The Ethical Ramifications of Recent Advances in Ovarian Transplantation

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Ovarian transplantation, for all its apparent novelty, has a long history: as Oktay and Yih observe, "The idea of fresh orthotopic autologous ovarian transplantation in humans is neither novel nor sophisticated; a New York surgeon reported on this technique as early as in 1906." However, fresh autologous transplantation -- removing the ovary from the same location to which it is retransplanted -- is not particularly useful in itself; rather, two modern advances, frozen autologous transplantation and heterologous transplantation, have returned ovarian transplantation to the spotlight. The former, made possible by improved cryopreservative technology, enabled a woman, Ouarda Touirat, whose ovaries were removed and frozen while she underwent chemotherapy, to become pregnant after ovarian retransplantation. Meanwhile, Dr. Sherman Silber’s transplant of fresh ovarian tissue between identical twins Melanie Morgan and Stephanie Yarber has transformed heterologous ovarian transplantation from a philosophical thought-experiment into a genuine possibility.

Before the above procedures become standard medical practice, they deserve an ethical analysis that is informed by up-to-date literature. When compared to ARTs such as embryo cryopreservation, ovarian transplantation has the advantage of avoiding the creation or destruction of potential human life. However, as Robertson states in his discussion of an autologous ovarian transplant following cryopreservation,

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Although this advance is unlikely to generate the controversies that reproductive innovations such as surrogacy and cloning have, important ethical issues will arise if such techniques lead to premenopausal ovarian storage by healthy women or ovary donation from cadavers or fetuses.\(^5\)

The former issue Robertson raises relates to autologous transplantation, while the latter involves concern about heterologous transplants. Since many ethical problems in autologous transplantation also apply to heterologous transplantation, I will initially consider autologous transplantation, and then move on to issues unique to heterologous donation.

This call to consider ethical issues is not a demand for a halt or slowdown in progress -- in fact, I hope to do just the opposite. Effective ethical analysis will suggest new areas in which this technology might be useful and should be accelerated, while realistically assessing its limitations in other arenas. In particular, I hope to treat religious views not as a roadblock to technological progress, but as an encouragement to develop technologies that serve patients whose religious beliefs prevent them from using current ARTs.

**AUTLOGOUS TRANSPLANTATION**

Recent work on autologous ovarian transplantation has focused on cryopreservation of ovarian tissue, which enables strips of an ovary to be stored while ovary-damaging procedures, such as chemotherapy and radiotherapy, are performed on the patient.\(^6\) These strips can then be retransplanted into the patient after the therapy is complete.

The interim cryostorage of ovarian tissue produces ethical questions that parallel those raised by similar ARTs, such as oocyte and embryo cryopreservation. Imagine a patient who dies from complications of chemotherapy after her ovaries have been removed and cryopreserved. Had she had oocytes or embryos
preserved, her partner or other family members might want to use them for vitro fertilization and/or surrogate gestation. This produces two ethical challenges:

1) difficulties in confirming the deceased's intent to become a genetic parent
2) concern for the welfare of the offspring, who will lack a biological mother

(2) can be countered on the grounds that posthumous donation is analogous to anonymous oocyte or sperm donation, which is not thought to harm the offspring.7 However, this analogy is not perfect. Children of an anonymous oocyte donor will be unlikely to know the life story of their biological mother, while children of a posthumous donor will likely be raised with a full and perhaps saddening knowledge of their dead parent. Claim (1) seems even more troubling: imagine the case of a parent bringing grandchildren into the world against the wishes of a (now-dead) child, for example. Notwithstanding these issues, however, oocyte and embryo cryopreservation do make posthumous procreation possible.

In contrast, the ovarian tissue cryopreservation patient would likely be unable to procreate posthumously. Heterologous transplantation of the ovary would be fraught with immunological problems.8 Neither in-vitro ovarian maturation nor ovarian xenotransplantation into immunodeficient mice, which would avoid organ rejection problems, are medically mature technologies; the latter is also ethically and epidemiologically problematic.9 The ovary would therefore be unable to produce oocytes, because no location to which it might feasibly be transplanted would exist.

This limitation might be considered an advantage. Unlike a cryopreserved embryo, where the moral status of the embryo and the claim of the father must be considered, cryopreserved ovarian tissue would be an extension of the patient's body, only usable as long as she exists. However, whether this restriction is counted a benefit or a disadvantage, the appropriate disposal
procedure for "stranded" ovarian tissue in the case of donor death -- should it be discarded? stored indefinitely in hope of advances in transplant technology? donated to research? -- must be established before ovarian tissue cryopreservation moves from experimental technique to standard medical practice.

