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Preimplantation genetic testing for aneuploidy in uterus transplant patients

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Abstract: Uterus transplantation is an emerging treatment for uterine factor infertility. In vitro fertilization with cryopreservation of embryos prior is required before a patient can be listed for transplant. Whether or not to perform universal preimplantation genetic testing for aneuploidy should be addressed by centers considering a uterus transplant program. The advantages and disadvantages of preimplantation genetic testing for aneuploidy in this unique population are presented. The available literature is reviewed to determine the utility of preimplantation genetic testing for aneuploidy in uterus transplantation protocols. Theoretical benefits of preimplantation genetic testing for aneuploidy include decreased time to pregnancy in a population that benefits from minimization of exposure to immunosuppressive agents and decreased chance of spontaneous abortion requiring a dilation and curettage. Drawbacks include increased cost per in vitro fertilization cycle, increased number of required in vitro fertilization cycles to achieve a suitable number of embryos prior to listing for transplant, and a questionable benefit to live birth rate in younger patients. Thoughtful consideration of whether or not to use preimplantation genetic testing for aneuploidy is necessary in uterus transplant trials. Age is likely a primary factor that can be useful in determining which uterus transplant recipients benefit from preimplantation genetic testing for aneuploidy.

Keywords: IVF, PGT, PGT-A, preimplantation genetic testing for aneuploidy, uterine factor infertility, uterus transplantation

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Introduction

Uterus transplantation is an emerging surgical treatment that spans multiple disciplines including transplant surgery, gynecologic surgery, bioethics, high-risk obstetrics, and reproductive endocrinology. The demand for uterus transplantation has largely been driven by the patients and families directly affected by absolute uterine factor infertility (AUFI), a condition that affects an estimated 3–5% women worldwide by either congenital or acquired causes.[1,2] While there are alternative avenues for family building, including gestational surrogacy and adoption, these are not available or desired for some patients with AUFI, making uterus transplantation the only viable option for women seeking both biological and gestational motherhood.[3]

The past 8 years have shown a dramatic increase in the number of pregnancies following uterus transplantation.[4] Since the first birth following uterus transplant in Sweden reported in 2014, there have been at least 20 babies born following this procedure reported in the literature.[2] In the United States, there are currently three uterus transplantation clinical trials (Baylor Dallas, Cleveland Clinic, and Penn Medicine) that are actively recruiting patients, performing transplant procedures, and/or performing embryo transfers into transplant recipients.[5]

Currently, all centers in the United States perform uterus transplantation through clinical research protocols (ClinicalTrials.gov identifiers NCT02656550, NCT03307356, and NCT02573415). These protocols have several common features, including a timeline in which patients undergo embryo banking [including ovarian stimulation, oocyte retrieval, and in vitro fertilization (IVF)] prior to being matched to a living or deceased uterus donor depending on

the clinical trial. There is at present no consensus as to the optimal or minimum number of banked embryos needed prior to the transplant procedure; recommended inclusion criteria by the American Society for Reproductive Medicine (ASRM) state only that recipients should have a "sufficient number of good quality embryos."[6]

There is no standard definition of what constitutes a "good quality" embryo in the field of reproductive endocrinology. There is ongoing debate on whether and to whom aneuploidy screening through preimplantation genetic testing (PGT-A) should be offered with IVF.[7,8] Unlike early methods of PGT-A, modern methods involve comprehensive chromosome screening (CCS) using next-generation sequencing (NGS) of cells taken from trophectoderm (TE) biopsies of blastocysts; theoretically, such genetic testing should identify karyotypically abnormal embryos that otherwise appear morphologically normal and therefore reduce implantation failure and early pregnancy loss by exclusion of these embryos.[9] While earlier randomized trials suggested a benefit of PGT-A for women of all age groups, these trials faced significant criticisms, and PGT-A is currently not deemed to be standard of care by national society guidelines despite the widespread use of this technique in Assisted Reproductive Technology (ART) clinics. Recent randomized trials, including a large multicenter trial, have shown no benefit for PGT-A over traditional methods of assessing embryo competency.[10]

The importance of PGT-A in the context of uterus transplantation is worthy of debate. To our knowledge, the question of PGT-A in uterus transplantation has not yet been specifically addressed in the current body of literature. Due to the complex and risky nature of the uterus transplantation procedure, potential recipients must bank a sufficient number of high-quality embryos to be able to be listed for transplant.[11] Programs at national and international uterus transplant centers vary in their requirements for use of PGT-A. Previous studies of PGT-A have never included uterus transplant trial participants, who are likely younger and may be better prognosis for successful IVF than the average population undergoing in vitro fertilization. In this article, we explore the data available in the literature to determine the utility of PGT-A in uterus transplantation protocols.

