PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY (PGT-A)

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OUTLINE

- Introduction
- What is PGT-A?
- Evidences
- Guideline!

PGT-A

Preimplantation
Genetic Testing
for Aneuploidies

Helping you have a
successful pregnancy
and a healthy baby

PGT-A increases the chance of pregnancy

What is PGT-A?

PGT-A is a genetic test performed on the embryos produced through IVF.

It examines the chromosomal material of an embryo and can tell if the appropriate number of chromosomes are present.

This will help your physician select the best embryo for transfer and improve your chances of achieving a successful pregnancy.

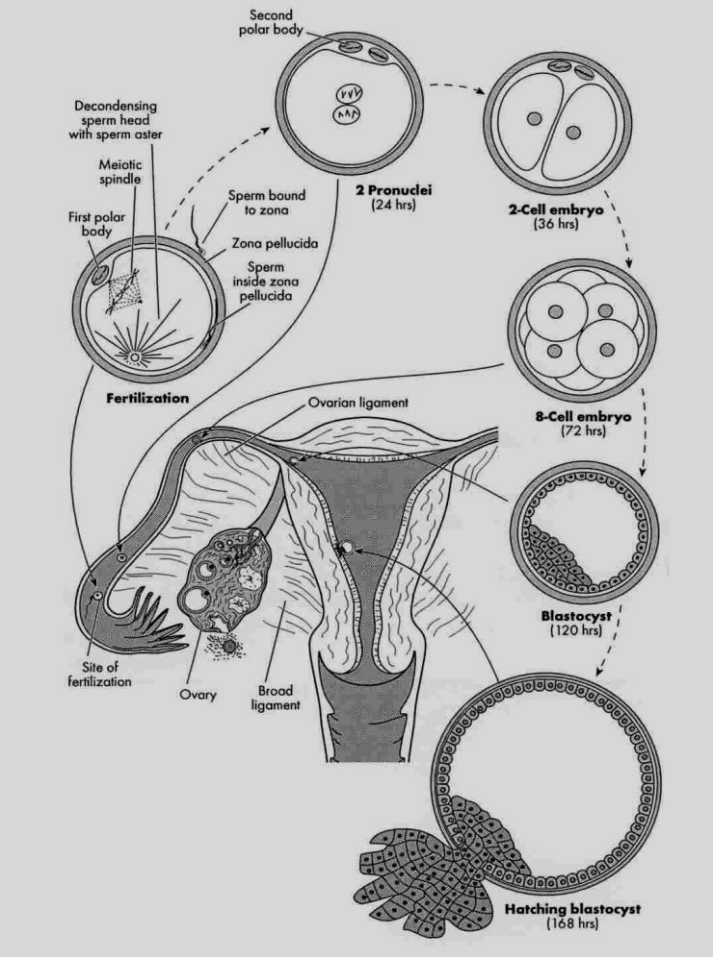
Unknown to the rest of the world, members of the scientific community have been making their own babies to order for quite some time now.

PGT-A: PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY

** A definitive tool in embryo selection on the grounds of euploidy

- Advanced female/maternal age (AMA)
- Recurrent implantation failure (RIF)
- Severe male factor (SMF)
- Recurrent Miscarriage (RM).

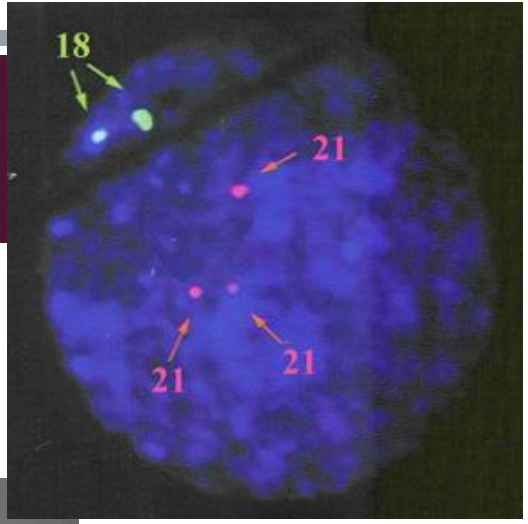
NOTE: It should be noted that couples with a history of RM have a high chance of successfully conceiving naturally that PGT-A for RM without a genetic cause is not recommended in a recent evidence-based guideline.

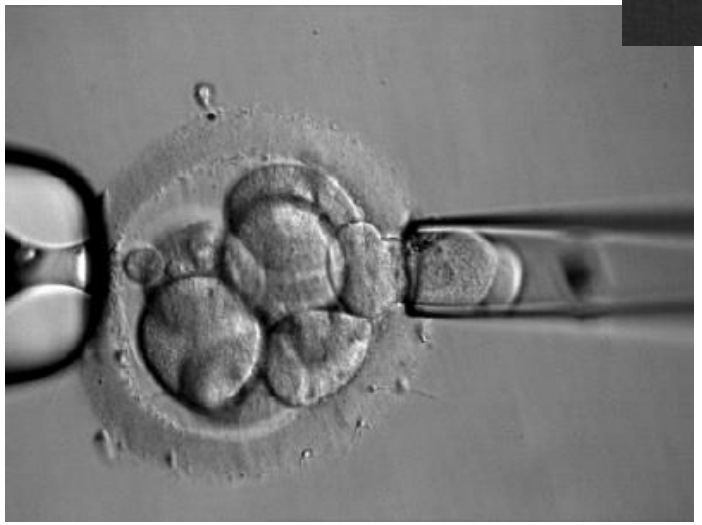


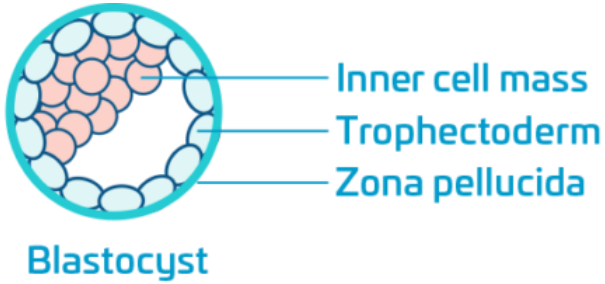
- Embryonic Development
  - In vitro = In vivo
- Aneuploidy common
  - 1st meiotic division
- Mitotic errors
  - Mosaicism

PGT-A

- Cleavage stage biopsy
- FISH analysis
- Widely utilized






Inner cell mass
Trophectoderm
Zona pellucida
Blastocyst


Low Power Laser
Assisted Hatching (AH)

