

THE ETHICS OF OVARIAN TISSUE TRANSPLANTATION: A TELEOLOGICAL PERSPECTIVE

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Abstract

Many female patients present with malignant and non-malignant conditions whose treatment causes infertility. Women who are diagnosed with neoplastic diseases before¹ or during² their reproductive years and undergo ootoxic therapies,³ those who undergo an oophorectomy due to non-malignant disorders,⁴ those of reproductive age at risk for premature menopause associated with genetic disorders, and those who have undergone conditioning regimens for bone marrow transplantation⁵ may experience partial or total loss of their fertility.⁶ Fortunately, in recent decades, medical science has witnessed dramatic improvements in chemo-⁷ and radiotherapy⁸ for neoplastic diseases together with noteworthy advances in fertility preservation techniques. Such advances have allowed more and more women who survive malignant and non-malignant illnesses⁹ to focus on improving their post-treatment quality of life, including the restoration of their fertility and the possibility of childbearing. Ovarian tissue cryopreservation¹⁰ and transplantation,¹¹ though still experimental,¹² hold out real promise¹³ for these women.

Here, I will conduct a teleological analysis of selected ethical issues¹⁴ from three clinical cases of women who experienced the reactivation of ovarian function and a live birth as a result of ovarian tissue transplantation (OTT). In case #1, a woman who experienced ovarian failure after cancer therapy for non-Hodgkins lymphoma subsequently conceived by means of IVF following a frozen-thawed ovarian autograft. In case #2, an infertile monozygotic twin conceived spontaneously as a result of a fresh ovarian graft¹⁵ from her fertile identical twin, and, in case #3, a woman who experienced ovarian failure after cancer therapy for stage IV Hodgkins lymphoma conceived spontaneously through autotransplantation of frozen-thawed ovarian tissue. Lastly, I will assess the ethics of case #4 in which a healthy woman has stored her ovarian tissue to prolong her reproductive life.

Part One— Ovarian Tissue Transplantation: What's Involved?

A. Collection and Cryopreservation of the Ovarian Tissue

Because of the ootoxic nature of chemo- and radiation therapies, the goal is to harvest ovarian tissue before the woman undergoes these therapeutic regimens. Theoretically, there are three ways of cryopreserving ovarian tissue: as fragments of ovarian cortex,¹⁶ as a whole ovary with or without its vascular pedicle, or as isolated follicles.¹⁷ In current practice, however, OT cryopreservation (and transplantation) is almost exclusively limited to avascular fragments of the ovarian cortex.¹⁸ Most primordial follicles are contained in the outer layer of the ovarian cortex and, fortunately, are less susceptible to cryoinjury than more mature oocytes. In the collection process via laparoscopy or

laparotomy, then, surgeons remove the millimeter-thick outer shell of the ovary, cut the cortex into strips around 1-3 mm in thickness and up to 1 cm² in total area, and allow the cryoprotectants to thoroughly penetrate the tissue. Each of these strips potentially contains thousands of primordial follicles capable of developing into mature oocytes or egg cells when thawed and transplanted.¹⁹ A slow-cooling technique was originally used to freeze the excised ovarian tissue. More recently, however, vitrification—a fast-cooling method of cryopreservation—has proven effective in reducing cryoinjury due to formation of ice crystals.²⁰

Before being frozen, however, each cortical strip must be examined both for the presence of primordial follicles and the absence of malignant cells. One of the primary risk factors of cryopreserving ovarian tissue from cancer survivors and, *a fortiori*, a critical ethical issue for those researchers who are experts in OTT and responsible for its ongoing refinement, is that of re-implanting malignant cells through the graft. For this reason, then, research clinicians insist that, prior to any cryopreservation of ovarian tissue, strict IRB oversight of OTT²¹ must require thorough examination of ovarian graft tissue to verify the absence of neoplastic cells.

B. Transplantation of the Ovarian Tissue

Only after the woman survives the therapeutic regimen that treated her disease, is declared disease-free, and is fit enough to request the replacement of her ovarian tissue for reproductive purposes will the surgeon thaw and then replace the cryopreserved tissue. The transplantation of ovarian tissue has been successfully attempted with various tissue sizes from cortical strips to the whole ovary either with or without the vascular pedicle. Typically, transplantation of fresh ovarian tissue would include a variety of tissue sizes, while transplantation of previously frozen ovarian tissue only uses cortical strips.

Ovarian tissue can be grafted orthotopically or heterotopically. Orthotopic transplantation involves the transfer of fresh or cryopreserved ovarian tissue to the ovary itself or the area surrounding the ovary: the peritoneum of the ovarian fossa, and/or to the remaining ovary.²² It is important to note that natural or spontaneous conception in the context of OTT can only take place with an orthotopic graft. To date, all the reported live births following OTT have resulted from orthotopically transplanted ovarian grafts.

Heterotopic transplantation involves the transfer of fresh or frozen ovarian tissue to locations outside the ovarian region: the arm, the forearm, the rectus abdominis muscle, and the subcutaneous tissue of the abdominal wall. Minimally invasive and providing easy access to mature eggs, ovarian tissue transplant to the abdominal wall or forearm is the heterotopic site of choice. Transplanting ovarian tissue heterotopically is easier and less risky than an orthotopic graft and allows easier monitoring of follicular growth.²³ Nonetheless, heterotopic transplantation necessitates IVF-assistance should the woman pursue conception.²⁴ Fertility researchers have proven that oocytes can be aspirated from heterotopically-grafted ovarian tissue, matured *in vitro*, and used for IVF-assisted pregnancy.²⁵ In some cases, both orthotopic and heterotopic grafts are combined in hopes that the heterotopic tissue will stimulate the orthotopic graft to produce ovarian hormones and mature oocytes more efficiently, thereby facilitating natural conception.²⁶

Some fertility researchers report that, following the freeze-thaw process, primordial follicles are able to tolerate ischemia for at least four hours.²⁷ Transplantation of strips of ovarian cortex is done without vascular reanastomosis. Hence, the health of the

graft depends on the growth of new blood vessels, and the vigor of ovarian function depends on a good blood supply to the ovarian graft. A newer, two-part transplantation technique appears to have resolved the problem of reducing the length of time between transplantation and neovascularisation²⁸ to avoid ischemic follicle depletion and loss of function and quality in the ovarian graft. Surgeons graft small pieces of cryopreserved ovarian tissue in the ovarian and peritoneal areas three days before the actual ovarian tissue transplant. The first graft increases the blood flow to the ovary by encouraging the graft to recruit its own blood supply via newly grown blood vessels, facilitating its principal goal: to make the ovaries more responsive to the action of hormones that induce them to release eggs each month.

