# Fresh Ovarian Tissue and Whole Ovary Transplantation

**Sherman J. Silber, M.D.**[1]

## ABSTRACT

A series of monozygotic (MZ) twin pairs discordant for premature ovarian failure presented an unusual opportunity to study ovarian transplantation. Ten MZ twin pairs requested ovarian transplantation and nine have undergone transplantation with cryopreservation of spare tissue. Eight had a fresh cortical tissue transplant, one of whom received a second frozen-thawed transplant after the first ceased functioning at 3 years. One had a fresh microvascular transplant. All recipients reinitiated ovulatory menstrual cycles and normal day 3 serum follicle-stimulating hormone levels by 77 to 142 days. Seven have already conceived naturally (three twice). Currently, seven healthy infants have been delivered out of 10 pregnancies. The oldest transplant ceased functioning by 3 years, but then she conceived again after a frozen-thawed secondary transplant. There was no apparent difference in return of ovarian function between the nine fresh ovarian grafts and the one frozen graft. Ovarian transplantation appears to restore ovulatory function robustly. Ten pregnancies, leading to seven healthy infants, including one after cryopreservation, bode well for application to fertility preservation.

**KEYWORDS:** Cryopreservation, fertility, menopause, monozygotic twins, ovary transplantation

Successful fresh human ovary transplantation was first reported between monozygotic twins discordant for premature ovarian failure (POF) using a cortical grafting technique.[1,2] Subsequently there have been a total of 9 consecutive successful ovary transplants with resumption of normal hormonal cycling and menstruation, with 10 pregnancies and 7 healthy infants born.[3–5]

The great majority of women enter menopause in their fifth or sixth decade of life, although ~1% undergo menopause prematurely (i.e., <40 years of age).[6–9] Among numerous causes, POF frequently has a genetic etiology, and normal menopausal age is strongly heritable judging by the greater concordance between monozygotic (MZ) than dizygotic twins.[10–12]

It was remarkable, therefore, to identify a MZ twin pair in which one sister had undergone menopause for unexplained reasons at 14 years of age, whereas the other, 24 years of age, was still fertile with three naturally conceived children, as well as normal ovulatory cycles and ovarian reserve.[1,3–5] 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 infant 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 article provides a clinical evaluation of nine of the cases that have already undergone transplantation,

[1]Infertility Center of St. Louis, St. Luke's Hospital, St. Louis, Missouri.

Address for correspondence and reprint requests: Sherman J. Silber, M.D., Infertility Center of St. Louis, St. Luke's Hospital, 224 South Woods Mill Road, St. Louis, MO 63017 (e-mail: silber@infertile.com).

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extending a preliminary report.[3] It includes the first case of cryopreserved cortical tissue in a noncancer patient and another showing results from a fresh microvascular ovarian transplant, a promising alternative strategy.[3,5,13]

## SUBJECT RECRUITMENT AND CONSENT

Ten (only nine underwent transplant) MZ twin pairs 24 to 40 years of age presented with discordant ovarian function, one sibling of each pair having undergone POF. Ovarian failure was diagnosed after at least 12 months of unexplained amenorrhoea accompanied by elevated serum levels of gonadotrophins. Their sisters, in contrast, still had normal menstrual cyclicity, and eight of the nine donors had successful pregnancy histories. None of the twin pairs was actively recruited. Each had inquired 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.[1,14] 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 gynecological 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 a onetime donation, with the hope that frozen banked tissue could serve as a backup if the first transplant failed.

## CLINICAL PROFILE

These studies were performed 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 might reach menopause slightly earlier than normal based on theoretical models and experimental studies[15,16] 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 gynecological procedures. Serum from peripheral blood was prepared for immunoassay of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol ($E_2$) 3 days after the start of menses in women who were cycling naturally but not on any specific day in those with POF. The antral follicle count (AFC) was recorded by transvaginal ultrasound scanning. Spare tissue becoming available during oophorectomy of the donor, and resection of the ovarian cortex in the recipient was prepared by fixation in Bouin's fluid, embedding in paraffin wax, and sectioning and staining with hematoxylin and eosin (Fig. 1A and B). In addition, much of the tissue was cryopreserved for future use.

