

Role of Calcium Ionophores for Artificially Activating Oocyte in Cases of Persistent Fertilization failure Despite ICSI-A Short Commentary

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AIM

In vitro fertilization laboratory is to get the best ratios between the number of oocytes retrieved and the ratio of embryo production which are highly viable. First step is obtaining the oocyte and sperm cells from the patients. Then to improve the success rates we use technologies that are available with us. One aim is to apply technologies that have been validated, are repeatable and are nonbiased techniques. As far as oocytes are concerned not many options are available as all will be treated for getting fertilization. But sperms are millions in numbers and only few get used. Can we improve the sperm path. Classically we use the conventional methods of sperm selection either by swim up or density gradient. There is need to try any kind of technology where molecular characteristics, are considered that are related to successful fertilization, embryo development along with live birth.

One has to improve sperm selection, for which some available options remain sperm binding assessment (PICSI), sperm head birefringence assessment, magnetic activated cell sorting (MACS), molecular targeting and real time morphology assessment (IMSI). The easiest method to increase efficiency is the use of calcium ionophore to get our aim.

Problem faced is in those patients where low fertilization is obtained. Which of sperm selection methods can be applied to increase the cycle outcome? After low fertilization one has to clearly define what low fertilization implies, should any kind of method be used to improve fertilization rates.

Of the 2 proposed strategies i.e selection and efficiency one is PICSI. PICSI is a sperm selection device which is being currently used by a prospective study. It is a method of sperm selection which utilizes binding to hyaluronic support. Since sperms have hyaluronic receptors which surround their heads and those cells that get selected by hyaluronic acid binding express less DNA fragmentation along with low apoptosis markers. Its benefits had been reviewed by McDowell et al [1]. As per McDowell et al there was not enough proof for recommending physiological intracytoplasmic injection (PICSI) or any other hyaluronic acid (HA) binding selection before ICSI. Further no studies are available regarding potential side effects of this method. A large ongoing multicentric study involving 16 centres in the United Kingdom known as HAP Select, that started in 2014, which finished recruiting 3238 patients by 2016. The mechanistic aim is to assess whether and how the chromatin state of HA-selected sperm corresponds with clinical outcome s-clinical pregnancy rates (CPR), LBR and pregnancy loss (PL). They were waiting for the results for the last live births and not published [2]. This trial is powered to detect a 5% difference (24-29%; p=0.05) in LBR >= 37 WKS Gestation. Selected residual sperm samples will be tested by one or more assays of DNA integrity [2].

MACS refers to a sperm selection method which is related to apoptosis and leads to externalization of phospholipid serine (PS; A molecule having high affinity for annexin V [AV]). Hence AV, i.e used as an apoptotic sperm marker is conjugated with magnetic microspheres, that are exposed to magnetic field in an

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affinity column, that it can separate apoptotic from non apoptotic sperm[3]. In 2013 a systematic review by Gil et al showed that MACS might improve pregnancy rates if used to complement the usual sperm selection techniques in ART. Only 1 RCT was reported, showing no improvement in outcome of ICSI[4]. MACS is a safe method and can be applied clinically since the report of Romany et al [5], showed that this technology does not increase or decrease any obstetric and perinatal outcomes In children who conceived.

Murugesu et al carried out a meta-analysis to investigate the effect of calcium ionophores like ionomycin and calcimycin (A23187), as a method for artificial oocyte activation(AOA) on pregnancy rates and fertilization[6]. They used RCT, prospective observational and retrospective trials. Studies included were infertile couples who were undergoing infertility treatment in which use of calcium ionophore was utilized. The author selected 14 studies and found that AOA using calcium ionophore increased the overall clinical pregnancy rate and live birth rate /embryo transfer with odds ratio over 3 fold change. Further the effect of calcium ionophore addition was reflected in the intermediate variables like fertilization, cleavage, blastocyst and implantation rates. On applying a meta-regression analysis that found an increase in the quality of the study with the effect of calcium ionophore significantly more pronounced as far as overall outcome rates were concerned. Although not much importance is given to this topic with not much weightage given by scientific community. This helps in selecting methods once fertilization failure is persistent despite ICSI, whatever be the primary cause in cases where ICSI gives poor results.

Thus if there is need for a choice between improved sperm selection or efficacy, this evidence favours use of AOA with calcium ionophore as the primary method

for improving treatment success.

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