A second issue involves safety and patient access. Respect for patient autonomy suggests that ovarian cryopreservation could be permissible even in the absence of clear medical indications such as cancer:

The autonomy of both males and females should be respected. Each person should be able to take measures to preserve his or her fertility whether threatened by disease or voluntary chosen interventions (such as vasectomy) or life-plan considerations (the wish to have a child later).10

Ovarian cryopreservation promises women the same fertility-preservation options that sperm banking currently offers men. As well, cryopreservative technology could remove age-related gender inequalities both by decreasing the danger of aneuploidy caused by aging ovaries and by allowing reproductive potential to continue beyond current menopause. As such, ovarian cryopreservation seems potentially both practically and ethically beneficial to patients who are not in danger of cancer. As Dr. Sherman Silber's infertility clinic states, "Ovarian tissue freezing is a new solution for these women who feel that by the time they do get married, or are otherwise ready to start a family, they will have lost all of their fertile eggs due to the aging process."11

However, the greater invasiveness and lower effectiveness of ovarian cryopreservation upsets the comparison with sperm banking. The ESHRE Task Force argues that the surgery is not medically beneficent:

Whilst the use of frozen-thawed sperm has become routine, the case is different for reproductive tissue cryopreservation. In view of the lack of suc-
cess and clinical applications in the case of ovarian tissue, this application should not be offered to women as a means to preserve their fertility potential when there is no immediate threat to their fertility.¹²

Robertson argues for a ban by invoking another ethical principle, that of non-maleficence:

[T]he burdens of elective oophorectomy would seem so much greater than the benefits that a physician who performed an oophorectomy in this situation might well be violating the medical ethical principle *primum non nocere.*¹³

The clash between autonomy and beneficence/non-maleficence suggests a combination of both principles. Given that women have no fertility preservation method as effective as sperm banking—embryo freezing requires a partner, oocyte freezing is still unreliable,¹⁴ and both require risky, expensive, and complicated ovarian stimulation—experimental research into ovarian tissue cryopreservation should be encouraged and accelerated as a means to gender equity. Simultaneously, concern for gender equity implies that strong standards, possibly including restrictions on availability of oocyte cryopreservation outside of experimental studies, must be enforced to ensure that society does not foist unsafe fertility management treatments on women rather than providing support for fertility choices that do not involve invasive surgery, such as flex-time work and maternity leave. This demand for evidence is no different from what is expected of any other ART; the issues of gender equity simply make it more important.

Finally, I will consider an surprising possibility for autologous ovarian transplantation. Retransplantation can be performed either heterotopically, where the ovary is retransplanted to another site in the body (often the forearm), or orthotopically, where the ovary is returned approximately to its
prior location in the pelvis. The latter method allows for "natural" pregnancy rather than egg retrieval followed by IVF:

In theory, natural pregnancy might be achieved via orthotopic transplantation (an autograft placed near the infundibulopelvic ligament) if the fallopian tubes remain intact and the transplant does not become sequestered under the peritoneum.

This method, orthotopic transplantation, worked exactly as described above in the case of Ouarda Touirat: "We should stress that conception arose spontaneously since neither ovarian stimulation nor IVF had been done." Orthotopic transplantation, since it does not necessitate IVF, offers fertility preservation to patients who, for religious reasons, would not consent to oocyte or embryo cryopreservation or to oocyte retrieval from a heterotopic transplant followed by IVF. Faiths that reject IVF include Eastern Orthodoxy and Roman Catholicism, as well as some interpretations of Jewish tradition. Thus, ovarian cryopreservation and transplantation could potentially succeed in preserving fertility in religious patients where other ARTs currently cannot.

Heterologous Transplantation

Heterologous transplantation introduces an entirely new set of ethical questions, many of which relate to organ transplantation and gamete donation rather than gamete cryopreservation. The first is that of immunological rejection. It is possible that Silber's transplant between identical twins will remain a special case: "The risk of tissue rejection means that ovary transplants of this sort are only really practical with identical twins and there just aren't many pairs out there that this could help." However, Silber is described as believing that "such a transplant could be useful between non-related women, but only if anti-rejection medicines became safer." Even with such improvements, the
risk of rejection remains high:

[A]llografting ovarian tissue is an enormous inconvenience compared with oocyte donation: it requires ongoing immunosuppressant treatment to avoid graft rejection. The burden of immunosuppressant treatment is known for vital grafts such as the kidney, heart liver, or lung; is it permissible to accept such a risk for an organ and nonvital function as the ovary and fertility?

