ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Perinatal outcomes in children born after fresh or frozen embryo transfer: a Catalan cohort study based on 14,262 newborns

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Objective: To ascertain whether perinatal outcomes are affected by vitrification and/or controlled ovarian hyperstimulation (COH).
Design: Register-based cohort study.
Setting: Not applicable.
Patient(s): Women undergoing in vitro fertilization (IVF) between 2008 and 2012 using autologous or donated eggs who had a singleton pregnancy delivered from the 24th week onward.
Intervention(s): Fresh embryo transfer (ET) or frozen-thawed ET in women undergoing IVF.
Main Outcome Measure(s): Primary outcome birthweight, and secondary outcomes gestational age at delivery, small for gestational age, mode of delivery, and perinatal mortality.
Result(s): In the autologous egg population, newborns from the fresh ET group had lower birthweight than the frozen-thawed ET group (3,152.9 $\pm$ 545.5g and 3,343.2 $\pm$ 532.3g, respectively), and this difference persisted even after adjusting for confounding factors, and the newborns had a higher risk of being small for gestational age (SGA). In contrast, among egg-donor recipients undergoing ET, the mean birthweight did not differ between the groups (3,165 $\pm$ 604.15 g and 3,143.60 $\pm$ 604.21g in the fresh and frozen-thawed ET groups, respectively); however, in the adjusted regression model birthweight was statistically significantly higher in the fresh ET group than the frozen-thawed ET group. The risk of SGA remained comparable between the fresh versus frozen-thawed ET groups. We observed no statistically significant differences in perinatal mortality between groups either in the autologous egg population or in the donor recipient group.
Conclusion(s): Perinatal outcomes are negatively affected by COH and not affected by the vitrification process. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Assisted reproduction technology, egg donation program, perinatal outcomes, vitrification

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One of the most important advances in reproductive medicine over the past decade has been the introduction of vitrification as a technique for embryo cryopreservation after in vitro fertilization (IVF) (1–4). Vitrification uses a combination of cryoprotectants at high concentrations to obtain remarkable shrinkage of the cell before rapid cooling, thus preventing the chilling effect observed with slow cooling. In 2007, Kuwayama (5) described the efficacy of this technique for cryopreservation of both oocytes and embryos in humans. Advances from this procedure have resulted in increased embryo survival and higher transfer rates (6) as well as an increase in the rate of delivery per embryo transferred, as reported by European and U.S. registries (3, 7).

Several studies have compared reproductive and perinatal outcomes after fresh embryo transfer (ET) and

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frozen-thawed ET (FET), and have reported that vitrification is associated with increased clinical pregnancy rates (7) and improved perinatal outcomes (8, 9), such as a lower risk of low birth weight (LBW) (1, 2, 4, 10–13), preterm birth (PTB) (1, 2, 11, 13, 14), and being small for gestational age (SGA) (2). However, other studies have shown a higher rate of post-term births, macrosomia, and being large for gestational age (LGA) as well as increased perinatal mortality in the FET group (3, 15). Therefore, there has been no conclusive evidence about the safety and effects of vitrification in the resulting offspring.

Perinatal outcomes are affected not only by the quality of the embryo transferred but also by the endometrial environment. Among women undergoing controlled ovarian hyperstimulation (COH), the endometrium is thought to be exposed to higher levels of estradiol and progesterone during the follicular and luteal phases as compared with nonstimulated cycles or endometrial priming for FET. This hyperestrogenism could lead to biochemical alterations during implantation and placentation, which may affect obstetric and perinatal results (16, 17). Alternatively, it has also been suggested that the improved perinatal outcomes may be due to the vitrification and thawing processes, which filter out poor-quality embryos and allow only stronger embryos to survive and implant (6, 14). Studies have suggested that the pregnancy rates from egg donation are similar in fresh ET and FET (18, 19). For the recipient, egg donation avoids the negative effects on endometrial development associated with COH, which is necessary for the development of multiple oocytes. Regardless of the type of ET performed, fresh ET or FET, patients who receive donated eggs have similar endometrial priming and comparable estradiol and progesterone levels. Therefore, egg donor recipients may be the best model to study differences in perinatal outcomes related to the embryonic component (fresh versus frozen) because the endometrial environment is similar for both groups.

Our study ascertained whether perinatal outcomes are affected by vitrification and/or COH. To achieve this goal, we analyzed two populations: women using autologous eggs who were exposed to COH to obtain the embryos, and women who used donor eggs and did not undergo hyperstimulation processes. The perinatal outcomes were evaluated in both population groups according to the type of ET performed.

MATERIALS AND METHODS

Study Design and Setting

We conducted a register-based cohort study using prospective data from the Department of Health of the Regional Government of Catalonia between 2008 and 2012. Although information from previous years was available, we only selected data from this period because the vitrification technique was first implemented in Catalonia in 2007 (20).

The registry, known as FIVCAT (IVF Registry of Catalonia), has been active since 1993 and is a mandatory, official, annually updated registry to which all public and private centers authorized to perform assisted reproduction techniques (ART) in Catalonia must report their activity. During the study period, the number of such centers increased from 29 in 2008 to 36 in 2012, and the number of IVF cycles performed increased as well: from 14,452 to 20,342 (20, 21).

The ART centers are in charge of collecting and submitting individual data (per cycle) to FIVCAT. Information about patients' background and the multiple items of the treatment protocol was obtained from various sources: medical charts, patient questionnaires, and/or laboratory tests. Monthly validation of the submitted data is performed by registry staff to detect imperfect or missing data using checklists generated by statistical software (20).

This study was approved by the clinical research ethics committee of our institution (CEIC-Parc de Salut Mar, Barcelona), and was conducted in accordance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (last amended in the 64th WMA General Assembly, Fortaleza Brazil, October 2013) and according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies (22).

Participant Selection and Data Collection

Two clearly differentiated populations were considered eligible for the study: women undergoing IVF using autologous oocytes and women undergoing IVF using donor eggs. Despite their differences, several essential aspects remained the same: the study period and the IVF laboratories.

Both populations were classified according to the type of ET performed, fresh ET versus FET. Only study participants who became pregnant and delivered after the 24th week were included. Exclusion criteria included pregnancies delivered after the 45th week, patients with a missing value for the main variables (birthweight [BW] and gestational age), multiple pregnancies, and singleton pregnancies arising from therapeutic embryo reduction to avoid the potential biases inherent to these types of pregnancies and the effects of the proinflammatory reaction after embryo reduction (Fig. 1).

We analyzed baseline characteristics such as maternal age (actual full years, corrected with +0.5 years), duration of infertility, sperm source, and the number of embryos transferred as well as obstetric and perinatal outcomes. No information about the egg donors was included because these individuals are anonymous. However, Spanish legislation stipulates that they must be 18 to 35 years old. The fertilization techniques used during the study period were IVF, intracytoplasmic sperm injection (ICSI), or combined IVF-ICSI.

The primary outcome was BW, measured in grams. Secondary outcomes included gestational age at delivery, BW according to gestational age, being SGA, mode of delivery, and perinatal mortality. We categorized BW as normal ($\geq$2,500 g and $\leq$4,500 g), low ($\geq$1,500 g and $<$2,500 g, LBW), very low ($<$1,500 g, VLBW), or macrosomia ($>$4,500 g) (19). Gestational age at delivery was categorized as at term ($\geq$37 and $\leq$42 weeks), early preterm ($<$32 weeks), moderate to late preterm ($\geq$32 and $<$37 weeks), and post-term ($>$42 weeks). Being SGA, defined as having a birthweight in the 10th percentile or below (23), was also considered in the analysis.