Factors associated with large-for-gestational-age infants born after frozen embryo transfer cycles

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Objective: To examine trends of frozen embryo transfer (FET) proportions and large-for-gestational-age (LGA) incidence and determine risk factors for LGA infants after FET.

Design: Retrospective cohort study.

Setting: Not applicable.

Patient(s): Frozen embryo transfer cycles.

Intervention(s): None.

Main Outcome Measure(s): Singleton LGA infant.

Result(s): The percentage of FETs increased from 20%–74% of transfers, whereas the rate of LGA among FET singleton births decreased from 18%–12% during 2004–2018. In a subanalysis of 127,525 FET-associated singleton live births during 2016–2018, patient factors associated with LGA were higher-than-normal maternal body mass index (BMI, 25.0–29.9 kg/m²; adjusted relative risk [aRR], 1.31; 95% confidence interval [CI], 1.26–1.36; BMI, 30.0–34.9 kg/m²; aRR, 1.48; 95% CI, 1.41–1.55; and BMI, >35 Kg/m²; aRR, 1.68; 95% CI, 1.59–1.77) and 1 prior birth vs. none. Low maternal BMI (<18.5 vs. 18.5–24.9 kg/m²) and cycles involving patients who were non-Hispanic (NH) Asian/Native Hawaiian/Pacific Islander, NH Black, or Hispanic (compared with NH White) were at lower risk of LGA infants. Cycle factors associated with LGA included gestational carrier use (aRR, 1.25; 95% CI, 1.16–1.34) and donor sperm (aRR, 1.17; 95% CI, 1.10–1.25).

Conclusion(s): Although the number and proportion of FET cycles increased from 2004–2018, the rate of LGA after FET decreased. Maternal BMI, parity, and race/ethnicity were the strongest risk factors for LGA infants after FET. (Fertil Steril Rep 2022;3:332–41. ©2022 by American Society for Reproductive Medicine.)

Key Words: Frozen embryo transfer, large-for-gestational-age, obstetric outcomes, in vitro fertilization
cycles are associated with increased birth weight, particularly large-for-gestational-age (LGA) infants (6–10). In contrast, it is well documented that fresh embryo transfers are associated with an increased risk of infants that are small for gestational age and with a lower risk of LGA (11, 12). However, the relationship between FET cycles and LGA infants is not well understood (13).

Known risk factors for LGA infants, in both ART and naturally conceived pregnancies, include maternal factors such as diabetes (both preexisting and gestational), obesity, prior macrosomic infant (birth weight > 4,000 g), postterm pregnancy, multiparity, excessive weight gain in pregnancy, maternal race and ethnicity, and infant male sex (12, 14–23). A recent study compared birth weight by method of conception and found that after controlling for several factors, including maternal age, body mass index (BMI), maternal hypertension and diabetes, smoking, and fetal sex, birth weight was significantly higher after FET than that after fresh embryo transfer or natural conception (12). A recent study from China demonstrated an association between increased prepregnancy maternal BMI (> 23 kg/m² per that study) and LGA/macrocosmia after FET (24). Other studies have identified several potential factors related to the freezing of embryos, including cryopreservation techniques, longer exposure to culture media, and absence of a corpus luteum, that may contribute to an increased risk of LGA from FET (13, 25–27).

There are adverse maternal and fetal outcomes associated with LGA. The maternal risk of adverse outcomes is specifically increased in the case of a term macrosomic infant, largely because of the actual size/weight (as opposed to being large for any gestational age, i.e., preterm infant), and includes the increased risk of Cesarean birth, postpartum hemorrhage, intrapartum intrauterine infection, and third- and fourth-degree perineal lacerations (22, 28). An important increased risk to an LGA/macrocosmic infant is shoulder dystocia, which can lead to fetal injuries, such as clavicle fracture, or brachial plexus damage, which can cause permanent nerve palsy (29). Other long-term fetal effects of LGA/macrocosmia include the increased risk of obesity and insulin resistance later in life; some studies also suggest a predisposition to cardiovascular disease (28). A recent systematic review reported that children born with high birth weight and/or LGA have mildly elevated risks of certain childhood malignancies, both type 1 and 2 diabetes, breast cancer, and several psychiatric disorders (30).

Although previous studies, some of which were cited earlier, investigated associations between FET cycle properties and birth weight, few assessed whether a constellation of specific patient and ART cycle characteristics increases the risk of LGA. Additionally, it is unknown whether the many changes in embryo culture and cryopreservation over the last 2 decades have led to alterations in the risk of LGA after FET.

