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COMMENTARY

Monozygotic twinning in the IVF era: is it time to change existing concepts?

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Monozygotic twinning (MZT) is a rare phenomenon among humans. Its incidence after natural conception is about 0.4% of births [1, 2]. However, there seems to be an increased rate of MZT following assisted reproduction technology procedures. In 1984 [3], the first case of MZT associated with IVF was reported. Soon after, Edwards and colleagues called attention to the fact that the conditions of embryonic growth in vitro might influence the incidence of identical twinning [4]. However, this opinion was not in agreement with the observation that artificial induction of ovulation, per se, without IVF treatment, increased the MZT rate [1]. The initial observations on a series of cases of monozygosity in IVF cycles led authors to suggest a link between the physical condition of the zona pellucida, hatching, and the generation of identical twins [5]. The advent of prolonged culture conditions [6] allowed the evaluation of embryo development and the selection of the "best" embryo for transfer at the blastocyst stage. This approach should decrease the number of multiple gestations resulting from the transfer of multiple cleavage stage embryos. However, the emergence of an increased rate of monozygosity after blastocyst transfers was soon associated with the extended culture protocols [7]. Several other publications followed [2, 8–20]. The reported rate of MZT associated with IVF treatment and blastocyst transfer can be as high as 5 and 6% [14]. Our group experienced the case of a quintuplet gestation, after the transfer of two blastocysts [19].

The common observation among cases described in the literature of monozygosity associated with IVF treatment is the occurrence of more gestational sacs than embryos transferred, particularly with blastocyst transfers. The reason for the appearance of MZT after ART procedures is not clear. Our group suggested that the two blastocysts underwent two different splitting processes, possibly caused by zona pellucida manipulation during ICSI. The splitting should have occurred at a similar time between the two embryos, giving rise to MZ dichorionic twins and MZ monochorionic triplets. However, other authors do not agree with this hypothesis [11, 21]. Cassuto and colleagues [21] claim that exogenous factors and culture conditions may alter preimplantation embryo function. In their study, the incidence of MZT was low (around 0.4%) regardless of the culture time, prolonged culture, or day-3 transfers, and there was no difference between IVF and ICSI. However, when there was a change in methodology and an additional medium was used for 48 h in the prolonged culture protocol, the prolonged culture time increased MZT for both ICSI and IVF patients, to a threshold of 5%, more than ten times higher than their original MZT rate using the standard protocol. Thus, it seems reasonable to suggest that prolonged culture conditions did not increase the incidence of MZT, but unfavorable, suboptimal culture conditions could influence the appearance of monozygosity.

In addition to the unclear origin of monozygosity associated with human IVF, the intriguing aspect of MZT in assisted reproduction cycles is the fact that it challenges established concepts. According to the academic literature, MZ dichorionic diamniotic (DD) twins are generated after splitting of an embryo at the two-to-four cell stage, that is, before blastomeres have differentiated into two distinct cell populations, inner cell mass and trophectoderm. However, the observation of a human cleavage stage embryo splitting in half has never been documented in more than 30 years of ART procedures [20, 22]. As Dr. Kyono wisely points out in his article [20], "One possible reason for the common belief that embryo splitting occurs in the two-cell stage is that it is widely known that we can produce monozygotic DD twins by splitting an embryo artificially at the two-cell stage. This manipulation produced monozygotic DD twins in sheep [23], cows [24], and mice [25]."

The present JARG issue brings the detailed analysis by Sundaram and colleagues of four cases of monozygotic DD

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twinning generated after the transfer of a single blastocyst in downregulated, controlled FET cycles (excluding the possibility of concomitant spontaneous pregnancy). This study provides further support for the notion that human blastocysts might cleave spontaneously into two viable blastocysts, a phenomenon that would result in a MZDD twin pregnancy. Based on their own experience and a careful literature review that identified an additional eight cases in which a single embryo transfer resulted in monozygotic multichorionic multiples, the authors propose a re-evaluation of the existing monozygozitic twinning theory to contemplate the observed multichorionic gestations occurring after the advent of IVF treatment. In view of the literature evidence and the present report by Sundaran and colleagues, we believe that there is need to reconsider current concepts on the origins of monozygotic twins especially in the context of ART practices such as extended culture. Moreover, it is important to mention that with the increased utilization of blastocyst transfer (eSET, dSET), the associated risk for monozygosity should not be ignored in face of the possible adverse health outcomes for newborns and mothers alike.

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