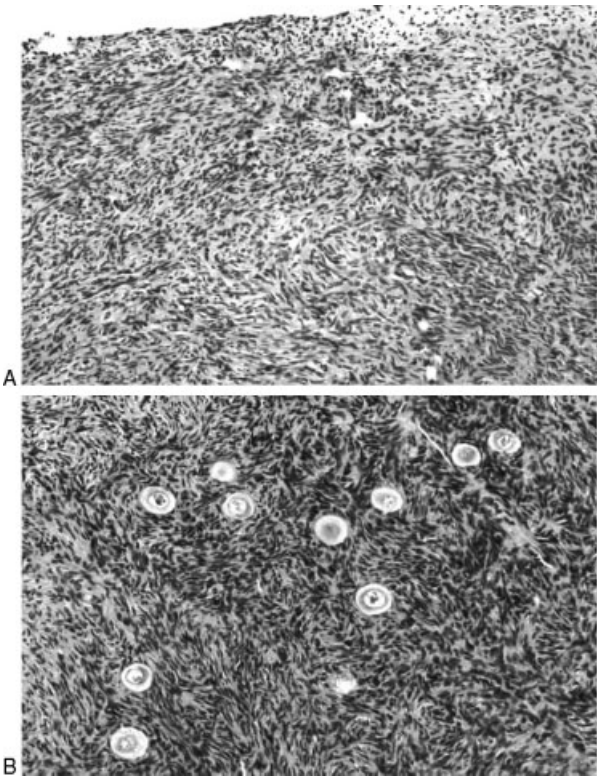


**Figure 1** (A) The absence of primordial or preantral follicles in ovarian biopsies of this candidate for ovarian transplantation compared with (B) that in her fertile sister.

## GENETIC STUDIES

DNA fingerprinting confirmed the genetic identify 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.[1] 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 2 weeks of confirming negativity for the human immunodeficiency virus type 1 and hepatitis B and C viruses. Under

general anesthesia, one ovary was removed from donors using laparoscopy or minilaparotomy. For the eight 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 or four pieces of approximately equal size for grafting, one piece to each recipient ovary. The remaining half of the cortical tissue was cryopreserved in 1.5 M 1,2-propanediol and 0.2 M sucrose by slow freezing to liquid nitrogen temperatures.[17,18] 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); hemostasis was controlled with microbipolar forceps, and irrigation with heparinized saline was performed to avoid formation of a hematoma 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 hemostasis were rigorous to avoid adhesion formation. The same procedure was used for frozen-thawed tissue to replace the first graft that may have 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. In the one case of bilateral absence of an ampulla, the graft was attached to the Fallopian tube isthmus.

## WHOLE OVARY TRANSPLANTATION

To transplant an intact ovary, the donor ovary was removed by clamping the infundibular pelvic ligament at its base to obtain maximum length. The veins (3 to 5 mm) were easily identified, but the ovarian artery

