Genetic factor in abortion

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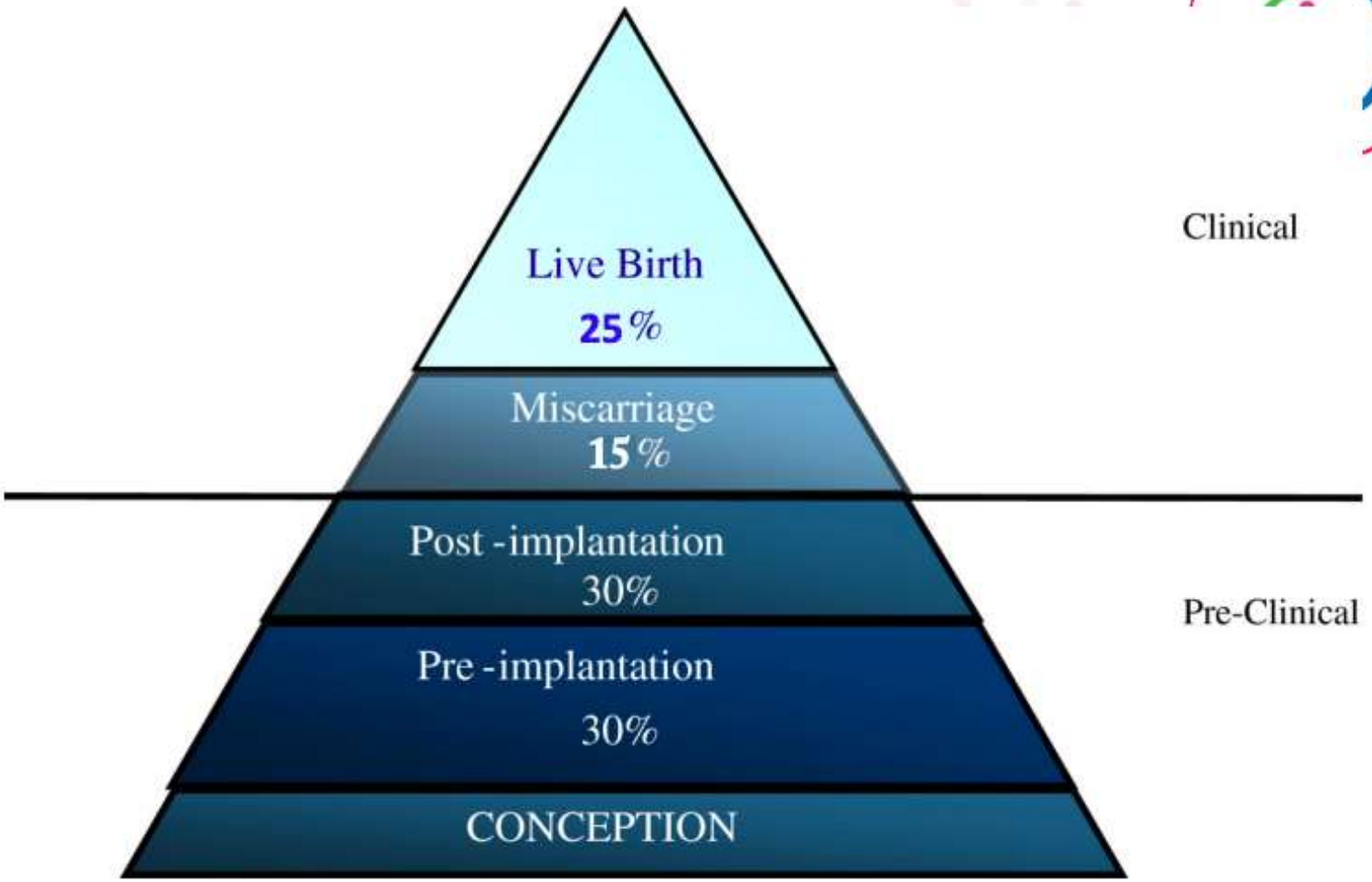
Chromosomal abnormality in abortion

- The first chromosomally abnormal abortion was reported in 1961.
- Chromosomal abnormality is approximately responsible for half of the clinically diagnosed abortions in the first trimester.
- About 50% of them are autosomal trisomy, 20% monosomy XO, 20% polyploidy and 10% variety of other abnormalities

The pregnancy loss iceberg

An overview of the outcome of spontaneous human conceptions



75% of embryos are lost before delivery

Most of those loses are in the period BEFORE implantation

There are two common types of abnormalities that occur in early pregnancy losses

Developmental

Genetic abnormalities

Most pregnancies that miscarry early are morphologically abnormal

chromosomal aberrations in miscarriage

- 50±60% of abortuses are chromosomally abnormal in women with two or more miscarriages
- 67.3% in women with two or more miscarriages.
- 29% in women with three or more miscarriages (mean 4.7).

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- As the number of miscarriages increases, the chance of a fetal chromosomal aberration decreases.

