The Role of PGT A in IVF

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- The diagnostic platforms used to perform PGT-A 2.0 have improved considerably in recent years.

- Current data strongly support the use of technologies that are capable of simultaneously evaluating the ploidy status of all 23 chromosome pairs

(Brezina and Kutteh, 2015; Brezina et al., 2016).

- Therefore, other more limited technologies, including FISH, are discouraged.
- The use of more comprehensive and reliable analytical platforms such as
  - single nucleotide polymorphism (SNP) array,
  - quantitative polymerase chain reaction,
  - array comparative genomic hybridization (aCGH) and
  - next-generation sequencing (NGS)

PGT A 2.0

- Strengths
  - PGT-A 2.0 is the strongest and most evaluated technique
  - PGT-A 2.0 improves embryo selection, which improves implantation rates and pregnancy rates.
  - PGT-A 2.0 decreases miscarriages.
  - PGS 2.0 increases the chance of a healthy, term, singleton delivery

PGT A 2.0

- Weakness
  - Mosaicisms
  - PGT-A 2.0 does not improve pregnancy rate per cycle
  - Invasiveness and complexity of the technique.
  - Laboratory management reliability and poor consistency between centres.
  - Costs of the technique.
  - Over diagnosed embryos.

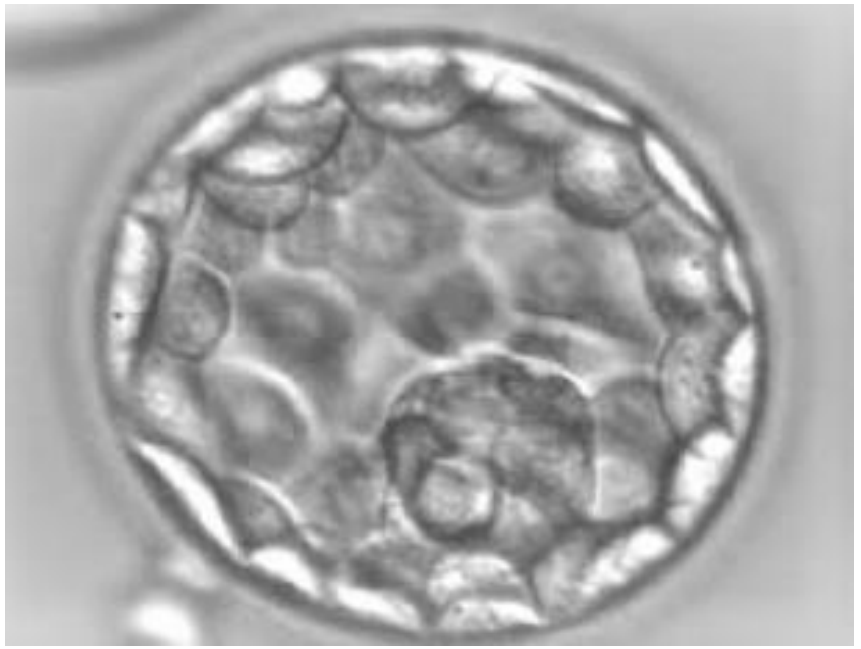
PGT-A 2.0 is the strongest and most evaluated technique

- PGT-A 2.0 presents a high level of consistency and reproducibility in different centres and with different embryologists

- Error rates with all methods of 24-chromosome aneuploidy detection are low (1–2%), but clinical error rates with diagnoses of partial aneuploidy, mosaicism or partial mosaicism are still unknown.

PGT-A 2.0 improves embryo selection, which improves implantation rates and pregnancy rates

- Several studies suggest that PGT-A 2.0 performed at the blastocyst stage with whole-genome screening seems to be a unique procedure, providing an accurate assessment of embryo ploidy, while maintaining high implantation potential .



- (Brezina et al., 2016; Capalbo et al., 2013; Forman et al., 2013; Fragouli et al., 2014; Lee et al., 2015; Minasi and Greco, 2014; Minasi et al., 2017; Scott et al., 2013; Ubaldi et al., 2017).

PLoS One. 2015; 10(10): e0140779.
Published online 2015 Oct 15. doi: 10.1371/journal.pone.0140779
PMCID: PMC4607161
PMID: 26470028

Can Comprehensive Chromosome Screening Technology Improve IVF/ICSI Outcomes? A Meta-Analysis

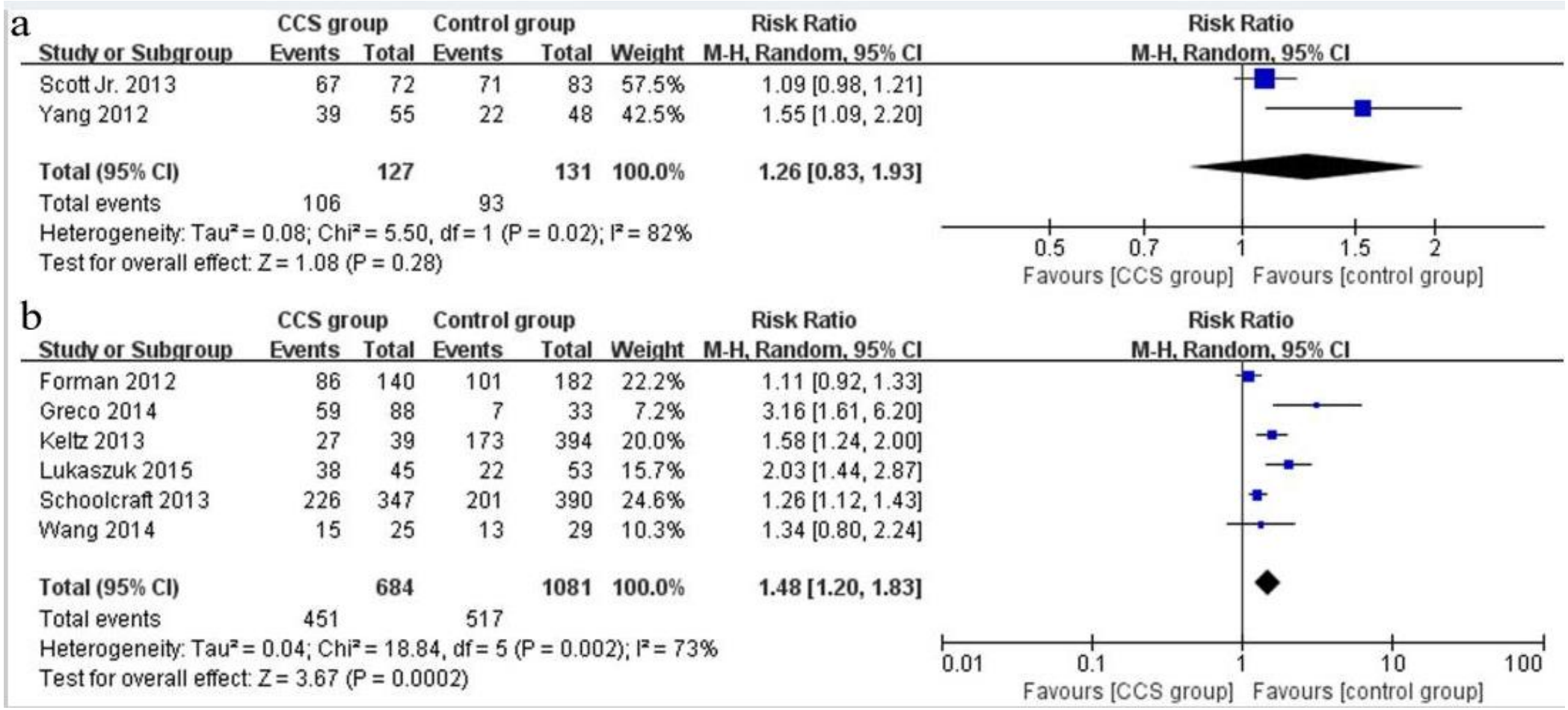
Minghao Chen,[#1] Shiyou Wei,[#2] Junyan Hu,[#3] and Song Quan[1,*]