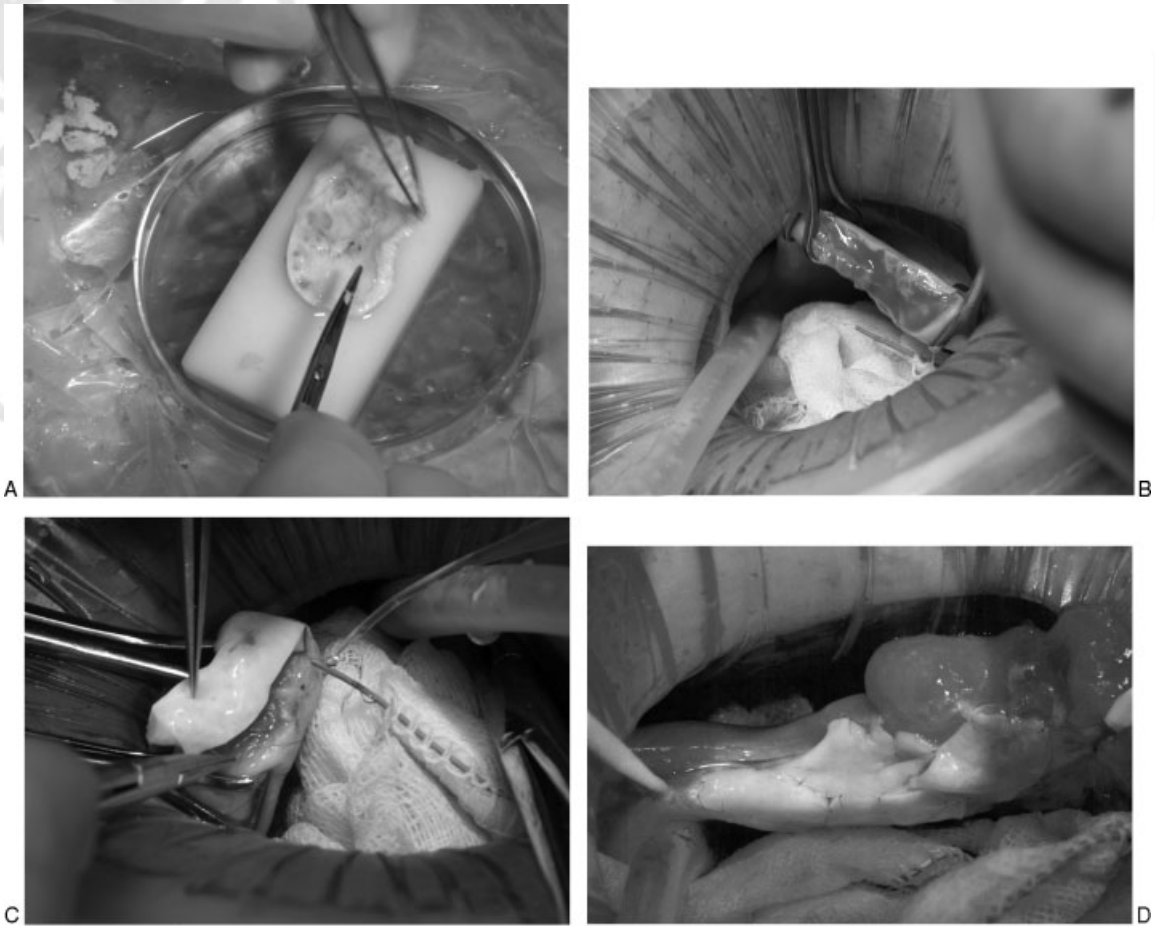


**Figure 2** Steps in the procedure of ovarian transplantation between monozygotic twin sisters. (A) Petri dish on ice. (B) Preparation of recipient ovarian medulla. (C) Attaching donor cortical tissue to recipient ovarian medulla. (D) Attaching thawed donor cortical tissue for retransplant to the recipient.

