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Reproductive genetics at a crossroads: the challenges posed by hominid pregnancy loss

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"It seems evident that most of "humanity" dies before, not after birth and that perhaps only one-third survive from earliest beginnings until birth or the end of the first year of life. As many as 50% of all human ova may have a chromosome abnormality with over 99% mortality, making this type of genetic defect not just the commonest cause of death prenatally and the cause of a substantial proportion of the malformations of abortuses and fetuses, but the commonest cause of death in humans altogether."

Opitz, The Farber Lecture, 1987

Few would argue that one of the most common statements in the reproductive medicine literature is that of the association between chromosomal abnormalities and pregnancy loss. The words of John Opitz noted above, and the foundational awareness he and others have fostered over the years, continues to underscore the frailties and failures of hominid reproduction.

Medical genetics broadly, and reproductive genetics in particular, have evolved to now embrace a spectrum of subdisciplines spanning the fields of molecular genetics, genomics, and epigenetics. And the advances being made to better understand the root causes of infertility have now identified an array of candidate genes suspected of acting at many levels of the hypothalamic-pituitary-gonadal axis making attempts to tease apart the complex relationships between genes and the environment among the most pressing challenges of the day for reproductive medicine (1). Many intractable aspects of gamete and embryo quality have accordingly been mapped to specific mutations with immediate clinical relevance that may or may not be resolvable with available technologies (2).

Despite these concrete measures of progress in the larger domain of genetic determinants of human reproduction, reproductive medicine has retained and expanded upon many well-documented features of early development that for the well-informed practitioners of human ARTs was founded on those very principles Opitz first drew our attention to so many years ago (3). Moreover, the stark reality that perhaps the human zygote is the unfortunate beneficiary of the lax and error-prone behaviors typical of the human oocyte spindle, proceeding through meiotic progression would then be construed as a bad habit "inherited" by the zygotic mitotic spindles as evidenced by ongoing studies on mosaicism (4). Such "bad behavior" underlies much of the genetic testing debate of recent years yielding a level of chaotic discourse that might only be paralleled by the widely supported claims of cell division chaos manifest in the cleavage stage human zygote suggested by some to be a trigger for selective elimination in the spirit of theories like self-correction to make resultant blastocysts pseudo-homogeneously euploid and therefore high on the list of transferrable embryos with the greatest developmental potential (5).

While to many with business interests in the PGT arena ensconced in the belief that such testing truly adds benefits to clinical outcomes, the deep and dark reality of chromosome instability in the human embryo, mirroring in so many ways that of cancer progression, is that it stands as a prominent feature of our earliest beginnings in the hominid life cycle commanding attention by all stakeholders who seek assistance to start a family (6).

Thus, while reproductive genetics continues to make headway in identifying gene-environment interactions as core attributes to the moving target that is human reproduction, maybe it is time for our discipline to take a deeper dive into the phenomena of genetic mosaicism that is both inclusive of, and capable of contextualizing, something a bit more than what chromosomes alone can tell us (7).

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