



A tale of two studies: now is no longer the best of times for preimplantation genetic testing for aneuploidy (PGT-A)

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Received: 25 January 2020 / Accepted: 30 January 2020 / Published online: 5 February 2020
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Abstract

Preimplantation genetic testing for aneuploidy (PGT-A) does not create normal embryos, but selecting a viable embryo for a fresh transfer has the potential to deliver an extra effect for live birth from a stimulated cycle by evading the attrition associated with embryo cryopreservation. Improved genetic tests are now available for selecting viable embryos; however, current embryo cryopreservation techniques also have a superior survival rate, which means it is now possible to transfer most morphologically suitable embryos from a stimulated cycle one at a time. The cumulative live birth rate from a stimulated cycle is now unlikely to be superior compared with morphological assessment alone, with any benefit likely to be associated with a reduction in the risk of miscarriage and the time to pregnancy. This communication offers a perspective on the likely benefit and disbenefit of PGT-A based on the outcome of modern-day clinical studies. Caution should be advised regarding offering PGT-A to every woman. Quantifying the likely miscarriage benefit and live birth disbenefit for an appropriate patient group may help to better inform couples who might be considering adding aneuploidy screening to their treatment cycle.

Keywords Preimplantation genetic testing · Aneuploidy screening · Single-embryo transfer

The primary unit of benefit for assisted conception is a healthy live born baby. Effective selection techniques to identify viable embryos should in principle help to optimise the process. Preimplantation genetic testing for aneuploidy (PGT-A) does not create normal embryos, but selecting a viable embryo for a fresh transfer has the potential to deliver a superior cumulative live birth rate (an extra effect for live birth) from a stimulated cycle by evading the attrition associated with embryo cryopreservation [1]. However, hypothetical studies have argued that not-testing is likely to be superior to testing [2, 3], that the predictive value of genetic testing, even at the blastocyst stage, is too low for clinical use [4], and that PGT-A results in a substantial loss rate of potential live births [5].

In the past, embryo transfer typically occurred on day 2 and slow-freezing of surplus embryos was inefficient, occasioning the transfer of several embryos when available, and a risk of

multiple pregnancy with clinical complications. This was the best time for PGT-A to be effective, where aneuploidy of maternal origin could be detected by testing the polar bodies. Unfortunately the fluorescence in situ hybridisation (FISH) technique available at the time was typically restricted to detecting the copy number of only a few chromosome pairs [6]. Advances in assisted reproductive technology (ART) included reliable in vitro culture to the blastocyst stage. Testing on day 3 became common using FISH for 5–8 chromosome pairs [7] but was likely to be complicated by the nature of the cleavage-stage embryo [8] and the suboptimal diagnostic accuracy of the FISH technique [9]; this approach was eventually shown in randomised control trials to be ineffective in most people's hands [10]. Trophoctoderm sampling on day 5/6 is currently the moment of choice and facilitates the use of new advanced genetic testing techniques for all 23 pairs of chromosomes, to exclude embryos with aneuploidy prior to transfer. However, current embryo cryopreservation techniques have a superior survival rate [11], which means it is now possible to transfer most morphologically suitable embryo from a stimulated cycle one at a time. Using a current selection technique, the cumulative live birth rate from a stimulated cycle is now unlikely to be superior compared with morphological assessment alone, with any benefit likely to be associated with a reduction

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10815-020-01712-x>) contains supplementary material, which is available to authorized users.

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in the risk of miscarriage and the time to pregnancy [1]. In a hypothetical trial for a first stimulated cycle [3, 12], using an ideal test (100% diagnostic accuracy and no chance of miscarriage following testing), it was estimated that only around 1 in 19 (54/1000) women were likely to benefit by avoiding a clinical miscarriage without reducing their chance of a healthy baby (and in a shorter time period). Around 1 in 4 (273/1000) women were likely to pay more for no benefit, which increased to 1 in 2 (449/1000) when the diagnostic accuracy was reduced to that typically expected in practice [3, 12].

