Best Practice & Research Clinical Endocrinology & Metabolism xxx (2018) 1–14

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

9

Cryostorage and retransplantation of ovarian tissue as an infertility treatment

Christiani A. Amorim, DMV, PhD, Professor [a, *],
Ellen Cristina Rivas Leonel, MSc [a, b], Yousri Afifi, MD, PhD [c],
Arri Coomarasamy, MD, M.R.C.O.G., Professor [d, e],
Simon Fishel, PhD, FRSB, Professor [f]

[a] *Pôle de Recherche en Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Avenue Mounier 52, bte. B1.52.02, 1200, Brussels, Belgium*
[b] *Department of Biology, Institute of Biosciences, Humanities and Exact Sciences, São Paulo State University, Rua Cristóvão Colombo, 2265 Jardim Nazareth, 15054-000, São José do Rio Preto, São Paulo, Brazil*
[c] *Department of Obstetrics and Gynaecology, Birmingham Women's NHS Foundation Trust, Birmingham, United Kingdom*
[d] *Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, B15 2TT, United Kingdom*
[e] *Birmingham Women's and Children's NHS Foundation Trust, Mindelsohn Way, Birmingham, B15 2TG, United Kingdom*
[f] *CARE Fertility Group, John Webster House, 6 Lawrence Drive, Nottingham Business Park, Nottingham, NG8 6PZ, United Kingdom*

ARTICLE INFO

Article history:
Available online xxx

Keywords:
cryopreservation
transplantation
ovarian tissue
ovarian follicles
fertility preservation
cancer patients

While still considered an experimental procedure in most countries, ovarian tissue cryopreservation and transplantation has been increasingly applied worldwide to restore fertility in patients with malignant and non-malignant pathologies with risk of premature ovarian insufficiency. It has yielded more than 130 live births up to now and almost all transplanted patients recovered their ovarian function. This study summarizes ovarian tissue cryopreservation and transplantation indications, procedures, their efficacy and main results and proposes different strategies to improve this strategy. Although the main focus of this study is on ovarian tissue cryopreservation and transplantation as a strategy to restore fertility, we believe that it is also important to discuss other applications for this approach.

* Corresponding author.
E-mail addresses: christiani.amorim@uclouvain.be (C.A. Amorim), ellenleonel@yahoo.com.br (E.C.R. Leonel), yousri.afifi@bwnft.nhs.uk (Y. Afifi), a.coomarasamy@bham.ac.uk (A. Coomarasamy), simon.fishel@carefertility.com (S. Fishel).

https://doi.org/10.1016/j.beem.2018.09.002
1521-690X/

Introduction

Recent progress in oncology has significantly increased the survival rates in cancer patients, giving rise to a new issue for cancer survivors: fertility restoration after disease remission. In women, treatments, such as chemo/radiotherapy, can be very harmful to the ovaries, often causing loss of both endocrine and reproductive functions. For this reason, different strategies have been proposed to preserve/restore their fertility. When gonadotoxic treatment cannot be delayed, ovarian tissue cryobanking appears to be the most promising way of preserving a patient's fertility. This technique is also the sole means of safeguarding fertility in prepubertal girls. At present, autotransplantation is the only option able to re-establish ovarian function from cryopreserved ovarian tissue in cancer survivors.

Ovarian tissue cryopreservation (OTC) and transplantation (OTCT) has also been increasingly proposed to patients with non-malignant pathologies with risk of premature ovarian insufficiency (POI) [1]. Indeed, OTCT has been offered to women undergoing oophorectomy for benign ovarian conditions (ovarian tumours or torsion and endometriosis) or bone marrow or stem cell transplantation (patients with thalassemia major or aplastic anaemia), patients with endocrine or genetic diseases (Turner syndrome and galactosemia) or autoimmune diseases that required chemotherapy (severe lupus carditis, glomerulonephritis and Beḥcet's disease) [1,2]. OTCT in patients with oncologic or non-oncologic diseases has resulted in restoration of endocrine function in around 93% of cases [3] and more than 130 live births to date [4]. Despite these successful results, it is still considered an experimental procedure in most countries. Hopefully, with the increasing amount of data demonstrating its efficacy and safety, it will become an established practise in the near future, as it already is in Israel [5].

Although the most common indication for OTCT is fertility restoration, it can be also proposed as a strategy to postpone menopause in healthy women [6]. A couple of centuries ago it was unusual for a women to live long enough to experience menopause, nowadays with the significant increase of life expectancy, women may spend almost half of their lives in menopause. This syndrome can result in different pathological conditions that permanently affect women's wellbeing, such as osteoporosis, heart diseases, diabetes, hypertension, sexual dysfunction, dementia and depression [7]. OTCT could be a physiological option to provide serum levels of female hormones, avoiding the risks linked to pharmacological hormone replacement therapy whilst promoting a positive impact on women health status and quality of life. It is also worth mentioning that postponing menopause would result in a significant decrease in healthcare costs associated with its side effects.

While an increasing number of centres worldwide have been offering OTCT to their patients, there is still no consensus on the cryopreservation and transplantation procedures. Probably because protocols have been empirically developed and vary among laboratories, and we still do not fully understand the effect of cryopreservation and transplantation on the ovarian tissue. OTCT success rate varies from 23% to 41% [4]. Finally, it is also important to highlight that most centres do not have standardized guidelines for quality control and quality assurance when implementing an OTC program and this can affect the outcomes of this strategy [8].

In this review, we will summarize OTCT procedures, their efficacy worldwide, propose improved strategies, and discuss the potential for further applications.

Cryopreservation procedures

Ovarian tissue retrieval and preparation prior cryopreservation

Despite of being a relatively simple procedure, ovarian tissue retrieval and preparation should be carefully executed in order to avoid any unnecessary damage to the biopsy. Tissue preparation includes removal of the medullary part and cutting the cortex into a pre-established size that allows for permeation of cryoprotectant agents (CPA) and effective reestablishment of blood perfusion and follicle activity after grafting, and to avoid excessive follicular loss [9].

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

Slow freezing versus vitrification

There is no consensus regarding the optimal procedure to cryopreserve ovarian tissue. While an increasing number of groups have been adopting vitrification procedures [10], most centres still apply conventional freezing, which has resulted in a greater number of live birth. Interestingly, human ovarian tissue freezing protocols [12,13] are usually adaptations of the protocol developed by Gosden et al. [11] for sheep ovarian tissue. In most protocols, DMSO is the CPA of choice [12–15], but some groups use propylene glycol [16,17] or ethylene glycol [18]. Sometimes, sucrose is also added [16,18] with the aim to decrease the risk of cryoinjury.