C. Possible Reproductive Outcomes

Most often, transplantation of ovarian tissue has two goals: to restore hormone production and to facilitate follicular development in order to achieve pregnancy. A 2007 survey²⁹ of reproductive outcomes of OTT reported that the transplantation of ovarian tissue did establish ovarian function after premature ovarian failure (POF). In a review of 46 unique cases,³⁰ OTT was used to treat POF in 27 women, to prevent POF in 15, to treat infertility in 2 and accidentally in 1. For 23 women in POF at the time of OTT, ovarian function was restored. After six months of ovarian restoration, however, four women experienced recurrent ovarian failure. Women receiving fresh grafts showed an increased likelihood for the return of their ovarian function and a decreased likelihood for recurrent ovarian failure. Insufficient data disallow evaluation of long-term (>12 mos) ovarian function. Of the 27 women who underwent an OTT, 25 sought pregnancy. Eight of these achieved nine pregnancies for a 12-month cumulative pregnancy rate of 37%. Four of the eight women who conceived had frozen-thawed ovarian grafts and four had fresh grafts. Five women achieved pregnancy spontaneously; three women got pregnant via IVF and embryo transfer. By the close of the survey period (June 2007), three of the pregnant women had given birth to full-term babies, and four women still had ongoing pregnancies. Two of these deliveries followed the autotransplantation of frozen-thawed ovarian tissue and the third was after heterologous transplantation of fresh cortical tissue between twin^s discordant for POF. As of 2009,³¹ the orthotopic autotransplantation of cryopreserved ovarian tissue had resulted in the birth of five healthy babies worldwide.

Part Two— Ethics Analysis: From a Teleological Perspective

My approach to adjudicating the ethics of OTT—that of a teleological prudential personalism³²—represents a middle course between a pragmatic and deontological ethics, between, on the one hand, those who solve ethical problems based less on principle and more on emotion or on subjective pragmatism and, on the other, those who adjudicate moral issues based on obedience to absolute principles or authoritative laws. As such, my analysis of the ethics of OTT in its varied applications is *personalist* and *teleological*. It is based, first, on an *a posteriori*, realistic understanding of (1) the basic needs/goals of the human person and human nature that comes from empirical induction and (2) the human fulfillment (personal and communal) that is derived from the realization of these needs.

When you or I think about ourselves or observe other human persons informally—or academically within the life and social sciences—two contrasting facts about humans

stand out. Though an individual, each of us is at the same time someone who exists “with” and “for” another and someone who finds fulfillment not in solitude but in communion with others, in an ever-expanding set of communities. We recognize that while each of us is unique, each person is also a member of the same species, *homo sapiens*; each of us lives in one global human community and strives for the same goals, goals that can only be reached by common action. In other words, empirical observation helps us see that every person is a “dynamic system of needs” and, as such, is teleologically defined by these basic needs or goals in their hierarchy: to preserve life, to procreate, to live in society, and to know the truth. So, from conception forward, every human person has physical needs for safety and security as well as nourishment and health that are the primary means for satisfying other, “higher” needs. These needs are higher in the sense of being spiritual needs, needs that make it possible for human beings to transcend the goals they share with plants and animals. So, our empirical study of human nature advises us that every human person needs a good family life, needs the truth of reason and of faith that leads to sound self-understanding—who we are and for what or for whom we are made—needs to know and love others, and, preeminently, needs to know and love God.

Based on both empirical and existential experience, we also conclude that what constitutes a reasonable system of ethics or moral human behavior is for human persons to satisfy these basic needs and the needs of others in a harmonious way, both in their order of necessity and in their order of importance. Acting consistently to realize their basic needs in themselves and in others leads human beings to an integrated *ethos* of happiness: the goods of life, health, security, and human dignity; the good of a personalized sexuality, a loving family, and society; the good of true self-knowledge and wisdom. In short, when you and I fulfill our basic human needs in their order of importance, we are ethical persons—naturally fulfilled and happy. Conversely, when you and I freely act in ways that abuse, destroy, or thwart our basic needs, we act against our basic personal and communitarian goods/values that comprise human flourishing. Or, to state it differently, when we arrest or circumvent our basic human goals, we act irrationally, failing to realize integral human fulfillment in a free and intelligent way.

Second, my personalist and teleological analysis is based on moral principles that, *a priori*, arise from knowledge of these basic human needs (every human being needs to preserve life, to procreate, to live in society, and to know the truth) and expatiate their content. Personalist principles are, therefore, capable of guiding people to intelligently analyze the ethics dimensions of concrete situations and to help them realize integral human fulfillment both individually and culturally through consistently choosing personal and communal good in their actions. Two personalist moral principles, pertinent to the OTT cases I analyze here, will illustrate my point.

