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# Opinion: contemporary insights into the efficacy of Preimplantation Genetic Testing for Aneuploidy (PGT-A) by mining the Society for Assisted Reproductive Technology (SART) database

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## ANEUPLOIDY AND THE PURPOSE OF PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY (PGT-A)

Chromosome abnormalities (predominantly aneuploidy: extra (trisomy) or missing (monosomy) chromosomes) are collectively the leading cause of in vitro fertilisation (IVF) failure, pregnancy loss and developmental delay in humans.[1] As such, the technique of PGT-A has been practiced for over 30 years[2] to try and mitigate this problem. The purpose of PGT-A is to treat patients at risk of transmitting aneuploidy, especially in high-risk referral categories. The hope is that live birth rates (LBR) and miscarriage rates following IVF can be improved through its use.

PGT-A is a clinical treatment protocol in which 5–10 cells are biopsied from the trophectoderm of a blastocyst-stage IVF embryo. This germ layer will eventually become the placenta, not the fetus, if the embryo is allowed to develop. As such, trophectoderm biopsy should have minimal or no detrimental effect on future foetal development if performed professionally by an expert embryologist.[3 4] The biopsied cells are then analysed genetically to establish if they contain the normal 46 chromosomes per cell (euploidy). If aneuploidy is detected, then selective transfer of euploid embryos becomes the most likely option. Referral categories for PGT-A include repeated implantation failure, recurrent miscarriage and male infertility; however, the most common is advanced maternal age.[5 6] For example, a woman of 42 years has a 39% chance of miscarriage and only a 15% chance of a successful live birth per embryo transfer if she does not undergo PGT-A treatment. Moreover, when PGT-A indicates that all cells from a trophectoderm biopsy are aneuploid (ie, all have (an) extra or missing chromosome(s)), then the outcome will hardly ever be a live birth. That is, at least three non-selection trials[4 7 8] and one unblinded cohort study[9] indicate that, in 267 embryos transferred in which aneuploidy (all cells) was detected, only three (1%) led to successful live birth outcomes.

## SOCIETY FOR ASSISTED REPRODUCTIVE TECHNOLOGY (SART) AND PGT-A

The SART in the USA recently released its findings for treatment cycles up until 2020.[10] It, in agreement with the aforementioned trials,[4 7–9] clearly suggests that *PGT-A improves live birth rates per embryo transfer*, even in young patients. PGT-A also evidently reduces the risk of miscarriage, and this translates to a shorter time to achieve a healthy baby compared with multiple IVF cycles not involving PGT-A. The evidence is as follows. The vast majority of US IVF clinics report to SART, and looking at its report in detail for the year 2022,[10] 82 291 retrievals employed PGT-A and 56 290 did not. These extremely large numbers sit alongside randomised clinical trials (RCTs) in the panoply of evidence-based medicine surrounding PGT-A. RCTs prospectively randomise patients to a treatment or control group arm to determine which has the better outcome but typically involve far fewer patients than can be found in the SART database. Non-selection trials also adopt the strict principles of an RCT in that the outcome is



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blinded to both patient and practitioner at the time of treatment. Whether RCTs attest to the efficacy of PGT-A is a matter of debate. One interpretation of the data is that all RCTs treating patients over 35 years of age show improved pregnancy results per embryo transfer.[11–16] Questions arise, however, among critics who might argue that some or all of these analyses are post hoc and not the primary purpose of the study. By common consent, results are not so clear for younger patients[11–19] since the rate of chromosome abnormalities is lower in them. Realistically, no RCT is likely to be sufficiently well-funded to reach the large numbers needed to establish a trend for younger patients. The SART database,[10] nonetheless, provides these large numbers.

