Review Article

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The Time has come: Gestational Carrier and the Use of Pre-implantation Genetic Testing (PGT)

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Abstract

Purpose of review: Gestational carrier reproduction is restricted in much of the industrialized world due to complex ethical issues between the intended parents (IP) and the gestational carrier (GC), as well as safety concerns for the GC. Over 3% of all embryo transfers done in the United States involve GCs. Recent review has revealed high perinatal risks associated with assisted reproductive technologies (ART) for GCs. Compared to spontaneous conception, which the GC is familiar with, GCs using IVF have increased risk for twins and triplets of 20 and 46 fold, respectively. The resultant perinatal mortality rates are increased 4-6 fold. Costs in the first year of life for multiples are 5 to 20 times greater than for singletons. As GC cycles continue to increase, we must develop strategies to reduce perinatal risks for GCs and their offspring.

Recent findings: Recent advances in IVF with pre-implantation genetic testing allow detection of euploidy for all 24 chromosomes. Elective single embryo transfer has reduced the risk of multiple pregnancy, preterm delivery and perinatal morbidity for women across the age spectrum.

Summary: Elective euploid single embryo transfer, through the use of PGT, allows for very high pregnancy rates while reducing perinatal morbidity to natural levels. Both multiple gestation and miscarriage are dramatically reduced. Implementation of this technology in GCs will greatly enhance the safety of pregnancies, protecting this vulnerable population of altruistic women.

Keywords: Gestational carrier, Pre-implantation genetic testing (PGT), Elective single embryo transfer (eSET), Euploid embryos

Abbreviations: IP: Intended Parents; GC: Gestational Carrier; Assisted Reproductive Technologies (ART); PGT: Pre-implantation Genetic Testing

Introduction

A gestational carrier (GC) is a woman who carries and delivers a pregnancy for another individual or couple. She is selected to carry the pregnancy because of a history of prior healthy term pregnancy and live birth. The egg and sperm are typically from the IPs, combined through the use of in vitro fertilization (IVF), cultured into embryos in the lab and then placed into the uterus of the GC [1]. GCs are often used when uterine disease or

serious medical condition precludes the intended parent (IP) from carrying a pregnancy or would pose a significant risk of death or harm to the woman or the fetus. They are also used by male same sex couples and more rarely by single men who desire to become fathers. The use of GCs is increasing in the United States, approaching 3.5% of all ART cycles in 2015 (Figure 1). As IVF success rates are improving, women unable to carry pregnancies on their own are seeking alternatives to adoption for genetic

children [2,3]. Adoption in itself is a time intensive process with its own rigorous selection criteria for IPs, which can limit its accessibility for many couples and individuals. Uterine transplantation is experimental and not yet available except in very rare circumstances. However, GCs offer a viable solution. Due to limitations on gestational surrogacy in other countries owing to concerns about coercion, there are a significant number of non-US residents who participate in cross border reproduction. The use of GCs by non-US residents has risen from 2% of the total GC cycles in 2005 to 19% in 2013 (Figure 1) [2].

Figure 1: Graph showing increase in utilization of Gestational Carrier through Assisted Reproductive Technology in the United States, as reported to the Centers for Disease Control.

According to recommendations from the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE), a GC should be between the ages of 21 and 45 years and have at least one child. Her previous pregnancies should have been full-term and uncomplicated [1,4]. She should not have had more than 5 deliveries total or more than 3 prior C-Sections. She may be known to the IP, such as a family member, or an unknown carrier identified through an outside agency. Given these eligibility criteria and the experience of childbirth, one might presume that GCs are familiar with the risks pregnancy. However, the GC is not only exposed to the more commonplace risks of singleton pregnancy, but also the burden of extensive medical, serologic, and psychological screening, hormonal preparation of the uterus, as well as the family burden of carrying a term pregnancy for the IP. In addition there are significant pregnancy risks added using ART, such as the increased risk of ectopic pregnancy, hypertensive disorders of

pregnancy and multiple gestation due to the transfer of more than one embryo. In fact, a recent study of the trends and outcomes survey of GC IVF cycles in the US between 1999-2013 revealed that of 30, 297 GC cycles, 78.6% had more than 1 embryo transferred (an average of 2.1 embryos are transferred per cycle.) There was also a 30% multiple pregnancy rate and a 18% risk of miscarriage for the carrier [2].

