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7

Transplantation of ovarian tissue

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Since the first live birth after orthotopic transplantation of frozen–thawed ovarian tissue, >40 babies have been born. It is time to consider fertility preservation in women as one of the foremost challenges of the next decade and to offer women facing the risk of induced or iatrogenic premature menopause the best chances of becoming mothers.

Heterotopic transplantation has also been attempted, with consistent restoration of endocrine function; nonetheless, its clinical value remains questionable as it may not provide an optimal environment for follicular development, possibly because of differences in temperature, pressure, paracrine factors and blood supply.

Finally, orthotopic allo-transplantation of fresh human ovarian tissue has been successfully attempted between monozygotic twins and also between genetically different sisters.

The next step in this field will be the development of an artificial ovary, using, as a support, a biodegradable scaffold made of an alginate matrigel matrix onto which isolated preantral follicles and ovarian cells can be grafted.

Introduction

Significant developments in cancer therapy over recent decades have led to a dramatic improvement in survival rates, and many cancers can now be cured, raising the important issue of subsequent

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quality of life [1]. Unfortunately, treatments such as chemotherapy, radiotherapy and/or surgery result in premature ovarian failure (POF) in some instances, robbing these women of the chance of conceiving a child [2–6].

This is particularly pertinent for young women wishing to start a family once in disease remission. Indeed, the number of new cases of invasive cancer in women in the USA was approximately 790,740 in 2012, and around 10% of these cases were in women aged <45 years [7].

Non-malignant systemic diseases like autoimmune and haematological disorders may also require chemotherapy or radiotherapy, often associated with bone marrow transplantation (BMT) [8,9]. Impairment of ovarian function after BMT is generally linked to increased age at the time of treatment and use of total body irradiation prior to transplantation [10,11].

Ovaries are particularly sensitive to cytotoxic drugs, especially alkylating agents, which are likely to lead to gonadal dysfunction [11–14]. Cyclophosphamide is the alkylating agent implicated in causing most damage to oocytes and granulosa cells depending on dose, while a combination of abdominal ionizing radiation and alkylating agents leaves almost 100% of patients infertile [15–17].

Pelvic radiation therapy also causes POF, with exposure levels of 5–10 Gy known to be toxic to oocytes [15]. Indeed, the human oocyte is very sensitive to radiation and as little as <2Gy may be enough to destroy 50% of primordial follicles [12,15].

This review evaluates the techniques and results of ovarian tissue transplantation.

The ovarian reserve

The term *'ovarian reserve'* typically describes the population of primordial follicles in the ovary constituting what has been called the 'true' ovarian reserve [18]. In assisted reproduction, this term refers to the population of small growing follicles, namely small antral follicles detected by vaginal ultrasonography.

Initiation of the resting primordial follicle reserve begins during fetal life, when around 100–2000 primordial germ cells colonize the genital ridges and embark upon a massive proliferation process that culminates in 7×10^6 potential oocytes at mid-gestation, but approximately 85% of these potential oocytes are lost prior to birth [18,19]. The number of follicles continues to decline throughout reproductive life, during which time only ~450 monthly ovulatory cycles occur. Most follicles undergo atresia during the growth phase, involving their degeneration and subsequent resorption. Cyclic folliculogenesis and ovulation, with massive follicular atresia and ageing-induced apoptosis, result in ovarian atrophy and reduced fertility [18–20].

Various mechanisms have been proposed to account for the decline in fertility experienced by women >40 years of age, including poor oocyte quality characterized by abnormalities in the meiotic spindle, shortened telomeres or chromosome misalignment [21,22]. At menopause (occurring on average at 50–51 years of age), some 1000 primordial follicles remain (Fig. 1). While mitotically active germ cells have been documented in mouse and human ovaries [23], their presence and capacity for neo-oogenesis remain contentious [24].

Fertility preservation: different options

Fertility preservation options in cancer patients give these women the opportunity to become mothers when they have overcome their disease. Alternatives include embryo cryopreservation [2], immature or mature oocyte cryopreservation [25] and ovarian tissue cryopreservation (see Ref. [1] for review).

