Polygenic testing for IVF embryo selection in Singapore: Proceed with caution

Posted on May 16, 2024

By Alexis Heng Boon Chin, Lee Wei Lim, and Sayyed Mohamed Muhsin

Singapore, like most affluent East Asian countries, has seen a drastic decline in total fertility rates (TFR) in recent years. In 2022 and 2023, the TFR hit new lows of 1.04 and 0.97 children per woman, respectively. This has dire implications for the country's future economic growth, as well as national security due to the projected shortfall in conscripted military manpower.

In typical Singaporean fashion to seek high-tech solutions to any outstanding problem, Government policymakers have increasingly leveraged new assisted reproductive technologies (ART) to overcome the country's demographic challenges, with generous subsidies for IVF treatment at public hospitals. Nevertheless, in its eagerness to embrace new ART to boost its dismal birthrates, Singapore should beware that the unregulated and wanton misuse of some new technologies could instead backfire and result in the opposite effect of further lowering fertility rates.

The example discussed here is highly complex predictive genetic testing for optimizing the health and intelligence of IVF embryos, technically referred to as preimplantation genetic testing for polygenic risk scores (PGT-P). Currently, PGT-P has not yet been approved for clinical application in Singapore, so it is timely to propose safeguards for future clinical trials.

Complex traits such as good health, intelligence, skin complexion and height, are determined by the combined interactions of several genes with the environment. Polygenic risk scores (PRS) can estimate an individual IVF embryo's likelihood of developing such complex multi-factorial traits by analyzing the combination of specific genetic variants within its genome. There are minimal risks with PGT-P, unlike human germline editing, due to the absence of permanent genetic modifications that can be transmitted to future generations.

In an era of ultra-low fertility rates, prospective parents inevitably invest more money, time and effort on their fewer children, very often resulting in unrealistic and unreasonable parental expectations, with the phenomenon of "tiger parenting" being commonplace in Singapore. Nevertheless, the major confounding challenge to every parent's great expectations and best-laid plans is the unpredictability and randomness of the natural fertilization

process, which involves mixing and recombining genes from the egg and sperm to produce new genetic variants. This often results in siblings born from the same pair of parents differing so much in looks, health and academic performance.

Hence, there is no guarantee that the offspring of high-achieving parents may necessarily be high-achievers, with the risk that all the money, time, and effort invested in an "inherently mediocre" child will ultimately go to waste. The PGT-P technique thus attempts to overcome the randomness and unpredictability of the natural human fertilization process to yield the best possible outcome.

The PGT-P technique will likely be expensive. Besides the high costs of the technique itself, additional medical fees for IVF are also required. Healthy and fertile couples might deliberately and unnecessarily choose to conceive via IVF to avail themselves of embryo selection by PGT-P for optimizing the health and intelligence of their offspring. Social pressure may make resisting such predictive genetic testing difficult if it becomes trendy. Prospective parents might feel guilty for not utilizing PGT-P to give their offspring the best start in life. As a result, many prospective parents desiring two or more children may ultimately decide to have just one superior "genetically optimized" child due to the high costs involved.

However, the efficacy of PGT-P is severely reduced by the small number and limited genetic variability of IVF embryos produced by the same pair of parents. When selecting specific polygenic traits within such a small sample size with limited genetic variability, the number of possible outcomes is very much limited.

Additionally, there are also other very obvious technical limitations. For example, the statistical probability of two dark-skinned parents conceiving a child with fair complexion by predictive genetic testing will always be low because most genes predisposing to fair skin are simply absent in those parents. The same can be said of two short parents attempting to beget a tall offspring.

Nevertheless, the actual effectiveness of PGT-P may not really matter. Because prospective parents naturally and instinctively desire the best future for their offspring, these thus represent particularly lucrative business opportunities for fertility clinics, which may deceive and exploit patients with their aggressive sales pitches and slick marketing gimmicks.

Hence, the following stringent regulatory safeguards are thus proposed. These include (i) Restricting the application of PGT-P only for the prevention of clinically relevant polygenic disease traits, (ii) Securely blocking patients' access to the raw genomic DNA sequencing data of their IVF embryos, (iii)

Validating diagnosis of polygenic disease traits in the prospective parents/grandparents of IVF embryos, and restricting PGT-P only for preventing specifically-diagnosed polygenic disease traits, and (iv) Mandating rigorous and comprehensive genetic counseling for IVF patients considering PGT-P.

There is a dire need to prevent abuse of the PGT-P technique and protect the interests and welfare of patients if its clinical application is to be permitted in Singapore.

Paper title: Regulatory safeguards needed if preimplantation genetic testing for polygenic risk scores (PGT-P) is permitted in Singapore

Authors: Alexis Heng Boon Chin, Lee Wei Lim, and Sayyed Mohamed Muhsin

Affiliations:

AHBC: Singapore Fertility and IVF Consultancy Pvt Ltd., Singapore

LWL: The University of Hong Kong, Hong Kong SAR, China

SMM: International Islamic University Malaysia, Malaysia

Competing interests: None declared

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