A series of monozygotic twins discordant for ovarian failure: ovary transplantation (cortical versus microvascular) and cryopreservation

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BACKGROUND: A series of monozygotic (MZ) twin pairs discordant for premature ovarian failure presented an unusual opportunity to study ovarian transplantation. METHODS: Ten MZ twin pairs requested ovarian transplantation and eight have undergone transplantation with cryopreservation of spare tissue. Seven had a fresh cortical tissue transplant, one of whom received a second frozen–thawed transplant after the first ceased functioning at three years. One had a fresh microvascular transplant. RESULTS: All recipients reinitiated ovulatory menstrual cycles and normal Day 3 serum FSH levels by 77–142 days. Six have already conceived naturally (one twice). Currently, two healthy babies have been delivered, and another three pregnancies are ongoing. The oldest transplant functioned for 36 months, resulting in one child and one miscarriage. She conceived again after a frozen–thawed secondary transplant. There was no apparent difference in return of ovarian function between the eight fresh ovarian grafts and the one frozen graft. CONCLUSIONS: Ovarian transplantation appears to restore ovulatory function robustly. Successful pregnancies, including one after cryopreservation, bode well for application to fertility preservation.

Keywords: cryopreservation; fertility; menopause; monozygotic twins; ovary; transplantation

The great majority of women enter menopause in their fifth or sixth decade of life, although ~1% undergo menopause prematurely, i.e. before 40 years of age (Coulam et al., 1986; Riboli et al., 2002; Luborsky et al., 2003; Goswami and Conway, 2005). Among numerous causes, premature ovarian failure (POF) frequently has a genetic aetiology and normal menopausal age is strongly heritable judging by the greater concordance between monozygotic (MZ) than dizygotic twins (Snieder et al., 1998; de Bruin et al., 2001; van Asselt et al., 2004).

It was remarkable, therefore, to identify a MZ twin pair in which one sister had undergone menopause for unexplained reasons at age 14 years, whereas the other, aged 24, was still fertile with three naturally conceived children, as well as normal ovulatory cycles and ovarian reserve (Silber et al., 2005). After the sterile twin received a graft of ovarian tissue from her sibling, she conceived naturally during the second menstrual cycle, and delivered a healthy baby at full-term. This case of discordant twins is not unique, however, and nine other twin pairs have subsequently consulted our center for ovarian transplantation in preference to conventional oocyte donation. The present paper provides a clinical evaluation of eight of the cases that have already undergone transplantation, extending a preliminary report (Silber and Gosden, 2007). It includes a novel report of cryopreserved cortical tissue and another showing results to date from a fresh microvascular ovarian transplant, a promising alternative strategy (Bedaiwy and Falcone, 2007).

Materials and Methods

Subject recruitment and consent

Eight MZ twin pairs aged 24–40 years presented with discordant ovarian function, one sibling of each pair having undergone POF by 34 years of age (one had primary amenorrhoea). POF was diagnosed after at least 12 months of unexplained amenorrhoea accompanied by elevated serum levels of gonadotrophins (one case had undergone bone marrow transplantation, indicating her POF was iatrogenic). Their sisters, in contrast, still had normal menstrual cyclicity, and six of the eight had successful pregnancy histories, and only one
miscarriage was reported (Donor for Case 2, i.e. 2D). None of the twin pairs was actively recruited. Each had enquired about treatment to restore normal reproductive endocrine function with fertile potential after hearing reports of the first successful ovarian transplant in a twin pair in 2005, as well as from researching an earlier testis transplant report for anorchia (Silber, 1978; Silber et al., 2005). The patients volunteered many reasons for preferring transplantation to conventional oocyte donation technology. Some of them had previous failures with donor oocyte cycles, or the twin had the opportunity to donate an ovary at the same time as having surgery for other gynaecologic problems (such as fibroids or cysts). All of them found the possibility of natural conception attractive. In some cases, the twins lived far apart (even in different countries) and the donors preferred to make a single visit for one-time donation, with the hope that frozen banked tissue could serve as a backup if the first transplant failed.

