Reviewing novel processes: Egg activation with calcium ionophore

Strategic delivery:	☒ Safe, ethical effective treatment	☐ Consistent outcomes and support	☐ Improving standards through intelligence
Details:			
Meeting	SCAAC February 2018		
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Output:			
For information or decision?	For decision		
Recommendation	The Committee is asked to: • consider the literature and outcomes report (Annex 2) and discuss the efficacy and safety profile of calcium ionophore • advise the HFEA on whether a more detailed outcomes report on the use of calcium ionophore on patients in UK clinics is needed in addition to the outcomes report • advise if this raises any concerns which might lead them to recommend that calcium ionophore should be removed from the authorised processes list.		
Resource implications	Possible paper to the Statutory Approvals Committee if SCAAC recommend that calcium ionophore should be removed from the authorised processes list		
Implementation date	N/A		
Communication(s)	N/A		
Organisational risk	☒ Low	☐ Medium	☐ High
Annexes	Annex 1: List of authorised processes Annex 2: Outcomes report		

1. Introduction

1.1. As the UK regulator of fertility clinics, the Authority maintains a list of authorised processes, which are arranged under each of the licensable activities permitted by the Act (see Annex 1). If a centre wishes to carry out a process which does not appear on the list, it must apply to the Authority for permission.

1.2. As part of considering a novel process application, SCAAC should agree that the process is sufficiently different from the processes currently authorised as to be considered 'novel'. The Committee should also provide a view on whether the process is effective and whether there is any evidence to indicate that it is unsafe.

1.3. A standard operating procedure (SOP) was put in place in 2015 to clearly outline the application stages for novel processes, which includes the application being put forward to the Statutory Approvals Committee for approval and an outcomes report from the clinic on the safety and efficacy of the process being submitted to the Executive two years after the process is approved. This report should cover the safety and efficacy of the process such that the Committee can discuss any concerns about the process being either unsafe or ineffective. If concerns are raised the Committee may consider recommending that the process is removed from the authorised processes list. This decision would have to be agreed by SAC.

1.4. Calcium ionophores are a type of substance that increases concentration of calcium ions when applied to an egg, which in turn activates the egg so that fertilisation can occur.

1.5. The use of calcium ionophore for gamete activation precedes the novel process SOP. In the absence of an outcomes report from one applying clinic, HFEA inspectors have collected information from clinics that have used calcium ionophore (Annex 2). SCAAC considered gamete activation as a novel process in June 2012 and concluded that there was no evidence that the process was unsafe. Subsequently, egg activation using calcium ionophore was added to the list of authorised processes, with a precaution that the process should only be used in selected patients such as those with PLCζ deficiency.

1.6. This paper provides an overview of research on gamete activation using calcium ionophore published since June 2012. The purpose of this literature review is to provide an update on studies done on calcium ionophore use, in case there is any new evidence that might affect the committee's view on the safety of the process.

2. Literature review

Randomised studies

2.1. A randomised clinical trial (Eftekhar et al., 2013) retrieved 313 oocytes from 38 women who had teratoospermic (a condition where men have abnormal sperm)

partners and divided them into two groups: a control group which underwent routine ICSI and a treatment group which underwent activation by calcium ionophore. There were no significant differences observed in fertilisation, cleavage and pregnancy rates.

2.2. A randomised study by Aytac et al. (2015), assessed the effect of calcium ionophore on 296 patients with diminished ovarian reserve whose partners had normal sperm parameters. No significant differences in fertilisation rates, clinical pregnancy or ongoing pregnancy were observed after use of calcium ionophore.

2.3. A randomised study by Aydinuraz et al. (2016) assessed the use of calcium ionophore on fertilisation, cleavage rates and embryo quality in sibling oocytes. Out of 194 oocytes collected from women with a history of low fertilisation rates and accompanying teratozoospermia, half were given calcium ionophore and the other half were controls. No differences were found in the fertilisation and cleavage rates, however the oocytes treated with calcium ionophore were less likely to produce top quality embryos in terms of per fertilised oocytes and per cycle.

Observational studies

2.4. The first prospective multicentre study on calcium ionophore (Ebner et al., 2012) in cases of severe male factor infertility observed a significant increase in fertilisation rate from 34.7% in a previous ICSI cycle to 56.9% in a subsequent cycle with calcium ionophore treatment. There was also a significant increase in live birth rate, and there were no malformations.