Qing-Yuan Sun, Editor

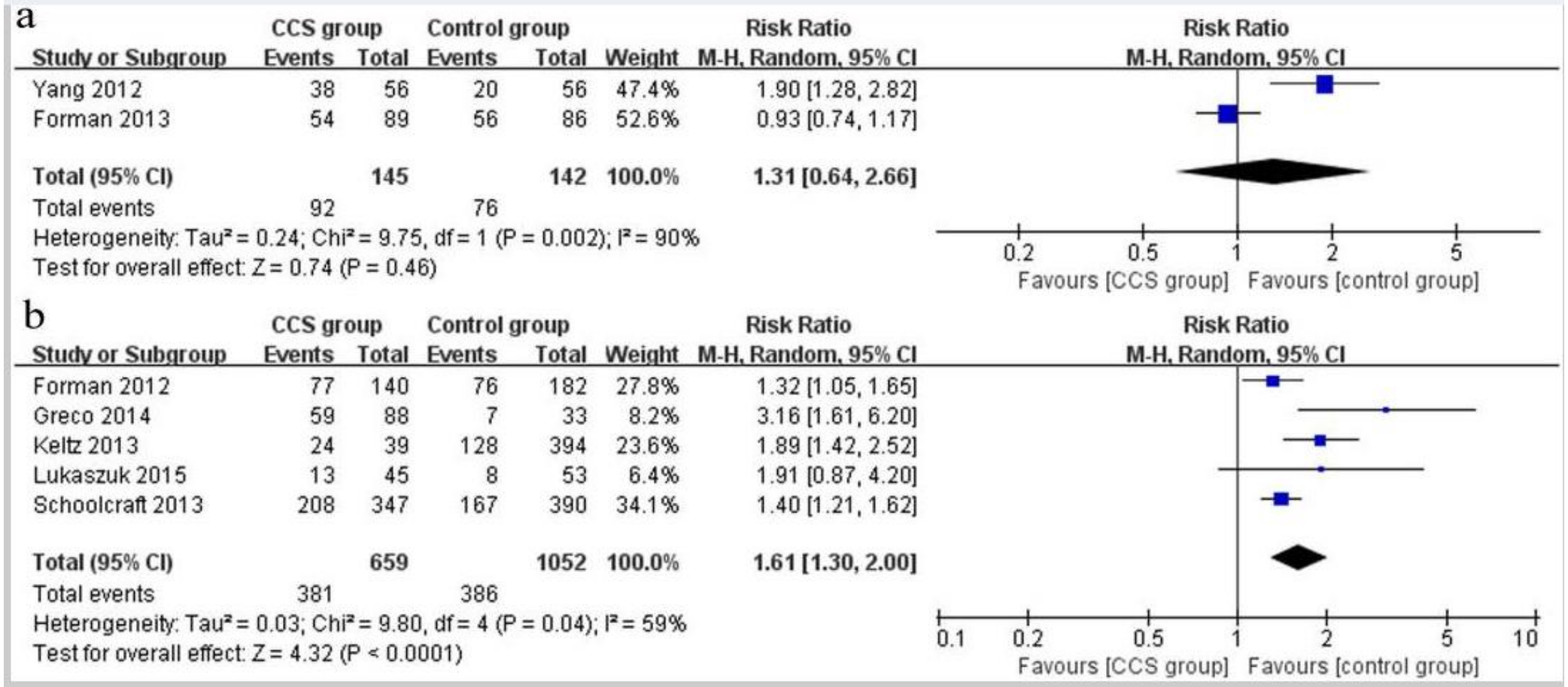
4 RCT and Seven cohort studies included in a meta-analysis.