**Clinical profile**

These studies were carried out with informed consent under a protocol approved by the Institutional Review Board and the Ethics Committee of St. Luke’s Hospital, St. Louis, MO. The donors were informed that they may reach menopause slightly earlier than normal based on theoretical models and experimental studies (Gosden et al., 1989; Faddy et al., 1992) and were aware of the relative risks associated with unilateral oophorectomy. Harvesting a large biopsy was judged to be no greater burden or risk but would have provided less tissue for fertility restoration.

The reproductive history of each twin pair was reviewed and ovarian function was investigated by standard gynaecological procedures. Serum from peripheral blood was prepared for immunoadsorption of FSH, LH and estradiol (E2) three days after the start of menses in women who were cycling naturally, but not on any specific day in those with POF. Some prospective donors had been taking birth control pills or were pregnant at the time of presentation, rendering hormone measurements meaningless. The antral follicle count (AFC) was recorded by transvaginal ultrasound scanning. Spare tissue becoming available during oophorectomy of the donor and resection of ovarian cortex in the recipient was prepared by fixation in Bouin’s fluid, embedding in paraffin wax, sectioning and staining with haematoxylin and eosin (Fig. 1a and b).

**Genetic studies**

DNA fingerprinting confirmed the genetic identity of all eight twin pairs, who were also screened for common genetic causes of POF. Peripheral lymphocytes were prepared as DNA for testing genetic polymorphisms at 15 loci (Paternity Testing Corporation, Columbia, MO), and cultures (and in some cases spare ovarian medullary tissue) were karyotyped by the G-banding technique and fluorescent in-situ hybridization. DNA was also screened for the number of CGG repeats in the *FMR1* gene using Southern blot analysis or the polymerase chain reaction for fragile X syndrome (Silber et al., 2005). In addition, genomic DNA and lymphoblastoid cell lines were prepared for future genetic studies of the twin pairs.

**Cortical ovarian tissue transplantation**

The patients were scheduled for surgery within two weeks of confirming negativity for the human immunodeficiency virus type 1 and hepatitis B and C viruses. Under general anaesthesia, one ovary was removed from donors using laparoscopy or minilaparotomy. For the seven undergoing cortical tissue harvesting, the whole ovary was transferred to a Petri dish for dissection with a scalpel and toothed forceps. It was felt important to prepare a cortical tissue slice no thicker than ~1.0 mm to facilitate rapid revascularization while keeping the tissue constantly irrigated with ice-cold Leibovitz L-15 medium (Fig. 2a). The pared cortex was divided into three pieces of approximately equal size for grafting, one piece to each recipient ovary. The remaining third was cryopreserved in 1.5 M 1,2-propanediol and 0.2 M sucrose by slow freezing to liquid nitrogen temperatures (Newton et al., 1996; Gook et al., 1999). Remnants of trimmed tissue were set aside for histology and genetic studies.

The recipients were prepared by minilaparotomy via a 3.5 cm incision above the pubis. For cortical tissue transplantation, recipient ovaries were resected to expose medullary tissue (Fig. 2b); haemostasis was controlled with microbipolar forceps and irrigation with heparinised saline was performed to avoid formation of a haematoma between donor and recipient tissues. The tissue graft was trimmed to the dimensions of the exposed surface of the recipient organ and attached using 9-0 interrupted sutures under an operating microscope (Fig. 2c). The medullary bed was sutured to the under surface of the cortical graft with 9-0 sutures to maintain tight tissue approximation. Irrigation and meticulous pinpoint haemostasis were rigorous to avoid adhesion formation. In the case of bilateral absence of an ampulla (3R), the graft was attached to the Fallopian tube isthmus. The same procedure was used for 1R when she needed frozen–thawed tissue to replace the first graft that had ceased to function (Fig. 2d). After removing the first graft to accommodate the new one, the discarded tissue was prepared by histology and found to be completely devoid of follicles. All patients were released from the hospital the following morning, and had a rapid and uneventful recovery.

