Do Assisted Reproductive Technologies Implicate Epigenetic Risks?

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Introduction

Recent estimations suggest that 1 in 10 people of reproductive age are infertile. There is a high percentage of couples requesting the use of Assisted Reproductive Technology (ART). Although some risks due to the use of this technology have been described, ART are considered safe. However, there is some controversy about ART contribution to increased epigenetic risk in offspring. After commenting the genetic imprinting cycle and their relation with ART, epigenetic risks due to this technology will be revised.

Genetic imprinting

Imprinted genes has either a paternal or maternal expression *(figure 1)*. Errors in the imprinting marks can be responsible for human diseases such as Angelman Syndrome (AS) or Beckwith-Widemann Syndrome (BWS).

Genomic imprinting requires sex-specific marks in the genome which imply a resetting of these marks in every generation. The imprinting cycle *(figure 2)* consists in three phases:

- **Erasure**: takes place in the primordial germ cells (PGCs).
- **Establishment**: takes place during the germ cells development. Imprinting marks are acquired earlier in the development in male gametes than in females.
- **Maintenance**: during the early embryo development there is a general demethylation of the genome that does not affect imprinted genes.

ART and imprinting

The use of ART necessarily involves the acquisition and sometimes manipulation of gametes, zygotes or embryos during the time when imprinting takes place. The most discussed procedures used in ART as possible inductors of imprinting errors are:

- **Superovulation**: premature release of oocytes
- **In vitro maturation of oocytes**: abnormal environment for the gametes maturation
- **The use of suboptimal sperm**: immature imprinting marks
- **In vitro fertilization**: abnormal environment
- **ICSI**: stress due to the procedure
- **Embryo culture**: abnormal environment when general demethylation occurs

ART and human disease

Since 2002 several studies have been published describing an increased risk of AS and BWS after the use of ART, and especially after the use of IVF and ICSI.

Angelman Syndrome

Neurodevelopmental disorder
(1 in 16.000 births)

In a general population 5% of AS cases are due to imprinting errors

The 35'3% of ART-associated AS have aberrant imprinting.

Beckwith-Widemann Syndrome

Overgrowth disorder with
(1 in 13.700 births)

In a general population 50-60% of BWS cases are due to imprinting errors

The 58'7% of ART-associated BWS have aberrant imprinting

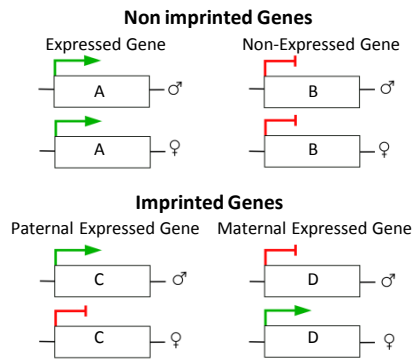

Figure 1. Non-imprinted genes are expressed from either both alleles (gene A) or none of them (gene B). Imprinted genes have a monoallelic expression, therefore they allow only the paternal allele (gene C) or the maternal allele (gene D) expression.

Adapted from: *Eroglu et al. Semin Reprod Med.* 2012;30:92-104

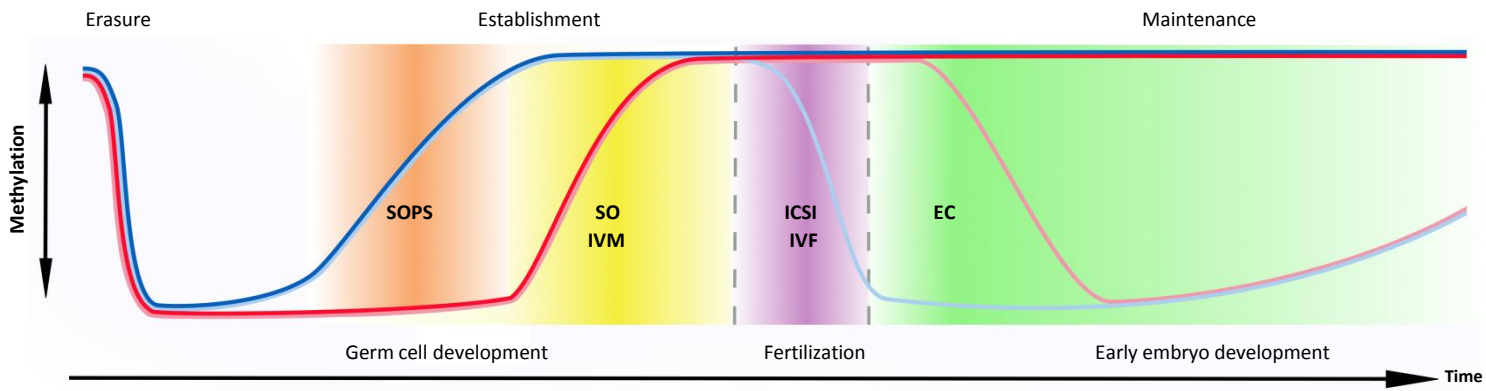

Figure 2. Methylation dynamics during germ cells development, fertilization and early embryo development. Methylation dynamics of paternal and maternal imprinted genes are shown by the dark blue and dark red lines respectively. Light blue and light red show the methylation dynamics of paternal and maternal non-imprinted genes respectively. The phases during development when ART procedures may induce imprinting errors are: SOPS =suboptimal sperm, SO = superovulation, IVM =in vitro maturation of oocytes, IVF = in vitro fertilization, ICSI =intracytoplasmic sperm injection, EC = embryo culture.

Adapted from: *Lucifero et al. Hum Reprod Update.* 2004;10:3-18

Conclusions

Considering the overlap between the majority of epigenetic reprogramming events during the gametogenesis or the embryonic development and the timing of ART, it is possible that suboptimal conditions in ART may induce imprinting errors. But, is there a real risk?

Yes, there are risks

There is an increased number of ART-associated imprinting disorders caused by aberrant imprinting

No, there are no risks

The recent cohort studies have failed to confirm the association between ART and imprinting disorders

MORE STUDIES ARE NEEDED

Glossary

ART: all treatments or procedures used for the purpose of achieving a pregnancy. ART includes, but it is not limited to, handling of human gametes or of embryos, in vitro fertilization, embryo transfer and gametes or embryo cryopreservation. ART does not include assisted insemination.

Infertility: a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.

Epigenetics: gene expression regulation based on changes in the chromatin structure that is not dependent on the DNA sequence and is inheritable.

Imprinted genes: genes that have a monoallelic expression due to an epigenetic regulation.

Selected Bibliography

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