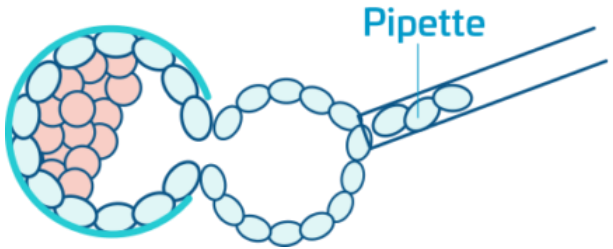
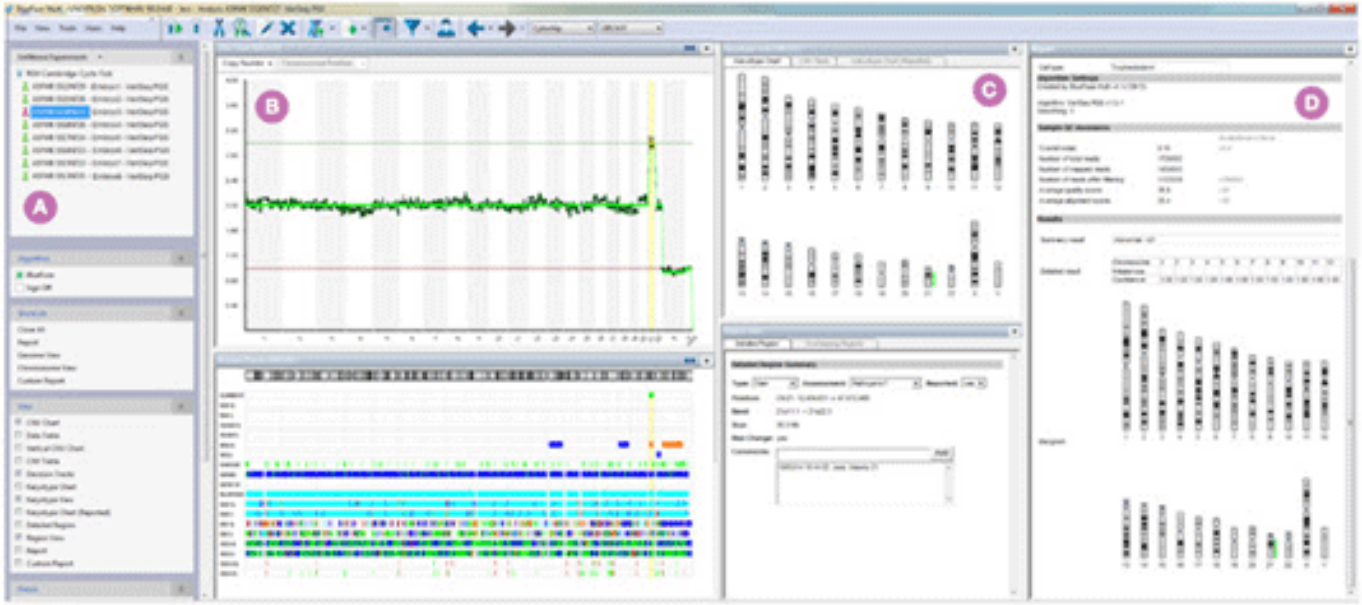
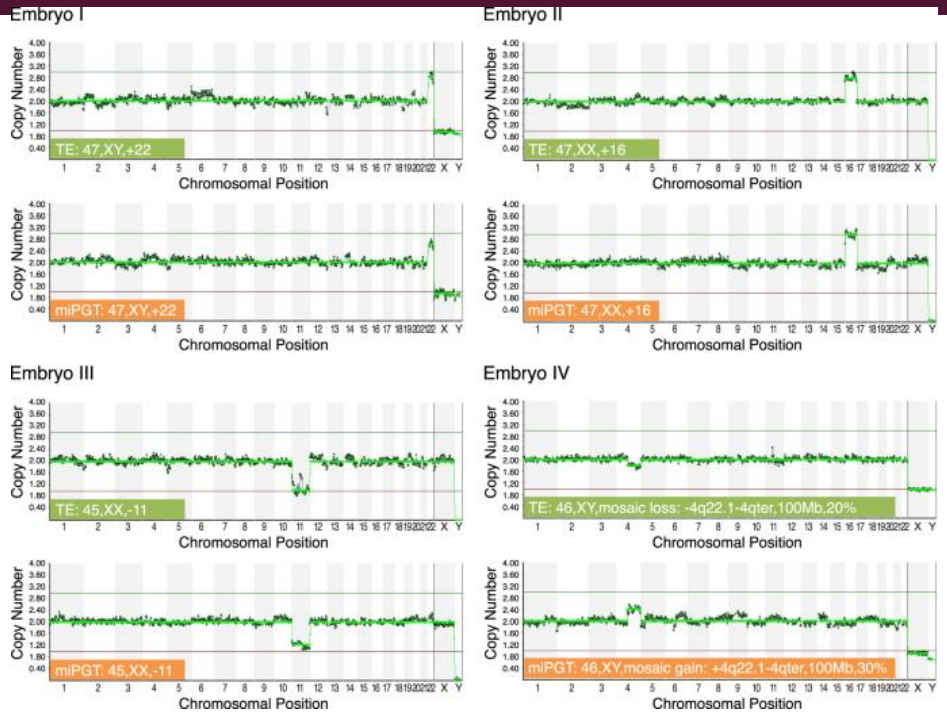

Pipette

Figure 2: BlueFuse Multi Software Delivers a Complete Data Analysis and Information Management System



BlueFuse software provides a complete solution for analyzing, storing, and reporting VeriSeq results. A. Sample database shows experimental information. B. Profiles for the sample (top) and DecisionTrack information (bottom). C. Karyotype chart for whole-genome view (top) and region view with the opportunity to annotate (bottom). D. Reports per embryo or per cycle (embryo report shown).

GENOMIC DATA



How is PGT-A done?

PGT-A adds one extra step to the IVF process. Here are the steps:

Hormone stimulation

Fertility drugs are given to develop a number of eggs (stimulated cycle).

