Difference in birth weight of consecutive sibling singletons is not found in oocyte donation when comparing fresh versus frozen embryo replacements

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Objective: First, to assess if there are any differences in birth weight or gestational length in newborns from egg-donation pregnancies delivering singletons, originating from either fresh or frozen-thawed embryos when they were developed and delivered within the same mothers. Second, to determine if there are any clinical, phenotypic, or laboratory factors influencing this relationship, including the origin of the oocyte (same or different donor), the order of the children (first fresh or first frozen-thawed embryo transfer), the embryo freezing technique (vitrification or slow freezing), the in vitro embryo culture length, and the duration that embryos remained frozen.
Design: Retrospective cohorts study.
Setting: University-affiliated infertility centers.
Patient(s): A total of 360 women undergoing oocyte donation (OD), delivering (>28 weeks) at least two babies, each one from a single pregnancy, originating from at least one fresh and one frozen-thawed embryo transfer, controlling maternal and laboratory characteristics, to test the effect of embryo freezing on children size (n = 731).
Intervention(s): None.
Main Outcome Measure(s): Birth weight, gestational age, weight percentile, being large for gestational age (LGA), small for gestational age (SGA), size out of normal range (ONR = LGA + SGA), and macrosomy.
Result(s): From fresh versus thawed embryos, respectively, mean birth weight of children was 3,183.7 g versus 3,226.4 g, gestational age was 272.1 days versus 268.8 days, and mean weight percentiles were 47.6 versus 50.1. The proportions and corresponding odds ratios (ORs) from fresh versus thawed embryos, respectively, were for LGA 13.6% versus 11.3% (OR 0.81), for SGA 9.4% versus 12.5% (OR 1.37), for ONR 23.1% versus 23.8% (OR 1.04), and for macrosomy 0.3% versus 0.8% (OR 3.1). After adjusting for clinically relevant variables, the ORs were for LGA 0.96, for SGA 1.40, for ONR 1.20, and for macrosomy not computable. None of the stated measures were significantly different. Also, independent analyses run on the origin of the oocytes, cryopreservation technique, cleavage stage of the embryos, and time that embryos remained frozen did not reveal any significant trends.
Conclusion(s): This study comparing siblings from OD cycles, and eliminating the independent variables that affect early events in pregnancy, revealed no difference in duration of gestation and live birth weights between fetuses obtained after the replacement of fresh or frozen embryos. Moreover, no clinical, phenotypic, or laboratory factors appeared to be relevant, once statistically controlled. (Fertil Steril® 2015;104:1411–8. ©2015 by American Society for Reproductive Medicine.)
Key Words: Birth weight, frozen embryo transfer, oocyte donation, large for gestational age, small for gestational age, macrosomia

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In vitro fertilization (IVF), and assisted reproductive technologies (ART) in general, are well established methods for treating infertility. Current efforts are primarily directed toward reducing complications in the mother and newborn infant. To this end, the most effective method so far has been the introduction, albeit too slowly, of single-embryo transfer (SET) in many programs around the world.

An increasing body of literature is appearing that analyzes perinatal parameters and short-, medium-, and long-term effects while controlling for prematurity. Furthermore, it has been observed that ART singleton pregnancies are associated with an increase in low birth weight (LBW) whose etiology is still not fully understood (1). One largely held belief is that the laboratory handling of the early stages of human life may bring epigenetic disorders that, in some way and at some point in life, may lead to the onset of disease. A link between laboratory procedures, epigenetic disorders, and offspring weight has already been established in nonhuman animal experiments (2).

Of particular interest is the potential effect of freezing protocols on future children, which is increasingly used in daily practice, especially after the introduction of vitrification of oocytes and embryos where it has been extremely successful (3–5).

Several studies have shown that children born through the transfer of frozen-thawed embryos have fewer neonatal complications and greater birth weight than children born after IVF with fresh embryo transfer (7). In fact, birth weight with frozen-thawed embryos appears to be very similar to natural conceptions (8, 9, 12). Some studies indicate that these fetuses may actually be large for their gestational age (LGA) (12–16), although other reports have not found differences in birth weight between children from fresh versus frozen embryo replacements (17).

These discrepancies are the consequence of the many variables that influence perinatal outcomes and specifically birth weight. On the maternal side, the cause of infertility, body mass index (BMI), parity, and ovarian stimulation in fresh versus frozen cycles, are important variables to consider. When the laboratory procedures are analyzed, the method of embryo freezing and the number of days of embryo culture are independent factors that have been shown to influence birth weight at early-cleavage and blastocyst stages (18).

Oocyte donation (OD) is a well established method of third-party reproduction. Our OD program has provided important clues about the pathophysiology of human infertility, such as the influence of endometriosis, adenomyosis (19), or fibroids (20) on implantation. When trying to analyze the influence of embryo freezing on birth weight, OD provides the advantage of eliminating ovarian stimulation in the recipient, which is, in our accounting, the most important variable determining perinatal outcomes after the number of embryos replaced. Moreover, the best model for studying the effect of embryo freezing on birth weight is to compare siblings in women who have delivered children from both fresh and frozen cycles, which helps to eliminate other confounding variables.