In this article, we examined the trends in FET and fresh cycles performed and the rate of LGA among singleton live births after FET cycles between 2004 and 2018 using data from the National ART Surveillance System (NASS). We then conducted a subanalysis among FET cycles in 2016–2018 that resulted in singleton live births to identify the characteristics of the cycle, including the characteristics of the ART patient with the cycle, that increase the risk of LGA infants. We hypothesized that multiple maternal and cycle characteristics at the time of egg retrieval are associated with the increased risk of LGA after FET.

**MATERIALS AND METHODS**

Data for this study were obtained from the Centers for Disease Control and Prevention’s NASS, which was mandated by the Fertility Clinic Success Rate and Certification Act (Fertility Clinic Success Rate and Certification Act of 1992, Public Law No. 102–493, October 23, 1992) and, as a result, includes information on nearly all (98%) ART cycles performed in US fertility clinics (2). Since 1995, the NASS has collected cycle-level data on patient characteristics, infertility diagnoses, reproductive history, clinical parameters for ART procedures, and resultant pregnancies and births. In this analysis, the subject and unit of analysis is the FET or fresh embryo transfer cycle. The characteristics of the ART patient involved with the cycle are referred to as patient factors. For the subanalysis, we restricted our analyses to FET cycles that resulted in singleton live birth.

**Trend Analysis**

We analyzed 1,993,742 embryo transfer cycles reported to the NASS from 2004–2018 to examine the trends in the proportions of FET vs. fresh embryo transfers. We then examined the rate (%) of LGA among 575,107 cycles resulting in singleton live births conceived from frozen vs. fresh embryo transfer during this time period. Large-for-gestational-age was defined as an infant birth weight (grams) for gestational age (weeks) of >90th percentile according to a gestational age-specific population-based reference by Talge et al. (31). This birth weight reference is based on singleton live births between 22 and 44 weeks of gestational age to US resident women in 2009–2010. Non-LGA was defined as an infant birth weight for gestational age of ≤90th percentile.

**RETROSPECTIVE COHORT ANALYSIS**

To examine factors associated with the risk of LGA after FET, we then conducted a retrospective cohort subanalysis of FET cycles performed during 2016–2018 that resulted in singleton live births (n = 135,512). We excluded cycles that used donated embryos (n = 2,301) and those with unknown infant sex (n = 933) or birth weight (n = 4,125). In addition, we excluded cycles with gestational age of <22 weeks or >44 weeks (n = 378). We further excluded cycles with implausible infant birth weights (n = 250) according to previously published criteria by Alexander et al. (32). Our final analytic cohort was 127,525 FET cycles resulting in singleton live births.

To identify the potential risk factors for LGA after FET, we compared the characteristics of ART patients (age, race/ethnicity, BMI, smoking status, and maximum follicle-stimulating hormone level), maternal reproductive history (parity, gravidity, and reason for ART/infertility
diagnosis), IVF and transfer cycle characteristics (year of cycle start, clinic region, number of thawed embryos transferred, oocyte source, stimulation protocol used for oocyte retrieval, number of oocytes retrieved, use of intracytoplasmic sperm injection, use of assisted hatching, preimplantation genetic testing, embryo quality, and sperm source and collection method), and cycle pregnancy factors (number of fetal heartbeats and infant sex) between LGA and non-LGA outcomes. Because certain IVF cycle characteristics (e.g., stimulation protocol, intracytoplasmic sperm injection, and preimplantation genetic testing) collected during oocyte retrieval are not always carried forward to subsequent FET cycles in the NASS, we used the date of retrieval to link FET cycles to their original oocyte retrieval cycles to obtain relevant data related to retrieval.

To identify cycle characteristics independently associated with LGA after FET, we performed a multivariate modified Poisson regression analysis, including patient factors (age, race and ethnicity, BMI, maximum follicle-stimulating hormone level, parity, gravidity, and reason for ART) and IVF and transfer cycle factors (year of cycle start, clinic region, oocyte source, use of a gestational carrier, use of assisted hatching, use of preimplantation genetic screening, IVF stimulation protocol, number of oocytes retrieved, sperm source, sperm collection method, number of fetal heartbeats, and infant sex). A missing category was created for variables with missing observations to retain observations in the multivariate model. Although most variables had <2% missing data, a larger proportion of missing data were noted for some variables, including patient race/ethnicity (44%) and maternal BMI (15%), as well as for those variables obtained from the initial retrieval cycle.