Egg retrieval

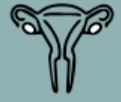
Eggs are retrieved from the ovaries and sperm are added to the eggs to create embryos.

Embryo development and biopsy

Embryos are grown in the laboratory for 5-6 days.
At this time, two types of cells are distinguishable: the cells that will develop into the placenta and the cells that will become the baby.
A few cells are removed from the future placenta for genetic testing to minimise the risk that the developing fetus is harmed.

PGT-A

Chromosomal testing is performed on the cells that are removed.
The time it takes to get PGT-A results can vary from days to weeks and depends on the method used and where the testing takes place.
Embryos are frozen until test results are available.



Embryo transfer

If the test shows that there is one or more normal embryos, one is thawed and transferred to the woman's uterus. Any remaining normal embryos will be kept frozen for transfer later if the first transfer does not lead to a pregnancy.

PGT-A: Advantages vs Disadvantages

Advantages	Disadvantages

• PGT-A reduces the risk of having a child with a chromosomal abnormality.
• For women who have had unexplained miscarriages, PGT-A can reduce the risk of future miscarriages.
• PGT-A can reduce the risk of having to make difficult decisions about whether to terminate or continue a pregnancy where the fetus has a chromosomal abnormality.[1]
• For women over the age of 36 PGT-A can reduce the risk of miscarriage and the number of embryo transfers to achieve a pregnancy.[2,3]
	• PGT-A does not increase the overall chance of having a baby.[4]
	• PGT-A is expensive and is in addition to the costs of IVF. The cost of PGT-A is not covered by Medicare.
	• Embryos may not survive the biopsy procedure.[5]
	• Due to technical challenges, there is a small chance that the test results may not reflect the true health of the embryo.
	• Some embryos have a mixture of normal and abnormal cells. This is called **mosaicism.** This can cause a false positive or false negative PGT-A result.[6]
	  • **A false positive result** means that the few cells that are tested show abnormalities, while the remaining cells are chromosomally normal. Based on the test result, an embryo that may have led to the birth of a healthy baby may be discarded.
	  • **A false negative result** means that the few cells that are tested are normal while the remaining cells are chromosomally abnormal. Based on the test result, a chromosomally abnormal embryo may be transferred.
	• Sometimes no embryo is suitable for transfer. Your doctor will discuss your results and options with you.
	• Embryos may not survive the thawing process.

Homer HA. Preimplantation genetic testing for aneuploidy (PGT-A): The biology, the technology and the clinical outcomes. Aust N Z J Obstet Gynaecol. 2019;59(2):317-24.

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human reproduction open

ESHRE PAGES

ESHRE PGT Consortium good practice recommendations for the detection of structural and numerical chromosomal aberrations†

ESHRE PGT-SR/PGT-A Working Group, Edith Coonen [1,2,‡,*], Carmen Rubio [3,‡,*], Dimitra Christopikou [4], Eftychia Dimitriadou [5], Julia Gontar [6], Veerle Goossens [7], Maria Maurer [8], Francesca Spinella [9], Nathalie Vermeulen [7,*], and Martine De Rycke [10,11]

