



Australian Government
Department of Health and Ageing



Australia and New Zealand Horizon Scanning Network

ANZHSN

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Horizon Scanning Technology Prioritising Summary

Ovarian tissue cryopreservation and transplantation for fertility preservation

August 2007



Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical



Royal Australasian
College of Surgeons

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ISBN

Publications Approval Number:

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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from departments in all states and territories, the Australia and New Zealand governments; and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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PRIORITISING SUMMARY

REGISTER ID: S000049

NAME OF TECHNOLOGY: OVARIAN TISSUE CRYOPRESERVATION AND TRANSPLANTATION

PURPOSE AND TARGET GROUP: PATIENTS WITH A HIGH RISK OF PREMATURE OVARIAN FAILURE

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | | |
|--|-------------|-----|
| <input type="checkbox"/> Yes | ARTG number | N/A |
| <input type="checkbox"/> No | | |
| <input checked="" type="checkbox"/> Not applicable | | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials underway or completed	Limited Use	Widely Diffused
United States	✓		
France	✓		
Israel	✓		

IMPACT SUMMARY:

Ovarian tissue transplantation has emerged as a potential method of preserving fertility in women who are at a high risk of premature ovarian failure (POF); particular in young women and children undergoing chemotherapy and/or radiotherapy. In Australia, several fertility centres offer cryopreservation of ovarian tissue as an 'insurance' for future fertility. Given the high rates of cancer in Australia, it is likely that ovarian transplantation, once proven effective, would diffuse rapidly as a means of preserving fertility. If adopted, the procedure would be performed by a gynaecologist within a specialist medical centre.

BACKGROUND

Medical advances in the diagnosis and treatment of childhood, adolescent and adult cancer have greatly increased the life expectancy of premenopausal women suffering from various cancers. Consequent to this, there is a growing population of adolescent and adult long-term survivors of childhood malignancies who are at risk of fertility problems due to premature ovarian failure (POF) (Donnez et al. 2006). Studies have shown that the ovaries are extremely sensitive to cytotoxic treatment, particularly alkylating agents (cyclophosphamide, busulfan, melphalan, chlorambucil, dacarbazine, ifosfamide, procarbazine, nitrogen mustard, and thiotepa) as well as ionising radiotherapy; both of which are utilised extensively in cancer treatment. Follicular destruction due to cancer treatment regimens generally results in the loss of both endocrine and reproductive functions (Donnez et al. 2006).

To date, several techniques have been explored to preserve fertility in cancer patients; one of them being autotransplantation of cryopreserved embryos. Although this technique is theoretically sound, it has some inherent limitations. Embryo cryopreservation is only suitable for patients of pubertal age, has a partner/willing to use donor sperm, and is suitable to undergo a cycle of ovarian stimulation; which is not possible if chemotherapy has to be initiated immediately or when stimulation is contraindicated according to the type of cancer (Donnez et al. 2006). A second method of preserving fertility is oocyte cryopreservation; however studies have revealed relatively low levels of efficacy, with pregnancy and delivery rates ranging from 1% to 5% per frozen oocyte (Stachecki and Cohen 2004, Borini et al. 2006, Levi Setti et al. 2006).

In view of the limitations of embryo and oocyte cryopreservation and transplantation, researchers have proposed the use of ovarian tissue as a potential alternative. To date, it is the only suitable option for prepubertal girls and patients who require immediate chemotherapy; it enables the preservation of hundreds of primordial follicles without the need of ovarian stimulation. In addition to this, evidence suggests that primordial follicles are less susceptible to cryoinjury due to their smaller size, slower metabolic rates and the absence of zona pellucida (Marhhom and Cohen 2006). There are two main surgical approaches for the transplantation of ovarian tissue: orthotopic or heterotopic. Theoretically, natural spontaneous pregnancy may be achieved via orthotopic transplantation, where the ovarian tissue is transplanted back into the pelvic cavity, as long as the fallopian tube remains intact. Heterotopic transplantation on the other hand is conducted at subcutaneous sites such as the forearm or abdomen; and *in vitro* fertilisation would be required to achieve pregnancy (Marhhom and Cohen 2006).

CLINICAL NEED AND BURDEN OF DISEASE

The Australian Institute of Health and Welfare has projected that the age standardised incidence rate of cancer in women is projected to increase by 2% from 393.3 per 100,000 women in 2001 to 402.9 per 100,000 in 2011, with a 95% prediction interval from 380.5 to 428.6. Meanwhile the number of new cancer cases in women is projected to increase by 29% from 40,578 in 2001 to 52,356 in 2011, with a 95% prediction interval from 49,356 to 55,777 (AIHW 2005). Approximately 750 children and adolescents are

diagnosed with cancer in Australia and New Zealand every year and approximately 75% of these patients are expected to be long-term survivors (Heath and Stern 2006).

