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Perspective

# The Safety and Effectiveness of Artificial Oocyte Activation

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## DESCRIPTION

Artificial oocyte activation is an intervention aimed at increasing the intracellular calcium ion levels of oocytes after sperm-oocyte fusion, which has been proven to improve clinical outcomes in patients with Oocyte Activation Deficiency (OAD). However, due to safety and efficacy concerns, Artificial Oocyte Activation (AOA) is not currently recommended as a routine technique for enhancing clinical outcomes but may be beneficial for specific patients with explicit indications.

Artificial oocyte activation is an intervention aimed at elevating the intracellular calcium ion levels of oocytes following spermatozoon-oocyte fusion. It can mitigate the fertilization failure problems resulting from oocyte activation deficiency.

Intracellular calcium oscillations are a crucial event in oocyte activation [1]. The majority of oocyte activation failures result from insufficient intracellular calcium oscillations, as the rise of calcium ions is necessary for oocytes to enter anaphase and complete meiosis. AOA can simulate intracellular calcium oscillations through mechanical stimuli, electrical pulses, and chemical stimuli. Therefore, it can improve the fertilization rate and even clinical outcomes in patients diagnosed with OAD [2-4].

However, why is AOA still not a routine practice in Assisted Reproductive Technology (ART)? It is due to safety concerns. Although there are many methods of AOA, calcium ionophores such as ionomycin and A23187 are the most well-known and commonly used [5,6]. Nevertheless, the calcium ion increase caused by ionomycin and A23187 is still different from that during physiological fertilization. These calcium ionophores cause a single increase in calcium ions, but physiological fertilization involves repeated calcium oscillations. In addition, achieving a precise match between artificial calcium ion release and physiological levels is challenging. Deviations from the optimal range of calcium ion concentration may lead to distinct gene expression patterns [7]. Therefore, the use of AOA carries potential risks.

Strontium chloride has been demonstrated to induce calcium oscillations and oocyte activation in mouse models [8]. However, the use of strontium chloride for clinical AOA remains controversial as its ability to cause calcium oscillations in human oocytes is still under debate [9]. Even if it does induce calcium oscillations in human oocytes, the resulting model may differ from physiological conditions. Therefore, the use of strontium chloride for AOA also carries potential risks.

Some previous studies have indicated that AOA may result in epigenetic defects [10,11]. Our prior study has also demonstrated that AOA could potentially increase the risks of chromosome structural abnormalities, transcriptional regulation deficiencies, and epigenetic impairments [12]. However, other investigations have reported no significant difference in the prevalence of major or specific birth defects between the AOA group and the traditional Intra-Cytoplasmic Sperm Injection (ICSI) group [13]. Why do these findings appear inconsistent? It may be due to the survivorship bias [12].

All newborns have undergone repeated screening in the ART. Although AOA may impair the developmental potential of oocytes and embryos, both oocytes and embryos possess a robust capacity for self-repair. Some of them are able to repair the damage and pass screening. These screened embryos can develop into healthy babies, but that does not mean AOA has no negative effect on embryos. The negative effects are only repaired. As for the embryos that are incapable of repairing the damage, they will fail to develop into blastocysts and consequently be excluded from transfer. They will be eliminated in the screening. Therefore, solely comparing the incidence of birth defects between ART offspring born from Assisted Oocyte Activation (AOA) and those without AOA may not be sufficient to comprehensively evaluate the safety of AOA. It is possible that AOA could have potential long-term effects on the health of ART offspring [10].

In fact, AOA is usually performed immediately following ICSI. This indicates that AOA is working during the recombination of parental genetic material. It is hard to avoid having an adverse effect on chromosome structure, transcriptional regulation, and epigenetics. Our previous study demonstrated changes in gene expression related to these processes within the AOA group [12].

In general, some studies have proven that AOA can improve

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fertilization rates and clinical outcomes for some specific patients, such as those who experience failed fertilization after ICSI or exhibit 100% abnormal morphology of the sperm head [14]. However, some other studies have indicated that AOA is not omnipotent. It cannot improve the fertilization rate and embryo quality for patients with recurrent embryo developmental problems after ICSI [15] or Multiple Morphological Abnormalities of the sperm Flagella (MMAF)[12]. Therefore, considering the safety and efficacy of AOA, it is not recommended as a routine technique for enhancing clinical outcomes at present. However, it may be beneficial for specific patients with explicit indications.

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