Cryopreservation of ovarian tissue is the only available option for prepubertal girls and women who cannot delay the start of chemotherapy [1,17,26]. The age of the patient should be taken into account, because the follicular reserve of the ovary is age-dependent [5]. It is well documented that fertility becomes compromised during the mid-30s; for this reason, the procedure should probably not be offered to women after the age of 38 years. In many centres, the limit is fixed at 35 years [1,3].

Orthotopic autotransplantation of cryopreserved human ovarian tissue

The main aim of ovarian tissue cryopreservation is to restore fertility. This method involves reimplantation of ovarian cortical tissue into the pelvic cavity (orthotopic site) or a heterotopic site like the forearm or abdominal wall, once treatment is completed and the patient is disease-free [1].

Orthotopic refers to implantation in the pelvic cavity on the remaining ovary, close to it or in the uterine environment. Heterotopic means clearly outside the peritoneal cavity [1].

Techniques of orthotopic autotransplantation

Two techniques may be used depending on the presence or not of at least one remaining ovary.

1. If at least one ovary is present, the technique starts with decortication of the ovary. A large piece of ovarian cortex is removed to have access to the medulla (Fig. 2) and its vascular network [1,27]. According to microsurgical techniques, ovarian cortical pieces are then fixed with the use of 7/0 or 8/0 propylene stitches [1,27–30], or simply placed on the medulla and fixed with Interceed® or fibrin glue. In the series published by Andersen's group [28,31], ovarian tissue is deposited on the medulla after making an incision in the cortex; the tissue is thus placed in a subcortical area.
2. If both ovaries are absent, a peritoneal window may be created in two steps, as in the case published in 2004 [32], to induce angiogenesis before the grafting procedure, or in one step, as recently described [33]. The incision for this peritoneal window is made on the anterior leaf of the broad ligament in an area where a vascular network is visible (retroperitoneal vessels; Fig. 3). The fragments are placed in the window and subsequently covered with Interceed®, the edges of which are fixed with fibrin glue. The peritoneal window method may also be applied if a non-functional ovary is still in place.

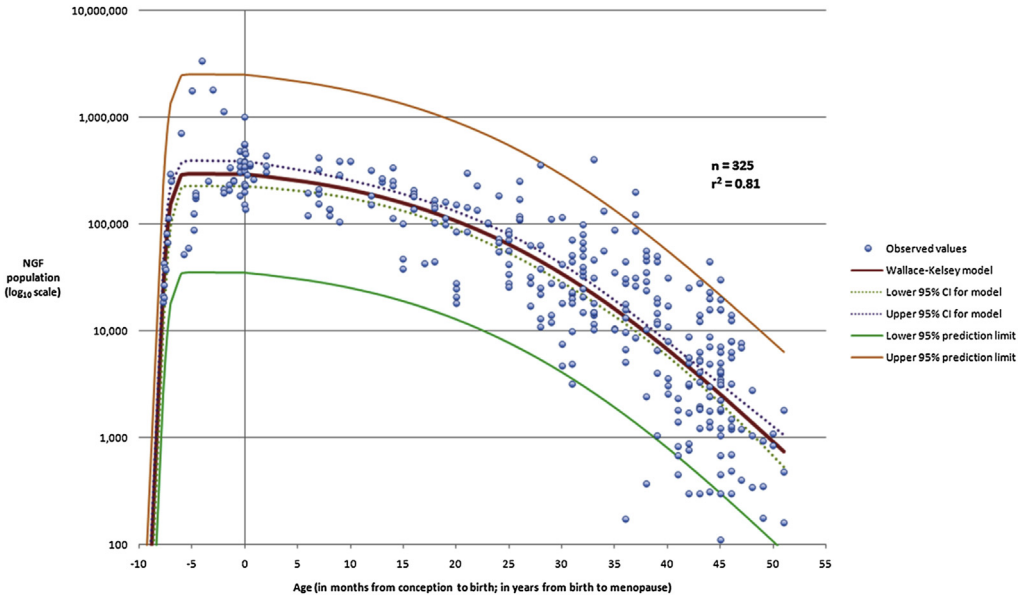

Fig. 1. The ovarian reserve: the model that best fits histological data according to Wallace and Kelsey. The ovarian reserve is depicted throughout a woman's life, from conception to the age of 55 years. The *Y*-axis illustrates the number of primordial follicles constituting the ovarian reserve. After an initial increase (germ cell formation), the ovarian reserve starts to diminish even before birth, resulting in only ~1000 follicles present at menopause. This figure is adapted from Wallace, W. H. & Kelsey, T. W. from *PLoS ONE* 27, e8772 (2010), published under an open-access license by PLoS.