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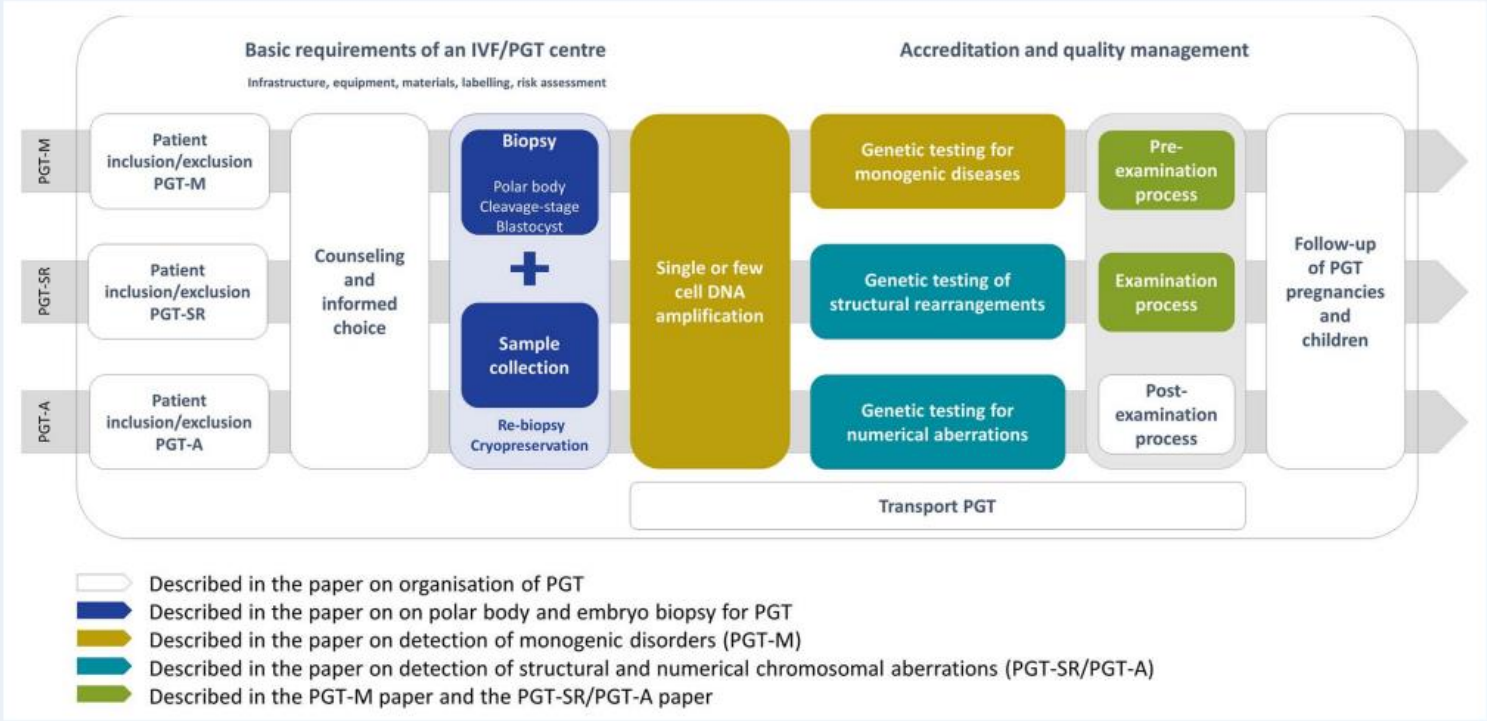
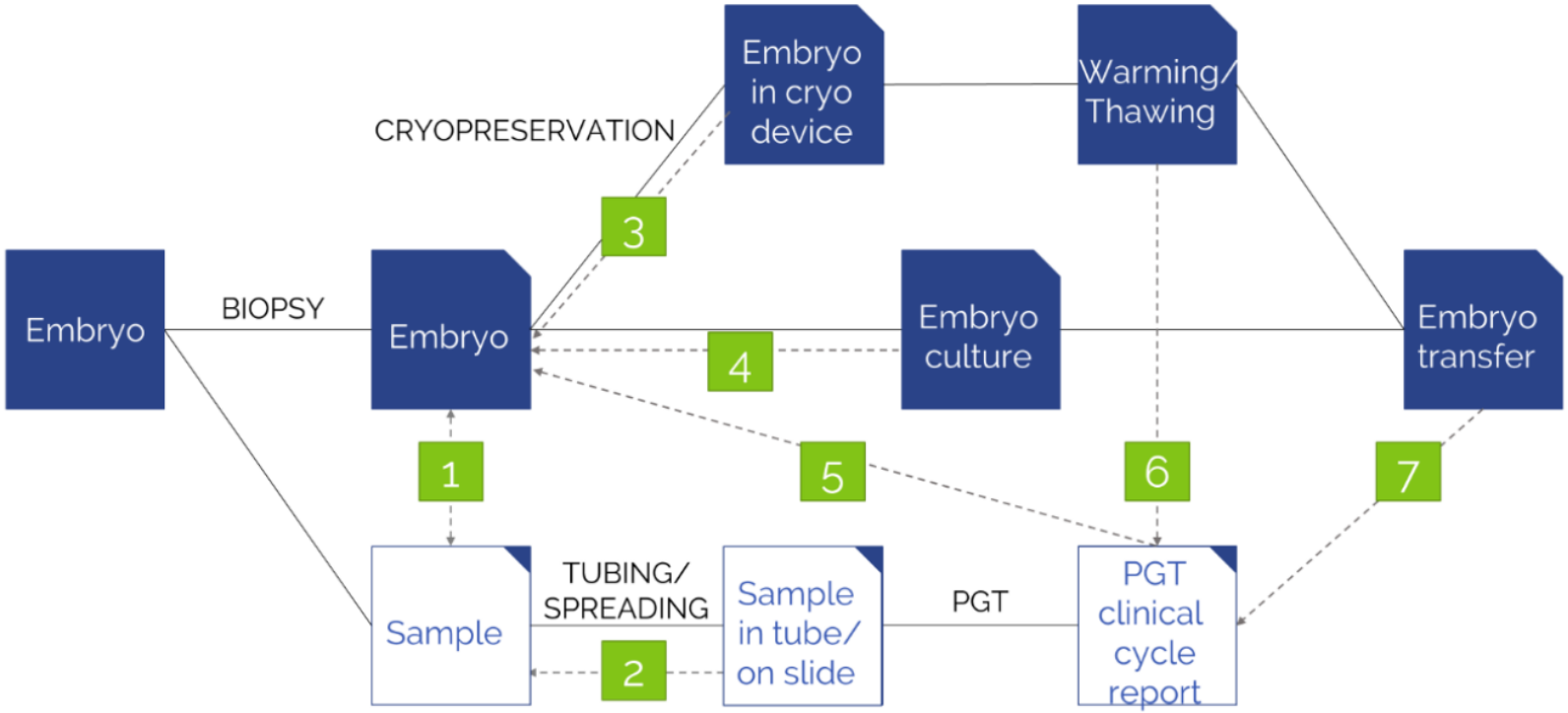


Figure 1 Overview of the IVF/PGT process, and how all aspects are covered by one of the four recommendations papers. IVF: *in vitro* fertilisation, PGT: preimplantation genetic testing.



Outline of the biopsy and genetic testing procedure with indications of the 7 critical steps where labelling and sample identification should be confirmed.

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REVIEW

PGT-A: who and when? A systematic review and network meta-analysis of RCTs

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ABSTRACT

Purpose Wide controversy is still ongoing regarding efficiency of preimplantation genetic testing for aneuploidy (PGT-A). This systematic review and meta-analysis, aims to identify the patient age group that benefits from PGT-A and the best day to biopsy.

Methods A systematic search of the literature was performed on MEDLINE/PubMed, Embase and Cochrane Central Library up to May 2020. Eleven randomized controlled trials employing PGT-A with comprehensive chromosomal screening (CCS) on Day-3 or Day-5 were eligible.

Results PGT-A did not improve live-birth rates (LBR) per patient in the general population (RR:1.11; 95%CI:0.87-1.42; n=1513; I^2=75%). However, PGT-A lowered miscarriage rate in the general population (RR:0.45; 95%CI:0.25-0.80; n=912; I^2=49%). Interestingly, the cumulative LBR per patient was improved by PGT-A (RR:1.36; 95%CI:1.13-1.64; n=580; I^2=12%). When performing an age-subgroup analysis PGT-A improved LBR in women over the age of 35 (RR:1.29; 95%CI:1.05-1.60; n=692; I^2=0%), whereas it appeared to be ineffective in younger women (RR:0.92; 95%CI:0.62-1.39; n=666; I^2=75%). Regarding optimal timing, only day-5 biopsy practice presented with improved LBR per ET (RR: 1.37; 95% CI: 1.03-1.82; I^2=72%).

Conclusion PGT-A did not improve clinical outcomes for the general population, however PGT-A improved live-birth rates strictly when performed on blastocyst stage embryos of women over the 35-year-old mark.

Keywords Systematic Reviews · Randomized Controlled trials · Infertility · Assisted Conception · Genetics · Clinical Guidelines

Table 2 Summary of findings.