Morphological criteria VS (CCS)-based PGT-A 2.0

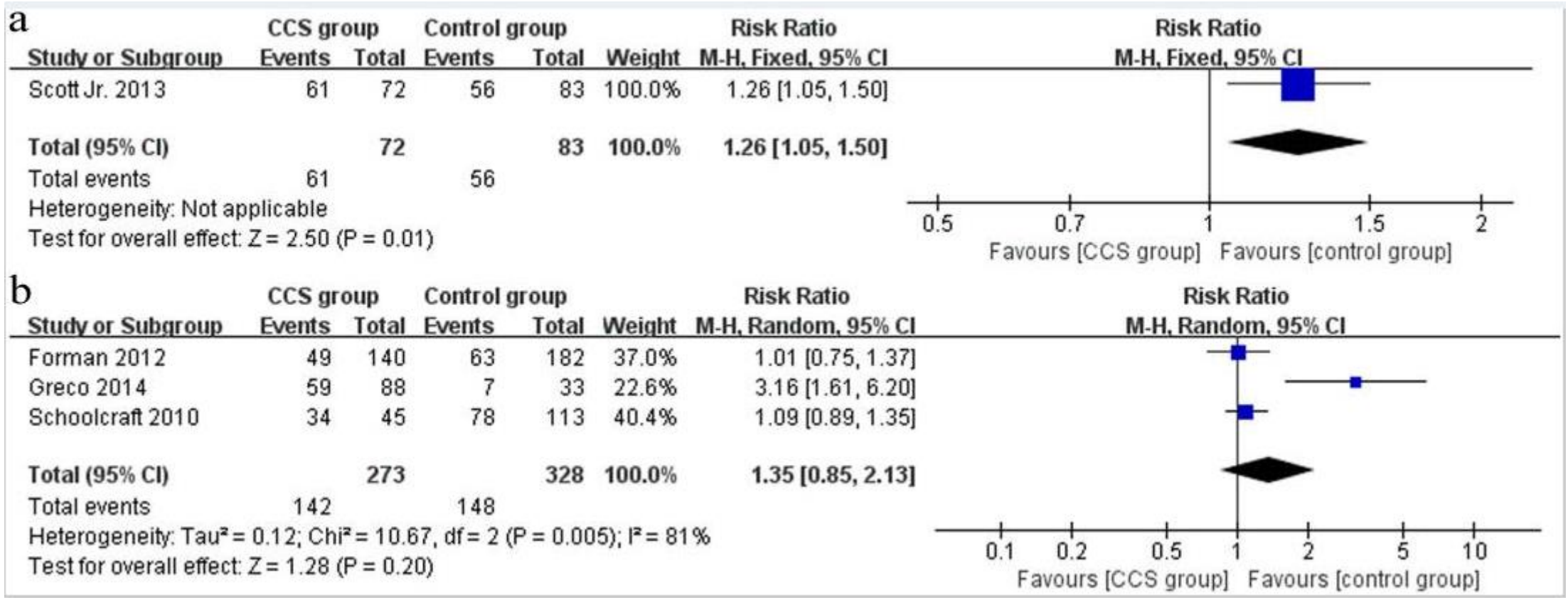
Implanation



On going pregnancy Rate

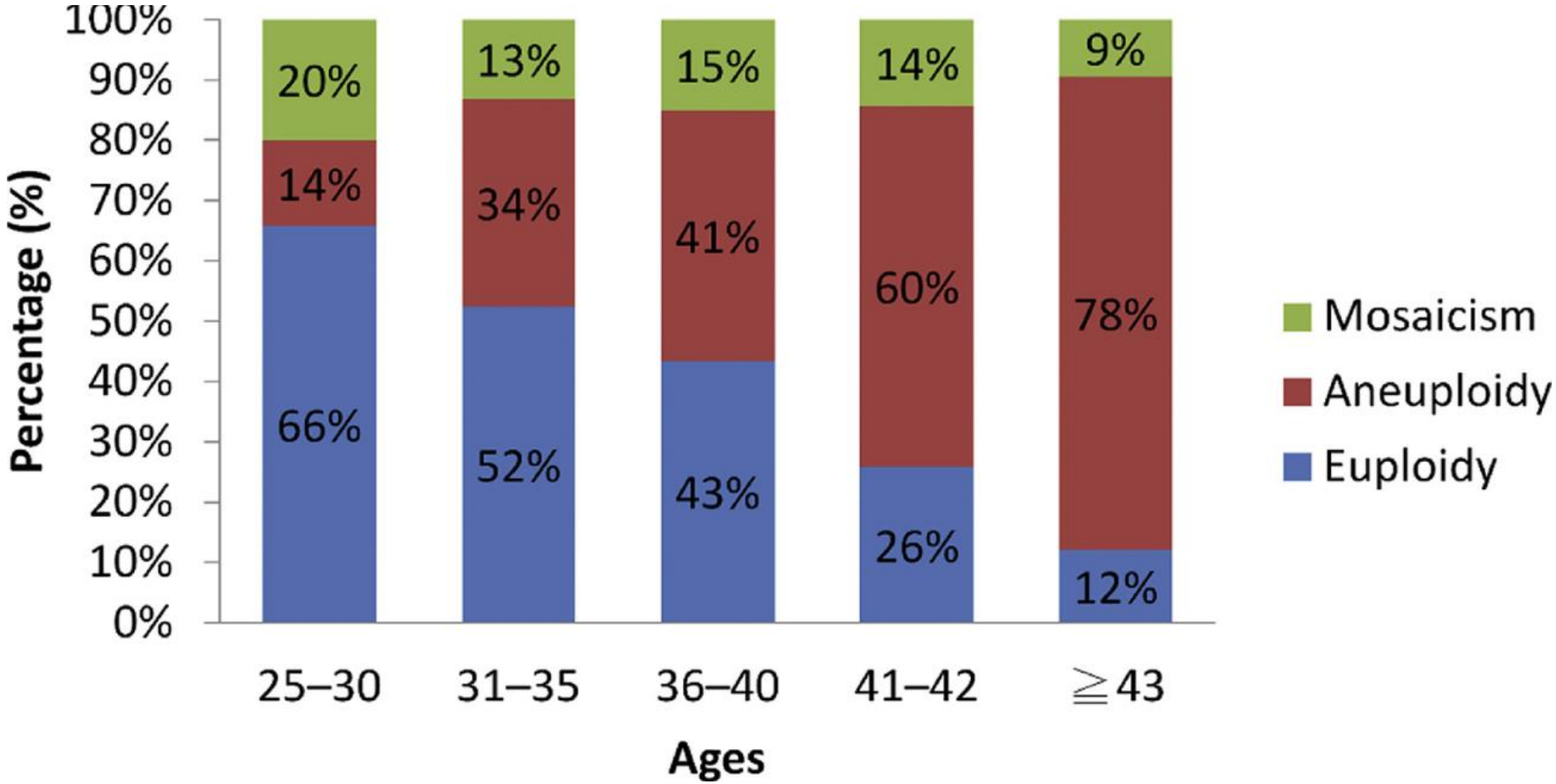


Live Birth rate



- In those women at high risk of producing aneuploid embryos (AMA, repeated implantation failure [RIF] or recurrent pregnancy loss [RPL)], a lower level of evidence has been found as the data obtained came only from observational studies

- (Dahdouh et al., 2015; Lee et al., 2015).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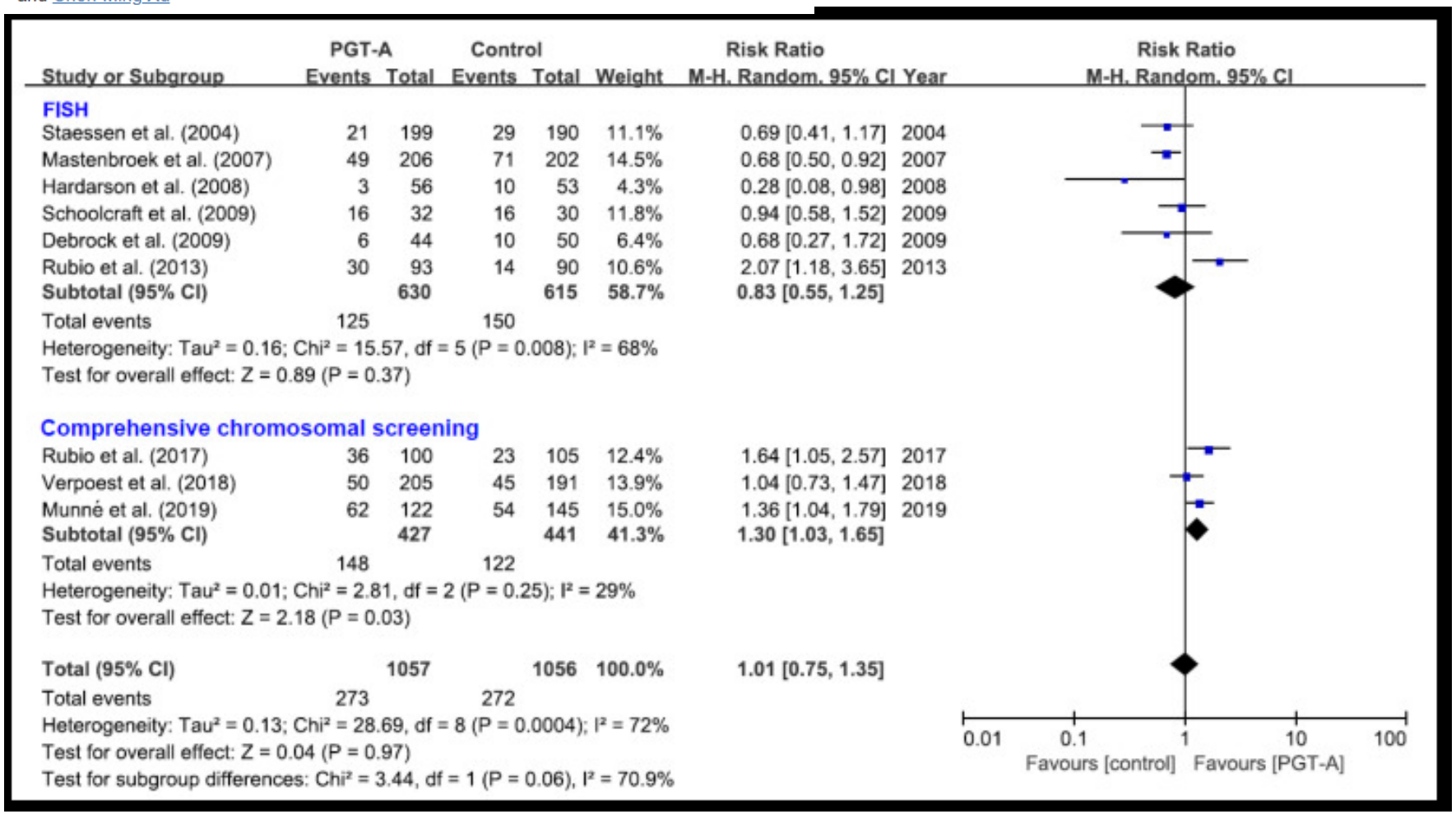
Ages
Mosaicism
Aneuploidy
Euploidy

