ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Oocytes with smooth endoplasmic reticulum clusters originate blastocysts with impaired implantation potential

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Objective: To study whether embryos derived from oocytes presenting a smooth endoplasmic reticulum cluster (SERC) are less likely to develop into blastocysts and implant.
Design: Transversal study.
Setting: Private university-affiliated in vitro fertilization (IVF) center.
Patient(s): Total of 7,609 oocytes obtained from 743 intracytoplasmic sperm injection (ICSI) cycles.
Intervention(s): Oocytes split between the SERC-positive cycles (with at least one SERC-positive oocyte) and the SERC-negative cycles (only oocytes free of SERC).
Main Outcome Measure(s): Embryo implantation.
Result(s): A statistically significantly higher mean number of follicles (24.0 ± 10.5 vs. 19.6 ± 10.5), retrieved oocytes (17.8 ± 8.3 vs. 14.3 ± 8.0), and mature oocytes (13.5 ± 6.2 vs. 10.6 ± 5.9) were observed in the SERC-positive cycles as compared with SERC-negative cycles. The implantation rate was statistically significantly lower in SERC-positive cycles as compared with SERC-negative cycles (14.8% vs. 25.6%; odds ratio 0.61; 95% confidence interval, 0.44–0.86). When only cycles with in which none (0) or all the blastocysts transferred had implanted (100%) were analyzed, the mean implantation rate per transferred blastocyst in the SERC-negative group was 20.5%; no blastocysts derived from SERC-positive oocytes implanted.
Conclusion(s): The occurrence of SERC impairs embryo implantation. Careful oocyte observation that takes into account the presence of SERC should be part of embryo selection strategy before transfer. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Blastocyst, embryo implantation, ICSI, oocyte morphology, smooth endoplasmic reticulum

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Embryo selection for transfer is a key element in in vitro fertilization (IVF). The selection of high-quality embryos increases pregnancy rates and decreases multiple pregnancies as it enables restrictions on the number of transferred embryos. Usually embryos are selected for transfer based on their morphologic features on days 1, 2, 3, and 5 of development (1). Additionally, oocyte quality assessed on day 0 can also be taken into account for embryo selection, considering the vital role played by the oocyte in the embryo developmental process (2).

In fact, several studies have shown that embryo quality and implantation potential may be influenced by oocyte quality (3–8). The typical evaluation of the oocyte quality is based on extra and intracytoplasmic morphologic features, such as first polar body morphology, perivitelline space size and granularity, zona pellucida defects, shape anomalies, and the presence of refractile bodies, dense cellular granulation, vacuoles, and smooth endoplasmic reticulum (9).

Smooth endoplasmic reticulum is a type of organelle that forms an interconnected network of flattened, membrane-enclosed sacs or tubes. These can be

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distinguished from fluid-filled vacuoles because they are not filled with fluid and not separated from the cytoplasm by a membrane (10, 11). One of the key roles of smooth endoplasmic reticulum in the oocyte is storage and redistribution of calcium, which is responsible for cell activation in the course of fertilization (11, 12). A smooth endoplasmic reticulum cluster (SERC) is an intracytoplasmic dimorphism that has been suggested to interfere with calcium stores and oscillations during fertilization, and may have a negative effect on embryo development and implantation (13).

Previous studies have shown that compromised fertilization, embryo development, pregnancy rates, and obstetric and neonatal outcomes (8,14–17) result when oocytes presenting with SERC are injected and the embryo thus derived is transferred. In 2011 the Alpha Scientists in Reproductive Medicine and European Society of Human Reproduction and Embryology (ESHRE) Special Interest Group of Embryology recommended not inseminating oocytes that presented with SERC because they might be associated with an increased risk of abnormal outcomes (18). However, more recently a study showed that healthy babies could be obtained using oocytes presenting with SERC (13).

Thus, information regarding the clinical significance of oocytes presenting with SERC is sparse and controversial. We investigated whether embryos derived from oocytes presenting SERC are less likely to develop into blastocysts and implant. Additionally, we examined the predictive factors for the occurrence of SERC.

