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Uterine transplantation: A maternal-fetal medicine perspective

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ABSTRACT

Uterine transplantation is a novel approach to solving a clinical problem faced by women with uterine factor infertility whose desire to parent includes a desire to give birth. The ethical precepts used for other solid organ transplants are helpful in developing normative frameworks for understanding this experimental therapy. Nevertheless, both fetal and neonatal risks complicate this calculus and therefore it is useful to incorporate analyses used in other realms of maternal-fetal medicine to understand and justify this research. Preliminary data on maternal and neonatal outcomes from the many centers exploring this technique are encouraging, but as these techniques move into mainstream care, ongoing vigilance will be necessary to ensure that women and their families are afforded similar protections required of research protocols.

Uterine transplantation is a captivating topic for the myriad ethical issues it raises. Many of these issues have been analyzed extensively in the literature since the marvel of solid organ transplantation was first realized in the 1950s. But we have now been collecting data on uterine transplantation since the first successful birth in 2015[1] and the questions raised have morphed very quickly from "Can we do this?" to "Should we do this?" and "How should we do this?" The good news for patients and the public is that bioethicists have been front and center in participating in and helping to inform the rolling out of this innovative treatment for rare forms of infertility. The model for such an integrative role of ethics in uterine transplantation programs grew out of similar programs in high risk obstetrical procedures such as the repair of fetal meningomyelocele trials.[2] The goal of this review is to outline some of the key issues these transplantations raise from the perspective of maternal-fetal medicine, a field well acquainted with the dilemmas that may arise in maximizing outcomes for both pregnant women and their fetuses.

Beneficence: why uterine transplantation is good

In order to justify uterine transplantation, we need to delineate what good we are trying to achieve. And the obvious answer, of course, is that we are allowing women (and couples) to have babies that they were unable to conceive and carry themselves. Specifically, these are women who have absolute uterine factor infertility (AUFI) that may be congenital (eg the Mayer-Rokitansky-Kuster-Hauser syndrome) or acquired, often due to a premenopausal hysterectomy (eg for fibroids or obstetric hemorrhage).[3] It is estimated

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that 15 million women worldwide may have AUFI and might benefit from access to uterine transplantation.[4]

If the goal were simply to help people parent, then adoption would be a much easier solution; or, if they wanted a genetic connection to their offspring, then surrogacy provides this path. And for many women with uterine factor infertility, adoption or surrogacy are acceptable, even desired options.[5] It should be noted, however, that for many women, adoption and surrogacy are not feasible due to financial and/or legal constraints: in many countries (eg much of Europe including Germany, France, Italy, Spain, and Portugal) surrogacy is illegal.

But for some women with uterine factor infertility, their desire to parent is compounded by a desire for something less tangible, but equally vital: a desire to *bear* a child. Now, of course, this wish is inexorably linked to extremely personal and sometimes politically and philosophically thorny notions of womanhood and motherhood, but it is clear that for a subset of women with AUFI, uterine transplantation provides a path to fulfill this ineffable goal by actually growing, carrying, and birthing a baby.[6] (See Fig. 1.) The justification for uterine transplantation cannot stand unless these fundamental truths are accepted: for some women, it is not enough merely to parent; and for some women, adoption and surrogacy are not acceptable, feasible, or even legal options.[7]

Non-maleficence: is uterine transplantation safe?

"Will pregnancy be safe for me and my baby?" and "Will I have a successful pregnancy?" are two of the most common questions that maternal-fetal medicine specialists are asked in a preconception consultation. Being able to answer these questions is crucial in providing women with substantive information prior to pursuing uterine transplantation. To quote Dr. Michael Grodin, "Good Ethics Requires Good Facts." Women cannot be supported in their uterine transplantation endeavors unless we have reliable data to give them on success rates and safety outcomes: this is why we need well-designed research on uterine transplantation.

In 2021, uterine transplantation remains experimental and research on this treatment rightly focuses on both success rates (live births) and safety (maternal and neonatal morbidities). In a recent review over 50 transplants had been performed with 16 live births.[8] And while these data are encouraging, the numbers are small enough to warrant ongoing skepticism and the need for well-designed and monitored research protocols to ensure maternal and neonatal safety. [This review will not address the safety and ethical issues of living donor uterine transplantations as these are less concerning to the maternal-fetal medicine specialist, despite comprising an array of significant ethical concerns.]