By allowing newborn infants from different donors to be compared in the same recipient, OD provides a unique opportunity to test genetic influence on birth weight.

Freezing has gained a lot of interest in ART since the introduction of vitrification of oocytes and embryos (3, 4). Although currently available perinatal outcomes are reassuring (5, 11), no study has compared birth weight in relation to the freezing-thawing procedure. Moreover, no study has contemplated the possible effect of the total period of time that embryos are frozen on birth weight.

Based on the above information, we have designed a retrospective cohort study from our OD database to gain insight into the influence of embryo freezing on birth weight and gestational age. This study included consecutive singleton sibling pairs, where one sibling was born after fresh transfer and the other sibling after frozen embryo transfer, in either order. The main objective of the study was to assess the crude and adjusted risks of being small for gestational age (SGA), LGA, or macrosomic in fresh and frozen embryo transfers. Additionally, we addressed the genetic influence of the biologic mother by looking at those cases that delivered children from different donors. We also analyzed as independent variables the mother's age on birth weight, the origin of the first child (fresh vs. frozen-thawed embryos), the cryopreservation method employed (vitrification vs. slow freezing), the developmental stage of the embryo (cleavage stage vs. blastocyst), and the time embryos had been frozen before replacement.

MATERIALS AND METHODS

Patients

This was a retrospective study of sibling cohorts of singletons born to mothers undergoing OD for any indication from January 2000 to June 2014. Each included patient delivered a single baby after the replacement of fresh or frozen embryos in different pregnancies that went beyond the 28th week of gestation. The study was approved by the Ethics Committee of the Instituto Valenciano de Infertilidad (IVI), (identification code no. 1406-BCN-033-DG). The protocols for endometrial preparation have been reported elsewhere (21). The embryo culture conditions (22), slow embryo freezing (23), and vitrification (3, 23) have also been extensively described in previous publications. Patients with embryos undergoing preimplantation genetic screening were not included in our study.

Data Collection

Data were obtained through the export of relevant variables from our database, and analyses were carried out by the data analysts and computer information systems team. The data were anonymous, following all rules regarding the protection of personal data. OD patients with at least two children born after week 28 in single deliveries, which resulted from fresh and frozen embryo transfers, in either order, where the data register was available, were included in the analysis. Pregnancies with initial number of sacs >1 were excluded.

Main outcome measures were weight, gestational age, SGA (defined as birth weight below the 10th percentile), LGA (identified as birth weight above the 90th percentile), weight out of the normal range (ONR, considering LGA + SGA), weight percentile, and macrosomy (>4,500 g).

We calculated their corresponding SD score (*z*-score) for each newborn by means of the equation $z = (x - \mu)/\sigma$, where x is the weight of the child, μ is the national mean weight of babies born at the same gestational age and of the same sex (reference group), and σ is the SD of the reference group. The *z*-score, or standard normal deviate, is a measure of the variation in the actual birth weight relative to that expected.

Statistical Analysis

Categoric and continuous variables are expressed in the text and tables as proportions and means with 95% confidence intervals (CIs), respectively.

Categoric data were compared with the use of χ^2 tests, and continuous variables were compared with the use of *t* tests.

Nonparametric tests were not used, because either the sample size per group was >30 cases and normal distribution can therefore be assumed (per the central limit theorem) or normal distribution was observed after testing by means of the Kolmogorov–Smirnoff test. A *P* value of < .05 was considered to be statistically significant.

The associations between the main categoric outcome variables and the study variable (having transferred fresh or frozen embryos from which single-sibling live births were achieved) were assessed with the use of logistic regression analyses and are shown with their corresponding crude odds ratios (ORs) while controlling for potentially confounding factors. Because the data set included known or potentially correlated data (e.g., from siblings coming from the same patients, oocyte donors, protocols, etc.), the generalized estimating equation (GEE) method with random effects in the multivariate logistic regression context for correlated data, was used to assess differences in the weight-related outcomes between the two groups studied (fresh vs. frozen embryos transferred) while adjusting for theoretically relevant variables. Models and adjusted odds ratios (AdjORs) and their 95% CIs were estimated with each method to evaluate the relative odds for frozen-thawed embryos compared with the reference group of fresh embryos.

Confounding factors were selected on the basis of their clinical relevance and previous knowledge. The variables used to adjust ORs were maternal and donor ages, height, weight, BMI, the use of donor sperm, if the oocytes were previously vitrified or not, the day of embryo transfers (day 3 or day 5), and the use of frozen or fresh sperm.

Parity, although clinically relevant, was not included as a variable for a number of reasons, but most crucially because each patient participated in both fresh and frozen groups, and therefore parity was equal between the groups, avoiding any influence on the reported findings.