Based on the basic human need to procreate (and the correlative goods of sexuality and offspring), we can formulate the principles of (a) personalized sexuality and (b) family-oriented sexuality:

- (a) We, like higher animals, reproduce and raise our offspring sexually. Just as our need to eat is supported by physical pleasure, so is our need to procreate. But, for human persons, the need to propagate the human species is also achieved by sexual acts of intercourse that are expressive of a personal union of committed love between husband and wife and of mutual love for their offspring.³³

(b) The gift of human sexuality must be used in marriage in keeping with its intrinsic, indivisible, specifically human teleology. It should be a loving, bodily, pleasurable expression of the complementary, permanent self-giving of a man and woman to each other which is open to the perpetuation and expansion of this personal communion through the family they responsibly beget and educate.³⁴

My ethical assessment of OTT, then, will not be focused on whether those who choose to access this reproductive technique are doing so out of obedience to rules or emotivist urgings or to realize the greatest good for the greatest number or any other consequentialist goals. I will adjudicate this fertility preservation technique *prudentially*, that is to say, using personalist principles to wisely discern whether OTT, in the four settings analyzed here, promotes a personal and communitarian ethics of authentic love. The principal adjudicative question I ask is this: Would a woman, choosing to access OTT in these various applications, realize her full human personhood and the happiness of her spouse and child?³⁵

*Case #1: IVF Conception and Live Birth Following Ovarian Autotransplant*³⁶

In some centers, all of the women entering the OTT study are offered assisted reproductive services (IVF) to increase their chances at conception, since the lifespan and quality of the grafts were largely unknown.³⁷ At the Chaim Sheba Medical Center in Tel Hashomer, Israel, Dror Meirou and his colleagues reported a live birth after IVF,

following the transplantation of thawed cryopreserved ovarian cortical tissue into the ovaries of a 28-year-old woman who had ovarian failure after high-dose chemotherapy for non-Hodgkin's lymphoma. Ovarian tissue (containing many primordial follicles) was harvested after administration of a second-line conventional chemotherapy regimen, before treatment with high-dose chemotherapy. The patient's menses ceased after the high-dose chemotherapy. During the ensuing 24 months, the amenorrhea persisted and laboratory testing consistently revealed high levels of follicle-stimulating hormone and luteinizing hormone and undetectable levels of anti-müllerian hormone and inhibin B—findings consistent with ovarian failure.

At 24 months post-treatment, the woman requested reimplantation of her cryopreserved ovarian tissue in order to restore her fertility. With approval from the institutional review board³⁸ and with her informed consent, the patient underwent a laparotomy during which strips of her thawed ovarian tissue were transplanted to the left ovary and small fragments were injected into the right ovary. Only the ovarian strips in the left ovary resumed function.³⁹ Eight months post-transplantation, the patient menstruated spontaneously. Basal levels of antimüllerian hormone were found in concentrations consistent with early-stage developing follicles. Then a rise in inhibin B levels characteristic of ovulatory women was identified. An ultrasound study showed a preovulatory follicle in the left ovary. Nine months post-autotransplantation, the patient had a second spontaneous menstrual period. IVF was performed; a single mature egg was collected (via transvaginal follicle aspiration) and fertilized in vitro with her husband's sperm. Two days later, a 4-cell embryonic human being was transferred to the mother's uterus. Repeated ultrasonography showed a normal pregnancy, and at 38 weeks 5 days of gestation, the patient delivered a healthy-appearing female infant.

Case #1: Ethics Analysis

Any female patient who experiences iatrogenic loss of fertility needs to preserve her life by pursuing good health. In this case, that need is satisfied through the OTT procedure—up to a point. Certainly, the collection⁴⁰ and cryopreservation of her ovarian tissue fulfills that need since healing—the restoration of her fertility—was the intent of those initial steps. But, with the patient’s (informed) consent to transplant her ovarian tissue heterotopically, she necessarily limited herself and her husband⁴¹ to an IVF-assisted conception (predicated, of course, on the success of the graft, i.e., on whether it restored ovarian function and produced oocytes capable of being used *in vitro*). In the technological act of producing their child with the assistance of IVF, the woman and her husband forfeited a nexus of basic human goods. Specifically, they frustrated their need for a sound self-understanding, for responsible self-determination, for integral fulfillment as parents, and for a family life in which the child learns the meaning of true love from their parents’ life-giving love—all values that follow directly from the satisfaction of the need to procreate in a truly prudential way.

Is such a sweeping indictment defensible, you ask? Yes, and for very cogent personalist reasons. In the first place, the patient and her husband were deprived of the (good of) knowledge that comes from discovering and respecting the laws of their sexual nature, especially the principle of the radical interdependence between the unitive and procreative dimensions of their sex acts. Knowledge of this truth—that having babies demands, activates, and defines the couple’s act of sexual union—would have helped the couple make sense of the mystery of their sexuality and the transcendent drama of their commendable desire for a child. Deprived of this wisdom—the good of conceiving a child within the only context worthy of human dignity—the patient and her husband were depersonalized, reduced to by-standers of, and suppliers of, fertilization material for a sterile laboratory procedure in which strangers presided over the genesis of their child.

Second, instead of benefiting from the important psychological good of being the personification of his parents’ love—connected to the protection, security, and, yes, intimacy of their bodily union—the child is reduced to an end-product controlled by scientific technology. The child, just as tragically as his parents, is also depersonalized and objectified.

Third, by pursuing an IVF-assisted pregnancy, the patient and her husband are denied the familial good of knowing each other—as mother and father—in their child who is conceived within their act of love, and the child is deprived of knowing himself as a beloved son or daughter in and through his parents’ bodily act of mutual self-gifting.

And, fourth, the patient’s choice of IVF placed the child’s basic need to preserve his life at great risk. What if, at her embryonic stage and before being transferred to her mother’s uterus, the child had been found to be genetically or chromosomally abnormal and either disposed of immediately or donated to destructive embryonic stem cell research? Or, what if she were tagged as a “spare” or “extra” embryo and relegated to the surrealistic suspension of cryopreservation?

Thus, for all these reasons, the answer to the question posed initially—Would a woman, choosing to access OTT to achieve an IVF-assisted pregnancy, realize her personal happiness and that of their spouse and child?—is in the negative.

Case #2: Spontaneous Conception in an Infertile Monozygotic Twin Following Ovarian Transplant from the Fertile Twin

The OTT procedure between monozygotic twins discordant for fertility (one twin was fertile, the other was prematurely infertile) was conducted by Dr. Sherman Silber and his colleagues after approval from the ethics review committee of St. Luke's Hospital and after informed consent from both women. Prior to the collection of ovarian tissue, both women were screened for hepatitis B and C viruses, and, two weeks before surgery, the recipient twin was taken off the oral contraceptives intended as hormone-replacement therapy. The surgeon removed the donor twin's left ovary under general anesthesia, and then dissected it, on ice, into strips 1 to 2 mm in thickness.