- Most chromosomal aberrations are chance recurrences. Additionally, the patient who loses a chromosomally abnormal fetus has a greater chance of a live birth than the patient losing a euploid embryo

FISH

- FISH used for PGT-A, following blastomere biopsy of cleavage stage embryos. However, a number of studies failed to show any benefit in the live birth rate, especially amongst older women
- almost half of the top-quality blastocysts are aneuploid

FISH

- the mosaic nature of cleavage stage embryos, in addition to the ability to only screen a limited number of chromosomes, contributed to the poor initial outcomes following PGT-A using FISH and thus the decline in implementation of this technique

Types of CCS

- array comparative genomic hybridisation (CGH)
- single nucleotide polymorphism (SNP) arrays
- quantitative polymerase chain reaction (qPCR)
- next-generation sequencing (NGS)

- CCS can also be undertaken on biopsies taken at different stages of embryo development, including day 1 zygote (polar bodies), day 3 cleavage-stage (1 or 2 blastomeres), or day 5 or 6 blastocyst stage embryos (3–10 trophectoderm cells).

Success of PGT-A

- Amongst studies whereby improved LBR with PGT-A are not recognised benefits
- the success of PGT-A was deemed to be age-dependent. This is exemplified by one study whereby improved rates with PGT-A were only observed in women above 35 years old.

effect of different chromosomal abnormalities in embryo development

- Only 20.2% of autosomal monosomies developed into blastocysts
- Trisomies also impaired embryo development; only 34.7% formed blastocysts.
- Most haploid embryos arrested before cavitation, and triploid and tetraploid embryos had lower rates of development to the blastocyst stage.
- the less severe aneuploidies may present as recurrent miscarriage.

It is against this background that assisted reproductive technologies (ARTs) have been used to treat recurrent miscarriage. The aim of physicians to allow childless couples to have children. There are two approaches:

- ✓ pre-gestational preimplantation diagnosis of known chromosomal aberrations (PGD) or screening for a variety of possible chromosomal aberrations (PGS)
- ✓ surrogacy

- PGS/PGD assumes that the embryo is abnormal, and the patient should receive a normal embryo.

Surrogacy assumes that the embryo is normal and that the maternal environment must be substituted.

- assessed the fetal karyotype in abortuses of patients with parental aberrations:
- 73% were euploid and 27% aneuploid.

Genetic techniques

- conventional karyotyping
- fluorescence in situ hybridization (FISH)
- array-CGH
- next generation sequencing (NGS), SNP arrays, whole genome screening (WGS) and whole exome screening (WES) have not yet been extensively investigated in genetic analysis of pregnancy tissue following pregnancy loss but may be useful in the near future

Chromosomal assessment

- Analysis by conventional karyotyping is limited by the failure of tissue culture and the fact that it does not distinguish between maternal contamination and a normal (euploid) female fetus
- FISH is limited as it only uses probes for certain chromosomes, and therefore does not necessarily detect the chromosomal cause of the miscarriage.
- Array CGH is a better technique, and currently preferred technique, looking at all chromosomes and avoiding the limitations associated with karyotype and FISH, but may identify clinically irrelevant findings

Recommendation

Genetic analysis of pregnancy tissue following pregnancy loss is not routinely recommended but it could be performed for explanatory purposes.

For genetic analysis of the pregnancy tissue following pregnancy loss, array-CGH is recommended based on a reduced maternal contamination effect.

array-CGH

- The preferred method of genetic analysis
- This is not limited by tissue culture failure or false negative results due to maternal cell contamination.

- Parental karyotyping can be recommended based on genetic history (for instance in case of the previous birth of a child with congenital abnormalities, offspring with unbalanced chromosome abnormalities in the family, or detection of a translocation in the pregnancy tissue). For other couples, the benefit of the test is limited as the chances of finding an abnormality are very low

Recommendations

Parental karyotyping could be carried out after individual assessment of risk for diagnostic purposes

For couples with a parental chromosome abnormality, about one third of pregnancy losses are caused by parental chromosome abnormality; the other losses are aneuploidies, unexplained or a contribution of another underlying factor might exist.

Male factors

KEY QUESTION: DOES THE QUALITY OF THE MALE GAMETES CONTRIBUTE TO RPL?

- Abortion has long been considered an issue stemming exclusively from female causes.
- If a man achieved a pregnancy, his gametes were deemed normal and any loss of the pregnancy was believed to be from female anomalies, ranging from genetic, endocrinologic or anatomical factors to autoimmune diseases.
- Although together, these factors only account for an estimated 50-60% of RPL, leaving 40-50% of RPL remaining unexplained. Possible male factors have not been satisfactorily addressed or taken into account in these numbers.

paternal age with spontaneous miscarriage during the first trimester of

- A meta-analysis investigating the association of advanced paternal age with spontaneous miscarriage during the first trimester of pregnancy showed that there is an increased risk for miscarriage for male age categories 30-34, 35-39 and 40-44 and this risk was higher for the ≥45 age category (du Fossé, et al., 2020).

DFI

- Sperm DNA damage is associated with advanced paternal age and caused by unhealthy lifestyles (such as smoking, obesity and excessive exercise). It is recommended that clinicians advise male partners of couples with RPL of these connections and suggest ways to prevent sperm DNA damage caused by unhealthy lifestyles.

