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LETTER TO EDITOR

Effect of A23187 ionophore treatment on human blastocyst development—a sibling oocyte study

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To the Editor,

Maintenance of calcium homeostasis within the oocyte and associated embryo is a key physiological function in normal preimplantation development. Any deficiency in available Ca^{2+} levels, which cannot be compensated by the cells, could automatically affect Ca^{2+}-dependent processes, such as oocyte activation and mitosis. While bringing up calcium artificially by means of ionophores to restore fertilization (which is known as artificial oocyte activation [AOA]) is a common technique in IVF laboratories, evidence to use the same chemical compound to overcome associated downstream problems, such as mitotic inactivity or arrest, is rather new [1]. Impaired mitotic activity can manifest in several ways, such as developmental delay, including reduced blastocyst formation at a given time or arrest, which are generally summarized under the category "developmental problems."

As little is known about how to rescue such cycles, the recent well-designed study by Mateizel et al. [2] is of importance. These authors tested the effectiveness of a ready-to-use ionophore (calcimycin) in improving the utilization rate in a patient cohort with a history of transfer cancelation or less promising transfers due to suboptimal embryo quality. In this sibling oocyte study [2], no significant difference in the ability of embryos to reach good quality on day 5 was observed between the ionophore-treated and untreated groups, which led them to conclude that the ready-to-use ionophore is not helpful in cases with embryo developmental problems.

However, this conclusion appears premature and is worthy of discussion. According to their material and method section, Mateizel et al. [2] exclusively included patients who had presented embryos of moderate-to-poor quality in a previous cycle. Additionally, they have powered their study to detect a 15% increase in utilization rate, a key performance indicator that per definition is based on good embryo quality. Moreover, the rather rough classification of embryo grades, for example, attributing a 4-cell embryo without fragments on day 3, the same potential as a 10-cell embryo with 25% of fragments, indicates that the plain morphological appearance is weighted over the rate of mitosis. However, there is no evidence in the literature suggesting that ionophore usage might improve embryo quality, although it is said to increase the cleavage rate and result in a stage-appropriate cell number [1, 3]. Therefore, it may be assumed that a certain proportion of patients in the recent publication [2] was not the classical patients showing "developmental problems" and would not have been first candidates for ionophore treatment a priori. This theory is supported by the fact that remarkable rates of excellent/good quality day 3 embryos (70.3%) and blastocyst formation (38.3%) were observed even without supporting Ca^{2+} balance in the current study [2].

Irrespective of this obvious conceptual confusion within embryologists, it is obvious that not all patients lumped together under the term "developmental problems" will benefit from a 15-min ionophore treatment at first instance [1, 2, 4]. In our clinic, it is common practice [5] that patients with developmental problems in whom a single ionophore stimulus failed to improve the outcome were transferred to a double ionophore application regimen (two ionophore stimuli separated by 30 min). Promising results in terms of blastocyst formation and pregnancy outcome [5] support the idea of personalized responsiveness to artificial Ca2 + recruitment, meaning that some patients might need different stimuli or more potential stimuli than others [6]. Therefore, a more powerful ready-to-use ionomycin [7] could serve as an important component in treating patients with obvious developmental problems. Alternatively, one could consider the timing of ionophore application in patients with "developmental problems." It is questionable whether providing

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calcium as early as oocyte activation is tolerable, particularly since the fertilization rate is not affected in this subgroup of patients. There is indeed evidence that later ionophore application up to 44 h following ICSI [8] would be a feasible and probably more physiological option.

However, as long as good-quality evidence from prospective RCTs is missing, clinical embryologists must carefully determine whether to use ionophores. Particularly in patients with less specified indications, such as "developmental problems," there is a considerable risk of overtreatment.

Declarations

Conflict of interest T.E. is a consultant for Gynemed and has received payment for expert testimony outside the submitted work. O.S. has no conflicts.

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