Larsen et al. (2003) reported that female teenagers treated for cancer have a four-fold increased risk of POF, and this risk increases by a factor of 27 in women aged between 21 and 25 years. Studies on chemotherapeutic agents have highlighted the high risk of POF after treatment, with one study stating that the administration of 5g of cyclophosphamide can result in complete amenorrhea in women over 40 years of age (Shalet 1980), and another study highlighting that a combination of various chemotherapeutic agents can result in further gonadal toxicity; with 89% of patients aged >25 years and 20% of patients aged <25 years experiencing amenorrhea at the time of treatment (Schilsky et al. 1981). Ionizing radiation associated with alkylating agents directed to the adominal region is also associated with POF, rendering almost 100% of patients infertile after treatment; with one study highlighting that a dose of 5 to 20Gy to the ovary is sufficient to completely impair gonadal function (Wallace et al. 2005).

DIFFUSION

At the time of writing, fertility preservation techniques are available in Australia and New Zealand but the proportion of cancer patients utilising these facilities is unclear. Oocyte or ovarian tissue conservation is offered to postpubertal females in at least 10 centres within Australia and New Zealand (Heath and Stern 2006). Methods of ovarian conservation include ovarian freezing (cryopreservation) and ovarian transposition. There are no known centres which offer oocyte freezing or *in vitro* fertilisation and embryo freezing as a method of preserving fertility (Heath and Stern 2006).

It is likely the ovarian tissue transplantation will play a significant role in preserving fertility if it is proven to be effective.

COMPARATORS

Comparators to ovarian tissue cryopreservation and transplantation include:

- Embryo cryopreservation
- Oocyte cryopreservation

SAFETY AND EFFECTIVENESS ISSUES

A substantial amount of research has been conducted to determine the safety and efficacy of ovarian tissue cryopreservation and transplantation; a cross section of these studies, particularly studies which have resulted in conception after transplantation, will be discussed below. Results for both orthotopic and heterotopic transplantation will be briefly discussed as well

a) Safety

One of the key safety issues associated with the autotransplantation of grafts is the risk of viral (e.g. HIV and hepatitis virus) and cancer cell transmission. Research has shown that

cancers have been shown to recur in patients in remission after the replacement of autologous cryopreserved bone marrow. This therefore raises the possibility that blood-borne cancers such as leukaemia, systemic cancers such as lymphoma and metastasising cancers may be transmitted back to the patient via ovarian tissue grafts (Wood et al. 1997). This in turn has serious implications on the clinical application of this technique; however it should be noted that this is not an inherent risk associated with ovarian tissue transplantation alone as it is a major risk for embryo and oocyte transplantation as well. None of the included studies reported any incidences of viral transmission or relapse of cancer due to the transplantation of cryopreserved ovarian tissue.

b) Effectiveness

Autotransplantation of cryopreserved ovarian tissue

Various studies have been performed to assess the efficacy of autotransplantation of cryopreserved human ovarian tissue and the results of several studies are summarised in a review by Donnez et al. (2006). Overall, autotransplantation of cryopreserved human ovarian tissue appears to be capable of restoring ovarian function. All 13 studies¹ included within the review on orthotopic ovarian tissue transplantation (orthotopic and heterotopic) by Donnez et al. (2006) reported recovery of ovarian function² after transplantation. The recovery of ovarian function occurred within 2 to 8 months of transplantation³ and in some cases resulted in successful pregnancy and live birth⁴.

The first reported case of pregnancy and live birth as a result of successful transplantation (orthotopic) of cryopreserved ovarian tissue was reported in a 25-year old woman who presented with clinical stage IV Hodgkin's lymphoma (Donnez et al. 2004). Ovarian cortical tissue (5 biopsies) was retrieved via laparoscopy from the left ovary. When the patient was declared completely disease free seven years after chemotherapy, a large strip and 35 small cubes of frozen-thawed ovarian tissue were implanted into a furrow created by the peritoneal window adjacent to the ovarian vessels and fimbria on the right side. At 4-months post transplantation, laparoscopy revealed a follicular structure in the area of tissue transplantation; biopsy and analysis confirmed the presence of viable primordial follicles and a follicular structure with inhibin A-marked cells. From 5 to 9 months after reimplantation, ultrasonography revealed the development of a follicle followed by corpus luteum formation with every menstrual cycle at the reimplantation site. At 11 months post-implantation, the patient became pregnant. It should be noted that the conception was spontaneous and occurred without ovarian stimulation or *in vitro*