On the other hand, since vitrification requires higher concentrations of CPAs, which can be potentially toxic to cells and follicles, procedures for human ovarian tissue usually apply a combination of different permeable CPAs [17,19,20] to decrease the specific toxicity of individual CPAs [21]. However, the only reported live birth obtained from vitrified ovarian tissue was when a single permeable CPA (ethylene glycol) was used [22,23].

It is important to bear in mind that it is not possible to affirm which is the optimal OTC protocol. According to Meirow et al. [24] and Suzuki [25], since we cannot quantify the primordial follicle population in the ovarian fragments before and after cryopreservation and transplantation, it is impossible to calculate the protective effect of a given OTC protocol.

Main findings

Since there is no worldwide registry of ovarian autotransplants [10], we do not know precisely the success rate of OTC. However, Gellert et al. [26] examined all peer-reviewed reports of OTCT and showed that there are 318 transplantations of cryopreserved ovarian tissue worldwide. In this group, 95% of the patients recovered their ovarian function and the pregnancy rate was as high as 40.5% [26]. Regarding the graft life span, in some cases, it can be more than 10 years [27].

Validation of new cryopreservation protocols

Currently, there is no optimal procedure to cryopreserve human ovarian tissue. While a few of the current protocols can yield pregnancies and live births, all of them offer different types and degrees of damage to ovarian tissue and follicles [21]. Aiming to improve follicular survival, numerous groups worldwide have been working on the development or optimization of OTC protocols. While at first some results seem encouraging after an initial analysis of follicle morphology [28], ultrastructure [29], viability [30], the conclusive proof of ovarian tissue function after thawing/warming are follicular development and hormone synthesis. For that, the optimal approach to evaluate an OTC protocol is the transplantation. Xenotransplantation of thawed/warmed tissue to an immunodeficient animal allows the assessment of ovarian tissue activity reestablishment and follicle ability to survive and develop after cryopreservation. It is more relevant to the clinical setting in comparison to in vitro culture, since it simulates the autotransplantation procedure in terms of post grafting ischemic stress [31]. Using animal models for studies of human reproduction, such as non-human primates [32], sheep [33] and cows [19] is another excellent strategy to validate OTC protocols as it can evaluate restoration of ovarian function and fertility.

Transplantation of ovarian tissue

Surgical aspect of ovarian tissue preservation

Surgical technique of ovarian tissue retrieval and transplantation are crucial for the success of OTC. As OTC is a developing process, there is no consensus on the technique in both literature and clinical practice. The principles of surgical techniques are based on three points: (i) ovary anatomical and histological architecture; (ii) microsurgical principles of the conservative surgery, which aims to preserve the ovarian and graft function by reducing the traumatic and ischaemic damage, and (iii) biological principles of graft survival and its incorporation into the host tissue. We will outline the current

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

reported techniques with the critical assessment of its impact and success and propose a standard technique to be adopted.

Ovarian tissue retrieval

Ovarian tissue retrieval (OTR) aims to collect enough tissue with follicular volume that could stand some loss (due to ischemia or freezing) and still can function after transplantation for a reasonable duration of time. On the other hand, OTR should also have a minimal impact if any on the existing and future ovarian function. An ovarian function could be affected due to the reduction in the reserve or due to direct or energy mediated damage of the remaining ovarian tissue.

OTR could be done by removing one of the two ovaries (oophorectomy) or removing part of the ovarian cortex (partial decortication) or having small ovarian biopsies. A systematic review of all published literature related to OTR techniques concluded that unilateral oophorectomy was the chosen technique in 11% of cases, partial decortication (removal of 1/3 to 1/2 of one ovary) in 79% of cases and ovarian multiple biopsies in 8% of cases [34].

Removal of the whole or most of one of the ovaries is expected to be associated with a significant reduction of the ovarian reserve. However, its impact on the ovarian function (hormonal and fertility) is far less than expected. The three largest population studies [35–37] of the age of menopause in patients who had unilateral oophorectomy in comparison to those with intact ovaries revealed no significant difference in the risk of early or premature menopause between the two groups with around 1-year difference in the age of menopause. The studies included different populations with nearly similar outcomes. However, a study with smaller numbers of patients suggested an increased risk of early menopause after unilateral oophorectomy [38]. In the view of this, partial decortication or biopsies may be preferable than oophorectomy, except in cases with a very high risk of premature ovarian failure [3,4].

There is contradicting evidence regarding the impact of ovarian surgery (cystectomy, endometrioma excision, wedge resection) on ovarian reserve. The studies, which showed some impact, have been attributed to (i) loss of some follicular tissue; (ii) traumatic injury of ovarian tissue or its blood supply, or (iii) energy-mediated damage of the ovarian tissue or its blood supply [39]. All haemostatic methods used during ovarian cystectomy have been shown to have a potentially harmful effect on the nearby ovarian tissue and could possibly compromise ovarian reserve. Deckers et al. [40] reported a systematic review of all haemostatic methods during endometrioma excision and its impact on ovarian reserve. They suggested that diathermy is more detrimental to ovarian reserve than alternative haemostatic methods. According to the best available evidence, the use of monopolar coagulation should be avoided and the bipolar diathermy should be used with cautious, even avoided when possible during endometrioma excision in women who desire to have children. The same conclusion was made by the studies looking at ovarian cysts in general. It makes sense to use such evidence to address the surgical technique of the ovarian decortication or ovarian biopsy on the function of the remaining ovarian tissue.

Another important aspect of the retrieval is the adhesiogenesity. Adhesion formation can be associated with pain and distortion of tubo–ovarian axis, which might compromise the chance of spontaneous conception.

The following technique of ovarian decortication is developed by ProFaM (UK) and aims to develop the evidence base standard technique for decortication:

- Four port laparoscopy is used and the ovary is gently supported;
- Diluted vasopressin is injected by the fine needle to stretch the ovarian cortex and reduce the bleeding from the ovarian tissue;
- 2/0 stay stitch of the ovary is used for manipulating the ovary and applying traction on the cortex during the retrieval;
- Outlining the strip by using a curved micro scissor, 1–1.5 mm deep cuts of rectangular strip account 1/3 to ½ of the ovary as agreed in the consent;
- Shaving the cortical strip from the underlying hilum with use of the scissor is done;
- Retrieval of the tissue after pulling on the stay stitch through opened valve trocar;
- One or two simple inverted stitches using prolen 5/0 for edge approximation.

