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COUNTERCURRENT

Why PGT-A, most likely, improves IVF success

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ABSTRACT

Preimplantation genetic testing for aneuploidies (PGT-A), with its vocal advocates and opponents, is at the epicentre of a perpetual, often heated, debate. The main issues include the following. First, how do we interpret the existing evidence-base? Around 100 retrospective and single-centre studies, two non-selection trials and at least two meta-analyses point to its efficacy in improving live birth rates, although randomized controlled trials are more mixed. Second, what should be done in relation to euploid/aneuploid mosaicism? Recent data suggest that low-level mosaic pregnancies can proceed uneventfully to term, so intelligent interpretation of the diagnostic data is appropriate. Third, what is the stance of the Human Fertilisation and Embryology Authority? The 'traffic light' system is much debated and is perhaps best described as well-intentioned, but misguided in places. Fourth, what is the motivation of people who maintain their point of view despite the evidence? Sadly, the presentation of new empirical evidence polarizes, rather than reconciles, opinion. Too many have made a career out of either promoting or denigrating PGT-A for them to back down easily. Finally, how can we find common ground and move forward? All patients should be counselled in a non-directive manner on whether to embark on PGT-A, summarizing for them the *whole evidence base* so they can make up their own mind.

INTRODUCTION AND THE CHALLENGE

Preimplantation genetic testing for aneuploidies (PGT-A) is arguably the most hotly debated area of reproductive medicine, with vocal advocates and opponents. The nature of the controversy is multifaceted and, in effect, both sides of the argument have valid points. With over 20 years of ongoing controversy, however, neither side can possibly be completely right, or wrong. Breaking down the issue as follows can shed some light:

- How do we interpret the existing evidence base, including the randomized controlled trials (RCT)?
- Mosaicism: what should be done when results show clear evidence of normal and abnormal cells?
- What is the stance of the Human Fertilisation and Embryology Authority (HFEA), and is it appropriate?
- What is the motivation of people who maintain their point of view in spite of the evidence?
- How can we find common ground and move forward?

THE EVIDENCE BASE

Around 100 retrospective studies, using comprehensive chromosome screening (array comparative genomic hybridization or next-generation sequencing) and trophectoderm biopsy involve a direct comparison of PGT-A with regular IVF cycles. Comparing the implantation rate, ongoing pregnancy rate (OPR) and/or live birth rate (LBR), most report significant benefits of PGT-A (*Griffin and Ogur, 2018*; *Victor et al., 2020*). Of course, these can be criticized. They are not RCT and thus we cannot be entirely certain that the control and test groups are matched, nor can we be sure that there was no bias (however inadvertent) in participant selection.

Sanders and colleagues (*Sanders et al., 2021*) presented 3 years' of HFEA data, from 2016 to 2018, on LBR per embryo transfer and per treatment cycle. Approximately 190,000 cycles,

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KEY WORDS

Debate
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Traffic lights

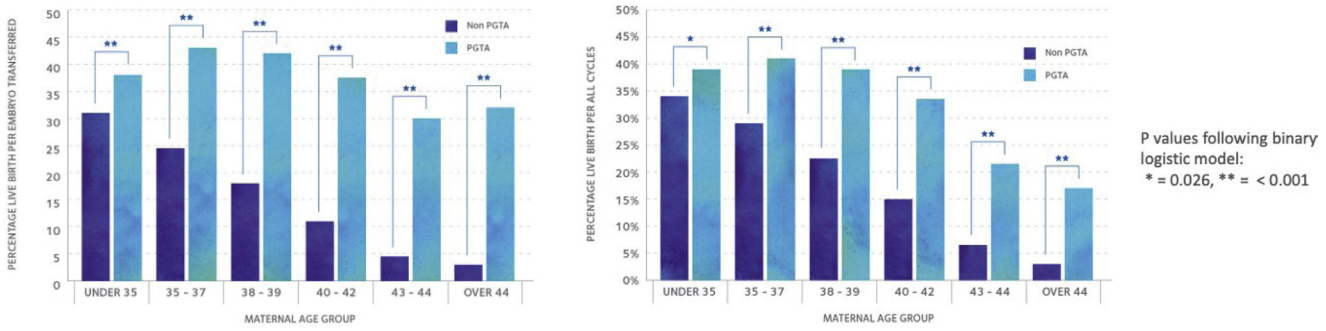

FIGURE 1 Live birth rate per embryo transferred (left) and per treatment cycle started (right) (adapted from *Sanders et al., 2021*). PGTA,

of which 2464 involved PGT-A, are summarized in FIGURE 1. All age groups (even the under-35s) show a significantly higher LBR when PGT-A is used, with approximately *5–10-fold differences* in the older cohorts. Although this study has no pretentions to being an RCT, it begs the question 'if these data do not demonstrate the benefits of PGT-A, how are the hugely significant differences, and the evident maternal age effect, explained?' It is of course theoretically possible that, in the PGT-A group, better-prognosis women were selected, increasingly so as they got older. This possibility is, however, vanishingly unlikely: women undergoing PGT-A especially older ones) are not selected because they have a good prognosis; quite the opposite.