Similarly to approaches from previous publications (16), we then calculated the OR and AdjOR for different categories, namely: the use of the same or different donor within the children obtained; the first child obtained with fresh or frozen embryos; the embryo freezing technique (slow freezing vs. vitrification); the day of embryo transfer (4 categories, combining the days of the fresh and frozen embryos transferred); and the time that the embryos remained frozen (categorized in quartiles).

TABLE 1

Risk of weight alterations depending on the embryo's origin, fresh or frozen transfer, and same or different oocyte donor among siblings.

	Same donor (n = 523)		Different donor (n = 182)		
Parameter	**Fresh (n = 262)**	**Frozen (n = 261)**	**Fresh (n = 91)**	**Frozen (n = 91)**	***P* value: same, different**
Gestational age (d)	272.4 (270.2–274.7)	271.5 (269.8–273.30)	270.5 (266.7–274.3)	272.5 (269.8–275.2)	ns, ns
Birth weight (g)	3,197.4 (3,114.6–3,288.22)	3,249.1 (3,176.8–3,321.5)	3,127.2 (3,001.2–3,252.4)	3,138.3 (3,030.5–3,246.2)	ns, ns
Percentile	47.1 (43.3–50.8)	52.3 (48.5–56.0)	48.6 (42.5–54.7)	45.7 (39.6–51.9)	ns, ns
z-Score	−0.04 (−0.140 to 0.131)	0.08 (−0.38 to 0.199)	−0.12 (−0.33 to 0.88)	−0.10 (−0.28 to 0.08)	ns, ns
SGA (%)	9.5	12.2	9.6	9.1	ns, ns
LGA (%)	13.3	11.3	8.5	9.1	ns, ns
Macrosomy (%)	0.3	0.8	0	1.1	ns, ns
ONR (%)	22.8	23.5	18.1	18.2	ns, ns
	Fresh vs. frozen		**Fresh vs. Frozen**		
	Crude OR (n = 523)	**Adjusted OR (n = 487)**	**Crude OR (n = 182)**	**Adjusted OR (n = 167)**	
SGA	1.52 (0.88–2.60)	1.89 (0.85–4.21)	0.94 (0.35–2.56)	0.65 (0.17–2.53)	ns, ns
LGA	0.73 (0.44–1.20)	0.82 (0.38–1.74)	1.08 (0.39–3.00)	0.64 (0.31–6.78)	ns, ns
Macrosomy	2.02 (0.18–22.36)	NA	NA	NA	ns, ns
ONR	1.03 (0.69–1.52)	1.29 (0.72–2.31)	1.01 (0.47–2.14)	0.95 (0.33–2.73)	ns, ns

Note: Data presented as %, mean (SD), or OR (95% CI); n = 705. LGA = large for gestational age; ONR = out of normal range (LGA + SGA); ns = nonsignificant difference; SGA = small for gestational age.

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All statistical analyses were performed with the use of the Statistical Package for Social Sciences, version 22 (SPSS).

RESULTS

Study Population

A total of 360 women were included in the study, resulting in 731 single pregnancies. Out of them, a total of 369 children were the result of a fresh embryo transfer, and 362 single pregnancies resulted from a frozen-thawed embryo transfer. In other words, some patients had more than one child coming from either fresh or frozen-thawed embryos, but only one per group was recorded, in a consecutive manner, for comparisons. Some missing data on particular variables led to minor sample size recalculations.

Indications for OD were advanced maternal age (n = 131; 36.5%), low response to gonadotropins (n = 105; 29.2%), endometriosis (n = 30; 6.9%), genetic factor (n = 7; 2.0%), recurrent miscarriage (n = 8; 2.2%), polycystic ovary (n = 3; 1.0%), and those without a defined or unique indication (n = 79; 22.2%). Moderate male factor (n = 241; 66.8%), severe male factor (n = 51, 14.2%), and normozoospermia (n = 36; 10.0%) were also recorded. Donor sperm was used in 32 cases (8.9%).

For the entire cohort population, the mean gestational age was 270.5 days (95% CI 267.5–273.4) with a mean weight of 3,204.8 g (95% CI 3,159.2–3,250.5). The mean weight percentile was 48.8 (95% CI 46.6–51.1), and *z*-score 0.08 (95% CI −0.07 to 0.08). There were four cases of macrosomy (0.6%), 78 cases of SGA (10.9%), 89 cases LGA (12.5%), and 167 cases of ONR (23.4%). Male children represented 52.1% of all children involved in this study.

Regarding adverse events, one child died a few days after delivery owing to severe sepsis. Other minor health problems (e.g., congenital scoliosis, vitiligo) unrelated to significant modifications of child weight were also found.

Supplemental Table 1 (available online at www.fertstert.org) presents some epidemiologic characteristics of the cycles for fresh and frozen embryo transfers, such as the age and BMI of the patient when she received the embryos that resulted in the compared newborn infants, as well as some of the donors' characteristics and parameters related to the OD cycle that may influence the results. As shown, the patients were significantly older ($P<.05$) when they received frozen embryos compared with fresh. A significant ($P<.05$) shift toward the replacement of blastocysts in the frozen group was also observed.