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

Ovarian tissue transplantation

Graft take is a term used to describe the process of incorporation of the graft tissue into the host bed. There are four stages of the process of graft take: (i) fibrin adhesion; (ii) plasma imbibition; (iii) revascularisation with inosculation and capillary ingrowth, and (iv) remodelling with complete revascularisation and adhesion in normal histological architecture. The success of graft take depends on the extent and speed of the vascular perfusion.

Ovarian tissue transplantation (OTR) is either orthotopic or heterotopic (Table 1). Orthotopic transplantation implies the grafting of cortical strips to their natural site (the ovary) or very close to the natural site with similar environmental condition (pelvic peritoneum or broad ligament). Heterotopic transplantation implies grafting the ovarian tissue outside the natural location and environment. Different sites have been reported including forearm, abdominal wall, subperitoneal space and chest wall [41].

Positive graft survival has been reported in both types of transplantation, including hormonal and follicular activities (Table 1). However, all but two of the reported pregnancies happened in the patients having orthotopic OTT suggested the very significant superiority of this site for the fertility restoration [26]. This has been explained by a study showing that oocytes collected from heterotopic grafted ovarian tissue exhibited lower embryo developmental potential than orthotopically OTT [26]. Therefore, one can conclude that orthotopic OTT is the recommended method for fertility restoration and it can also be the standard method for hormonal restoration in the absence of fertility desire.

Orthotopic OTT has been reported with similar success either in the ovary (after decortication) whether the ipsilateral or the contralateral one of the retrieval side, or the peritoneal pouch in the region of the pelvic wall close the ovary or in combinations of these options. The systematic review of the reported transplantation sites revealed that 86% were orthotopic, 8% were heterotopic and 6% were combined orthotopic and heterotopic. In the orthotopic group, nearly 40% was ovarian, 37% was peritoneal and 24% was combined ovarian and peritoneal [26].

There is a broad consensus regarding the route used for surgical access. Nearly all of the centres favoured the laparoscopic access. However, robotic surgery and mini laparotomy have also been reported.

The amount of transplanted tissues depends on the amount of the frozen tissue, desired frequency of transplantation and aim of transplantation. Gellert et al. [26] reported that the average amount of transplanted tissue at the first OTT corresponded to 46% of the total amount of the frozen tissue, with an average area of 294 mm. In the second OTT, an average amount of 37% of the frozen tissue with an average of 263 mm, while the third transplantation used an average of 38% with an average area of 455 mm.

Three essential steps with variable techniques have been reported for OTT:

1 Extracorporeal preparation of the strips either by microscopic suturing to produce a bigger strip using nylon 9/0 [42] or suturing the strips into biological scaffold-like Alloderm [43] to produce a bigger piece and might help with revascularisation. Many units are not using either technique [3].

Table 1
Orthotopic versus heterotopic OTT.

	Heterotopic OTT	Orthotopic OTT
Nature of procedure	Less invasive	More invasive
Site of transplantation	Forearm, abdominal wall, sub-peritoneal	Ovary and/or peritoneal pocket
Environment for follicular development	Suboptimal	Optimal
Spontaneous pregnancy	Unfeasible	Very feasible
Fertility	Not well demonstrated	Well demonstrated
Access for monitoring	Easy access	May be difficult
Hormonal function	Well demonstrated	Well demonstrated
Duration of graft	6 months to 7 years	2–10 years
Removal of the graft	Very feasible	Challenging
Future use	Hormonal replacement	Fertility restoration

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

2 Decortication of the ovary by removing similar size strip of the non-functioning cortex to the intended graft. Strict haemostasis is undesirable, as little bleeding will produce a better fresh host environment for the graft and better revascularisation.
3 Fixation of the graft to the ovarian decorticated host tissue. This can be achieved either by micro-suturing or glue fixation or both depending on the local protocol [3,4].

Peritoneal transplantation can be carried out immediately after peritoneal pocket preparation or as a second transplantation in a second surgical procedure. One peritoneal pocket has been usually used but two-pocket transplantation has also been reported. Peritoneum was incised without coagulation. Management of the strips and its fixation are similar to above. Peritoneum is either closed over the strips or left for spontaneous adaptation. Suturing will provide better fixation which might improve the graft take. However, it might increase the trauma or initiate a granulomatous reaction, which can affect the survival [3]. Further research is required to provide the best way of OTR.

To improve the revascularisation, there are two supplementary steps that can be applied:

1 Stem cell infiltration to the host tissue [44];
2 Two surface revascularisation either by tunnelling the ovarian tissue under the cortex or sticking vascularised omental graft over the transplanted tissue.

The period from OTT to restoration of the graft function has been on average of 4 months with 1.5 months standard deviation [3,26]. Following transplantation, it is recommended to commence the patients on hormone replacement to lower the high follicular stimulation hormone for two months in order to avoid the overstimulation of the graft once it resumes its activities (graft burn out).

Bechman et al. [45] reported one single complication linked to transplantation surgery in their centralised network for OTCT, the FertiPROTEKT. In 37 OOT procedures, only 1 (1.4%) had a conversion from laparoscopy to laparotomy with no other intraoperative or postoperative complications. The complication rate of less than 1% has been reported as well by Meirow et al. [46]. We can therefore conclude that OCT is a safe technique with low complication rate similar to the risk of diagnostic laparoscopy.

Explicit histological examination of the ovarian tissue before transplantation was reported in 50.7% of the transplantation [3].

Cryopreservation and transplantation of ovarian tissue: main centres and networks worldwide

The success of OTCT has led to numerous service providers setting up and offering the services to various patient groups, particularly girls and women requiring fertility preservation before cancer treatment. Although professional bodies have taken a conservative view, still regarding OTC as an 'experimental' technique, clinical practice has moved forward; for instance, robust OTC clinical services have been in place for over a decade in Belgium, Denmark, Israel and Spain [1,3,5,26,27]. In this section, we provide a brief overview of some of the main centres and networks offering OTC.

