The Ethics of Heterologous Ovarian Transplantation

by

Janetta Brundage

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This thesis was presented

by

Janetta Brundage

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and approved by

Greer Donley, Associate Professor, Law

Thesis Advisor/Dissertation Director: Lisa Parker, Professor, Bioethics

The Ethics of Heterologous Ovarian Transplantation

Janetta Brundage, MA

University of Pittsburgh, 2022

This project examines the ethical permissibility of heterologous ovarian transplantation to treat infertility, ovarian insufficiency, or both. Based on currently available data regarding the procedures' risks, outcomes, and alternatives, it argues that the procedure is ethically permissible under a research protocol to treat ovarian insufficiency, but not infertility, because of the risks immunosuppression poses to potential future offspring. Reviewing the history and current empirical literature regarding heterologous ovarian transplantation, the project compares the procedure to relevant alternatives: hormone replacement therapy (HRT) and in vitro fertilization (IVF). It analyzes the risks and potential benefits for each of the parties immediately involved in heterologous ovarian transplantation: recipients and donors, as well as potential future children of recipients. Depending on the particular interests and values or conception of the good embraced by recipients and donors, and despite the alternative of hormone replacement therapy, heterologous ovarian transplantation can be an ethically permissible intervention for ovarian insufficiency. Because of the risks to fetal development presented by requisite immunosuppression in recipients, the procedure does not have an acceptable risk:benefit profile for treatment of infertility. The project concludes by addressing two concerns that may be raised in opposition to developing heterologous ovarian transplantation: that desires for the procedure are insufficiently autonomous or authentic, and that the procedure reinforces ethically problematic social norms and beliefs in biological essentialism. It concludes that considerations of justice and respect for the autonomy of

decision makers support studying and making available heterologous ovarian transplantation for treatment of ovarian insufficiency.

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1.0 Introduction

This project examines the ethical permissibility of heterologous ovarian transplantation to treat infertility, ovarian insufficiency, or both. I argue that heterologous ovarian transplantation for the treatment of ovarian insufficiency, but not for the treatment of infertility, is currently ethically permissible under a research protocol, contingent on currently available data regarding the procedures' risks, outcomes, and alternatives. I organize my argument by examining the risks and potential benefits for each of the parties immediately involved in heterologous ovarian transplantation: recipients and donors, as well as potential future children of recipients. I argue that, depending on the particular interests and values or conception of the good embraced by recipients and donors, the procedure can have a favorable risk:benefit ratio and be an ethically permissible intervention for ovarian insufficiency. In contrast, because of the risks immunosuppression may present to a developing fetus, I argue that the procedure is not ethically permissible as an intervention to treat infertility.

The thesis comprises two parts. The first provides background based on empirical research to date that is relevant to consideration of ovarian transplantation (heterologous and otherwise). It is broken into four sections: historical background, comparison to in vitro fertilization (IVF), comparison to hormone replacement therapy (HRT), and special consideration of immunosuppressive medications. The second part explores the ethical implications of heterologous ovarian transplantation, often providing comparisons to other already well-established medical procedures and decisions deemed ethically permissible. I analyze implications of heterologous ovarian transplantation for donors, recipients, and future children. I also respond briefly to concerns that pursuing heterologous ovarian transplantation reinforces stereotypical

notions of femininity and problematically prizes biological aspects of parenthood over its social components. I argue that the fact that individuals' pursuit of heterologous ovarian transplantation may be influenced by problematic social norms does not undermine the autonomy of their decisions to participate in the procedure either as donors or recipients. Further, I argue that even if pursuing research on heterologous ovarian transplantation reinforces social norms deemed problematic, this does not provide justifiable reason not to study and develop the procedure. Considerations of justice and respect for the autonomy of decision makers support studying and making available heterologous ovarian transplantation without special concern for the role of social norms in shaping the decisions of those seeking to participate as donors or recipients.

2.0 Empirical Research

2.1 Background: History and Empirical Research regarding Ovarian Transplantation

2.1.1 Pre-21st Century Ovarian Transplantation

Ovarian transplantation dates back to the late 1800s, when in 1863 Paul Bert experimented (unsuccessfully) with xenotransplantation of rabbit ovaries (Gosden, 2008). By the end of the century, Robert Morris was performing ovarian transplantation in humans (Gosden, 2008). Morris's most notable case involved heterologous transplantation of ovarian tissue biopsies from a 33-year-old donor to a recipient suffering from secondary amenorrhea due to polycystic ovarian disease. Many years later the recipient reportedly had three children, which baffled Morris, who knew heterologous ovarian grafts were prone to failure (even though he didn't know these failures were because of the recipient's immune response to the donated tissue). Roger Gosden acknowledges, "Most modern commentators have discounted [Morris's] 1906 claim [that the recipient had three children as a result of the ovarian transplant], although we cannot rule out the possibility that the case had a lucky genetic combination" (Gosden, 2008, p. 672).

Though these first forays in ovarian transplantation seemed promising, by the mid 20th century researchers had become skeptical of its usefulness, with the exception of a particular form of autotransplantation called Estes' operation, which was performed in an effort to increase fertility. In the 1950s and 60s researchers learned more about immunogenicity, though many still believed that "in the hierarchy of antigenicity the ovaries are among the more anergic tissues, having fewer antigen presenting cells than, for example, skin and liver and therefore being more

readily tolerated with mild or no immunosuppression" (Gosden, 2008, p. 676). These hopes were dashed in the 1980s when several different research groups demonstrated that immunosuppressants were necessary for allograft survival, resulting in a general loss of interest in studying ovarian allotransplantation. Once in vitro fertilization (IVF) was established at around the same time even Estes' operation faded from clinical discourse.

There was then little interest in ovarian transplantation until significant advances in the 1990s in cancer treatment for young people opened up a new era of research. Because of these advances, many children, adolescents, and young adults were now surviving to the age where they would desire children, but the treatments they had undertaken to control their cancer were often gonadotoxic, destroying hormone production as well as fertility. Harvesting ovarian tissue and cryopreserving it during cancer treatment, then transplanting back into the body, became an intriguing proposal to preserve fertility as well as ovarian function in general. This particular application of autotransplantation has garnered significant interest over the past two decades and has progressed to being on the brink of moving from experimental research to standard clinical practice (Khattak et al., 2022).

2.1.2 Recent Autologous Transplantation Research

Today, modern advances in technology have changed how ovarian transplantation is performed. The advent of cryopreservation has allowed for the preservation of ovarian tissue over an extended period of time. This development, along with the increasing demand for the procedure before cancer treatment, means "the most commonly practiced approach to ovarian transplantation is the reimplantation of small pieces of cryopreserved ovarian tissue that were removed from the patient before treatment" (Bedaiwy et al., 2008a, p. 2033). Cryopreservation of ovarian tissue can

be done in several different ways: “as fragments of ovarian cortex, as entire ovary with its vascular pedicle or as isolated follicles” (Donnez et al., 2006, p. 521). Remarkably, transplantation outcomes are extremely comparable between using fresh tissue and cryopreserved tissue (Bedaiwy et al., 2008b; Silber et al., 2015). The removal of ovarian tissue or even an entire ovary can be done laparoscopically (Bedaiwy et al., 2008a). While small pieces of tissue are most common, larger pieces of the ovary and also the whole ovary can and have been transplanted.

Such transplantation is largely successful, with around 95% of recipients experiencing a restoration of endocrine function (Anderson, 2018; Donnez & Dolmans, 2017). The duration of this function varies, depending mostly on the donor’s ovarian reserve—more specifically the number of primordial follicles in the donated tissue, which varies from person to person (Silber et al., 2015; Donnez & Dolmans, 2017). Richard Anderson cautions however that even though the “number of surviving primordial follicles following thawing may provide some useful information…the duration of restored endocrine function cannot be predicted reliably” (Anderson, 2018, p. 251). Silber et al. performed a series of ¼ to ½ ovary transplants and, at the time of publication, had found graft function to vary widely from two years to over eight years (Silber et al., 2015). Donnez & Dolmans report similar results, with a mean duration of endocrine function of four to five years with some grafts lasting up to seven years (Donnez & Dolmans, 2017). Andersen & Kristensen note that in their experience one patient with 55% of an ovary transplanted had endocrine function for almost seven years, while another who had 62% of an ovary transplanted incredibly had the graft function for at least 10.5 years—once again the tissue was still functional at the time of publication (Andersen & Kristensen, 2015). Restoration of fertility is also often achieved, with pregnancy attained an estimated 30% to 50% of recipients (Anderson, 2018; Dolmans & Donnez, 2021; Bedaiwy et al., 2008b). It is thought that generating fertility

requires a higher ovarian reserve than generating endocrine function, which usually translates to a larger piece of grafted tissue being necessary for fertility restoration (Andersen & Kristensen, 2015). Transplantation can be performed orthotopically, with the tissue grafted to the usual place an ovary would reside, or heterotopically, with the tissue grafted somewhere else in the body such as the abdominal wall or into the arm. There is limited research on the difference in success rates for orthotopic and heterotopic transplantation, but preliminary results seem to suggest that orthotopic is the superior approach both for endocrine function and fertility (Dolmans et al., 2021).

2.1.3 A Special Case: Transplantation between Identical Twins

Transplantation between identical twins exists in the space between autologous and heterologous transplantation. While technically still autologous because the individuals are genetically identical (albeit with epigenetic differences), transplantation between identical twins still involves taking tissue from one person and transplanting it into a separate individual (Silber & Gosden, 2007). Such transplantation requires donors to undergo a medical procedure from which they do not directly benefit—an important difference from other autologous transplantation. Silber et al. first presented a case report of ovarian transplantation between identical twins in 2005. The recipient sister had previously tried two cycles of IVF to achieve pregnancy, but was unsuccessful, and refused to try egg donation again (Silber et al., 2005). Ovarian tissue was transplanted from her identical twin sister, and she soon conceived naturally, eventually delivering a healthy baby girl (Silber et al., 2005). Only a couple years later, Silber and Gosden reported they had seen ten pairs of monozygotic twins at their center for ovarian transplantation consultation, and had carried out the procedure for seven of those pairs (as of publishing), resulting in a total of

five pregnancies, four of which were conceived naturally and the other achieved through IVF (Silber & Gosden, 2007).

2.1.4 History of Heterologous Ovarian Transplantation

While hundreds of autologous ovarian transplants have been performed in the 21st century, the same cannot be said for heterologous transplantation of ovaries, i.e., transplantation between genetically distinct individuals. Indeed, the list is so short that cases can be confined to two research groups: Donnez et al. and Mhatre et al.