J Clin Med. 2021 Sep; 10(17): 3895.
Published online 2021 Aug 30. doi: 10.3390/jcm10173895
PMCID: PMC8432243
PMID: 34501345

Different Strategies of Preimplantation Genetic Testing for Aneuploidies in Women of Advanced Maternal Age: A Systematic Review and Meta-Analysis

Wei-Hui Shi,[1,2,†] Zi-Ru Jiang,[3,†] Zhi-Yang Zhou,[1,2] Mu-Jin Ye,[1,2] Ning-Xin Qin,[4] He-Feng Huang,[1,2,3] Song-Chang Chen,[2,3,*] and Chen-Ming Xu[1,2,3,*]



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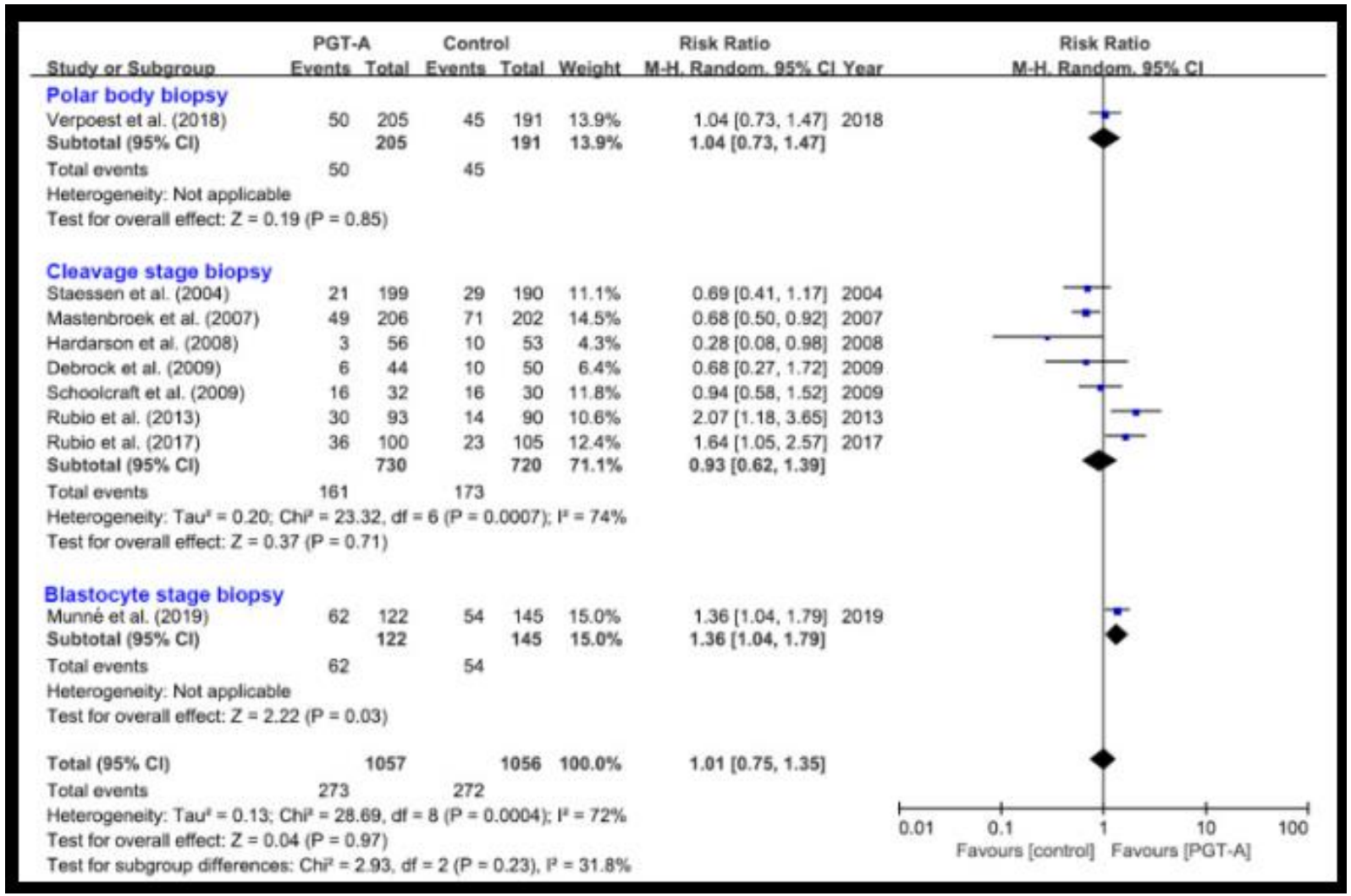


- Some ongoing RCT are being conducted on different patient populations (e.g. AMA [NCT02868528]) patients with male factor infertility [NCT02941965] to clarify the role of this technology in these populations.

- Early figures suggest that the benefits of testing embryos for common chromosomal abnormalities, include: increased ongoing implantation and pregnancy rates per transfer, decreased miscarriage rates per patient, and faster time to pregnancy when compared to conventional embryo scoring by morphology alone.

PGT-A 2.0 decreases miscarriages

In one 40-year review of 8319 specimens,
trisomy was the most common chromosome abnormality

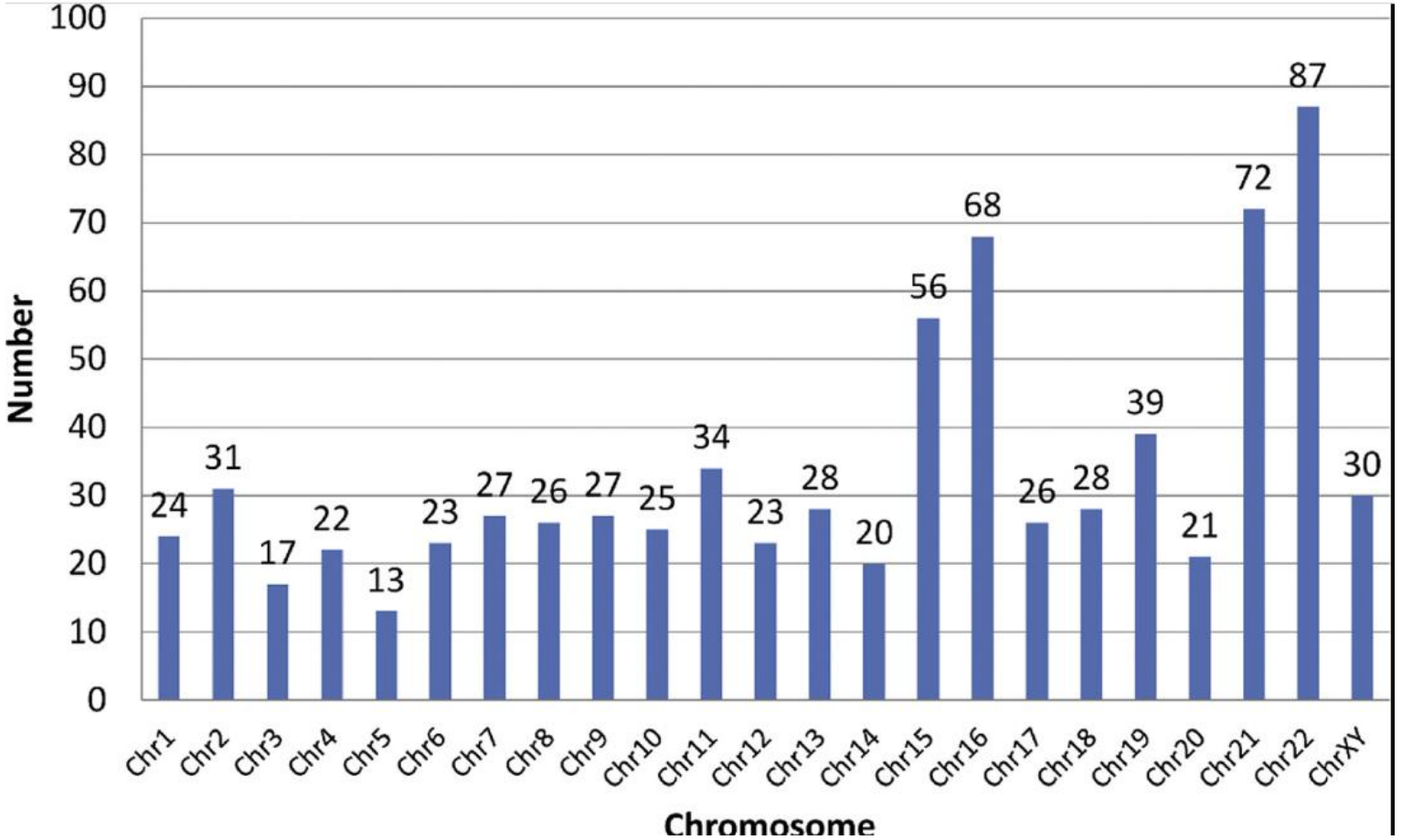
trisomies 16, 22, 15, and 21
were found to be the most common