PRO: PGT-A should be utilized for all uterus transplant patients

PGT-A is widely performed by IVF centers today.[12,13] Current indications for PGT-A include advanced maternal age, prior chromosomally abnormal pregnancy or child, multiple implantation failure, recurrent miscarriage, severe male factor infertility, egg donation cycles, or good prognosis patients transferring a single embryo.[14] Proposed benefits of PGT-A in the general population include improved implantation rates and cost-effectiveness and decreased miscarriage rates, risk of multiples, abnormal offspring, time to pregnancy, and emotional burden.

There are unique considerations regarding PGT-A within the uterus transplant population. The primary theoretical benefit of PGT-A is the reduction in exposure to immunosuppression by a shortened window to pregnancy achieved via euploid blastocyst transfer. Until the time of graft removal, recipients must receive immunosuppression to prevent rejection of the transplanted uterus. Traditional immunosuppressive regimens consist of a combination of calcineurin inhibitors such tacrolimus and cyclosporine, as well as steroids and other agents including mycophenolate and/or azathioprine.[1] These regimens are adjusted for pregnancy to avoid the teratogenic effects of mycophenolate, but even the obstetric regimens are associated with known maternal toxicities (e.g., renal toxicity, related to tacrolimus and cyclosporine levels), which may or may not be reversible following hysterectomy and discontinuation of immunosuppressants. There is no knowledge whether decreased glomerular filtration rate (GFR) in uterine transplant patients can be reversed after hysterectomy or without immunosuppressants. It is not currently known whether the delay in pregnancy would significantly impact a patient's GFR after transplant or whether there is significant recovery of the GFR after the graft is removed; however, retrospective case studies have shown renal toxicity is a common occurrence among the uterus transplant population. However, the longer the duration of exposure, the greater the risk of these toxicities, including risk of graft rejection and/or infection. Thus, it is of paramount importance to minimize exposure of immunosuppressive medications by decreasing the time to pregnancy in uterus transplant recipients.[15] A recent randomized clinical trial of 205 older women aged 38–41 years found that PGT-A not only increased delivery

rates and decreased miscarriage rates but also shortened the time interval to pregnancy by 7 weeks compared with similar untested embryos.[14] If PGT-A can truly decrease the amount of time to a healthy life birth, then that would be of fundamental importance in counseling women considering uterine transplant in regard to PGT-A; although this has not been the outcome of such studies, if this was further proven it could be. A retrospective analysis of 2093 older women undergoing IVF with PGT-A also found a significantly shorter time to pregnancy leading to live birth of 35 days on average compared with embryo assessment with morphology alone.[16]

Ovarian stimulation, oocyte retrieval, and embryo cryopreservation generally occur prior to uterus transplantation. Given that Mayer–Rokitansky–Küster–Hauser syndrome is the most common indication for uterus transplantation and that these patients on average have normal ovarian reserve, uterine factor infertility patients selected for clinical trials typically are predicted to respond favorably to controlled ovarian stimulation.[17] Therefore, unlike women undergoing IVF who have underlying infertility diagnoses, potential uterus transplant candidates typically have less difficulty generating sufficient embryos. Women 26–37 years old in the general IVF population have a $<10\%$ rate of euploid embryo; this rate may be even lower in women with uterine factor infertility.[18]

The ASRM recommends a single embryo be transferred at a time in all uterus transplant patients.[6] Therefore, stringent protocols for embryo selection are of great importance. Morphology selection alone does not avoid the transfer of aneuploid embryos.[19] A randomized study comparing PGT-A with CCS versus morphology selection alone found improved implantation and pregnancy rates and fewer miscarriages among good-prognosis IVF patients after PGT-A.[20] Optimization of embryo competence may result in increased success of single-embryo transfer. Ensuring that a euploid blastocyst is transferred may translate to decreased time to pregnancy and decreased rate of spontaneous abortion due to aneuploidy.

The proposed benefits of PGT-A in the general population include improved implantation rates and cost-effectiveness as well as decreased miscarriage rates, risk of multiples, abnormal offspring, time to pregnancy, and emotional burden. The question arises whether PGT-A can deliver on these proposed benefits for uterus transplant recipients. Studies of the general IVF population show conflicting results regarding implantation and miscarriage rates using PGT-A. A meta-analysis of randomized controlled trials (RCTs) comparing implantation and clinical pregnancy rates with PGT-A with CCS compared with routine IVF using embryo morphology selection criteria found significantly improved implantation and clinical pregnancy rates with PGT-A with CCS.[21] A separate meta-analysis of four RCTs and seven cohort studies found improved implantation, pregnancy, and live birth rates with decreased miscarriage rates in PGT-A with CCS compared with morphological assessment alone.[22] Improved outcomes have been noted in young, good-prognosis patients and in older patients. A single-center retrospective observational study of egg donation cycles in frozen embryo transfers comparing single-embryo versus double-embryo transfers found significantly improved live birth rate per embryo transfer in both own recipient uterus and gestational carriers after double-embryo transfer with PGT-A and a similar trend with single-embryo transfer.[23] Scott and colleagues recently published findings from a decision analytic model using clinical data and assumptions from the literature investigating the cost-effectiveness of PGT-A. This model reviewed 8998 patients less than 43 years old undergoing IVF in 74 different IVF centers and found that for patients with more than one embryo, PGT-A is cost-effective and can decrease time to pregnancy by up to 4 months.[24]

