REPRODUCTION
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Female fertility preservation: past, present and future

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Abstract

Anti-cancer therapy, particularly chemotherapy, damages ovarian follicles and promotes ovarian failure. The only pharmacological means for protecting the ovaries from chemotherapy-induced injury is gonadotrophin-releasing hormone agonist, but its efficiency remains controversial; ovarian transposition is used to shield the ovary from radiation when indicated. Until the late 1990s, the only option for fertility preservation and restoration in women with cancer was embryo cryopreservation. The development of other assisted reproductive technologies such as mature oocyte cryopreservation and *in vitro* maturation of oocytes has contributed to fertility preservation. Treatment regimens to obtain mature oocytes/embryos have been modified to overcome various limitations of conventional ovarian stimulation protocols. In the last decades, several centres have begun cryopreserving ovarian samples containing primordial follicles from young patients before anti-cancer therapy. The first live birth following implantation of cryopreserved-thawed ovarian tissue was reported in 2004; since then, the number has risen to more than 130. Nowadays, ovarian tissue cryopreservation can be combined with *in vitro* maturation and vitrification of oocytes. The use of cryopreserved oocytes eliminates the risk posed by ovarian implantation of reseeding the cancer. Novel methods for enhancing follicular survival after implantation are presently being studied. In addition, researchers are currently investigating agents for ovarian protection. It is expected that the risk of reimplantation of malignant cells with ovarian grafts will be overcome with the putative development of an artificial ovary and an efficient follicle class- and species-dependent *in vitro* system for culturing primordial follicles.

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Introduction

By age of 39 years, one of every 51 women will have been diagnosed with cancer (Chung *et al.* 2013). Advances in anti-cancer treatment have resulted in higher survival rates (Feigin *et al.* 2008, Chung *et al.* 2013), but one of the side effects is ovarian failure. Thus, the number of cancer survivors coping with this problem is expected to grow.

The ovarian damage induced by anti-cancer chemotherapy is correlated with patient age at the time of treatment, the type and dose of the agents used and the duration of treatment (Abir *et al.* 1998, 2008, 2016, Brougham & Wallace 2005, Wallace *et al.* 2005, Feigin *et al.* 2008, Chung *et al.* 2013). In general, alkylating agents pose the highest risk, especially when they are combined with abdominal-pelvic radiation. The degree of radiation-induced impairment depends on the radiation dose, location of the ovaries relative to the radiation field, fractionation schedule and age at treatment (Abir *et al.* 1998, Brougham & Wallace 2005, Chung *et al.* 2013).

The evolution of assisted reproductive technologies (ART) has facilitated the development of methods and strategies to preserve fertility in patients with cancer. These include pharmacological protection of the ovary against the gonadotoxic compounds used in anti-cancer treatment and ovarian transposition when indicated, as well as cryopreservation of oocytes, embryos or ovarian tissue before initiation of anti-cancer therapy (Fig. 1). Some of these fertility preservation methods are also used in women with medical indications other than cancer and in women who seek fertility preservation for social reasons.

Means of ovarian protection

Anti-gonadotoxic treatment

Currently, the only pharmacological means of ovarian protection during chemotherapy is gonadotrophin-releasing hormone (GnRH) agonist; however, its efficiency remains controversial (Rodrigez-Wallberg & Oktay 2012, Hickman *et al.* 2016, Salama *et al.* 2016,

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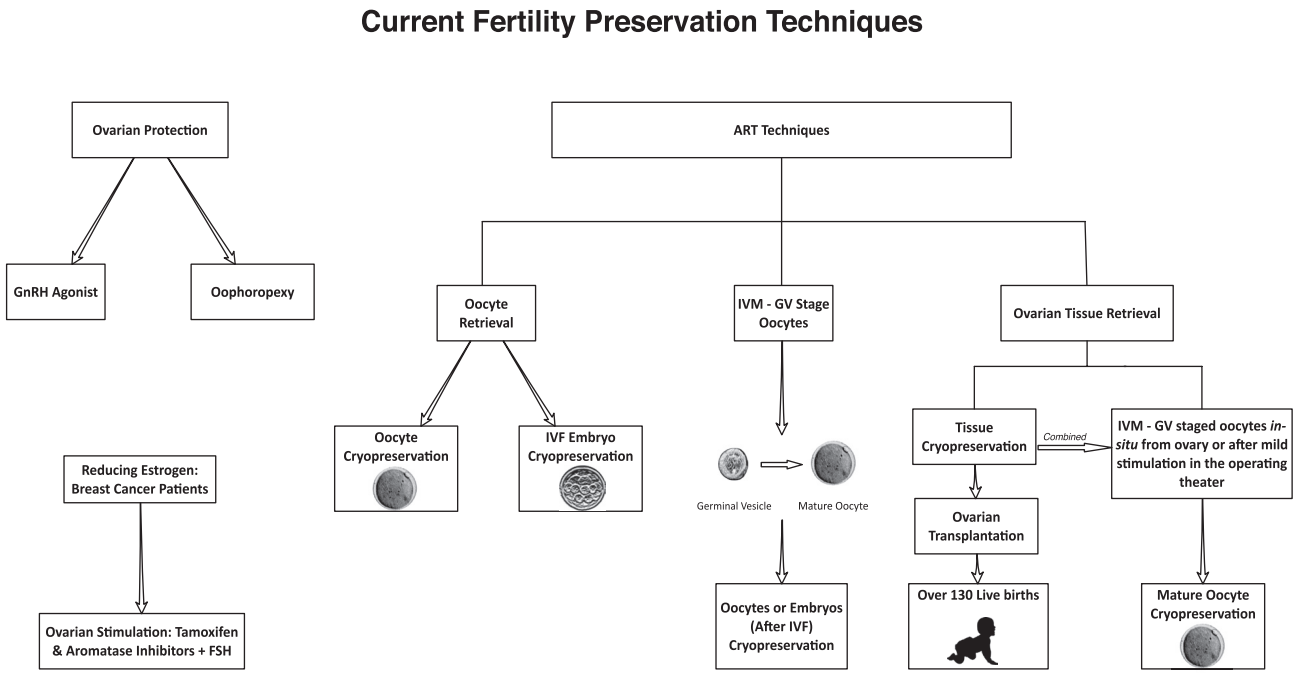

Figure 1 Current fertility preservation techniques. FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; GV, germinal vesicle; IVF, *in vitro* fertilization; IVM, *in vitro* maturation.

