Why is preimplantation genetic testing for aneuploidy (PGT-A) important?

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ORIGINAL ARTICLE

WILEY Reproductive Medicine and Biology

Assisted reproductive technology in Japan: a summary report for 2015 by The Ethics Committee of The Japan Society of Obstetrics and Gynecology

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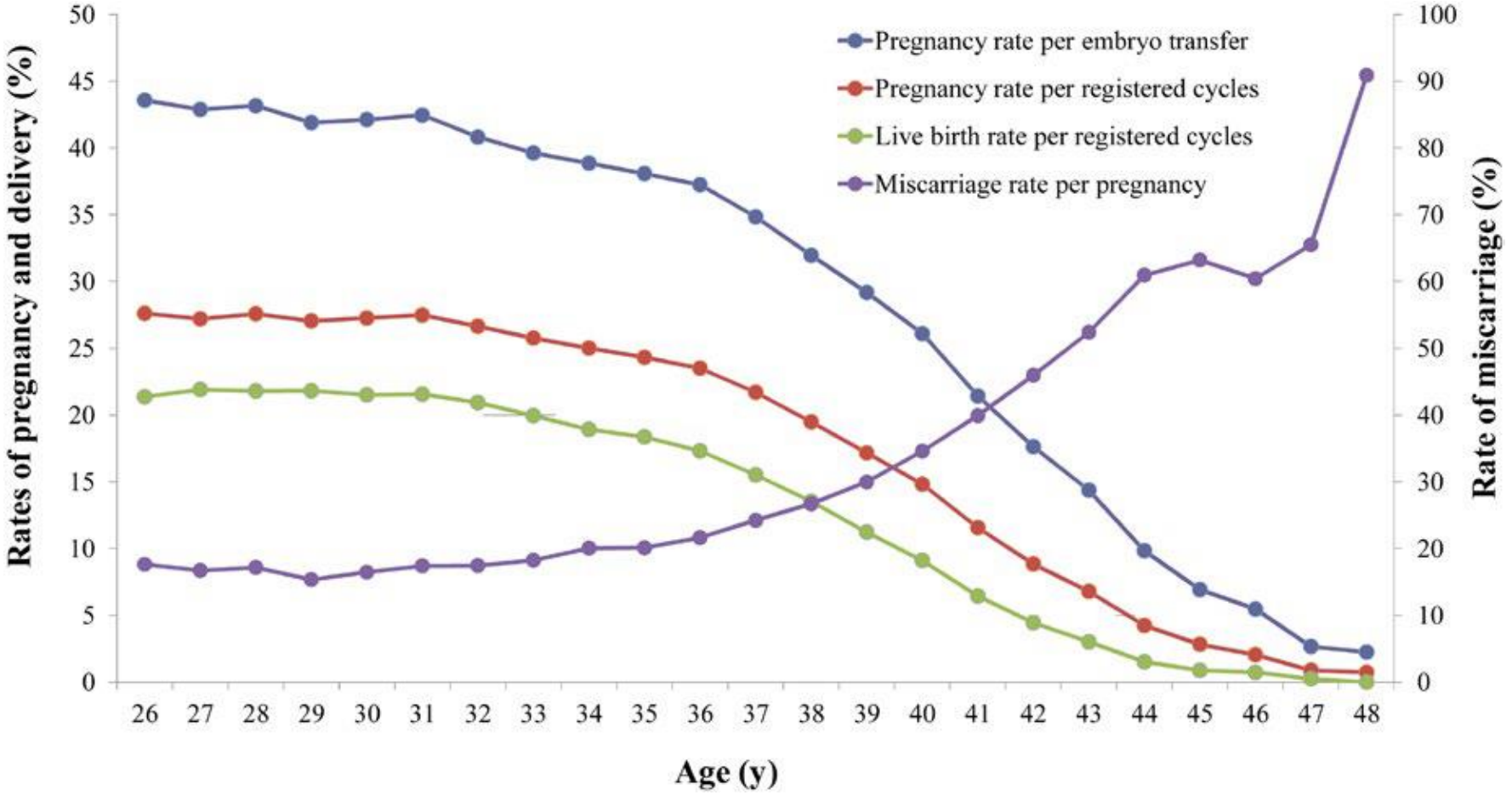
Saito et al (2018) Reprod Med Biol 17, 20