Donnez et al. report work with three pairs of sisters who were not genetically identical but who also had a very specific prior medical history. Several years prior to the ovarian transplantation one of the sisters in each pair had undergone chemotherapy/radiotherapy and subsequently had received a bone marrow transplant from her sister (Donnez et al., 2010). As a result, when Donnez et al. tested for immunocompatibility, "HLA group analysis revealed complete chimerism (HLA compatibility) between the two sisters, proving that no immunosuppressive treatment would be necessary, although the two sisters were genetically non-identical" (Donnez et al., 2007, p. 2654). Interestingly, in the first case report Donnez et al. explicitly note that they discussed oocyte donation with the sisters but the donor sister "expressly asked to be the tissue donor and refused to undergo ovarian stimulation for oocyte donation" (Donnez et al., 2007, p. 2657). More detail is not given about the donor's reasons for refusing oocyte donation. All three recipients experienced restoration of hormonal ovarian function (Donnez et al., 2010), and one recipient subsequently became pregnant and gave birth to a live child (Donnez et al., 2011).

Cases reported by Mhatre et al. most closely resemble what heterologous ovarian transplantation could look like if the procedure became widespread. Most people with primary ovarian failure are not prior recipients of bone marrow and do not have an identical twin; thus the problem of immunocompatibility is most often going to have to be resolved with immunosuppressing drugs. Mhatre et al. describe two cases of patients with Turner Syndrome who received ovarian transplantation with donation from either their genetically distinct sister or their mother (Mhatre et al., 2005). The recipients were then started on an immunosuppressing drug regimen that was eventually tapered to a lower maintenance dose; importantly, though, it could not be completely withdrawn. While both patients experienced normal menstrual cycles post-transplantation, no mention was made of pregnancy or any attempts to conceive, though it is certainly possible that neither of the recipients had pursued pregnancy by the time of study publication.

In describing the benefits that ovarian transplantation would offer the recipients, Mhatre et al. appeal to now-outdated information. In particular, they state (without giving a citation) that hormone replacement therapy increases the risk of cancer, offering ovarian transplantation as a method of providing hormonal benefit without the increased cancer risk (Mhatre et al., 2005). Similarities and differences between hormone replacement therapy and ovarian transplantation are considered in greater detail below, but for now it is sufficient to state that those claims are now known to be inaccurate with respect to Turner Syndrome patients (Elsheikh et al., 2002; Bösze et al., 2006; Campo-Engelstein, 2011; Committee on Gynecologic Practice, 2017; Viuff et al., 2019, Viuff et al., 2020). In fairness, Mhatre et al. published their paper in 2005—prior to the more robust of the analyses cited, and only a few years after the famous Women's Health Initiative study linking hormone replacement therapy to breast cancer in 2002 (Writing Group for the Women's

Health Initiative Investigators, 2002). More disturbingly, Mhatre et al. also reference the scale of antigenicity, stating that "there is a great deal of laboratory evidence that the ovary lies close to the bottom due to histocompatibility antigens being fewer or less capable of stimulating an immune response," and citing a single study from 1962 to support this claim (Mhatre et al., 2005, p. 1396). As previously mentioned, this theory had been repeatedly debunked in the 1980s, decades before Mhatre et al. carried out their research (Gosden, 2008). The justifications cited by Mhatre et al. demonstrate the importance of using up to date information to appropriately counsel patients about the risks and benefits of ovarian transplantation and its alternatives; patients cannot give informed consent if they are presented with false information. Were these two arguments the only justifications for heterologous ovarian transplantation, it would seem that there would be no real indication for performing the procedure.

But, Mhatre et al. also justify ovarian transplantation with reference to benefits that continue to be pertinent. Their claim that "ovarian transplant will offer [Turner Syndrome patients] spontaneous menstruation, ovulation, and reproductive function" is still applicable to current understanding of what ovarian transplantation could offer that alternatives cannot (Mhatre et al., 2005, p. 1396). Mhatre et al. specifically note that a couple years after the procedure their first patient was "leading a meaningful normal life pattern. She feels like a complete woman psychologically" (Mhatre et al., 2005, p. 1397). This patient was previously on hormone replacement therapy (HRT), and it appears that this sense of normality and completeness was not something that HRT could provide to her. Their report documents at least one instance in which a patient determined that an alternative to heterologous ovarian transplantation did not meet her needs.

2.1.5 Heterologous Ovarian Transplantation Harms and Risks of Harms to Living Donors

The probability and magnitude of harm to a living donor of ovarian tissue is uncertain. Bjelland et al. note, "Since early menopause is associated with increased mortality and morbidity, it is important to have reliable knowledge on whether or not unilateral oophorectomy influences the age at menopause" (Bjelland et al., 2014, p. 836). Donnez and Dolmans assert that several small biopsies of an ovary would have little to no effect on the age of menopause or fertility and that even removal of a whole ovary would not have a large effect (Donnez & Dolmans, 2018). Yasui et al. found that women who had undergone removal of one ovary (unilateral oophorectomy) had a median age of menopause that was 1.2 years earlier than those who had not had an ovary removed, similar to findings by Bjelland et al. (Yasui et al, 2012; Bjelland et al., 2014). Additionally, Yasui et al. found that unilateral oophorectomy was associated with a 4-fold risk of menopause before the age of 45, consistent with findings by Cramer et al. (Yasui et al., 2012; Cramer et al., 1995). "The estimated association of a unilateral oophorectomy at the age at menopause is similar to the association of smoking, and smoking is considered to significantly reduce the age at menopause" (Bjelland et al., 2014, p. 840). Yasui et al. also mention studies that have shown unilateral oophorectomy is associated with increased risk for cognitive impairment, dementia, parkinsonism, as well as "mortality from neurological and mental diseases" (Yasui et al., 2012, p. 253). The risk to any particular donor is likely to depend on the donor's follicular reserve because a lower follicular reserve means more tissue would need to be harvested for the recipient (Silber et al., 2015). Long-term effects on donors should be carefully studied during a research-only phase before allowing heterologous ovarian transplantation to become more widely available. Moreover, given the timeframe for health-related and psychological effects to manifest, it would be highly desirable for research or FDA monitoring to continue regarding these effects

following the introduction of heterologous ovarian transplantation into standard care, if indeed that introduction occurs.

As for the procedure itself, risks to the donor depend on the method. The procedure can be done laparoscopically to reduce the risks of surgery. The type of anesthesia varies. Silber et al. note that they gave the donor general anesthesia in their first ovarian transplant between identical twins, but do not mention whether they continued this practice in their subsequent procurements (Silber et al., 2005). Mhatre et al. used general anesthesia for their first donor but only local anesthesia for their second (Mhatre et al., 2005). The length of hospital stay post-procurement also might vary, with Mhatre et al. discharging one of their donors on day five, and Donnez et al. calling their procedure a "one-day surgery" (Mhatre et al., 2005; Donnez et al., 2011, p. 1387).

2.2 Comparison to In Vitro Fertilization (IVF)

For a thorough ethical analysis, it is necessary to compare ovarian transplantation to oocyte donation/IVF, since this is the current standard of care treatment for infertility[1]. Like ovarian

[1]It could be argued that both adoption and gestational surrogacy are also alternatives to heterologous ovarian transplantation, but because neither of these options involves gestating the pregnancy oneself only a brief note will be included here. It should be noted that "adoption can be a long and difficult administrative procedure" (Bruno & Arora, 2018, p. 6). For some, it can be so long and difficult that, practically speaking, adoption is not an available option. Additionally, adoption often costs between $20,000 and $50,000, which means that it is as expensive or more expensive than other methods of having children (Mushro, 2022).

Gestational surrogacy is also significantly different from ovarian transplantation. In gestational surrogacy, the intended parent does not carry the pregnancy; some will find this a desirable feature, while others find it undesirable.

transplantation, oocyte donation allows recipients to carry a pregnancy themselves. Oocyte donation also has the benefit of a high pregnancy rate even for persons with ovarian failure, at around a 40% success rate per treatment cycle for this population when using fresh oocytes, similar to current estimates for ovarian transplantation (Elsheikh et al., 2002). It should be noted, however, that compared to oocyte donation ovarian transplantation has had significantly less time to be optimized (Anderson, 2018; Dolmans & Donnez, 2021; Bedaiwy et al., 2008b). Additionally, unlike with heterologous ovarian transplantation, whether the oocyte is fresh or cryopreserved does seem to impact pregnancy rate to a significant extent, with fresh oocytes giving the best results (Elsheikh et al., 2002).

Without special circumstances like cases of donation between identical twins or a prior bone marrow donor/recipient pair, ovarian transplantation will require ongoing immunosuppression to maintain an ovarian graft, which would not be necessary in the case of oocyte donation. Neither oocyte donation nor heterologous ovarian transplantation would allow the patient to bear a genetically-related child, though in either case the donor could be a close family member if some percentage of genetic overlap is desirable.

Surrogacy also shifts control and decision-making from resting squarely and indeed solely on the intended parents' side, as it introduces the possibility of the surrogate having some decisional authority with regard to the pregnancy. This is a reason that "gestational surrogacy is commonly represented as a [legally] 'risky' alternative" to gestating the pregnancy oneself (Castanos et al., 2011, p. 71). In the case of people with primary ovarian insufficiency, oocyte donation would be required in addition to gestational surrogacy. Gestational surrogacy is also likely the most expensive method of having children, with costs often ranging from $100,000 to $200,000 (Braverman, 2022).

For both the recipient and the donor, the experience of ovarian transplantation is different from assisted reproduction with oocyte donation. The preparation for oocyte recovery is quite arduous and involves injecting medications into one's belly for several days. The medications can have serious side effects, ranging from the uncomfortable (mood changes, bloating) to the life-threatening (kidney disease) (Campo-Engelstein, 2011). "Ovarian hyperstimulation syndrome, which seriously affects about 6% of women receiving the drugs" is a condition which can cause severe pain, blood clots, and even death in some cases (Pearson, 2006, p. 607; Mayo Clinic Staff, 2021). These would be risks for the donor, not the recipient, who would only undergo a much less invasive procedure to transfer the embryo. Also, as Donnez et al. note, ovarian transplantation is likely to involve a much lower time commitment by the donor, which may be preferable (Donnez et al., 2011). Unlike with oocyte donation, however, the ovarian tissue donor is likely to have to stay in the hospital at least a night, which is a reason a potential donor may prefer oocyte donation to ovarian tissue procurement (Mhatre et al., 2005; Donnez et al., 2011). Nevertheless, Donnez et al. note that in one case "the sister refused to donate oocytes after gonadotrophin stimulation, but was willing to undergo one-day surgery to donate an ovary" (Donnez et al., 2011, p. 1387).