Also, in the case of an ovarian tissue recipient, immunosuppressant treatment not only affects the woman herself, but may also produce worse pregnancy outcomes such as prematurity and low birth weight. While it is true that many healthy children have been born to immunosuppressed patients, accepting additional risk to the newborn as a result of a treatment primarily intended to produce a healthy newborn seems both illogical and in potential violation of the neonate's best interests.

Like Henderson and Robertson, I can conceive of few situations where oocyte donation would not be equally effective at bringing about desired reproductive outcomes and less hazardous to all individuals concerned. While oocyte donation did fail in the St. Louis case, heterologous transplantation was made drastically safer by the twins' genetic identity. Thus, heterologous transplantation seems biologically interesting but medically limited.

One exception might be in religious cases where IVF and/or egg donation are taboo: if the donated ovary is considered to belong to the gestational mother rather than to the donor, then, through heterologous transplantation, a child could be born through natural pregnancy to a previously infertile woman. The genetic parentage of the child might be considered unimportant. There is support for this line of thought in Jewish practice. Given Silber’s admirable grasp of the Jewish halachic tradition and its impact on ART treatments, he may have foreseen this option when he made the optimistic comments above.
The Jewish idea stated above raises questions about the status of the ovary. The ovary, unlike other frequently transplanted organs such as the kidney, is both an endocrine and a germline tissue. As a germline tissue, it has the capability to continue the genetic line of the ovary donor. Given this difference, does agreeing to organ donation involve agreeing to ovary donation? Robertson sees this as a possibility:

Women while alive might sign organ donor cards that encompass ovarian donation when they die, or families might consent to donate the ovaries of deceased young women for preservation and later reproductive use by infertile couples.\textsuperscript{27}

However, the scenario Robertson envisions involves the use of the ovary purely as a source for oocytes, rather than as an organ to be transplanted into the body. We do not permit organ transplant recipients, even recipients of other nonessential organs such as corneas, to use donor organs for purposes other than implantation into their own bodies; nor do we authorize the next of kin to donate or sell a deceased person's organs to private individuals. Thus, I would argue that "heterologous transplantation" as described by Robertson is really postmortem gamete donation, not organ donation. In Britain, for example, this redefinition would prohibit their use without explicit permission from the donor herself.\textsuperscript{28} I do not argue that postmortem gamete donation is wrong – just that it is not organ transplantation.

In contrast to the procedure Robertson outlines, a donated ovary could in fact be transplanted into the body of the recipient. As well as for the religious reasons outlined above, this might be done in order to reap health benefits: "[A]lllografting has a large advantage over oocyte donation, that of reestablishing the endocrine functions of the ovary and thus enabling the grafted patient to avoid need for replacement hormones."\textsuperscript{29} Dr. Silber considered this beneficial effect when making the decision to perform ovarian transplantation.\textsuperscript{30} It could be argued that if a ovarian transplant were performed from a cadaver donor, the
reproductive potential of the ovary could be considered a case of double effect, and the transplant be considered an organ donation rather than a gamete donation. Consider McCarty's example of double effect:

A doctor who believed that abortion was wrong, even in order to save the mother's life, might nevertheless consistently believe that it would be permissible to perform a hysterectomy on a pregnant woman with cancer. In carrying out the hysterectomy, the doctor would aim to save the woman's life while merely foreseeing the death of the fetus. Performing an abortion, by contrast, would involve intending to kill the fetus as a means to saving the mother.31

Thus, on the double effect model, one could believe that gamete donation was wrong without donor consent and still transplant an ovary into a recipient, as long as the aim was organ transfer rather than egg transfer.

However, aside from the immunological problems already discussed, there are two arguments against this approach. First, there are other ways, such as hormone replacement therapy, to restore hormone levels in the body. It is likely that a human ovary will be more effective; however, this may not justify the potential violation of the donor's wishes. Second, the ovary's reproductive function could be separated from its endocrine function: donor ovary recipients who are not authorized to use the gametes contained in the ovary could be required to undergo sterilization or use a near-perfect contraceptive method. This would undermine the claim of double effect. Despite these concerns, I believe that the double effect claim is compelling, given that the ovary's reproductive and endocrine functions are so closely related. It seems counterintuitive to consider a part of one's own body to have a right against one that it be treated in a certain way. Therefore, to respect the donor's will, I would argue that, rather than limiting the rights of organ recipients over their
bodies, germline organ donation ought to be separated from somatic organ donation in donor consent forms.