Meanwhile, the recipient underwent a minilaparotomy through a 3.5-cm incision above the pubis. The cortex of each streak ovary was resected . . . exposing the entire raw surface of the medulla. No follicles were observed. Hemostasis was meticulously controlled in the medulla . . . and continuous irrigation with heparin-treated saline in order to prevent the formation of a hematoma under the graft, but at the same time care was taken to avoid impairing revascularization by minimizing the amount of cautery. A section of approximately one third of the donor ovarian cortex was laid over the raw medulla of each ovary in the recipient and sutured onto the medulla The remaining third of the donor ovarian cortex was cryopreserved after equilibration . . . and slow cooled in an automated freezer. Tissue from the ovaries of both women were fixed in Bouin's fluid for histologic examination.

Seventy-one days post-transplantation, the development of a mature follicle, the presence of estradiol, levels and a proliferative uterus signaled that ovulation had occurred. At eighty days, the woman had her first postoperative menses, lasting one day. Her ovaries then remained quiescent until 48 days later when another mature follicle was found sonographically. At 141 days post-transplant, the recipient twin's FSH and LH levels had decreased to post-ovulatory levels and a second heavy period ensued.

On day 176 post-transplant (five weeks after her second menstrual cycle), an ultrasound study revealed a normal intrauterine pregnancy that occurred spontaneously. At seven weeks, an ultrasound showed a normally developing intrauterine pregnancy, and at 22 weeks another ultrasound showed the baby was developing normally. At 38 weeks gestation, the recipient twin vaginally delivered a healthy baby girl.

Case #2: Ethics Analysis

It is true that the woman in this study chose OTT to fulfill her basic need to procreate, but, examining the outcomes of using OTT in the context of a syngeneic graft, we see such a choice sabotages rather than realizes the procreative good. More, the choice thwarts some of the recipient twin's basic sexual, psychological, and familial needs and those of her husband and child. For although the donated graft made the recipient fertile, it was not really *her* fertility that was restored; although the ovarian graft allowed the recipient to achieve a pregnancy, it wasn't really *her* biological child who was conceived. Although the recipient twin conceived the child within an act of sex between her and her husband, it was not a genuine act of complete reciprocal self-gift of their sexual bodies since it included her sister's eggs rather than the gift of *her* oocytes. And although the

graft recipient brought a healthy baby to term, the biological reality is that her sister is the baby's genetic mother.

Thus, although the patient's husband could know and understand himself as father in and through the baby, the patient could not come to the correlative knowledge of her motherhood through the baby. And as the baby matures and begins to reflect on her own conception, I would predict she will seek out her biological mother (her aunt) in much the same way adopted children do, feeling the need to be connected somehow to the biological mother and father whose genomic self-gift they personify.

And, with a tragic irony, since the choice of OTT for monozygotic twins discordant for fertility necessarily involves imprudent actions from both twins, the personal and communal harm experienced by the infertile twin is duplicated in the personal and familial life of the fertile twin. And, since a healthy society is inextricably linked to the well-being of the basic cell of the family, the choice of OTT for monozygotic twins discordant for fertility, *a fortiori*, injures the larger society and culture as well. In sum, a woman who would choose OTT under these circumstances would realize neither her personal fulfillment nor the comprehensive happiness of her spouse, her child, and her twin sister.

Case #3: Spontaneous Conception and Live Birth Following Ovarian Autotransplantation⁴²

In 1995, the ethics committee of the Catholic University of Louvain approved a protocol to examine the safety and efficacy of the cryopreservation of ovarian tissue for women who were in treatment-induced ovarian failure as a result of high doses of chemotherapy.

In 1997, a woman with stage IV Hodgkin's lymphoma presented at the Catholic University's Gynecology Research Unit. After obtaining her informed consent, researchers collected five biopsy samples laparoscopically—each about 12-15 mm long and 5 mm wide—from the left ovary. The surgeons cut four biopsy samples of ovarian cortex into 70 small cubes of 2X2 mm, and one strip of 12X4 mm was left whole. All ovarian fragments were suspended in a cryoprotective medium, placed into precooled cryogenic vials filled with a Leibovitz medium, cooled in a programmable freezer, and eventually transferred to liquid nitrogen. Following the laparoscopy, the patient underwent hybrid chemotherapy and was amenorrheic shortly after initiation of the chemo. After chemo- and radiation therapy, the patient's FSH, LH, and estradiol levels all confirmed castration, and POF was confirmed three months later. In June of 1998, the woman was given hormone replacement therapy and then stopped in 2001, since she wanted to achieve a pregnancy. After a thorough examination, she was declared cancer-free. The surgeons did the first laparoscopy seven days before reimplantation to create a peritoneal window in order to induce angiogenesis and neovascularisation in the area. Although there was a small corpus luteum on the left ovary, the patient's LH and FSH returned to castration levels.

Surgeons then did a second laparoscopy seven days later and removed a biopsy sample, 4-5 mm in size, from both ovaries which was cryopreserved, thawed, and immediately transferred to the operating theater.

We pushed the large strip and 35 small cubes of frozen-thawed ovarian tissue into the furrow created by the peritoneal window very close to the ovarian vessels

and fimbria on the right side. No suture was used. An extensive neovascular network was clearly visible in this space. We used vital fluorescent staining to confirm survival of primordial follicles after freeze-thawing.⁴³

After prolonged discussion between oncologists and the patient, surgeons performed a third laparoscopy to check the viability of the grafts, to insure the absence of malignant cells, and to reimplant the remaining ovarian cortical cubes. At the site of reimplantation, the follicular structure that was previously identified at vaginal echography was seen and biopsied. The grafted cubes were also biopsied and checked for follicle survival. The remaining 32 ovarian cubes were transplanted on the right side and a slight reduction in LH and FSH was recorded, consistent with follicular development in the grafted area. Five to nine months after reimplantation, ultrasonography revealed a mature follicle and a corpus luteum. This began restoration of consecutive monthly menstrual bleeding. At 9.5 months after reimplantation, FSH concentrations peaked and then returned to normal levels 7 days later. After three weeks, a ripe follicle appeared “clearly outside the right ovary,” while both native ovaries were well visualized and “obviously atrophic.” From this ovulation, the patient conceived spontaneously. Eighteen days post-ovulation, a clinical pregnancy was confirmed through human chorionic gonadotropin concentrations and vaginal echography. Vaginal ultrasonography confirmed a viable intrauterine pregnancy 8 weeks later. At term, the woman gave birth to a healthy girl.

