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 have 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-Wiedemann 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 inducers 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 10,000 births)

- In a general population 5% of AS cases are due to imprinting errors
- The 35-38% of ART-associated AS have aberrant imprinting.

Beckwith-Wiedemann Syndrome
Overgrowth disorder
(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

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?

Selected Bibliography