Senra *et al.* 2017). Another advantage of the use of GnRH agonist is that it abolishes the monthly menstrual bleedings during chemotherapy and may, therefore, prevent chemotherapy-induced menorrhagia. GnRH agonist binds GnRH receptors at the anterior pituitary (Blumenfeld & Evron 2015, Hickman *et al.* 2016), stimulating luteinizing hormone and follicle-stimulating hormone (FSH) secretion. Prolonged activation of the receptor leads to desensitization and downregulation of gonadotrophin secretion. It is thought that in the ovary, GnRH agonist decreases vascularity, thereby reducing the concentration of the chemotherapeutic agents. GnRH agonist might also inhibit the recruitment of primordial follicles, although the development of unilaminar follicles is considered FSH independent, and they do not express gonadotrophin receptors (Blumenfeld *et al.* 2007, Blumenfeld & Evron 2015).

The protective effects of GnRH agonists on the ovary have been investigated mainly in patients with lymphoma and oestrogen-receptor-positive breast cancer (Rodrigez-Wallberg & Oktay 2012, Lumachi 2015). In patients with Hodgkin's lymphoma, negative findings were reported in the initial study after a 2-year follow-up (Waxman *et al.* 1987) and in two studies performed almost three decades later (Demeestere *et al.* 2016, Hickman *et al.* 2016). In patients with breast cancer, specifically oestrogen-receptor-negative early-stage disease, one study found that the addition of GnRH agonist to chemotherapy was associated with a higher pregnancy rate and lower ovarian failure rate than chemotherapy alone (Moore *et al.* 2015). Most other studies in similar patients reported a reduction in the premature ovarian failure rate (Hickman *et al.* 2016), although some observed that GnRH agonist was inefficient unless tamoxifen was included in the treatment protocol (Vitek *et al.* 2014, Kasum *et al.* 2015). In 2013, The American Society for Reproductive Medicine recommended the use of GnRH agonist in combination with other fertility preservation methods (Practice Committee of American Society for Reproductive Medicine 2013, Lambertini *et al.* 2016). A very recent meta-analysis (Senra *et al.* 2017) assessed 13 randomised control studies of patients treated for breast cancer ($n = 1099$) or lymphoma ($n = 109$). GnRH agonist had a significant protective effect against premature ovarian insufficiency/amenorrhea in the breast cancer group but not in the lymphoma group. Furthermore, the rate of spontaneous pregnancy after completion of treatment was higher in women who received GnRH agonist with chemotherapy than in those treated with chemotherapy alone. Despite these positive results, the authors point out that the quality of evidence was low in all the studies.

Ovarian transposition

Young patients scheduled for pelvic irradiation may undergo oophoropexy to shield their ovaries or move them as far as possible from the radiation field (Leporrier *et al.* 1987, Brougham & Wallace 2005, Feigin *et al.* 2008, Rodriguez-Wallberg & Oktay 2012, Arian *et al.* 2017). Because of the risk of spontaneous relocation of the ovaries, the procedure should be performed in close

proximity to the radiation treatment. Some extent of protection has been documented, but scattered radiation and alterations in ovarian blood supply limit the success rate to approximately 50% (Damewood *et al.* 1990, Clough *et al.* 1996, Zinger *et al.* 2004, Lee *et al.* 2006, Feigin *et al.* 2008). The procedure may also complicate future oocyte retrieval and promote some ovarian dysfunction and cyst development. There are reports of spontaneous conception following oophoropexy. In some cases, a combined approach of transposition of one ovary with tissue retrieval for cryopreservation from the other ovary may be considered (Martin *et al.* 2007, Feigin *et al.* 2008).

Controlled ovarian stimulation protocols for obtaining mature oocytes/embryos for fertility preservation

Stimulating the development of multiple follicles is a prerequisite in ART to maximize the yield of aspirated oocytes (Fauser & Van Heusden 1997, Macklon *et al.* 2006). This is crucial in patients with cancer undergoing egg collection for fertility preservation, because they usually have time for only a single attempt before commencing chemotherapy. Conventional controlled ovarian hyperstimulation (COH) protocols use gonadotrophin preparations, and GnRH analogues are added to improve their efficiency by decreasing cycle cancellation and increasing the yield of mature oocytes (Arslan *et al.* 2005, Fatemi *et al.* 2012, Shrestha *et al.* 2015). However, in patients with cancer, the standard protocol needs to be modified to encounter three main limitations.

1. COH protocols pose a high risk of ovarian hyperstimulation syndrome (OHSS), a serious and potentially fatal complication (Aboulghar & Mansour 2003), especially when the aim is to obtain as many oocytes as possible for future use. Several recent trials (Engmann *et al.* 2008, Devroey *et al.* 2011, Youssef *et al.* 2014) have supported earlier suggestions that OHSS may be prevented if final follicular maturation is induced by GnRH agonist instead of human chorionic gonadotrophin (hCG) (Itskovitz *et al.* 1991, Lewit *et al.* 1996). In patients with cancer, GnRH agonist trigger was shown to have similar or better results than hCG trigger with a higher yield of metaphase II oocytes (Oktay *et al.* 2010, Reddy *et al.* 2014). Therefore, the standard regimen in cycles for fertility preservation now includes gonadotrophin stimulation, GnRH antagonist (to prevent premature luteinisation) and GnRH agonist (to trigger final maturation).
2. Conventional start protocols may cause a significant delay in anti-cancer treatment because stimulation begins at the early follicular phase of the menstrual cycle. Therefore, in patients with cancer undergoing COH for fertility preservation, GnRH antagonist may be administered at any stage of the cycle ('random start'). When given during the luteal phase, it induces abrupt luteolysis, such that gonadotrophin treatment can be initiated immediately instead of waiting for the next menstrual period (von Wolff *et al.* 2009, Bedoschi *et al.* 2010). It has been reported that in random-start protocols, oocyte retrieval may be performed irrespective of the phase of the cycle without compromising oocyte yield and maturity (Cakmak & Rosen 2013, Kuang *et al.* 2014*a*). Double ovarian stimulation during the follicular and luteal phases might be a feasible option for retrieving more oocytes for future use (Kuang *et al.* 2014*b*).
3. Standard COH protocols cause a significant elevation in circulating oestradiol levels. There is no clear evidence that short-term exposure to supra-physiologic oestradiol levels may induce the proliferation or dissemination of oestrogen-receptor-positive breast cancer cells. Nevertheless, to avoid potential risks, women with breast cancer undergo specific stimulation regimens that include tamoxifen to negate the effect of oestradiol at the receptor level or aromatase inhibitors to abolish oestradiol biosynthesis (Oktay *et al.* 2006*a*). Initially, these agents were used alone as ovarian-stimulating agents, and later, in combination with FSH to increase the yield of mature oocytes (Oktay *et al.* 2003, 2005, Ben-Haroush *et al.* 2011). The limited data available suggest that embryo cryopreservation after COH with aromatase inhibitors and FSH results in pregnancy rates comparable to those expected in a non-cancer population undergoing *in vitro* fertilization (IVF) (Oktay *et al.* 2015). The regimens seem to have a good safety profile, with no reported increase in cancer recurrence or mortality in tamoxifen-treated patients (Meirow *et al.* 2014, Shapira *et al.* 2015), and no evidence of a decline in relapse-free survival rates in women co-treated with aromatase inhibitors (Oktay *et al.* 2005, Azim *et al.* 2008, Kim *et al.* 2016, Rodgers *et al.* 2017).

