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Preimplantation genetic testing for aneuploidy (PGT-A) in the USA avoided nearly 15 000 miscarriages and over 6500 preterm births in 2023: an opinion

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ABSTRACT

Recently, through analysis of Society for Assisted Reproductive Technology (SART) data, we provided evidence that preimplantation genetic testing for aneuploidy (PGT-A) improves implantation, miscarriage and pregnancy rates per egg retrieval. In this review (using 2023 SART data), we concentrate more closely on pregnancy loss, preterm birth and elective single embryo transfer (eSET). Aneuploidy causes ~65% of pregnancy losses and we ask: (1) what is the association between pregnancy loss and PGT-A (with/without eSET)?; (2) is there an association between (very) preterm birth and PGT-A?; (3) how many pregnancy losses or (very) preterm births were avoided using PGT-A?; and (4) how many could have been avoided using PGT-A? Significant associations were observed between miscarriage rate and PGT-A: a greater rise associated with maternal age in the PGT group. The youngest age group showed a significant effect of PGT, the oldest PGT patients having a similar miscarriage rate to the youngest not using it. Effects were greater in the eSET group, and there was a significant difference in favour of PGT when considering the rate of (very) preterm birth. We calculate that ~14 983 miscarriages were avoided by using PGT, and that ~11 419 could have been avoided if PGT had been used; ~6619 (very) preterm births were avoided by using PGT and ~3636 could have been avoided. These analyses complement clinical trial studies with profound implications for the use of PGT-A; moreover, although groups are not randomised nor matched as in trial studies, sheer force of numbers suggests that we are observing genuine biological phenomena.

FURTHER INSIGHTS FROM THE SOCIETY FOR ASSISTED REPRODUCTIVE TECHNOLOGY DATABASE

Preimplantation genetic testing for aneuploidy (PGT-A) continues to be one of the most controversial areas of reproductive medicine. Debates, often quite heated, persist in scientific and medical forums, but with consensus emerging that PGT-A does not improve cumulative live birth rate (CLBR), but does improve live birth rate per embryo transferred (LBR PET).[1 2] The conflict, however, appears now to be switching to discussions about which of the two metrics is most important to patients, with continued discourse about 'intent to treat' criteria and its relevance. We[3] recently collated Society for Assisted Reproductive Technology (SART) data finding that, in 2022, in the USA alone, among 138 581 cycles (82 291 with PGT-A (59.4%), 56 290 (40.6%) without), PGT-A appeared to improve LBR PET, implantation rate, miscarriage rate and pregnancy rate per egg retrieval. While we accept that patients were not 'matched" in the PGT and non-PGT groups and the results are thus open to statistical criticism, we contend that the sheer force of numbers and the magnitude of the differences provide strong evidence that the observed effects reflect genuine biological phenomena.[3]

The latest SART database (https://sartcorsonline.com/Csr/Public?ClinicPKID=0&reportingYear=2023&newReport=True#patient-first-attempt) is now reporting all PGT cases for 2023 and, while some of these will constitute PGT-M (PGT for monogenic disorders) and PGT-SR (PGT for structural chromosomal rearrangements) treatment cycles, the vast majority (over 90%) are PGT-A. Moreover, most PGT-SR cases now inherently include screening for all chromosomes and some PGT-M regimes also include PGT-A concurrently. It is thus estimated that at least 95% of PGT cases in the USA involve some form of comprehensive chromosome screening. It is a reasonable assumption, therefore, that the numbers for PGT-A

alone and PGT in general are broadly comparable. In our previous paper,[3] we focused our attention primarily on live birth rates; in this review, we concentrate more closely on pregnancy loss and preterm birth.

