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Imprinting methylation and assisted reproductive technology

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Assisted reproductive technology (ART) is an important treatment for infertile people of reproductive age and is also known as fertility treatment. The processes of ART involves the isolation, handling and culture of early embryos, which may result in alterations in genomic methylation at specific loci and influence the proper establishment and maintenance of genomic imprints. Recent studies have identified an increased incidence of imprinting disorders via ART. In this article, we reviewed that the ART may be prone to induction of imprinting methylation errors during embryonic development. Further studies are necessary to elucidate the safety of ART in this field.

Key words: imprinting; methylation; assisted reproductive technology (ART); disoder; epigenetics

In the past decades, the efficiency of human assisted reproductive technology (ART) has improved. We have witnessed important new developments such as vitrification, ovulation stimulation, *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), oocyte *in vitro* maturation (IVM), gamete/embryo cryopreservation blastocyst culture and methods for genetic analysis of human embryos. These are important treatments for infertile people of reproductive age and increasingly produce children. ART has been responsible for the birth of 5 million infants worldwide[1], while debates on their safety have been generated. Changes in DNA methylation and the frequency of imprinting disorders have been linked

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with ART. Recent studies have identified an increased incidence of imprinting disorders via ART, including cases of Beckwith-Wiedemann syndrome (BWS, NIM130650), Angelman syndrome (AS, NIM105830) and Silver-Russell syndrome (SRS, OMIN 180860)[2].

The processes of ART involves the isolation, handling and culture of early embryos, exposing the developing epigenome to many external stresses[3], which may result in alterations in genomic methylation at specific loci and influence the proper establishment and maintenance of genomic imprints[4].

Epigenetic modifications include DNA methylation, remodelling of nucleosomes, higher-order chromatin reorganization, histone modification, and regulation by noncoding RNAs[5]. DNA methylation is the most commonly studied epigenetic process in relation to imprinting syndromes[6].

Genomic imprinting is an epigenetic process that silences one parental allele, resulting in monoallelic expression[7]. Imprinted genes play an important role in mammalian fetal growth and development. Evidence has emerged showing that genes that are paternally expressed promote fetal growth, whereas maternally expressed genes suppress growth. Early investigations suggested that children born as a result of ART had higher risk of diseases with epigenetic aetiologies including imprinting disorders caused by a lack of maternal methylation at imprinting control elements. Aberrant expression of some imprinted genes has been linked to a number of human diseases, developmental abnormalities and malignant tumors[8].

DNA methylation and genomic imprinting

The field of epigenetics encompasses the study of heritable changes in gene expression that occur without a change in the DNA sequence. The epigenetic modifications that are imposed during gametogenesis act as primary imprint markers to distinguish the maternal and paternal alleles[9]. The most likely candidate for the gamete mark is DNA methylation. DNA methylation is an epigenetic regulator of gene expression and acts as an important molecular mark underlying the parental-specific expression of genes subject to genomic imprinting. It has been observed in the vicinity of most imprinted genes. In some instances, the methylation is present on the inactive gene, suggesting a role for DNA methylation in silencing of the gene[10].

Genomic imprinting, the allele-specific expression of certain genes, accounts for the requirement for both paternal and maternal genomes in normal development and plays an important role in regulating embryonic growth[11]. It is a gamete-specific modification that causes differential expression of the two parental alleles. The erasure establishment and maintenance of imprints are dynamic process that must be correctly reprogrammed with every reproductive cycle. DNA cytosine methylation (methyltransferase) regulates imprinted gene expression. Differentially methylated regions (DMRs) are commonly associated with