K. Hardy, P.J. Hardy, P.A. Jacobs, K. Lewallen, T.J. Hassold

Temporal changes in chromosome abnormalities in human spontaneous abortions: results of 40 years of analysis

Am J Med Genet, 170 (2016), pp. 2671-2680

Number of chromosomal errors detected. The number of chromosomal errors, including whole chromosome aneuploidy (monosomy and trisomy), structural aneuploidy and mosaicism, detected in each chromosome. Chromosomes 22, 21, 16, and 15, in that order, were most frequently affected.



JOURNAL ARTICLE

Pregnancy outcomes following *in vitro* fertilization frozen embryo transfer (IVF-FET) with or without preimplantation genetic testing for aneuploidy (PGT-A) in women with recurrent pregnancy loss (RPL): a SART-CORS study

S J Bhatt, N M Marchetto ✉, J Roy, S S Morelli, P C

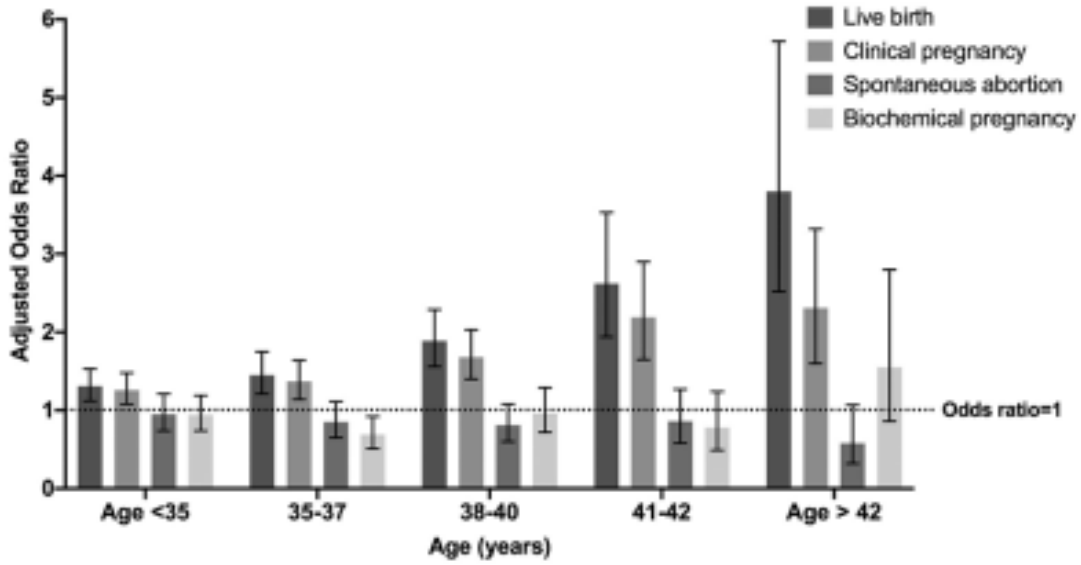
Human Reproduction, Volume 36, Issue 8, August
https://doi.org/10.1093/humrep/deab117
Published: 24 May 2021 **Article history** ▾

Table II Overall outcomes in women with recurrent pregnancy loss undergoing frozen embryo transfer (FET) with or without preimplantation genetic testing for aneuploidy (PGT-A).

	Recurrent pregnancy loss	
	No PGT-A	**PGT-A**
Cycles (n)	4116	4288
Live birth, n (%)	1381 (33.6)	2047 (47.7)
Spontaneous abortion, n (%)	517 (12.6)	463 (10.8)
Ectopic pregnancy, n (%)	27 (0.7)	19 (0.4)
Biochemical pregnancy, n (%)	474 (11.5)	425 (9.9)
Not pregnant, n (%)	1717 (41.7)	1334 (31.1)

Adjusted odds ratio for pregnancy outcomes in women with recurrent pregnancy loss undergoing IVF-frozen embryo transfer (IVF-FET) with or without preimplantation genetic testing for aneuploidy (PGT-A) use.

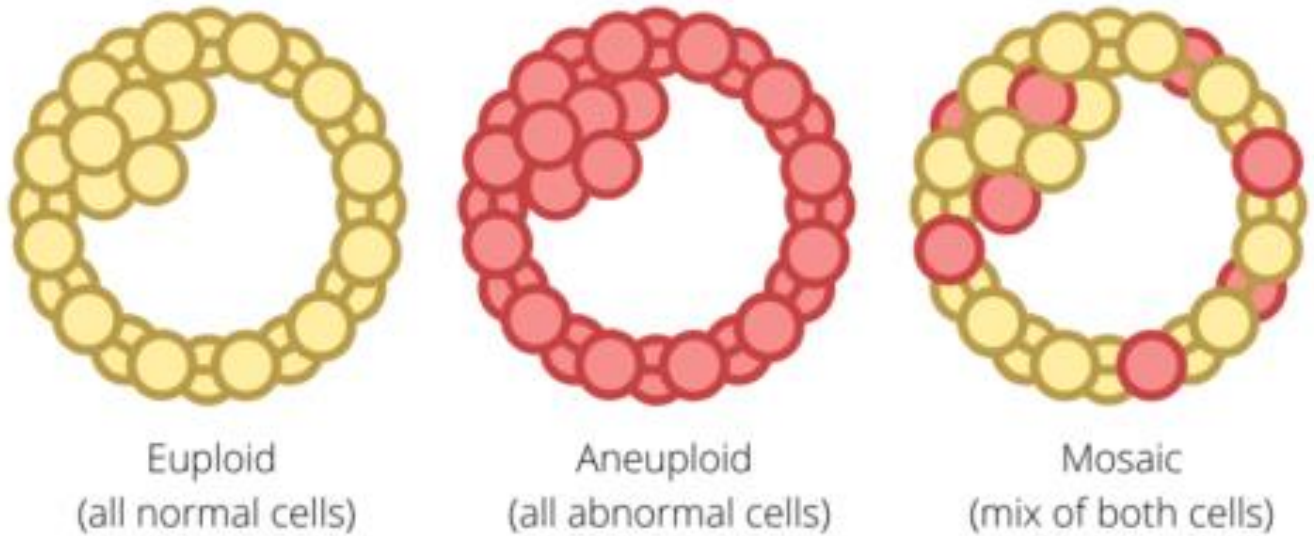
Figure 1. Adjusted odds ratio for pregnancy outcomes in women with recurrent pregnancy loss undergoing IVF-frozen …