Pregnancy rate per embryo transfer
Pregnancy rate per registered cycles
Live birth rate per registered cycles
Miscarriage rate per pregnancy
Rates of pregnancy and delivery (%)
Rate of miscarriage (%)
Age (y)
0
5
10
15
20
25
30
35
40
45
50
0
10
20
30
40
50
60
70
80
90
100
26
27
28
29
30
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- Chromosome aneuploidy is common in human gametes and preimplantation embryos and is a major cause of developmental arrest, IVF failure, miscarriage and rarely affected live births
- No clinical or ethical justification for transferring aneuploid embryos following IVF
- Aneuploidy testing (PGT-A) is the most effective embryo selection method so far reported
- Genetic imbalance causing implantation and developmental failure acts downstream of all other embryo viability factors
- For routine application, PGT-A should be (1) non-invasive or minimally invasive, (2) accurate, (3) inexpensive and (4) straightforward to interpret

Rosenwaks and Handyside (2018) Fert Stert 110, 351

Origin and types of aneuploidy

Meiotic

Mainly maternal in origin (10x)
Exponential increase in women above 35y
80% of spontaneous abortions associated with maternal meiotic errors

Fertilisation

Digynic and diandric triploidy
Haploidy

- Affects whole embryo
- Trisomic rescue rare and risk of uniparental isodisomy
- With few exceptions non-viable

Mitotic

Karyotype-wide eg tetraploidy
Non-disjunction or anaphase lag
Chromosome breaks
Tripolar and other abnormal cleavage divisions

- Affects only part of the embryo (mosaic)
- Grossly aneuploid cells eliminated before blastocyst formation
- Others likely eliminated after implantation

Technologies for PGT-A

Chromosome counting

- Karyotyping
- Fluorescent in situ hybridisation

Copy number analysis

- Quantitative fluorescent real time PCR
- Low read depth next generation sequencing (NGS)

Genotyping

- SNP genotyping by array and karyomapping

Combined genotyping and copy number analysis

- SNP genotyping by array with karyomap and allele-specific intensity analysis
- SNP genotyping by NGS and copy number analysis

Copy number analysis vs genotyping

Copy number analysis

- Accurate high resolution copy number quantitation
- Moderately accurate discrimination of full and mosaic changes
- Only XXY triploidy detectable
- Lower cost