**Figure 1:** Case R2 showing (a) the absence of primordial or preantral follicles in ovarian biopsies of this candidate for ovarian transplantation compared with (b) that in her fertile sister.
Subsequently, the recipients kept a menstrual calendar and record of attempts to conceive naturally, except for case 3R, who will require IVF, and 8R, who has chosen to remain childless at present. On Day 3 of menstrual cycles, blood was drawn for assaying serum FSH levels and samples were subsequently taken at various intervals depending on circumstances, i.e. where the patients were living. A delay of more than two weeks after the expected time of menses prompted the testing of serum hCG. After a positive pregnancy test, abdominal ultrasound was used to verify the presence of a fetal sac and heartbeat at standard times during pregnancy.

**Whole-ovary transplantation**

To transplant an intact ovary, the donor ovary (8D) was removed by clamping the infundibular pelvic ligament at its base in order to obtain maximum length. The veins (3–5 mm) were easily identified, but the ovarian artery (0.3 mm) was not grossly visible. The entire specimen was placed in Leibovitz medium at 4°C and two veins and one artery were dissected and isolated under the operating microscope. Germinal vesicle oocytes were aspirated from antral follicles for *in vitro* maturation and vitrification at the metaphase II stage. Meanwhile, the recipient’s infundibular pelvic ligament was clamped at the base and transected close to her ovary (8R). The donor’s ovarian veins were then anastomosed to the recipient’s with 9-0 nylon interrupted sutures, and the ovarian arteries were anastomosed with 10-0 nylon interrupted sutures (Fig. 3a–d). When the microvascular clamps were removed, blood flow was observed by fresh bleeding from the surface of the ovary where a cortical slice had been taken for cryopreservation as a backup.

**Results**

**Patient profiles**

The clinical profiles of all eight twin pairs who have undergone ovarian transplantation between siblings are summarized in Table I. The recipients had become menopausal 2–26 years prior to case presentation, and at ages ranging from 13–34 years. All 16 women had normal 46, XX karyotypes and were free of *FMR-1* premutations. Serum hormone profiles confirmed POF in the recipients, with FSH being >50 mIU/ml, with LH and E2 levels also in post-menopausal ranges. Moreover, sonographic inspection verified the complete absence of antral follicles in both ovaries, confirmed by histology of ovarian tissue which revealed a complete absence of primordial and growing follicles (Fig. 1a). Apart from case 3R, the reproductive tracts of the other seven recipients were unremarkable, apart from diminutive ovaries. Case 3R reported that she had adrenarche but never experienced menarche, nor any menstrual cycles. At surgery, she was found to have bilateral absence of ovaries, tubal ampullae and fimbriae, although the isthmus and uterus were normal. In contrast to the recipients, their sisters had normal ovarian...
morphology, AFCs and Day 3 FSH levels (Table I). Histology confirmed that primordial follicles were located <1 mm below the ovarian surface. Four donors had previously undergone controlled ovarian stimulation for oocyte donation, and had demonstrated a normal ovarian reserve at that time. They strongly resisted suggestions to repeat this procedure. In cases 4D and 5D, the ovarian reserve of the donor was more marginal based on AFCs ($n = 11$ and $10$, respectively), though this had not prevented one of them becoming pregnant (Table II).

Apart from differential fertility, the twin pairs were generally in good health, apart from some issues that had no obvious association with POF. Case 4D had been treated successfully more than four years earlier for acute lymphoblastic leukaemia using a bone marrow transplant from her sister, who has never had cancer. She also had a large nevus birthmark on her face, unlike her sister who had no such birthmark. Case 6R required bilateral surgery during childhood for carpal tunnel syndrome, which is very unusual without obvious cause in someone so young, and she also had a rare eyelid tumour. Case 8R was suffering from severe osteoporosis, which reflected her refusal of estrogen replacement since entering menopause at 15 years of age.

Obstetric details were available for six of the ten twin pairs consulting our center (including two pending transplantation). Two were monochorionic-diamniotic, one was dichorionic-diamniotic and three were monochorionic-monoamniotic, which was a surprisingly high incidence since mono/mono is normally ~2% ($P < 0.0005$).

**Post-operative results**

All eight twin pairs underwent orthotopic ovarian isoctransplantation between April 2004 and January 2007. The recipients continued to cycle for about three years or were pregnant at the time of writing. Day 3 FSH levels returned to normal by 4.5 months of surgery (Fig. 4a), soon after ovulation had recommenced, judging by the results of BBT or home ovulation detection kits monitored by the patients themselves. Table II records that the refractory period for resuming menses after transplantation was 63–100 days, with the majority of subsequent cycles in the normal range of duration.

