

# Ovarian Tissue Transplants Look Promising

BY CHRISTINE KILGORE

Recently published reports from both sides of the Atlantic on ovarian tissue transplants suggest that the grafts have reasonable longevity and offer support for the development of cryopreservation and transplantation as a method of fertility preservation, U.S. experts told this news organization.

In a report from Denmark published online in *Human Reproduction*, investigators described the case of a woman who gave birth to her second child almost 3 years after six strips of frozen and thawed ovarian tissue were transplanted back to her ovary (2010 Feb. 25 [doi:10.1093/humrep/deq033]).

The woman became pregnant with her first child after mild ovarian stimulation soon after the transplant, but conceived naturally for her second pregnancy.

Another report published online in the American Society for Reproductive Medicine's journal *Fertility and Sterility* describes pregnancies and healthy babies in two groups of patients: a series of women who had premature ovarian failure and received a fresh donated ovary from a monozygotic twin and several women who had cryopreserved tissue transplanted (2010 Feb. 19 [doi:10.1016/j.fertnstert.2009.12.073]).

"What all this research suggests is that we're developing a body of evidence that indicates that it's possible to freeze and thaw ovarian strips and transplant them back," resulting in successful preg-

nancies, said Dr. William Gibbons, ASRM president and professor and division director for reproductive endocrinology and infertility at Baylor College of Medicine in Houston. "Definitely, researchers have demonstrated proof of concept," he said.

Comparing outcomes after fresh and frozen transplantation, as was done in the *Fertility and Sterility* report, is important for understanding the extent to which follicles are lost from cryopreservation, compared with ischemia, he noted.

Among the nine women described in the report who had transplantations of fresh ovarian tissue from their monozygotic twins, 12 pregnancies have occurred without assisted reproductive technology (ART) and eight healthy babies have been born to six of these women thus far, reported Dr. Sherman Silber of the Infertility Center of St. Louis and his associates.

Each of the women returned to regular menses and ovulatory cycles 60-130 days after one-quarter to one-third of the donor ovary was transplanted as a cortical slice, and conception often occurred within the first year after surgery. One woman conceived after 3 years, however, and another had her second child more than 4 years after her transplant, they reported.

One of the women who had given birth to a healthy child after the transplant of fresh ovarian tissue became menopausal after about 3 years and had a second transplant of some of her twin's

tissue that had been frozen. She became pregnant and gave birth to another healthy child. The patient again became menopausal another year-and-a-half later, had a second frozen graft, and was carrying her third child at the time of publication.

Another patient described in the report had a healthy ongoing pregnancy following a frozen transplant of tissue that she had cryopreserved 11 years earlier before treatment for Hodgkin's lymphoma.

Overall, the experience of these patients shows that pregnancy results after frozen transplantation are "as robust" as after fresh transplantation, although the duration of function may be shorter, Dr. Silber said in an interview.

"We used to think that freezing doesn't do any damage, and that the only damage is from ischemia," he commented. "Now, our thinking has flipped. ... Lengthy ischemia does not appear to be a major issue."

Research has shown, meanwhile, that with standard "slow freezing" cryopreservation techniques, ovarian tissue loses about 50%-60% of its eggs. Dr. Silber said he is finding that vitrification—a "fast-freeze" process, in essence—may be more effective, resulting in percentages of viable oocytes that are "remarkably similar" to those found in fresh tissue grafts.

Reports of ovarian tissue transplants in cancer patients have generated questions about whether pregnancies are indeed

achieved from eggs in the transplanted strips rather than eggs in the original ovary.

Dr. Silber said that, in the cases he and his associates looked at, they found no follicles during "intensive examinations" of patients' existing ovaries.

And in the European paper, Dr. Erik Ernst of Aarhus (Denmark) University Hospital and his colleagues reported that a biopsy obtained from the ovary in situ of their patient "revealed no remaining follicles upon histological examination."

The patient treated in Denmark had previously had her left ovary removed because of a dermoid cyst involving the whole ovary. Approximately one-third of the right ovary (13 strips) was removed prior to chemotherapy for Ewing's sarcoma.

Among Dr. Silber's patients, there have been few miscarriages to date and no birth defects or obstetric complications associated with transplantation.

