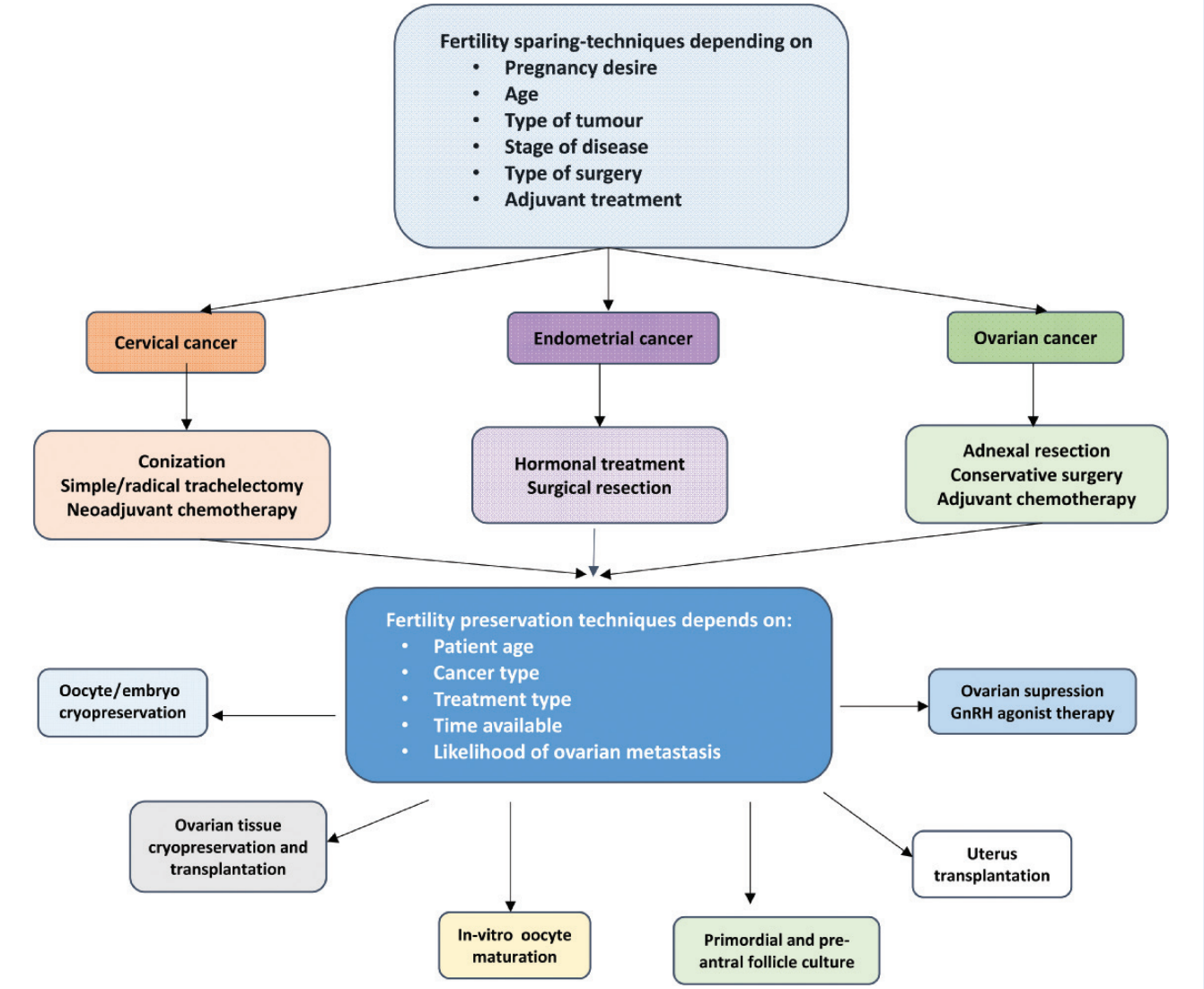

Figure 2 Summary diagram on the different fertility sparing options in gynaecological cancer patients.

with a range of specialists. Helping patients to understand the implications of their condition for their future life, and to choose fertility preservation options accordingly, should be a core goal of decisional counselling services (Figs 1 and 2).

Conclusions

Several fertility-sparing techniques are available for selected endometrial, cervical and ovarian cancer cases. Moreover, ART may help achieve pregnancy in such patients, and show good obstetric outcomes with apparent oncological safety. Available data are based mainly on retrospective studies and case series, but no data from randomized prospective trials have been published. Available data could support the conservative management of patients with fertility-sparing needs, although each case must be evaluated individually and discussed with the patient.

Authors' roles

I.Z., M.C., M.D., A.R. and J.G.-V. participated in the design of the paper, in database searching, in data extraction and analysis, and in the writing, revision and final approval of the manuscript.

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