

Preimplantation genetic testing for aneuploidies (PGT-A) should be used in all IVF cycles in women over the age of 35 years for optimising reproductive outcomes and minimising adverse sequelae.

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Advancing age is unequivocally linked to adverse reproductive outcomes, including a reduction in fecundity and implantation rates, and an increased risk of miscarriage and foetal chromosomal abnormality. This physiological phenomenon has been attributed to a higher frequency of chromosomal mis-segregation during maternal meiosis, resulting in aneuploidy, the risk of which increases as age advances, and in an exponential fashion from the age of 35 onwards.

Preimplantation genetic testing for aneuploidies (PGT-A), as its name suggests, encompasses the screening of embryos, generated using in vitro fertilisation (IVF) technology, for aneuploidy. It facilitates embryo selection by allowing the opportunity to prioritise chromosomally normal embryos for transfer to the uterus. The transfer of embryos adjudged to be euploid using modern PGT-A methods is associated with higher implantation, ongoing pregnancy and delivery rates with reduced pregnancy loss compared to unscreened embryos (Scott et al. *Fertil Steril.* 2013;100:697-703), thus mitigating the negative clinical impact maternal age has upon reproductive outcomes.

Several previous studies, including randomised controlled trials (RCTs), showed a benefit of modern PGT-A strategies for patients of all ages. However, a recent RCT was only able to show a reproductive benefit to women > 35 years, with an ongoing pregnancy rate of 50.8% vs 37.2% in the control group (Munne et al. *Fertil Steril.* 2017; 108: 3, e19). In another multi-centre RCT, specifically targeted to women aged between 38-41 years, the delivery rate after the first embryo transfer was more than double when using PGT-A for embryo selection compared to controls (52.9% vs 24.2%), the mean number of transfers needed to achieve a live birth was

approximately half (1.8 vs. 3.7), as was the time to pregnancy (7.7 vs. 14.9 weeks). Moreover, the miscarriage rate was reduced dramatically by more than 14-fold (2.7% vs. 39.0%; Rubio et al. *Fertil Steril*. 2017; 107:1122-9.). Another recent study showed similar findings, with shorter treatment time, less failed cycles and lower miscarriage rate, but additionally demonstrated a significant cost-effectiveness benefit in all women >35 years with >1 available embryo. (Neal et al. *Fertil Steril*. 2019; 110; 5: 896-904).

Whilst it could be argued that double embryo transfer can achieve similar ongoing pregnancy rates, the transfer of a single euploid embryo virtually negates the risk of twin pregnancy, reducing it from more than half of cycles affected (53.4%) to 0%. (Forman et al. *Fertil Steril*. 2013; 100: 110-7). As such, not only would PGT-A reduce the obstetric and neonatal complications associated with multiple gestation, but it would also offer additional economic benefits by reducing the inherent costs of treating the associated morbidity.

Lastly, it is well known that adverse IVF outcomes, such as failed implantation and miscarriage, are associated with negative psychological sequelae, including mood disturbance, reduced quality of life and decreased perceived femininity. There is often subsequent adverse impact on relationships, particularly with partners but also with family and friends. Therefore, optimising outcomes and reducing adverse events with PGT-A will almost certainly be associated with significant psychological benefit. Moreover, reducing the number of unsuccessful transfers and time taken to achieve a livebirth should reduce time off work and increase time spent socially, thereby minimising impact on quality of life.

Women over the age of 35 who embark on IVF treatment should be counselled and offered PGT-A prior to embryo transfer. Rather than suffer the psychosocial, physical and economic burden associated with miscarriage, an increased number of failed embryo transfers, high risk of aneuploid pregnancy and a longer time to achieve pregnancy, PGT-A offers a cost-effective opportunity to optimise reproductive outcomes and minimise adverse impact on quality of life.

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