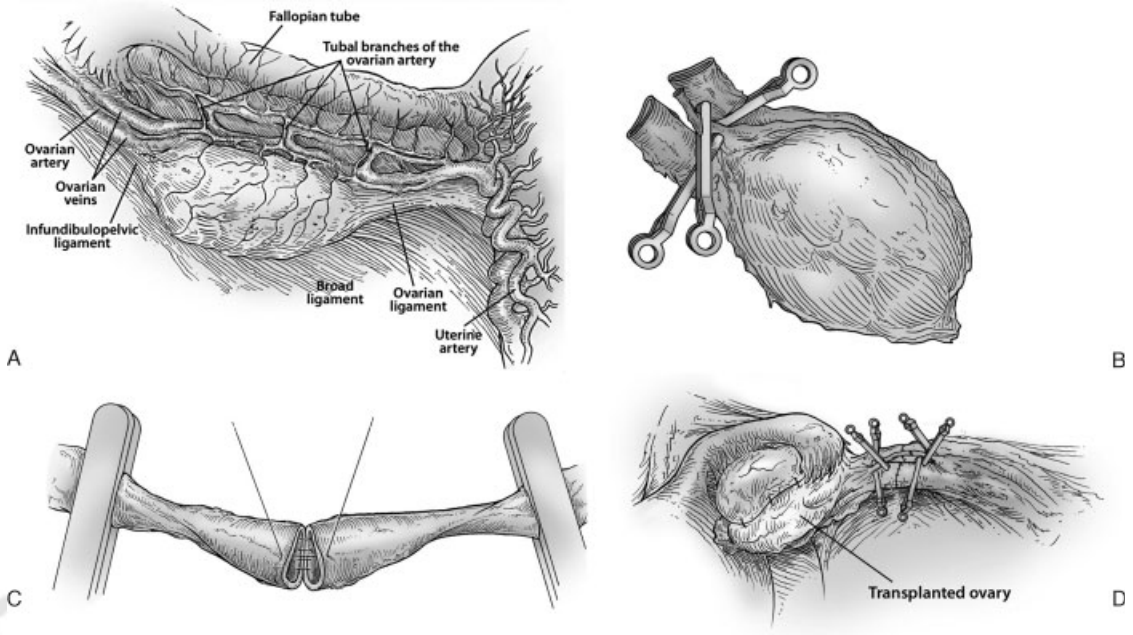


**Figure 3** Steps in the procedure of intact ovary microvascular transplantation. (A) Depiction of donor oophorectomy. (B) Microsurgical isolation of donor ovary blood supply. (C) End-to-end anastomosis of ovarian blood vessel. (D) Completed anastomosis of ovarian artery and veins.

(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. 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.

Obstetrical details from the twin births were only available for 6 of the 10 twin pairs consulting our center. Two were monochorionic-diamniotic, one was dichorionic-diamniotic, and three were monochorionic-monoamniotic, which was a surprisingly high incidence because mono/mono is normally ~2% ($p < 0.0005$). It is clear that late splitting predisposes the twins to discordant germ cell deficiency.

## POSTOPERATIVE RESULTS

All nine pairs underwent orthotopic ovarian isotransplantation between April 2004 and April 2008. The recipients continued to cycle over 3 years, although three of them whose donor had low AFC <10 only functioned for 2 years. 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 basal body temperature or home ovulation detection kits monitored by the patients themselves). The refractory period for resuming menses after transplantation was 63 to 100 days, with most subsequent cycles in the normal range of duration.

The first case, a 25-year old recipient, became pregnant the first time after her second menses without medical assistance, and she 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 postmenopausal (82 mIU/mL FSH, 34 mIU/mL LH, and 13 pg/mL $E_x$). After transplanting cryopreserved spare tissue, her hormones again returned to premenopausal levels after 4 months, a delay identical to her fresh transplant (Fig. 4B). She conceived again without any intervening menses ~5 months after her retransplant.

The second woman became pregnant at 39 years of age without medical assistance after her fifth menses, 8 months after transplantation. She too delivered a healthy baby girl at full term. At this time two recipients did not become pregnant, although both continue to cycle. One is unable to conceive naturally because of congenital absence of Fallopian tube ampullae and ovaries. Another had a marginal AFC and was 41 years of age. One woman had a microvascular transplant and is