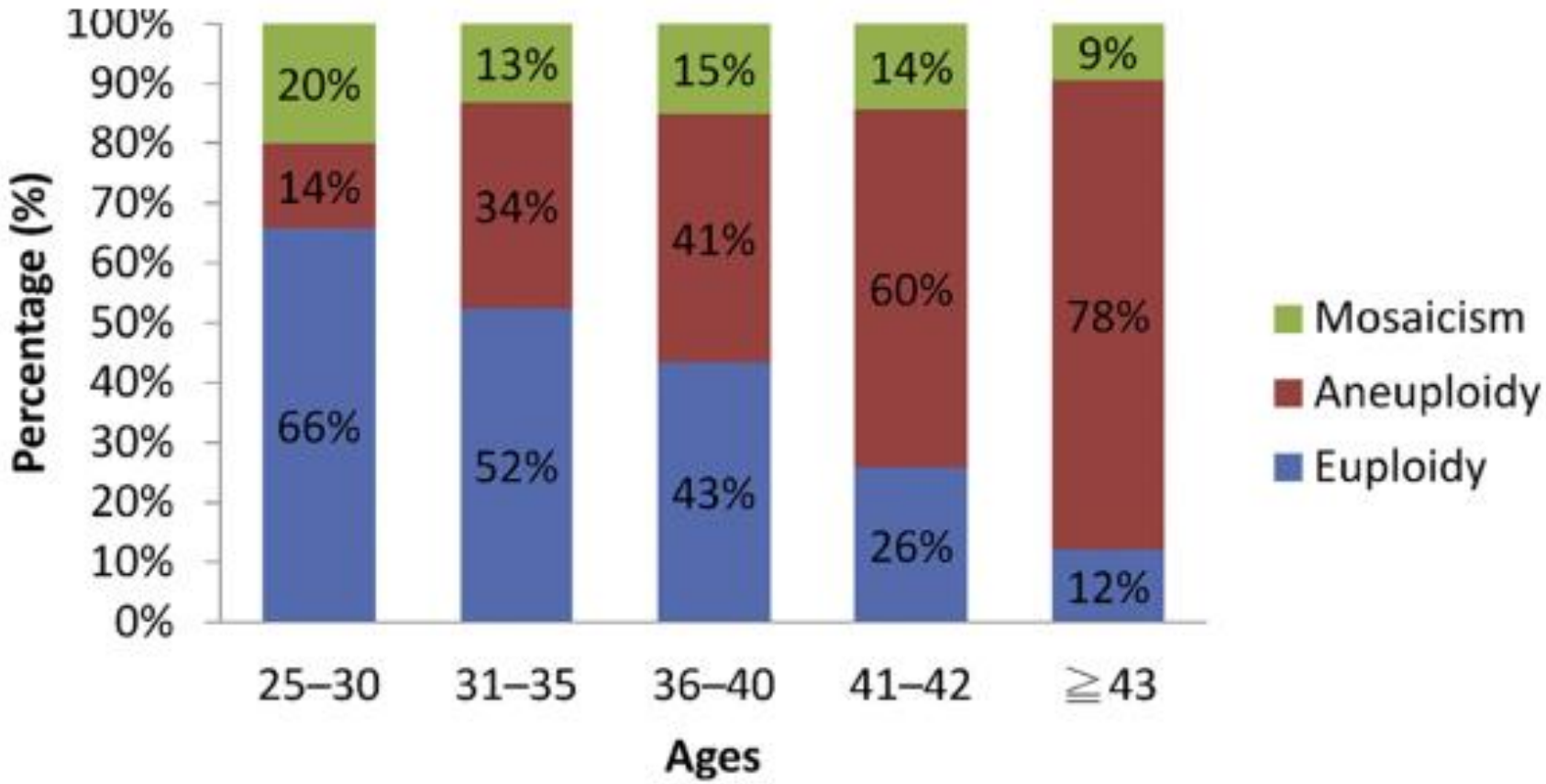


Hum Reprod, Volume 36, Issue 8, August 2021, Pages 2339–2344, https://doi.org/10.1093/humrep/deab117

Weaknesses

Mosaicisms


Euploid
(all normal cells)
Aneuploid
(all abnormal cells)
Mosaic
(mix of both cells)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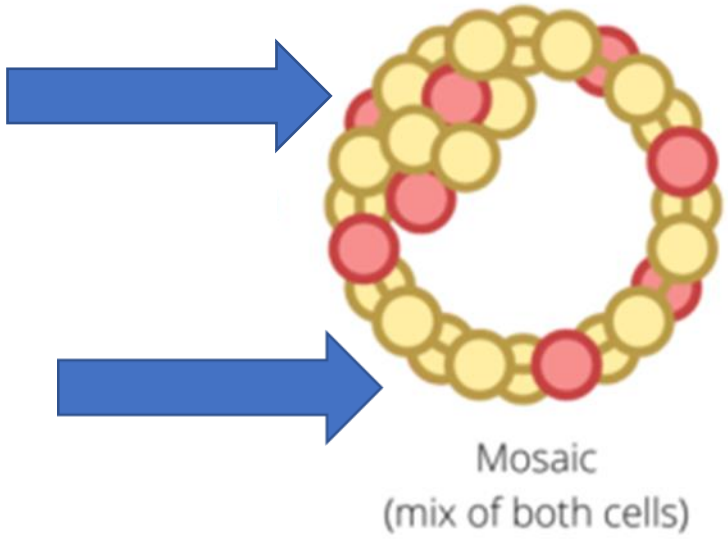
Ages
Mosaicism
Aneuploidy
Euploidy

Mosaicisms

- Mosaicism is thought to be less common in blastocyst-stage embryos than in previous stages (Brezina and Kutteh, 2015), so current data strongly support obtaining an embryo biopsy at this point in time (Dahdouh et al., 2015).

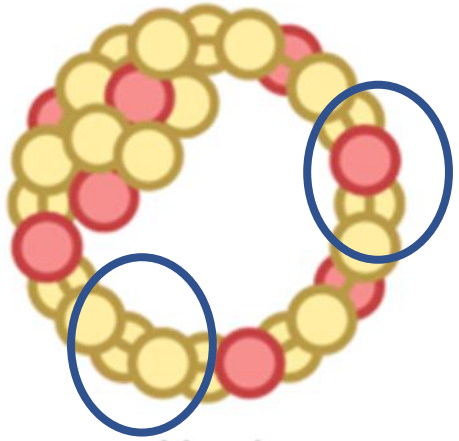
Mosaicisms

- However, discordance in the ploidy status between the inner cell mass and the trophectoderm is still relatively common (Brezina and Kutteh, 2015).



Mosaicisms

- Embryo rebiopsy studies in mosaic embryos show that the reproducibility of trophectoderm biopsy demonstrating mosaicism is only 41–58%, and that trophectoderm biopsy of 5 cells may not be representative of the degree of mosaicism of the entire embryo.