Current fertility preservation and restoration options

Cryopreserving mature oocytes

The first birth from a cryopreserved oocyte was reported in Australia in 1986 (Chen 1986, Jadoul & Kim 2012). However, this method did not yield optimal results for many years (Oktay *et al.* 2006*b*, Jadoul & Kim 2012). Vitrification, introduced in the late 1990s in Japan and Australia for freezing embryos and oocytes (Mukaida *et al.* 1998, Kuleshova *et al.* 1999, Rienzi *et al.* 2017), was abandoned thereafter until the early 2000s when studies using improved protocols reported a live birth rate of 40% for vitrified-warmed oocytes (Cobo *et al.*

2008, Ata *et al.* 2010, Jadoul & Kim 2012), and delivery rates similar to those for pregnancies from fresh oocytes (Grifo & Noyes 2010, Pavone *et al.* 2016). So far, the use of cryopreserved oocytes has not been associated with an increase in congenital anomalies (Chian *et al.* 2008, Noyes *et al.* 2009, Jadoul & Kim 2012).

Unlike embryo cryopreservation, oocyte cryopreservation does not require sperm and is, therefore, better suited to single patients. However, studies in patients with cancer are limited because in many cases, anti-cancer treatment cannot be postponed, and there is no time for hormonal stimulation (Massarotti *et al.* 2017). This may explain the paucity of reports on the routine use of oocyte cryopreservation for this patient group. In one relatively large study of 176 patients with cancer who underwent oocyte cryopreservation by either slow freezing or vitrification (Druckenmiller *et al.* 2016), 10 patients returned for fertility restoration. The live birth rate was 44% per embryo transfer cycle, similar to patients without cancer. One report described a patient with a *BRCA1* mutation and suspected ovarian cancer in which standard oocyte collection was ruled out because of malignant cell spillage risk. Mature oocytes were retrieved after mild hormonal stimulation directly from the oophorectomized ovaries and vitrified (Pereira *et al.* 2017).

Cryopreserving in vitro*-matured germinal vesicle (GV)-stage oocytes*

In vitro maturation (IVM) of rabbit oocytes was first reported in 1935 (Pincus & Enzmann 1935) and was followed more than 30 years later by IVM of human germinal vesicle (GV)-stage oocytes (Edwards *et al.* 1969). In the 1990s, there was new interest in improving this technique: In Korea, oocytes retrieved from oophorectomized tissue underwent IVM and were subsequently used for donation (Cha *et al.* 1991), and in Australia, immature oocytes surgically collected from small antral follicles of patients with polycystic ovaries syndrome (PCOS) underwent IVM and were subsequently inseminated, resulting in one live birth (Trounson *et al.* 1994). Thereafter, mild hormonal stimulation was applied, before oocyte pick-up, in patients with PCOS (Chian 2004, Son *et al.* 2008, Fadini *et al.* 2009, Son & Tan 2010, Hourvitz *et al.* 2015). In Canada, immature oocytes were retrieved without hormonal stimulation from ovaries of patients with cancer, subjected to IVM and vitrified either before or after fertilization (Rao *et al.* 2004). The first live births using frozen-thawed embryos from *in vitro*-matured oocytes of cancer survivors were reported in Singapore (Prasath *et al.* 2014), Belgium (Segers *et al.* 2015) and the United States (Uzelac *et al.* 2015). Immature oocyte collection was reported also during caesarean section for subsequent IVM and vitrification (Ben-Haroush *et al.* 2010, 2017).

It is noteworthy that IVM of GV-stage oocytes for fertility preservation eliminates the risk of reseeding cancer (Rao *et al.* 2004, Chian *et al.* 2014). Moreover, it allows for fertility preservation without exposing the patient to hormonal stimulation and without any delay in the anti-cancer treatment (Huang *et al.* 2010). However, it is not yet known if vitrified-warmed *in vitro*-matured oocytes yield similar results to vitrified-warmed mature oocytes obtained after standard ovarian stimulation (Chian *et al.* 2009, Ellenbogen *et al.* 2014).

Cryopreserving embryos

The first pregnancy from cryopreserved embryos was reported in Australia in 1983 (Trounson & Mohr 1983), and the first baby born after blastocyst cryopreservation was reported 2 years later (Cohen *et al.* 1985). Since then, embryo cryopreservation has become a routine procedure in IVF laboratories (Herrero *et al.* 2011). Like for oocytes, slow freezing was used initially, and vitrification is currently the method of choice.

Embryo cryopreservation in patients with cancer has been documented from 2006 (Oktay *et al.* 2006*b*, Yang *et al.* 2007, Courbiere *et al.* 2013, Dolmans *et al.* 2015). Comparison of patients with and without cancer (before chemotherapy) who underwent IVF and embryo cryopreservation showed no difference in the number of collected oocytes, fertilization rate, number of live births and birth complications, although the patients with cancer had fewer good-quality embryos (Robertson *et al.* 2011, Dolmans *et al.* 2015, Pavone *et al.* 2016). Embryo cryopreservation also requires sperm and is not always suitable for single patients or young girls. Moreover, similar to the situation with mature oocytes in many patients with cancer, anti-cancer treatment cannot be postponed, and there is no time for hormonal stimulation (Massarotti *et al.* 2017). It is noteworthy that IVF is not recommended after one or two chemotherapy courses, as the number of embryos is very low, and they might be an increased risk of congenital malformations (Jadoul & Kim 2012).

