The future of human uterine transplantation: can minimally invasive techniques provide a uterus suitable for transplant?

Interest in uterine transplantation for the treatment of uterine factor infertility (UFI) has grown exponentially over the past several years. Following the first birth from this procedure in September 2014 (1), multiple centers worldwide have announced plans to perform clinical trials of uterine transplant. A prominent consideration in creating a protocol is whether to select a living or a nonliving donor model and whether a minimally invasive technique can be successfully used to minimize living donor risk. Indeed, in each of the three reports of living donor transplants from Sweden, Saudi Arabia, and Texas, there has been a major donor complication reported (1, 2). Although the theoretical benefits of a minimally invasive approach for a living donor are clear, questions remain as to whether laparoscopic or robotic retrieval is ethically and/or technically feasible, and also whether these uteri can result in the sina qua non of uterine transplantation, which is the live birth of a healthy infant. In this issue of *Fertility and Sterility,* Wei et al. (3) present the first robotic-assisted procurement of a uterus and subsequent transplantation, which has remained in situ for 12 months of follow up. The authors should be commended for their novel surgical approach in both the use of minimally invasive techniques for recovery of the uterus as well as successful use of the utero-ovarian veins to provide venous drainage for the graft. In addition, in contrast to early attempts at uterine transplantation in humans, the authors performed this procedure as part of a clinical trial with appropriate ethics board approval and also demonstrated success in animal studies initiated several years prior to their attempt in a human subject.

From a bioethical standpoint, the first step in designing clinical trials is identifying potential risks and benefits and minimizing risks to the participants through careful study design. Scientific approaches should be developed that maximize potential benefits to the individual and society, and done so in a way that these benefits outweigh the risks (4). Unlike most clinical research, where risks and benefits affect a single group of research participants, in the case of transplant research, risks and benefits apply to two individuals who participate in the study: the donor and the recipient. Further, it is not sufficient to consider the donor and recipient as separate entities. Instead, it is necessary to address how exposures to one may directly affect the other. This calls for a careful calculus to limit the risks that the donor is asked to take on as research participant in the anticipation that risks will result in greater benefit for the recipient.

As uterine transplant remains an experimental procedure, it is critical to view the risks and benefits to donor and recipient in this research context. Preemptive steps must be taken in experimental design and conduct to minimize risks and maximize benefits, particularly when a novel approach is taken to one or more aspects of successfully described uterine transplant procedures. Specific to this article (3), it is yet premature to conclude that a modified surgical approach, such as the one described, benefits both the donor and the recipient more than other approaches to the procedure. A modified approach may have a shorter surgical time, thereby reducing the risks to the donor associated with anesthesia and surgery. And although a minimally invasive approach poses clear potential benefits, it may also introduce additional and yet uncharted risks, leading to a reconsideration of the fundamental assumptions that made the clinical research ethical. For instance, the risks of premature surgical menopause, as occurred here in the donor, are well recognized. Thus, there should be a justifiable reason for exposing donors to both this risk as well as the risks of hormone therapy (or the consequences to health from the lack thereof) which may be required subsequently. However, at the present it is not clear if the benefits associated with shorter surgical times sufficiently outweigh these additional potential risks to the donor. The risks of premature surgical menopause as well as the risks of potential hormone therapy, in addition to the uncertainty associated with new approaches to uterine transplant, must be fully disclosed to potential donors in the informed consent process.

In considering the risks and benefits, it is also necessary to consider the recipient. As of yet, it is not clear if this modified approach to graft retrieval will, in fact, increase the chances of a successful pregnancy. This factors into the fundamental question of whether the risks presented to the donor from oophorectomy are outweighed by benefit to the recipient. Without these data, the question of the optimal risk-benefit ratio of this approach cannot be answered. Furthermore, this modified approach potentially introduces additional risks that must be addressed in the informed consent process. First, the authors (3) note the use of the utero-ovarian vein from the donor to provide venous drainage of the graft. In time, it may become clear how significantly this approach may reduce donor recovery times or, ultimately, pregnancy and pregnancy outcomes. It is also important to recognize the composite risk for a series of novel modification used in combination are unknown. There are several ways in which this surgical approach diverged from the approach previously used successfully in Sweden. The use of the utero-ovarian vein, the use of the surgical robot, the performance of the anastomosis beginning with the vagina rather than with the blood vessels, the use of a recipient with a recent vaginal reconstruction, and the use of robot, either individually or in combination may affect the risk:benefit ratio and, ultimately, alter the chances of a healthy live birth. For this reason, those conducting research in uterine transplant must structure a thoughtful and meticulous informed consent process that assists those considering transplant.

In addition to the ethical considerations important in a new procedure, there are technical challenges to be noted from this report. It is imperative that transplanted uteri have adequate vascular inflow and outflow; the vascular pedicles required for these procedures are significantly

longer and larger caliber than what would be afforded by a simple hysterectomy. When attempting a minimally invasive approach, although the uterine artery can typically be easily delineated, the dissection of the uterine vein (as was successfully used in the Swedish trial) will present a formidable challenge even for the most skilled surgeons due to close proximity to the ureter, thin walls, and numerous branches. Indeed, in this report, the authors describe that robotically, the uterine veins could not be isolated, and therefore the utero-ovarian vessels were used for venous drainage instead. Proof of concept preclinical studies using the utero-ovarian veins for venous drainage of a transplanted uterus have been successfully performed in baboons (5). Further in the recent series of five human living donor transplants from Texas, short segments of the utero-ovarian vessels obtained via laparotomy were successfully used (1). Although this does appear to be a promising new direction for uterine transplantation, Wei et al. do not indicate that the use of utero-ovarian veins had been trialed by their group in animal models or human deceased donor practice cases prior to attempting use in their human subject.

It should be noted that the use of the utero-ovarian veins allowed for a short donor surgical time in this case. At 6 hours, this compares favorably to the two prior published series of living donor uterine transplants from Sweden and Texas, with reported recovery times for the living donors of 10–13 hours and 8–9 hours, respectively (1, 2). Recovery times in deceased donors are shorter as swift dissection can proceed without concern for donor injury.

In contrast to organ recovery, reimplantation of the uterus in the recipient was relatively long at 8 hours and 50 minutes compared to the Swedish experience, which was on average 4 hours and 46 minutes ± 30 min (2). In the Texas report, which also used the utero-ovarian veins, the reimplantation took 4.5–6 hours (1). The length of time for reimplantation factors into warm ischemia time (the time between removing the uterus from ice and reperfusion of the graft). The effects of longer warm ischemia times on uterine transplants is unknown but longer times could potentially compromise graft viability.

Finally, although this study and others will increase optimism for the possibility of a minimally invasive uterus retrieval, no current protocols in humans or animals have yet reported a successful pregnancy using a minimally invasive approach. Although resumption of menstrual function occurred in this case report within two months of transplant, it is unknown whether a uterus drained by the utero-ovarian vessels will be able to support and sustain implantation and ongoing pregnancy in humans.

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