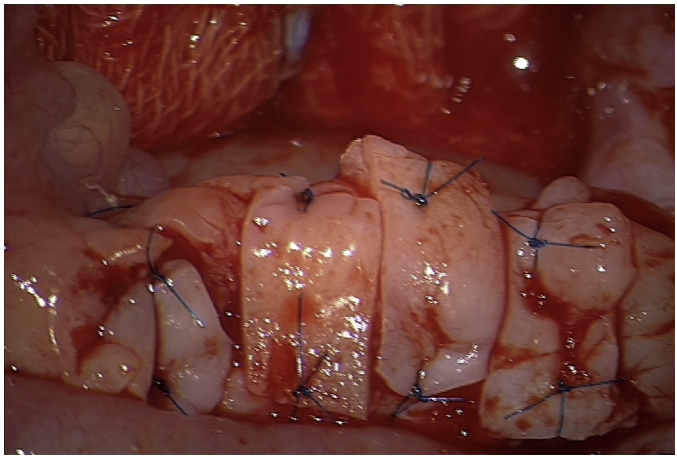

Fig. 2. Ovarian cortex reimplantation on the ovarian medulla. Large pieces of thawed ovarian cortex are sutured to the medulla. From Donnez et al., 2006.

Restoration of ovarian activity

In a series of 60 cases of frozen–thawed ovarian tissue reimplantation, restoration of ovarian activity was observed in all cases but three, where no follicles were present in the reimplanted tissue, highlighting the importance of evaluating follicular density before making the decision to reimplant [28]. In this series (including Danish, Spanish and Belgian teams), the peritoneal reimplantation window created close to the ovarian hilus or in the ovarian medulla proved to be equally efficient in both cases, at least for restoration of ovarian activity (as evidenced by follicular development and circulating steroid levels). Large strips (8–10 × 5 mm) and small cubes (2 mm^3) of tissue were both shown to effectively restore ovarian endocrine function (Fig. 4).

In all instances, it took 3.5–6.5 months after reimplantation before a rise in oestradiol (E2) and a decrease in follicle-stimulating hormone (FSH) were detected (mean 4.5 months). The time interval between implantation of cortical tissue and the first E2 peak is consistent with data obtained from sheep and humans, although some variation may be observed and explained by a difference in follicular reserve at the time of cryopreservation (Fig. 4) [1].

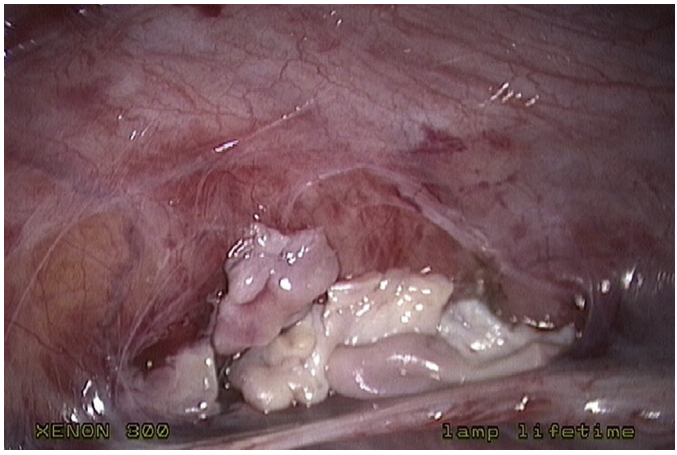

Fig. 3. Ovarian cortex reimplantation in a peritoneal pocket. Large pieces of ovarian cortex are placed in a peritoneal pocket. From Donnez et al., 2012.