Case # 3: Ethics Analysis

Any woman who, as the female patient in this case did, chooses an orthotopic ovarian graft in hopes of restoring her fertility and achieving a pregnancy would also satisfy her need for health and survival, procreation, married friendship, family, and society in an integrally fulfilling way, both personally and interpersonally. By that I mean, the woman could reap the same concomitant human goods as did the female patient of this fourth case did. She would benefit from sound knowledge about the truth of personalized sexuality and the demands arising from the dignity of human procreation, reproductive health, a child conceived within a loving act of interpersonal union between wife and husband, a sturdy family built on the familial truth of the interpersonally-generated knowledge of what it means to be a loving parent and a beloved child, and a society which flourishes in a way commensurate with the strength and health of each family. In sum, then, were any woman to choose OTT under the circumstances described in this third case, she would not only help to realize her own personal fulfillment but would also take an important first step to promote the wholesome development of her spouse, her child, and the society at large.

Case #4: The Removal and Cryopreservation of Ovarian Tissue from a Healthy Woman to Postpone Childbirth

The *Wall Street Journal* reports⁴⁴ that the Infertility Clinic of St. Louis is one of the few or perhaps the only fertility center in the U.S. that performs cryopreservation of ovarian tissue for healthy women wanting to postpone pregnancy. The center’s director, Dr. Sherman Silber, is a pioneer in OTT and believes the technique ought also to be made available for healthy women. The procedure will work well, Silber insists, if women freeze their tissue in their 20s or 30s rather than waiting until their late 30s or 40s to do so. The goal of the St. Louis Center in making the cryopreservation of ovarian tissue

available for healthy women is to give these patients the reproductive advantage of transplanting their own youthful eggs when they are older.

A healthy patient in her early 30s underwent elective surgery at the St. Louis Center to collect her ovarian tissue, to cryopreserve it, and to re-transplant it in the event she had “a hard time getting pregnant in the future when she might be too old.” Source? The patient wanted to postpone pregnancy until after her husband secured his degree and earned a tenured university teaching position. Subsequent to removal and cryopreservation of her ovarian tissue, this patient conceived spontaneously, i.e., without help from her frozen reserves. Nevertheless, she confesses she is grateful that she made the decision to bank her tissue should she have needed the graft to help her overcome difficulty in conceiving the next time.

Case #4: Ethics Analysis

The *Wall Street Journal* interviewed Dr. Silber about his highly disputed promotion of OTT for healthy women. Defending his program, Silber argued:

What is the difference between losing your fertility from aging of your ovary or from cancer treatment? Either way you are losing your fertility, and freezing either your eggs or your ovarian tissue can preserve that fertility.⁴⁵

My response to Silber speaks to the way I would evaluate any case of a healthy woman who chooses OTT to prolong fertility into her late reproductive (or even menopausal) years, as did the woman in case #4. I strongly disagree with Silber’s egalitarian view that a healthy woman’s choice of OTT is the same as that of a woman with the iatrogenic loss of her fertility. The two cases—treatment-induced sterility of young women in their 20s and 30s and the natural waning of fertility in women in their mid-30s, 40s, and 50s—have distinct existential and ethical profiles. The loss of fertility in a reproductive-age woman represents a health deficit which she needs to restore in order to regain not only procreative but also systemic health. But a woman’s natural loss of fertility in mid-life, when she is heading toward retirement and her “senior” years, is a built-in (natural) protection against harm both to the woman and to possible children she might bear. From a health perspective alone, women in their late 40s and early 50s, short on optimal health, stamina, and energy, are more susceptible to pregnancy complications. From a sensible child-rearing perspective, is it fair to submit the child of elementary age to the predictable taunts of his classmates because his mother looks more like the child’s grandmother than mother? Is it fair to require the involved father to measure up to the challenging spiritual and physical demands of fathering that are routinely and logically required of younger dads? And is it fair to the larger society to weaken the family, its basic building block, because children are more likely to lose their parent or parents at an age when they still, or perhaps most, need their presence? To use cryopreservation of ovarian tissue to facilitate the deliberate postponement of childbirth and child-rearing until the twilight years of reproductive health, best of motives notwithstanding, is imprudent, unreasonable, and, therefore, unethical. But it is ethical to reverse, by moral means, the iatrogenic loss of fertility.

Other ethicists⁴⁶ argue that a woman’s right to reproduce in whatever way she likes at whatever time she likes trumps any objections to the use of OTT by healthy women that “appeal to nature.” They argue that the reaction that “nature’s boundaries are there

to be respected, not transgressed” and the familiar claim of popular-press reports that fertility preservation techniques such as OTT are ““playing God”” or ““tinkering with nature”” do not make “convincing moral arguments.”⁴⁷ But the natural law or prudential personalism that I appeal to here is not a matter of boundaries or limits but of our natural human needs for food, health, friends, and truth. If we fail to meet these needs in their order of importance, we simply cannot be happy (as in fulfilled) and we will not be acting ethically. These natural needs and the principles derived from them are the bottom line for assessing the morality of OTT or of any other concrete choices of life.

In sum, then, any healthy woman who would choose OTT to prolong ovarian function in the waning years of her fertility would not only thwart her own personal fulfillment but also would threaten the wholesome development of her spouse, any child she might conceive, and the society at large.

Conclusion

Of the four cases examined here, only the circumstances of the third case—spontaneous conception and live birth following ovarian autotransplantation—prove to promote a personal and communitarian ethics of authentic love by helping the woman who chooses it realize not only her full human personhood but the happiness of her spouse and child.