The first case, a 25-year-old recipient (1R), became pregnant the first time after her second menses without medical assistance, and subsequently delivered a healthy baby girl in 2005 following an uneventful pregnancy. After nursing for several months, she resumed menses and during the seventh cycle conceived naturally a second time, but this pregnancy miscarried. Three years after her transplant, she ceased cycling and hormone levels, which were measured monthly, became post-menopausal ($82$ mIU/ml FSH, $34$ mIU/ml LH and $13$ pg/ml $E_2$). After transplanting cryopreserved spare tissue, her hormones again returned to premenopausal levels after four months, a delay identical to her fresh transplant (Fig. 4b). She conceived again without any intervening menses approximately five months after her re-transplant.

Case 2R became pregnant at 39 years of age without medical assistance after her fifth menses, eight months after transplantation. She too delivered a healthy baby girl at full-term. Case 4R did not become pregnant until after the eighth menses and required oocyte retrieval for IVF during a natural cycle. This patient subsequently returned to a post-menopausal state, but has frozen ovarian tissue remaining for a re-transplant.

At this time, neither recipients 3R nor 5R are pregnant, although both continue to cycle. Case 3R was unable to conceive naturally, for reasons stated above, and 5R had a marginal AFC and was 41 years old by the time of first ovulation.

Case 8R was the only one to have a microvascular transplant and is continuing to cycle regularly seven months post-surgery (Table II). Her Day 3 FSH and LH fell to the lowest levels of

Figure 3: Steps in the procedure of intact ovary microvascular transplantation: (a) depiction of donor oophorectomy, (b) microsurgical isolation of donor ovary blood supply, (c) end-to-end anastomosis of ovarian blood vessel, (d) completed anastomosis of ovarian artery and veins
all the recipients (3.4 and 0.4 mIU/mL, respectively), and her post-operative ultrasound appeared normal.

All patients remain pleased with their decision to undergo transplantation, and even the patient requiring IVF preferred this option. Overall, out of the six recipients with patent Fallopian tubes, five have conceived thus far, and one of them three times.

**Discussion**

Including the first MZ twin pair presenting for ovarian transplantation in 2004, there have been eight comparable cases so far in whom the procedure has been performed, with two others pending. The twins were characterized by ovarian discordancy, a phenomenon that is not as rare as first assumed (Gosden et al., 2007). The ovaries with POF were diminutive, fibrous and completely lacking follicles at any stage, while serum gonadotrophins were correspondingly elevated and E2 was low. None of the medical histories provided an explanation for POF with afollicular ovaries in the recipients, except for 7R who had received chemotherapy. The clinical histories of POF in the other seven were idiopathic and consistent with congenital deficiency of germ cells. According to a mathematical model (Faddy et al., 1992), the follicle reserve at birth must be very small to account for POF as early as adolescence or young adulthood.

With a single exception, the reproductive tracts of the recipients were structurally normal and both ovaries were present, albeit as ‘streaks’ in some cases. In the agonadal case (3R), the tubal ampullae were bilaterally absent, indicating a concurrent Müllerian anomaly (Dueck et al., 2001). In mice, null mutations of Wil1 and Sf1 cause failure of ovarian development (Kreidberg et al., 1993; Luo et al., 1994), but their kidneys and adrenal glands are abnormal. The LIM homeodomain gene, Lhx9, is a more plausible candidate gene for a mutation in this woman, although Fallopian tubes are not known to be affected (Birk et al., 2000).

**Table I.** A series of monozygotic twins discordant for premature ovarian failure undergoing sister to sister ovarian transplantation: reproductive endocrinology before the transplant and pregnancy history before and afterwards.