Cryopreservation and transplantation of ovarian tissue

Ovarian tissue transplantation in rabbits was reported already in 1863 in France and again 30 years later in Austria (Gosden 2008). In 1895, a New York surgeon transplanted human ovaries from donors or cadavers to 26 infertile women, one of whom gave birth to three children (Morris 1895, 1906, Oktay & Buyuk 2004, Gosden 2008). These attempts continued moderately around World War II, and ceased after IVF was clinically established.

Following the development of cryopreservation techniques, researchers successfully restored ovarian function to oophorectomized sheep using sliced frozen-thawed ovarian tissue (Gosden *et al.* 1994, 2013, Baird

et al. 1999). Thereafter, studies of cryopreservation of human ovarian tissue reported normal follicular morphology after thawing (Hovatta *et al.* 1996), follicular survival (Newton *et al.* 1996, Oktay *et al.* 1998) and development of follicles to antral stages after implantation into immunodeficient mice (Oktay *et al.* 1998). The optimal cryoprotectant for slow freezing of human ovarian tissue has not yet been established (Hovatta *et al.* 1996, Newton *et al.* 1996, 1998, Gook *et al.* 1999), although most centres still use Gosden's protocol of dimethylsulfoxide (Newton *et al.* 1996, 1998). The efficiency of vitrification for freezing human ovarian tissue remains controversial (Amorim *et al.* 2011, Abir *et al.* 2017).

Initially, frozen ovarian tissue was transplanted to heterotopic sites such as the forearm (Oktay *et al.* 2004) with resumption of ovarian function and embryo development following IVF. Thereafter, the ovary became the most common grafting location (Meirow *et al.* 2005). The first live births from implanted frozen-thawed ovarian tissue were reported in Belgium (Donnez *et al.* 2004) and Israel (Meirow *et al.* 2005); to date, more than 130 live births have been documented worldwide (Donnez & Dolmans 2017).

One of the main dangers of grafting ovarian tissue is reseeding the cancer (Chung *et al.* 2013). This risk applies mostly to haematological malignancies but may also be relevant to non-haematological cancers such as Ewing sarcoma and neuroblastoma (Abir *et al.* 2010, 2014, Chung *et al.* 2013, Greze *et al.* 2017). It cannot be ruled out by pathology examinations and immunohistochemical markers; therefore, reimplantation should be preceded by the application of specific molecular markers (minimal residual disease) (Abir *et al.* 2010, 2014, Chung *et al.* 2013). Researchers have suggested that the ovarian tissue might first be transplanted to immunodeficient mice to observe if it disseminates cancer (Dolmans *et al.* 2013). So far, there is one report of a live birth after implantation of ovarian tissue in a survivor of leukaemia (Meirow *et al.* 2016, Shapira *et al.* 2018).

Despite the encouraging results after human ovarian implantation (Donnez & Dolmans 2017), grafting is immediately followed by extensive follicular loss, probably due to the ischaemia induced by slow graft revascularization (Abir *et al.* 2011, Friedman *et al.* 2012). Therefore, methods to improve and hasten graft vascularization and to reduce apoptosis are needed (see: Future Prospects).

Cryopreserving in vitro*-matured oocytes combined with ovarian tissue*

In 2008, a preliminary study from Canada described four women in whom immature oocytes were aspirated directly from retrieved ovarian tissue followed by IVM and vitrification (Huang *et al.* 2008). Since then, this strategy has been adopted by various centres (Hourvitz *et al.* 2015, Abir *et al.* 2016, Fasano *et al.* 2017). One group studied more than 100 patients with cancer who underwent mild ovarian stimulation before immature oocyte collection and ovarian tissue retrieval (Hourvitz *et al.* 2015). The oocytes were collected directly from the tissue or in the operating theatre, and the maturation rate was more than 50%. The mature oocytes were vitrified in parallel with slow ovarian freezing.

This approach is applicable to young and even prepubertal girls (Revel *et al.* 2009, Abir *et al.* 2016, Fasano *et al.* 2017), who account for the large percentage of blood cancer cases and in whom the risks of reseeding cancer with ovarian implants might be high (Feigin *et al.* 2008). In one study, immature oocytes were collected from more than 40 patients aged 2–18 years either chemotherapy naïve or after chemotherapy (Abir *et al.* 2016). As many as 31 immature oocytes were recovered from an ovary of a 5-year-old girl before anti-cancer therapy. The oocyte maturation rate in young girls was low (10–30%) and the number of atretic oocytes upon collection was high (~30%) (Revel *et al.* 2009, Abir *et al.* 2016, Fasano *et al.* 2017). The developmental capability of oocytes collected at early ages is unknown.

Future prospects

Despite the progress in fertility preservation options for young patients with cancer, several problems still remain and researchers worldwide are working on improving the following technologies (Fig. 2):

1. Developing effective ovary protective substances.
2. Improving ovarian grafting by increasing post-implantation follicular survival.
3. Eliminating the risk of reseeding malignancies with ovarian grafts by either:
   a. Transplantation of an artificial ovary that contains matrix-embedded isolated follicles;
   b. Application of a successful IVM system for primordial follicles

Potential new pharmacological gonadoprotective agents

Various new gonadoprotective agents are currently being tested, mostly in mice (Roness *et al.* 2014). These include sphingosine-1-phosphate (S1P), a ceramide-promoted cell-death inhibitor that blocks doxorubicin-induced oocyte apoptosis and imatinib, a tyrosine kinase inhibitor and anti-cancer agent (Perez *et al.* 1997, Morita *et al.* 2000, Kaya *et al.* 2008, Zelinski *et al.* 2011). S1P was found to protect follicles against radiation in mice, rats, primates and implanted human ovarian tissue and the monkey offspring had no abnormalities. However, it has a short plasma half-life and cannot be administered systemically (Perez *et al.* 1997, Morita & Tilly 2000, Kaya *et al.* 2008, Soleimani *et al.* 2011).