## DOES PGT-A 'WORK' AND BY WHAT MEASURE?

When addressing what might be a simplistic question of 'Does PGT-A work?', the first point to make is that we need to *consider carefully what we are measuring*. Most RCTs focus their attention on cumulative LBR, that is, will a healthy live birth ensue, regardless of the time period?[5 6] This is a source of unending frustration to many practitioners of PGT-A since it is not, theoretically, anything that PGT-A can, nor was ever designed to, improve. In a given pool of embryos, some may be euploid and thus have a good chance of live birth, and others may be aneuploid with little or no chance.[4 7–9] Cumulatively, if the family keeps trying with successive embryo transfers not involving PGT-A, then a euploid one, if it exists, will eventually be found and transferred. Thus, cumulative LBR cannot theoretically be improved by PGT-A, nor indeed any means of embryo selection.[5 6] Times may be changing, however, as recent evidence suggests that PGT-A may be used on embryos previously discarded because of an inappropriate number of pronuclei.[20–22] The pronucleus check is standard in IVF practice, and only those single-cell zygotes that clearly display two pronuclei (deriving from the nuclei of the sperm and the egg) are transferred. With PGT-A now shown to identify normally euploid embryos that previously had zero, one, three or four pronuclei, the potential for it to identify new embryos, and hence improve cumulative LBR, could be realised in the future.[21 22] When we consider LBR per treatment cycle, then the story is similar to that of cumulative LBR. If a euploid embryo exists, then PGT-A should not improve this; if, however, a time scale (6 or 12 months to pregnancy is not unusual) is put on a successful treatment cycle, or if a significant number of people give up on their treatment cycle before becoming pregnant, then PGT-A can be beneficial by this measure. This has been the topic of some debate in recent years.[23 24] Where is it very difficult to argue the efficacy of PGT-A, however, is in LBR per embryo transfer. Here, numerous lines of evidence attest to this. LBR per embryo transfer is higher with PGT-A than without it, even in younger patients.[4 7 8 22] This measure is calculated as the number of pregnancies resulting in live births divided by the number of embryo transfer attempts.[22] When PGT-A treatment is used, there is only a mild (but admittedly significant) decrease in LBR per embryo transfer associated with maternal age (57.2% in <35 years old compared with 49.6% at >42 years old) (figure 1). Contrast this, however, to an over threefold decrease when PGT-A is not used (45.2% (<35) to 14.8% (>42) figure 1). Even in younger patients (<35), the LBR per embryo transfer is significantly higher (p<0.001) when using PGT-A than when not (figure 1). If we compare this to the combined results of all RCTs involving young