- Evidence shows that lifestyle modifications of the male partner (cessation of smoking, a normal body weight, limited alcohol consumption, physical activity) could improve the clinical outcomes of couples experiencing RPL.

DFI

- Semen of men in the RPL had significantly reduced viability, normal morphology and total progressive sperm and a higher mean percentage of DNA damaged sperm
- A higher miscarriage rate in high -DNA fragmentation index (DFI) group compared to the low-DFI group
- male age and lifestyle risk factors
- HA selection by PICSI: less DNA damage , lower miscarriage

Role of maternal age in repair DFI

- In the case of fertilization, sperm DNA fragmentation can to some extent be repaired by the oocyte.
- However, with advancing age, the oocyte quality is deteriorating, together with its repair capacity .
- This supports the hypothesis that the impact of paternal age on miscarriage, mediated by an increased DFI, is more present in interaction with higher maternal age.

- Higher miscarriage rate in women beyond 35 years and partners with high sperm DFI, compared to couples with similarly high sperm DFI and younger women (Liang et al., 2019).

Male factor

It was concluded that in couples with RPL, male factors such as paternal age, sperm quality, occupational exposure, and lifestyle (smoking, alcohol consumption and soft drugs) should be assessed in addition to female factors

Advanced paternal age

- Advanced paternal age may also be linked to increased sperm aneuploidy
- It is suggested that due to continual spermatogenesis, the male gamete is less vulnerable to age-related non-disjunction aneuploidies than its female counterpart

Male factors

- markers of Y chromosomal deletions
- sperm aneuploidy
- chromatin integrity to DNA damage

Recommendations (updated 2022)

In couples with RPL, it is recommended to assess lifestyle factors in the male partner (paternal age, smoking, alcohol consumption, exercise pattern, and body weight).

Assessing sperm DNA fragmentation in couples with RPL could be considered for diagnostic purposes.

PGD vs PGS

- PGD describes a case group in which the indication for the investigation is “hereditary disease in future parents”, while PGS describes a case group that has “suspected genetic disorders at the level of gametes and embryos”.
- The terminology has recently been “officially” changed: PGD was changed to “structural rearrangement testing (PGT-S)" and “monogenetic

PGS and prevention of miscarriage:

- ✓ There is still risk of miscarriage 16-30% after PGS
- ✓ We can not completely avoid the miscarriages
- ✓PGS improve pregnancy rate in those patients
- ✓Combined with AMA there is a very small chance for euploid embryo and for deliver a healthy baby

Aneuploidy in the preimplantation stage

oocyte aneuploidies

- meiotic event
- There is a higher rate of aneuploidy in the oocyte, when compared with the rate of full aneuploidy in blastocyst and cleavage stages.
- lower chance for full aneuploid embryos to develop or the presence of some mechanisms that are involved in aneuploidy correction, which would change a full aneuploid embryo to a mosaic or fully corrected embryo.

Aneuploidy in the cleavage stage

- The majority of cell division abnormalities in the early embryo occur in the cleavage stage.
- High frequency of mosaicism and limited numbers of cells available for biopsy, it seems that there is inadequate scientific justification to perform preimplantation genetic screening (PGS) at the cleavage stage.

embryo self- correction.

The trophectoderm blastocyst biopsy: The aneuploidy rate can be around 70% in day 3 versus approximately 20%-50% in the blastocyst with significant degree of embryo self- correction.

mechanisms of aneuploidy correction

- Proposed mechanisms include the loss of an extra chromosome and gaining a copy of a missed chromosome.

Aneuploidy correction

- presence of some mechanisms that are involved in aneuploidy correction, which would change a full aneuploid embryo to a mosaic or fully corrected embryo.

- High frequency of genomic instability during the first cell divisions of the embryo, it seems that oocyte analysis is not a good stage to predict an embryo's genetic status.

Some aneuploid embryos might miss the chance for development to the blastocyst stage,

Self-correction of aneuploidies until the blastocyst stage

- Santos et al. have compared aneuploidy rates in days 4, 5 and 6 embryos.
- the increase in rate of relatively normal embryos (with more than 60% normal cells) was 6% for day 4, 37% for day 5, and 58% for day 6 .
- According to the authors, the reduction in percent of aneuploid cells resulted from increased death and a decreased division rate in aneuploid cells.

- Co-culture of these embryos with the endometrial layer might be effective in increasing the selfcorrection rate due to communications between the embryo and endometrial cells, such as exchange of growth factors
- Apoptotic pathways are activated during the blastocyst stage

Comparison of different stages for embryo biopsy

Blastocyst stage is more advantageous for PGD.

- aneuploidy correction in blastocyst stage
  So genetic evaluation in blastocyst stage improve LBR and decrease spontaneous abortion
- Advanced paternal age related to autosomal aneuploidy

As the number of miscarriages increases, the chance of a fetal chromosomal aberration decreases.

FISH: screen a limited number of chromosomes

CGH array at blastocyst stage is the best method for diagnosis the cause of abortion


Thanks for Your attention