We have also attempted to capture the reported success rates of the main centres and networks, although this endeavour is made difficult by at least three factors. Firstly, there is often a long interval between ovarian tissue retrieval and transplantation; although several thousands of women have now had ovarian tissue preservation, only a few hundreds have had transplantation [3,26]. Such a small sample size results in imprecise estimates of success. Secondly, there is much heterogeneity in the population (e.g. indication for OTC, female age, baseline ovarian reserve, and co-morbidities) and the techniques (e.g., amount and dimensions of the surgical specimen retrieved, freezing and thawing techniques, and transplantation approaches) that providing a single success rate is of limited practical value. Thirdly, there is no consistent reporting of the success rates by the various centres, presumably at least partly because of the first two issues, making it difficult to make an overall assessment of success rates.

European centres and networks

'The ESHRE Working Group on Oocyte Cryopreservation in Europe' carried out a questionnaire survey of 34 European countries in 2015 to understand oocyte and ovarian tissue preservation practices

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

at the country level [47]. The questionnaires were returned by 24 countries, of which 12 reported to have an OTC service (Table 2); this is likely to be an incomplete list as countries like UK and Spain (which are known to have OTC services) were absent from the list.

During the 5 years from 2010 to 2014, a total of 4474 OTCs and 185 OTTs were reported in the 12 European countries. As these data exclude UK and other countries that did not complete the questionnaire, the true numbers are likely to be over 5000 OTCs and over 200 OTTs during this period, giving estimated averages of 1000 OTCs/year and 40 OTTs/year in Europe. For comparison, 34,705 oocyte cryopreservations were reported during this 5 year period, of which 10.9% (~3800) were for women with 'serious' conditions such as cancer. These figures thus indicate similar numbers of oocyte and ovarian tissue cryopreservation procedures being carried out for cancer patients.

Germany, France and Belgium and Denmark have the greatest experience with OTC and OTT.

Germany: FertiPROTEKT

FertiPROTEKT was originally established in Germany in 2006 and has now expanded to include other German-speaking countries, Austria and Switzerland. It is a network of over 100 university and non-university centres. FertiPROTEKT provides clinical guidelines, sets standards of practice, offers practice workshops, and audits practice and outcomes. FertiPROTEKT network is a considered a robust blueprint for an OTC network, and a similar model has been adopted for a regionally centralised cryobank in Beijing, China [48].

FertiPROTEKT accepts girls and women of up to 37 years with an age-appropriate ovarian reserve [49], and excludes patients with high risk for ovarian metastasis (e.g. haematological malignancies). Pregnancies can be achieved naturally or through in vitro fertilization. For instance, FertiPROTEKT Bonn cryobank reported a success rate of 9 pregnancies in eight patients from a total of 24 women who had transplantation, which is consistent with wider FertiPROTECT pregnancy rates of approximately 30% of transplanted women [49].

Belgium

The pioneering Belgian OTCT group from Catholic University of Louvain was the first to achieve a live birth after transplantation of frozen-thawed ovarian tissue in 2004 [12]. They have continued to be one of the leaders in the field with important research and refinements in the surgical and laboratory aspects of OTC and OTT. In the 15 year period from 1997 to 2012, 582 patients had ovarian tissue preservation and by 2012, 11 patients had undergone transplantation. Currently, they have reported 15 live births after OTCT and a pregnancy rate of 33% [50].

Table 2
Numbers of ovarian tissue cryopreservation and transplantation procedures in 12 European countries (modified from Shenfield et al. [47]).

Country	Ovarian tissue cryopreservation between 2010 and 2014	Ovarian tissue transplantation between 2010 and 2014
Austria	147	1
Belgium	624	23
Denmark	346	34
Estonia	38	0
Finland	57	4
France	1096	29
Germany	1499	69
Italy	399	11
Netherlands	56	5
Norway	100	3
Slovenia	14	0
Switzerland	98	6
Total	4474	185

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

France

France is only second to Germany in the number of OTCs carried out in Europe (Table 2), yet there is limited information on coverage across France and success rates. The available evidence suggests the success rates of OTT are similar to other European countries; for example, the DATOR group, which developed the French protocol for ovarian tissue autografting, reported six children born after 15 ovarian tissue transplantations, performed between 2007 and 2016 [51].

United Kingdom

Ovarian tissue preservation is offered in Edinburgh [52], Oxford and Southampton in the UK. The Edinburgh team has carried out important research into efficient tissue freezing and long-term storage of ovarian tissues. In 1994, they were the first to demonstrate that spontaneous ovarian cycles and fertility can be restored by auto-transplantation of ovarian cortex in an animal [11]. The UK coverage of OTC service, however, remains patchy. Many girls and women who may benefit from OTC are not offered the procedure, even when they have no other alternatives for fertility preservation (for example, pre-pubertal girls). A new national service is currently under development through a private-public partnership.

Non-European centres

OTC and OTT are available in many non-European countries, including the USA, Israel, South Korea, Japan, China and Singapore. Israel is one of the leaders in OTCT [5,24,46,53] and this technique is no longer considered an experimental procedure. The Fertility Preservation Centre at Tel-Aviv University, Israel, published its success rates in 2016: after transplantation ($n = 20$), there was endocrine recovery in 93%, conceptions (both natural and IVF) in 53%, and live births in 32% [5]. On the other hand, there is limited published evidence on success in the other aforementioned countries [22,23,42,54–59].

Future applications of this strategy

Recovery of ovarian function - teenager patients

Preserving fertility used to be considered only for those at risk of becoming sterile as collateral damage to potentially life-saving medical therapy. Further, infertility was considered of secondary importance to trying to save a life, and many patients were (and still many are) not referred on to specialist clinics for fertility preservation. It soon became apparent by survivors of sterilizing cancer therapy that a major effect on their relative quality of life was how they felt about being sterile. In such cases egg donation was the only option for those wishing to become pregnant. In recent years embryo freezing (if appropriate) following by technical improvements to encourage egg freezing became an option for patients with benign disease and cancer, which was endorsed by the American Society for Reproductive Medicine [60]. However, these methods are only appropriate for postpubertal women, and for those for whom cancer therapy can be delayed. OTC is remains the only option for perpubertal girls, women who cannot delay chemotherapy or those who should not undergo follicular stimulation for egg retrieval; indeed, several rounds of egg retrieval may be essential to maximize opportunity of a live birth [61]. As increasing numbers of prepubertal girls and postpubertal women survive cancer, and more women with benign disease who may lose ovarian function prematurely seek efficacious methods to preserve their fertility, alternatives to egg freezing have become a clinical imperative. The prospects of using OTC today not only removes the need for ovarian stimulation, it provides the opportunity for conception in vivo as well as in vitro for females of all ages who need to preserve their fertility.