On the contrary, two recent randomized control trials failed to find significant differences in pregnancy outcomes using PGT-A in good-prognosis patients.[10,25] One study randomly assigned 220 couples younger than 36 years old with at least two good-quality blastocysts to frozen embryo transfer (FET) of either single best euploid or single best unknown-ploidy blastocyst. This study did not demonstrate a significant difference in live birth rates between the groups. However, due to the small sample sizes within the groups, the study may not be sufficiently powered to generalize the results. Furthermore, the impact of technical expertise of embryo biopsy may also impact the efficacy of PGT-A, and this was performed at a single center.[25] A prospective, multicenter randomized control trial was also recently performed to

evaluate the efficacy of NGS-based PGT-A after single FET if there were at least 2 blastocysts available to biopsy. Six hundred sixty-one women were randomized to either morphology with PGT-A or morphology alone for embryo selection. This study did not find a significant difference between miscarriage, implantation, or live birth rates between the groups. However, this was an intention-to-treat analysis which included 42 patients within the PGT-A group that did not have any blastocysts to biopsy or transfer and thus may have impacted the outcomes.[10] This may imply a possible detrimental effect of embryo biopsy on outcomes. This conclusion would contradict previously published results of an RCT showing equivalent sustained implantation rates after blastocyst biopsy compared with unbiopsied blastocysts.[26] New noninvasive biopsy technology and sequencing platforms are being developed that may help mitigate any potential iatrogenic errors arising from the biopsy itself as well as errors related to mosaicism.

Uterus transplant recipients are women with restricted options for achieving motherhood who wish to achieve pregnancy and as such may be considered a vulnerable population.[6] Recipients are exposed to known and unknown risks as part of their participation in clinical trials and require significantly more resources than typical IVF patients. By the time they enter into IVF, potential transplant recipients have already undergone an exhaustive screening process and can anticipate undergoing treatment with immunosuppressive agents in addition to multiple surgeries for the goal of carrying and delivering a biological child. Furthermore, uterus transplant pregnancies require a high level of medical attention, which results in increased anxiety and stress.[27] Thus, unnecessary mental and social pressures on these patients should be avoided if possible. Most aneuploid embryos do not implant or result in miscarriage.[28] A retrospective review of 15,169 IVF patients undergoing TE biopsy with CCS found the rate of aneuploidy increases predictably with age from 20% at age 26 to 85% at age 43.[18] As expected, the rate of spontaneous miscarriage increases with age from 10% to more than 65%.[28] Difficult reproductive decisions regarding the management of aneuploid pregnancies and the disposal of surplus embryos once one to two pregnancies have been achieved may be influenced by the unique scenario of uterus transplantation. Furthermore, the emotional toll of miscarriage may impact this population differently than others. Euploid embryo transfer may help to avoid these challenging situations.

Technical considerations in situations of miscarriage or termination of pregnancy related to aneuploidy should also be considered in the setting of uterus transplantation. Little data are available as to the optimal technique, risks, and long-term sequelae of performing a dilation and curettage in a chronically immunosuppressed patient with a transplanted uterus, and in each of these domains there may be differences from typical patients. First, immunosuppression and chronic steroid use increase the risk of infection and adrenal crises perioperatively. Second, increased thrombotic risk in pregnancy and after surgery may complicate the course of a uterus transplant patient. Finally, recipients with a history of AUFI secondary to congenital absence of a uterus often develop a vaginal stricture at the site of the anastomosis, which may result in difficulty visualizing and accessing the cervical os for dilation and curettage.[29] In these patients, surgical complexity and adverse outcomes could be significant even for this minor procedure which is typically considered a low-risk and low-complexity procedure. Although mid-trimester evacuation has not been required or attempted in a uterus transplant recipient, this would likely present an even more challenging scenario. Thus, attempts to avoid these surgeries and the complications thereof with the use of PGT-A to decrease risk of aneuploidy-associated miscarriage should be a priority.

CON: PGT-A should not be universally performed for uterus transplant patients

Many arguments against the use of PGT-A in uterus transplant candidates include the same arguments against its universal use in the general population, including the inherent limitations of PGT-A, the possible harm of biopsy to embryos with live birth potential, the questionable efficacy of PGT-A in improving live birth outcomes, and increased costs. Specifically for uterus transplantation patient, the use of PGT-A may possibly delay the patient's entry into a transplant waiting list.