For the recipient, both oocyte donation (specifically embryo implantation) and ovarian transplantation involve some type of anesthesia, but ovarian transplantation is likely to require a longer hospital stay, likely because of the need to closely monitor the function of the new graft. As an example, Mhatre et al. note that one of their ovarian graft recipients stayed in the hospital for 15 days post-transplant (Mhatre et al., 2005).

Finally, it is not immediately apparent whether the procedures involved in heterologous ovarian transplantation would be more or less expensive than oocyte donation and assisted reproduction. In vitro fertilization (IVF) can cost from $15,000-$30,000 per cycle (including both

oocyte recovery and embryo implantation), and multiple cycles may be necessary to achieve pregnancy (Conrad, 2022; Silber, 2008). Medications make up approximately 35% of this cost (Conrad, 2022). Additionally, given that nearly all people with primary ovarian insufficiency cannot produce their own oocytes (one main reason for their infertility), they would need to obtain oocytes from another person, likely increasing the cost significantly; in 2010, IVF with donor oocytes was approximately $18,000 more expensive than IVF using the intended parent's own oocytes (C. N. Y. Fertility, 2021). This additional cost is largely due to the compensation given to donors (usually between $5000 and $10,000 per cycle), but additionally includes fees associated with the agency providing the eggs, as well as costs of travel and medical evaluation (Santilli, 2022; C. N. Y. Fertility, 2021).

In comparison to IVF, heterologous ovarian transplantation as organ donation in the U.S. is restricted to altruistic donation solely (i.e. without compensation) by the Uniform Anatomical Gift Act (National Conference of Commissioners on Uniform State Laws, 2009). Autologous ovarian reimplantation cryopreservation and surgery costs around $9,000-$13,000 (Silber, 2008). However, in the context of heterologous ovarian transplantation, the cost of the surgery may be significantly higher as additional expertise would likely be necessary to deal with the added immunocompatibility concerns and donor work-up. To enable cost comparison, (both for individuals and for insurers, healthcare systems, and society) additional tracking and analysis of the immediate and longer-term costs of heterologous ovarian transplantation would be needed. It is unclear at present whether the costs of heterologous ovarian transplantation (were it to become more widely practiced) would be borne by the patient themselves (akin to IVF) or by health insurance companies (like other organ transplants).

Additionally, as explained in section 2.1.2, ovarian autografts seem to last a maximum of around ten years, with five years being more common. A second surgery might[2] be needed to remove the graft, adding medical risks and financial costs. Due to the possibility of graft rejection, ovarian allografts might have an even shorter lifetime than autografts, potentially requiring multiple surgeries throughout the recipient's life, both to replace the graft with new tissue as well as remove possibly remove old tissue. The immunosuppressive medications themselves add another significant cost. For the maintenance doses Mhate et al. prescribed, the cost for prednisolone without insurance would likely be at least $175 per month, and cyclosporine would be at least $300 (as a rough estimate)[3] (GoodRx, n.d.). Immunosuppressive medications alone then could easily cost $5,700 a year. The recipient would need to be on these medications for the duration of the time with the graft. So, for people who would be satisfied with only a few years of graft function, heterologous ovarian transplantation might be less expensive than oocyte donation, but the longer they need the graft/grafts to function, the more likely it is that oocyte donation would be a less expensive option.

In summary, IVF is likely to cost $15,000-$30,000 per cycle, possibly a little more with the additional medical and coordination costs associated with the donor and with the possibility of

[2] Determining the best course of action for managing a failed graft is not necessarily straightforward. For some solid organs (like the heart) the failed graft must be removed before retransplantation because of physiological constraints; there is insufficient space in the cavity for a second graft. But, for kidney grafts, where there is space in the body for multiple grafts, whether to remove a failed graft, either in the case of retransplantation or when switching to dialysis, remains controversial (Dinis et al., 2014). Space considerations would not be an issue for ovarian transplantation, and thus, the importance of removing a failed ovarian graft is likely to be unclear.

[3] Estimates were made using GoodRx discounts for prices in the Pittsburgh PA area in October 2022.

multiple cycles being needed. If there is no altruistic donor available there will also be an additional cost of $5,000-$10,000 per cycle for donor eggs. The surgery for heterologous ovarian transplantation, based on current costs of surgery for autologous ovarian transplantation, is likely to be a one-time cost of at least $9,000-$13,000, but likely higher due to the fact that two people will need to be evaluated instead of one. In addition to the surgery, heterologous ovarian transplantation also requires ongoing immunosuppression to maintain the graft and possibly a second surgery to remove the graft later in life. The cost of immunosuppressive medications is likely to add at least $5000 a year for every year the graft is maintained. So, IVF imposes higher initial costs, but the costs of ovarian transplantation significantly increase the longer the graft is kept, with the breakeven point being keeping the graft for between one and three years depending on the exact prices a person would be offered for both heterologous ovarian transplantation and IVF.

2.3 Effects of Immunosuppression

There is one major difference between heterologous ovarian transplantation and other methods of assisted reproduction: the effects of the immunosuppressing drugs that recipients will almost certainly have to take in order to prevent their immune system from rejecting the graft. Because these drugs will have to be used either to generate hormonal function or to restore fertility, these effects should also be kept in mind when comparing heterologous ovarian transplantation to hormonal replacement therapy.

There are a wide variety of immunosuppressing medications that each have their own uses, benefits, and harms. It is difficult to tell at this stage what the best medications for heterologous

ovarian transplantation would be because very few operations have been performed. The drugs Mhatre et al. used are the only immunosuppressing drugs that have been used in human ovarian transplantation to date. Regarding both of their patients, Mhatre et al. note that a combination of cyclosporine and prednisolone was used (Mhatre et al., 2005). After initial higher doses in the immediate days post-transplant, the prednisolone was lowered to a maintenance dose of 0.2mg/kg/body weight which along with 4mg/kg/body weight of cyclosporine are presumably going to be daily medications for the rest of the recipient's life (or at least the life of the graft) (Mhatre et al., 2005).

Prednisolone[4] can have a variety of side effects; the more serious of which include increased susceptibility to infection, eye problems including glaucoma, high blood pressure (Mayo Clinic Staff, 2020). In many cases for which prednisolone is prescribed, these sides effects or risks of side effects are straightforwardly outweighed by the potential benefits of the drug, from treating severe asthma to preventing rejection of a life-saving organ.

There has long been concern about the effects Prednisone on a developing fetus, with human studies dating back over half a century; suspected effects include lower birth weight, prematurity, and increased incidence of oral clefts, which can have physiological and cosmetic impact and require surgery to correct (Centers for Disease Control and Prevention, 2020; Park-Wyllie et al., 2000). However, it is difficult to disentangle whether these outcomes are associated with Prednisone, or instead with the underlying conditions which the drug is prescribed for (Park-

[4] Prednisolone and Prednisone are nearly equivalent pharmacologically. Prednisone is a prodrug, which is converted to Prednisolone in the liver. When used in a patient with a healthy liver, the effectiveness of the medications is equivalent at identical dosages (Torres, 2019). Therefore, I occasionally refer to studies done with Prednisone since the results should be applicable to Prednisolone treatment as well.

Wyllie et al., 2000). Thus, it is possible that for a patient population with an entirely different indication for Prednisolone use (i.e. primary ovarian insufficiency) these increased risks may not apply. Further research into the use of immunosuppressive medications for heterologous ovarian transplantation specifically is likely to shed some light on whether the risk of these negative effects for the heterologous ovarian transplantation population is comparable to the risk in other indications populations. Park-Wyllie et al. report a statistically significant difference in birth weight and incidence of prematurity among newborns of those using Prednisone, though they also note that the vast majority of the babies born to mothers on Prednisone were of appropriate birth weight (139/157); for the controls 158/168 were of appropriate weight (Park-Wyllie et al., 2000). Nevertheless, low birth weight and prematurity are concerning and associated with higher mortality and other negative consequences (Mayor, 2016; Population Reference Bureau, 2009).

Regarding oral clefts and Prednisolone, a meta-analysis by Park-Wyllie et al. found an overall odds ratio of 3.35[5] for cleft palates and Prednisone use—in other words, babies born to mothers using Prednisone were approximately 3.5 times as likely to develop some form of an oral cleft than babies born to mothers not on this drug. This is certainly an important risk, and one that those pursuing heterologous ovarian transplantation should be made aware of were the procedure to be offered to them. Yet, it is also important to keep in mind that oral clefts only occur in about 1 out of every 1000 births, so even a 3.5-fold increase in risk still means the likelihood of an oral cleft is only 3.5 out of every 1000 births (Park-Wyllie et al., 2000). Furthermore, the overall risk

[5] Park-Wyllie et al. note that this could be an overestimation since studies that find no difference in a particular effect of treatment are less likely to be published.

of major malformations is comparable between babies of Prednisone-exposed mothers and controls and remains at about 3% (Park-Wyllie et al., 2000; Schatz et al., 1975).

Cyclosporine "has a proven place as first-line therapy in the prophylaxis and treatment of transplant rejection" (Bedaiwy et al., 2008a, p. 2046). Serious side effects of the drug can include increased risk of infections, cancer, high blood pressure, and kidney damage (Medline Plus, n.d.) But as with Prednisolone, these risks are likely outweighed by its benefits for the person taking it, since this is a drug that is often prescribed for preventing rejection of a life-saving organ transplant.

Cyclosporin can also have effects on a developing fetus. Like Prednisolone, Cyclosporin is associated with prematurity and low birth weight, though the association does not always reach statistical significance. Once again it is hard to tell whether the association is with the drug or the underlying indications for which the mothers are taking the drug, which emphasizes the need for research specifically focused on the use of immunosuppressive medications in the context of heterologous ovarian transplantation to treat infertility/primary ovarian insufficiency (Bedaiwy et al., 2008a). Cyclosporin can be toxic to fetuses at high doses (25-100 mg/kg maternal body weight) but was found not to be toxic at a dose of 10 mg/kg maternal body weight, which is 2.5 times the dose that Mhatre et al. described using in their ovarian transplantation recipients (Bedaiwy et al., 2008a). Several studies have concluded that Cyclosporin does not increase the rate of congenital malformations (Bedaiwy et al., 2008a).