Does the ovary resumes its function normally?

Following OTT ovarian function can be measured by follicular growth, recurrence of menstruation but, most importantly by successful pregnancies. In a recent review [26], 95% of OTT (ovarian tissue

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

transplantation) cases (n = 318) could be classified as having restored ovarian function, which took on average 4.0 months for follicular function. They reported 131 pregnancies with 46% (87) live births, all of whom underwent bilateral oophorectomy. Forty-four deliveries occurred from spontaneous conception, and of these 84% were menopausal before pregnancy. Of the 43 deliveries following IVF 75% were menopausal before successful conception. It was further reported that in three women who were menopausal before OTT, each had a consecutive pregnancy resulting in three contiguous deliveries of healthy babies. Donnez et al. [3] reported a woman of 17 years who delivered three times after one orthotopic OTT in the ovary following OTC for a neuroectodermal tumour. A woman of 22 years recently gave birth following OTC when aged 12 and OTT at 20 following IVF at the CARE Fertility Clinic, London.

A woman having had OTC aged 24 conceived 4 times after orthotopic transplantation in Israel [61] and in Denmark a woman having had OTC aged 27 due to Ewing Sarcoma had three healthy babies, the third nearly six years after six pieces of OTT [62].

Predicting the life-span of grafts has been difficult because of varying parameters of OTC, the women themselves, such as their age, and grafting techniques employed in the different clinics worldwide. Women of the same age may have different ovarian size by as much as 4–12 ml volume, and the period of ovarian function may vary from one year to up to 10 years [27]. Even when the most effective and consistent OTC and grafting methods are developed individual female circumstances will remain. This will always make accurate predictions of outcome as difficult as any reproductive program, such as IVF for example.

However, because of current success, and in different clinics around the world, experienced practitioners recently called for OTC and OTT no longer to be considered experimental [63].

Menopause postponement

Successful OTC and OTT may eventually be of considerable health benefit to women. For the first time in human evolution it is expected that most women will be in the menopause considerably longer than at anytime in history. Life expectancy for most girls born today in advanced nations is expected to reach and exceed 100 years [64]. The population of US women older than 80 years is expected to increase by more than 15 million over the next three decades [65], and demographic data do not support life spans beyond the eighth decade as a frequent naturally occurring event [66,67]. Octogenarians of bygone eras were only those who were the most vigorous [68], but contemporary medical science does not favour only those best selected to survive menopause-induced somatic aging [69]. Such population dynamics, coupled with the sequalae of hypo-oestrogenic environment of menopause such as increased risk of cardiovascular disease, osteoporosis, vasomotor symptoms, depression, urinary incontinence, sexual dysfunction, diminished cognitive function [70–77], for example, is a major increasing health economic issue, especially in economically advanced nations. Examples from North America demonstrate that just for osteoporosis the medical expense in Canada was estimated to rise from Can$1.3 billion in 1993 to approximately Can$32.5 billion in 2018 [78], and in the USA the cost of treating broken bones was approximately $18 billion in 2006 [79] highlight the concerns.

The risks of the long term hypoestrogenic state may be alleviated to some extent by hormone replacement therapy (HRT) when started early in perimenopausal state, but this is believed to benefit women for only a relatively short number of years of the expected menopausal period; and HRT is not for all women. The question of increased risk of breast cancer and cardiovascular disease has been raised but this has been shown to have none to marginal increase [70]. Furthermore, although HRT is designed to mimic monthly ovarian steroid injection, drug therapy never equates to natural rhythmical transitions of physiological hormone secretion. Hence the call for ‘new strategies for long-term osteoporosis prevention’ [80]. OTC/OTT would make use of the huge endogenous store of ovarian follicles that would otherwise undergo atresia, and over time improved cryopreservation techniques is likely to improve this opportunity.

Have we now reached the point where declining birth rates, aging first time mothers and evidence of increasing infertility, along with the need to develop new strategies for postponing the menopause? We would argue ‘yes’. It is well established that women with one ovary have no reduction in their fertility potential as a woman with two ovaries [81]. Although about 20% fewer mature follicles are

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

produced by women with one ovary, there is a compensatory hypertrophy equally reducing atresia [81]; and the age at menopause is only marginally affected by unilateral oophorectomy, by around one year [35,36] thereby having little effect on fertility per se should the tissue be removed when young. Balanced against the prospect of a significant period of menopause postponement this would support the medical benefit and use of OTC/OTT as a potential health economic strategy. Reports of women having experienced at least a decade of menstrual activity following a menopausal state, and the report from Anderson and Kirstensen [80] of a woman experiencing more than 10.5 years having used only 62.5% of her cryopreserved ovarian tissue, makes OTC/OTT seem eminently sensible. The evidence thus far has been gathered mainly from women who have not had their ovarian tissue stored at a young age for the purpose of postponement of the menopause, but for fertility preservation, usually for cancer or benign disease. From the discussions above there is every good reason to predict that the preservation of young ovarian tissue that was not utilised for fertility and becomes available solely for menopause postponement may procure beneficial longevity of the premenopausal on most women [80,82].

Ethics

Would it be ethical to remove and cryopreserve ovarian tissue for menopause postponement? Would it be ethical, or less unethical, if OTC were undertaken for the purpose of fertility preservation, for medical or non-medical purposes, but used for postponing the menopause? Indeed, would it be unethical to prevent a woman with stored ovarian tissue from using it to postpone the menopause? What ethical principles are at stake?

Autonomy of patients has been one of the five pillars of ethical consideration. People have (or should have) a right to their personal reproductive proclivity and healthcare options, and to use whatever means is technically possible within the confines of what is deemed safe and appropriate medical practice. Notwithstanding this ethical right, mixed regulation and legislature across varying geographical regions in the field of assisted conception in particular often places such decision making outside of true ethical principles and more in the realm of social acceptance; which itself changes over time. As a right, with proper informed consenting procedures patients should be free to make choices; and those choices may indeed be a hedge on their future health opportunity, especially if medical science appears to be moving conclusively in that direction. Exampling assisted conception further; oocyte preservation for fertility preservation a decade ago would not be recommended except in cases of medical emergency because the efficacy of the technology at that time was poor. Today, with advanced vitrification procedures guidelines have changed and egg freezing for non-medical fertility preservation is welcomed and practiced by thousands of women. Would women who would wish to consider OTC today for either or both fertility preservation and delaying menopause, and who were adequately informed of the state of knowledge be thankful to be denied if indeed in a decade's time their tissue could have procured an additional 10–15 years pre-menopausal physiology? Are we currently at the point where, in appropriately experienced hands it could be considered unethical to deny those requesting OTC?