2.5. A long-term follow-up study was conducted by Vanden Meerschaut et al. (2014), assessing neonatal and neurodevelopmental outcomes in 21 children between the ages of 3-10 years old who were born following activation by calcium ionophore. No birth defects were reported at birth. The children were tested on their cognitive, language and motor development as well as their behaviour. The scores obtained fell within normal ranges.

2.6. A case report by Karaca et al. (2015) described the use of calcium ionophore on a patient whose partner had globozoospermia. After oocyte activation, a healthy baby was born.

2.7. A prospective study by Ebner et al. (2015) analysed the effect of calcium ionophore in 101 patients who had fertilisation abnormalities in a previous ICSI cycle. The previous cycle was designated as the control group. There was a significantly higher fertilisation rate in the study cycles (48%) compared to the control cycles (25%) with a p value of <0.001.

2.8. Another prospective study looked at patients who had poor embryo development in a previous cycle (Ebner et al., 2015b). Application of calcium ionophore led to increased rates of cleavage to 2-cell stage, blastocyst formation and clinical pregnancy. The study suggested development incompetence of embryos could be an additional indication for ionophore treatment.

2.9. A study by Darwish and Magdi (2015) looked at the use of calcium ionophore in four women who had previous ICSI failures where embryos arrested development. Fertilisation rate increased after calcium ionophore application and one patient delivered two healthy babies.

2.10. A retrospective cohort study by Miller et al. (2016) looked at pregnancy and neonatal outcomes including birth defects after ICSI with and without use of activation by calcium ionophore. In a sample of 678 cases, where 595 were ICSI pregnancies and 83 were ICSI pregnancies with calcium ionophore, there were no differences in birth defects or other outcomes.

2.11. The risk of chromosome segregation errors was measured in a study by Capalbo et al. (2016). There was no evidence to suggest activation by calcium ionophore leads to errors compared with normally activated oocytes. A suggestion was given that calcium ionophore is to be used selectively on patients with specific indications such as PLCζ deficiency, globozoospermia and previous failed fertilisation.

2.12. A meta-analysis by Murugesu et al. (2017) that included fourteen studies found that activation with calcium ionophore increased fertilisation, cleavage, blastocyst and implantation rates as well as overall clinical pregnancy rate per embryo transfer (OR=3.48) and live birth rate (OR=3.44).

3. Conclusion

3.1. Studies included in this literature review generally report that oocyte activation using calcium ionophore may be effective for selected patients with previous ICSI failures. Whilst there is some observational evidence to suggest an increase in fertilisation rates, the randomised studies summarised in this review did not confirm these findings.

3.2. Only one study involved follow up of children in later years where the children were found to display normal neurodevelopment. More follow up studies should be done to further understanding on whether calcium ionophore is safe to use.

3.3. The Committee is asked to:

- consider the literature and outcomes report (Annex 2) and discuss the efficacy and safety profile of calcium ionophore
- advise the HFEA on whether a more detailed outcomes report on the use of calcium ionophore on patients in UK clinics is needed in addition to the outcomes report
- advise if this raises any concerns which might lead them to recommend that calcium ionophore should be removed from the authorised processes list.

4. References

Aydinuraz, B. et al., 2016. Artificial oocyte activation after intracytoplasmic morphologically selected sperm injection: A prospective randomized sibling oocyte study. *Human Fertility*, 119(4), pp. 282-288. Available at https://doi.org/10.1080/14647273.2016.1240374.

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Ebner, T. et al., 2015. Live birth after artificial oocyte activation using a ready-to-use ionophore: a prospective multicentre study. *Reproductive biomedicine online*, 30(4), pp. 359-365. Available at https://doi.org/10.1016/j.rbmo.2014.11.012.

Ebner, T. et al., 2015b. Treatment with Ca2+ ionophore improves embryo development and outcome in cases with previous developmental problems: a prospective multicenter study. *Human Reproduction*, 30(1), pp. 97-102.

Eftekhar, M. et al., 2013. Effect of oocyte activation with calcium ionophore on ICSI outcomes in teratospermia: A randomized clinical trial. *Iranian journal of reproductive medicine*, 11(11), pp. 875-882.