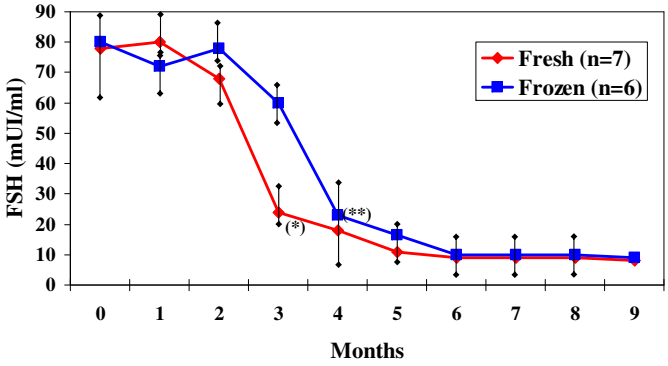

Fig. 4. FSH values after orthotopic reimplantation of frozen–thawed (■) and fresh (◆) ovarian tissue. $^{*}p < 0.05$: A significant decrease in FSH was observed 3 months after fresh ovarian tissue transplantation. $^{**}p < 0.05$: A significant decrease in FSH was observed 4 months after frozen–thawed ovarian tissue transplantation in women who had not received chemotherapy before cryopreservation. Fresh tissue (red) (mean ± SEM) ($n = 7$). Frozen tissue (blue) (mean ± SEM) ($n = 6$ women who had not received chemotherapy before cryopreservation).

Pregnancies

More than 40 live births worldwide have been reported so far [1]. Among them, 30 were published in peer-reviewed papers [27–46] (Table 1). Table 1, published in 2013 in a review, shows the 22 first live births reported in the literature [28]. This report summarizes data from three groups in Spain, Denmark and Belgium; 11 of the 60 patients became pregnant (including two ongoing pregnancies at 24 and 30 weeks), and six of these women have already delivered 12 healthy babies. Since publication, five more women have conceived in this series, achieving an ongoing pregnancy rate of 27%. More than 50% of pregnancies were obtained naturally.

Mean gestational age at delivery was over 38½ weeks in case of singleton pregnancies. Mean birth weight in singleton pregnancies was >3300 g.

In some centres, most deliveries were by caesarean section. In the series at the Department of Gynaecology and Obstetrics of the Catholic University of Louvain, Cliniques Universitaires Saint-Luc, all

Table 1
Series of 30 live births after transplantation of frozen-thawed ovarian cortex (see Refs. 27–46).

References	Cryopreservation procedure	Graft site	Live birth	
			Spont.	IVF
Donnez et al., 2004, 2010, 2011, 2012, 2013	SF	Peritoneal window (two steps) Ovarian medulla	+ +++	++
Meirow et al., 2005, 2012	SF	Beneath the ovarian cortex	+	+++
Demeestere et al., 2007	SF	Ovarian and peritoneal windows (two steps)	++	–
Andersen et al., 2008, 2009, 2011, 2012, 2013	SF	Subcortical ovarian pocket Ovarian medulla	++ +	+ +
Silber et al., 2008, 2010, 2012	SF	Ovarian medulla	+ +	–
Piver et al., 2009 Roux et al, 2010	SF	Ovarian and peritoneal windows (one and two steps)	+ +	–
Sanchez et al., 2009	SF	Ovarian medulla	–	++ (twins)
Revel et al., 2010, 2012	SF	Peritoneal window (slice)	–	+ +
Dittrich et al., 2012	SF	Peritoneal window	+	–
Revelli et al., 2013	SF	Ovarian medulla	+	
Stern et al., 2013	SF	"Heterotopic" pelvic site		++
Callejo et al., 2013	SF	Ovarian medulla		+
Garcia Rada, 2013	SF	Peritoneal pocket		+

There are abstracts reporting live births in Germany, South Africa and Spain, for a total of >10 additional live births.

babies ($n = 9$) were delivered vaginally (six after frozen–thawed ovarian tissue transplantation and three after fresh tissue transplantation).

