EFFECTS OF ASSISTED REPRODUCTIVE TECHNOLOGIES ON GAMETE AND EMBRYO EPIGENETICS AND POSTNATAL IMPRINTING DISEASES

BIBLIOGRAPHIC REVIEW

Bachelor's degree final project
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INTRODUCTION

1-4% of children born in developed countries come from assisted reproductive technologies (ART). Although the techniques used are safe, in the course of these there are critical steps that could alter the correct establishment of epigenetic marks in both gamete and embryos.

EPIGENETIC WAVES AND ASSISTED REPRODUCTIVE TECHNOLOGIES

1. **Gametogenesis wave:** erasure and parental allele-specific *de novo* DNA methylation. In male germline it finishes before birth while in female's oocytes, methylation will not be completed until fertilisation.
2. **Embryo wave:** retrotransposons and imprinted genes are protected from demethylation. In blastocyst stage, methylation will be again introduced to differentiate every tissue.

Two waves take place in parallel with performance of various ART procedures increasing the possibility of epigenetic errors and transmitting imprinting syndromes.

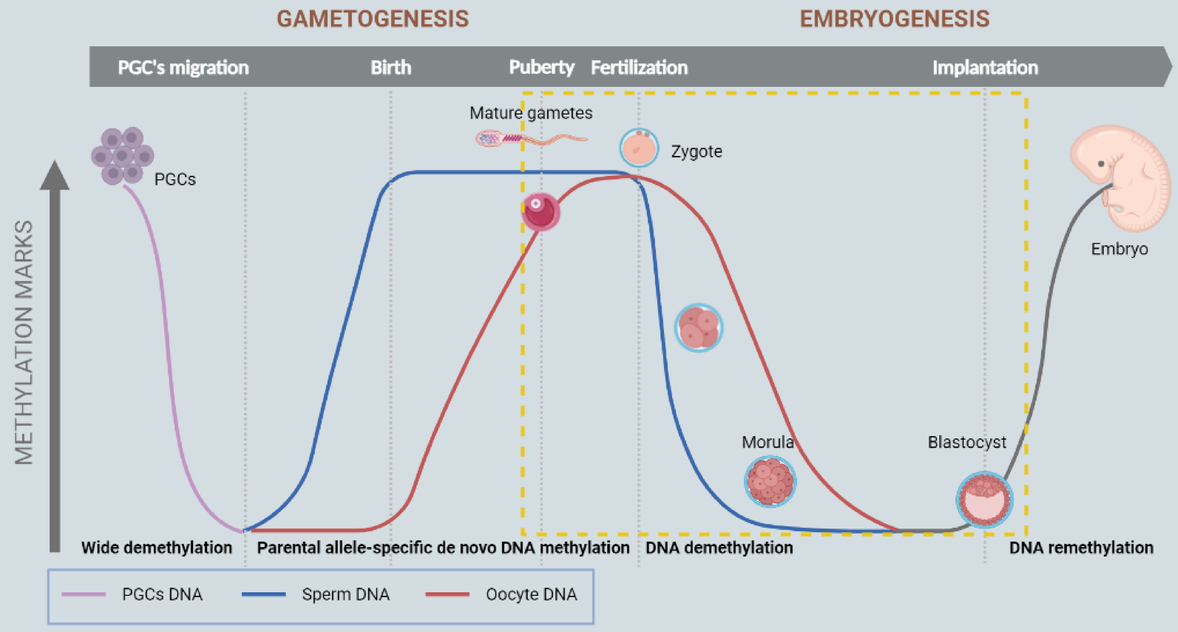

***Figure 1**: Variation in methylation levels during the processes of human gametogenesis and embryogenesis. Yellow square marks the ART actuation timing. Adapted from www.app.biorender.com template.*

OBJECTIVES AND METHODOLOGY

The main objective is to discover if there is a higher prevalence of epigenetic-based diseases in individuals conceived by ART and which are the most common illnesses related to this treatments. Also another objective is identify the most critical steps and techniques used.

