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COMMENTARY

Assisted yes, but where do we draw the line?

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Abstract In a recent report in *Reproductive Biomedicine Online* by Ebner et al., a comprehensive multi-centre study was presented on the use of a calcium ionophore, A23187, to artificially activate oocytes from patients who had poor fertilization rates in previous cycles. Under physiological conditions, the calcium increase in oocytes at activation is caused by influx and release from specific stores and ion channels, and has precise temporal, quantitative and spatial patterns. Calcium ionophores may release Ca^{2+} in an uncontrolled fashion from intracellular stores that would not normally be involved in the activation process. Ionophores, including A23187, have a multitude of effects on cell homeostasis, not yet defined in oocytes, that may have long-term effects, for example on gene expression. We suspect that the successful births reported by Ebner et al. are a result of the overriding influence of the injected spermatozoa, rather than the effect of the ionophore; nevertheless, such an invasive non-physiological approach to assisted reproduction techniques is worrying, especially as epigenetic effects may result in future generations.

KEYWORDS: calcium increases, caution, ionophore, oocyte activation

Dynamics of the calcium increase at oocyte activation

Calcium release is one of the first indications of oocyte activation in all animals (Stricker, 1999), with many studies showing aesthetically pleasing images of oocytes loaded with calcium-sensitive dyes 'lighting up' at activation. It is not so simple. The calcium increase is caused by both influx and release (Santella et al., 2004) from specific stores and ion channels, with temporal, quantitative and spatial patterns that need to be respected. The signal transduction pathway generating the intracellular Ca^{2+} liberation is still unknown. Several different calcium release mechanisms exist in oocytes, depending on the type of receptor located on the intracellular calcium store. Furthermore, the calcium increase does not occur alone. Simultaneously, and obviously in conjunction, there is a massive cortical re-organization of this large cell involving cytoskeletal elements, the plasma membrane and a cascade of cell–cycle kinases. All activation events are propagative and also have temporal, quantitative and spatial patterns (Dale et al., 2010). Fortunately, much has been published on animals across the animal kingdom that is allowing us to build up a larger picture.

In echinoderms, ascidians and mammals, intracellular Ca^{2+} increases occur in the form of a single wave or oscillations starting at the sperm attachment site and then spreading to the antipode. It is thought that the spermatozoon triggers activation locally by releasing a soluble sperm factor into the cortex. Candidates are a sperm-specific phospholipase, PLC zeta, a complex of several non-specific factors, or a post-acrosomal WW domain-binding protein (Dale et al., 2010). Whatever the mechanism, the signal originates at the point of sperm–oocyte fusion and traverses the oocyte in a wave. Several studies in mammals have shown that alterations in the precise pattern of calcium release or influx at oocyte activation influences later developmental traits (Miao et al., 2012). When sperm–oocyte membrane interaction is bypassed, as in intracytoplasmic sperm injection (ICSI), the Ca^{2+} oscillations show a delayed and truncated pattern, with the Ca^{2+} increases starting from an arbitrary cortical region, not far from the vicinity of the injected sperm head, indicating that the oocyte cortex where sperm oocyte interaction normally

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