Mosaicisms

- Therefore, there is still a chance of misdiagnosis with PGT-A 2.0 from the biopsy based purely on the biology of the developing embryo.

- This represents a biological limitation that is not possible to overcome even with the best diagnostic techniques

(Brezina et al., 2016).

Mosaicisms

- High-resolution NGS succeeds in detecting mosaicism in the vast majority of trophectoderm biopsies in which it is present, and the frequency of false-positive and false-negative results appears to be low.

(Munné et al., 2017)

Fertility and Sterility asrm

ORIGINAL ARTICLE | VOLUME 115, ISSUE 5, P1212-1224, MAY 01, 2021

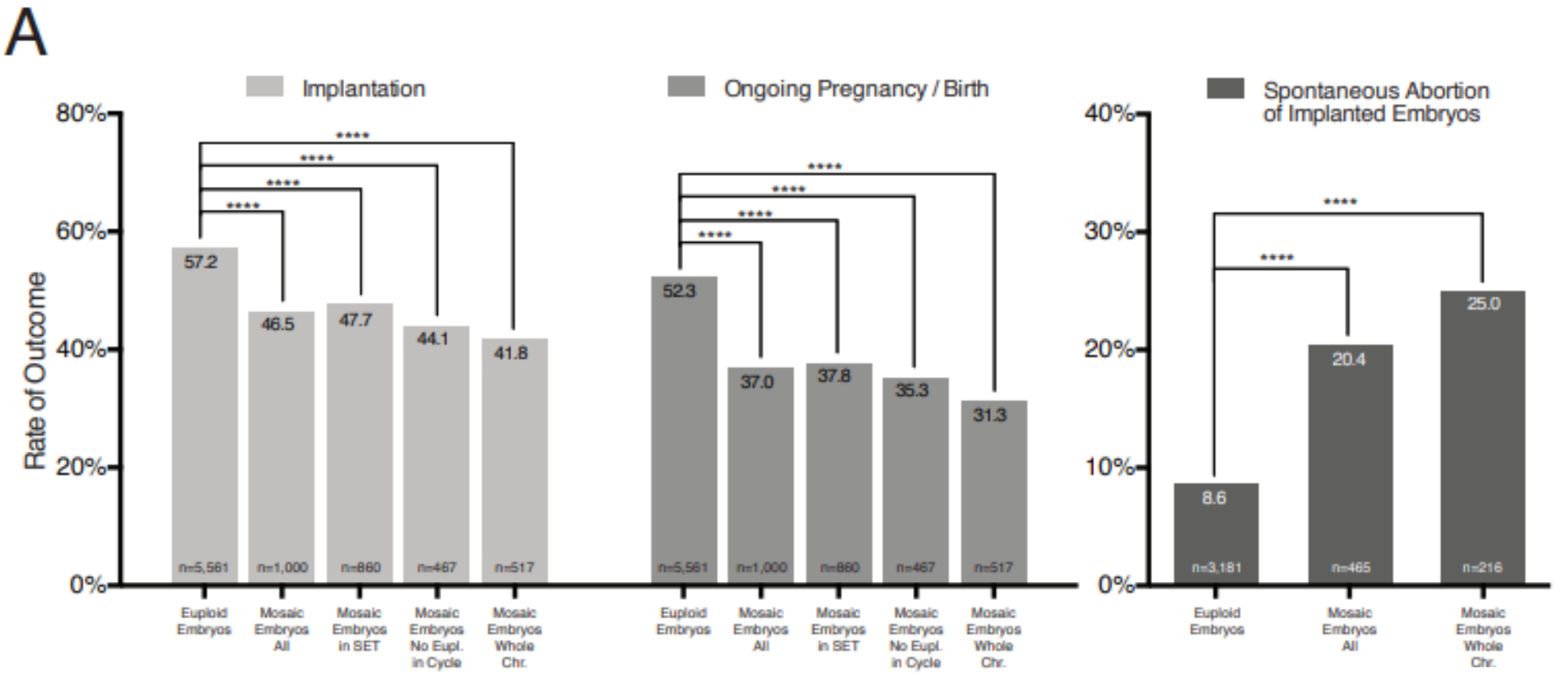
PDF [500 KB]

Using outcome data from one thousand mosaic embryo transfers to formulate an embryo ranking system for clinical use

Manuel Viotti, Ph.D. • Andrea R. Victor, M.S. • Frank L. Barnes, Ph.D. • ... Maria Giulia Minasi, M.Sc. • Ermanno Greco, M.D. • Santiago Munné, Ph.D. • Show all authors

Published: March 05, 2021 • DOI: https://doi.org/10.1016/j.fertnstert.2020.11.041 •

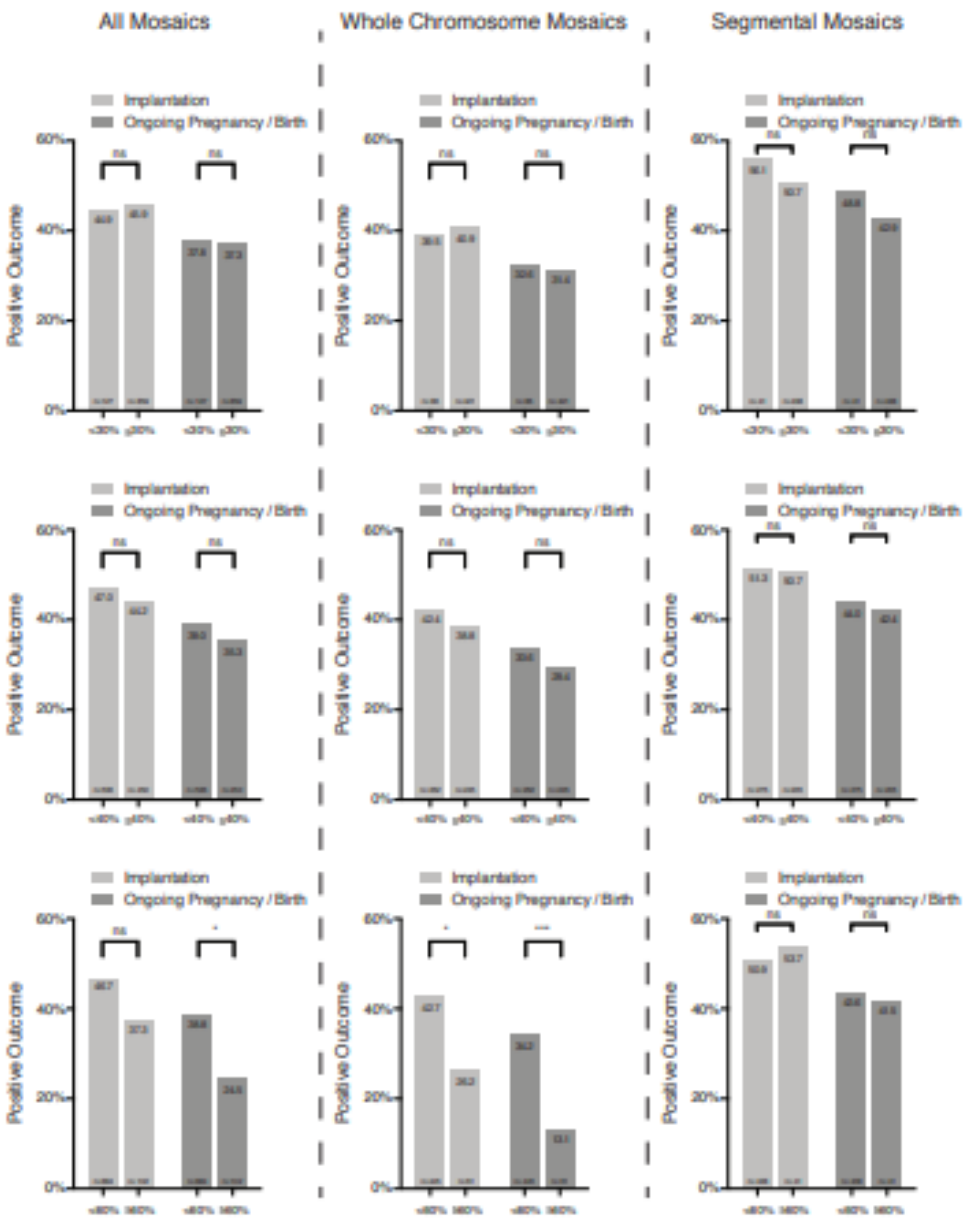
Clinical outcomes of transferred euploid and mosaic embryos, with controls.
Comparison of the euploid group to various mosaic sub-groups.



