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Case Report

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The First Livebirth Using Warmed Oocytes by a Semi-Automated Vitrification Procedure

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Abstract

Background: The first successful livebirth using warmed oocytes (vitrified by the GAVI™ system) is reported in this paper. Embryologists throughout the world have vitrified oocytes using a manual technique which is susceptible to error and variation. In this era of automated laboratory procedures, vitrification was made semi-automatic by using the GAVI™ system.

Case Presentation: Donor oocytes were initially vitrified using the GAVI™ system. They remained in the clinic's oocyte bank until they were allocated to the patient. Donor oocytes were warmed as per Genea BIOMEDX protocol and inseminated to create embryos. Resulting embryos for the 42-year-old patient were cultured to the blastocyst stage, biopsied to perform PGT-A, using next generation sequencing and subsequently vitrified. The patient underwent a single euploid transfer in a frozen embryo transfer cycle which resulted in a healthy livebirth.

Conclusion: The introduction of a semi-automated system should minimize the risk to the oocytes, standardize the procedure worldwide and potentially reduce the laboratory time taken by the embryologists. This case report demonstrates the safety of the technology used for vitrification, but larger randomized studies need to be performed to demonstrate the safety and efficacy of newer technologies like the GAVI™ system before adopting it as a standard laboratory procedure.

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Introduction

Embryo and sperm cryopreservation are routinely performed in most *in vitro* fertilization laboratories. However, after oocyte vitrification, lower survival and implantation rates were reported compared to embryo cryopreservation (1, 2). The need to find a robust and reproducible technique alternative to vitrification and storing oocytes, both from patients and donors, encouraged the Centre for Reproductive and Genetic Health (CRGH) to use GAVI™, a novel semi-automated vitrification system. GAVI™ is designed to provide automated cryoprotectant exposure to oocytes and embryos and can be sealed to minimize the chance of human error (3, 4).

Case Presentation

A 42-year-old patient and her 42-year partner attended the clinic after eight years of secondary infertility. In 2007, the patient conceived naturally but pregnancy was terminated when Edwards' Syndrome was diagnosed. In 2009, the couple conceived naturally again, and a healthy girl was born. They subsequently opted for fertility treatment in 2012. Following a failed cycle in another unit, the patients attended the CRGH in 2018 for further treatment and were diagnosed with unexplained infertility. The couple underwent three cycles of ovarian stimulation using their own gametes in order to batch embryos on day 3 of development using Vit Kit-Freeze (FUJIFILM Ir-

vine Scientific). A total of eleven day 3 embryos were cultured to the blastocyst stage in order to perform Preimplantation Genetic Testing for Aneuploidies (PGT-A). Two blastocysts underwent trophectoderm biopsy; cells were sent to IGENOMIX UK LTD for next generation sequencing. Both embryos were diagnosed as having complex abnormality. Next, the couple decided to use donor oocytes to maximize their chances.

Treatment: Oocytes used in the treatment were donated by a 33-year-old oocyte donor who underwent ovarian stimulation following a short antagonist protocol. Fifteen oocytes were collected and after cumulus removal, fourteen metaphase II oocytes were identified. They were vitrified 40 hours post hCG using GAVI™ as previously described by Roy et al. (5). Prior to loading the oocytes into the pod, gametes were cultured for 5 minutes in VitBase in an ungassed incubator. In the meantime, the media vials and the cartridges containing the tips and seals used by GAVI™ were loaded. Finally, the oocytes were loaded individually or in pairs in each pod and pods were loaded into the GAVI™ system. Oocyte vitrification program was initiated and once it had finished, pods were submerged directly into liquid nitrogen.

Oocytes were stored until they were allocated to the couple for treatment. The couple accepted all fourteen oocytes from oocyte bank of clinic. All fourteen were warmed as per Genea BIOMEDX protocol.

Seven oocytes survived the warming procedure and were inseminated by intracytoplasmic sperm injection (ICSI) using partner's sperm, 2 *hr* post warming (41 *hr* post hCG). After injection, oocytes were placed in Embryoscope™ (Vitrolife) for uninterrupted culture (Sage 1-Step, Cooper-Surgical). At 16±2 *hr* post insemination, fertilization was assessed, and all seven oocytes showed signs of fertilization. On day 3 of embryo development, six out of the seven embryos were classified as top quality or very good quality. In total, three embryos reached the blastocyst stage; one embryo was biopsied on day 5 and two other embryos were biopsied on day 6 of embryo development for PGT-A. Embryos were vitrified immediately post biopsy (Sydney IVF Blastocyst Vitrification Kit, COOK Medical) and cells were sent to IGENOMIX UK Ltd for testing.

Both day 6 blastocysts came back as euploid while day 5 blastocyst came back as aneuploid (+5, -6, +13) (Figure 1).

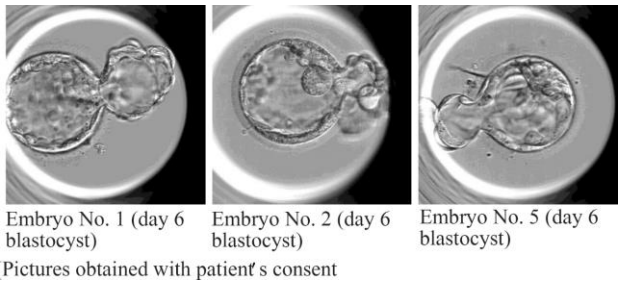

Figure 1. Pictures of the obtained blastocysts

In February 2018, the patient underwent a medicated frozen embryo transfer. One euploid embryo was warmed (Sydney IVF Blastocyst Warming Kit, COOK Medical™) and transferred into the middle of the uterine cavity on day 6 of progesterone administration. Two weeks later, the patient had a positive pregnancy test which was confirmed by blood test (BETA HCG 361.0 IU/L). Four weeks post embryo transfer, the patient attended a pregnancy scan, which showed a viable singleton pregnancy. Non-invasive pre-natal test (NACE™, IGENOMIX UK Ltd) performed at 10 weeks and 6 days of pregnancy confirmed a gestation with low risk for chromosomal abnormalities. Results were consistent with a male fetus.

Outcome: A healthy boy (2900 grams) was born at 38+0 weeks of gestation in October 2019 delivered via a caesarean section. The baby was fit and well at the time of submission of this manuscript.

Ethical Approval and patient consent: Patient's written consent was obtained.

Discussion

To our knowledge, this is the first live birth obtained using donor oocytes vitrified by GAVI™. Despite the survival rate in this case (7 out of 14 oocytes, 50%) being below both our average and the "gold standard" for oocyte vitrification quoted by Kuwayama (6) and Kuwayama et al. (7), fertilization rate, embryo quality and blastocyst formation rates were still equivalent to those obtained with fresh oocytes. Two euploid embryos were obtained from three blastocysts demonstrating the GAVI™ system was unlikely to have caused any aberrations or alterations in chromosomal status of the oocytes. Pregnancies have been reported in the medical literature following the use of the GAVI™ system. However, this case report describes a healthy livebirth using this technique.

Conclusion

The semi-automated vitrification method used in this case could be a first step towards the total automatization of oocyte vitrification. Semi-automated or totally automated systems would allow us to maintain a better control of temperature that oocytes and embryos are exposed to, minimize embryo handling, minimize differences in the cryoprotectant concentrations and optimize the balance between equilibration and vitrification timing. However, larger randomized studies need to be performed to demonstrate the safety and efficacy of newer technologies like the Gavi™ system before adopting it as a standard laboratory procedure.

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Conflict of Interest

Authors have no conflict of interest to declare.

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