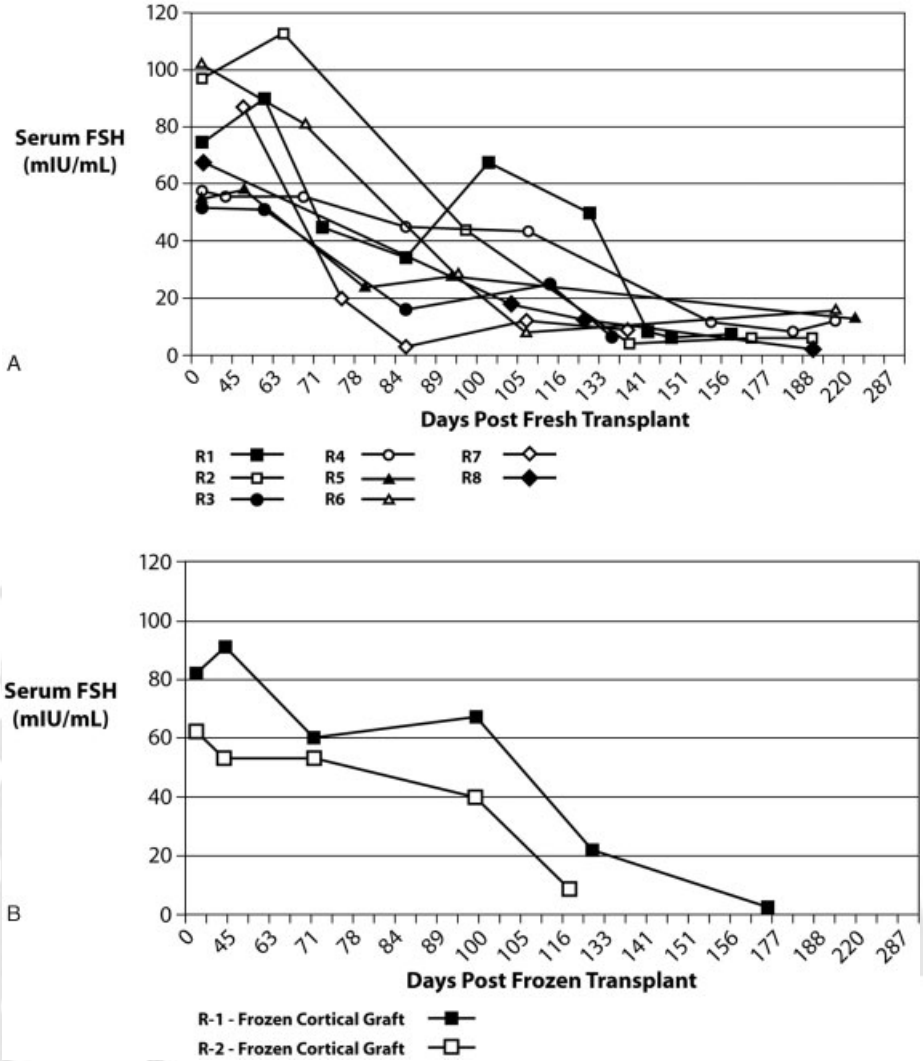


**Figure 4** (A) The eight fresh transplant cases showed a dramatic decline in day 3 serum follicle-stimulating hormone (FSH) by 80 to 140 days postoperatively corresponding approximately to the resumption of menses. The results of the microvascular whole ovary transplant are not significantly different from cortical grafts. (B) After a frozen cortical retransplant, serum FSH declined again to normal levels, similar to those of fresh transplants.

continuing to cycle regularly. Her day 3 FSH and LH fell to the lowest levels of all the recipients (3.4 and 0.4 mIU/mL, respectively), and her postoperative ultrasound appeared normal. She became pregnant and delivered a healthy infant 2 years later.

All patients remain pleased with their decision to undergo transplantation, and even the patient requiring in vitro fertilization (IVF) preferred this option. Overall, of the 8 recipients with patent Fallopian tubes, 7 have conceived thus far with 10 pregnancies and 7 live births.