Genotyping

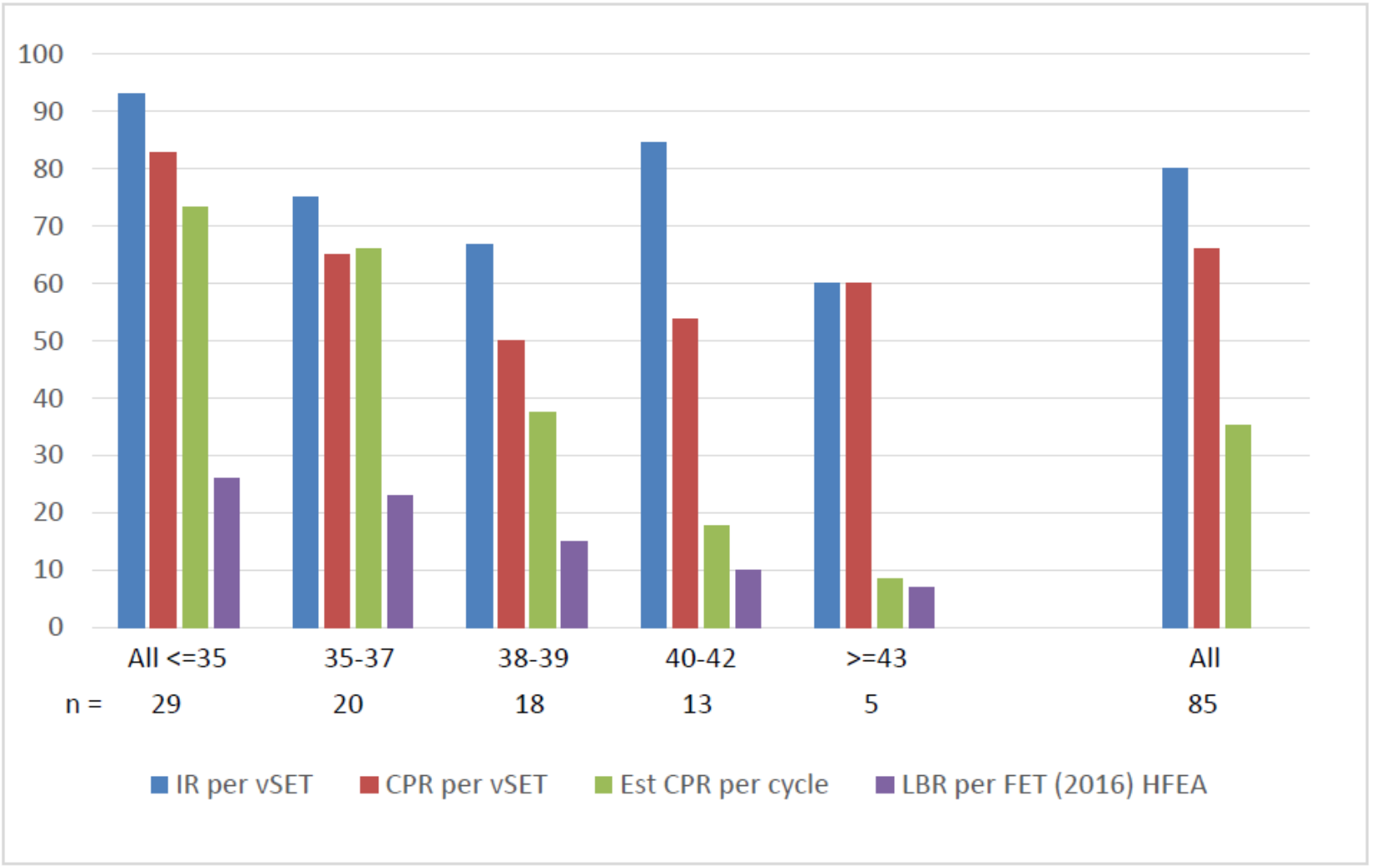
- Directly identifies meiotic trisomies, monosomies and deletions
- Highly informative including parental origin of aneuploidies and abnormally fertilised triploid and haploid embryos
- Moderately accurate quantitation
- Embryo ‘fingerprinting’ and detection of contamination
- Need for parental DNA
- Higher cost

One by One and One by One Plus

- IVF/ICSI, blastocyst culture in time lapse incubator and low oxygen, optional trophectoderm biopsy and NGS-based PGT-A, ‘freeze all’ by vitrification and single vitrified-thawed blastocyst (vSET) transfer in later managed cycles for all patients
- Prospective cohort study of 155 patients and 222 cycles from January 2016 to December 2017 with 85 vSET outcomes to end of March 2018
- Average maternal age 39 years
- All patients suitable for IVF

Gorodeckaja et al (2018) Human Fertility in press

% Clinical pregnancy/delivery rate per single vitrified-thawed blastocyst transfer (vSET)