The debate is ongoing about offering PGT-A as an add-on to IVF/ICSI [13]. The purpose of this communication is to offer a perspective on the likely benefit and disbenefit of PGT-A based on the outcome of modern-day clinical studies. A model published previously [1] is used to extrapolate what the outcome might be if embryos are transferred one at a time until one ongoing clinical pregnancy or live birth occurs, or until all the embryos are used (a full cycle). The model estimates the numbers of ongoing pregnancies or live births, clinical miscarriages, and embryo transfer procedures when the diagnostic accuracy and vitrified-warmed survival rates are varied from 100% for different numbers of available morphologically transferable embryos without testing. The probabilities transferring one embryo at a time were estimated for 6 study reports using the approach detailed in the [Electronic supplementary material](#). The studies encompass microarray comparative genomic hybridisation (aCGH) testing of polar bodies [14] and cleavage-stage blastomeres [15–17], and blastocyst-stage trophoctoderm samples using aCGH [18, 19] and next-generation sequencing (NGS) [20] (Table 1). Two of these studies [19, 20] are presented below and the findings discussed.

Salient features of the STAR trial [20] are explained in detail in the [Electronic supplementary material](#), and the model outcomes are presented in Fig. 1. With a prevalence of non-

viable morphologically transferable embryos of 54.3%, the likelihood of an abnormal test result correctly predicting no ongoing pregnancy was estimated to be 57.6% and the likelihood of a normal test result correctly predicting an ongoing pregnancy was 50.0%. The PGT-A ongoing pregnancy rate per embryo transferred was superior (50.0% vs 45.7%) indicating that testing was more effective than a conventional morphological assessment alone to select a viable embryo, however, with 52.6% fewer ongoing pregnancies overall due to the exclusion of viable embryos with false positive test results.

Testing was more effective than a morphological assessment alone for an ongoing clinical pregnancy when 5 or more embryos were available for transfer or testing. For 100,000 women with 7 morphologically transferable embryos (the average from the study report) and considering only up to 1 transfer attempt, the numbers of women with an ongoing pregnancy are 48,717 with PGT-A and 45,687 without testing (difference 6.6%). Following a full cycle for 100,000 women, there are 79,694 (79.7%) vs 98,032 (98.0%) ongoing pregnancies (difference – 18.7%). There are 15,593 vs 20,283 miscarriages (difference – 23.1%) and 159,385 vs 214,573 transfers (difference – 25.7%). Approximately 1 in 21 women are likely to benefit by avoiding a clinical miscarriage, with the disbenefit of a reduction in the number of women with an ongoing pregnancy of around 1 in 5.

The STAR trial evaluated if PGT-A could increase the chance of having an ongoing pregnancy for a single embryo transferred but did not achieve statistical significance. The majority of women included were aged less than 35 years (55%); with a prevalence of non-viable morphologically transferable embryos estimated to be 54.3%, the likelihood of an abnormal test result correctly predicting no ongoing pregnancy (PPV) was 57.6%, compared with 58.3% and 91.9% (ongoing pregnancy) for the Yang et al. study [18],

Table 1 Summary of PGT-A studies assessed and outcome measures

Clinical study	Maternal age (years)	Type of study and primary outcome	Biopsy moment	Test	Prev. (%)	PPV (%)	NPV (%)	Excl. (%)	Benefit* (CM)	Disbenefit (LB/OP)
Yang et al. [18]	<35	Prospective pilot OP	Day 5	aCGH	58.3	91.9	69.1	8.7	1 in 9	1 in 126
Rubio et al. [15]	38–41	RCT LB	Day 3	aCGH	82.8	91.8	50.0	37.6	1 in 3	1 in 4
Verpoest et al. [14]	36–40	RCT LB	PB	aCGH	87.0	92.5	22.9	37.7	1 in 6	1 in 3
Munné et al. [20]	25–40	RCT OP	Day 5/6	NGS	54.3	57.6	50.0	52.6	1 in 21	1 in 5
Munné et al. [20]	35–40	Post hoc OP	Day 5/6	NGS	62.8	70.6	50.8	50.2	1 in 6	1 in 3
Lee et al. [16, 17]	37–45	Retrospective LB	Day 3	aCGH	90.9	95.6	29.1	39.1	1 in 12	1 in 3
Sato et al. [19]	35–42	Prospective pilot LB	Day 5/6	aCGH	78.4	91.1	52.4	29.3	1 in 18	1 in 6

