EPIGENETICS AND THE ASSISTED REPRODUCTIVE TECHNIQUES

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-Wideman Syndrome, Angelman Syndrome and Prader-Willi Syndrome.
2. Due to parental subfertility or infertility.

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

In human, the most important modifications are: DNA methylation and the Histone modifications. They are placed in approximately 60 genes in genome, called IMPRINTED GENES 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.

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.

A. Hormonal Treatment: (Gonadotropins) It can affect to the remetilation femenine-specific in a dose-dependent manner.
B. Maturation oocyte culture: It can also affect to the remetilation femenine-specific.
C. Treatment ICSI o FIV: Some studies affirm that ICSI has additional risks in relation to FIV, although others point out there are not.

D. Embryo culture medium: Some papers affirm that culture stays in culture can explain the increased imprinting defects in ART children. Each species requires a different medium, it is difficult to improve it.

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).

- ART Singletons versus non-ART singleton have:
  - ↑ Risk of Birth defects (mainly urogenitalts)
  - ↑ Neonatal intensive care needed
  - ↑ Low birth height (< 2500 g)
  - ↑ Risk of perinatal mortality
- ART Twins versus Non-ART twins have:
  - ↑ Risk of being delivered by caesarean section
  - Neonatal intensive care needeed
- 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 subfertility.
- 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 responsible of the increased imprinting disorders in ART children.

References: