Epigenetic concerns in assisted reproduction: update and critical review of the current literature

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More than 4 million children have been born through the use of human in vitro fertilization (IVF), a technology that emerged only 35 years ago and is still dynamically evolving. Despite its very good initial safety profile, reports of increased prevalence of human perinatal problems and evidence obtained from animal experiments raise concerns that the occurrence of epigenetic anomalies might be increased as a result of infertility etiologies, ovarian stimulation, and extracorporeal handling and culture of gametes and embryos. This issue's Views and Reviews section aims to describe the basic mechanisms of epigenetics and to summarize the current knowledge obtained from animal experiments and human IVF practice, to shed light on the possible association between epigenetic disturbances and assisted reproduction technologies. (Fertil Steril® 2013;99:605–6. ©2013 by American Society for Reproductive Medicine.)

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Epigenetic mechanisms govern development and regulate gene expression in diverse cell types of the organism, which otherwise carry the same genomic DNA sequence. Metaphorically, the nucleotides of the DNA sequence are the letters of a complex text, and the epigenetic labels are the spaces, punctuation, sentences, paragraphs, and style that make the sequence a meaningful text (1). The major types of epigenetic markers that control gene expression are DNA methylation at CpG dinucleotides, covalent modifications of histone proteins, and noncoding RNAs (2, 3). They are established, read, and erased by specific protein complexes, which control each cell's transcriptional machinery to maintain mitotically heritable differences in gene expression potential without altering the DNA sequence. The process of imprinting, stable allele labeling according to parental origin to assure correct monoallelic expression, occurs during gametogenesis in specific domains (4). Such epigenetic mechanisms are subject to environmental and developmental influences (5, 6). Gametogenesis and early embryonic development are events of major global epigenetic alterations, so when they are impaired, altered, or performed in vitro, the accompanying epigenetic processes might be easily disturbed. The nature, extent, and significance of these changes and their relevance to human assisted reproduction technologies (ART) are the focus of this section.

To the extent of present knowledge, the performance of human ART is not associated with a clear increase of epigenetic disorders in the resultant embryos and children. Such epigenetic changes are more frequent than DNA mutations, but their contribution to human phenotypic variation and disease states is currently not entirely understood. The rarity of frank imprinting disorders (such as Prader-Willi and Angelman syndromes), and the late expression of milder conditions associated with epigenetic disturbances (such as obesity and type II diabetes) make the association with ART difficult to prove. The only exception to this is the higher prevalence of the Beckwith-Wiedemann syndrome in children born after ART (7), but even in this case the etiology is more likely to be the parental background of infertility rather than the procedure (8, 9).

However, animal studies indicate that there may be differences in the methylation patterns of various genes as a consequence of ART process and/or the etiology of infertility (10). In quite a few models, superovulation and in vitro culture of oocytes were shown to effect the epigenome of the derived embryos/offspring (11). On the other hand, epimutations in sperm may be largely associated with impaired male subfertility (12). In animal models, the in vitro embryo culture conditions also have an

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established epigenetic effect on the cultured embryos (13, 14). Although significantly improved since human IVF was first performed, it is difficult to assume that even the current standardized optimized culture conditions mimic the endogenous environment perfectly.

Currently, it is difficult to assess the existence of an association between human ART and epigenetic disturbances. It is also currently impossible to determine the relative contribution of preexisting biology to epigenetic disturbances versus that added by ART. All these considerations must be taken into account when contemplating infertility treatments. In this section of Views and Reviews, the currently available animal and human data are thoroughly and critically reviewed by the leading authors of the field. The basic principles and concepts of epigenetics are presented in a lucid manner to facilitate the discussion of the more complex topics. The evidence contemplating epigentic disturbances with (in vivo) gametogenesis in the clinical setup (ovulation induction and abnormal spermatogenesis) is presented, as well as the impact of in vitro culture on the epigenome of gametes and embryos, and the relevance to human ART is discussed. Although no significant association between epigenetic anomalies and human ART can be presently established, the summation of this evidence warrants future caution and continued observation.

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