Objective

Since the publication of Barker's hypothesis in 1992, the impact of the uterine environment on de novo epigenetic programming during early embryogenesis has been regarded as a critical mechanism linking nutritional and metabolic factors in utero with the development of complex diseases in offspring. A study conducted by DeBaun, M., et al. identified 7 ART children in the BWS Registry. Of them, 5 had been conceived via ICSI. Their methylation analyses are exquisitely relevant to the developmental outcomes of ART embryos. At the Washington University BWS registry, the frequency of ART was 4.7%. Relative to the general population, this presents an estimated six-fold increase of BWS in ART children. Although both were matured in the same medium, CAPS-PCR for ICSI and IVF mice embryos at 98.5% analyzed. Although both groups were matured in the same way, 18% of the loci reflected over a 5-fold change in expression level. Surprisingly, this indicates that in vitro fertilization is a process that induces major changes in the genome, even in the absence of fertilization. A different study found that hypermethylation of H19 gene has been linked to Silver-Russell syndrome, a condition characterized by growth retardation and asymmetry. Conversely, hypomethylation can induce BWS, an overgrowth syndrome. Approximately 40% of stillbirths recommended for ICSI have elevated amounts of DMRs in the offspring, implying sperm DNA hypermethylation can lead to adverse pregnancy outcomes. While the data suggest a link between ART and increased DNA methylation, more research is needed to understand the underlying mechanisms and develop targeted interventions.

Abstract

Material and methods

Two studies analyzed the congenital anomalies of specifically ICSI-derived embryos. Both were experimental studies that compared conventional IVF and ICSI. One study used KOSM as a model for the latter cultured embryos, while the other utilized DNA methylation patterns at various stages. Another analysis of the effects of ICSI on the methylation of loci H19, Peg3, and Sryn in mice. The former used HI. Studies of DNA methylation systems commonly used for in vitro maturation: Whitten's, KOSM, using amino acids (KOSMA), human tubal fluid (HTF), Global Medium, PFL-M2, and G15-12, or the latter currently being used at human clinics. For homone-treated groups of this study, ICSI was considered an ethical option. ICSI produced 6.2% UI human chorionic gonadotropin (EGC) was followed by 6.2% UI human chorionic gonadotropin (HCG). HCG were administered to female mice for two studies, which focused particularly on the effects of sperm DNA methylation of 5.5% of EGCG followed by 5.3% of HCG to two groups of mice, with one group afterwards subjected to ICSI and the other to natural mating. The frequency of disruptive LITZI and H229 methylation after ART leading to BWS was quantified in a final study that revealed differences between ICSI and IVF, or from ICSI. Lymphocytes or biopsy samples from 6 of 7 ART children were then epigenetically analyzed at LITZI and H19.

Results

Hypomethylation of H19 has been linked to Silver-Russel syndrome, a condition characterized by growth retardation and asymmetry. Conversely, hypermethylation can induce BWS, an overgrowth syndrome. Approximately 40% of stillbirths recommended for ICSI have elevated amounts of DMRs in the offspring, implying sperm DNA hypermethylation can lead to adverse pregnancy outcomes. While the data suggest a link between ART and increased DNA methylation, more research is needed to understand the underlying mechanisms and develop targeted interventions.

Discussion

The generation of data and images presented by the various studies of this research was made possible by the support of the Society for Maternal-Fetal Medicine and the Genetics and Ultrasound Foundation. Of one such includes bisulfite sequencing, which isolates the methylated cytosine of DNA. Visual detection was made possible by immunofluorescence staining and gel electrophoresis. From its association with ART, the information provided here lends insight to the extreme plasticity of fetal epigenetic programming, a potential vessel for development of predispositions to disease and abnormalities. Understanding this mechanism gives a different lens to epigenome and disease prevention.

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References