The majority of pregnant women were <30 years old. In Donnez's group, a woman whose tissue was cryopreserved at the age of 17 years and reimplanted at the age of 25 years has already given birth to three healthy babies in <3 years. In Andersen's group as well, a woman has delivered three healthy babies after cryopreservation and reimplantation. It is important to stress that all babies born were healthy and that no recurrence of the initial disease was observed.

Since then, case reports and abstracts have described >10 additional pregnancies in different countries (South Africa, Germany, Israel, Spain, Denmark and Australia). The slow-freezing procedure was used in all cases. The fact that >50% of women were able to conceive naturally constitutes a good argument in favour of orthotopic reimplantation.

Orthotopic versus heterotopic

In theory, ovarian tissue can be transplanted orthotopically (into the pelvic cavity, onto the ovarian medulla or inside a specially created peritoneal window) or heterotopically (to the abdominal wall, forearm, rectus muscle, etc.) [47–49]. Nevertheless, the clinical value of heterotopic reimplantation remains questionable (Table 2). Heterotopic sites may not provide an optimal environment for follicular development, possibly because of differences in temperature, pressure, paracrine factors and blood supply [1,28]. However, restoration of endocrine function has been demonstrated consistently after heterotopic ovarian transplantation. In a very recent study by Kim [49], all five patients recovered endocrine function 3–5 months after grafting of frozen–thawed ovarian tissue to the space between the rectus muscle and rectus sheath.

According to Oktay et al. [47,48] and Kim [49], the advantages of transplanting ovarian tissue to heterotopic sites include: 1) avoidance of invasive procedures, 2) easy recovery of oocytes, 3) cost-effective technology when repeated transplantation is required, and 4) feasibility even in case of severe pelvic adhesions that preclude orthotopic transplantation.

It has been claimed that one pregnancy recently occurred after this procedure; however, the fragments were placed in the retroperitoneal space through a small incision (the fragments were visible at second-look laparoscopy) and, for this reason, the technique should be considered as orthotopic reimplantation in a peritoneal window [45].

Orthotopic transplantation of fresh human ovarian tissue

Between monozygotic twins

The first successful ovarian allograft between monozygotic twins resulting in a pregnancy was published by Silber et al. in 2005 [29]. The efficacy of this technique was confirmed by a series of ovarian allografts between monozygotic twins published by the same authors in 2008 [50] and 2012 [46].

Table 2
Advantages and disadvantages of heterotopic and orthotopic sites for ovarian tissue transplantation.

	Heterotopic site (subcutaneous)	Orthotopic site
Advantages	• No limitation of the number of fragments transplanted • Easy transplantation procedure • Easy access for follicular monitoring and oocyte collection	• Possibility of natural conception • Restoration of fertility demonstrated • Favourable environment for follicular development
Disadvantages	• Restoration of fertility not yet demonstrated • IVF procedure required • Effect of the local environment on oocyte quality is unknown	• Number of fragments transplanted limited by ovarian size • Invasive transplantation procedure

Ovarian allografting between monozygotic twin sisters one of whom had Turner syndrome was also successful [51]. The fact that there was only atrophic ovarian tissue (streak ovaries) supports the notion that the origin of the oocyte resulting in 2 pregnancies and 2 live births was the transplanted tissue. In our case, the follicular density of the donor ovarian specimen was high and recovery of ovarian activity in the recipient occurred 3 months after reimplantation. Silber et al. [46] and Donnez et al. [27] both reported that the time to first menses after transplantation of fresh tissue is slightly sooner (1 month) than after grafting of frozen–thawed tissue. This interval corresponds to the development of primordial follicles to the antral follicle stage, but it is also possible that one or two growing follicles, having survived the reimplantation procedure and subsequent ischaemic period (estimated to be between 3 and 5 days), could reach the preovulatory stage earlier than would be expected of primordial follicles [51].

Between genetically different sisters

Donnez et al. [52,53] demonstrated that ovarian function may also be restored after allografting of the ovarian cortex between genetically different sisters and the first live birth after this procedure was reported. It was proved by genetic analysis that the baby born originated from an oocyte from the ovarian tissue donor.