## DISCUSSION

Including the first MZ twin pair presenting for ovarian transplantation in 2004, there have been nine comparable cases so far in whom the procedure has been performed. The twins were characterized by ovarian discordancy, a phenomenon that is not as rare as first assumed.[19] The ovaries with POF were diminutive, fibrous, and completely lacking follicles at any stage, serum gonadotrophins were correspondingly elevated, and $E_2$ was low. None of the medical histories provided an explanation for POF with afollicular ovaries in the recipients, except for one who had received chemotherapy. The clinical histories of POF in the other eight were idiopathic and consistent with a congenital deficiency of germ cells. According to a mathematical model,[16] 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, the tubal ampullae were bilaterally absent, indicating a concurrent Müllerian anomaly[20]

There may be nongenetic explanations for discordancy because MZ twins, like animal clones, are not phenotypically identical and other, nonovarian discordancies were observed in three twin pairs. One clue to ovarian discordancy might be the momoamniotic, monochorionic twin pregnancies, which were more frequent than expected.[21] The embryos are presumed to arise from late splitting postimplantation, perhaps as late as the primitive streak. If so, late splitting may be a risk factor for decreased ovarian reserve through misallocation of germ cell precursors, or perhaps epigenetic factors may affect the follicle reserve also. Correspondingly, there is an excess of imprinting defects in twin pregnancies.[22]

Conventional oocyte donation is the first line of treatment for patients with POF who want to become pregnant. Nevertheless, the robust results obtained in every case of this series of isogenetic twins offer confidence in ovarian transplantation as an alternative strategy for overcoming sterility. Although the surgery might seem more burdensome than oocyte retrieval, it is a straightforward and uneventful outpatient procedure, which has been effective in all nine cases in restoring menstrual cycles and enabling establishment of viable pregnancies. After ovarian transplantation, the patients were able to attempt natural conception every month without medical assistance. Accepting the risks of surgery, the procedure avoids the specific risks associated with IVF, notably ovarian hyperstimulation syndrome and multiple pregnancy, and moreover, it allows spare tissue to be cryopreserved in the event of graft failure. The number of successful retransplants will depend on the age of the patient and the number of follicles surviving, but the results of fresh and frozen cortical tissue from the first patient suggests that fertile potential may be restored cumulatively for over 8 years by serial transplantation.

Ovarian cortical grafting was chosen for the first eight 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 advantageous for rapid revascularization, as well as for successful cryopreservation.[2,17,23–27] Heterotopic sites have produced no successful pregnancies to date, and our patients preferred the chance of natural conception.[28–31] In the last case, a whole ovary microvascular approach was adopted at the patient's request in the hope of maximizing the functional longevity of her transplant.[5] We suspect follicle ischemia was minimal, as predicted from transplants of intact rat ovaries using vascular anastomosis.[32]

There was remarkable consistency between subjects in the return of menses after ovarian transplantation. The refractory period of ~3 months was similar to autotransplants in the sheep model[2] and consistent with estimates of the time taken for small follicles to grow to ovulatory size in humans.[33] In some case reports of transplantation in cancer patients, a longer refractory period of up to 9 months has been reported,[25,26,34] 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. Although this evidence suggests that follicle dynamics are relatively normal once the transplant is fully active, the follicle reserve might be compromised by ischemia. Graft longevity might be affected by graft ischemia time or by cryopreservation damage. This is now the subject of intense study.[27]

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 the future, and the major application is likely to be for fertility preservation in cancer patients and possibly other women who need to delay childbearing. Although neither ovarian autografts nor isografts should present any problem of histocompatability, 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 reported in 2007.[35] Tolerance may apply in that rare circumstance, but mild immunosuppression would be acceptable and effective for some other cases.[36] Reassuringly, well-matched (human leukocyte antigen) kidney transplant recipients on immunosuppression have favorable obstetrical outcomes.[37]

At the time of this writing, we are only aware of four other births or ongoing pregnancies after reimplanting frozen ovarian tissue, and these were all for cancer patients.[25,26,38,39] 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. We had no such concern in this series, which offers a better chance to evaluate this technique in both fresh and frozen grafts from the same individual. No such concerns applied to the healthy twins, and the evidence from this series of the effectiveness of both fresh and frozen transplants offers hope that cryopreserved ovarian tissue can benefit other patients.

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