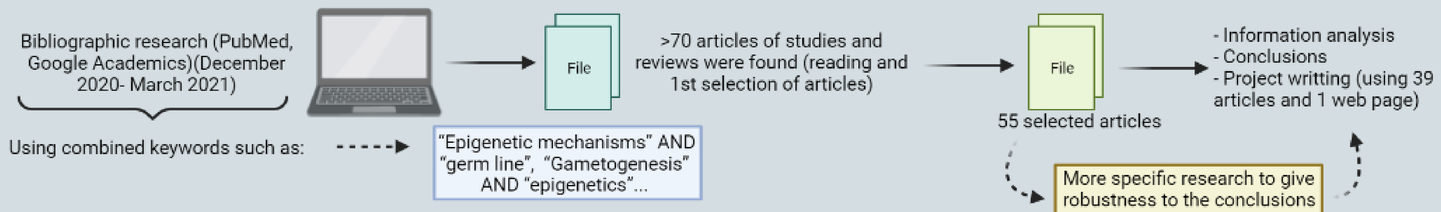

***Figure 2**: Summary of the methodology used in the final degree project.*

STATE OF THE ART AND RESULTS

More prevalence of **Silver-Russell syndrome** (SRS), **Beckwith-Widemann syndrome** (BWS) and **Angelman syndrome** (AS) caused by imprinting errors in ART's population has been detected.

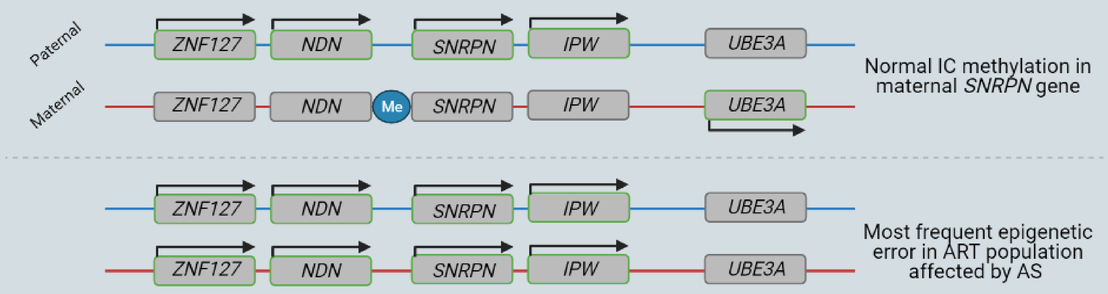

***Figure 3**: Scheme of normal methylated alleles and alleles with the most frequent imprinting errors that cause AS in the ART population. Adapted from Hitchins MP et al. 2003.*

Prader-Willi syndrome, retinoblastoma, maternal hypomethylation syndrome, transient neonatal diabetes mellitus and pseudohypoparathyroidism Type 1B have not been found to be over-represented in population born through ART, probably due to lack of studies or the rarity and low incidence of these diseases.

Nevertheless, some authors claim that there is a direct causal association between the ART and these pathologies.

***Table 1**: Incidence and molecular mechanisms of BWS, SRS and AS in general and ART population.*

Syndrome	General incidence	ART incidence	Molecular mechanisms in general population	Molecular mechanisms in ART population
BWS	1:13,000	x6 times higher	40-50% loss of methylation in maternal IC2	90% loss of methylation in maternal IC2
SRS	1:3,000-100,000	x6-12 times higher	33-67% loss of methylation in IC1	Hypomethylation of IC1
AS	1:15,000	Unknown	Maternal deletion or paternal uniparental disomy	71% loss of methylation of maternal *SNRPN*