Allografting has the potential to restore not only ovarian activity but also natural fertility. The first oestradiol peak was detected 3.5–6 months after transplantation, the interval depending on follicular density.

It is particularly important to stress that the recipient had received bone marrow from her human leucocyte antigen (HLA)-compatible sister. Transplantation of organs like kidneys has already been performed between HLA-compatible sisters who have previously undergone BMT, with one sister acting as donor to the other. Indeed, Hamawi et al. [54] reported six cases of kidney transplantation after BMT, the kidney donor being the BMT donor in all cases. The patients did not receive immunosuppressive treatment and there was no sign of rejection. Hamawi thus concluded that BMT recipients who receive a kidney from their bone marrow donor do not require immunosuppression.

In our case, HLA group analysis revealed complete chimerism (HLA compatibility) between the two sisters. It was therefore proposed that ovarian tissue be grafted from the sister who had already donated bone marrow to the recipient sister with POF.

The artificial ovary: the future of grafting procedures

In case of suspicion of malignant cells in ovarian tissue [55,56], an alternative is to obtain mature oocytes with the help of the so-called artificial ovary. Isolation of primordial follicles and their transfer onto a scaffold to create an artificial ovary will, of course, eliminate the risk of transmission of malignant cells. Human preantral follicles can be successfully cryopreserved before and after isolation without impairing their ability to survive and grow in vitro [57]. Indeed, survival and growth of preantral follicles from vitrified human ovarian tissue have been demonstrated, as have survival and growth of isolated follicles enclosed in biomatrices [58,59].

The first step in developing an artificial ovary, namely a biodegradable scaffold (consisting of an alginate matrigel matrix) onto which isolated preantral follicles and ovarian cells can be grafted, was accomplished in 2012 [58]. Transplanted beads were able to degrade, enabled vascularization and elicited a low inflammatory response [60].

Conclusion

In conclusion, since the first live birth after orthotopic transplantation of frozen–thawed ovarian tissue [29], >40 babies have been born. It is time to consider fertility preservation in women as one of the foremost challenges of the next decade and to offer women facing the risk of induced or iatrogenic premature menopause the best chances of becoming mothers.

Providing patients and/or parents (in case of minors) with an accurate assessment of the risk to fertility is challenging, as it is almost impossible to predict how a disease will develop [17]. This is why evaluating the likelihood of POF after chemotherapy or radiotherapy is often highly problematic. It is

further compounded by the fact that the ovarian reserve varies greatly from one woman to the next, also affecting the chances of developing POF. For this reason, fertility preservation counselling should be offered to all girls and women with their reproductive potential at risks of developing POF. Strict criteria were recently used by the team of Wallace [9] to predict the risks of POF after treatment. It is also important that mental health professionals, reproductive endocrinologists and paediatricians collaborate with oncologists to optimize both patient care and quality of life after therapy.

Only a small percentage of patients at the risk of POF are referred to specialists to discuss fertility preservation options and, of this number, only a few actually undergo fertility preservation procedures because of social, economic or technical constraints. Furthermore, women are increasingly having children later in life for social or financial reasons, which automatically puts them at greater risk as the incidence of most cancers increases with age [1].

Disclosure

J.D. has nothing to disclose. M.M.D. has nothing to disclose.

Conflict of interest statement

The authors report no conflict of interest.

Practice points

- Orthotopic homo-transplantation of frozen–thawed ovarian tissue is today perfectly feasible, with >40 babies having been born.
- Orthotopic allo-transplantation of fresh human ovarian tissue can also be successful between monozygotic twins, as well as between genetically different sisters.
- Heterotopic transplantation results in a consistent restoration of endocrine function, but it may not provide an optimal environment for follicular development.

Research agenda

- Study optimal conditions for heterotopic homo-transplantation of fresh and/or frozen –thawed ovarian tissue to obtain oocytes for in vitro fertilization and embryo transfer.
- Further develop the so-called artificial ovary to be utilized when there is suspicion of malignant cells in the ovarian tissue. Explore the option of utilizing biodegradable scaffolds made of alginate matrigel matrices.

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