From fresh versus thawed embryos, respectively, mean birth weight of children was 3,183.7 g (95% CI 3,115.0–3,252.4) versus 3,226.4 g (95% CI 3,166.3–3,243.2), gestational age was 272.1 days (95% CI 270.1–274.0) versus 268.8 days (95% CI 263.1–274.5), and mean weight percentiles were 47.6 (95% CI 44.5–50.8) versus 50.1 (95% CI 46.8–53.3).

The proportion and ratios from fresh versus thawed embryos, respectively, were: for LGA 13.6% versus 11.3% (OR 0.81, 95% CI 0.52–1.27); for SGA 9.4% versus 12.5% (OR 1.37, 95% CI 0.85–2.2); for ONR 23.1% versus 23.8%

TABLE 2

Risk of weight difference depending on the embryo's origin, fresh or frozen transfer, and the order of the embryo transfer (fresh first or frozen first).

Parameter	Fresh first (n = 617)		Frozen first (n = 82)		*P* value: fresh first, frozen first
	Fresh (n = 310)	Frozen (n = 307)	Fresh (n = 40)	Frozen (n = 42)	
Gestational age (d)	272.1 (270.0–274.3)	271.2 (269.6–272.8)	270.7 (266.1–275.3)	276.1 (272.7–279.4)	ns, ns
Birth weight (g)	3,166.9 (3,091.5–3,242.3)	3,216 (3,151.1–3,282. 1)	3,267.3 (3,076.2–3,458.4)	3,254.9 (3,096.3–3,413.2)	ns, ns
Percentile	46.3 (42.9–49.7)	51.1 (47.7–54.6)	56.6 (46.8–66.4)	46.8 (37.33–56.3)	ns, ns
z-Score	−0.05 (−0.18 to 0.07)	0.03 (−0.08 to 0.14)	0.11 (−0.20 to 0.42)	0.09 (−0.17 to 0.35)	ns, ns
SGA (%)	9.0	12.4	15.0	14.3	ns, ns
LGA (%)	14.2	10.7	10.0	14.3	ns, ns
Macrosomy (%)	0.3	1.0	0	0	ns, ns
ONR (%)	23.2	23.1	25.0	28.6	ns, ns
	Fresh vs. Frozen		**Fresh vs. Frozen**		
	Crude OR (n = 617)	**Adjusted OR (n = 540)**	**Crude OR (n = 82)**	**Adjusted OR (n = 78)**	
SGA	1.42 (0.85–2.38)	1.60 (0.76–3.40)	0.94 (0.28–3.21)	1.37 (0.20–9.31)	ns, ns
LGA	0.73 (0.45–1.18)	0.82 (0.39–1.73)	1.50 (0.39–5.77)	0.84 (0.12–6.16)	ns, ns
Macrosomy	3.05 (0.32–29.47)	NA	NA	NA	ns, ns
ONR	0.99 (0.68–1.45)	1.18 (0.68–2.06)	1.20 (0.45–3.20)	1.32 (0.31–5.68)	ns, ns

Note: Data presented as %, mean (Sd), or OR (95% CI); n = 699. Abbreviations as in Table 1.

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(OR 1.04, 95% CI 0.74–1.47); and for macrosomy 0.3% versus 0.8% (OR 3.1, 95% CI 0.3–29.7). Mean *z*-scores were 0.28 (95% CI −0.13 to 0.09) versus 0.04 (95% CI −0.06 to 0.14), respectively.

After adjusting for clinically relevant variables, minor changes were noted including the AdjORs: LGA 0.96 (95% CI 0.50–1.87); SGA 1.40 (95% CI 0.72–2.71); ONR 1.20 (95% CI 0.73–1.97); and macrosomy not computable. No statistically significant differences between groups in any comparisons were found.

The Biologic Mother's Genetic Contribution to Birth Weight

Table 1 analyzes the perinatal outcomes comparing fresh and frozen embryos originating from the same (n = 266) or different (n = 94) donor. Data comparing fresh and frozen embryos with the same donor are found in the first two columns. No differences in gestational age or weight were observed between groups, and therefore the percentages of SGA, LGA, and macrosomy were similar. Similar comparisons were performed in the other two columns when the origin of the oocytes was different for a particular recipient. Again, no differences were found between groups with any of the variables tested (Table 1).

The Influence of Mother's Age

Table 2 analyzes the age of the mother at embryo transfer. As can be seen, there are more fresh-first cases, because the usual procedure is to first attempt a fresh transfer and then to try with frozen if the initial transfer is unsuccessful. The percentage of pairs where the first child came from fresh cycles was 89%, and those pairs coming from the frozen-thawed embryo transfer first, and from fresh cycles afterward, represented 11%. In this comparison, the age of the mother was not found to influence birth weight. Also, some patients delivered a child after replacement of frozen embryos and tried again a second and successful cycle with fresh oocytes, from either the same or a different donor. This population is compared in the other two columns of Table 2 to assure that age is not an relevant variable influencing the duration of pregnancy or birth weight.