Patient or population: Couples undergoing IVF
Settings: Assisted reproduction units
Intervention: Preimplantation genetic testing for aneuploidy (PGT-A)
Comparison: Morphological or morphokinetic evaluation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect(95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk for control group	Corresponding risk for the PGT-A group			
Live-Birth	**414 per 1000**	**431 per 1000** (360 to 588)	RR: 1.11 (0.87 to 1.42)	1513 (6)	⊕⊖⊖⊖**very low** [a,b]
`Live Birth - ≤35 years old	**481 per 1000**	**405 per 1000** (298 to 669)	RR: 0.92(0.62-1.3-9)	666 (3)	⊕⊖⊖⊖**very low** [a,b]
Live Birth - >35 years old	**290 per 1000**	**379 per 1000 (305 to 464)**	**RR: 1.29(1.05-1.6-0)**	692 (4)	⊕⊕⊕⊖**moderate** [c]
Ongoing Pregnancy	**432 per 1000**	**474 per 1000 (389 to 825)**	RR: 1.31 (0.90-1.-91)	933 (3)	⊕⊖⊖⊖**very low** [a,b]
Miscarriage	**197 per 1000**	**101 per 1000 (49 to 158)**	**RR: 0.36 (0.17-0.73)**	912 (7)	⊕⊕⊖⊖**low** [a]
Miscarriage - ≤35 years old	**161 per 1000**	**133 per 1000** (60 to 232)	RR: 0.73 (0.37 to 1.44)	383 (3)	⊕⊕⊖⊖**low** [a]
Miscarriage - >35 years old	**279 per 1000**	**104 per 1000** (33 to 326)	RR: 0.37 (0.12 to 1.17)	221(2)	⊕⊕⊕⊖**moderate** [d]
Clinical Pregnancy	**521 per 1000**	**546 per 1000 (495 to 714)**	RR: 1.14 (0.95 to 1.37)	1824 (9)	⊕⊖⊖⊖**very low** [a,b]
Clinical Pregnancy - ≤35 years old	**570 per 1000**	**503 per 1000** (388 to 770)	RR 0.96 (0.68 to 1.35)	679 (3)	⊕⊖⊖⊖**very low** [a,b]
Clinical Pregnancy - >35 years old	**406 per 1000**	**434 per 1000** (361 to 520)	RR 1.07 (0.89 to 1.28)	510 (2)	⊕⊕⊕⊕**high**
Cumulative Live Birth	**368 per 1000**	**512 per 1000** (416 to 604)	**RR 1.36 (1.13 to 1.64)**	580 (4)	⊕⊖⊖⊖**very low** [b,c]

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the

CONSIDERATIONS

- There is still an ongoing controversy regarding its effectiveness
- In 2019, the Preimplantation Genetic Diagnosis International Community (PGDIS) published a position statement, concluding that PGT-A improved implantation, pregnancy, and live-birth rates
- But this statement has been rebutted in literature! 
- Fact!: effectiveness of PGTA programs may differ and be subject to factors such as a poor or efficient biopsy directly affecting subsequent analysis and outcome
- This may be the underlying factor leading to the contradicting data, as patients may not be adequately profiled. To elaborate on that, undoubtedly maternal age should be the major criterion in decision-making, as aneuploidy rates increase when maternal age is over 35 years.

CONSIDERATIONS

- From the IVF cycle's performance perspective, the number and quality of embryos available for biopsy can be a defining factor in deciding whether PGT-A is beneficial.
- Furthermore, it has been observed that women with diminished ovarian reserve, auto-immune disorders, the implication of certain causes of male infertility, and other lifestyle factors have been associated with higher risk for embryo aneuploidy.

PGT-A: CONCLUSIONS

- Information about the embryo
  - Sex, ploidy
- Increased implantation rate in 1st ET
  - Age > 35
- Added cost
  - Not cost-effective for attainment of pregnancy
- Large percentage of potential implantations lost
  - 50% in the STAR trial
  - Need for additional egg retrievals

PGT-A: CONCLUSIONS

- Logical and appealing
  - Requested by patients
- Currently overused
  - Applied inappropriately
  - Marketed with very poor data
- Imperfect but improving
- Integral part of fertility treatment of the future

Thank you for your attention!

Questions