2.4 Hormone Replacement Therapy vs. Ovarian Transplantation: Focus on Turner Syndrome

In addition to offering fertility benefits, ovarian transplantation has the potential to restore/initiate ovarian endocrine function. Indeed, the production of endogenous hormones is one major distinction between ovarian transplantation and established methods of assisted reproduction. Stimulating production of endogenous hormones would be clinically useful in many cases (for example, treating gender dysphoria or ovarian insufficiency secondary to another condition), but would likely be of particular use to individuals with primary ovarian insufficiency. While most causes of primary ovarian insufficiency are idiopathic one well-known cause is Turner Syndrome,[6] which both patients of Mhatre et al. had (Committee on Gynecologic Practice., 2017; Mhatre et al., 2005). Turner Syndrome is a condition in which a person is born with only one copy of the X chromosome and no Y chromosome; it can manifest in all cells or in only some (known as mosaicism) (Turner Syndrome Clinic, 2019). Currently, hormone replacement therapy "is necessary to induce puberty, to maintain secondary sex characteristics, and to facilitate uterine growth [and] appropriate peak bone mass" (Viuff et al., 2019, p. 469). Additionally, Turner Syndrome is associated with some neurocognitive issues; HRT can improve some of these (e.g., memory, reaction time) (Ross et al., 2000). Heterologous ovarian transplantation could theoretically offer these health benefits as well, and constitute an alternative to HRT.

Because heterologous ovarian transplantation would replace the need for exogenous hormones or hormone replacement therapy (HRT), it is useful to compare these two approaches to

[6] Turner Syndrome is sometimes called Turner's Syndrome.

hormone delivery, which is the project of the following sections. The effects of HRT have been studied for decades, though the clinical significance of the data has not always been clear. What is clear is that HRT is likely to be much less expensive than heterologous ovarian transplantation—with prices for HRT drugs in the tens of dollars per month instead of the hundreds previously noted for heterologous ovarian transplantation immunosuppressive medications (Kirkley, 2020).

Historically, one major concern regarding HRT has been that it increases cancer risk—particularly breast cancer risk. As noted above, this was one reason Mhatre et al. decided the risk:benefit ratio of heterologous ovarian transplantation was superior to that of HRT (Mhatre et al., 2005). Lisa Campo-Englestein notes that the perceived health risks of HRT may make heterologous ovarian transplantation more appealing to some people (Campo-Engelstein, 2011). HRT is indeed associated with breast cancer risk, as well as cardiovascular issues, as indicated by the landmark Women's Health Initiative (WHI) clinical trials (Writing Group for the Women's Health Initiative Investigators, 2002). However, the results of the WHI trials were inappropriately extrapolated beyond the study population of post-menopausal women to suggest that these increased risks were present for all populations—including those with primary ovarian insufficiency—resulting in increased reluctance to prescribe HRT (Freel & Mason, 2018).

Research has continuously shown that the results of the WHI trials are not applicable to Turner Syndrome patients or other patients with primary ovarian insufficiency. One of the first indications that the cancer risks might be different for this population came from Bösze et al., who noted that none of their 62 Turner Syndrome patients ever developed any form of breast cancer, despite many being on HRT for decades (Bösze et al., 2006). Most compellingly, Viuff et al. matched over 1000 patients with Turner Syndrome each with 100 age-matched controls to investigate the impact of HRT on cancer and other health risks by comparing the patients with

Turner Syndrome to the controls as well as to each other (Viuff et al., 2019, Viuff et al., 2020). They found no increased risk of cancer for patients with Turner Syndrome on HRT in comparison to those not on medication (Viuff et al., 2020). Viuff et al. also found reduced reports of hypertension and stroke in women with Turner Syndrome on HRT compared to women with Turner Syndrome not on HRT (Viuff et al., 2019). Consistent with this evidence, the American College of Obstetrics and Gynecology notes: "The results from the Women's Health Initiative trials related to menopause therapy are not applicable to young women with primary ovarian insufficiency whose exposure to physiologic estrogen has been withdrawn prematurely" (Committee on Gynecologic Practice, 2017, p. 2). Furthermore, they emphasize, "When [HRT] is withheld from women with primary ovarian insufficiency because of extrapolation of good epidemiologic evidence from the wrong population, those women may experience negative health consequences" (Committee on Gynecologic Practice, 2017, p. 2). This means that if a person with primary ovarian insufficiency seeks heterologous ovarian transplantation solely for the purpose of avoiding the negative health effects of HRT (for example, a perceived increased risk of cancer), then the appropriate response to this patient would be to educate them about what is currently known about these risks, rather than offering heterologous ovarian transplantation.

2.4.1 Method of Delivery for Hormone Replacement Therapy

The procedure for heterologous ovarian transplantation has already been briefly described. To compare heterologous ovarian transplantation to HRT, it is useful to understand the mechanism of HRT drugs as well. There are two main forms of HRT: an oral form and a patch/gel form that delivers the medication transdermally. For people with primary ovarian insufficiency, estrogen is the main (and sometimes only) hormone given. Currently, for most people with primary ovarian

insufficiency, “there remains no gold standard recommendation on the preferred type of HRT” (Freel & Mason, 2018, p. 43). The main clinical indication for using one over the other is that the transdermal form avoids first-pass hepatic metabolism (i.e., bypasses most of the metabolism in the liver) and is “therefore ideal in women with liver disease or hypertriglyceridemia,” (Elsheikh et al., 2002, p. 125) or hypertension, or any combination of these conditions (Ostberg & Conway, 2003). Transdermal delivery also more closely mimics natural physiology, as estrogen is normally secreted directly into the systemic circulation (Klein et al., 2018). Transdermal estrogen may also have an association with better regulation of blood pressure than oral estrogen (Freel & Mason, 2018). Oral estrogen, in contrast, is absorbed through gastrointestinal tract and “reaches the systemic circulation only after absorption into the portal venous system and metabolism by the liver, thus exposing the liver to a greater dose of estrogen than the rest of the body” (Klein et al., 2018, p. 1795). Transdermal estrogen is not associated with any increased risk of blood clots whereas oral estrogen (including estrogen-based birth control pills) presents a slight increase of risk, with an estimated 1 in 1000 people per year developing blood clots as a result of using oral estrogen medications (Vinogradova et al., 2019; Cleveland Clinic, 2022).

Yet, even with these purported benefits of the transdermal route, most women opt for oral estrogen for several reasons (Ostberg & Conway, 2003). Topical hypersensitivity to transdermal estrogen can develop, for example, which makes transdermal delivery less desirable for some (Ostberg & Conway, 2003). Contraceptive pills are a satisfactory form of HRT and can be more convenient (Klein et al., 2018). Additionally, because ‘normal women’ also take birth control pills, taking birth control pills may be less stigmatizing than taking a medication solely designed to replicate physiologic levels of hormones (Committee on Gynecologic Practice, 2017). However, because birth control pills are not designed to replicate physiological levels of hormones and are

instead designed to prevent ovulation, which requires a much higher level of hormones, birth control medications have a much higher dosage of hormones than medications specifically designed for HRT (Committee on Gynecologic Practice, 2017). For those specifically interested in mimicking physiological levels of hormones to the greatest extent possible, birth control pills therefore are not as desirable. Researchers stress that the "route of administration should be individualized taking into account patient preference and coexisting illness" (Elsheikh et al., 2002, p. 125; Klein et al., 2018).

2.4.2 'Natural' Hormones

There are obvious differences in methods of hormone delivery between HRT drugs and ovarian transplantation. But there are also significant similarities. Estrogen—specifically Estradiol (E_2) is the natural form of estrogen secreted by the body. E_2 is available as HRT—but HRT can also include Ethinyl Estradiol (a synthetic estrogen) and Equine Estrogens, which are a collection of over 100 different forms of estrogen (Klein et al., 2018). Some argue in favor of E_2 for strictly medical purposes, making the argument that "by using human-identical hormones, doctors get a better, more predictable response and reduce the likelihood of complications or side effects" (University of Utah Health, 2019, n. p.). Additionally, because E_2 is biologically identical to the estrogen human ovaries produce, E_2 could serve an aesthetic role for some people who have a psychological desire for their body to function in a way as close as possible to a 'natural' or 'normal' person's body. So, if a person with primary ovarian insufficiency is interested in 'natural hormones'—i.e. the same hormones that would be produced physiologically, HRT remains an option that can accommodate that desire.

The desire for 'naturalness' also extends past the hormones themselves to their origin. Richard Anderson notes that ovarian "transplants would provide a source of endogenous hormones, secreted in physiological concentrations in a cyclical manner, which may in itself be of benefit to the patient…Benefits may be psychological as well as physiological" (Anderson, 2018, p. 251). One seeker of heterologous ovarian transplantation—Joy Lagos—specifically contrasted it with HRT, as described by her husband: "[HRT] does help lots, but will never match her own body producing exactly what she needs" (Campo-Engelstein, 2011, p. 167). However, Anderson also cautions that further research would have to be done to establish whether ovarian transplantation physiologically works as well as HRT (Anderson, 2018). Notably, HRT is easier to manipulate—dosages and therefore the levels of hormones can easily be changed. The same cannot be said for ovarian transplantation. Ovarian transplantation may be more at risk of resulting in "erratic and insufficient hormone production" (Anderson, 2018, p. 251). There may indeed be an assumption by some that what is 'natural' (i.e., hormones produced from an ovary) is inherently better at replicating physiologic function than something manmade like HRT. [7] This assumption may or may not be borne out by the data in the case of heterologous ovarian transplantation, and is additional area where further research is necessary. It is unclear whether Lagos and her husband were assuming that ovarian transplantation would inherently lead to a more physiologically consistent hormone profile (which is at present unclear), or whether they were specifically arguing that the fact that the hormones came from an ovary and not a pill, patch, or gel was *itself* what was

[7] Of course, the operation to insert the ovary would also be 'manmade'. Since the hormones still come from a 'natural source' (i.e., the ovary), however, to some recipients, heterologous ovarian transplantation could seem more natural than conventional HRT.

desirable (which was more in line with what Mhatre et al. and their patients claimed) (Mhatre et al., 2005). Physiological results can be studied. Individuals' preferences or judgments as to what is valuable may also be studied, but individual preferences and values will remain individual. If some people value having their own body produce hormones, HRT will never afford that desired outcome, while ovarian transplantation may. Nevertheless, the facts that their own body and its original organs did not produce such hormones and that medical assistance was required may also detract from the fulfillment of this desire. Research regarding these psychosocial aspects of ovarian transplantation should accompany the procedure's development.

3.0 Ethical Analysis

Ethical analysis of heterologous ovarian transplantation—a determination of whether and for what purposes heterologous ovarian transplantation may be permitted—does not rest solely on the risks and potential benefits of the procedure, even in comparison to the risk:benefit profile of alternatives. In addition to the objectively ascribable health-related effects of heterologous ovarian transplantation and alternatives, the personal preferences and values of the donor and recipient are relevant, and this section will consider them in more detail. This section will also consider in greater detail the well-being and rights of the donor and recipient, as well as the well-being of any future child of the recipient who would be born following heterologous ovarian transplantation. In light of these more detailed considerations, this section will argue that it is permissible to develop heterologous ovarian transplantation and enable its choice over alternate procedures to achieve the goal of endocrine function, but that it is not an appropriate intervention to treat fertility because of the relatively greater risks to future offspring that it presents compared to alternative interventions. This argument will give substantial weight to the personal preferences and values of recipients. It will conclude that the importance of these values and preferences can justify the likely somewhat greater medical or health-related risks, as well as costs, of heterologous ovarian transplantation, but likely not the imposition of even slightly greater health risks on future offspring.

