Two Ovarian Transplants Result in Normal Births

BY KATE JOHNSON
Montreal Bureau

Two recent births that were made possible by maternal ovarian transplant procedures were achieved with markedly different techniques and approaches.

U.S. expert Sherman Silber, M.D., of St. Luke's Hospital, St. Louis, performed an ovarian allotransplant between 24-year-old identical twins, one of whom had premature ovarian failure. The procedure restored the patient's fertility and her ability to conceive naturally (N. Engl. J. Med. 2005;353:58-63).

In Israel, the transplant performed by Dror Meirow, M.D., of Chaim Sheba Medical Center in Tel Hashomer, and colleagues was an autotransplant of a 28-year-old cancer patient's previously frozen healthy ovarian tissue. Conception was achieved through in vitro fertilization (N. Engl. J. Med. 2005;353:318-21).

In the U.S. patient—a woman who had experienced premature ovarian failure at age 14—laparoscopic examination and ovarian biopsy showed atrophic, elongated ("streak") gonads with no follicles and a small uterus with an otherwise normal reproductive tract. Her donor sister had three children who had been conceived naturally, and she had been using oral contraception in the year preceding the procedure.

The donor's ovary was laparoscopically removed and the cortical tissue dissected ex vivo. Meanwhile, the recipient underwent a minilaparotomy during which the cortex of each streak ovary was resected, exposing the raw surface of the medulla.

Hemostasis was meticulously controlled with the use of pinpoint microbipolar forceps and continuous irrigation with heparin-treated saline to prevent the formation of a hematoma under the graft. The amount of cautery was also minimized to avoid impairing revascularization.

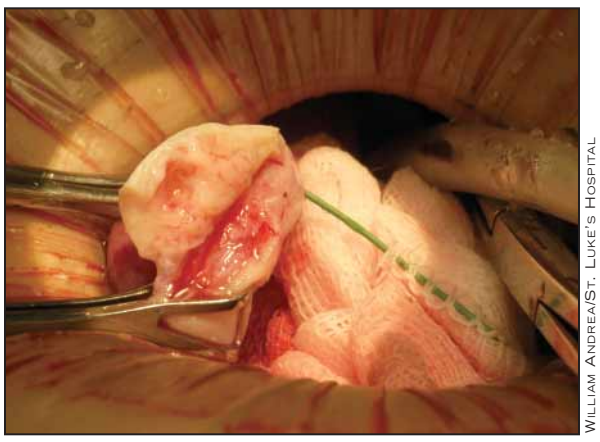
One-third of the donor ovary was sutured onto the raw medulla of each recipient ovary, and the remaining third was frozen. Analysis of spare tissue from the recipient's ovaries confirmed that there was extensive fibrosis and that there were no follicles.

Both sisters returned home 1 day after the procedure.

At 71 days after transplantation, a 14-mm follicle was observed in the recipient, her serum estradiol level was 154 pg/mL, and her uterine lining was 8 mm thick. Her first postoperative menses occurred at 80 days, although it lasted only a single day. Her ovaries remained quiescent until 128 days after the procedure when another 14-mm follicle was observed. Her serum estradiol level was 193 pg/mL, and the thickness of her uterine lining was 10 mm. At 142 days after the procedure, she had a heavy menstrual period.

On day 26 of her second menstrual cycle, her β-hCG level (828 mIU/mL) indicated that she was pregnant, and 5 weeks after her second menstrual period, a normal intrauterine pregnancy was confirmed by ultrasound. She gave birth vaginally to a healthy infant at 38 weeks' gestation.

"It is extremely unlikely that the restoration of ovarian function in this patient after transplantation was due to residual follicles in the streak ovary of the recipient," Dr. Silber and his associates wrote. "She had a decade-long history of amenorrhea with elevated gonadotropin levels on all occasions on which they were measured and no detectable follicles on pathologic examination."



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One-third of the donor twin's ovary was sutured to each ovary of the recipient twin in the U.S. case.

The Israeli transplant patient had experienced ovarian failure after high-dose chemotherapy for non-Hodgkin's lymphoma. Ovarian tissue containing many primordial follicles was harvested and frozen before she underwent high-dose chemotherapy but after she had undergone a second-line conventional chemotherapy regimen.

The patient remained free of disease 24 months after undergoing chemotherapy, at which point she requested autotransplantation of the thawed ovarian tissue. Strips of the tissue were transplanted to the left ovary, and small fragments were injected into the right ovary. Menstruation resumed spontaneously 8 months later, and baseline levels of antimüllerian hormone, which were previously undetectable (consistent with ovarian failure), were high—consistent with the presence of active follicles in an early stage of growth.

This was followed by a rise in inhibin B to levels reported in ovulatory women. At this time, ultrasonography revealed a preovulatory follicle in the left ovary.