Could this position bring us to beneficence, such that the balance of risks and future benefit may support intervention requested by the sufficiently informed patient? We could argue that the current state of OTC/OTT in experienced hands offers the opportunity to promote patient well-being, not just physically, but emotionally - especially in high-income countries where there is rising concern over fertility, and, possibly within a decade, apprehension over having little other than HRT to offer women approaching 40 years in the menopausal state.

The principle of non-maleficence (*primum non nocere*) 'do no harm' is essential to any ethical consideration. As described, ample data now exists demonstrating no material effect on a woman's fertility should she have one of two ovaries removed, and no evidence of only part of one of two ovaries. The possible effect of an induced early onset of menopause by approximately one year is balanced against the potential to delay menopause for considerably much longer. Arguments against the use of OTC stating that survival is not uniform, varying from a few months to several years, are unsatisfactory. In vitro fertilization, for example, is not denied because many women fail to achieve a pregnancy, or there is variable outcome such as failed egg collection or failed fertilisation; not to mention treatments for terminally ill patients that reduce quality of life with little hope of significantly

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

prolonging life. Well defined data now exists on the material benefit of OTC/OTT in high proportion of patients.

It is true today, that OTT/OTT for non-medical reasons – and at this juncture includes the postponement of menopause – would be unlikely to satisfy 'justice': the principle of fairness and equity. But neither does spreading the burden of cost equally across society of several key therapies or even assisted conception in all its forms adequately adhere to this principle. The cost and the manner in which medical science has developed in modern times has precluded this; but it is to be hoped that the benefits that may accrue from OTC/OTT will over time become economically sensible for many societies offering all encompassing healthcare options.

Last, but no least, the principle of 'veracidity' must be seen to be adhered to at all times.

What about the concerns of much older women who, still menstruating, may become pregnant – heralding the feared era of geriatric obstetrics! There will be several strategies to deal with this, each will be personalized. Initially graft survival will be considered with the prospect of its longest surviving potential on the parameters available, and in association with the age of the woman. If the OTT is solely for hormone replacement consideration heterotopic transplantation is an option. If women do not wish to have menstrual bleeding then endometrial ablation is also an option, but as a further medical procedure that requires detailed discussion.

Practice points

- OTCT has been successfully applied worldwide to preserve fertility in cancer patients and women with different types of benign conditions that have a negative impact on their fertility.
- Proper assessment of the risk of ovarian failure, existing ovarian reserve and patient choice have to be taken into account for the amount of the ovarian tissue needs to be retrieved
- Microsurgical principles need to be adopted to reduce the risk of graft's damage and compromising ovarian function.
- Ultimately, OTCT could be also be applied as an alternative to recover ovarian function in teenager patients and postpone menopause in older women.

Research agenda

- Cryopreservation and transplantation procedures for human ovarian tissue need to be optimized.
- Creation of a worldwide OTCT registry is recommended to aid standardize outcomes.
- Study on systematic and local factors that can improve the revascularisation of the graft.
- Development of scaffolds to aid grafting of smaller ovarian tissue fragments.

Funding

The authors would like to acknowledge the financial support from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for the grant (2016/22947-8) to E.C. Rivas Leonel. C.A. Amorim as a research associate for the FRS-FNRS.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Jadoul P, Dolmans MM, Donnez J. Fertility preservation in girls during childhood: is it feasible, efficient and safe and to whom should it be proposed? Hum Reprod Update 2010;16:617–30.