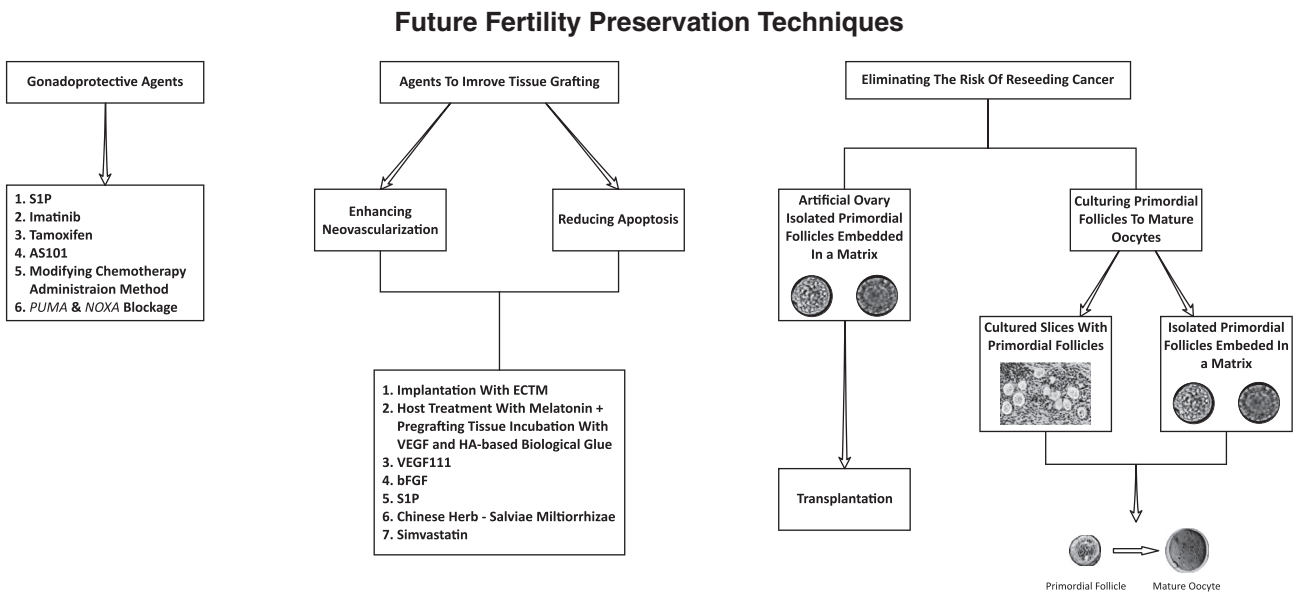

Figure 2 Future fertility preservation techniques. bFGF, basic fibroblast growth factor; ECTM, decellularized human extracellular matrix; HA, hyaluronan; S1P, sphingosine-1-phosphate; VEGF, vascular endothelial growth factor.

Another gonadoprotective agent might possibly be imatinib, a specific tyrosine kinase enzyme inhibitor, that its co-administration with cisplatin rescued murine ovarian follicles (Gonfloni *et al.* 2009, Maiani *et al.* 2012), but promoted oocyte death in another study (Kerr *et al.* 2012*a*). GNF-2, another tyrosine kinase inhibitor, protected primordial and primary murine follicles exposed to cisplatin *in vitro* (Maiani *et al.* 2012).

Promising results have been reported for tamoxifen, a selective oestrogen receptor modulator used for oestrogen-sensitive cancers (Roness *et al.* 2014). In rat studies, tamoxifen administered during chemotherapy reduced chemotherapy-induced follicle loss and doxorubicin-induced oocyte fragmentation (Ting & Petroff 2010). When administered during γ-irradiation, it restored fertility and normalized anti-Mullerian hormone (AMH) and insulin-like growth factor 1 levels (Mahran *et al.* 2013). In another study in mice, granulocyte colony-stimulating factor with/without stem cell factor was combined with high-dose alkylating agents, increasing micro-vessel density and decreasing follicle loss (Skaznik-Wikiel *et al.* 2013).

AS101 is a nontoxic immune modulator that directly inhibits the PI3K/PTEN/Akt signalling pathway (responsible for primordial follicle development) with anti-apoptotic and anti-inflammatory effects (Kalich-Philosoph *et al.* 2013). The combination of AS101 with cyclophosphamide in female mice inhibited primordial follicle activation and reduced granulosa cell apoptosis without an increase in foetal malformations in pups.

Using a novel approach, one group attempted to modify the method of chemotherapy administration by encapsulating arsenic trioxide, used to treat against haematological malignancies, in nanobins (Ahn *et al.* 2013). When administered to mice, ovarian damage was reduced.

Others suggested that gene therapy may play a potential role in follicle protection against radiation (Kerr *et al.* 2012*b*). Mice lacking the pro-apoptotic *puma* and *noxa* genes were found to be protected from γ-irradiation-induced follicular apoptosis and produced healthy offspring.

Methods for enhancing follicular survival after implantation

Recent years have witnessed the development of a range of novel methods intended to increase vascularization and promote follicular survival after transplantation. The three-dimensional (3D) decellularized extracellular matrix (ECM) consists of molecules that form ECM preserved in their natural ultrastructural architecture (Amorim & Shikanov 2016). The transplantation of human ovarian tissue together with a decellularized ECM to mice led to normal primordial follicle survival, and auto-transplantation of the human ovarian tissue with the matrix resulted in two pregnancies and one live birth (Oktay *et al.* 2016).

Others took advantage of the antioxidant activity and anti-apoptotic effect of melatonin and vitamin E, both free-radical scavengers, and the anti-inflammatory and anti-apoptotic effect of hyaluronan, a component of the ECM (Abir *et al.* 2011, Friedman *et al.* 2012). By treating the host with melatonin concomitant with incubation of the human ovarian graft with hyaluronan-based biological glue +vitamin E+ vascular endothelial growth factor A (VEGF-A), neovascularization was enhanced and apoptosis was reduced.

Promising results were obtained when ovarian tissue was auto-transplanted to murine hosts after the administration of recombinant human erythropoietin (Mahmoodi *et al.* 2014). One group improved angiogenesis when the VEGF111 isoform, which is resistant to proteolysis and has a relatively long plasma half-life, was added to collagen type I during transplantation of ovarian cortical samples from sheep to immunodeficient mice (Labied *et al.* 2013). Incubating human ovarian slices with basic fibroblast growth factor (bFGF) before implantation into immunodeficient mice was found to improve angiogenesis, increase granulosa cell proliferation and decrease apoptosis; VEGF had no effect on bFGF action (Kang *et al.* 2016). In light of the high concentrations of growth factors, including vascularisation enhancers, in platelet- rich plasma, researchers transplanted human ovarian tissue together with platelet-rich plasma from the patient's blood and achieved one live birth (Callejo *et al.* 2013).

Continuous graft-directed administration of S1P with a subcutaneous pump to murine hosts accelerated neo-angiogenesis, reduced tissue hypoxia and decreased follicular apoptosis (Soleimani *et al.* 2011). Injection of an extract of the Chinese herb *Salviae miltiorrhizae*, used for treating ischaemic diseases, into immunodeficient mice grafted with human foetal ovarian tissue facilitated vascularisation and improved primordial follicle preservation (Wu *et al.* 2010). The administration of simvastatin, which has antioxidant, anti-ischaemic and anti-inflammatory effects to mice before auto-transplantation of vitrified-warmed or fresh mouse ovarian tissue portions protected the ovary against ischaemia, decreased follicular apoptosis, activated the Akt1 signal pathway and improved revascularization (Lee *et al.* 2015*a*,*b*, Cohen *et al.* 2016).