Endnotes

- 1 A. J. Jakimiuk and W. Grzybowski report that one in 600 girls will develop cancer (mostly leukemia, central nervous system, embryonal, lymphoma, and soft tissue or bone cancers). The life expectancy of young women battling these diseases has been so dramatically improved that they and their treating physicians expect a 90% chance of being cured. These statistics raise another ethics issue beyond the scope of this paper: the need to discuss fertility preservation options with prepubertal girls as well as with younger and older women facing iatrogenic loss of fertility *pre-therapy*, since restoration of reproductive capacity is important for their psychophysical well-being post-therapy [“Ovarian tissue preservation, present and clinical perspectives,” 32 *Gynecological Endocrinology* 2(2007):87].
- 2 OTT is also indicated for women in their thirties who will be treated for breast, ovary, uterine or cervix cancer, for oophorectomy due to non-malignant disorders (cf. fnnt 4), or for autoimmune diseases requiring gonadotoxic therapy [Jakimiuk, “Ovarian tissue preservation,” 90].
- 3 Ovaries are very sensitive to cytotoxic treatment and are at different levels of risk for premature ovarian failure (POF) from alkylating agents and from radiotherapy, depending on doses, irradiation schedule, and patient’s age when starting radiation [Ibid, 88].
- 4 OTT is suggested for women with non-malignant diseases: (1) those who have undergone uni/bilateral oophorectomy after presenting with a benign ovarian tumor, severe and recurrent endometriosis, BRCA-1 or BRCA-2 mutation carriers, (2) women at risk of premature menopause in the case of Turner’s syndrome, family history, or from benign diseases requiring chemotherapy: autoimmune diseases such as systemic lupus, rheumatoid arthritis, Behcet’s disease and Wegener’s disease and (3) women who undergo a bone marrow transplant because of benign hematological diseases such as sickle-cell anemia, thalassemia major and aplastic anemia, or autoimmune disease unresponsive to immunosuppression. [J. Donnez et al., “Ovarian tissue cryopreservation and transplantation: a review,” 12 *Human Reproduction Update* 5(2006):521].
- 5 The conditioning regimen for bone marrow transplantation represents “the most gonadotoxic regimen with an ovarian failure rate after treatment exceeding 90% (I. Demesteere et al., “Orthotopic and heterotopic ovarian tissue transplantation,” *Human Reproduction Update* (Advance Access published May 27), (2009):2). Hematopoietic stem cell transplantation (peripheral blood or BMT) have been used increasingly in recent decades for non-cancerous diseases such as benign hematological disease (sickle cell anemia, thalassemia major and

- aplastic anemia) and for women suffering from autoimmune diseases previously unresponsive to immunosuppressive therapy (systemic lupus erythematosus and autoimmune thrombocytopenia) [Donnez, "Ovarian tissue cryopreservation," 521].
- 6 Jakimiuk, "Ovarian tissue preservation," 87-88.
 - 7 Chemotherapy with alkylating agents that involve high risk of sterility for the female patient include cyclophosphamide, busulfan, melphalan, chlorambucil, dacarbazine, procarbazine, ifosfamide, thiotopa and nitrogen mustard; women are at medium risk from alkylating-like agents cisplatin and carboplatin and at low risk for gonadal dysfunction from methotrexate, bleomycin, 5-fluorouracil, actinomycin-D, mercaptopurine, and vincristine. "The type and doses of chemotherapeutic agents influence the progression to ovarian failure with alkylating agents increasing the risk of POF by a factor of 9. . . . Larsen et al reported a four-fold increased risk of premature ovarian failure (POF) in teenagers treated for cancer, and a risk increased by a factor of 27 in women between 21 and 25 years of age. . . . It is thus obvious that high doses of alkylating agents, irradiation and advancing age increase the risk of gonadal damage." (Donnez, "Ovarian tissue transplantation," 519). Demesteere et al. report that premenopausal women treated with alkylating agents have a 68% risk for POF ("Orthotopic and heterotopic," 2).
 - 8 "The effective sterilizing [radiation] dose is a dose of fractionated radiotherapy (Gray [Gy]) that causes POF immediately after treatment in 97.5% of cases. . . . For younger women and children it is likely that a total dose of 20 Gy over six weeks would produce permanent sterility, with 95% confidence. In women aged 40 years it has been shown that a permanent menopause may be induced by 6 Gy" [Jakimiuk, "Ovarian tissue transplantation," 88].
 - 9 By the year 2010, approximately one in every 250 people in the adult population will be childhood cancer survivors [Donnez et al., "Ovarian tissue cryopreservation," 519; Jakimiuk, "Ovarian tissue preservation," 87]. Presuming half of these survivors are women, the possibility of using OTT after sterilizing treatment to restore fertility would be a welcome option for a sizeable number.
 - 10 Cryopreservation, the process of preserving and storing living systems in a viable condition at low temperatures for future use, is accomplished, prior to the transplantation of the ovarian graft, using two different techniques: slow-cooling (older method, less effective) and fast-cooling or bitrification (newer method, more effective). Cf. *fn* 20.
 - 11 Jakimiuk, "Ovarian tissue preservation," 89.
 - 12 The Ethics Committee of the American Society for Reproductive Medicine recommends that the OTT procedure only be done in specialty centers and under IRB oversight and approval [83 *Fertility and Sterility* 6(2005):1622]. Women who are candidates for fertility preservation techniques need to be counseled about the availability of OTT and its experimental nature so they can properly weigh benefits against risks in giving their informed consent. For the sake of informed consent for these women and for those who will opt for OTT after it is introduced into mainstream clinical practice, future research by OTT experts needs to optimize the freeze-thaw process, resolve the difficulty of transient graft ischemia, and perfect the tests to detect cancer cells in the transplanted tissue (multiple biopsies submitted to thorough histological examination: molecular genetic techniques: polymerase chain reaction, flow cytometry, fluorescence in situ hybridization and cytogenetics) [Jakimiuk et al., "Ovarian tissue preservation," 87, 90-91]. In addition, Mohamed A. Bedaiwy et al. call for a "multicenter controlled clinical trial with sufficient follow-up (5 years) to systematically evaluate the efficacy of this procedure before wide clinical utilization" ["Reproductive outcome after transplantation of ovarian tissue: a systematic review," 23 *Human Reproduction*, 12(2008):2716].
 - 13 The Ethics Committee of the American Society for Reproductive Medicine reports that the only established method of fertility preservation, embryo cryopreservation, requires that the female patient who suffers iatrogenic infertility be of reproductive age, have a partner or use donor sperm, and be capable of a cycle of ovarian stimulation (which of course is impossible when hyperstimulation is contraindicated in certain types of cancer) and able to put off chemo- or radiological therapy long enough to go through the IVF process of producing embryos. Furthermore, another fertility preservation technique, oocyte cryopreservation, which could be performed in single women, has proved ineffective with pregnancy and delivery rates ranging from 1% to 5% per frozen oocytes. Thus, for prepubertal women and for cancer patients who