Embryo Cryopreservation Method

Table 3 addresses the method of freezing-thawing, comparing slow freezing and vitrification. There were no differences in gestational age or birth weight at delivery between fresh and frozen embryos, regardless of the method used for embryo cryopreservation. Accordingly, the rate of birth weight alterations (SGA, LGA, ONR, macrosomy) was not different.

Embryo Developmental Stage

Table 4 presents a comparison of the embryo developmental stages and whether they were fresh or frozen embryos. As can be seen, there were no differences among the different groups compared, showing that the developmental stage of

TABLE 3

Weight difference depending on the embryo's origin, fresh or frozen transfer, and the freezing protocol (slow freezing or vitrification).

	Slow freezing (n = 108)			Vitrification (n = 475)		
Parameter	**Fresh (n = 54)**	**Frozen (n = 54)**	***P* value: fresh vs. frozen**	**Fresh (n = 237)**	**Frozen (n = 238)**	***P* value: fresh vs. frozen**
Gestational age (d)	273.2 (269.3–277.2)	270.6 (265.5–275.6)	ns, ns	272.0 (269.7–274.2)	272.2 (270.4–273.9)	ns, ns
Birth weight (g)	3,308.3 (3,141.7–3,474.8)	3,270.8 (3,086.9–3,454.8)	ns, ns	3,157.6 (3,073.2–3,242.0)	3,217.1 (3,143.4–3,298.9)	ns, ns
Percentile	53.6 (45.3–61.9)	54.7 (46.3–63.1)	ns, ns	45.9 (41.9–49.9)	50.2 (46.3–54.2)	ns, ns
z-Score	0.18 (−0.09 to 0.45)	0.12 (−0.19 to 0.42)	ns, ns	−0.07 (−0.21 to 0.07)	0.03 (−0.09 to 0.15)	ns, ns
SGA (%)	11.1	16.7	ns, ns	10.1	13.0	ns, ns
LGA (%)	9.3	11.1	ns, ns	15.6	11.3	ns, ns
Macrosomy (%)	0	0	ns, ns	0.4	1.3	ns, ns
ONR (%)	20.4	27.8	ns, ns	25.7	24.4	ns, ns
	Fresh vs. Frozen			**Fresh vs. Frozen**		
	Crude OR (n = 108)	**Adjusted OR (n = 97)**		**Crude OR (n = 475)**	**Adjusted OR (n = 458)**	
SGA	1.60 (0.53–4.86)	1.08 (0.14–8.23)	ns, ns	1.33 (0.78–2.34)	2.09 (0.90–4.87)	ns, ns
LGA	1.23 (0.35–4.28)	NA	ns, ns	0.69 (0.41–1.18)	0.91 (0.44–1.90)	ns, ns
Macrosomy	NA	NA	ns, ns	3.01 (0.31–29.17)	NA	ns, ns
ONR	1.50 (0.617–3.67)	1.73 (0.320–9.401)	ns, ns	0.93 (0.61–1.41)	1.41 (0.79–2.53)	ns, ns

Note: Data presented as %, mean (SD), or OR (95% CI); n = 583. Abbreviations as in Table 1.

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TABLE 4

Weight difference depending on the embryo's origin and fresh or frozen transfer, categorized by embryos' developmental stage at replacement.

	ECS both (a) (n = 293)		ECS and blastocyst (b) (n = 216)	
Parameter	**Fresh (n = 149)**	**Frozen (n = 144)**	**Fresh (n = 109)**	**Frozen (n = 107)**
Gestational age (d)	274.2 (271.9–276.5)	272.1 (269.7–274.5)	273.0 (269.3–276.7)	273.0 (270.7–275.3)
Birth weight (g)	3,263.4 (3,165.2–3,361.6)	3,227.7 (3,125.4–3,230.9)	3,131.6 (3,006.2–3,256.9)	3,238.0 (3,139.8–3,336.2)
Percentile	50.6 (45.8–55.5)	51.4 (46.3–56.5)	43.8 (38.2–49.5)	49.9 (44.2–55.7)
z-Score	0.10 (−0.06 to 0.27)	0.05 (−0.11 to 0.21)	−0.01 (−0.03 to 0.09)	0.06 (−0.10 to 0.22)
SGA (%)	10.7	11.8	7.3	11.2
LGA (%)	10.7	11.1	15.6	11.2
Macrosomy (%)	0.7	1.4	0	0.9
ONR (%)	21.5	22.4	22.9	22.4