¹ Oktay and Karlikaya 2000; Radford et al. 2001; Callejo et al. 2001; Kim et al. 2004a; Oktay et al. 2004; Donnez et al. 2004; Meiorow et al. 2005; Schmidt et al. 2005; Wolner-Hanssen et al. 2005; Donnez et al. 2006; Oktay 2006; Demeestere et al. 2006; and Donnez et al. [unpublished data]

² "Recovery of ovarian function" for patients who received heterotopic autotransplantation *does not* infer restoration of the menstrual cycle; rather the growth of follicles within the subcutaneous site.

³ Recovery of ovarian function was determined by measuring oestrogen (E₂), follicular stimulating hormone, and leutenising hormone levels, follicular development, ovulation and in some cases inhibin B and anti-Mullerian hormone levels.

⁴ Studies included in the review by Donnez et al. (2006) which reported live birth include: Donnez et al. (2004), Meiorow et al. 2005, Oktay (2006) and Demeestere et al. (2006).

fertilisation. Progesterone treatment was initiated as the investigators were uncertain if the transplanted tissue can sustain ovarian steroid hormone support during pregnancy (Donnez et al. 2004). Oktay and Tilly (2004) challenged the validity of the results presented by Donnez et al. (2004), stating that the chemotherapy regimen utilised carried a low probability of POF (approximately <20%); and that the raised concentrations of follicle stimulating hormone at 3 months post-chemotherapy may not be sufficient to indicate permanent ovarian failure. Therefore, there is a possibility that ovulation may have occurred from the native ovary and not from the transplanted ovarian tissues (Oktay and Tilly 2004).

In 2005, the second live birth after orthotopic autotransplantation of cryopreserved ovarian tissue was reported by Meirow et al. (2005) in a 28-year old woman who experienced POF after chemotherapy for non-Hodgkin's lymphoma. The patient was menopausal for 24 months before requesting ovarian transplantation. Strips of thawed ovarian tissue were transplanted into the left ovary while small fragments were injected into the right ovary. Spontaneous menstruation was observed 8 months after transplantation and the patient experienced a rise in antimullerian hormone and inhibin B levels, indicating the presence of active, early-stage, growing follicles. Ultrasonography confirmed the presence of a preovulatory follicle within the left ovary. At 9 months, a second spontaneous menstrual period was observed and *in vitro* fertilisation was performed. Normal foetal growth and development was confirmed via repeat ultrasonography and a healthy female infant was delivered via caesarean section after 38 weeks of gestation (Meirow et al. 2005). However, due to the fact that the cryopreserved ovarian tissue was transplanted into the pre-existing ovary of this patient, there is a small possibility that the ovulation may have been from the native ovary.

In 2006, Demeestere et al. (2006) reported a naturally conceived pregnancy in a woman who underwent orthotopic and heterotopic transplantation of cryopreserved ovarian tissue. Ovarian tissue was retrieved after one cycle of chemotherapy in November 1999. Following the completion of chemotherapy, the patient experienced 2 years of complete amenorrhoea and hormone therapy was initiated. At 4-years, the patient requested ovarian tissue transplantation which was conducted by the implantation of 18 ovarian tissue fragments (3 within the ovary and 9 within the peritoneal pocket, 6 subcutaneously above the left abdominal incision used for the trocar). The first spontaneous ovulation was observed 148 days post transplantation. Follicular development was observed in all three transplantation sites; with large follicles within the ovarian site, one dominant follicle within the peritoneal site and follicles <13mm in size within the heterotopic/subcutaneous site. In August 2005, the patient experienced her sixth luteinising hormone peak at day 11 of her cycle (E^2 410pg/ml); 13 days later the patient experienced vaginal bleeding. The presence of a viable intrauterine pregnancy was confirmed via ultrasonography after the investigators detected the presence of human chorionic gonadotrophin. Unfortunately, the patient experienced a miscarriage at 7 weeks of gestation due to aneuploidy. It is unclear if the miscarriage was related to the procedure (Demesteere et al. 2006).