<table>
<thead>
<tr>
<th>Twin Pair</th>
<th>Age at menarche (years)</th>
<th>Age at menopause (years)</th>
<th>Age at TP (years)</th>
<th>FSH (mIU/ml)</th>
<th>LH (mIU/ml)</th>
<th>Estradiol pg/ml</th>
<th>Antral follicle count</th>
<th>Pregnancy historya</th>
</tr>
</thead>
<tbody>
<tr>
<td>1D</td>
<td>11</td>
<td>–</td>
<td>24</td>
<td>OC</td>
<td>OC</td>
<td>OC</td>
<td>24</td>
<td>3/0/3</td>
</tr>
<tr>
<td>1R</td>
<td>11</td>
<td>14</td>
<td>28</td>
<td>82</td>
<td>34</td>
<td>13.0</td>
<td>0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>1RCb</td>
<td>10</td>
<td>38</td>
<td>49</td>
<td>96</td>
<td>24</td>
<td>71</td>
<td>20</td>
<td>2/1/1</td>
</tr>
<tr>
<td>2R</td>
<td>16</td>
<td>22</td>
<td>25</td>
<td>7.4</td>
<td>9.9</td>
<td>61</td>
<td>33</td>
<td>0/0/0</td>
</tr>
<tr>
<td>3R</td>
<td>14</td>
<td>PA</td>
<td>PA</td>
<td>53</td>
<td>23</td>
<td>16</td>
<td>Agonal</td>
<td>0/0/0</td>
</tr>
<tr>
<td>4D</td>
<td>13</td>
<td>28</td>
<td>34</td>
<td>9.4</td>
<td>5.2</td>
<td>32</td>
<td>11</td>
<td>2/0/2</td>
</tr>
<tr>
<td>4R</td>
<td>13</td>
<td>28</td>
<td>57</td>
<td>34</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>5D</td>
<td>12</td>
<td>40</td>
<td>6.2</td>
<td>–</td>
<td>–</td>
<td>10</td>
<td>0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>5R</td>
<td>11</td>
<td>14</td>
<td>54</td>
<td>70</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>6D</td>
<td>14</td>
<td>26</td>
<td>OC</td>
<td>77</td>
<td>56</td>
<td>0</td>
<td>0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>6R</td>
<td>14</td>
<td>25</td>
<td>101</td>
<td>41</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>7D</td>
<td>11</td>
<td>33</td>
<td>7.5</td>
<td>2.9</td>
<td>44</td>
<td>30</td>
<td>0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>7R</td>
<td>11</td>
<td>30</td>
<td>77</td>
<td>56</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>8D</td>
<td>14</td>
<td>–</td>
<td>37</td>
<td>OC</td>
<td>OC</td>
<td>–</td>
<td>2/0/2</td>
<td>–</td>
</tr>
<tr>
<td>8Rc</td>
<td>13</td>
<td>15</td>
<td>81</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>0/0/0</td>
</tr>
</tbody>
</table>

aPregnancies/pregnancy losses/live births or ongoing; bsecond transplant (cryopreserved tissue); cmicrovascular intact whole-ovary transplant. OC, currently using oral contraception; PA, primary amenorrhoea; TP, transplant.

**Table II.** Initiation of menstrual cycles, duration of ovarian function, and establishment of pregnancy in recipients of ovarian isografts (TP).