3.1 Considerations Regarding Recipients

3.1.1 Exploration of Harms and Potential Benefits of Heterologous Ovarian Transplantation to Recipients

Heterologous ovarian transplantation offers what some recipients consider important benefits not afforded by other interventions. For those using it to seek pregnancy and parenthood, heterologous ovarian transplantation offers a significantly different experience from other methods of assisted reproduction. It allows recipients not only the possibility of gestating their own fetus, but also the possibility of experiencing 'natural conception' or at least avoiding some parts of IVF. It also affords the knowledge that one will have been responsible for the 'follicular maturation' that resulted in the pregnancy, another unique feature of heterologous ovarian transplantation compared to other interventions. Both of these features were highlighted by Donnez et al. when describing one of their patient's reasons for pursuing ovarian transplantation (Donnez et al., 2011). Thus, heterologous ovarian transplantation could be a desirable intervention for a person wanting to generate gametes from their own body and experience conception that is as nonmedicalized as possible.

For those seeking treatment of ovarian insufficiency, heterologous ovarian transplantation also offers benefits that are not found in other treatment methods. Many people will be satisfied in receiving hormones in drug form, but as shown in section 2.4.2, there are those who find that method inferior to hormones from an ovary for psychological or values-based reasons. Elson notes that "traditional normative definitions of biological women include individuals who are born with a uterus and two ovaries" (Elson, 2003, p. 750). In particular, while the uterus is associated with childbearing, the ovaries are often seen as the seat of femininity, as they are the source of sex

hormones (Elson, 2003). Elson studied women who had undergone gynecological surgery. She found that "a number of respondents ranked themselves against other women who had undergone hysterectomies, based on whether ovaries were removed or how many ovaries or parts of ovaries had been excised" and constructed what Elson terms a 'hormonal hierarchy' (Elson, 2003, p. 754). In particular, "a substantial proportion of respondents who experienced simple hysterectomies [without bilateral oophorectomy] expressed great relief that they were able to keep their ovaries, which they viewed as necessary to preserve both their femaleness and their femininity" (Elson, 2003, p. 758). Some who were able to keep their ovaries or part of an ovary expressed pity for those who could not (Elson, 2003). Importantly, women expressed these responses even though ovary removal is more invisible compared to, for example, mastectomy. These responses suggest that one's personal conception of femininity/womanhood is still important to one's sense of identity or self-concept even if it is not immediately socially visible. Thus, access to heterologous ovarian transplantation could be a way for some women with primary ovarian insufficiency to gain a sense of biological femininity that HRT cannot provide[8]. While some women found that HRT could serve as an 'ovary prosthesis' (Elson, 2003), others considered HRT inferior to the 'real thing', as was seen with one of the patients reported by Mhatre et al. (Mhatre et al., 2005). For those women, heterologous ovarian transplantation has the potential to improve their self-conception and provide them a sense of "wholeness" (Rodriguez & Campo-Engelstein, 2011).

Some might question the value of the benefits recipients seek and argue that they seem trivial in light of the risks of the procedure. However, in other contexts patients are allowed to advance their personal, idiosyncratic values or pursue idiosyncratic goals in medicine even though

[8] Trans women also might benefit from this aspect of heterologous ovarian transplantation.

others do not share the vision of a good life advanced by the medical pursuit of those goals. Many cosmetic procedures fall into this category; not everyone sees the purported benefits of a face lift, breast augmentation, or Botox as outweighing their risks. Even reconstructive procedures like introducing a testicular implant after orchiectomy or breast reconstruction following mastectomy, are viewed by some as not worth the risks or as acceding to and reinforcing social norms that would better be challenged. Not all transgender people seek gender affirming surgeries, or may only pursue those surgeries for which the risk:benefit ratio seems favorable to them.

What these examples reflect is the generally accepted view in both society and the medical profession, that it is the balance of risks and potential benefits of a procedure *for the patient(s) involved*, not the view of the majority in society that matters for a procedure meeting standards of safety and effectiveness in order to be offered. Of course, safety and effectiveness are standards that are themselves grounded in social norms. If a procedure's risks were evaluated in terms of the benefits perceived by those who oppose or find no value in a face lift, breast reconstruction, or gender affirming surgeries, the procedure's risks could not be justified. Instead, the goal or good to be achieved if the procedure is effective (i.e., achieves it) must be assumed as valuable in making this assessment.

In the case of heterologous ovarian transplantation, just as for other procedures that introduce risks in service of patients' personal values and life goals (e.g., gender affirming surgery), counseling may enable patients to explore their own values and to determine whether the procedure is right for them. Additionally, in heterologous ovarian transplantation, a candidate evaluation process may serve some of the same roles as in organ transplantation (Organ Procurement and Transplantation Network, 2021), aesthetic surgery (Wildgoose et al., 2013), or gender affirming surgery (Coleman et al., 2022).

However, requiring counseling also has the potential to be stigmatizing and unnecessarily reduce access to procedures. The potential benefits of mandating counseling—and indeed whether benefits of counseling occur when that counseling is mandated—should be studied. It may be that its potential benefits are not outweighed by its burdens or that mandating it obviates those benefits. Future research should investigate, in particular, the role of the counselors for recipients (and donors), how the counseling and candidate evaluation processes can best be kept distinct, and the effect of both processes on the psychological fulfillment of donors and recipients following their procedures.

3.1.2 Subjective Good vs. Physiological Good: Body Integrity Identity Disorder

Tension between patients' idiosyncratic views of their own well-being and medical professionals' duty to avoid harm—a tension evident in heterologous ovarian transplantation given potentially less risky alternatives to achieve socially recognized goals if not patients' personal, idiosyncratic goals—arises in other medical contexts. Medical ethics discussions of surgical intervention for Body Integrity Identity Disorder (BIID), a condition in which a patient desires amputation of a healthy body part, reveal relevant points for consideration of heterologous ovarian transplantation. The debate about treating BIID is often framed as whether to favor the patient's own conception of their good, and therefore carry out the procedure, or understand the duty of nonmaleficence to refer to avoiding physiological harm, and therefore refuse to perform the amputation (Müller, 2009). In addition to pitting uncommon psychological desires or needs (involving an individual's own, uncommon self-concept) against common conceptions of physical well-being (involving a species typical, well-working intact body), the debate is fueled by the empirical uncertainties surrounding the condition and whether amputation proves to be an effective

treatment for it (Müller, 2009; Barrow & Oyebode, 2019). It is unclear whether amputation is the only option or most effective way to address the psychological need. It is also unclear whether amputation will actually have the psychological benefits the patient desires (Müller, 2009; Barrow & Oyebode, 2019). Even if it does, those who focus on the physiological harm of amputation would argue that a medical professional's duty of nonmaleficence would dictate that amputation not be performed even for psychological benefit, particularly given the possibility that psychological counseling or psychopharmacological could, or could eventually, address the BID patient's psychological need (Müller, 2009). At issue is whether resolution of the psychological need warrants and outweighs the physical harms that come with the amputation.

In their argument in favor of amputation as a treatment for BIID, Bayne and Levy argue that four conditions must be met for the procedure to be considered ethically permissible: (i) the patient endures serious suffering due to their condition; (ii) the treatment is likely to provide relief from this suffering; (iii) this relief cannot be obtained by any other (less drastic) means; and (iv) the benefits are worth the harms of the procedure (Bayne & Levy, 2005). The reason to require that these criteria be met is to ensure that the harms of the procedure are justified in virtue of being outweighed by the benefits sought. The same analysis can be performed for heterologous ovarian transplantation with respect to the ovary recipient.

Regarding (i), that the patient endures serious suffering due to their condition, as with BIID patients' conception of themselves as a person who should be an amputee, gender expression and opinions about childbearing can be part of one's fundamental identity as a person. Preventing fulfillment or expression of that identity when the means exist to enable such identity expression could be seen as failing to prevent serious suffering. It is possible, even probable, that not all people who might desire what heterologous ovarian transplantation can offer have such strong desires.

But, the case reports presented above suggest that some people do have a strong enough interest in outcomes uniquely provided by heterologous ovarian transplantation that they have been willing to undergo experimental surgery to further that interest.

Regarding condition (ii), that the treatment is likely to provide relief from this suffering, Johnston and Elliot argue that "it would be short-sighted to embark on yet another surgical treatment for a psychiatric condition without first subjecting it to the rigorous standards of research and ethical review that have come to characterize sound scientific medicine" (Johnston & Elliot, 2002, p. 434). This suggestion of caution should apply to heterologous ovarian transplantation as well, and this is a good reason to restrict initial instances of heterologous ovarian transplantation to the realm of research alone while both medical, physiological outcomes and psychological outcomes and patient satisfaction are studied. The need to characterize the nature, magnitude, and likelihood of the desired benefits of the procedure is a reason to pursue research on the procedure, and not a reason to prohibit it altogether. Based on case reports by Mhatre et al., there is hope that heterologous ovarian transplantation would provide desired psychological benefits, as one of the results reported was that the patient "feels like a complete woman psychologically" (Mhatre et al., 2005, p. 1397). The research on autologous transplantation seems to suggest that the desire for natural conception may also be achieved through heterologous ovarian transplantation, though, if heterologous ovarian transplantation is eventually approved under a research protocol to treat infertility, further research should focus on both the extent to which heterologous ovarian transplantation results in natural conception and the extent to which the recipient feels satisfied by the experience.

Condition (iii), that this relief cannot be obtained by any other (less drastic) means, is also likely fulfilled for some indications for heterologous ovarian transplantation. If the person only

desires to carry their own child, then this could be achieved through IVF, likely suggesting heterologous ovarian transplantation would not be worth the additional burdens the procedure brings. But, heterologous ovarian transplantation also offers benefits that cannot be achieved through assisted reproduction, namely the psychological benefits of living according to one's conception of a good life regarding gender expression and childbearing.