PGT-A AND PREGNANCY LOSS

The association between aneuploidy and pregnancy loss is well established, with aneuploidy leading to ~65% of first trimester miscarriages. A degree of consensus pertaining to PGT-A can be found in the field when considering miscarriage rate. In the UK, PGT-A is now deemed by the Human Fertilisation and Embryology Authority (HFEA) to be safe and effective in reducing the chances of pregnancy loss (though, curiously, not yet for older women (over 35) where the effect of aneuploidy is greater) (https://www.hfea.gov.uk/treatments/treatment-add-ons/pre-implantation-genetic-testing-for-aneuploidy-pgt-a/). In these measures, intent-to-treat criteria are not an issue since both PGT-A and non-PGT-A groups have already undergone an embryo transfer and a pregnancy has already been established. Moreover, the question of whether a loss of pregnancy occurred is a binary measure and metrics can be gathered relatively without bias from both groups, each of which can be broken down into age categories.[3]

PGT-A AND PRE-TERM BIRTH

Preterm birth (in addition to low birth weight, with which it is associated) is a leading cause of considerable psychological, health and financial cost to families around the world. It is rising in Western countries and, for instance, ~10% of births in the USA are classed as such.[4 5] Preterm birth is a major cause of neonatal death as well as long- and short-term infant disability and morbidity. Alongside the well-established respiratory and neurocognitive morbidities, others may impact adversely on health in later life, such as altered adipose tissue partitioning, ectopic fat deposition, hypertension and insulin resistance. Indeed, there is a huge economic burden of preterm birth running into the tens of billions of dollars per year in the USA, equating to tens of thousands per child. In addition to its effects in pregnancy loss, for preterm birth, aneuploidy is also an issue, it follows, therefore, the PGT-A should reduce the incidence of the phenomenon.[6–10]

ELECTIVE SINGLE EMBRYO TRANSFER

In this study, we also paid closer attention to the issue of elective single embryo transfer (eSET). The percentage of in-vitro fertilisation (IVF) cycles that involve eSET has risen worldwide in the last 10–20 years. That is, previously, multiple embryo transfer was more widespread, particularly when treating patients of advanced maternal age, as this was seen to be the most effective transfer strategy to maintain acceptable levels of live birth in clinics. The disadvantage to this strategy is that it encourages a higher incidence of multiple births, pregnancy loss and obstetric complications including preterm birth.[11 12] Alternatively, once a euploid embryo is identified following PGT-A, eSET is an efficient strategy to ensure an acceptable LBR PET, largely independent of maternal age. Increased use of PGT-A is thus one of the reasons why there are now higher levels of eSET as reported by SART.[13]

METHODOLOGY

The SART data for 2023 can be found online at https://sartcorsonline.com/Csr/Public?ClinicPKID=0&reportingYear=2023&newReport=True#patient-second-attempt. For this study, we filtered the data for year 2023 only and included or excluded 'only PGT' and 'only eSET'. Then, by selecting 'show cycle characteristics', we generated the results, which were converted to graphs using Microsoft Excel. Results were combined for 'first transfer only', 'second transfer only' and 'additional transfers/long term freezes' and all were in the 'patient's own eggs' category. In this analysis, we considered the categories of 'miscarriage rate', 'pre-term birth' and 'very pre-term birth'. The results were already broken down into five 'age of woman' categories (<35, 35–37, 38–40, 41–42 and >42). Because of very small numbers in some subcategories, the 'pre-term birth' (before 37 weeks of pregnancy) and 'very pre-term birth' (before 32 weeks) results were combined and, for this new category, the '41–42' and '>42' combined to a single category (>41). Results were either expressed as 'PGT' or 'non-PGT' (two categories) or PGT/non-PGT, with or without eSET (four categories) as line graphs. Statistically significant differences between groups were established using the 'N-1' χ^2 test (Source is MedCalc Software Ltd. Comparison of proportions calculator. https://www.medcalc.org/calc/comparison_of_proportions.php (V.23.2.8; accessed 17 July 2025)). In order to answer the question of 'how many incidences of pregnancy loss or (very) pre-term birth were avoided by use of PGT-A' we took the miscarriage/(very) preterm birth total numbers in the PGT group, readjusted the reported rate in this group to the rate on the non-PGT group, generating a hypothetical second number of miscarriages/(very) preterm births, then subtracted one from the other. Similarly, we used a reciprocal approach to ask the question of 'how many could have been saved if PGT-A had been used' for the non-PGT group.