Fortunately, we have a great deal of data on the safety of pregnancy in the setting of other solid organ transplantations, especially vis-à-vis fetal exposures to immunosuppressive drug regimens. Women who undergo uterine transplantation require maintenance therapy with a variety of immunosuppressant medications that have long track records for safety, particularly in women who have renal allografts.[9] Immunosuppressant medications such as tacrolimus and azathioprine do not seem to be teratogens. It should be noted that maternal-fetal medicine specialists counsel women about the risks and benefits of taking potentially teratogenic (eg some

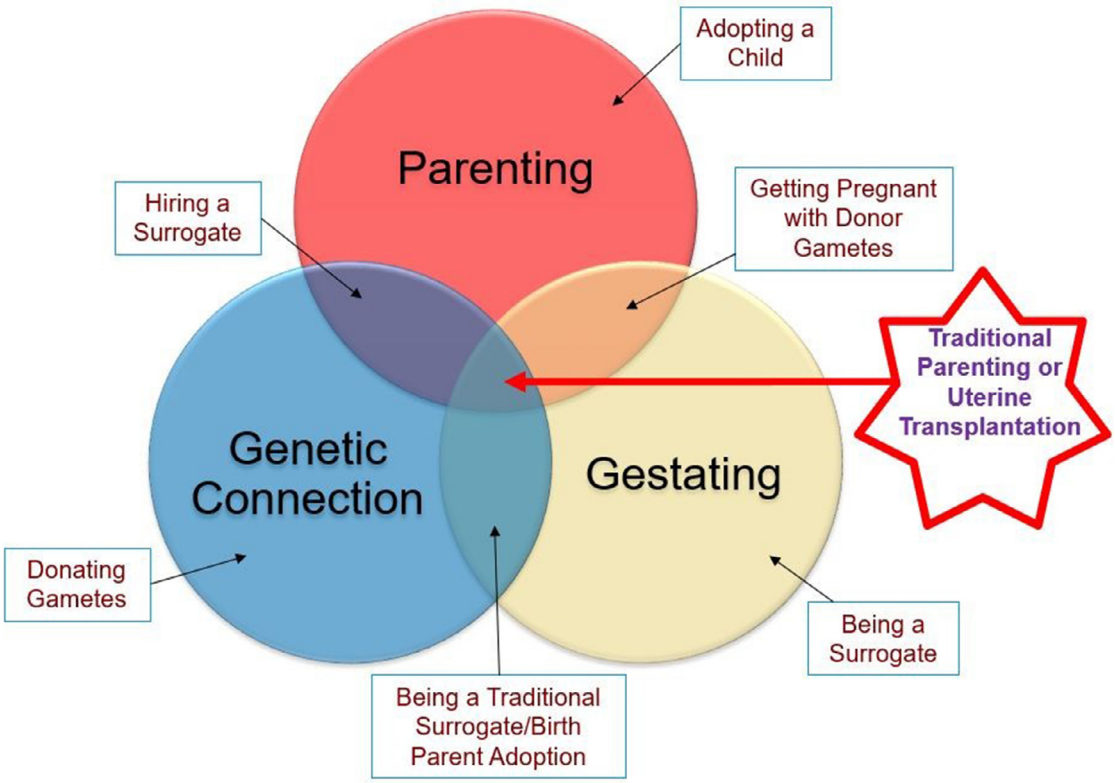

Fig. 1 – Goals of Having or Making a Baby

antiepileptic medications) or addictive substances (eg opiates) in pregnancy and the pharmacologic risks to fetuses and neonates. Often, we conclude that the risks of these medications are worth the health benefits conferred to the pregnant woman. The medications used for uterine transplant recipients don't seem to be exceptionally risky.

But teratogenicity is only one aspect of fetal safety; another important one is the risk of prematurity. The reported gestational ages of babies delivered after uterine transplantation has ranged from 31-37 weeks with the majority being born in the late preterm period.[10] And while this may, on the surface, seem encouraging, the deleterious health effects of prematurity cannot be ignored in this calculus: neonates born before 39 weeks' gestation are more likely to face a number of morbidities ranging from asthma to intellectual disability. But, of course, most babies do fine and while relative risks of morbidity are important and real, they do not translate to high absolute risks. And these risks are not any greater than those for women contemplating any number of challenging pregnancies that may have risks of prematurity that are as high if not higher than the risks we are seeing after uterine transplantation: for example, women with uncomplicated multiple gestations face similar risks of prematurity. So while the risks of prematurity need to be understood and conveyed to women contemplating these surgeries – the principle of autonomy and its close relative, informed consent, require this – the prematurity risk (at least from the data we have so far) do not seem to be so inordinately high that we as maternal-fetal medicine specialists should be any more wary of these pregnancies as we are of other high-risk pregnancies.

The final fetal risk to explore is growth restriction. These pregnancies have every reason to be at higher risk for growth restriction, if only because the blood flow to the uterus may be tenuous and predispose to placental insufficiency. The actual risk of IUGR, however, does not seem to be that worrisome, at least from the early data we have on neonatal outcomes.[11]

The maternal risks associated with uterine transplantation also require our consideration. The transplantation process by design requires several major surgeries for women: the initial transplantation, the cesarean section(s), and then a hysterectomy to remove the transplant after she has completed her childbearing (this is usually after one or two children). Women face problems of being on immunosuppressants, even if only for a few years. And the pregnancies after uterine transplantation have been associated with increased risks of preeclampsia.[12] Women are often willing to take great risks to have a baby, and maternal-fetal medicine specialists have set the bar quite high before we start recommending against pregnancy. Until maternal mortality risks reach double digits, most women are not told that pregnancy is contraindicated. And while uterine transplantation is associated with some clear maternal morbidities, the data we have to date speaks to generally good outcomes for these women, and certainly no risks at the level of those which become suspect for maternal-fetal medicine specialists (eg Marfan's disease with dilated aortic roots, pulmonary hypertension, severe cardiomyopathy).