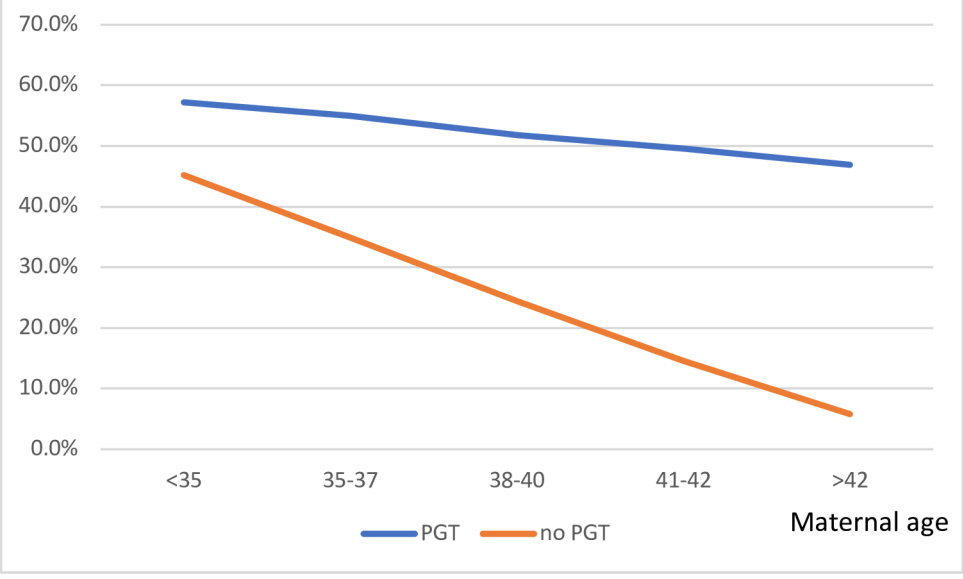


**Figure 1** Live births rate per embryo transfer. PGT, preimplantation genetic testing.



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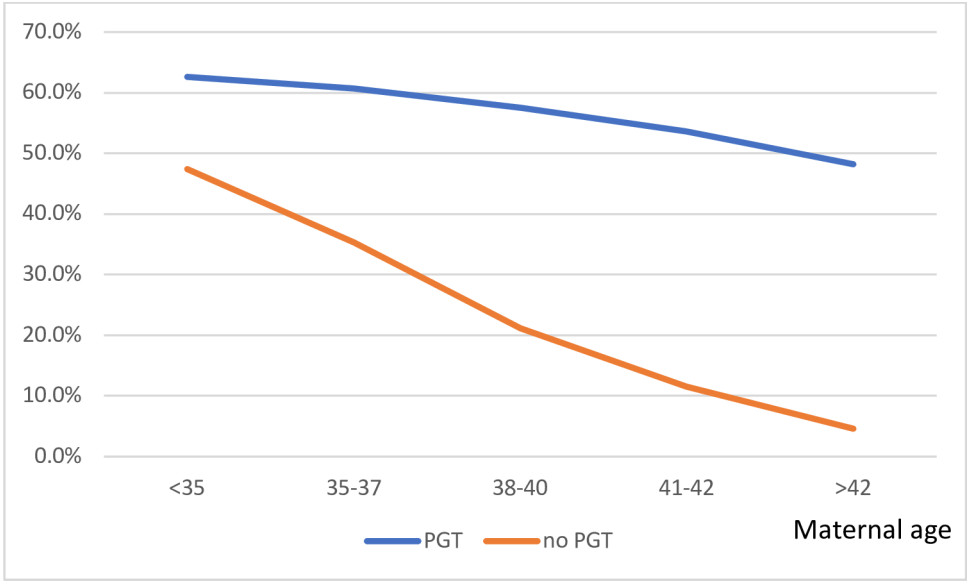


**Figure 2** Implantation per maternal age. PGT, preimplantation genetic testing.

patients,[11–19] we see a similar significant increase in LBR per embryo transfer after PGT-A ($p<0.025$).

In summary, is PGT-A effective in improving LBR? For cumulative LBR—no; for LBR per treatment cycle—maybe, and for LBR per embryo transfer—yes.

## IMPLANTATION RATES AND PGT-A

Implantation rate can be defined as the number of embryos that implant divided by the number of embryos transferred. As aforementioned, overall LBRs decrease with advancing maternal age due to chromosome abnormalities in embryos.[1] However, if we transfer euploid embryos as determined by PGT-A, then the *implantation rates only minimally decrease with advancing maternal age* (figure 2). After PGT-A, implantation rates decline only from 62.6% in younger patients (<35) to 48.6% in women aged >42 years. In contrast, without PGT-A, the decline goes from 47.4% in women aged <35 to 4.6% in those aged >42 years—an order of magnitude reduction (figure 2).

Indeed, *implantation rates are higher after PGT-A, even in young patients*, that is, 62.6% with PGT-A versus 47.4% without PGT-A in women aged <35, a highly significant difference ($p<0.001$). In other words, according to the SART database, a woman aged >42 years has a higher implantation rate following PGT-A (53.6%) than a woman aged <35 years not using it (47.4%) (figure 2).

## PGT-A AND PREGNANCY LOSS

According to the data, *PGT-A reduces the chance of pregnancy loss*. More than 60% of first-trimester pregnancy losses are due to chromosome abnormalities, and this increases with advancing maternal age.[1] In PGT-A patients younger than 35 years compared with patients over 42 years, the miscarriage rate rises only marginally with age (11.5% vs 14.8%; figure 3). Significant, but small, compared with when PGT-A is not used, where it more than doubles from 14.9% to 39.1% (figure 3). Indeed, the miscarriage rate for older (>42) patients using PGT-A (14.8%) is nearly identical to that of younger patients (<35) not using it (14.9%). In younger patients, evidence of a significant benefit of PGT-A could be only usually observed with a large dataset like the SART database,[10] and the difference (11.5% PGT-A vs 14.9% non-PGT-A), though small, is indeed significant ($p<0.01$). Interestingly, this difference is similar in magnitude to that seen by combining all the RCTs.[11–19]

## PREGNANCY RATE PER EGG RETRIEVAL

According to the data, PGT-A apparently *improves the pregnancy rate per egg retrieval* (figure 4). This is somewhat counterintuitive since the beneficial effect of PGT-A is to avoid the transfer of abnormal embryos that would not normally lead to live births. Assessing pregnancy rates per egg retrieval means that the selection has not yet been taken into consideration. This significant improvement in pregnancy rates per retrieval with PGT-A is possibly due to patients with fewer embryos not being recommended to have PGT-A on the basis that they have lower odds of conceiving. For this reason, we contend that implantation, pregnancy rates and LBRs per embryo transfer, not per egg retrieval (figures 1–3), are better measures to assess PGT-A efficacy. It is worth noting, however, that the proportion of retrievals resulting in transfers is similar between PGT-A and non-PGT-A cycles, that is, 54% versus 56%.