Thus it would seem that for recipients, heterologous ovarian transplantation may fulfill condition (iv), that the benefits are worth the harms of the procedure. The weighing of the risks and potential benefits of heterologous ovarian transplantation is extremely subjective and dependent on that particular person's conception of a good life. If the indication for heterologous ovarian transplantation involved a trivial interest (based on the perspective of the patient), then it might be ethically permissible to prohibit or actively discourage the procedure, particularly given the existence of alternatives that can provide the physiological outcomes associated with heterologous ovarian transplantation (i.e., pregnancy or treatment of symptoms of ovarian insufficiency). The psychological interests that people have in seeking heterologous ovarian transplantation are not trivial. Heterologous ovarian transplantation may enable recipients to express a fundamental part of their identity. It is plausible that, if a person is deeply concerned with a particular benefit uniquely afforded by heterologous ovarian transplantation, the harms and risks of harms associated with immunosuppression and surgery may be tolerable to that person. Ostensibly, this is what patients reported by Mhatre et al. decided when, in addition to consenting to the risks associated with an experimental surgical procedure, they took on the burden of immunosuppressive medications to maintain the function of their grafts.

At the same time, heterologous ovarian transplantation involves nontrivial burdens and risks to donors, which is not a consideration in the case of BIID. The next section considers these risks to donors and whether they can be justified.

3.2 Considerations Regarding Donors

3.2.1 Exploration of Harms and Benefits of Heterologous Ovarian Transplantation to Donors

Even if heterologous ovarian transplantation offers a permissible balance of risks and potential benefits to the recipient this does not by itself necessarily mean the procedure overall is ethically permissible. By definition, heterologous ovarian transplantation involves the use of another person's ovary or ovarian tissue. It is crucial to determine whether it is permissible to allow a person to donate an ovary. Section 2.1.5 established that heterologous ovarian transplantation presents more than minimal risk to donors. Donors have to undergo an invasive surgery that can have permanent effects on their health. Egg donation also requires anesthesia but typically does not require staying overnight at a hospital. Egg donation, however, does require the donor to take drugs which can have significant side effects for several weeks before the donation, which is not required for ovarian tissue donation. In neither case are the health risks so great that it would be utterly unreasonable to permit a donor to incur them *tout court*. It should also be noted that to some extent heterologous ovarian transplantation would be reversible. Were the donor to experience early menopause and desire to have some of their tissue transplanted back, that would still be possible as long as the tissue had been cryopreserved and there was enough remaining for such a

procedure. The donor would likely experience the same high success rates as other instances of ovarian autologous transplantation. While it would not be the ideal scenario for the donor to have to undergo an additional surgery, and the risks of the surgery/surgeries are not reversible themselves, nevertheless this option may exist for many donors.

Moreover, the risks of heterologous ovarian transplantation are not different in kind from other living organ donation procedures. Living kidney, liver segment, bowel segment, and lung lobe donation are also invasive procedures that can have serious complications and long-term effects, which may present greater health risks, as donors continue to have an interest in the function of their remaining kidney and liver, bowel, or lung tissue. These procedures have been considered ethically permissible for approximately 30 years (liver and lung) to 70 years (kidney), largely because these risks to donors are considered in relation to the life-saving potential of making the donation and lack of good alternatives for the recipient, including the poor quality of life of those relying on kidney dialysis while awaiting cadaveric transplantation (Childress & Liverman, 2006).

Ethical analyses establishing the acceptability of a donor's incurring health-related risks take into account the potential benefits to the recipient and available alternatives for the recipient, as well as the donor's conception of the good that may be advanced by being a donor (Spital & Taylor, 2007). Family members often have an interest in the health and well-being of their other family members. In other words, it could be part of a twin's, sibling's, parent's, or other relative's conception of the good to donate to save the life of a family member who would die while waiting for a cadaveric donor organ. Donors themselves explicitly argue that the benefit of offering restoration of health or saving the life of their loved one vastly outweighs the health consequences they faced as a result of their donation (Spital & Taylor, 2007). Subsequently, it has been

recognized that being altruistic and donating an organ or organ segment to an unrelated recipient is part of some people's conceptions of the good and is conducive to their well-being; following careful candidate evaluation that includes scrutiny of their motives, such altruistic donors are now accepted (Reichman, 2017; National Kidney Foundation, n.d.). As in other cases of donation and transplantation, research should also examine how the outcomes experienced by the recipient affects the donor in the short- and long-term.

To determine whether heterologous ovarian transplantation offers an opportunity for the donor to pursue important personal value-related interests, it is critical to ascertain whether the donor values the particular prospective recipient or values the life plan or values of prospective ovary recipients in general. Decisions about childbearing and perspectives on gender are often some of the most fundamental and personal aspects of a person's identity. The donor's own ideas regarding these interests or their perception of the importance of these interests in the mind of the intended recipient are likely to be the source of motivation for their desire to donate in the first place. In Silber's first ovarian transplant between identical twins, for example, the donor "donated an ovary to [her] twin sister because, as a mother of three, she deeply understood the importance of motherhood in her own life and saw how its absence was adversely affecting her sister" (Rodriguez & Campo-Engelstein, 2011, p. 414). Becoming an ovarian allograft donor thus has the potential to further major interests of the recipient, and thus of the donor insofar as her interests encompass those of the recipient. Thus, just as these subjective values can justify a recipient accepting risks of heterologous ovarian transplantation, the interests of the donor can outweigh the health-related risks a donor faces. Therefore, ovary procurement for heterologous ovarian transplantation should not be deemed impermissible on the basis of a paternalistic concern for donors' health-related well-being.

3.2.2 Informed Consent of Donors

Even if donors' altruism and the alignment of donation with their conception of the good justifies creation of the opportunity to donate ovaries, they must be enabled to give their informed, voluntary consent to the procurement. The same ethical concerns arise with regard to ovarian donation as with other organ donation. The fact that many living related organ donors make the decision to donate prior to learning the risks of donation and thus do not fully engage in the decision-making process required for informed consent is troubling to some (Spital & Taylor, 2007). It would be worthwhile to examine whether this same problem arises for ovary donation, given that ovarian transplantation is not a life-saving procedure and thus may not exert such an overwhelming influence on prospective donors, particularly those emotionally related to the recipient, so as to short-circuit the deliberation required for informed consent.

Just as for other instances of organ donation, the candidate evaluation process for ovary donation should not only determine the suitability of the organ and rule-out undue health risks to the donor, but also determine insofar as possible whether the prospective ovary donor has any social or psychological features that may complicate the donation or render it ethically problematic. In other organ donation contexts, for example, a donor's being too involved in the recipient's outcome is considered problematic, as the donor could suffer psychological harm if the operation is not successful, if the donor does not receive the social regard or self-esteem (or other psychological outcome) sought, or in the case of emotionally related donor-recipient pairs, if their relationship is damaged (Olbrisch et al., 2001). In addition to these concerns, with heterologous ovarian transplantation, the donor could be too invested in achieving the recipient's goals related to childbearing or gender identity. Or, the donor might have an unrealistic or undesired (by the recipient) expectation of involvement in the recipient's or a future child's life. Using known (non-

anonymous) egg donors has had a similar potential to generate conflict over parenting decisions made by the recipient that the egg donor disagrees with (Gurevich, 2020).

Prospective ovary donors would need to consent not only to candidate evaluation and procurement procedures and their attendant risks, but also to any long-term follow-up implemented to study psychosocial and health-related outcomes. The content of disclosure of the risks and potential benefits of donation should evolve over time to include what becomes known about these psychosocial and health-related outcomes. Because the donor's decision is interconnected with the risks, potential benefits, and alternatives recipients face, the donor informed consent process is complicated and the information to be disclosed would evolve for the foreseeable future.

Heterologous ovarian transplantation has the potential to result in 'genetic parenthood' for the donor, and thus involves different interests than other organ donation opportunities. Genetic parenthood, as used herein, is defined as being the producer of the gamete that (combined with another) resulted in another human person. A person can be a genetic parent and a parent in another sense, such as being a social parent, a person who raises a child. Or, they can be solely a genetic parent, having no other relationship with the person who arose from their genetic material.

People often have a strong interest in whether to become a genetic parent or not. Barton et al. have found that about half of their study population said they would not want even their surviving partner to be able to use their gametes, and similarly only about half supported the overall notion of posthumous reproduction (Barton et al., 2012). People can feel very strongly that 'genetic parenthood' is synonymous with 'parenthood' in general, both in terms of rights and responsibilities. Courts have historically taken the concept of 'genetic parenthood' seriously. In *Davis v. Davis*, Junior Davis emphasized that if children were to arise from cryopreserved preembryos containing his sperm, he would view those children as his own and would fight for

custody of them (*Davis v. Davis*, 1992). The Tennessee Supreme Court concluded "that an interest in avoiding genetic parenthood can be significant enough to trigger the protections afforded to all other aspects of parenthood." (*Davis v. Davis*, 1992). Importantly for consideration of heterologous ovarian transplantation, the court also noted that "the technological effect that someone unknown to these parties could gestate these preembryos does not alter the fact that these parties, the gamete-providers, would become parents in that event, at least in the genetic sense" (*Davis v. Davis*, 1992). Therefore, the possibility that one may become a 'genetic parent' as a result of ovarian donation is a possibility that should be disclosed to prospective donors during the informed consent procedure. Whether it should be considered a risk or a potential benefit of donation would depend on the donor's values and thus should be disclosed in a neutral manner that does not prejudge whether genetic parenthood would be a good or bad, desired or undesired, outcome.

3.2.3 Ethical Considerations Related to Deceased Ovarian Donation

That informed consent for ovarian donation must include the material information that genetic parenthood could result from use of the donate ovary has implications for whether to procure ovaries from deceased organ donors for heterologous ovarian transplantation. Instead it may be ethically preferable to restrict donation to those who are able to give contemporaneous informed consent, or perhaps to those who have given specific informed consent for posthumous procurement of their ovaries.

To some extent, employing deceased donors is ethically appealing, as they would not be subject to iatrogenic physical harm of donation as living donors are. However, because ovarian

transplantation has the potential to lead to genetic parenthood for the donor, it involves different interests than other organ donation opportunities.

There is currently no provision for an adequate disclosure and informed consent process as part of common schemes to enroll as an organ donor. Therefore, ovarian donation should not be part of standard organ donation processes like signing up to be an organ donor at the Department of Motor Vehicles. Instead, posthumous ovarian donation should be subject to a more rigorous informed consent process, likely involving presentation of information by a professional familiar with the genetic implications of the decision to donate. Although consenting for deceased ovarian donation should be more rigorous than consenting for other solid organ donations, there could be an acceptable method of obtaining informed consent for ovarian donation after death; however, at the present time there is not an acceptable established practice. Until such a practice is established, ovarian donation should be limited to living donors who undergo an informed consent process commensurate with the risks and potential benefits they face.