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

[2] The Practice Committee of the American Society for Reproductive Medicine, Practice Committee of the Society for Assisted Reproductive Technology. Ovarian tissue and oocyte cryopreservation. Fertil Steril 2008;90:S241–6.
[3] Donnez J, Dolmans MM, Pellicer A, et al. Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. Fertil Steril 2013;99:1503–13.
[4] Donnez J, Dolmans MM. Fertility preservation in women. N Engl J Med 2017;377:1657–65.
[5] Meirow D, Ra'anani H, Shapira M, et al. Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. Fertil Steril 2016;106:467–74.
[6] Amorim CA, Gonçalves PB, Figueiredo JR. Cryopreservation of oocytes from pre-antral follicles. Hum Reprod Update 2003;9:119–29.
[7] Dalal PK, Agarwal M. Postmenopausal syndrome. Indian J Psychiatr 2015;57:S222–32.
*[8] Andersen CY, Bollerup AC, Kristensen SG. Defining quality assurance and quality control measures in connection with ovarian tissue cryopreservation and transplantation: a call to action. Hum Reprod 2018;33:1201–4.
[9] Prasath EB. Ovarian tissue cryopreservation: an update. J Hum Reprod Sci 2008;1:50–5.
*[10] Ladanyi C, Mor A, Christianson MS, et al. Recent advances in the field of ovarian tissue cryopreservation and opportunities for research. J Assist Reprod Genet 2017;34:709–22.
[11] Gosden R, Baird DT, Wade JC, et al. Restoration of fertility to oophorectomized sheep by ovarian autografts stored at -196 degrees C. Hum Reprod 1994;9:597–603.
[12] Donnez J, Dolmans MM, Demylle D, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet 2004;364:1405–10.
[13] Poirot CJ, Martelli H, Genestie C, et al. Feasibility of ovarian tissue cryopreservation for prepubertal females with cancer. Pediatr Blood Canc 2007;49:74–8.
[14] Roux C, Amiot C, Agnani G, et al. Live birth after ovarian tissue autograft in a patient with sickle cell disease treated by allogeneic bone marrow transplantation. Fertil Steril 2010;93:2413.e15–9.
[15] Dittrich R, Lotz L, Keck G, et al. Live birth after ovarian tissue autotransplantation following overnight transport before cryopreservation. Fertil Steril 2012;97:387–90.
[16] Gook DA, Edgar DH, Stern C. Effect of cooling rate and dehydration regimen on the histological appearance of human ovarian cortex following cryopreservation in 1, 2-propanediol. Hum Reprod 1999;14:2061–8.
[17] Keros V, Xella S, Hultenby K, et al. Vitrification versus controlled-rate freezing in cryopreservation of human ovarian tissue. Hum Reprod 2009;24:1670–83.
[18] Ernst E, Bergholdt S, Jørgensen JS, et al. The first woman to give birth to two children following transplantation of frozen/thawed ovarian tissue. Hum Reprod 2010;25:1280–1.
[19] Kagawa N, Silber S, Kuwayama M. Successful vitrification of bovine and human ovarian tissue. Reprod Biomed Online 2009;18:568–77.
[20] Herraiz S, Novella-Maestre E, Rodríguez B, et al. Improving ovarian tissue cryopreservation for oncologic patients: slow freezing versus vitrification, effect of different procedures and devices. Fertil Steril 2014;101:775–84.
*[21] Amorim CA, Curaba M, Van Langendonckt A, et al. Vitrification as an alternative means of cryopreserving ovarian tissue. Reprod Biomed Online 2011;23:160–86.
[22] Kawamura K, Cheng Y, Suzuki N, et al. Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment. Proc Natl Acad Sci USA 2013;110:17474–9.
[23] Suzuki N, Yoshioka N, Takae S, et al. Successful fertility preservation following ovarian tissue vitrification in patients with primary ovarian insufficiency. Hum Reprod 2015;30:608–15.
[24] Meirow D, Roness H, Kristensen SG, et al. Optimizing outcomes from ovarian tissue cryopreservation and transplantation; activation versus preservation. Hum Reprod 2015;30:2453–6.
*[25] Suzuki N. Ovarian tissue cryopreservation using vitrification and/or in vitro activated technology. Hum Reprod 2015;30:2461–2.
*[26] Gellert SE, Pors SE, Kristensen SG, et al. Transplantation of frozen-thawed ovarian tissue: an update on worldwide activity published in peer-reviewed papers and on the Danish cohort. J Assist Reprod Genet 2018;35:561–70.
[27] Jensen AK, Kristensen SG, Macklon KT, et al. Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark. Hum Reprod 2015;30:2838–45.
[28] Amorim CA, David A, Van Langendonckt A, et al. Vitrification of human ovarian tissue: effect of different solutions and procedures. Fertil Steril 2011;95:1094–7.
[29] Fabbri R, Vicenti R, Macciocca M, et al. Morphological, ultrastructural and functional imaging of frozen/thawed and vitrified/warmed human ovarian tissue retrieved from oncological patients. Hum Reprod 2016;31:1838–49.
[30] Merdassi G, Mazoyer C, Guerin JF, et al. Examination of viability and quality of ovarian tissue after cryopreservation using simple laboratory methods in Ewe. Reprod Biol Endocrinol 2011;9:78.
[31] Amorim CA, Dolmans MM, David A, et al. Vitrification and xenografting of human ovarian tissue. Fertil Steril 2012;98.1291.e2-1298.e2.
[32] Amorim CA, Jacobs S, Devireddy RV, et al. Successful vitrification and autografting of baboon (*Papio anubis*) ovarian tissue. Hum Reprod 2013;28:2146–56.
[33] Massadier J, Courbiere B, Lornage J, et al. Technical aspects of laparoscopic ovarian autograft in ewes after cryopreservation by slow-cooling protocol. Reprod Domest Anim 2010;45:8–12.
[34] Beckmann MW, Dittrich R, Findeklee S, et al. Surgical aspects of ovarian tissue removal and ovarian tissue transplantation for fertility preservation. Geburtshilfe Frauenheilkd 2016;76:1057–64.
*[35] Bjelland EK, Wilkosz P, Tanbo TG, et al. Is unilateral oophorectomy associated with age at menopause? A population study (the HUNT2 Survey). Hum Reprod 2014;29:835–41.
[36] Yasui T, Hayashi K, Mizunuma H, et al. Factors associated with premature ovarian failure, early menopause and earlier onset of menopause in Japanese women. Maturitas 2012;72:249–55.
[37] Rosendahl M, Simonson MK, Kjer JJ. The influence of unilateral oophorectomy on the age of menopause. Climacteric 2017;20:540–4.
[38] Cramer DW, Xu H, Harlow BL. Does 'incessant' ovulation increase risk for early menopause? Am J Obstet Gynecol 1995;172:568–73.