A non-selection trial (*Tiegs et al., 2021*) supports the use of PGT-A. The authors concluded that there was *a 0% LBR following aneuploid diagnoses*. In a related model system (cattle) study of 1700 embryos (including sibling analysis), euploid diagnoses had a 59.3%/46.5% OPR/LBR compared with a 4.2%/4.0% OPR/LBR for aneuploid diagnoses (*Silvestri et al., 2021*). Employing reanalysis 'as if for an RCT', however, the improvement in OPR/LBR was 6.2%/5.7% (barely statistically significant), begging the question 'what does the patient actually want to know?' Is it 'can you identify (and therefore not transfer) any of my embryos that have little chance of becoming a live birth' or 'does PGT-A statistically improve the chances of LBR overall?' Identical data (as in this case) can answer 'yes' for the first, and 'no' for the second.

In the literature there are seven PGT-A RCT that include comprehensive chromosome screening analysis (all but the most recent are reviewed in *Victor et al., 2020*). Opponents disregard the earlier ones because of concerns surrounding 'intention-to-treat' criteria, leaving the ESTEEM and STAR trials (*Munne et al., 2019*; *Verpoest et al., 2018*) for consideration. Opponents are quick to point out that the primary outcomes of both indicate that PGT-A is not effective. PGT-A proponents, however, argue that they, and all RCT thus far performed, show at least some positive PGT-A outcomes. With the STAR trial (*Munne et al., 2019*), the study retrospectively reanalysed the older age group, finding a significant benefit. Opponents argue that you cannot do this. Nonetheless, the STAR trial and the SART study (culminated data from US IVF clinics) are near-identical (*Munne et al., 2019*), indicating statistically significant differences in the over-35 years age category.

At face value the most recent RCT (*Yan et al., 2021*) provides compelling evidence that PGT-A is ineffective. Even a cursory look at the data, however, suggests that it is not quite that simple. First, the outcome measure was cumulative live birth rate (CLBR). One has to wonder about the motivation of those who insist that CLBR is the most accurate measure of PGT-A success. Theoretically speaking, no method of embryo selection (including PGT-A) could improve CLBR as, eventually, the best embryo will be found for transfer. So, is the suggestion that embryos should not be selected for, for example, morphology or that patients do not prioritize LBR per cycle/transfer? This seems unlikely. Second, the participants of this study all had a good prognosis, with an average age of 29 years. In other words, this study provides evidence that PGT-A is ineffective in areas in which it was never designed to be effective. QED.

THE VALUE OF RCT

Although RCT undoubtedly provide the best study design, they do not necessarily give an indication of how well that study was performed. Compare the COVID vaccine RCT: favourable results give near-complete confidence that the jab can be globally administered as the procedure (a shot in the arm) is a simple one. PGT-A, on the other hand, has multiple steps involving complex protocols. An RCT therefore that shows no effect may either mean that there is no effect to be found, or that the clinics involved in the trial performed it sub-optimally. Equally, a favourable RCT gives an indication that it works well in the hands of those clinics involved in the trial, but not how effective it will be in new clinics that adopt it. For this reason, when asking questions about the efficacy of PGT-A, the *balance of evidence* needs to be taken into account. Most clinics are not going to perform RCT before adopting PGT-A.

What about the 'highest level' of scientific evidence, the Cochrane review? A recent study by Cornelisse and colleagues (*Cornelisse et al., 2020*) is somewhat disingenuous. It collates studies, including cleavage-stage biopsy fluorescence in-situ hybridization (FISH) studies, together with recent ones and concludes that, on balance, there is no evidence to support the use of PGT-A. Given universal acceptance that day 3/FISH PGT-A is no longer performed, one has to wonder about the authors' motivation for performing this review.