MATERIALS AND METHODS

Experimental Design, Patients, and Inclusion and Exclusion Criteria

Our transversal study included data from patients undergoing intracytoplasmic sperm injection (ICSI) from July 2011 to June 2014 at a private university-affiliated IVF center located in Brazil. The inclusion criteria were as follows: patients undergoing ICSI with fresh embryo transfer performed on day 5 of development. Patients who were undergoing ICSI with vitrified/thawed or donated oocytes, surgical sperm retrieval, sperm without progressive motility, vitrified/thawed embryo transfer, donated embryo transfer, or preimplantation genetic diagnosis or screening were excluded from the analysis.

Two analyses were performed. In the first analysis, the obtained oocytes were split between the SERC-positive group, in which the oocytes presented with SERC, and the SERC-negative group, in which the oocytes were free of SERC. The ICSI cycles' characteristics, such as female age, total dose of follicle-stimulating hormone (FSH) administered, number of follicles and oocytes obtained, fertilization rate, high-quality embryos available on day 2 and 3, blastocyst formation rate, number of high-quality blastocysts, and number of embryos transferred, were compared between the SERC-positive and SERC-negative oocytes.

In the second analysis, the ICSI cycles were split between the SERC-positive cycles, in which the cycles had at least one SERC-positive oocyte, and the SERC-negative cycles, in which the cycles had only SERC-free oocytes. The ICSI cycles' characteristics such as female age, total dose of FSH administered, number of follicles and oocytes obtained, fertilization rate, high-quality embryos on day 2 and 3, blastocyst formation rate, high-quality blastocysts, number of embryos transferred, and implantation, pregnancy, and miscarriage rates were compared between the SERC-positive and SERC-negative cycles. In a further analysis, to investigate the implantation potential of the embryos derived from SERC-positive oocytes, only cycles in which none (0) or all embryos transferred had implanted (100%) were analyzed. All patients signed a written informed consent form, and the study was approved by the local institutional review board.

Controlled Ovarian Stimulation

Ovarian stimulation was achieved by the administration of recombinant FSH (Gonal-F; Serono) on a daily basis until the visualization of at least one follicle $\geq$14 mm, at which time we began the administration of gonadotropin-releasing hormone (GnRH) antagonist, cetrorelix acetate (Cetrotide; Serono).

The ovulation trigger was provided by injection of recombinant human chorionic gonadotrophin (hCG, Ovidrel; Serono) when at least three follicles $\geq$18 mm were observed. Oocyte retrieval was performed 35 hours after the administration of hCG, through transvaginal ultrasonography.

Oocyte Preparation

Retrieved oocytes were maintained in culture medium (Global for fertilization; LifeGlobal) supplemented with 10% protein supplement (LGPS; LifeGlobal) and covered with paraffin oil (Paraffin oil P.G.; LifeGlobal) for 2 to 3 hours before cumulus cell removal. The surrounding cumulus cells were removed after exposure to a HEPES-buffered medium containing hyaluronidase (80 IU/mL; LifeGlobal). The remaining cumulus cells were then mechanically removed by gently pipetting with a hand-drawn Pasteur pipette (Humagen Fertility Diagnostics).

Oocyte morphology was assessed using an inverted Nikon Diaphot microscope (Eclipse TE 300; Nikon) with a Hoffmann modulation contrast system under $\times$400 magnification, just before sperm injection (5 hours after retrieval). The presence of SERC in the ooplasm was recorded (Fig. 1). Oocytes that had released the first polar body were considered mature and were used for ICSI.

ICSI

We performed ICSI according to the methods described by Palermo et al. (19). Sperm selection was analyzed at $\times$400 magnification using an inverted Nikon Eclipse TE 300 microscope. The injection was performed in a microinjection dish prepared with 4-μL droplets of buffered medium (Global with HEPES; LifeGlobal) and covered with paraffin oil on a heated stage at 37.0°C $\pm$ 0.5°C in an inverted microscope. Fertilization was confirmed by the presence of two pronuclei and the extrusion of the second polar body approximately 16 hours after ICSI.

Embryo Quality and Transfer

To evaluate the cleavage-stage morphology, the following parameters were recorded: the number of blastomeres, the

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