RCT, randomised controlled trial; LB, live birth; OP, ongoing pregnancy; PPV, positive predictive value—the likelihood that an abnormal test result correctly predicts non-viability; NPV, negative predictive value—the likelihood that a normal test result correctly predicts viability; CM, clinical miscarriage; Prev., prevalence of non-viable morphologically transferable embryos; Excl., proportion of viable embryos excluded due to false abnormal test results; Benefit, the number of women likely to avoid a clinical miscarriage; Disbenefit, the likely reduction in the number of women with a live birth/ongoing pregnancy

*An overestimate; there is a bias in favour of testing caused by more women with more than 1 miscarriage without testing

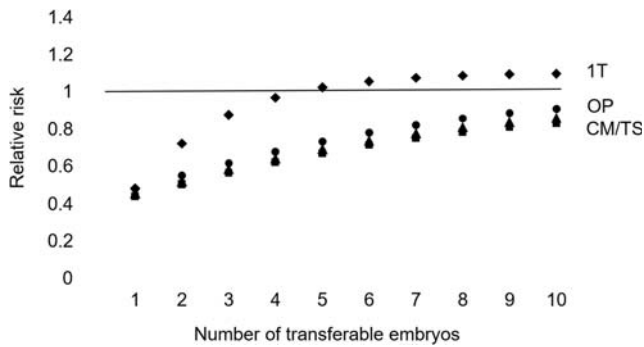


Fig. 1 The STAR trial [20]. The theoretical relative risk for PGT-A compared with a conventional embryo morphology assessment with a single-embryo transfer. Ongoing pregnancy considering only up to 1 transfer attempt (1T). Ongoing pregnancies (OP), clinical miscarriages (CM), and transfer procedures (TS) for a full cycle

87.0% and 92.5% (live birth) for the ESTEEM trial [14, 21], and 82.8% and 91.8% (live birth) for the Rubio et al. trial [15] (Table 1).

The post hoc analysis of older women aged 35 to 40 years found a significant increase in the OPR per embryo transfer (50.8% vs 37.2%). With a prevalence of non-viable morphologically transferable embryos of 62.8% (greater), the likelihood of an abnormal test result correctly predicting no ongoing pregnancy was estimated to be 70.6% (higher) and the likelihood of a normal test result correctly predicting an ongoing pregnancy was 50.8% (similar). The PGT-A ongoing pregnancy rate per embryo transferred was superior (50.8% vs 37.2%) indicating that testing was more effective than a conventional morphological assessment alone to select a viable embryo, with 50.2% fewer ongoing pregnancies overall due to the exclusion of viable embryos with false positive test results.

Testing was more effective than a morphological assessment alone for an ongoing clinical pregnancy when 4 or more embryos were available for transfer or testing. For 100,000 women with 5 morphologically transferable embryos and considering only up to 1 transfer attempt, the numbers of women with an ongoing pregnancy are 44,587 with PGT-A and 37,241 without testing (difference 19.7%). Following a full cycle for 100,000 women, there are 61,592 (61.6%) vs 88,403 (88.4%) ongoing pregnancies (difference – 30.3%). There are 9777 vs 26,193 miscarriages (difference – 62.7%) and 121,196 vs 237,381 transfers (difference – 48.9%). Approximately 1 in 6 women are likely to benefit by avoiding a clinical miscarriage, with the disbenefit of a reduction in the number of women with an ongoing pregnancy of around 1 in 3. Although PGT-A is a better test for this older age group and more effective to avoid miscarriage, including the transfer of all available cryopreserved embryos, the cumulative OPR is inferior.