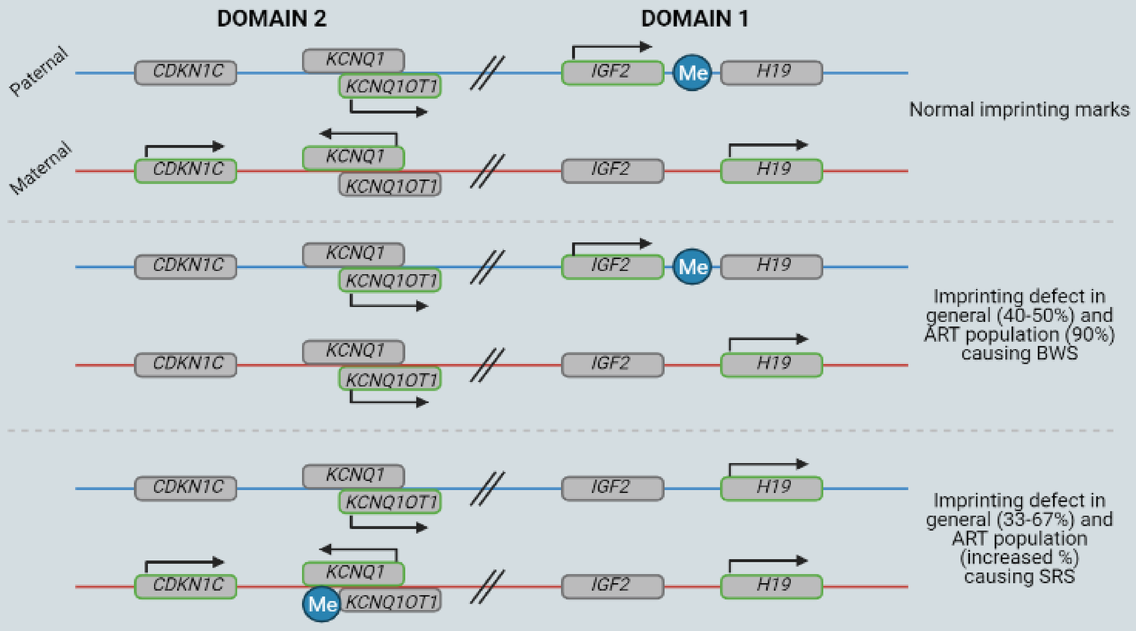

***Figure 4**: Scheme of normal methylated alleles and alleles with the most frequent imprinting errors caused by BWS and SRS in the ART population. Adapted from Weksberg R et al. 2010.*

▶ Techniques and conditions that may introduce epigenetic and imprinting errors:

- Controlled ovarian hyperstimulation (COH) / superovulation
- Embryo culture
- Infertility

▶ Techniques and conditions that are not shown to cause imprinting and epigenetic-based diseases:

- Use of immature sperm, advanced maternal age, oocyte in vitro maturation, In vitro fertilization and intracytoplasmic sperm injection, cryopreservation and vitrification.

CONCLUSIONS

A higher prevalence of imprinting diseases has been found in ART population.

↳ AS, BWS and SRS are more frequent in ART population than in general group.

Embryo culture, COH/superovulation and infertility

Nonetheless, these diseases and syndromes are really uncommon and the risk after ART is very low, so they are safe techniques for usance in humans.

LIMITATIONS

- Imprinting and epigenetic-based diseases are really uncommon and have low frequency.
- The number of participants in each study is small (small "*N*").
- There are fewer births thanks to ART than naturally conceived and large number of ART babies are not followed after conception.
- It is difficult to analyse the effect of each individual technique because some of them always go together. Also infertility is present in most cases producing an extra-effect.

More studies with a larger N and better follow-up of ART-born individuals are needed.

MAIN REFERENCES: **Amor Dj et al.** *Hum Reprod*. 2008;23(12):2826–34 // **Cui X et al.** *Exp Ther Med*. 2016;12(4):1973–9 // **Deangelis Amet al.** *Semin Reprod Med*. 2018;36(3–4):221–32 // **Hattori H et al.** *Clin Epigenetics*. 2019;11(1):1–12 // **Jacob S et al.** *Pediatr Res*. 2005;58(3):437–46 // **Kuhtz J et al.** *Epigenetics*. 2014;9(12):1648–58 // **La Rovere M et al.** *International Journal of Molecular Sciences*. 2019;20(17):4169 // **Laprise SL.** *Mol Reprod Dev*. 2009;76(11):1006–18 // **Marshall KI et al.** *Mol Reprod Dev*. 2018;85(2):90–105 //**Menezo Y et al.** *International Journal of Molecular Sciences*. 2019;20(6):1342 // **Osman E et al.** *Semin Reprod Med*. 2018;36(3–4) // **Uk A et al.** *Eur J Med Genet*. 2018 Sep 1;61(9):518–23.