Artificial ovary

Artificial ovaries containing isolated follicles might serve as a revolutionary means of restoring fertility without the danger of reseeding the cancer (Amorim & Shikanov 2016). The ground work for the development of the artificial ovary was laid in the early 1990s (Gosden 1990, 2013, Carrol & Gosden 1993) using fresh (Gosden 1990, Telfer *et al.* 1990) and cryopreserved (Carrol & Gosden 1993) isolated murine ovarian follicles embedded in fibrin or plasma clots or collagen gels transplanted into ovaries of sterile mice leading to the birth of offspring.

The isolation of human primordial follicles, first reported in 1997 (Oktay *et al.* 1997), requires digesting enzymes such as collagenase (Oktay *et al.* 1997, Abir *et al.* 1999, 2001, 2008) or Liberase (Dolmans *et al.* 2006) (Fig. 3). To allow for folliculogenesis and blood vessel formation, the fragile isolated follicles need to be embedded in a 3D supporting matrix that degrades with time (Amorim & Shikanov 2016).

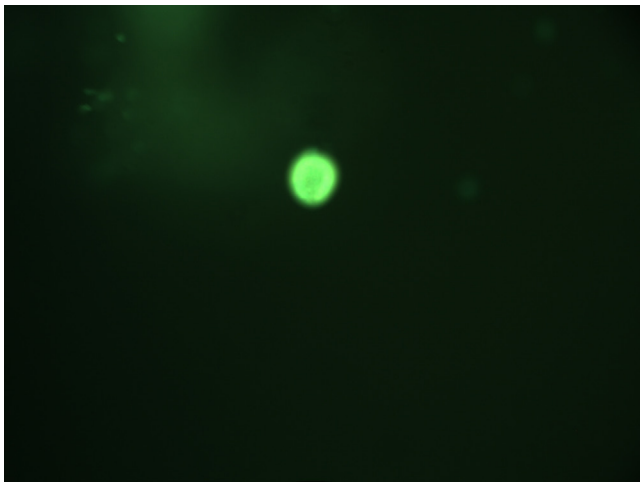

Figure 3 Fluorescent photograph of a viable isolated unilaminar follicle isolated human ovarian follicle from a 13-year-old girl stained exclusively with the green viability stain calcein acetoxymethyl (AM), a membrane-permeable live-cell labelling dye. Once the dye enters the cell, intracellular esterases cleave the AM ester group, making the membrane impermeable to the dye. Apoptotic and dead cells with compromised cell membranes do not retain calcein. Original magnification, ×400.

Initially, plasma clots were used as the supporting matrix for implantation into immunodeficient mice (Dolmans *et al.* 2007, 2008). Although follicular development to antral stages was obtained, plasma clots were found to have an inconsistent composition and to degrade quickly, thereby potentially promoting follicle loss. Therefore, researchers turned to hydrogels of alginate (Vanacker *et al.* 2012, 2014, David *et al.* 2017), which is produced from brown algae (Kedem *et al.* 2011*a*) or alginate combined with Matrigel, an ECM protein-rich gelatinous substance derived from mouse sarcoma cell lines. The alginate matrices proved to be flexible (Vanacker *et al.* 2012, 2014), but their rate of degradation was very slow, and vascularization was observed mainly in the grafts' periphery (Amorim & Shikanov 2016).

An alternative material is fibrin, a natural fibrinogen polymer, which gels in the presence of thrombin and provides hydrogels with mechanical dynamic properties (Amorim & Shikanov 2016). Fibrin is known to promote angiogenesis (Lesman *et al.* 2011). Although mouse follicles implanted in fibrin clots (Luyckx *et al.* 2013, 2014) showed low follicular recovery (Chiti *et al.* 2016), fibrin or fibrin supplemented with hyaluronic acid seemed promising for use for human preantral follicles (Paulini *et al.* 2016). The fibrin clots were more efficient at high concentrations (Smith *et al.* 2014), although live mouse pups were obtained only with the addition of VEGF (Kniazeva *et al.* 2015). Platelet lysates that contain many angiogenic factors also increased follicular recovery in fibrin clots (Rajabzadeh *et al.* 2015). By combining slow-degrading alginate with fibrin, researchers were able to

preserve the 3D follicular structure and gap junction communication between oocytes and granulosa cells (Zhou *et al.* 2015).

Embedding primary murine follicles in human and bovine decellularized ECM promoted the production of higher levels of oestradiol and inhibin B in the hosts, and the grafts initiated puberty in oophorectomized mice (Laronda *et al.* 2015).

The construction of a supporting matrix using a 3D printer with gelatin as ink has recently been described (Laronda *et al.* 2017). Preantral follicles from green fluorescent mice were embedded into these matrices and implanted into murine hosts. The implants became vascularised and the hosts gave birth to green fluorescent pups.

Others reported the use of the synthetic matrices polyetheleneglycol (PEG) superoxide dismutase (Kim *et al.* 2015), a free-radical scavenger, and polytetrafluoroethylene membrane (PTFE, TheraCyte), which is impermeable to cells but allows molecule diffusion through its pores (David *et al.* 2017). PEG superoxide dismutase supported primordial follicle survival (Kim *et al.* 2015), and PTFE effectively isolated the grafts from immune recognition, supported follicular growth and restored endocrine function to oophorectomized mice.

As artificial ovaries require the inclusion of stroma cells, the risk of cancer reseeding might not be completely eliminated (Vanacker *et al.* 2012, 2014, Soares *et al.* 2015). Fresh human medullary cells were shown to be the most efficient source of stroma cells (Soares *et al.* 2015).