This idea of the donor having interests in the state of the donated ovary suggests another question: whose ovary is it, really -- and whose child is its product? In the St. Louis case, this worry was diminished by the shared genetic identity of the twin sisters, but would be salient elsewhere. In the case of somatic tissues, the consensus is that they are the recipient's, but in germline donation cases, the donated tissues seem to remain the donor's. For example, in the case of oocyte transfer, the birth mother is considered simply a gestational surrogate for the donor's egg. Stephen Munzer argues that DNA identity is a necessary criterion for organ identity, and thus that the donor determines the eggs produced in their former ovaries:

Again, having the same DNA bears importantly on the genetic makeup of children conceived after the transplantation of gonads. Though rare, transplants of ovaries and testicles have taken place. The donor determines the genetic make-up of ova and sperm. This is obviously true in the case of ova, for at birth the ovaries of a female contain all the ova she will ever possess.32

Genetic determination alone, however, does not establish maternity. The parent of a clone would entirely determine the genetic make-up of the clone and of the clone's gametes, but it does not follow from this that she would be the parent of the clone's offspring. Thus, there must be something more than genetic identity or genetic determination to parenthood. I argue that a better definition of "parent of a child" would be "the individual whose ovary secretes the egg from which the child is produced." I also argue that, unlike other transplantable tissues such as ova or embryos, the ovary, once transplanted, becomes part of the transplant recipient's body.

A natural result analogous to that of heterologous ovarian transplantation is empirically present in the documented case
of a true hermaphrodite chimera; this person has one ovary and one testis, and thus two different germ cell lines. This person's offspring would not be merely the product of one of the two germ cell lines, but of the person. Heterologous ovarian transplantation similarly makes the recipient a germline chimera, just as bone marrow transplant recipients become somatic-cell chimeras. Just as the natural chimera's offspring, from either cell line, would be her own, the offspring would then arguably be the ovary recipient's, because they share their genetic material with one of the germ lines in her body and are produced by an egg from her ovary. While they are also genetically identical to the donor's germline and somatic cell lines, this does not imply that the donor is their parent.

I will close by noting the resemblance of this idea to the Jewish convention, discussed above, that defines the recipient of an ovarian transplant as the mother. Rosner retells this story:

A woman had been infertile for ten years, and rather than being required to divorce her husband, she underwent an ovarian transplant, and one year later gave birth. They asked Rav Kamelhaar: Is the donor of the ovary considered to be the baby's mother, or the woman who bore it? A very serious question! He answered with Solomon's wisdom: the baby belongs to the woman who bore it; though barren for ten years, it is possible that her own ovary produced the egg in the eleventh year of her marriage.

The ingenious Rabbi Kamelhaar might have been more right than he realized. Once the woman undergoes the transplant, the ovary really does, I argue, become "her own ovary."

This example brings ancient religious tradition, cutting-edge medical science, and the analytical tools of modern philosophy together to answer the questions that ovarian transplantation raises. As such, it perfectly encapsulates the project I discussed at the beginning of the paper -- one that advances and
guides new technologies rather than stymieing their progress. As ovarian transplantation matures medically and technologically, there will be many more opportunities both to benefit and to harm, and new ethical investigations will be required. However, the fundamental framework of ethical analysis as both interdisciplinary informed and forward-looking will remain central to these new efforts.

Notes


6. Oktay and Yih, 63.

7. Robertson, 445.


9. Ibid., 423-24


12. ESHRE Task Force on Ethics and Law, 461.

13. Robertson, 444. The English translation of the Latin is "First, do no harm."

15. Practice Committee of the American Society for Reproductive Medicine, 994.

16. Ibid.


27. Robertson, 445. Here, I would suggest a sidelight that brings out the gendered aspects of the debate. Would society be as sanguine if postmortem testicular removal and transplantation were proposed? I do not believe so.

28. Ibid.


34. Rosner, ibid.

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**Works Cited**


Robertson, John A. "Ethical Issues in Ovarian Transplantation and Donation." Fertility and Sterility 73:3


