Mono-pronuclear zygotes: a possible manifestation of androgenetic monospermic hydatidiform moles

To the best of our knowledge, the study by Zhou et al. (1) describes the first known case of an androgenetic monospermic hydatidiform mole (HM) resulting from a mono-pronuclear zygote following in vitro fertilization. This embryo subsequently developed into a "fair" blastocyst and was found to be euploid by preimplantation genetic testing for aneuploidy (PGT-A) and, after the transfer, led to the formation of an androgenetic monospermic HM. This case provides an interesting new perspective on how androgenetic monospermic HMs may manifest during assisted reproductive technologies (ARTs). In addition, it questions the traditional paradigm that mono-pronuclear zygotes ultimately arise as a consequence of haploid parthenogenetic activation or asynchronous pronuclear formation. Moreover, this fascinating report by Zhou et al. (1) also indicates that diploid androgenetic monospermic zygotes are capable of initiating embryonic development and are capable of producing morphologically normal blastocysts.

Since the initial discovery of androgenetic monospermic HMs in 1977, each of the proposed mechanisms for mole formation has remained hypothetical. The leading theory hypothesizes that a haploid spermatozoon fertilizes an oocyte that has lost its nuclear deoxyribonucleic acid (referred to as an "empty" oocyte). After fertilization, the paternal genome endoduplicates to reconstitute diploidy and facilitates continued embryo development. However, since the maternal and paternal genomes have different roles during development, these androgenetic diploid embryos yield the molar phenotype. However, this theory has remained hypothetical because "empty" oocytes are not a common observation in ART and an individual who produces only "empty" oocytes has not been reported. Although this may be partially due to the fact that after the germinal vesicle breakdown and before pronuclear formation, it is difficult to visualize the oocyte genome without fixation and immunofluorescence, the identification of these mono-pronuclear zygotes may instead demonstrate an alternative manifestation of the hypothesized "empty" oocyte.

Inspired by this study, we reviewed the occurrence of mono-pronuclear zygotes and their chromatin constitution in the literature (Supplementary Table 1). These data altogether indicate that mono-pronuclear zygotes are not uncommon in ART, accounting for approximately 5%–7% of all zygotes. Intriguingly, the frequency of mono-pronuclear zygotes in mice, approximately 6.6%, is extremely similar to that observed in humans (2). The examination of the available data highlighting the genetic constitution of human mono-pronuclear zygotes indicates that these cells are capable of initiating embryonic development and lead to the production of haploid, diploid, and/or mosaic embryos (3). As an example, the analysis of 176 cleavage-stage embryos derived from mono-pronuclear zygotes identified an eight-cell embryo with two Y-specific and two 18-specific signals (determined via fluorescence in situ hybridization), indicative of the penetration of an "empty" oocyte by a diploid spermatozoon or haploid spermatozoon with subsequent diploidization (3). In another report, investigators used H3K9me3, an antibody that stains only maternal chromatin, to determine the parental origin of the chromosomes and found that a fair proportion of zygotes (4.4%–24.4%) exhibited staining in the polar bodies but not in the pronucleus (2). These data suggest that these zygotes also contained only paternal chromatin and similarly may have arisen as a consequence of fertilization of an empty oocyte by a single spermatozoon that endoduplicated (2). The molar pregnancy reported by Zhou et al. (1) also appears to be another example of androgenetic zygote formation. In our work, we also have confirmed the production of androgenetic zygotes, this time, in mice. In this regard, using the *Mei1* knockout mouse model, we showed that meiotic abnormalities may produce oocytes capable of extruding their chromosomes into the first polar body (8% of the total). In addition, we demonstrated that 5% of *Mei1*$^{-/-}$ oocytes produce androgenetic zygotes (4). Despite their low frequency, which accords with the scarcity of recurrent androgenetic moles, the *Mei1*$^{-/-}$ mouse provides the first plausible model to begin to dissect the mechanism(s) responsible for "empty" oocyte formation.

Another significant point highlighted by Zhou et al. (1) is the limitation of PGT-A. Since PGT-A is entirely based on copy number, it consequently does not provide details on the parental origin of an embryo's nuclear material. Thus, to know the precise fraction of mono-pronuclear zygotes suitable for transfer, their ploidy and parental origin must be determined. If euploidy and biparental inheritance are established, mono-pronuclear embryos could provide a source of clinically useful embryos for patients where no other option is available. However, if both these criteria are not met, these embryos should not be used since they may lead to androgenetic HMs or other nonviable conceptions. This consideration is especially prudent given that the frequency of moles is higher in ART (0.3%–0.5% after in vitro fertilization/intracytoplasmic sperm injection) than in spontaneous conceptions (0.08%) (5). Finally, when replacing blastocysts derived from mono-pronuclear zygotes does occur, stringent monitoring of conceptions arising from such embryos must be maintained to continue to avoid molar pregnancies and their possible neoplastic complications.

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