Overall, the early safety data from many transplant programs seems to be encouraging for both women and their babies. Long-term data, of course, are wanting at this point in time.

Autonomy: supporting women's choices

What is key for all these risks discussed above – maternal and fetal safety concerns – is, of course, the need for informed consent. Women (and their partners) should not embark on this path without a clear understanding of what we know and don't know about outcomes for both the pregnant woman and her neonate after uterine transplantation. The protections afforded women within the confines of an IRB-approved research protocol will go a long way to ensuring that their volunteering for these protocols is well-informed and that ongoing safety concerns are found and addressed. Again, an equally important goal of these research programs besides helping women achieve parenthood is to produce generalizable data on outcomes and safety that can benefit future patients as well. Our support for women's autonomous decision-making in pursuing these unique parenting options is laudable, but only insofar as we can also provide them with accurate information about what outcomes they can expect and what risks they might be incurring for themselves and their children. This will require transparency on the part of the transplant programs and, as much as possible, collaborations between centers. A fine example of such collaboration is the International Society for Uterine Transplantation (ISUTx) whose mission is to:

1) facilitate networking between scientists, clinicians and para-medics worldwide;
2) advocate patient rights;
3) educate the public and medical professionals;
4) share current knowledge and new discoveries through the ISUTx website and the Congress of ISUTx;
5) promote multidisciplinary collaborative research;
6) develop consensus and guidelines on uterus transplantation;
7) establish and maintain an international registry of uterus transplantation cases with follow-up of patients, children and donors.[13]

When does innovation become therapy?

The innovative surgeons who developed the protocols and techniques that have led to successful uterine transplantation and the live births of apparently healthy neonates should be lauded.[14] Moreover, there has been great care in the development of these programs in the US to do so with the robust protections afforded patients in IRB-approved research protocols. The movement from innovation to research in this arena has been swift and welcome. But while most uterine transplantations are happening within IRB approved research protocols, there are already pressures to move these procedures out of the realm of research into the mainstream as standard therapy. Others have already addressed the obvious questions of payment and public funding of these procedures,[15] but the decision to move from research to clinical practice can be fraught with uncertainty and conflict. Indeed, there are few long-term outcome studies on the babies born

after uterine transplantation (the oldest child is barely school age), though it seems unlikely that the outcomes will be any worse than outcomes of other high risk pregnancies. There are sound arguments that both the maternal and neonatal outcomes reported to date are good enough that this no longer be considered experimental therapy. Likely, a consensus amongst the centers involved in these studies will have to be achieved, perhaps with some recommended constraints on and collaboration between future programs to ensure the continued safety of women and neonates. Similar to programs for fetal meningomyelocele repair, centers of excellence will likely be necessary to help protect the interests of future uterine transplantation candidates. As the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics concluded in 2011: "...the establishment of centers of excellence for those procedures that are particularly challenging and rare may help to optimize fetal and maternal outcomes."[16]

Other concerns

Even if the outcomes reported for women and neonates continue to look promising, as maternal-fetal medicine specialists we often think about and guard against worst-case scenarios. Given the low numbers of total pregnancies reported to date, the rare adverse pregnancy outcomes that will eventually befall some of these women need to be contemplated. These are IVF pregnancies and most will have undergone preimplantation genetic testing to screen for common aneuploidies, but major genetic and structural anomalies, acquired abnormalities such as fetal infections, and/or fetal demises will undoubtedly occur. Uterine transplant programs must prepare for these eventualities, ideally counseling women beforehand about these possible outcomes. Our normal management of abnormal pregnancies may be limited by the maternal anatomy – uterine evacuation procedures may be more difficult through a transplanted cervix, especially if there are vaginal strictures present as have been reported in the literature.[17] For similar reasons, the placement of cerclage (if necessary) may be more difficult, and of unknown efficacy in these patients. These concerns underscore the need for these research subjects – and eventually these patients – to have access to multidisciplinary teams that include maternal-fetal medicine specialists and family planning specialists.

Conclusions

Uterine transplantation is an innovative therapy for women with absolute uterine factor infertility. Its development as a clinical tool to help these women has been revolutionary and has demonstrated the power of international collaboration and the lure of the fame and media exposure these births have entailed. Ongoing vigilance and care will be necessary to protect women and their neonates as these techniques move out of research protocols and into standard care. Informed consent centered on a robust evidence base demonstrating what is the most beneficent care will be key in keeping these procedures safe and keeping patients' interests met.

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