3.3 Considerations Regarding Potential Future Children

3.3.1 Risks of Heterologous Ovarian Transplantation for Future Children

Heterologous ovarian transplantation presents some risks to the offspring of transplant recipients. The increased risk of cleft palates could be considered a serious problem, though it is typically treatable and thus not a lifelong problem. There *might* be a link between immunosuppressants used by a gestating person and risk of low birth weight and prematurity, conditions that as previously noted are associated with outcomes as severe as an increased risk of

death. However, even if there is an association between immunosuppressants and these harms, the overall probability of these harms actually manifesting is still likely to be very small. Further research could help identify more precisely the likelihood of any of those harms, but with what we know currently, it seems that heterologous ovarian transplantation is either likely to either have no effect on these factors or offer a minor increase in risk. Still, these risks to the fetus are sufficient to warrant caution in pursuing research on heterologous ovarian transplantation for the purposes of treating infertility. Research into heterologous ovarian transplantation for endocrine function may offer insights that determine the permissibility of heterologous ovarian transplantation as a treatment for infertility, and thus, research into heterologous ovarian transplantation for the purposes of restoring endocrine function should be carried out before determining whether to pursue research into heterologous ovarian transplantation for the purposes of fertility. Furthermore, in the initial human trials of heterologous ovarian transplantation for the purposes of restoring endocrine function, participants should employ contraception to avoid imposing risks on a developing fetus.

3.3.2 The Non-Identity Problem

In considering the impact of heterologous ovarian transplantation on a potential future child or children we must address what has been termed the ‘non-identity problem’, or whether a given action can still be wrong even if it in effect wrongs ‘no one’. Any children born via heterologous ovarian transplantation would not have existed but for that transplantation. Unless their life is so abhorrent that they would have been better off not being born at all, they are better off for the procedure having been performed since it was the only way to bring about their particular existence

and the particular sufficiently good life they now live[9]. Thus, even if there were any specific harms that heterologous ovarian transplantation would bring to a future child, the child could not argue that they themselves are worse off for the procedure having been performed. Where the child benefits from being brought into existence, the child cannot argue they have been harmed by the mechanism that was used to create them, even if they suffer even significant negative effects from that mechanism? Is there any way in which someone could argue that using such a mechanism is nevertheless wrong?

Derek Parfit argues that indeed it is possible for an action to be wrong even if it wrongs no one. The choice of whether to use heterologous ovarian transplantation as opposed to another method of having a child would be a same-number choice, one where the number of people that result from the choice will be the same but the identity of these people will differ depending on the choice (Parfit, 1986). To understand the morality of these choices, Parfit proposes the Same Number Quality Claim: "If in either of two possible outcomes the same number of people would ever live, it would be worse if those who live are worse off, or have a lower quality of life, than those who would have lived" (Parfit, 1986, p. 360). He also proposes that the wrongness of the action is the same whether a particular bad effect is felt by the same people when comparing choices, or different people when comparing choices, which he terms the "No Difference View" (Parfit, 1986). That is, even if no particular person is made worse off by a particular choice, it can still be wrong, and its wrongness depends on The Same Number Quality Claim. Adopting both the Same Number Quality Claim and the No Difference View, one cannot argue that heterologous

[9] A child born to the same person through oocyte donation and IVF would have a different existence and a different life.

ovarian transplantation cannot be wrong because it wrongs no one. Instead, one must examine the particular effects that heterologous ovarian transplantation will have and consider whether it would be better to choose any of its alternatives.

3.3.3 Balancing Harms that Harm Nobody and Harms that Harm Somebody

At this point, it is helpful to compare two cases that Parfit puts forth (Parfit, 1986). The first is the case of Jane. Jane, to summarize the salient points, has a disease that does not cause her any harm except that it kills her at the age of 40. Jane's disease will be passed on to any children that she has. In Jane's world, her only option of having a child is conceiving it herself; adoption and surrogacy are not options. Jane chooses to have a child despite knowing that it will die at the age of 40. Parfit then introduces the case of Ruth, where everything is identical to Jane's case except that Ruth's disease only kills males. Ruth can access IVF, and therefore would be able to ensure conceiving a girl. However, Ruth decides that IVF is too expensive and that she'd rather risk having a child with the disease. She is unlucky and has a son, who has the disease that will kill him at the age of 40. Parfit argues that regardless of what one thinks of Jane's choice, "there is clearly a greater objection to [Ruth's choice]. This is because Ruth has a different alternative." (Parfit, 1986, p. 376). Indeed, Parfit seemingly goes so far as to imply that Ruth's choice is wrong.

What Parfit fails to take into account in his analysis of these cases is that the same-number choice affecting the future child is not the only choice that is being made. There is also a same-person choice made at the same time—one that affects the gestating parent[10]. Parfit is quick to

[10] And additionally, for heterologous ovarian transplant, there is a same-person choice that applies to the donor as well.

dismiss Ruth's concerns over money as trivial, but the amount of money necessary for IVF has the potential to be life-altering for Ruth (or her future child for that matter). Furthermore, Parfit does not address the physical stress of IVF on the gestating parent, which could be significant. More fundamentally, he does not give us any understanding of how to balance the same-person effects of the choice with the same-number ones when they point to opposite choices being the right ones.

It is also important to note that Parfit's examples have the benefit of hindsight—he knows that Ruth will bear a child that has this condition. What if Ruth had borne a girl? Would her choice have still been wrong? Intuitively, it seems the answer should be yes, as the only difference was that in the case of bearing a girl, Ruth was 'lucky'. It seems that the contingent outcome of luck should not factor into the wrongness of a decision. As a parallel, it seems odd to judge more harshly a reckless driver who kills a pedestrian as they speed through a red light than a reckless driver who speeds through a red light where no pedestrian happened to be (Nagel, 1979). In both cases, the driver made the decision to drive recklessly knowing they might put someone in danger. Their moral luck, as Nagel puts it, should not impact judgement of whether their decision was good or bad. But, to turn back to Parfit's case, if Ruth bears a girl, it is more difficult to use the Same Number Quality Claim to say that her decision was wrong, since not only is her child not affected by the genetic condition, but Ruth also did not have to have the financial and physical burdens of IVF imposed on her. Indeed, from that perspective, taking the 'risk' was the better option since the child was no better off and Ruth certainly was.

Parfit's cases of Jane and Ruth cases are relevant to the discussion of the ethics of heterologous ovarian transplantation because the two cases help explain why the ethical permissibility of a lifesaving organ recipient pursuing pregnancy while taking immunosuppressive medications does not automatically mean that heterologous ovarian transplantation for the pursuit

of pregnancy is similarly ethically permissible. Jane's case arguably bears resemblance to, for example, a kidney transplant recipient choosing to gestate a child—there's no way for that person to stop taking the immunosuppressants so the choice is whether to gestate a child while on immunosuppressants, or not at all. Whereas, Ruth's case arguably bears more resemblance to heterologous ovarian transplantation, because in cases of heterologous ovarian transplantation it is not a matter of *whether* to conceive and gestate a child, but *how*. There is no reason to assume that IVF would be any less successful in achieving pregnancy than heterologous ovarian transplantation. In swapping Ruth's case for heterologous ovarian transplantation, Parfit would likely also argue that heterologous ovarian transplantation, when one has access to IVF as an alternative, is also wrong. But, despite the relevance of alternatives, as discussed above, Parfit's analysis fails to adequately consider both the same-person considerations and the moral luck considerations. Some other framework is necessary to weigh these considerations against the risk to the developing fetus.

Bonnie Steinbock offers some insights that might help resolve some of these tensions. She offers her own case (Steinbock, 2009): Betty is on a medication with the side effect that if she were to conceive a child while on the medication, the child would have a mild intellectual disability. But, Betty only has to take this medication for a few months and is advised to wait until she is off the medication to conceive. However, Betty wants to time the conception (and birth) of her child in accordance with her summer vacation and does not want to wait to conceive. So, she conceives while still on the medication and her baby is born with a mild intellectual disability[11] as predicted.

[11] In the time since Steinbock's paper was published, there has been somewhat of a cultural shift in how disabilities are viewed—particularly disabilities of this kind which explicitly do not impact quality of life to a significant extent.

Steinbock notes that Betty's desire to fit her child's conception in with her summer plans ordinarily "would be a good enough reason for not wishing to delay conception…So the question is, why isn't this a "good enough" reason here?" (Steinbock, 2009, p. 171). It seems that in Betty's actual case the negative effect on her child outweighs Betty's (arguably more trivial) interest, even though in other circumstances that same interest might be sufficient enough to weigh the balance in favor of the choice associated with the merely 'trivial' interest. Steinbock's analysis therefore does a better job of balancing the parent and child's interests than Parfit's analysis. At the end of the chapter, Steinbock proposes the following:

> Individuals who face reproductive decisions are morally required not to bring into the world children who will experience serious suffering or limited opportunity or serious loss of happiness, if this outcome can be avoided, without imposing substantial burdens or costs or loss of benefits on themselves or others, by bringing into the world different individuals who will be spared these disadvantages (Steinbock, 2009, p. 172)

Thus, the relevant factors are the degree of suffering of the child (i.e., whether it is serious), the probability of this suffering, and whether the parent would be subjected to a substantial burden in not choosing the outcome that would be superior for the child. This is the appropriate criterion to employ to assess the permissibility of heterologous ovarian transplantation with regard to potential harms to future offspring. And as such, whether a particular procedure entails an ethically

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The idea that a person with a mild disability is worse off than a person without one is arguably ableist, and an argument can be made that rather than seeking to 'correct' or avoid such disabilities we should be seeking to restructure society to be supportive of a wider range of intellectual phenotypes. Fortunately, Steinbock's argument does not depend on this particular condition, but rather that the condition involves a mild reduction in quality of life. To avoid embrace of the ableist assumptions, one may substitute any condition that results in a minor reduction in quality of life.

permissible level of harm to a developing fetus cannot be separated from the extent to which the mother benefits from the procedure, nor vice versa.

The risk:benefit ratio for the gestating parent depends on that person's own values and conception of a good life. Some people might not care whether the conception of the child occurs in their own body or through IVF, or whether hormones originate from their own body or are provided from external sources. For those people, choosing IVF over heterologous ovarian transplantation is likely not a substantial burden or does not result in a significant loss of benefit. For those people, the risks to the fetus would likely outweigh any benefits of the procedure, and it would be appropriate to counsel them to pursue other options which better suit their goals (like IVF or HRT).[12] However, for the person who cares deeply about either 'conceiving naturally' (as they define 'natural') or having hormones produced within their own body, choosing IVF over heterologous ovarian transplantation could result in a significant loss of psychological benefit.