This paper explores the risks of gestational carrier pregnancy and calls attention to carriers as an altruistic and vulnerable population of women who are looking to help other couples experience the joy of parenting sometimes at the expense of their own medical safety [5]. It also describes recent advances in assisted reproductive technologies including elective single embryo transfer (eSET) and pre-implantation genetic testing (PGT), which we argue can help dramatically increase the safety of GCs by allowing for SET without compromising pregnancy outcomes. Additionally, we highlight the tenuous legal environment present in much of the world, where GC is not permitted because of divergent ethical principles at play when the interests of the IP and GC disagree, which may place the welfare of the GC at risk. We believe that to simultaneously increase singleton pregnancy rates, term delivery, GC safety, and live birth rates per embryo transfer, PGT and eSET should be encouraged if not required for every IP using GC services.

Gestational carrier demographics

Fuchs et al. conducted a survey of 222 gestational carriers in the United States that well characterized the demographics of the GC population [6]. The majority had education beyond high school with nearly 40% having a bachelor's degree or more, 75% had a household income of greater than \$50K, and 94% had private health insurance. The mean number of children was 2.7 prior to surrogacy. In studies that have assessed contacts between the GC and the IPs, in the vast majority of cases, contact was harmonious and regular [7,8]. The frequency of contacts decreased over time while the quality of the relationships seemed to continue [9]. The rate of postpartum depression ranges from 0-20% , which is comparable to rates in the general population estimated to range between 10-20% per the CDC [7].

Among IPs using GC for infertility, the most common diagnosis causing their infertility was uterine factor, followed by a host of medical conditions for the intended mother including immunologic disorders, chromosomal disorders in the intended mother (i.e., Turner's

mosaicism) or other serious systemic disease. The mean age of the patients utilizing GC services was 37.6 years, implying advanced maternal age effects on the ovaries in the majority of these patients. Some IP utilized both donor oocyte and GC services. For infertile women, this might have been due to advanced maternal age or infertility refractory to other treatment given the use of donor eggs offers far better prognosis. Another group using gestational carrier are same-sex couples.

Gestational carriers and risk of multiples

Choosing to pursue GC services takes a large emotional and financial toll on IPs. As such, IPs may be eager to pursue any means to improve their chances of live birth and avoid having to do additional cycles. Therefore, it comes as no surprise that multiple embryo transfer sounds like a convenient and reasonable choice to most IPs. As indicated by results from a recent survey of 339 infertility patients from two different clinics, 58.2% of participants preferred having twins to having one child at a time and 4.8% preferred triplets. The primary reasons for preferring twins were “avoiding a new IVF/ICSI attempt” (61.6%). Some endorse the perception that the rate and severity of complications in multiple pregnancies “are low” [10].

These perceptions are reflected in real world practice. In the US, ART clinics are required to report their data prospectively to the CDC. About 80% of the 475 IVF clinics in the US report to the Society of Assisted Reproduction Technology SART (2016), accounting for 91% of ART cycles in the U.S [11]. In the 10-year period from 2004 to 2013, there were 24,269 cycles using gestational carrier reported to SART. When using the eggs from infertility patients and GC, the live birth rate per embryo transfer was 38%, with 29% of all live births representing twins and 1.3% being higher order multiple gestation (HOM). Of the total number of embryo transfers, 25.3% ended in early or late miscarriage. When using donor eggs and GC, the live birth rate per embryo transfer was 52%, with 37% of all live births representing twins and 1.4% being HOM. Of the total number of embryo transfers, 17% ended in early or late miscarriage [11]. This is in stark comparison to naturally conceived pregnancies in the United States. For naturally conceived pregnancies, the incidence of live birth rate for of singleton, twins, and HOM is 98.4%, 1.5%, and 0.03%, respectively [12]. This equates to an increased risk of twins and HOM of 20 fold and 47 fold, respectively, for GC IVF cycles.

It is evident that more education of both clinics and

patients is needed. IVF conceived multiple gestations in GCs are associated with increased risk for a multitude of obstetric complications including preterm birth, postpartum hemorrhage, need for hysterectomy, preeclampsia and gestational diabetes [13]. Selective fetal reduction is an option in the case of multiples, but carries the risk of losing the entire pregnancy. It also poses the ethically challenging question of whether IPs have the right to request selective feticide when using a GC for fear of raising triplets. Does a GC have the right to choose selective feticide to decrease her own risk? Nonetheless, often given their circumstances, the decision of IPs to transfer two or three embryos is routine. Consequently, it is left to the ART physician and GC/IP legal teams to balance the risks to the GC with the goals of the IP.