MOSAICISM

What to do with a 'mosaic' diagnosis? Some say 'treat as abnormal and discard', some say 'assign a lower priority', some say treat 'as normal.' The reality is,

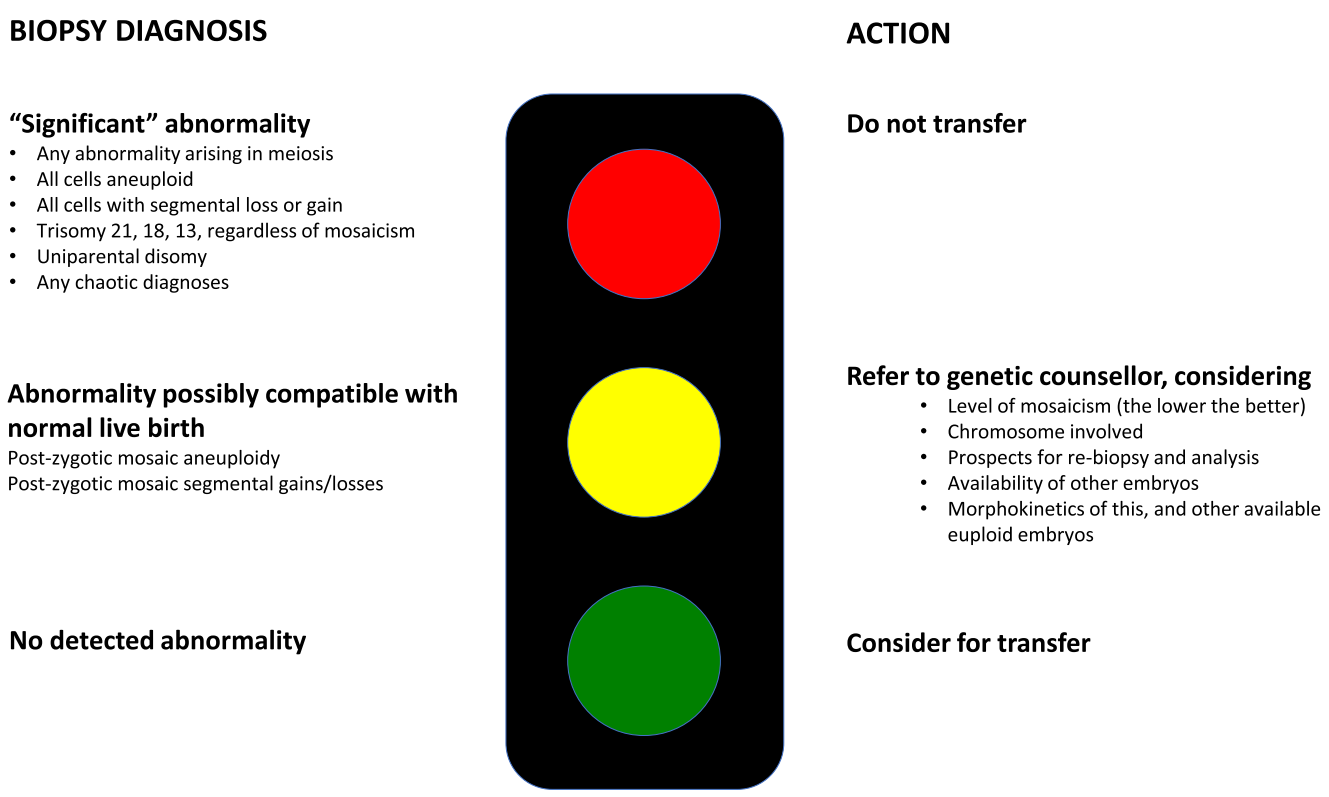

FIGURE 2 Some 'alternative traffic lights' to aid decision making for preimplantation genetic testing for aneuploidies.

however, far more complicated. Perhaps the terms 'normal embryo,' 'aneuploid embryo' and 'mosaic embryo' should not be used in this context because:

- diagnosis pertains to a biopsy 'window' of 5–10 cells, which may or may not be representative;
- evidence suggests that most human IVF embryos are mosaic and therefore aneuploid.

Rather, the terminology should refer to the *biopsy alone*, *not to the whole embryo*, and patients should be properly counselled to ensure they understand the ramifications of this to facilitate informed decision making.