	Fresh vs. Frozen		Fresh vs. Frozen	
	Crude OR (n = 293)	**Adjusted OR (n = 276)**	**Crude OR (n = 216)**	**Adjusted OR (n = 208)**
SGA	1.11 (0.54–2.23)	0.66 (0.25–1.75)	1.60 (0.63–4.07)	2.75 (0.65–1.67)
LGA	1.04 (0.50–2.17)	1.09 (0.39–3.69)	0.68 (0.31–1.51)	0.97 (0.28–3.33)
Macrosomy	2.09 (0.19–23.24)	NA	NA	NA
ONR	1.09 (0.63–1.89)	0.77 (0.37–1.60)	0.97 (0.51–1.84)	1.67 (0.64–4.39)

Note: Data presented as %, mean (SD), or OR (95% CI); n = 583. ECS = early cleavage stage; other abbreviations as in Table 1. [a]Each *P* value refers consecutively to each category: a) fresh vs. frozen in ECS both; b) fresh vs. frozen in ESC and blastocyst; c) fresh vs. frozen in blastocyst and ESC; d) fresh vs. frozen in blastocyst both.

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the embryo had no influence on duration of gestation or birth weight values.

Cryostorage Time

In Supplemental Table 2 (available online at www.fertstert.org) we analyze the influence on birth weight of the time embryos were frozen. To this end, the time that embryos were kept cryopreserved was divided into four quartiles. As shown, time of cryostorage did not influence birth weight or duration of pregnancy. Accordingly, the rate of birth weight alterations (SGA, LGA, ONR, macrosomy) was not different.

DISCUSSION

This study, based on our OD program and with the use of consecutive singleton sibling pairs, shows that cryopreservation has no positive or negative effect on the duration of pregnancy and birth weight of newborn infants. This is the first study to explore this concept with the use of the OD model. Regarding the individual variables that could influence this message, one was eliminated by the study design (controlled ovarian stimulation [COH]), BMI did not change, and although it was shown that women were older when frozen embryos were replaced, this did not lead to increased birth weight in this group (Supplemental Table 1).

Moreover, there was no observed influence of the freezing method used (slow freezing or vitrification), the genetics of the biologic mother, the stage of embryo development, or the cryostorage period. To further eliminate other confounding variables, we discarded pregnancies with more than one embryo implanted (vanishing twins), although infertility as an independent factor in OD patients can not be completely ruled out (1, 24, 25). Nevertheless, the study is based on a very robust model with a sufficient number of patients, adding strength to our findings.

These results contradict several earlier reports in which a higher weight (9, 11, 13, 26) and higher incidence of LGA and macrosomy were described in children from cryotransfers compared with fresh embryo transfers (12, 15, 16). Similarly, other reports have shown that the prevalence of low birth rates and SGA singletons conceived after the replacement of frozen embryos was reduced relative to that after fresh embryo transfers (6, 8–13, 15).

Our data are in line with studies reporting no differences in perinatal outcomes and birth weight of children born after the replacement of frozen embryos compared with those observed in naturally conceived singletons (9, 13, 17, 27), as well as with reports showing similar birth weights of naturally conceived babies after OD (28, 29).

Even though some publications describing increased weight and incidence of LGA are based on national registries and include many subjects, there is nearly always an implicit problem in these studies: the comparison of a COH with a non-COH cycle. The possible effect of COH on implantation and placental development is a variable that challenges many conclusions (1). With the use of the OD model, we eliminated the possible influence of COH on pregnancy outcome and weight of the newborn infant. COH is thought to create a diminished endometrial receptivity (30, 31) and a poor implantation environment (32). For example, placenta-associated plasma protein (PAPP) levels are lower in the first trimester of pregnancies obtained after COH, reflecting impairment of early implantation (32). Interestingly, decreases in PAPP levels have been associated with higher risk of SGA babies.

The absence of COH in the recipient mother indicates that the protocol of ovarian stimulation and the effects of high estrogen levels on the decidua, implantation, and early events in pregnancy are of paramount importance for determining some features of the newborn infant, particularly because we did not find differences in birth weight or SGA babies. However, an increase in weight resulting in LGA and

TABLE 4

Continued.

Blastocyst and ECS (c) (n = 22)		Blastocyst both (d) (n = 136)		
Fresh (n = 11)	**Frozen (n = 11)**	**Fresh (n = 68)**	**Frozen (n = 68)**	***P* value[a]: a, b, c, d**
263.8 (248.6–279.1)	274.2 (265.7–282.6)	269.6 (264.8–274.4)	269.2 (265.1–273.2)	ns, ns, ns, ns
2,929.56 (2,448.7–3,410.4)	3,130.9 (2,709.3–3,552.5)	3,171.4 (3,003.9–3,339.0)	3,194.1 (3,053.1–3,335.1)	ns, ns, ns, ns
50.9 (27.9–73.9)	43.4 (22.5–64.3)	46.9 (39.4–54.5)	53.33 (45.7–60.8)	ns, ns, ns, ns
−0.44 (−1.23 to 0.34)	−0.11 (−0.81 to 0.58)	−0.05 (−0.32 to 0.23)	−0.01 (−0.24 to 0.22)	ns, ns, ns, ns
0	9.1	11.8	17.6	ns, ns, ns, ns
18.2	18.2	14.7	10.3	ns, ns, ns, ns
0	0	0	0	ns, ns, ns, ns
18.2	27.3	26.5	27.9	ns, ns, ns, ns