PGT-A has several limitations. Even with advancement of PGT-A techniques from comprehensive cytogenetic methods such as array comparative genomic hybridization (CGH) to

more recent NGS, there have been reports of inaccurate PGT-A test results and discussions of its clinical efficiency.[8] The portion of the embryo that is biopsied, the TE, is known to divide at high rates, increasing the risk of mitotic errors. As a result of this, TE biopsy may lead to both false-positive and false-negative results. For example, an embryo may be reported as aneuploid when in fact the inner cell mass (ICM) is euploid.[8] This kind of false-positive result carries the potential to discard embryos that could otherwise lead to healthy live births. One study reports an approximate 10% false-positive rate.[30] Of note, false-positive rates may be even higher in young, low-risk patients such as women who are included in uterus transplant programs. In addition, embryos that result as mosaic or "no read" also may not be eligible for transfer.[31]

In addition, there may be some potential harm to the embryo from the biopsy procedure. The assertion that TE biopsy does not harm or decrease implantation rates of embryos derives primarily from one study that examined excellent-quality blasts that were all transferred within 3 h of biopsy in patients under the age of 35 who had a least two excellent-quality blastocysts (4AA or 4BB) available.[32] It is difficult to generalize these data beyond this group of individuals and IVF labs, as we cannot assume that these results apply to patients greater than the age of 35, those who have lesser quality embryos, or those who have cryopreserved embryos prior to use.[10]

Given the above concerns, the efficacy of PGT-A in embryo selection is an area of considerable debate. A recent RCT, the STAR trial, evaluated the benefit of NGS-based PGT-A for embryo selection in frozen embryo transfer patients compared with morphologic selection of embryos.[10] Their findings show that PGT-A in patients aged 25–40 years undergoing IVF with at least two blastocysts available for biopsy did not improve overall pregnancy rates when analyzed per embryo transfer or per intention to treat when compared with morphology-based embryo selection. When considering only those with age <35 years, the ongoing pregnancy rates (OPRs) at 20 weeks' gestation were 53% in the control group and 49% in the PGT-A group.[10] While the 35- to 40-year-old group had a higher OPR per embryo transfer after PGT-A (50.8% vs 37.2%; $p = 0.035$) compared with the <35-year-old group (49.3% vs 53.0%; $p = 0.58$), this was not significant when analyzed by intention to treat. The results of this study raise issues regarding PGT-A and its utility in all patients undergoing IVF. If ongoing pregnancy rates and live birth rates are not significantly improved in young patients undergoing PGT-A versus those with morphology-based selection criteria, then it may be unnecessary to require embryos to undergo biopsy, handling, and further manipulation prior to transfer. In the uterus transplantation population, this may mean that routine PGT-A testing may not offer an advantage in selecting embryos that are more likely to result in a live birth, especially when potential recipients are <35 years old. This is in line with anecdotal reports from active uterus transplant centers suggesting high implantation rates on initial transfer of untested embryos into young, good-prognosis uterus transplant recipients.

In fact, in patients younger than 35 years old, the use of PGT-A may result in an approximate 50% decrease in implantation potential.[33] As a result, use of PGT-A could cause some of these embryos with live birth potential to be discarded. To achieve the required number of PGT-A euploid embryos prior to uterus transplantation, participants may need to undergo additional cycles of ovarian stimulation, with each cycle carrying inherent risks such as hyperstimulation and thrombosis related to levels of supraphysiologic estrogen.

A final argument against universal PGT-A for uterus transplant candidates is increased cost. The average cost of PGT-A per IVF cycle is $5000.[34] While uterus transplantation costs are covered by research protocols at this time, IVF and PGT-A expenses may not be. In this case, such added costs put further emotional and financial burdens on this vulnerable population, who are highly motivated to gain access to limited spots on transplant lists. If PGT-A is considered an eligibility criteria for uterus transplant recipients, the incremental cost of needing to complete more IVF cycles to achieve the requisite number of PGT-A normal embryos will add to the overall cost for the uterus transplant candidate. Furthermore, when uterus transplantation is no longer considered experimental, issues related to cost and coverage will become even more pertinent. If PGT-A testing does not significantly improve reproductive outcomes, the additional

expense of PGT-A for a uterus transplant candidate cannot be justified.

Conclusion

Uterus transplant patients are a distinct subset of IVF patients. PGT-A may offer a decreased interval to pregnancy in a population that needs to minimize exposure time to immunosuppressive medications, limit risks of dilation and curettage, and prevent pregnancy complications. However, PGT-A adds cost and complexity with a questionable benefit to live birth rate in younger patients within this unique population. Until more data are available, decisions on whether or not to utilize PGT-A should be individualized for a given clinic and/or patient. Further discussion and research in this area are needed to develop clinical guidelines in the use of PGT-A for uterus transplant candidates.

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