Questions remain, however, about "what can be done with frozen ovarian tissue of the leukemia survivor if there happen to have been leukemic cells in that tissue," he and his associates wrote in their report.

"But for patients in whom there is no significant risk of ovarian metastasis, ovary tissue transplantation may now be ready for clinical use," they said, noting that at least 1 in 250 women of reproductive age is a cancer survivor. ■

*Disclosures: None was reported.*

## IM Progesterone Delays Luteal Phase Bleeding

BY PATRICE WENDLING

ATLANTA — Intramuscular progesterone delayed the onset of luteal phase bleeding, compared with Crinone 8% progesterone vaginal gel in nonpregnant women undergoing in vitro fertilization and embryo transfer in a prospective trial involving 365 patients.

"This isn't necessarily a good thing because it gives them false hope," lead researcher Dr. Elena Yanushpolsky said in an interview. "Patients think they're pregnant for a longer time when they're not, and the injections are painful."

Several meta-analyses as well as a recent large prospective, randomized trial have compared the efficacy of Crinone and intramuscular progesterone (IMP) for luteal phase support during in vitro fertilization (IVF) and reported similar pregnancy rates and IVF cycle outcomes.

However, a few studies observed an increased incidence of luteal phase bleeding in patients supplemented with Crinone.

In the current study, patient-reported luteal phase bleeding occurred with equal frequency among pregnant patients in the Crinone and IMP arms (22% vs. 19%). This was true for ongoing pregnancies (13% vs. 18%), as well as for failed pregnancies (40.5% vs. 21%).

Among nonpregnant women, however, the incidence of luteal phase bleeding was significantly higher at 56.5% in women treated with Crinone vs. 38% in those given IMP.

This effect was ameliorated by the administration of estrogen, according to Dr. Yanushpolsky and her col-

leagues at the Brigham and Women's Hospital in Boston.

"It's an issue of hormone metabolism, but not efficacy," she said.

Overall, pregnancy rates were similar at 67% among the 190 Crinone patients vs. 64% among the 175 IMP patients, the investigators reported in a poster at the

**VITALS** **Major Finding:** Among nonpregnant women, the incidence of luteal phase bleeding was significantly higher at 56.5% in women treated with Crinone vs. 38% in those given intramuscular progesterone.

**Data Source:** A prospective trial involving 365 patients.

**Disclosures:** The study was supported in part by EMD Serono Inc., which distributes Crinone. Dr. Yanushpolsky disclosed receiving compensation from Columbia Laboratories for time and travel expenses to present the data. Her coauthors disclosed being members of the scientific advisory boards for MediCult, Humagen, MidAtlantic Diagnostics, WIN Fertility, and EMD Serono.

annual meeting of the American Society for Reproductive Medicine.

There were no differences in age or day 3 follicle-stimulating hormone (FSH) levels between patients who experienced bleeding and those who did not, but those who had luteal phase bleeding had significantly lower pregnancy and delivery rates, and a significantly higher likelihood of failed pregnancy.

The investigators theorized that IMP may delay bleed-

ing because of some metabolite, while the addition of estrogen may play a role in delaying the breakdown of the endometrial lining in nonpregnant women given Crinone.

Dr. Yanushpolsky noted that anecdotally, clinicians were also reporting a low incidence of luteal phase bleeding with estrogen supplementation in women receiving either IMP or Crinone.

This prompted a post hoc analysis in 90 patients who received luteal estrogen supplementation in addition to their study medication, demonstrating that estrogen supplementation reduces luteal phase bleeding, but does not improve IVF outcomes.

Overall, patients supplemented with estrogen experienced significantly fewer episodes of luteal phase bleeding than those who did not receive estrogen (14% vs. 35%,  $P = .0002$ ).

This was true within the Crinone (17% vs. 38%) and IMP treatment arms (12% vs. 30%), and among nonpregnant (23% vs. 55%) and pregnant (10% vs. 24%) patients.

Pregnancy rates, however, were similar at 64% among those who received estrogen support vs. 65% among those who did not.

Likewise, there was no difference in pregnancy rates when patients received estrogen supplementation or did not in either the Crinone arm (65% vs. 67%) or IMP arm (63% vs. 62%).

Women in the study received either IMP 50 mg/day starting 24 hours after egg retrieval or Crinone 8% gel starting 48 hours after retrieval. Their mean age was 34 years. ■