Fresh vs. Frozen		Fresh vs. Frozen		
Crude OR (n = 22)	**Adjusted OR (n = 22)**	**Crude OR (n = 136)**	**Adjusted OR (n = 130)**	
NA	NA	1.61 (0.61–4.22)	8.59 (0.99–74.36)	ns, ns, ns, ns
1.00 (0.12–8.73)	NA	0.67 (0.24–1.87)	2.23 (0.32–15.47)	ns, ns, ns, ns
NA	NA	NA	NA	ns, ns, ns, ns
1.69 (0.22–12.81)	NA	1.08 (0.51–2.29)	7.66 (1.41–41.5)	ns, ns, ns, < .05

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macrosomy, which we failed to observe in our OD study, can not be explained with the use of this reasoning. It has been argued that epigenetic alterations related to culture and/or the freezing and thawing techniques might explain these pathologic increases in birth weight (16), similarly to the "large offspring syndrome" observed in nonhuman animal studies (33).

Why this phenomenon is not present in OD babies is unknown, but despite the fact that these babies are immunologically different from those resulting from natural conception (34), no difference in birth weight has been found between these groups, even in the event of preeclampsia, which is a common complication of OD gestations (35).

Other independent variables that may influence the weight of newborn infants and the incidence of SGA and LGA babies also were assessed in our study. One of the most controversial is embryo culture duration. In fact, some have reported that blastocyst culture significantly increased the risk of being born with higher weight (36) or even LGA (19), whereas others did not find increased birth weight (37). Our findings corroborate the latter publication in the sense that the embryo developmental stage does not appear to influence the duration of pregnancy or birth weight in OD pregnancies. In fact, we artificially replaced more blastocysts in the frozen-thawed group and no difference was noted (Supplemental Table 1), including in the extensive analyses included in Table 4.

The higher incidence of LGA babies described after frozen embryo transfer compared with fresh appears to occur in both slow freezing (16) and vitrification (11). However, no study has previously compared both techniques in a single center with the use of sibling cohorts. From our data it can be concluded that the technique used to cryopreserve the embryos has no influence on outcomes. Given that vitrification is increasingly used in modern ART, these data, together with other published observations on perinatal outcomes of vitrified oocytes and embryos (4, 5, 11), are reassuring.

A limitation of our study is that we were not able to adjust for the potentially confounding factors of gestational diabetes and preeclampsia, both of which are quite common in OD pregnancies (35), mainly owing to the fact that pregnancies were followed outside our institution. Therefore, although we could precisely collect the duration of pregnancy and birth weight, we did not have full information regarding other complications of pregnancy. However, even in the event of preeclampsia, no difference has been found in birth weight between OD and naturally conceived children (34).

Moreover, regarding the possibility of introducing a period effect in our data, considered as the consequences of introducing factors affecting outcomes that vary through time in a study, and the potential bias introduced by the fact that slow freezing has been replaced by vitrification in recent years, after reviewing our database we can confirm that this change was not sudden, and a transition period wide enough to disregard this point was found.

Major changes in the laboratory or medical protocols did not coincide with this procedure's introduction, meaning that both techniques, vitrification and slow freezing, have coexisted for several months, thus diluting such effect.

We also acknowledge that, to completely rule out any subtle negative effect of embryo freezing on children's features, a higher-powered sample would be desirable. To detect any slight impairment on children's perinatal parameters, thousands of cases must be analyzed, given the low prevalence or impact of some of them. Nevertheless, we can conclude that no clinically relevant effect on birth weight appeared in our otherwise well designed series.

In conclusion, our study with siblings from OD cycles, eliminating independent variables which affect early events in pregnancy, such as COH, shows no difference in duration of gestation and live birth weights between fetuses obtained after the replacement of fresh or frozen embryos.

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SUPPLEMENTAL TABLE 1

Descriptive characteristics of the compared groups.

Parameter	Fresh	n	Frozen	n	*P* value
Patient					
Mean age (y)	38.5 (38.0–38.9)	356	40.6 (40.1–40.7)	349	< .05
BMI (kg/m^2)	22.8 (22.4–23.2)	342	22.8 (22.4–23.2)	336	ns
Height (cm)	1.63 (1.62–1.63)	345	1.62 (1.62–1.63)	339	ns
Weight (g)	62.4 (61.4–63.4)	344	59.4 (58.4–60.4)	338	ns
Donor					
Mean age (y)	24.4 (23.4–25.3)	347	24.3 (23.3–25.3)	347	ns
BMI (kg/m^2)	22.6 (22.2–22.9)	343	22.5 (22.2–22.9)	344	ns
Height (cm)	1.63 (1.62–1.63)	347	1.62 (1.62–1.63)	347	ns
Weight (g)	59.6 (58.7–60.6)	343	59.4 (58.4–60.4)	344	ns
Oocyte donation					
Vitrified oocytes	22.2%	out of 356	25.8%	out of 349	ns
Donor sperm	3.9%	out of 356	4.4%	out of 349	ns
Day of embryo transfer					
ECS	77.0%	out of 356	43.9%	out of 349	< .05
Blastocyst	23.1%	out of 356	56.0%	out of 349	
Mean no. of embryos transferred	1.96 (1.91–2.01)		1.50 (1.44–1.56)		
Implantation rate (%)	62.8 (60.4–65.2)		78.9 (76.2–81.6)		

Note: BMI = body mass index; ECS = early cleavage stage; ns = nonsignificant difference.