In vitro *culture of ovarian follicles*

Secondary mouse follicles were first cultured at the end of the 1980s (Eppig & Schroeder 1989) and beginning of the 1990s (Cortvrindt *et al.* 1996, Spears *et al.* 1998). The first live born pups were reported in the United States of America in 1989 (Eppig & Schroeder 1989). The follicles were isolated either manually (Spears *et al.* 1998) or enzymatically (Eppig & Schroeder 1989), and growth was promoted by FSH. Cryopreserved-thawed secondary follicles also developed in culture (Cortvrindt & Smitz 2001). Additionally, FSH-induced early antral formation was described for cultured human secondary follicles after enzymatic (Roy & Treacy 1993) or mechanical isolation (Abir *et al.* 1997) (Fig. 4), and the findings were supported by later studies (Telfer *et al.* 2008, Xu *et al.* 2009*a*,*b*). Enzymatically isolated follicles require a supporting 3D matrix such as agar (Roy & Treacy 1993) or alginate hydrogel beads (Xu *et al.* 2009*a*), whereas mechanically isolated follicles do not (Abir *et al.* 1997, Telfer *et al.* 2008). However, efforts have shifted to produce culture systems for quiescent unilaminar follicles, as they account for most of the follicular population in mammalian ovaries (Gougeon

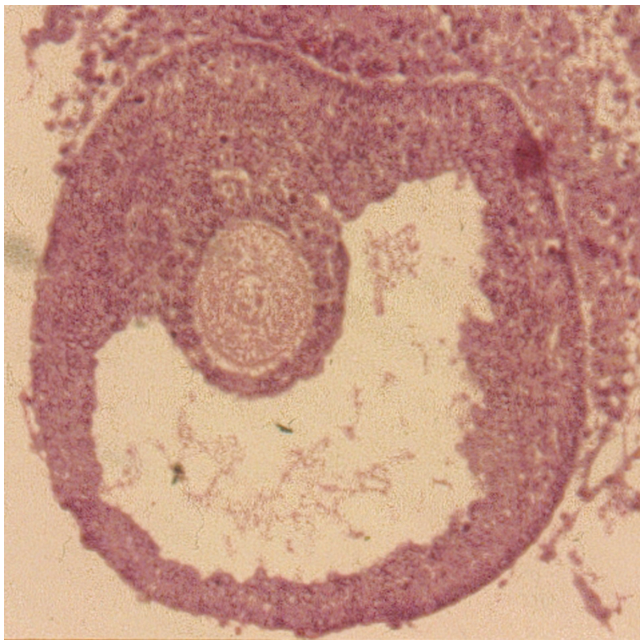

Figure 4 Section of small antral follicle obtained in culture that reached the early antral stages (850 µm) from secondary stages. Note the granulosa layer, the visibly normal oocyte, the theca layer and the antrum. Original magnification, ×200. Printed from Abir *et al.* (1997), with permission from Elsevier, licence number 4155820967732.

1996, Hovatta *et al.* 1996). The signals that promote their activation are still unclear (Abir *et al.* 2006).

Various growth factors have been shown to promote some activation of primordial follicles in humans (Abir *et al.* 2006, 2007, Garor *et al.* 2009, Kedem *et al.* 2011*b*, Streiter *et al.* 2016) including stem cell factor (Carlsson *et al.* 2006*a*), insulin and insulin-like growth factors (Yuan & Giudice 1999, Louhio *et al.* 2000, Stubbs *et al.* 2013), basic fibroblast growth factor (Garor *et al.* 2009, Wang *et al.* 2014), growth and differentiating factor 9 (Hreinsson *et al.* 2002, Kedem *et al.* 2011*b*), bone morphogenetic factor 15 (Kedem *et al.* 2011*b*) and VEGF165 with fetuin (Asadi *et al.* 2017). However, development was limited to early secondary stages. AMH activated cultured human follicles at low concentrations and inhibited growth at high doses (Schmidt *et al.* 2005, Carlsson *et al.* 2006*b*). High atresia levels were reported with the addition of leukaemia inhibitory factor to cultures of human primordial follicles (Younis *et al.* 2017).

It is now recognized that the *PI3K–PTEN–AKT* signalling pathway (Hsueh *et al.* 2015) regulates primordial follicle dormancy by sustaining high levels of phosphatidylinositol-biphosphate (PIP2) relative to low phosphatidylinositol-trisphosphate (PIP3). Growth factors probably disrupt this balance by elevating PIP3 levels, leading to the activation of quiescent primordial follicles. One PIP3-elevator was found to be deleterious to all the cultured human preantral follicles

(Lerer-Serfaty *et al.* 2013), whereas another, activated human primordial follicles (McLaughlin *et al.* 2014). Japanese researchers incubated sliced vitrified-warmed human ovarian tissue with PIP3-elevating substances ('*in vitro* activation') before ovarian implantation to women with primary ovarian insufficiency (Kawamura *et al.* 2013, 2015, Suzuki *et al.* 2015) leading to three clinical pregnancies.

The *HIPPO* signalling pathway is essential for organ size control. It is also responsible for follicular development and suppresses some tumours (Hsueh *et al.* 2015). The *HIPPO* pathway is more active in the stiff ovarian cortical region, where the primordial follicles are situated, than in the softer medullary region, leading to primordial follicle dormancy. When it is disrupted, various proteins including growth factors are activated, promoting cell growth and proliferation. Given findings that the fragmentation of ovarian tissue impairs *HIPPO* signalling, researchers suggested that the slicing procedure of ovarian tissue *per se* results in the growth of preantral follicles (Hsueh *et al.* 2015). This theory is supported by an early study showing that ovarian wedge sectioning is useful for promoting follicular growth in patients with PCOS (Stein & Leventhal 1935). Today, ovarian drilling by diathermy or laser (Farquhar *et al.* 2012) is applied for this purpose.

There are two approaches to the culture of primary and primordial follicles (Abir *et al.* 2006, 2007): using whole slices of ovarian tissue (organ culture) or using isolated primordial and primary follicles. Studies applying the first method reported the culture of human primordial follicles to the secondary stage only (Hovatta *et al.* 1997, Louhio *et al.* 2000, Hreinsson *et al.* 2002, Garor *et al.* 2009, Kedem *et al.* 2011*a*,*b*, Fabbri *et al.* 2012, Lerer-Serfaty *et al.* 2013, Lande *et al.* 2017, Younis *et al.* 2017), even after 32 weeks of culture (Fabbri *et al.* 2012). Therefore, at present, organ cultures are restricted to 1 week with the purpose of obtaining isolatable secondary follicles (Telfer *et al.* 2008, Kedem *et al.* 2011*a*, Lerer-Serfaty *et al.* 2013, Younis *et al.* 2017).