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

[39] Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol Metabol 2012;97:3146–54.
[40] Deckers P, Ribeiro S, Miyahara C, et al. Systematic review and meta-analysis of the effect of bipolar electrocoagulation during laparoscopic ovarian endometrioma stripping on ovarian reserve. Int J Gynaecol Obstet: Off Organ Int Feder Gynaecol Obstet 2018;140:11–7.
[41] Demeestere I, Simon P, Emiliani S, et al. Orthotopic and heterotopic ovarian tissue transplantation. Hum Reprod Update 2009;15:649–65.
[42] Silber S, Kagawa N, Kuwayama M. Duration of fertility after fresh and frozen ovary transplantation. Fertil Steril 2010;94:2191–6.
[43] Oktay K, Taylan E, Sugishita Y, et al. Robotic-assisted laparoscopic transplantation of frozen-thawed ovarian tissue. Minim Invas Gynaecol 2017;24:897–8.
[44] Manavella D, Cacciottola L, Desmet CM, et al. Adipose tissue derived stem cells in a fibrin implant enhance neovascularisation in a peritoneal grafting site: a potential way to improve ovarian tissue transplantation. Hum Reprod 2018;33:170–9.
[45] Beckmann MW, Dittrich R, Lotz L, et al. Fertility protection: complications of surgery and results of removal and transplantation of ovarian tissue. Reprod Biomed Online 2018;36:188–96.
[46] Meirow D, Leveron J, Eldar-Geva T. Pregnancy after transplantation of cryopreserved ovarian tissuein patients with ovarian failure after chemotherapy. N Engl J Med 2005;353:318–21.
[47] The ESHRE Working Group on Oocyte Cryopreservation in Europe, Shenfield F, de Mouzon J, et al. Oocyte and ovarian tissue cryopreservation in European countries: statutory background, practice, storage and use. Hum Reprod Open 2017;2017:hox003.
*[48] Liebenthron J, Montag M. Development of a nationwide network for ovarian tissue cryopreservation. Meth Mol Biol 2017;1568:205–20.
[49] Von Wolff M, Lawrenz B. FertiPROTEKT network for fertility preservation techniques before chemo- & radiotherapy. J fur Reproduktionsmedizin und Endokrinologie 2013;10:60–5.
*[50] Jadoul P, Guilmain A, Squifflet J, et al. Efficacy of ovarian tissue cryopreservation for fertility preservation: lessons learned from 545 cases. Hum Reprod 2017;32:1046–54.
[51] Amiot C, Pretalli JB, Frontczak S, et al. Six children born after 15 ovarian tissue transplantations: the French protocol for the development of ovarian tissue autograft in order to restore ovarian function (DATOR). Hum Reprod 2017;32:i365.
[52] Dunlop CE, Brady BM, McLaughlin M, et al. Re-implantation of cryopreserved ovarian cortex resulting in restoration of ovarian function, natural conception and successful pregnancy after haematopoietic stem cell transplantation for Wilms tumour. J Assist Reprod Genet 2016;33:1615–20.
[53] Kedem A, Yerushalmi GM, Brengauz M, et al. Outcome of immature oocytes collection of 119 cancer patients during ovarian tissue harvesting for fertility preservation. J Assist Reprod Genet 2018;35:851–6.
[54] Lee JR, Lee D, Park S, et al. Successful in vitro fertilization and embryo transfer after transplantation of cryopreserved ovarian tissue: report of the first Korean case. J Kor Med Sci 2018;33:e156.
[55] Kim SS. Assessment of long term endocrine function after transplantation of frozen-thawed human ovarian tissue to the heterotopic site: 10 year longitudinal follow-up study. J Assist Reprod Genet 2012;29:489–93.
[56] Kim SS, Lee WS, Chung MK, et al. Long-term ovarian function and fertility after heterotopic autotransplantation of cryobanked human ovarian tissue: 8-year experience in cancer patients. Fertil Steril 2009;91:2349–54.
[57] Donnez J, Silber S, Andersen CY, et al. Children born after autotransplantation of cryopreserved ovarian tissue. A review of 13 live births. Ann Med 2011;43:437–50.
[58] Oktay K, Bedoschi G, Pacheco F, et al. First pregnancies, live birth, and in vitro fertilization outcomes after transplantation of frozen-banked ovarian tissue with a human extracellular matrix scaffold using robot-assisted minimally invasive surgery. Am J Obstet Gynecol 2016;214. 94.e1-99.e1.
[59] Kyono K, Hashimoto T, Toya M, et al. A transportation network for human ovarian tissue is indispensable to success for fertility preservation. J Assist Reprod Genet 2017;34:1469–74.
[60] Practice Committees of American Society for Reproductive Medicine; Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril 2013;99:37–43.
[61] Cil AP, Bang H, Oktay K. Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis. Fertil Steril 2013;100:492–9.
[62] Andersen CY, Silber S, Bergholdt SH, et al. Long-term duration of function of ovarian tissue transplants: case reports. Reprod Biomed Online 2012;25:128–32.
[63] Donnez J, Dolmans MM, Diaz C, et al. Ovarian cortex transplantation: time to move on from experimental studies to open clinical application. Fertil Steril 2015;104:1097–8.
[64] Christensen K, Doblhammer G, Rau R, et al. Ageing populations: the challenges ahead. Lancet 2009;374:1196–208.
[65] Centers for Disease Control and Prevention. Years of healthy life – selected states, United States, 1993-1995. MMWR. Morb Most Weekly Rep 1998;47:5–7.
[66] Historical Census Browser. Retrieved April 25, 2010, from the University of Virginia, geospatial and statistical data center. 2004. June 2018, http://fisher.lib.virginia.edu/collections/stats/histcensus/index.html.
[67] Emery Thompson M, Jones JH, Pusey AE, et al. Aging and fertility patterns in wild chimpanzees provide insights into the evolution of menopause. Curr Biol 2007;17:2150–6.
[68] Jasienska G. Reproduction and lifespan: trade-offs, overall energy budgets, intergenerational costs, and costs neglected by research. Am J Hum Biol 2009;21:524–32.
*[69] Williams GC, Nesse RM. The dawn of Darwinian medicine. Q Rev Biol 1991;66:1–22.
[70] Lobo RA, Davis SR, De Villiers TJ, et al. Prevention of diseases after menopause. Climacteric 2014;17:540–56.
[71] de Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. Lancet 2010;376:911–21.
[72] Soules MR, Sherman S, Parrott E, et al. Executive summary: stages of reproductive aging workshop (STRAW). Fertil Steril 2001;76:874–9.
[73] Col NF, Guthrie JR, Politi M, et al. Duration of vasomotor symptoms in middle-aged women: a longitudinal study. Menopause 2009;16:453–7.

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002

[74] Simon JA, Reape KZ. Understanding the menopausal experiences of professional women. Menopause 2009;16:73–6.
[75] Carr MC, Kim KH, Zambon A, et al. Changes in LDL density across the menopausal transition. J Invest Med 2000;48:245–50.
[76] Do KA, Green A, Guthrie JR, et al. Longitudinal study of risk factors for coronary heart disease across the menopausal transition. Am J Epidemiol 2000;151:584–93.
[77] Ensrud KE, Ewing SK, Taylor BC, et al. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. J Gerontol Ser A Biol Sci Med Sci 2007;62:744–51.
[78] Goeree R, O'Brien B, Pettitt D, et al. An assessment of the burden of illness due to osteoporosis in Canada. J Obstet Gynaecol Can 1996;18:15–24.
[79] Ray NF, Chan JK, Thamer M, et al. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the national osteoporosis foundation. J Bone Miner Res 1997;12:24–35.
[80] Andersen CY, Kristensen SG. Novel use of the ovarian follicular pool to postpone menopause and delay osteoporosis. Reprod Biomed Online 2015;31:128–31.
[81] Lass A, Paul M, Margara R, et al. Women with one ovary have decreased response to GnRHa/HMG ovulation protocol in IVF but the same pregnancy rate as women with two ovaries. Hum Reprod 1997;12:298–300.
*[82] Wallace WHB, Kelsey TW. Human ovarian reserve from conception to the menopause. PLoS One 2010;5:e8772.

Please cite this article in press as: Amorim CA, et al.Cryostorage and retransplantation of ovarian tissue as an infertility treatment, Best Practice & Research Clinical Endocrinology & Metabolism (2018), https://doi.org/10.1016/j.beem.2018.09.002