- must have chemo or radiation immediately, OTT is an attractive alternative to embryo or oocyte cryopreservation (Donnez, "Ovarian tissue cryopreservation," 519).
- 14 Ethical issues that are important but will not be considered here include the following: ovary donation from cadavers or fetuses to be used as xenografts or heterogeneic grafts for infertile women who elect OTT as a way to achieve pregnancy, how informed consent protocols for prepubertal girls scheduled to undergo sterilizing treatment should be conducted (with or without the patient's consent/with or without parental presence and advice), the legal protocol that needs to be in place to insure proper disposition of banked ovarian tissue should the patient not survive treatment, the use of pre-implantation genetic diagnosis (PGD) to screen oocytes for inheritable conditions in the context of OTT with an IVF-assisted pregnancy, and whether refusing OTT for healthy women is gender-discriminatory by denying women the fertility extension that men enjoy.
 - 15 The technical term for a transplantation in which donor and recipient are identical twins is syngeneic transplantation.
 - 16 The ovarian cortex consists of ovarian follicles and stroma in between them. Included in the follicles are the cumulus oophorus, membrana granulosa (and the granulose cells inside it), corona radiata, zona pellucida, and primary oocyte. The corpus luteum from the follicles is also contained in the ovarian cortex. [Helga Fritsch and Wolfgang Kuehnel, *Color atlas of human anatomy*, Vol II: *Internal organs* (Stuttgart, Germany: Thieme Verlag, 2005), p. 270.]
 - 17 Primordial follicles within the ovarian cortex or isolated are less susceptible to cryoinjury because they have "a relatively inactive metabolism, as well as a lack of meiotic spindle, zona pellucida and cortical granules. The small size of primordial follicles also greatly facilitates penetration of cryoprotectant. In 1997, Oktay and his colleagues (Fertility Preservation Program, Department of Obstetrics and Gynecology, Weill Medical College of Cornell University) "developed an isolation technique for human primordial follicles using enzymatic digestion and microdissection and obtained high follicular viability rates with both fresh and frozen ovarian tissues." Nevertheless, Donnez et al. argue that the procedure of isolating primordial (ovarian) follicles "remains difficult" ["Ovarian tissue cryopreservation," 528].
 - 18 *Ibid.*, 521.
 - 19 In the ovaries, there is a continuous process whereby eggs (oocytes) are constantly being prepared for the maturation process. After menarche, it takes 3-6 months for eggs to develop and mature. As the eggs are developing, they transition from a primordial, to preantral, and then to an antral follicle. Antral follicles are visible by vaginal ultrasound. [Leon Speroff and Marc A. Fritz, *Clinical Gynecologic Endocrinology and Infertility*, (7th ed.; Philadelphia: Lippincott Williams & Wilkins, 2005), pp. 104-05.]
 - 20 "Initially introduced by Rall and Fahy for mouse embryos, vitrification involves the use of highly concentrated cryoprotectant solution combined with a high cooling rate (nearly 1500 C/min) in order to achieve a glassy, solid state without causing ice formation. First applied to human oocyte cryopreservation by Trounson, vitrification is easier, less expensive and does not require a programmable freezer that is mandatory for the conventional slow-cooling method" [Emre Seli & Jacob Tangir, "Fertility preservation options for female patients with malignancies," 17 *Current Opinion in Obstetrics and Gynecology* (2005): 303].
 - 21 Other OTT techniques that need to be standardized and optimized include the freeze-thaw method, metabolic injury, ischemic-reperfusion injury (after transplantation), the optimal graft site, and the quality of oocytes matured in a graft. A September 2004 practice bulletin from the American Society for Reproductive Medicine concluded that "the cryopreservation of both eggs and ovarian tissue for cancer patients holds great promise, but at this time should remain an investigational procedure with strict oversight and be provided at no charge to patients. The report further concluded that neither oocyte nor ovarian tissue preservation should be offered or marketed as a means to defer reproductive aging." HealthLink, "Cryopreservation of Oocytes or Ovarian Tissue," 2 [available at: http://www.healthlink.com/provider/medpolicy/policies/MED/cryopresrvation_oocytes.html] last accessed 8/4/2009].
 - 22 Demesteere, "Orthotopic and heterotopic," 10.
 - 23 For example, the pea-size lumps of mature eggs in ovarian tissue that is transferred to the arm are easy to see and relatively easy to aspirate for use in an IVF-assisted pregnancy [Ibid].