The optimal matrix for growing human primordial follicles in organ culture is unknown. Telfer and colleagues (2008) grew human primordial follicles *in vitro* without any culture matrix. Follicle survival was increased using Matrigel (Hovatta *et al.* 1997), and in later studies, better results were obtained with alginate scaffolds (Kedem *et al.* 2011*a*). Still, further improvement was reported when human ovarian slices were embedded and cultured in PEG-fibrinogen hydrogels (Lerer-Serfaty *et al.* 2013). Other ECM-like matrices have been investigated as well, human recombinant vitronectin (hrVit), small intestine submucosa (SIS) and human recombinant virgin collagen bioengineered in tobacco plant lines (CollPlant™) (Younis *et al.* 2017). CollPlant matrices and alginate scaffolds had a marginal advantage over hrVit coating and SIS matrices. In one study, slices of human ovarian tissue were cultured in test tubes under continuous agitation, and the follicles reached antral stage (Isachenko *et al.* 2006).

A two-step culturing system was utilized to grow murine (O'Brien *et al.* 2003, Jin *et al.* 2010), bovine (Mclaughlin *et al.* 2010) and human (Telfer *et al.* 2008) primordial follicles. The primordial follicles were first cultured in organ culture (ovarian slices), and secondary follicles were then isolated and further cultured. So far, *in vitro* follicular growth from primordial stage to functioning oocytes has been obtained with this method only in mice (O'Brien *et al.* 2003, Jin *et al.* 2010), with the birth of pups (O'Brien *et al.* 2003). The first mouse produced by this technique (Eppig & O'Brien 1996) sired many offspring, but it was abnormally obese, and postmortem evaluation revealed multiple internal malformations (Eppig & O'Brien 1996, 1998). In humans (Telfer *et al.* 2008) and cows (McLaughlin *et al.* 2010), this strategy resulted in small antral follicles. Recently, the same group retrieved GV-stage oocytes from human antral follicles cultured from the unilaminar follicle stage; ~10% of the initial primordial follicle oocytes underwent IVM and developed to metaphase II oocytes (McLaughlin *et al.* 2018).

In the second approach to follicular culture, a 3D supporting matrix is required because of the fragility of isolated primordial and primary follicles (Abir *et al.* 1999, 2001, 2006, 2007). In earlier studies, embedding isolated primordial follicles from mice (Torrance *et al.* 1989), cows (Schotanus *et al.* 1997) and humans (Abir *et al.* 1999, 2001) in collagen gels before culture (Green & Shikanov 2016) led to an increase in follicular size to the secondary stage without antrum development (Torrance *et al.* 1989, Abir *et al.* 1999, 2001). When isolated human primordial follicles were similarly treated, they too developed to the secondary stage (Abir *et al.* 1999, 2001). The increase in follicular size was achieved already within 24 h, probably because of the release of stroma cell inhibitors (Fig. 5). Only fully isolated human follicles grew in culture, whereas partially isolated follicles deteriorated in collagen gels, on ECM and on poly-L-lysine (Abir *et al.* 1999, Hovatta *et al.* 1999, 2001). Co-culture of human primordial follicles with stroma cells did not promote better follicular growth.

Today, alginate hydrogel beads are the most popular means of embedding and culturing isolated preantral follicles (Green & Shikanov 2016). They have been used mainly for murine follicles (Jin *et al.* 2010), but also for human unilaminar (Amorim *et al.* 2009, Camboni *et al.* 2013) and secondary follicles (Xu *et al.* 2009*a*,*b*). It seems that in primates, including humans, isolated unilaminar follicles require higher alginate concentrations than secondary follicles and murine follicles (Xu *et al.* 2009*a*,*b*, Jin *et al.* 2010, Hornick *et al.* 2012). Fibrin-alginate hydrogel beads were found to enhance the growth of encapsulated mouse secondary follicles and improve oocyte meiotic competence

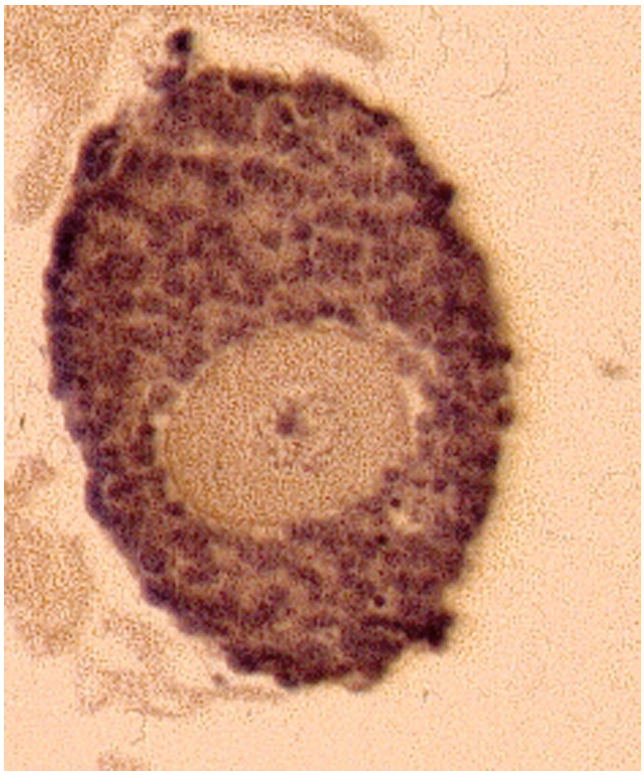

Figure 5 Micrograph of a normal secondary folliclere moved from collagen gel culture. Note that the normal oocyte is surrounded by several granulosa cell layers. Original magnification, ×400.

(Shikanov *et al.* 2009, 2011). However, in monkeys, this combination did not affect follicular survival, and the percentage of growing follicles was lower than with fibrin-only hydrogels (Xu *et al.* 2013).

Isolated mouse secondary follicles were embedded in 3D Matrigel resulting in development of antral follicles, expression of oocyte maturation genes (Xu *et al.* 2009*b*) and production of live pups (Higuchi *et al.* 2015). Hyaluronan, with or without ECM, increased oestradiol production of murine secondary follicles (Desai *et al.* 2012). PEG gels also maintained follicle morphology and accommodated a 17-fold follicle size increase of mouse follicles (Ahn *et al.* 2015). Others have attempted less successful non-scaffold systems mainly for rodent-isolated follicles (Green & Shikanov 2016).

Concluding remarks

Until the late 1990s, there was relatively little awareness among clinicians and patients of the gonadotoxic effects of anti-cancer therapy. Since then, major improvements have been made in various ARTs that can be applied for fertility preservation. In the future, it is expected that effective means to avoid reseeding of malignant cells with ovarian grafts such as artificial ovary and an *in vitro* culture system for primordial follicles will become available.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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