"The time from transplantation to recovery was compatible with the time needed for the growth and maturation of primordial follicles," Dr. Meirow and colleagues wrote. The next month, another spontaneous menstrual period occurred, after which modified natural-cycle in vitro fertilization was performed. A single egg was retrieved and fertilized, and a four-cell embryo was transferred to the uterus. A healthy infant was delivered by cesarean section at 38 weeks' gestation. ■

DRUGS, PREGNANCY, AND LACTATION

Antihyperlipidemic Agents

BY GERALD G. BRIGGS, B.PHARM.

The large antihyperlipidemic class of drugs can be subdivided into bile acid sequestrants, HMG-CoA reductase inhibitors, fibric acid derivatives, ezetimibe, and niacin. With the possible exception of familial hypercholesterolemia, there appears to be no maternal benefit for the treatment of hyperlipidemia during gestation. Nearly all reported pregnancy exposures have occurred accidentally. If treatment is required, only bile acid sequestrants are considered compatible in pregnancy and lactation.

Ezetimibe (Zetia) also appears to be low risk in gestation, but not in lactation. Because most drug-induced adverse effects (about two-thirds) in nursing infants have been reported during the first month after birth, delaying treatment of a nursing mother until after this period appears to be the best course.

Cholesterol is the precursor of bile acids that are excreted from the liver and gallbladder into the intestine to aid in the digestion of fat in food. Bile acid sequestrants—cholestyramine (Questran and various other names), colestipol (Colestid), and colesevelam (WelChol)—are anion exchange resins that form insoluble complexes with bile acids in the intestine. The complexes are then excreted in the feces, removing cholesterol from the system.

Cholestyramine has been used as a treatment for intrahepatic cholestasis of pregnancy and as an antidote for some types of diarrhea, chlordecone pesticide poisoning, and digitalis toxicity. Because bile acid sequestrants are not absorbed into the systemic circulation, they do not represent a direct risk to the embryo or fetus and are considered compatible with pregnancy (all are rated risk factor B) and lactation. However, the resins also bind fat-soluble vitamins (vitamins A, D, E, and K) in the gut, and deficiencies of these vitamins may result.

The six HMG-CoA reductase inhibitors (statins) are atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor, Altocor), pravastatin (Pravachol), rosuvastatin (Crestor), and simvastatin (Zocor). All are contraindicated in pregnancy (risk factor X). Case reports and surveillance studies have described healthy outcomes from a number of pregnancies inadvertently exposed in the first trimester and later. The largest number of cases (187) were reported with simvastatin, with 86 cases that could be evaluated: 74% had normal outcomes, 15% resulted in spontaneous abortion, 6% of cases demonstrated congenital anomalies, 4% of cases had effects related to prematurity, and 1% resulted in fetal death. Three of the five birth defect cases were not related to simvastatin because of the timing of exposure or the outcome was a known chromosome defect. The remaining two cases involved unilateral cleft lip and a clubfoot, neither of which appear to be attributable to simvastatin.

In contrast, a 2004 reference described 178 cases of first-trimester exposure to statins reported to the Food and Drug Administration. Among the 52 cases suitable for evaluation, there were 20 major malformations, some thought to be consistent with inhibition of cholesterol biosynthesis. All 20 defects involved a lipophilic statin (atorvastatin), cerivastatin (Baycol), lovastatin, or simvastatin. No defects were reported with pravastatin, a hydrophilic agent with low tissue penetration that is not associated with animal developmental toxicity. These results are controversial, and controlled studies are needed to determine if there is a causal relationship. Because all statins are probably excreted into milk, women taking these drugs should not breast-feed.

Among the fibric acid derivatives, only gemfibrozil (Lopid) has some human data. The other agent, fenofibrate (TriCor), has no human data. The animal data (developmental toxicity in two animal species at doses up to 10 times the human dose) for each drug suggest there may be a risk to the human embryo or fetus. Thus, the safest course is to avoid these drugs in pregnancy (both are risk factor C). Although there are no data, the drugs are probably excreted into milk, and women on these agents should not breast-feed because of the potential toxicity, such as tumors, in their infants.

Ezetimibe (risk factor C) selectively inhibits the intestinal absorption of cholesterol and related phytosterols. At doses up to 10 times the human dose, the drug is teratogenic in rats but not in rabbits. Human pregnancy exposures have not been reported. If therapy during pregnancy is mandated, ezetimibe appears to be a better choice than statins. There are no data on use during lactation, but the drug is probably excreted into milk. Toxicity is a potential concern, and nursing infants should be monitored for headache, diarrhea, arthralgia, pharyngitis, sinusitis, and other adverse effects observed in adults.

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