Viotti et al.Supplemental Fig. 1

Effect of mosaicism level on clinical outcomes.

Analysis of outcomes with different cutoffs defining low and high levels of mosaicism.



Viotti et al. Supplemental Fig. 2

< 30%

< 40%

< 60%

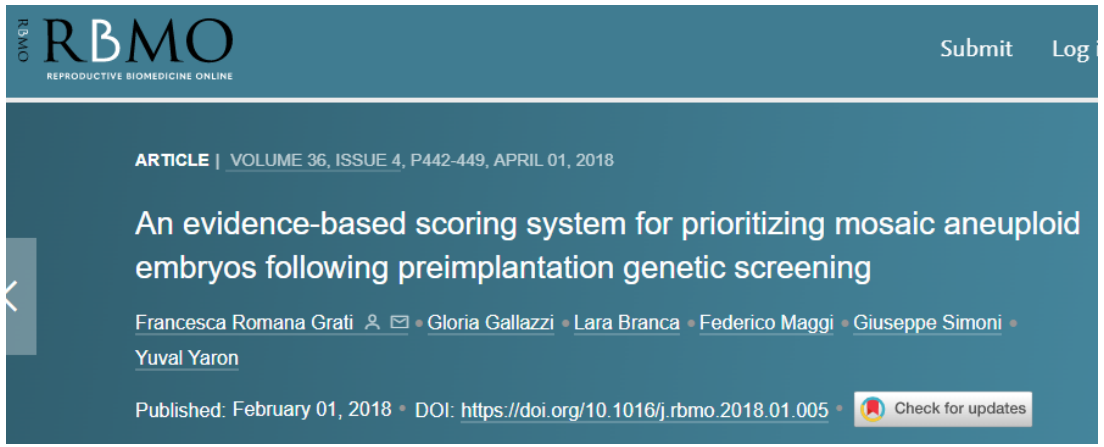
Mosaicisms

- If no euploid embryos are available and the patient is aware of and understands all the associated risks
- The most recent data suggest that the majority of embryos with 20–40% of aneuploid cells in their biopsy sample have an euploid inner cell mass and could be considered for transfer.
- Blastocysts with 40–80% of abnormal cells and those with complex mosaicism should be given the lowest priority for transfer or be excluded

Mosaicisms

- A scoring system according to the chromosomes involved in the mosaic has been developed to help clinicians in counselling patients, taking into account the risk of miscarriage or having an affected fetus

Mosaicisms



- Mosaic aneuploidies show different likelihoods of fetal involvement and may therefore be assigned one of the following arbitrary risk scores:
  - 3. High risk (>15%): trisomy 16, 18, 21 and 45,X, 47,XXY, 47,XXX
  - 2. Intermediate risk (5–15%): trisomy 14 and 20
  - 1. Low risk (1–4%): trisomy 13
  - 0. No risk (<1%): trisomies 1–12, 15, 17, 19, 22 and 47,XYY

PGT-A 2.0 does not improve pregnancy rate per cycle

- PGT-A 2.0 is associated with inconsistent results in terms of improving pregnancy rates
- It is essential to assess pregnancy rates by **‘intent to treat’**
- A retrospective cohort study analysing this found that IVF-PGT-A in women aged over 37 years improved live birth rates. However, when analysed per cycle, the PGT-A 2.0 advantage in this age group did not persist.

Invasiveness and complexity of the technique

- To date no sufficiently statistically powered study has clarified the impact of this procedure on reproductive competence of the embryo,

- High standards are required for blastocyst culture and cryopreservation, which is an important limiting factor for the widespread implementation of this strategy.

Costs of the technique

Loss of embryos

- PGT-A 2.0 is also associated with fewer embryos being available for transfer and/or cryopreservation.
- The proportion of embryos that are unsuitable for transfer is likely to vary among clinical settings, but it has been estimated to be somewhat relevant (Paulson, 2017: evidence level 5).
- For these reasons, individual programs may need to examine their own embryo implantation rates with and without PGT-A 2.0, calculate their embryo loss rate.

Over diagnosed embryos

- A false-positive diagnosis or failure to determine clinical significance may result in the discarding of
  - reproductively competent embryos
  - embryos with the ability to self-repair and eliminate aneuploid cells.

JOURNAL ARTICLE

IVF outcomes of embryos with abnormal PGT-A biopsy previously refused transfer: a prospective cohort study

Get access >

D H Barad ✉, D F Albertini, E Molinari, N Gleicher

Human Reproduction, Volume 37, Issue 6, June 2022, Pages 1194–1206,
https://doi.org/10.1093/humrep/deac063
Published: 12 April 2022 **Article history** ▾

- 50 patients have undergone 57 transfer cycles of 141 embryos.

- Transfer of PGT-A abnormal embryos resulted in 8 live births, 11 miscarriages and no voluntary terminations.

Lack of well-designed randomized studies and long-term data

- The lack of large well-designed RCT is one important limitation of PGT-A 2.0. Only three RCT have been published, all of which have been criticized because of poor study design (Forman et al., 2013; Scott et al., 2013; Yang et al., 2012).
- The pilot RCT by Yang and colleagues (Yang et al., 2012) included a small sample size of 45 young, good-prognosis patients.
- Scott and co-workers (Scott et al., 2013) performed an RCT on 72 good-prognosis women between the ages of 21 and 42 years who were randomized quite late, i.e. if they had at least two blastocysts available for analysis. Although the authors claimed that PGT-A increased implantation and delivery rates, there was a fundamental methodological flaw in the study's failure to account for the difference between the unit of randomization (patients) and unit of analysis (individual embryos).
- The third RCT studied 89 patients aiming to compare PGT-A and single-embryo transfer with the transfer of two embryos without genetic diagnosis (Forman et al., 2013). The same methodological problem encountered by the Scott trial was introduced but, even so, the wide confidence interval for pregnancy did not demonstrate a beneficial effect (Chen et al., 2015: evidence level 1a).

Lack of well-designed randomized studies and long-term data

- Intention-to-treat studies of deferred embryo transfer with and without PGT-A 2.0 and eventually of all transferred embryos will be required to fully assess the impact of contemporary PGT-A 2.0 (Meldrum et al., 2016: evidence level 5), and further studies evaluating long-term paediatric outcomes and the overall cost-efficacy of this approach are necessary (Forman et al., 2014).

Conclusion

Technology
Strengths
Weakness

Thank you very much