RESULTS

In the current database, at the time of analysis, a total of 415 953 cycles were reported to SART for 2023, 233 073 (56%) were recorded as PGT cases, whereas 182 880 (44%) did not involve PGT. This compared with the 2022 data[3] where 82 291 retrievals were reported with PGT-A (59.4%), and 56 290 (40.6%) without. This roughly threefold difference involves partly a greater number of patients taking up IVF as well as a greater proportion of clinics reporting to SART. Moreover, in our current analysis, we counted 'all cycles' whereas, before,[3] we

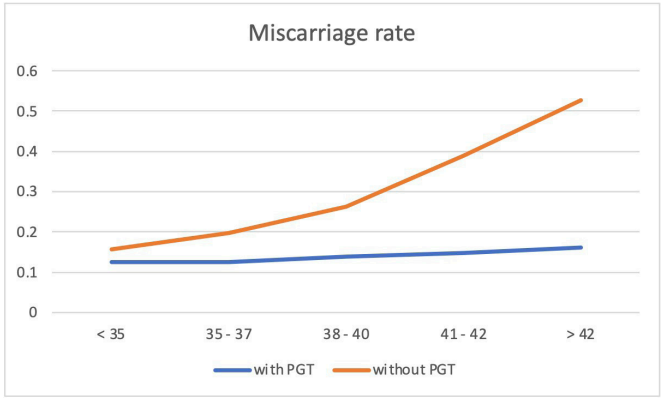

Figure 1 The association between miscarriage rate and PGT-A in five age groups. PGT, preimplantation genetic testing; PGT-A, PGT for aneuploidy.

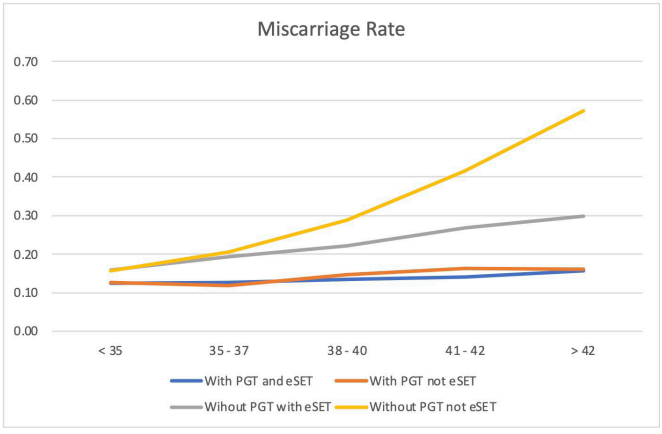

Figure 2 The association between miscarriage rate and PGT-A in five age groups with groups further divided into whether or not eSET had been employed. eSET, elective single embryo transfer; PGT, preimplantation genetic testing; PGT-A, PGT for aneuploidy.

counted only 'cycle starts'. Of these, 136 799 (32.9%) were reported as eSET, whereas 279 154 (67.1%) were not. This meant that 93 245 (22.4%) were both eSET and PGT, 139 828 (33.6%) were PGT but not eSET, 43 554 (10.5%) were eSET but not PGT and 139 326 (33.5%) were neither PGT nor eSET.

As previously reported,[3] the miscarriage rate increased marginally with age in the PGT group (rising from 0.12 to 0.16) but highly significantly (rising from 0.16 to 0.53) in the non-PGT group (p<0.0001). All age categories showed higher levels of miscarriage in the non-PGT group (p<0.0001), with the youngest age category in the non-PGT group showing a near identical level (0.16) to that of the oldest age category in the PGT group (figure 1).

Considering then the relative rates in each group (and acknowledging the effect of rounding errors), we calculate that 14 983 miscarriages were avoided by using PGT, whereas a further 11 419 could have been avoided if PGT had been used in the non-PGT group.

Breaking the numbers down further to subdivide into eSET and non-eSET, the greater effect was seen in the non-eSET group. That is, in the PGT group, miscarriage rates rose from 0.13 to 0.16, regardless of eSET; whereas, in the non-PGT group, eSET rose from 0.16 to 0.30 in the eSET subgroup, compared with 0.16 to 0.57 in the non-eSET subgroup (p<0.0001) (figure 2).

Considering now preterm birth and very preterm birth rates combined, again, we see a significant difference in PGT versus non-PGT groups (p<0.0001) (figure 3).

