Scientific and ethical considerations in using preimplantation genetic testing for polygenic disease

In the 44 years since the birth of Louise Joy Brown, the world's first infant conceived by in vitro fertilization (IVF), there has been intense focus on improving the IVF success rates. Live birth rates have drastically improved over the decades, from initial success rates of <10% per cycle, to more recent reporting of success rates of >50% per cycle for women aged <35 years (1). Several major developments in the field have contributed to the rapid advancement of IVF and remarkable improvements in success rates. Embryo culture systems have been modified to optimize embryo metabolism and development, and, as a result, more embryos from each cycle are generated for future use (1). The increase in success has been in parallel with reductions in procedural risk and patient morbidity. One of the major iatrogenic risks of IVF, namely ovarian hyperstimulation syndrome, has been effectively mitigated with gonadotropin-releasing hormone agonists as triggers for final oocyte maturation. The widespread implementation of single embryo transfer has drastically reduced both maternal and neonatal morbidities and mortalities. Emerging data are promising in demonstrating reduced rates of pre-eclampsia with the use of natural cycle frozen embryo transfer protocols that rely on corpus luteum formation for progesterone production. Although the past 44 years have worked toward increasing the likelihood of live birth, we anticipate that the next 44 years will bring into focus the goal of improving the long-term health outcomes of persons conceived by artificial reproductive technology.

The determinants of health outcomes are interplay between genetics and the environment. Preimplantation genetic testing (PGT) for aneuploidy and for monogenic disorders represent additional advancements in the field. Preimplantation genetic testing for aneuploidy allows for the selection of the single best euploid embryo for transfer and has been shown to improve the live birth rate and to reduce the miscarriage rate in older patients (2). Preimplantation genetic testing for monogenic disorders enables patients to test and selectively transfer an embryo unaffected by genetic disorders, such as spinal muscular atrophy or Tay-Sachs disease, that can lead to severe neonatal morbidity and mortality. More recently, embryo selection based on polygenic scores (ESPS) or PGT for polygenic disorders has emerged, with companies offering ESPS to screen for conditions that have polygenic inheritance, such as diabetes, hypertension, breast cancer, and schizophrenia (2). As opposed to single gene disorders, these conditions have a complex inheritance.

This *Fertile Battle* seeks to explain the scientific and ethical factors behind polygenic scores to select embryos for transfer. Dr. Nathan Treff discusses that all patients undergoing IVF should be informed of the option to select embryos on the basis of polygenic scores. Dr. Treff discusses that the use of PGT for polygenic disorders has been effectively demonstrated and that PGT for adult-onset diseases has been deemed ethical by the American Society for Reproductive Medicine for reasons of reproductive liberty. Further, he cites that this does not require a high number of euploid embryos to provide benefit. Additionally, he argues that the current practice of PGT for polygenic disorders involves prioritizing embryos with the lowest risk of disease and not discarding embryos with high-risk scores. Dr. Savulescu provides an ethical perspective and frames the discussion in terms of procreative autonomy. He notes that the benefit does not have to be large, especially in a setting of no additional risk. He discusses that individual decisions about reproduction are best made by the prospective parents and cites the principle of autonomy as a guiding force.

Dr. Shulman explains the perils of the use and limitations of embryo selection on the basis of polygenic scores. He describes the limitations of genome-wide association studies because of the inability to generalize the findings to populations outside European ancestry. Furthermore, he discusses that polygenic risk score calculations fail to consider environmental influences that are critical for the development and prevention of many conditions; therefore, he believes that testing will provide an incomplete and misleading risk assessment. Dr. Melo-Martin gives the ethical perspective and maintains that prediction and selection for nonmedical traits such as intelligence or height can contribute to an increase in social inequality. The guiding principle of beneficence is simply not met.

The questions whether polygenic scores will become a potential tool to help patients have the healthiest possible child or whether the medical and ethical limitations are too profound remain unanswered. A dose of caution must be maintained to avoid reducing the likelihood of a live birth in the attempt to select a "more favorable" embryo on the basis of polygenic scoring.

In striving for the best outcome, are we potentially eliminating the chance of conception?

This is the conundrum that PGT for aneuploidy imposes, particularly in situations where cleavage-stage embryos do not progress to blastocysts or PGT results are interpreted as a mosaic.

The latter is highly relevant at the present time, as many centers do not transfer mosaic embryos because of the fear of adverse outcomes. One group modeled the exclusion of low-grade or medium-grade mosaic embryos and demonstrated that the exclusion of these embryos from transfer would result in up to 36% reduction in the live birth rate (3). Preimplantation genetic testing for polygenic scoring will create many similar scenarios, if not more, especially in patients with low ovarian reserves who have very few blastocysts. Furthermore, the results of ESPS testing will add additional complex counseling to the already erudite discussions between reproductive endocrinologists and their patients. When patients seek this testing via direct-to-consumer marketing, it is unclear who assumes the risk when an "unfavorable" embryo is transferred or an unintended adverse outcome occurs from the transfer of the "healthiest" embryo.

We must all remember that before the advent of PGT, untested embryos were routinely transferred, and some of these embryos likely would have been interpreted as a mosaic or have unfavorable polygenic risk scores. Although implantation and live birth rates can be increased in select patients using PGT for aneuploidy, this comes at the cost of some patients forgoing a chance to achieve pregnancy by not having an embryo transfer. Ultimately, as physicians, our role is to understand and interpret data to help inform clinical decision-making at all levels. We must collectively balance the desire for embryo selection with the chance to achieve pregnancy. Often, these factors are exclusive, and it is our responsibility to understand the science, limitations, and ethics and to steer these discussions to best help patients individualize and prioritize reproductive goals.

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