Clinical outcome

85 vSETs in 74 patients to date

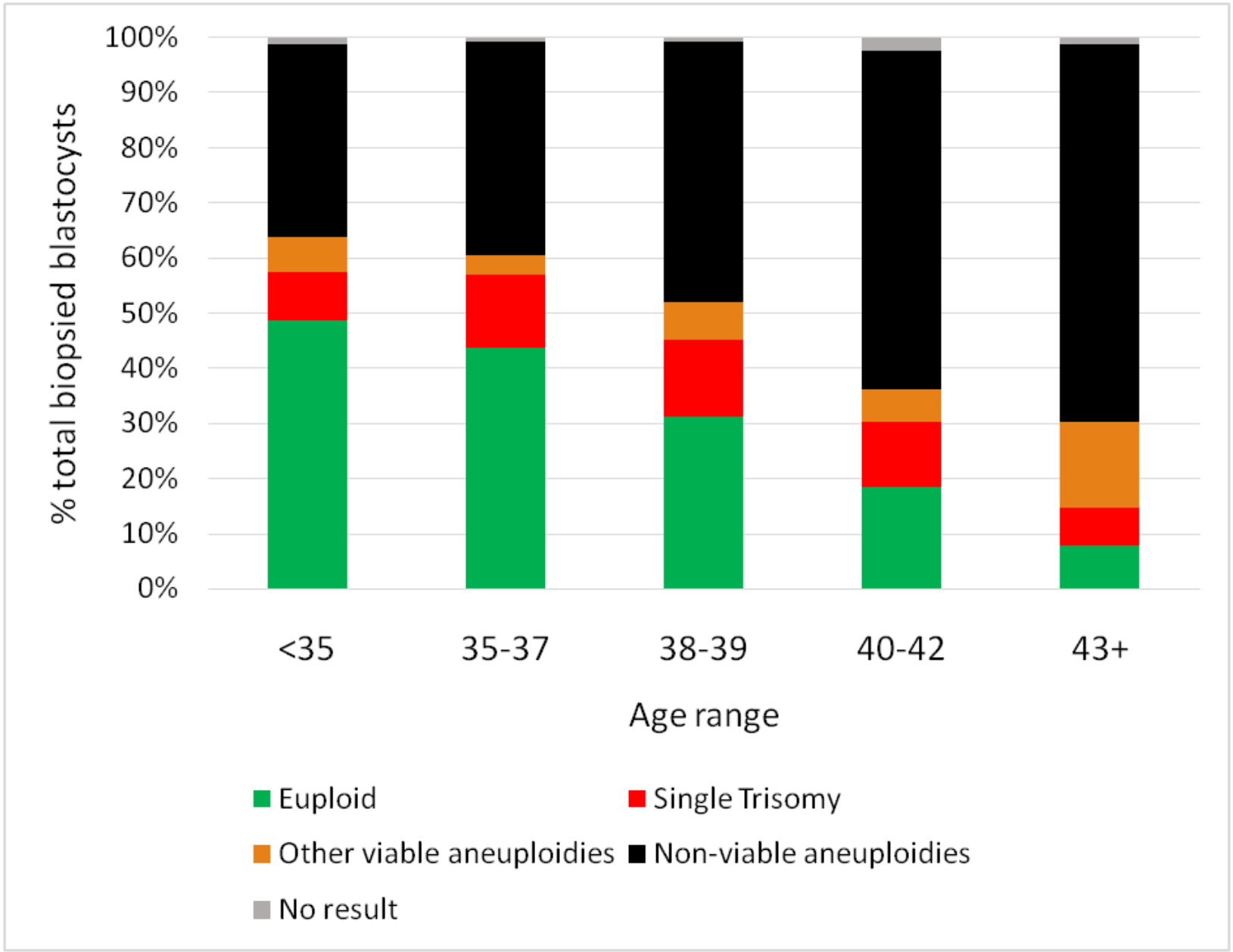
80% implantation rate per transfer

66% clinical pregnancy/delivery rate, all singletons

7 (8%) preclinical and 6 (7%) clinical losses

36/55 (65%) of pregnant/delivered patients have 126 (tested or untested) frozen blastocysts in storage

10/19 (53%) non-pregnant patients 19 frozen blastocysts and 15 patients have yet to have a transfers of 28 frozen blastocysts


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% total biopsied blastocysts
<35
35-37
38-39
40-42
43+
Age range
Euploid
Single Trisomy
Other viable aneuploidies
Non-viable aneuploidies
No result

Why is PGT-A important?

- Efficient embryo selection to facilitate single vitrified warmed blastocyst transfer and reduce redundant cycles and transfers
- Avoids the transfer of non-viable aneuploid embryos and reduces miscarriage rates
- Improved clinical management
- Promotes improved clinical and embryology standards

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