- 24 Seli & Tangir, "Fertility preservation options," 304. The choice of a heterotopic ovarian graft necessarily limits the patient to an IVF pregnancy because eggs brought to maturity outside the ovarian site are unable to participate in the natural series of events of an *in vivo* conception: viz., the transport of the oocyte by the fallopian tubes to the fertilization site (the ampulla of the tube) where it is fertilized by a spermatoocyte released during sexual intercourse.
- 25 M. Rosenthal et al., "Biochemical pregnancy after fertilization of an oocyte aspirated from a heterotopic autotransplant of cryopreserved ovarian tissue: case report," 21 *Human Reproduction* (2006):2006-2009.
- 26 In a case similar to #3 of this analysis in which a woman gave birth to a full-term, healthy baby girl following a natural conception, Demeestere et al. performed two heterotopic and orthotopic transplants "to recover a normal hormonal status and to increase, as much as possible, the chance of pregnancy" [L. Demeestere et al., "Fertility Preservation: Successful Transplantation of Cryopreserved Ovarian Tissue in a Young Patient Previously Treated for Hodgkins Disease," 12 *The Oncologist* (2007):1438-39].
- 27 Demesteere, "Orthotopic and heterotopic," 3.
- 28 Ovarian graft neovascularisation is the formation of new functional microvascular networks with red blood cell perfusion in the ovarian graft. Ischemia, or the restriction of blood flow to the graft, will ensue without the oxygen and nutrients to the ovarian tissue from newly formed microvessels. Cf. Donnez, "Ovarian tissue cryopreservation," 523, 525.
- 29 Bedaiwy et al. examined published studies on MEDLINE, EMBASE, Cochrane Systematic Reviews, CENTRAL, Web of Science and Scopus databases that gave "reproductive outcomes after OTT in humans up to June 2007" [Bedaiwy et al., "Reproductive outcome," 2709].
- 30 Ibid.
- 31 Demesteere et al., "Orthotopic and heterotopic," 3.
- 32 My teleological presentation of prudential personalism relies on class material from and lengthy discussions with Benedict Ashley, OP and then on the crystallization of those ideas in his book, co-authored with Kevin O'Rourke, OP: *Health Care Ethics: A Theological Analysis*, 4th edition (Washington, D.C.: Georgetown University Press) 1997. This philosophical analysis is confirmed and expanded in the teaching of the Roman Catholic Church which reflects on the meaning of marriage, procreation, personalized sexuality, and family (Cf. *Humanae Vitae* [1968]; *Donum Vitae* [1987]; *Dignitatis Personae* [2007]) and on a humanly fulfilling way of realizing the basic human needs of procreation and family. The basis for the Church's teaching on the meaning of human procreation and for its condemnation of IVF and contraception, for example, is the personalist truth behind the inseparability principle: the procreative and unitive dimensions of a loving act of marital sex are inextricably linked. The procreative dimension of the sex act—the capacity to create a new human being—demands, defines, and activates its unitive dimension (i.e., conceiving a child within the loving act of sex as opposed to producing a child in a sterile lab, outside the mother's body and outside an act of loving union between its parents). The unitive dimension of the marital sexual act—the interpersonal communion of husband and wife within the sex act—demands, defines, and activates its procreative meaning (i.e., the openness to life as opposed to the direct suppression of fertility through contraception or sterilization).
- 33 Ibid., 206.
- 34 Ibid., 212.
- 35 Ibid., 169.
- 36 Dror Meirou et al. reported the details of this case in: "Pregnancy after Transplantation of Cryopreserved Ovarian Tissue in a Patient with Ovarian Failure after Chemotherapy," 353 *NEJM* 3 (July 21, 2005): 318-321.
- 37 [Bedaiwy et al., "Reproductive outcome," 2716].
- 38 In their journal report, Meirou et al. do not explicitly reference or describe the histological examination of the ovarian tissue to prevent transfer of neoplastic cells via the transplanted graft. However, I presume that reference to prior IRB approval for transplantation implies that this safety issue had been appropriately handled.
- 39 Meirou et al. supply the details of their transplantation technique: "Three pairs of 5-mm transverse incisions were made in the left ovary through the tunica albuginea. With blunt

dissection, cavities were formed beneath the cortex for each of the three strips. Each piece of thawed ovarian tissue (1.5 by 0.5 cm in area and 0.1 to 0.2 cm in thickness) was gently placed in a cavity, and the incisions were closed with 4/0 Vicryl sutures. In the smaller, right ovary, tiny ovarian fragments immersed in oocyte wash buffer were injected beneath the cortex” [“Pregnancy after transplantation,” 320].

- 40 Since details of this study do not include marital status or origin of the male gametes, I will presume that the sperm used to produce the human embryo or embryos in Case #1 originated from the patient’s husband, not from a donor or from a man to whom she was not married. I will also presume, in Cases 2 & 3, that the spontaneous conceptions occurred within an act of marital intercourse. The ethical issues of the first three cases, then, do not include that of breaching the exclusivity of the couple’s marriage (with their promise to be parents only through each other) by introducing a sperm donation from someone other than the patient’s husband or by denying the right of every child to be born into a committed marriage or by using sperm from a man who is not married to the patient. However, in Case #2 (and that of any monozygotic female twin opting for a syngeneic graft), the ethics of breaching the exclusivity of marriage is evaluated because it was an obvious aspect of the case: conception resulted from donor eggs.
- 41 Sherman J. Silber et al. reported the details of this case in: “Ovarian Transplantation between Monozygotic Twins Discordant for Premature Ovarian Failure,” 353 *The New England Journal of Medicine* 1(2005):58-63.
- 42 *Ibid.*, 59-60.
- 43 J. Donnez et al. reported the details of this case in: “Livebirth after orthotopic transplantation of cryopreserved ovarian tissue,” 364 *Lancet* 2004:1405-10.
- 44 Sylvia Pagán Westphal reported the details of this account in: “Doctor Pioneers New Way to Extend Fertility: Freeze Ovary Tissue” *Wall Street Journal*, Thursday, April 26, 2007, front page (available: http://www.infertile.com/in_the_new/lay/WSJ-04-26-07.htm, last accessed: 11/3/09).
- 45 *Ibid.*, 2.
- 46 W. J. Dondor works within the Department of Health, Ethics & Society (HE&S), Maastricht University and The Netherlands and the Care and Public Health Research Institute, Maastricht University. G.M.W.R. De Wert is a member of Department of HE&S and The Netherlands Research Institute Growth & Development, Maastricht University. They adjudicate the ethics of the use of fertility preservation techniques by healthy women in “Fertility preservation for healthy women: ethical aspects,” *Human Reproduction*, Vol. 24, No. 8(2009): 1779-1785.
- 47 *Ibid.*, 1780.