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SUPPLEMENTAL TABLE 2

Risk of weight alterations depending on the embryo's origin, fresh or frozen transfer, and the period of time embryos remained cryopreserved.

	1st quartile (28–210 d) (n = 171)		2nd quartile (211–695 d) (n = 168)	
Parameter	**Fresh (n = 86)**	**Frozen (n = 85)**	**Fresh (n = 83)**	**Frozen (n = 85)**
Gestational age (d)	271.29 (267.5–275.8)	272.56 (269.87–275.26)	268.36 (269.97–276.76)	272.89 (270.65–275.14)
Birth weight (g)	3,098.08 (2,965.09–3,231.07)	3,142.21 (3,033.65–3,250.78)	3,336.79 (3,217.02–3,455.75)	3,329.45 (3,211.30–3,447.59)
Percentile	44.02 (37.33–50.71)	44.61 (38.29–50.93)	53.39 (47.59–59.61)	55.84 (49.39–62.29)
z-Score	−0.17 (−0.39 to 0.05)	−0.09 (−0.27 to 0.08)	0.22 (0.03–0.42)	0.21 (0.19–0.41)
SGA (%)	10.5	9.4	7.2	17.6
LGA (%)	16.3	13.9	6.0	7.1
Macrosomy (%)	0	0	1.2	2.4
ONR (%)	26.7	22.4	13.3	24.7
	Fresh vs. frozen		**Fresh vs. frozen**	
	Crude OR (n = 171)	**Adjusted OR (n = 164)**	**Crude OR (n = 168)**	**Adjusted OR (n = 163)**
SGA	0.89 (0.33–2.42)	0.99 (0.17–5.81)	2.75 (1.01–7.50)	3.91 (0.83–18.37)
LGA	0.76 (0.33–1.80)	2.15 (0.41–11.30)	1.18 (0.35–4.04)	1.37 (0.13–14.27)
Macrosomy	NA	NA	1.98 (0.18–22.22)	NA

Note: Data presented as %, mean (SD), or OR (95% CI). LGA = large for gestational age; ONR = out of normal range (LGA + SGA); ns = nonsignificant difference; SGA = small for gestational age.

Galliano. Ovum-donation siblings have similar birth weights. Fertil Steril 2015.

SUPPLEMENTAL TABLE 2

Continued.

3rd quartile (698–891 d) (n = 160)		4th Quartile (893–1,686 d) (n = 162)		*P* value
Fresh (n = 78)	**Frozen (n = 82)**	**Fresh (n = 80)**	**Frozen (n = 82)**	**1st, 2nd, 3rd, 4th**
273.81 (270.56–277.06)	272.57 (2691.59–275.55)	272.01 (267.39–273.83)	269.91 (265.99–273.83)	ns, ns, ns, ns
3,200.53 (3,056.63–3,344.42)	3,273.51 (3,146.45–3,400.57)	3,149.35 (2,985.12–3,813.58)	3,176.28 (3,033.89–3,318.67)	ns, ns, ns, ns
44.77 (37.50–52.90)	52.25 (45.56–58.92)	48.22 (41.22–55.20)	52.46 (45.40–59.52)	ns, ns, ns, ns
0.01 (−0.24 to 0.24)	0.12 (−0.09 to 0.33)	−0.08 (−0.35 to 0.19)	−0.34 (−0.24 to 0.19)	ns, ns, ns, ns
12.8	11.9	10.0	14.6	ns, ns, ns, ns
19.2	13.4	11.3	11.0	ns, ns, ns, ns
0	1.2	0	0	ns, ns, ns, ns
32.1	24.4	21.3	25.6	ns, ns, ns, ns
Fresh vs. frozen		**Fresh vs. frozen**		
Crude OR (n = 160)	**Adjusted OR (n = 145)**	**Crude OR (n = 162)**	**Adjusted OR (n = 155)**	
0.84 (0.32–2.20)	0.66 (0.14–3.26)	1.54 (0.56–4.00)	0.69 (0.16–3.13)	ns, ns, ns, ns
0.65 (0.29–2.53)	0.53 (0.11–2.53)	0.97 (0.37–2.59)	1.06 (0.21–5.31)	ns, ns, ns, ns
NA	NA	NA	NA	ns, ns, ns, ns

Galliano. Ovum-donation siblings have similar birth weights. Fertil Steril 2015.