Capalbo, A. et al., 2016. Artificial oocyte activation with calcium ionophore does not cause a widespread increase in chromosome segregation errors in the second meiotic division of the oocyte. *Fertility and sterility*,105(3), pp. 807-814. Available at https://doi.org/10.1016/j.fertnstert.2015.11.017.

Darwish, E. and Magdi, Y, 2015. A preliminary report of successful cleavage after calcium ionophore activation at ICSI in cases with previous arrest at the pronuclear stage. *Reproductive biomedicine online*, 31(6), pp. 799-804. Available at https://doi.org/10.1016/j.rbmo.2015.08.012.

Karaca, N. et al., 2015. A successful healthy childbirth in a case of total globozoospermia with oocyte activation by calcium ionophore. *Journal of reproduction & infertility*, 16(2), pp. 116-120.

Meerschaut, F. V., 2014. Neonatal and neurodevelopmental outcome of children aged 3–10 years born following assisted oocyte activation. *Reproductive biomedicine online*, 28(1), pp. 54-63. Available at https://doi.org/10.1016/j.fertnstert.2017.06.029

Miller, N. et al., 2016. Oocyte activation by calcium ionophore and congenital birth defects: a retrospective cohort study. *Fertility and sterility*, 106(3), pp. 590-596. Available at https://doi.org/10.1016/j.fertnstert.2016.04.025.

Murugesu, S. et al., 2017. Does the use of calcium ionophore during artificial oocyte activation demonstrate an effect on pregnancy rate? A meta-analysis. *Fertility and*

sterility, 108(3), pp. 468-482. Available at https://doi.org/10.1016/j.fertnstert.2017.06.029.

Annex 1: List of authorised processes

Licensed activity	Authorised processes
Procuring gametes	Egg collection Surgical sperm collection Ovarian tissue collection
Keeping gametes	Culture of eggs
Processing gametes	Semen preparation (including the use of reagents to increase sperm motility) Egg preparation In vitro maturation Thawing/re-warming gametes Egg activation using Calcium Ionophore (only in suitable patients* - see below for further guidance) Intrauterine culture of gametes and embryos (including insertion and removal of device, followed by transfer of embryo(s) to the same woman)'
Distribution of gametes	Transfer of sperm between centres Transfer of eggs between centres
Use of gametes	IUI GIFT IVF ICSI
Storage of gametes	Freezing of eggs Freezing of sperm Vitrification of eggs Freezing of testicular tissue (not for transplantation purposes unless a HTA licence is in place) Freezing of ovarian tissue (not for transplantation purposes unless a HTA licence is in place)
Storage of embryos	Freezing of pronucleate embryos Freezing of early cleavage embryos Freezing of blastocysts Vitrification of embryos Vitrification of blastocysts
Creation of embryos	IVF ICSI

Procuring embryos	Lavage
Keeping embryos	Culture system
Testing embryos	PGD PGS Polar body biopsy
Processing embryos	Culture Assisted hatching (mechanical, chemical, laser) Morphological grading Manipulation Thawing/re-warming of blastocysts and embryos Non-invasive assessments Intrauterine culture of gametes and embryos (including insertion and removal of device, followed by transfer of embryo(s) to the same woman)'
Distribution of embryos	Transfer of embryos between centres
Placing permitted embryo in a woman	Embryo transfer
Using embryos in training	Embryo biopsy Blastocyst biopsy Cryopreservation and thawing techniques Vitrification Assisted hatching (mechanical, chemical, laser) Embryo handling and manipulation Assessment of embryos

*The HFEA's Scientific and Clinical Advances Advisory Committee considered the use of Calcium Ionophore as an egg activation technique and highlighted the theoretical risks relating to embryo viability (eg, premature activation and triploid embryos).

Given the theoretical risks of using Calcium Ionophore, centres using it are expected to do so only in selected patients, such as those with PLCz deficiency. Centres are expected to document their rationale for using Calcium Ionophore for individual cases. As with all treatments and processes, centres should ensure that patients are fully informed about the efficacy and potential risks and that validation is carried out.

Prohibited processes

If a process does not appear on the list above, it may have been considered by the HFEA's Compliance Committee but determined to be inappropriate for use in clinical practice. This may have been because the Scientific and Clinical Advances Advisory Committee, on reviewing the evidence, has advised that there is not enough evidence of safety or efficacy about a particular process for it to be authorised for use in a clinical laboratory.

Annex 2: Outcomes reports

Content redacted for confidentiality