EPIGENETICS AND THE ASSISTED REPRODUCTIVE TECHNIQUES

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Introduction:

Several epidemiologic studies confirm that children conceived by Assisted Reproductive Technology have more genomic imprinting disorders than children conceived by spontaneous pregnancies.

In humans, there are two main hypothesis to explain this increase:

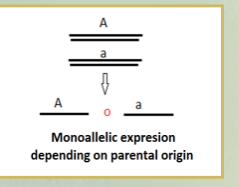
1- Due to the procedures of Reproductive Assisted Techniques (ART) by itself. Animal studies (mouse and cow) demonstrate this theory although human epidemiologic results are not too consistent to affirm it. There are three main disease related to ART: Beckwith-Widemann Syndrome, Angelman Syndrome and Prader-Willi Syndrome. [1]

2- Due to parental subfertily or infertily.

EPIGENETICS is the science referred to the modifications that does not affect at the DNA sequence of the individual *per se*, but to it's genetic expression. Those modifications are potentially heritable at the cellular level.

In human, the most important modifications are: DNA metilation and the Histone modifications. They are placed in approximately 60 gens in genome, called **IMPRINTED GENS** with the aim of assure it's monoallelic expression.

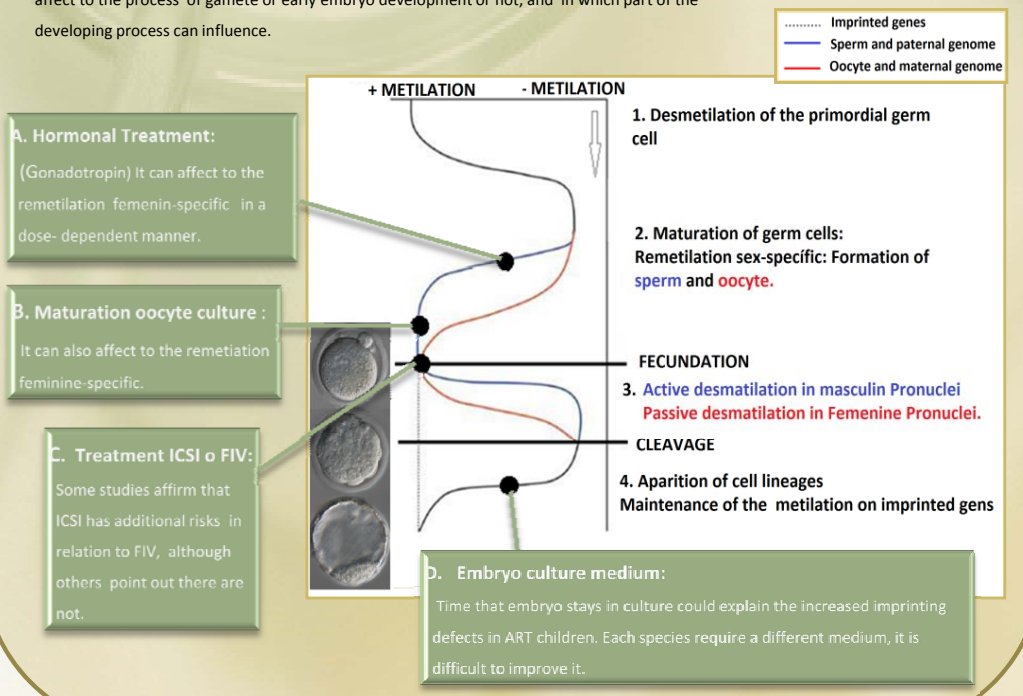
The phenomenon that allow the expression of one of the two alleles it is known as **GENETIC IMPRINTING.** [2]



Monoallelic expresion depending on parental origin

Possible effect of Assisted Reproductive Techniques (ART) to the natural epigenetic process of the gamete and early embryo development:

It has been analysed individually each technique that compose the Assisted Reproduction Technology, in order to see whether they can affect to the process of gamete or early embryo development or not, and in which part of the developing process can influence.



Epidemiologic results: Comparison between ART children and children conceived by natural pregnancies (No-ART):

Not all studies obtained the same results. Some of them, in order to dismiss problems associated to multiple birth, they made the comparison distinguishing two categories: Singleton births or multiple births (twins). [4]

- ART Singletons *versus* non-ART singleton have:
  - ↑ Risk of Birth defects (mainly urogenitals)
  - ↑ Neonatal intensive care needed
  - ↑ Low birth height (< 2500 g)
  - ↑ Risk of preterm birth (<37 weeks)
  - ↑ Risk of perinatal mortality
- ART Twins *versus* Non-ART twins have:
  - ↑ Risk of being delivered by caesarean section
  - ↑ Neonatal intensive care needed
- ART twins *versus* Singleton ART have:
  - ↑ Neonatal intensive care needed
  - ↑ Risk of poorer speech development

Conclusions:

- ❑ So far, studies have not been able to resolve if the increase of imprinting disorders observed in ART children is due to the techniques of ART by itself or maybe it is a consequence of parental sub/ infertility.
- ❑ There are important limitations on these studies: (size of the sample, short following time, bad accuracy in statistic studies and the ignorance of the possible genetic or epigenetic parental problem in each case.
- ❑ Epigenetic disorders are so rare that is very difficult to make a reliable database.
- ❑ There is a lack of knowledge in some epigenetic mechanisms.
- ❑ By extrapolating animal results, hormonal stimulation and embryo culture medium might be the main responsibles of the increased imprinting disorders in ART children.

References:
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3- Weaver J.R., Susiarjo M., Bartolomei M.S. Imprinting and epigenetic changes in the early embryo. Mamm Genome. 2009. 20: 532–543.
4- Davies M.J., Moore V.M., et al. Reproductive Technologies and the Risk of Birth Defects. N Engl J Med. 2012. 366, 1803-13.