The prospective study of Sato et al. [19] included women aged 35 to 42 years with no previous live birth and 2 or more

previous IVF-ET clinical miscarriages with at least 1 with aneuploidy (recurrent pregnancy loss (RPL)). Testing for every chromosome was done at the blastocyst stage by trophectoderm biopsy and using aCGH, and the model outcomes (see [Electronic supplementary material](#)) are presented in Fig. 2. With 78.4% prevalence of non-viable morphologically transferable embryos, the predictive value is estimated to be 91.1% for an abnormal test result and 52.4% for a normal test result. The PGT-A live birth rate per transfer is superior indicating that testing is more effective than a conventional morphological assessment alone to select a viable embryo, with fewer live births (29.3%) overall due to the exclusion from transfer of viable embryos with false positive test results.

For 100,000 women with 4 morphologically transferable embryos (the likely average for the study) and considering only up to one transfer attempt, the numbers of women with a live birth event are 37,862 with PGT-A and 21,621 without testing (difference 75.1%). Following a full cycle for 100,000 women, there are 46,245 (46.2%) vs 59,699 (59.7%) live births (difference – 22.5%). There are 7708 vs 13,267 miscarriages (difference – 41.9%) and 88,285 vs 276,116 transfers (difference – 68.0%). Approximately 1 in 18 women are likely to benefit by avoiding a clinical miscarriage, with the disbenefit of a reduction in the number of women with a live birth of around 1 in 6.

Investigations prior to the study included parental karyotyping, a cavity examination, and antiphospholipid syndrome. The likely miscarriage benefit is modest and may be because the study included women who have had an aneuploid miscarriage and who (counterintuitively) have a good prognosis. Detection of aneuploidy in products of conception explains the pregnancy loss and is likely to be sporadic; recurrent pregnancy losses which are chromosomally normal may be due to other factors which may persist next time. It is noted that the Japan Society of Obstetrics and Gynecology decided not to continue the pilot study and not to conduct a

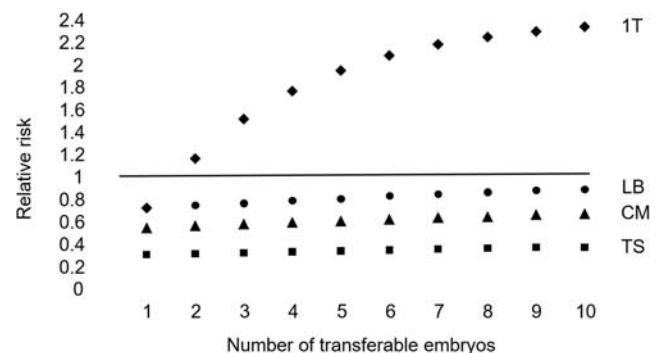


Fig. 2 Based on Sato et al. [19]. The theoretical relative risk for PGT-A compared with a conventional embryo morphology assessment with a single-embryo transfer. Live birth event considering only up to 1 transfer attempt (1T). Live birth events (LB), clinical miscarriages (CM), and transfer procedures (TS) for a full cycle

randomised controlled trial, and did not change the ruling that PGT-A is prohibited.

In conclusion, caution should be advised regarding offering PGT-A to every woman, and it should not be expected to improve the chance of having a baby when taking into account every morphologically transferable embryo from a stimulated cycle. The psychological burden of repeated implantation failure and spontaneous miscarriage of a much wanted clinical pregnancy can be severe, and it should be recognised that a reduction in the chance of a live birth might be of secondary concern to some women with a history of recurrent pregnancy loss. Gauging whether or not PGT-A is appropriate in an individual case is likely to be complex, and to depend on who is making the decision and how each couple is counselled. Quantifying the likely miscarriage benefit and live birth dis-benefit for an appropriate patient group may help to better inform couples who might be considering adding aneuploidy screening to their treatment cycle.

Authors' contributions The author is responsible for the content and writing of the paper.

Data availability Supplementary file is provided.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

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