The costs of multiples

A recent study by Lemos et al. compared the total all-care direct costs of combined obstetrical care from 27 weeks gestational age until delivery in addition to infant care from delivery until the first year of life. Twins and triplets were much more likely to spend time in a neonatal intensive care unit and 13 times more likely to be born premature, before 32 weeks gestation. This translates into a 7 and 28 fold increase in the risk of cerebral palsy for twins and triplets respectively [14]. The average direct costs for singleton, twin and triplet pregnancies were \$21,458 per delivery with singletons, \$104,831 with twins, and \$407,199 with triplets or more [15]. Costs after the first year of life are harder to estimate, but the long term health effects of prematurity likely persist into adulthood.

Perinatal mortality rates are also 4-fold higher for twins and 6-fold higher for triplets than for singletons. Multiple gestations are high risk pregnancies, which may be complicated by prematurity, low birth weight, pre-eclampsia, anemia, postpartum hemorrhage, intrauterine growth restriction, neonatal morbidity and high neonatal and infant mortality. Multiple gestation children may suffer long-term consequences of perinatal complications, including cerebral palsy and learning disabilities [16]. Of course, the emotional costs of complicated pregnancies for any pregnant women are high extending both to the IP and the GC [17].

Gestational carriers and single embryo transfer

Given the risks and costs we have outlined above, we need to increase safety for gestational carriers. Single embryo transfer seems like a sensible solution to reduce the risk of multiple gestation and the associated obstetric

complications for GCs. In an effort to promote singleton gestations, reduce twin gestation, and eliminate HOM, ASRM and the SART have developed guidelines to assist ART programs in determining the appropriate limit to the number of embryos to transfer. These guidelines have been incrementally refined since 2006, and have resulted in progressive reductions in the proportion of multiple gestations over time, with the expected benefit of decreasing the risk of preterm delivery and pregnancy complications [18-20]. Martin et al. recently examined a large database linking vital records in four states to the SART registry to examine the outcome of singletons conceived by eSET versus those conceived by non-eSET. After examining over nearly 500,000 non-ART and over 17,000 ART birth outcomes, they concluded that singletons conceived by ART and eSET have similar birth outcomes as naturally conceived singletons [21]. Despite these improved outcomes, in the most recent reporting years, a minority of patients have elected for single embryo transfer, 17% in our most common age group of 35-37 years [3]. Advancing maternal age drives the desire for multiple embryo transfer to the GC uterus. An average of 2.1 embryos is transferred in GC IVF cycles. While the mean number of embryos transferred has fallen, the multiple pregnancy rate and risk accrued by gestational carriers continues to be very high. This in part is due to IPs seeking to minimize their out of pocket expenses and maximize their chance for pregnancy through the transfer of 2 or 3 embryos. In fact, many IPs find twins or triplets desirable [21].

The ASRM guidelines have recommendations regarding gestational carrier, and request consideration of single embryo transfer. However, the guidelines also add a caveat that "additional embryos may be transferred based on the age of the genetic parent, in an effort to improve the probability of pregnancy" [1]. In another guideline, the ASRM states "In each of the above age groups, patients who do not meet criteria for a favorable prognosis may have an additional embryo transferred according to individual circumstances" [20]. In general, third party reproduction represents a higher stakes situation. Moreover, IPs are often very anxious for pregnancy, and consider themselves to have an unfavorable situation. Due to this ambiguity in phrasing and differences in interpretation, the guidelines may unintentionally promote the transfer of more than 1 embryo in GCs. Furthermore, the ASRM does not mention PGT for gestational carrier services.

Pre-implantation genetic testing

We believe the answer is single embryo transfer after pre-implantation genetic testing of the embryo for aneuploidy (PGT-A). Aneuploid embryos are the predominant cause of age related infertility [22,23]. The risk of trisomy in a clinically recognized pregnancy rises from 2-3% at the age of 30, to over 30% after the age of 40 [24]. Clinical aneuploidy testing for IVF began in the early 1990s with biopsy of a single cell from a cleavage stage embryo, and fluorescent in situ hybridization to test for the most common aneuploidies in chromosomes: X,Y,18,13,and 21 [25]. Modern PGT is a process by which an embryo undergoes biopsy at the blastocyst stage to remove a 5-10 trophectoderm cells, which are the cells destined to become the placenta rather than the embryo itself. The biopsy specimen then undergoes genetic analysis using a gene sequencing platform, with the ability to perform 24 chromosome screening for aneuploidy (PGT-A), or for diagnosis of a specific single gene mutation (PGT-M). Embryos with a normal complement of chromosomes are characterized as euploid, and those with missing or extra chromosomes as aneuploid. Sometimes these 5 cell biopsy results show a mix of normal and abnormal cells with more than one cell line present. These embryos are characterized as mosaic. How to proceed with the mosaic embryos is a matter of controversy, but beyond the scope of this paper. PGT-A allows for the identification and transfer of these euploid embryos. Embryo transfer occurs after the PGT results are known, typically into a prepared endometrial cavity depending on how long it takes for the results to return.