As with the miscarriage rate, we calculate that 6619 preterm or very preterm births were avoided by using PGT, and a further 3636 could have been avoided if PGT had been used in the non-PGT group.

DISCUSSION

The key message arising from this data is that thousands of miscarriages and (very) preterm births were likely avoided because of PGT-A in the USA in 2023. It also reinforces the need to use eSET, especially when PGT is not being employed and to avoid multiple embryo transfer. Ironically, PGT appears to negate the adverse effects of not employing eSET in terms of pregnancy loss; nonetheless, the obstetrical risks of multiple births should not be underestimated.

By performing this analysis of all cases reported in the USA, we appreciate that there are issues of equivalence. Groups are, in no way, matched and thus lack the rigour of controlled studies, including randomised controlled trials (RCTs). On the other hand, interrogation of these databases allows the analysis of larger sheer numbers not amenable to controlled studies, including RCTs, and thus the effects of any bias in group characteristics are, on the balance of probabilities, somewhat neutralised. As both the American Society of Reproductive Medicine and SART state that 'the routine use of blastocyst biopsy with aneuploidy testing in *all infertile patients* undergoing IVF treatment cannot be recommended'.[14] Similarly, the HFEA recommends using PGT-A for the prevention of miscarriage, but not to improve CLBR. In our previous study,[3] we posed the question of the extent to which criteria set out published by the national regulators should rely on RCT evidence alone, specifically

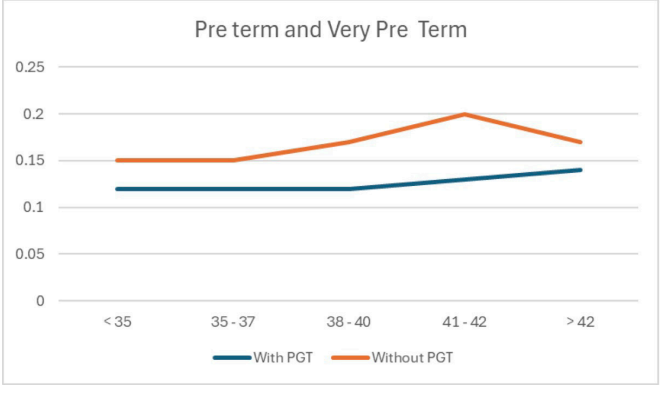

Figure 3 The association between (very) preterm birth rate and PGT-A in five age groups. PGT, preimplantation genetic testing; PGT-A, PGT for aneuploidy.

investigations 'intent to treat' criteria. Studies such as the one presented here[3] provide an alternative source of information intended for patient benefit. In this study, and that previous one,[3] we raised the issue of benefits in using PGT-A in younger patients. In this review, we double down on this, extending our analyses to preterm birth and eSET. PGT-A, most likely, will still be controversial for some time. Times are changing, however, and the wisdom of relying solely on RCTs to inform patients undergoing assisted reproduction needs to be challenged. Most of the evidence now is clear that PGT-A facilitates a significantly improved LBR PET, a reduced pregnancy loss rate, an improved time to first pregnancy and, according to this study, a reduced chance of preterm birth.[1–3] An obvious next step now is for genetic counsellors to initiate studies on patient attitudes pertaining to what is most important for them: the above issues or CLBR. Such studies may help resolve the current conflict and debate. Finally, although an improvement in CLBR following PGT-A is not theoretically possible since PGT-A has not, to date, 'created' new embryos for analysis, recent studies have provided evidence through which this might change. Al Hashimi *et al* and (two papers) Capalbo *et al* analysed both non 2PN (non-two pro-nuclear) and PQEs (morphologically poor-quality embryos[15–17] that would so far not be considered for transfer), finding that many were chromosomally normal and led to live births. This approach has the potential to make use of PGT-A to improve CLBR, and future studies will reveal whether it is sufficiently impactful to make a significant difference.

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Competing interests DG is Editor in Chief of BMJ Connections, Clinical Genetics and Genomics. SM is CEO of Overture Life and Scientific Director of Progenesis. AG and KM are both employed by Cooper Surgical.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval All the data presented in this study was extracted from a publicly available database and thus no ethical scrutiny was required.

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