Recent studies have revealed a hitherto undiscovered plasticity and a propensity for self-correction of aneuploidy in human IVF embryos (*Coticchio et al., 2021*). Irregular cleavage can generate chromosome abnormalities that may result in developmental arrest, or be confined to cells excluded from the blastocyst. Mitotic chromosome errors can generate mosaic blastocysts, but there may be selective death or clonal depletion of aneuploid cells, resulting in a euploid embryo. In other words, the embryo, if the number of aneuploid cells is relatively low, may ultimately develop normally because of self-correction, so could be from embryos eligible for transfer. This should be taken into account, for example, when embryos are of particularly good morphology compared with others diagnosed as euploid (*Viotti et al., 2021*).

Embryos diagnosed as mosaic *may be transferred*, especially if there are no (or very poor quality) embryos defined as euploid available. Capalbo and co-workers (*Capalbo et al., 2021*) suggest that low-level mosaic diagnoses have a similar implantation potential to euploid ones (note that *Yan et al. [2021]* did not transfer embryos with mosaic diagnoses). Viotti and colleagues (*Viotti et al., 2021*) suggest that LBR are highest when no mosaicism is detected, slightly lower in the 20–49% mosaicism range and lower again in the 50–80% range. Combining this with the study from Tiegs and collaborators (*Tiegs et al., 2021*) in which 100% aneuploid diagnoses led to 0% live births (the study did not detect mosaicism), *there is no real justification for transferring embryos in which 100% of cells have been diagnosed aneuploid*.

WHAT DOES THE REGULATOR SAY?

From 2018, the HFEA considered adjunct IVF treatments (termed 'add-ons') and assessed them using a 'traffic light' system. After an initial awarding of red/amber for contemporary PGT-A, this was downgraded to two (and then, most recently, one) red lights. Although well intentioned, there were several flaws in how this system was managed:

- There were no green lights. None of the treatments received a green light; in fact there was no provision for one because, if the 'add-on' fulfilled all the criteria, it was considered 'routine' and did not fit the inclusion criteria.
- Procedures such as endometrial scratch, strangely, received an amber light (the highest available) despite much less supporting evidence.
- Saying there is 'no evidence that PGT-A is effective' is factually incorrect (see above).
- To license a treatment, yet give it red lights, appears somewhat hypocritical.

THE NATURE OF THE PGT-A DEBATE

Opponents typically argue that PGT-A is not properly validated, and that clinicians *must always* wait for RCTs (with intention-to-treat criteria) before introducing a new technology because:

- any treatment not validated by RCT should only be part of a trial;
- clinics are motivated by the need to be ***seen*** to be innovating and the money associated with charging patients for 'the latest' therapy, despite proper supporting evidence.

Proponents, however, argue that there *is* sufficient evidence justifying PGT-A and that

- innovation is good; clinics that tend not to innovate typically have lower success rates;
- in reproductive medicine it is ***not always possible*** to wait for an RCT; they can take years and are poorly funded (unlike drug trials), treatment benefits may already be obvious, the appetite to perform the RCT may have waned, and recruitment is difficult because participants do not want to be in the control arm.

Sadly, the presentation of new empirical evidence only seems to polarize, rather than reconcile, opinion. Too many people have made a career out of either promoting or denigrating PGT-A to want to back down easily.

SUMMARY

On balance I feel that common ground can be found, but that the weight of evidence points to PGT-A being effective and safe with the following caveats:

- Single-centre and cohort retrospective studies largely point to a higher implantation rate, OPR and LBR and a reduced miscarriage rate following PGT-A, especially in the advanced maternal age (AMA) category.
- Multicentre analyses point to efficacy in the over 35 years age categories (and *Sanders et al. [2021]* also indicate this in the under 35 years group).
- The results of RCT are mixed and some clinics may want to wait until they are more convincing.

Patients should be informed clearly and concisely that the CPR should not be improved until further evidence is presented. For AMA, recurrent pregnancy loss and recurrent implantation failure, patients should be pointed to the non-selection trials, and informed clearly that while the evidence specifically for RPL and RIF is not absolute, these are complex conditions and they might consider that it is possible to accurately identify at least those embryos that are destined not to lead to live births. For male factor infertility, and all other IVF, the case is not yet proven but evidence is mounting. In terms of what to do about mosaic embryos, I suggest the scheme outlined in FIGURE 2.

Genetic counsellors should look at the origin of the aneuploidy (remembering that new systems, e.g. from Cooper and Igenomix, can do this, and meiotic errors rarely lead to live births) and appreciate that reported the percentage abnormality is of the *biopsy*, and not necessarily of the whole embryo. In this spirit, all patients should be counselled in a non-directive manner on whether to embark on PGT-A, summarizing for them the *whole evidence base* so they can make up their own minds.

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