Oktay (2006) described the incidence of spontaneous conception and live birth after heterotopic ovarian transplantation in a woman who received six courses of

chemotherapy and radiotherapy for Hodgkin's lymphoma. This treatment did *not* result in POF as alkylating agents were not utilised. Later, the patient relapsed and underwent autologous hematopoietic stem cell transplantation (HSCT); her left ovary was removed and cryopreserved before HSCT. After remaining in menopause for 2.5 years after HSCT, the patients requested for ovarian transplantation and the ovarian tissue was subcutaneously transplanted to the suprapubic area. A viable pregnancy was detected via ultrasound at a later date and a healthy female child was delivered at 40 weeks of gestation. It should be noted that the ovulation occurred from the native ovary and hence the pregnancy could not be attributed to the autotransplantation of ovarian tissue (Oktay 2006). This study highlights the importance of caution when interpreting spontaneous pregnancies in transplant patients with intact ovaries (especially in orthotopic transplantation) as there is a possibility, albeit low, that the conception may be due to ovulation of the native ovary and not from the transplanted ovarian tissue.

Transplantation of donor-sourced ovarian tissue

In 2005, a 24-year old prematurely menopausal woman achieved spontaneous conception and delivery after receiving syngeneic ovarian transplantation from her monozygotic twin sister. Ovarian function was restored within 3 months after transplantation and the patient conceived during the second menstrual cycle. A healthy female infant was born at 38 weeks gestation (Silber et al. 2005). Although ovarian transplantation between monozygotic twins will be rare; this report provides additional evidence that ovarian function can be restored and natural conception and successful pregnancy can be achieved after transplantation of ovarian tissue.

Researchers have also explored allogenic transplantation of donor ovaries as a means of restoring ovarian function in patients suffering from ovarian dysgenesis (Turner's syndrome) (Mhatre et al. 2005). As with other allogenic transplantations, issues relating to immunogenic compatibility and the use of immunosuppressants have been researched extensively. The latest study by Mhatre et al. (2005) on two patients who received donor ovaries reported successful establishment of menstrual cycles with the aid of cyclosporine and prednisolone. In one patient, spontaneous menstruation and ovulation was observed up to 2.5 years post-transplantation (Mhatre et al. 2005).

COST IMPACT

The cost of ovarian tissue cryopreservation and transplantation in Australia is not known. Overall, the cost of the procedure can be separated into four parts: the cost of the surgical act, which should be similar to a standard laparoscopy; ovarian cryopreservation which should be similar to the cost of cryopreserving testicular sperm after testicular dissection; the annual cost of ovarian tissue storage and the cost of transplantation (Poirot et al. 2002). In Australia, the cost of cryopreservation and storage of ovarian tissue is not covered by Medicare. A medical infertility treatment facility in Australia, Repromed, stated that the cost of frozen embryo transfer is approximately \$880 with a Medicare rebate of \$176; this should be somewhat similar for ovarian transplantation (Repromed 2007).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

The transplantation of cryopreserved ovarian tissue raises several ethical issues. It is possible for women beyond the age of menopause to receive these cryopreserved ovarian tissues as a method of hormone replacement therapy. In addition to this, the technique could also facilitate older women having access to their own 'young' eggs which were cryopreserved at an earlier date. In Australia, *in vitro* fertilisation centres limit the use of donor eggs to women within the reproductive age span; therefore the storage of a woman's own ovary from a younger age may prevent its usage at an older postmenstrual age (Wood et al. 1997).

In the case of *cancer*, ovarian tissue should not be transplanted into other women on medical grounds; due to the fact that the procedure would require the use of anti-rejection/immunosuppressive drug such as cyclosporine, which increases the risk of malignant disease (Wood et al. 1997).

OTHER ISSUES

It should be noted that cryopreservation and transplantation of ovarian tissue may be utilised in women with non-cancerous diseases as well, such as benign haematological diseases (sickle cell anaemia, thalassaemia major and aplastic anaemia) and autoimmune diseases previously unresponsive to immunosuppressive therapy (Donnez et al. 2006).

SUMMARY OF FINDINGS

The success of orthotopic ovarian transplantation in restoring spontaneous menstrual cycles is well documented within the scientific literature. A handful of case reports have reported live births as a result of autotransplantation of cryopreserved ovarian tissue; indicating that this procedure is capable of preserving fertility and does not appear to cause any visible harm to the infant. Despite the encouraging results to date, it is important to note that this procedure is still experimental and peer reviewed reports on live births have only just recently begun to surface.

HEALTHPACT ACTION:

At the time of writing, there are no clinical guidelines for the management of POF in Australia, resulting in varying clinical practices across Australia. The NHMRC and Cancer Australia will be advised of the evidence available on this technology; however no further assessment is warranted. This technique will therefore be archived.

NUMBER OF STUDIES INCLUDED

Total number of studies 6
Case reports

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SEARCH CRITERIA TO BE USED:

Ovary*/transplantation
Cryopreservation*
Infertility, Female/surgery*
Ovarian transplant