## MISCELLANEOUS POINTS

Given all of the above, some final points that we can make are contrary to some popular claims that *PGT-A is not experimental*. Rather, it is a standard of care now commonly practiced in the majority (59.4%) of



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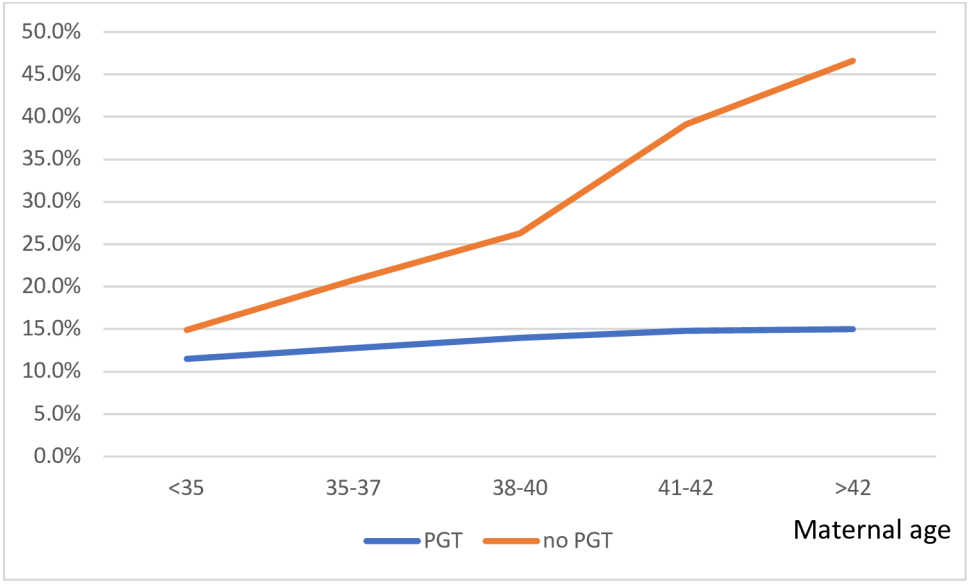


**Figure 3** Miscarriage per maternal age. PGT, preimplantation genetic testing.

IVF treatments in the USA.[10] This proportion varies from country to country, but some clinics now use it routinely in all IVF cycles. There is no room for complacency; however, PGT-A is not 100% accurate and has a 0%–4% misdiagnosis rate, meaning that the above results could be improved further. Suboptimal biopsy (which can lead to poor genetic results or embryonic arrest) and contamination of cells from the mother are all factors that could improve PGT-A.[5 6] On the issue of improvement, it would be amiss of us not to mention the issue of mosaicism, specifically when euploid and aneuploid cells are detected in the biopsy. This topic is dealt with in far greater detail elsewhere in the literature.[5 6] Suffice it to say, however, that where mosaicism appears in the biopsy, live birth can still ensue, but, as a general rule, the greater the proportion of abnormal cells, the less likely the chances of live birth.[25–27] Nonetheless, those biopsies that harbour predominantly euploid cells show very little difference in LBR compared with those biopsies where no aneuploidy was found at all.[25–27]

## SART DOES NOT RECOMMEND PGT-A FOR ALL PATIENTS

The latest recommendation from the American Society of Reproductive Medicine and SART itself[28] is that 'the routine use of blastocyst biopsy with aneuploidy testing in *all infertile patients* undergoing IVF treatment cannot be recommended'.[28] Those recommendations are solely based on RCT evidence and favour 'intent to treat' studies. As discussed above, combining all RCTs, however, there is a clear improvement in results in older patients and some evidence for younger ones. 'Intent to treat'