Early randomized control trials on PGT-A showed some potential harm (lower live birth rates), but more recent studies using the latest technologies have resulted in very high pregnancy rates, with implantation rates remaining stable across all age groups [26,27]. Scott et al. published a randomized controlled trial for the use of PGT using comprehensive chromosome screening and ART in 155 patients between 21-42 years of age. Patients had an average 2.0 embryo transferred in the control group and average 1.86 embryos transferred in the PGT group. The delivery rates were 47.9% and 66.4%, respectively, showing a statistical advantage to using PGT. The twin gestation rate was presumed to be high and was unfortunately not reported [22]. This early study of PGT showed a significant increase in the live birth rate over untested embryos.

Next Generation Sequencing (NGS) is the newest platform for 24-chromosome aneuploidy screening

and provides the highest genomic coverage. High-resolution NGS can detect unbalanced translocations, partial aneuploidies as small as 1.8-14 Mb, triploidy, and mosaicism when there are 20% or more abnormal cells present in the biopsy [28]. The clinical error rate of NGS is estimated to be between 1 and 2% [28]. A study by Friedenthal et al. described their experience with eSET after PGT using NGS compared to array comprehensive genetic hybridization (aCGH). In reviewing over 900 patients with mean age of 36, the ongoing pregnancy or live birth rate was 54.4% and 62% with aCGH and NGS testing, respectively. The early miscarriage rate was lower with NGS testing, 8.7% versus 15%. All pregnancies were singletons [29]. This early data speaks to the safety of this technology. Monozygotic twinning is possible with eSET, though a recent study shows that this occurs in approximately 1% of embryo transfers [30]. These refinements in technique have led many centers to routinely use PGT, and are echoed by the results of single euploid embryo transfer in our fertility center (Figure 2). National summary data from 2015 shows that 66% of patients transfer more than one embryo, and 23.7% of births are twins or more for a singleton live birth rate per transfer of 35.3% (Figure 3).

Figure 2: Graph showing the profound effect of age on miscarriage and trisomy amongst clinically recognized pregnancies. Reproduced from Hassold T, Hunt P. To err (meiotically) is human: The genesis of human aneuploidy. Nature Reviews Genetics. 2001.

The United States is one of the few industrialized countries where compensated GC is not restricted at the national level. There are variations in the legal climates between states [31]. In Europe, the use of gestational carrier services is not allowed in Austria, Bulgaria, Denmark, Finland, Greece, Italy, Malta, Norway, Portugal, Spain and Sweden. Altruistic GC is permitted in some of the U.S., as well as in Canada, Australia, and New Zealand [7]. The concern in some countries is based on religious tradition. For others, the legal status is precarious because of concerns regarding coercion of the surrogate mother. There is a fear that recruitment of GCs may selectively target disadvantaged and vulnerable women who would who may unwittingly accept the many risks detailed above, particularly the risks of miscarriage and multiple gestation, to feed their families. We have an opportunity now to champion single euploid embryo transfer to reduce pregnancy risks to those achieved with natural conception, to make this service safe, and to encourage practices that may allow our legislatures to embrace the technology permitting patients with uterine infertility, serious medical illness, and same sex partners to have a family, responsibly.

Figure 3: Original graph of data from the author's institution (CARS), showing how transferring a single euploid embryo to the prepared uterus allows very high singleton live birth rates, regardless of maternal age. Bars show multiple pregnancy rate per live birth using single euploid embryo transfer (0%), as compared to the multiple pregnancy rates reported by 2015 National Summary Report, Centers for Disease Control and Prevention. Inset shows the number of embryos transfer for each CDC age group.

Conclusions

The utilization of gestational carrier services is steadily increasing. Advancement in embryo cryopreservation, extended embryo culture with blastocyst selection, and pre-implantation genetic screening has facilitated the expansion of elective single embryo transfer with historically high singleton live birth rates at full term. The time has come to bring this enhanced safety to gestational carrier services. Embracing the improved safety with PGT-A and single euploid embryo transfer will protect gestational carriers, reduce multiples, reduce miscarriage, and remove a burden of morbidity. It will also help preserve the official availability of this service in the United States, and may allow it to be re-introduced in many Western countries where it has been banned. We call on our professional organizations and IVF programs world-wide to fully promote the use of single euploid embryo transfer for gestational carriers, to ultimately permit more patients with uterine infertility, serious medical conditions, and same sex partners to have a family. Additionally, we call on individual physicians to prioritize the safety of the GC, and protect their well-being as patients, and actively advocate for this group of altruistic individuals.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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