But, given that there are presently only a few case reports describing the psychological benefits of heterologous ovarian transplantation, present research is insufficient to determine whether a significant psychological benefit from heterologous ovarian transplantation is likely to be obtained. Of course, this is why more research should be conducted—to more precisely determine what benefits can be expected form heterologous ovarian transplantation. But, it one thing for a person to consent to an experimental study knowing that they may or may not see the

[12] Indeed, since the present discussion surrounds a wanted pregnancy, presumably these parents-to-be are interested in the welfare of their future child, and that future child's welfare is one of the factors they are (or should be) considering when deciding between procedures. Thus, patients who are not interested in the unique benefits of heterologous ovarian transplantation are likely to see IVF or HRT as a better choice for their needs even without pressure from external sources, including healthcare providers.

significant benefit they hope for, and quite another for a person to consent to an experimental study hoping to see a significant benefit for themselves but also know they are consenting to bring potentially serious harm on another (future) person. Consenting to harm for another for the purposes of pursuing benefit for oneself seems at least morally indecent, and may even be morally repugnant if the harms are large and the benefits are small.

One may argue in response to this that even if heterologous ovarian transplantation for the purposes of fertility is morally indecent, this does not mean that the procedure should be prohibited for the purposes of treating infertility; it is not the business of medical professionals to force someone to do the right thing. To give an extreme example, it is compelling to argue that a mother who is the only kidney donor match for their dying child should not be compelled by their doctors to donate; it is vitally important to respect the mother's wishes about what medical procedures she does and does not want to undertake. Yet, forced kidney donation is clearly a serious harm, whereas being denied heterologous ovarian transplantation to restore fertility is less clearly such a serious harm. This is why further research on the psychological benefits of heterologous ovarian transplantation is so crucial: to help determine whether the harm of being denied heterologous ovarian transplantation is a significant harm closer to that of forced kidney donation, or is better understood as mere inconvenience. Until that further research is realized, it is prudent to take a conservative approach and consider heterologous ovarian transplantation impermissible for the purposes of treating infertility. Therefore, people who use heterologous ovarian transplantation for ovarian insufficiency should employ contraception to avoid imposing risks on a fetus. The stronger a person's interests in benefits afforded uniquely by heterologous ovarian transplantation, the more likely those interests are to outweigh the risks to the donor and recipient, as well as the fetus. This

reasoning is consistent with Steinbock's balancing of maternal and fetal interests; as similarly, as presumed risk of harm to the fetus decreased, more weight was given to the mother's interests.

3.4 Pursuing Heterologous Ovarian Transplantation: Concerns about the Influence of, and Impact on, Social Norms

The risks and potential benefits associated with heterologous ovarian transplantation are not the only reasons that individuals' pursuit of the procedure—and even the scientific community's pursuit of is development—may be questioned. The reasons that people may seek heterologous ovarian transplantation or choose to donate an ovary not only are highly personal, but also reflect their embrace of socially constructed or socially reinforced views of childbearing and femininity. One might, therefore, be concerned that the availability of heterologous ovarian transplantation for ovarian insufficiency would perpetuate, or even exacerbate, problematic conceptions of womanhood that embrace biological essentialism or a reductive notion of what it means to be a woman or to be feminine. Similarly, one might be concerned that offering heterologous ovarian transplantation to address infertility reinforces the notion that particular biological connections (genetic and gestational) and experiences (e.g., conception without contemporaneous assistance and gestation) are so valuable that they warrant donors of ovaries incurring risks and recipients (and their future offspring) incurring risks associated with immunosuppression.

These concerns about the relationship of social norms of femininity, womanhood, and motherhood—or about a biological essentialism that underlies them—may take two forms. One line of concern would focus on the decision making of those seeking heterologous ovarian

transplantation (and to some extent the decisions of those who donate ovaries for the procedure). The concern would be that those engaging in heterologous ovarian transplantation are not acting on autonomous or authentic values, but are instead being duped by prevailing social norms regarding femininity or parenthood, or both. It might be argued that cultural norms of femininity lead those with ovarian insufficiency to make nonvoluntary decisions, at some risk to themselves—and to the donor—that they would not make but for those cultural norms (Parker, 1995). Similar arguments have been made about women's decisions to seek aesthetic surgery, including breast augmentation or breast reconstruction following mastectomy or injury. Feminist criticisms of women's decisions to seek such aesthetic surgery "question the authenticity of their values, criticize the origin of their desires" (Parker, 1995, p. 191) and hence "raise concerns about the ability of women, situated as they are in society and in the culture of beauty, to competently give consent that is voluntary or unconstrained" (Parker, 1995, p. 191).

In response to this concern, however, it should be noted that if a decision were only considered autonomous when it is made independent of any and all external pressures then almost no decision people make could meet this standard. Indeed, George Sher argues that even "if women's traditional preferences are largely or entirely shaped by sexual stereotypes…abolishing the prevailing stereotypes is likely only to clear the way for other, less systematic forms of conditioning. Hence, abolishing those stereotypes is unlikely to increase women's autonomy" (Sher, 1983, p. 46). Instead, a more appropriate standard for an autonomous decision is whether the decision-maker is free from coercion and is not forced into one option over another. It is ethically appropriate and indeed required by norms of medical decision making to take social values and pressures into account if they form part of the decision maker's own values (Buchanan and Brock, 1989). A person's conception of the good is always influenced, one way or another, by

external factors like their cultural context, social norms, and relationships. In the case of aesthetic surgery, such as breast augmentation, for example, it is noted that women choose to enhance their physical appearance, as they themselves define such enhancement. "Within the prevailing cultural context, physical appearance … is not merely a difference worth noting but also a difference that is tied to social regard, self-esteem, love, power, employment, and security" (Parker, 1995, p. 191); however, "self-esteem does not occur in a vacuum but in response to social pressures and rewards" (Pollitt, 1992, p. 329). As noted above, Elson found that some women considered retention of their ovaries essential to maintaining their femaleness and femininity even though oophorectomy is invisible compared to mastectomy (Elson, 2003). Though their physical appearance is not involved, their self-esteem and sense of identity ground their decision. So, the same arguments that support respecting women's decisions about their breasts in light of cultural norms of beauty may be made regarding people's decisions regarding ovarian function and womanliness.

Similar arguments may be made in support of donors' decisions to contribute their ovaries for heterologous ovarian transplantation in light of existing social norms—including norms that support women being givers and contributors to the projects of others—and in expectation of the benefits for recipients. Similar arguments could also be made in support of ovary recipients' choices to pursue heterologous ovarian transplantation to address infertility because they desire particular biological connections (genetic and gestational) and experiences. Here, it is the imposition on future offspring of the risks associated with immunosuppression, not concern about the autonomy of their desires and decision that renders the procedure ethically problematic.

The second focus of concern would be on the broader social implications of the practice of heterologous ovarian transplantation insofar as it not only embraces, but advances social norms that reflect and reinforce views that have negative effects on society and its relatively vulnerable

members (e.g., women, trans people, infertile people). It might then be argued that this is a reason not to encourage heterologous ovarian transplantation through research to optimize it or by making it more available.

Nevertheless, even if heterologous ovarian transplantation is considered to reinforce problematic social norms and is deemed contrary to feminist values and problematically pronatalist, "it is incumbent on the defender of a prescription that oppressed agents engage in self-sacrifice to explain why it is expressive of feminist values to recommend that victims of oppression make their lives worse than they already are" (Khader, 2020, p. 512). Marginalized individuals in society are often faced with the choice of whether to better their own situation by conforming to a problematic social norm or stereotype, or instead fight to dismantle the problematic assumption but take on personal risk or harm in doing so. An example of this dilemma would be a gay man deciding whether to come out to his family and risk losing their support, or remain in the closet and lose the opportunity to show his family a counterexample to the stereotypical caricatures they have in their minds. It is not obvious why members of a marginalized group should sacrifice their own good for the good of the marginalized group as a whole. Indeed, it would be unjust to place such a burden on members on marginalized groups, when this burden of group-responsibility is not placed on nonmarginalized groups. Instead, the burden of dismantling problematic social norms and stereotypes rightly falls on all members of society, rather than on the ones who are harmed the most by problematic norms and stereotypes. Considerations of justice and respect for the autonomy of decision makers within healthcare (and health research) thus support studying and making available heterologous ovarian transplantation without special concern for the role of social norms in shaping the decisions of those seeking to participate as donors or recipients.

4.0 Conclusion

To date, not much has been written about heterologous ovarian transplantation and even less has been written concerning the ethics of the procedure. This work should provide a foundation for understanding the relevant ethical concerns of heterologous ovarian transplantation and serve as a guide for future research. Heterologous ovarian transplantation has the potential to offer a significant benefit to the people who would seek it over available alternatives for treatment of ovarian insufficiency. If the risks that immunosuppression presents to a developing fetus can be addressed or reduced substantially (or if there are determined to be no such risks to the fetus), heterologous ovarian transplantation might eventually be explored and employed to treat infertility.

For heterologous ovarian transplantation to treat ovarian insufficiency, more research should be done to study and optimize the procedure for the sake of those who might benefit from it. In addition to studying and minimizing the physiological health-related risks associated with heterologous ovarian transplantation, research should examine whether the procedure is successful in promoting the recipient's conception of a good life and promotes it to a degree that warrants the risks and burdens heterologous ovarian transplantation presents in comparison to those of HRT. This would involve studying both the extent to which the procedure succeeds in achieving a particular outcome (e.g., the percentage of recipients who experience physiologically typical hormone levels post-transplant), as well as whether participants do indeed find these opportunities meaningful once they have experienced them. Findings from study of recipients would, in turn, inform prediction of whether donors' interests in benefitting recipients are likely to be served by donation.

Since, as currently understood, the risks that heterologous ovarian transplantation poses to a developing fetus are significant enough that pregnancy should be avoided, the initial studies of heterologous ovarian transplantation for the purposes of restoring endocrine function should only include participants who are willing to use a barrier method of birth control if and when they have heterosexual sexual intercourse. This is a common requirement for research under conditions where the intervention is known to pose risks to a developing fetus or where the intervention's effects on a developing fetus are unknown (Stewart et al., 2016). If a participant in a heterologous ovarian transplantation trial does become pregnant, and chooses to continue that pregnancy, the fetal effects of immunosuppression in the context of heterologous ovarian transplantation could be studied. Once the risks and benefits of heterologous ovarian transplantation for treating ovarian insufficiency are better understood, this information should be used to reevaluate the ethical permissibility of research on heterologous ovarian insufficiency for the purposes of treating infertility. If further research demonstrates that the landscape of harms and benefits is different from what current research suggests, then the conclusion that heterologous ovarian transplantation is ethically permissible for the purposes of treating ovarian insufficiency should be reconsidered.

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