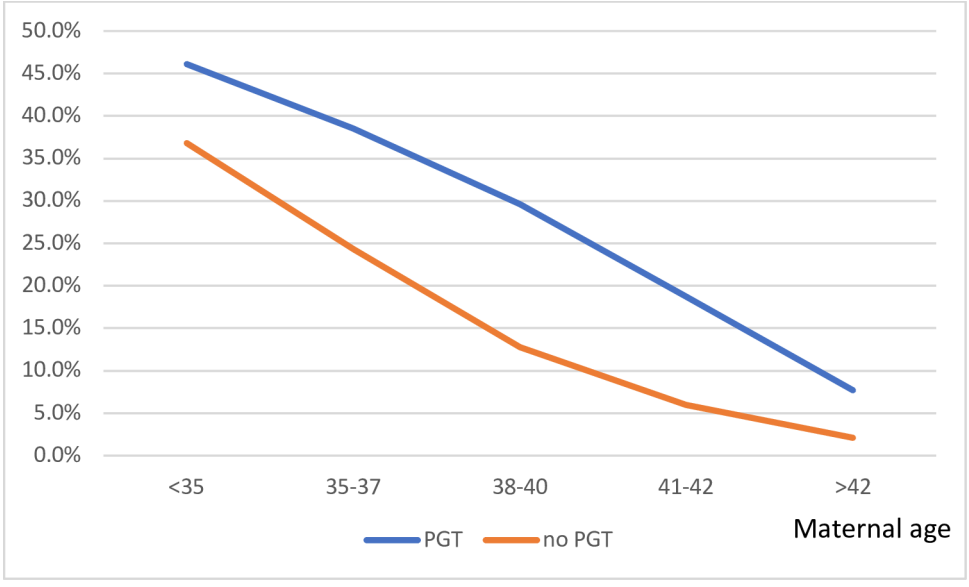


**Figure 4** Live birth per retrieval. PGT, preimplantation genetic testing.



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means that, before a couple starts the process of IVF, they decide whether to undergo PGT-A or not. Obviously, PGT-A is a selection tool; if there is nothing to select because there are not enough embryos produced, that cycle will not show an improvement in results. Also, here, we report the findings per egg retrieval or per embryo transfer (figures 1–4), not per intent to treat, meaning that some patients will not generate enough embryos to be treated by PGT-A and. therefore. not be included in the PGT-A arm of the study. Most probably, then they still get included in the non-PGT-A arm, which may contain worse prognostic patients. This is one argument for why SART does not recommend PGT-A for all patients, despite the evidence of their own database.[10 27] This bias, however, cannot affect miscarriage rates since in both groups, there has already been an embryo transfer. Indeed, both the SART data presented here (figures 1–4) and the combination of all RCTs[11–19] show a significant reduction in miscarriage rates, even in young patients. Similarly, if patients had embryos for transfer, the selection bias should be mild for implantation and LBR per embryo transfer, showing strong improvements both in the SART database[10] and when pooling the data of all these RCTs,[11–19] which are small in comparison.

## CONCLUSION

PGT-A remains a controversial topic, and the treatment is clearly not suitable for all patients. Patients are charged for it, and while an average IVF cycle is US$20 000 in the USA, an average PGT-A is an additional US$2500. More embryo transfers lead to more cost. The cost-benefit ratio therefore needs to be considered, as does whether the patients, psychologically, fall into the category of being more concerned with LBR per embryo transfer or with cumulative LBR. All will be different, and, for instance, some will not be persuaded by the time to first pregnancy benefits and reduction in miscarriage rate benefits that PGT-A brings. An alternative interpretation of the SART data presented here and the culmination of the RCTs is that PGT-A should perhaps be recommended for all patients except those that do not produce enough blastocysts from which to select. Even with a single embryo, however, it might be argued[29] that knowing whether it has a 1% or a 65% chance of live birth is money well spent.

## METHOD OF ANALYSIS

The SART data for 2022[10] can be found online at https://sartcorsonline.com/Csr/Public?ClinicPKID=0&reportingYear=2021&newReport=True. For this study, we filtered the data for the year 2022 only and included or excluded 'only PGT-A' finally then selecting 'show cycle characteristics' generated the results, which were converted to graphs using Microsoft Excel. A caveat here is that the SART data does not differentiate PGT-A (for aneuploidy) from PGT-SR (for structural chromosome abnormalities) or PGT-M (for monogenic diseases). Nonetheless, PGT-A cases constitute about 90% of all PGT, with the others making the final 10%.[10] Moreover, in recent years, most PGT-SR and PGT-M cases also include PGT-A, and therefore, the data are mostly accurate of the results expected for PGT-A.[10]

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