<table>
<thead>
<tr>
<th>Recipient</th>
<th>First menses Post-TP (Days)</th>
<th>Intermenstrual interval (median, range, days)</th>
<th>Pregnancy detected Post-TP (Days)</th>
<th>Cycle</th>
<th>Functional lifespan (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1R</td>
<td>80</td>
<td>62</td>
<td>167</td>
<td>2</td>
<td>975</td>
</tr>
<tr>
<td>1RCb</td>
<td>Pregnant</td>
<td>–</td>
<td>152</td>
<td>1</td>
<td>&gt;152</td>
</tr>
<tr>
<td>2R</td>
<td>93</td>
<td>25 (23–42)</td>
<td>250</td>
<td>5</td>
<td>&gt;815</td>
</tr>
<tr>
<td>3R</td>
<td>77</td>
<td>26 (20–51)</td>
<td>N/A</td>
<td>N/A</td>
<td>&gt;395</td>
</tr>
<tr>
<td>4R</td>
<td>82</td>
<td>25 (20–48)</td>
<td>286</td>
<td>8</td>
<td>739</td>
</tr>
<tr>
<td>5R</td>
<td>87</td>
<td>31 (28–38)</td>
<td>195</td>
<td>3</td>
<td>&gt;395</td>
</tr>
<tr>
<td>6R</td>
<td>82</td>
<td>25 (22–29)</td>
<td>336</td>
<td>9</td>
<td>&gt;430</td>
</tr>
<tr>
<td>7R</td>
<td>65</td>
<td>29 (20–40)</td>
<td>N/A</td>
<td>N/A</td>
<td>&gt;260</td>
</tr>
<tr>
<td>8Rb</td>
<td>100</td>
<td>27 (18–39)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aCryopreserved transplant; bMicrovascular intact ovary transplant. The symbol > indicates continuing to cycle or cycles interrupted by pregnancy—breast feeding.
Ovarian cortical grafting was chosen for the first seven procedures in preference to vascular anastomosis of the intact ovary because it is less invasive, carries minimal operative risk and reduces recovery time. The peripheral location of primordial follicles is likely advantageous for rapid revascularization, as well as for successful cryopreservation (Gosden et al., 1994; Newton et al., 1996; Oktay et al., 2001; Salle et al., 2002; Donnez et al., 2004; Meirow et al., 2005). Heterotopic sites might also give favourable outcomes, although no successful pregnancies have been reported to date and our patients preferred the chance of natural conception (Hilders et al., 2004; Kim et al., 2004; Oktay et al., 2004; Rosendahl et al., 2006).

In the eighth case, a whole-ovary microvascular approach was adopted at the patient’s request in the hope of maximizing the functional longevity of her transplant and providing the benefit of normal menstrual cycles. Judging from the five cycles she has had so far, as well as other endocrine signs of well-being, we suspect follicle ischaemia was minimal, as predicted from transplants of intact rat ovaries using vascular anastomosis (Wang et al., 2002).

There was remarkable consistency between subjects in the return of menses after ovarian transplantation. The refractory period of about three months was similar to autotransplants in the sheep model (Gosden et al., 1994), and consistent with estimates of the time taken for small follicles to grow to ovulatory size in humans (Gougeon, 1986). In some case reports of transplantation in cancer patients, a longer refractory period of up to nine months has been reported (Donnez et al., 2004, 2006; Meirow et al., 2005), but it is not clear whether the difference is due to technical aspects of surgery or patient selection, either of which could influence the speed of recovery and duration of graft function. While this evidence suggests that follicle dynamics are relatively normal once the transplant is fully active, the follicle reserve is bound to be compromised by ischaemia. Graft longevity is unpredictable and likely to be much shorter than normal ovaries in situ and, probably, shorter than whole-ovary transplants. It is less likely that the latency was due to cryopreservation per se, because the refractory time in Case 1 was virtually identical in fresh and frozen transplants.

This is the most extensive clinical series of orthotopic ovarian transplantation of which we are aware. Twins are unlikely to be the main candidates for this procedure in future, and the major application is likely to be for fertility preservation in cancer patients and possibly other women who need to delay childbearing. While neither ovarian autografts nor isografts should present any problem of histocompatibility, allografts are potentially at risk. Allografts might occasionally be considered if ovarian tissue is available from a young woman who previously donated bone marrow to the same patient, and the first such case was recently reported (Donnez et al., 2007). Tolerance may
apply in that rare circumstance, but mild immunosuppression would be acceptable and effective for some other cases (Mahtre et al., 2005). Reassuringly, well-matched (HLA) kidney transplant recipients on immunosuppression have favourable obstetric outcomes (Armenti et al., 2000).

We are only aware of four other births or ongoing pregnancies after re-implanting frozen ovarian tissue, and these were all for cancer patients (Donnez et al., 2004; Meirou et al., 2005; personal communications). This is not surprising for a new procedure involving patients who must delay transplantation until they are assured of long-term remission or await confirmation that their frozen tissue is free of malignant cells. No such concerns applied to the healthy twins, and the evidence from this series of the effectiveness of both fresh and frozen transplants gives hope that cryopreserved ovarian tissue can benefit other patients.

Acknowledgements

We thank Ellen Kutner and Sharon Fuller for help with preparation of this manuscript.

References


Submitted on August 15, 2007; resubmitted on January 14, 2008; accepted on January 23, 2008.