The χ² and Fisher’s exact tests were used to compare categorical variables between the LGA and non-LGA outcomes for FET cycles. We calculated the means for gestational age and infant birth weight for each of the 2 outcomes. Factors that were selected a priori or that were significantly associated with LGA in univariate analyses were included in the multivariate model. We estimated the adjusted relative risks (aRRs) and 95% confidence intervals (CIs) to determine cycle-level factors associated with the increased risk of LGA after FET (33). All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC), and the results were considered significant at a P value of <.05. Epidemiologic research using NASS data is approved by the institutional review board at the Centers for Disease Control and Prevention.

RESULTS

Trend Analysis

The number and proportion of FET cycles increased from 21,245 FETs (20% of all transfers) in 2004 to 121,521 FETs (74% of all transfers) in 2018 (Fig. 1A). In contrast, the percentage of frozen transfers resulting in singleton LGA infants declined from 18% in 2004 to 12% in 2018 (Fig. 1B). Similarly, the incidence of LGA infants after fresh embryo transfer decreased from 11%–9% during this period. The mean birth weight for singletons conceived via FET cycles declined from a mean of 3,364 g in 2004 to a mean of 3,310 g in 2018 (data not shown).

Subanalysis of FET Cycles

Among the 127,525 FET cycles during 2016–2018 that resulted in singleton live births, 16,374 (12.8%) cycles resulted in LGA infants and 111,151 (87.2%) cycles resulted in non-LGA infants. There were differences in the characteristics of the cycle and the ART patient with the cycle between FET cycles resulting in LGA and non-LGA infants (Table 1). Compared with the non-LGA infant cycles, cycles resulting in LGA infants were more likely to include non-Hispanic (NH) White patients (45.0% vs. 38.0%) and less likely to include NH Black (2.4% vs. 3.1%) or NH Asian, Native Hawaiian, or Pacific Islander (5.8% vs. 11.0%) patients and were more likely to include patients with a BMI of ≥25 kg/m² (43.4% vs. 34.6%) and higher gravidity and parity. Cycle factors associated with LGA included reason for ART (more likely to be male factor infertility or polycystic ovary syndrome and less likely to be diminished ovarian reserve), cycle started in 2016 or 2017, and cycles performed in clinics located in the South and Midwestern regions.

Large-for-gestational-age infants were less likely to have resulted from cycles that used preimplantation genetic testing. There was no observed difference in the quality of embryos that had been transferred between cycles resulting in LGA and non-LGA infants. Fewer infants with LGA were from cycles that resulted in pregnancies with >1 heartbeat at first obstetric ultrasound. Infants with LGA had slightly higher mean gestational age (39.0 vs. 38.8 weeks) at delivery. There was a small yet significant difference in the percentage of male infant sex, with 52.2% men in the LGA cohort and 51.4% men in the non-LGA cohort (P = .04). The mean infant birth weights were 4,098 and 3,210 g in the LGA and non-LGA cohorts, respectively.

In the adjusted model, several variables were significantly associated with LGA among FET cycles (Table 2). The risk of LGA directly increased with increasing maternal BMI (aRR of 1.31 [95% CI, 1.26–1.36] for a BMI of 25.0–29.9 kg/m²; aRR of 1.48 [95% CI, 1.41–1.55] for a BMI of 30.0–34.9 kg/m²; and aRR of 1.68 [95% CI, 1.59–1.77] for a BMI of >35.0 kg/m² compared with a BMI of 18.5–24.9 kg/m²) and increased parity (aRR of 1.36 [95% CI, 1.31–1.41] for 1 prior pregnancy and aRR of 1.38 [95% CI, 1.30–1.46] for ≥2 prior pregnancies compared with none). The use of a gestational carrier and that of donor sperm increased the risk of LGA (aRRs of 1.25 [95% CI, 1.16–1.34] and 1.17 [95% CI, 1.10–1.25], respectively).

There were several factors associated with a decreased relative risk of LGA among FET cycles. The risk of LGA was lower among cycles in which the patient race/ethnicity was NH Asian, Native Hawaiian, or Pacific Islander (aRR, 0.55; 95% CI, 0.51–0.59); NH Black (aRR, 0.64; 95% CI, 0.59–0.71); or Hispanic (aRR, 0.83; 95% CI, 0.76–0.89) than that among cycles that involved NH White patients. The risk of LGA infants was also reduced among cycles in which the maternal BMI was lower than normal (<18.5 vs. 18.5–24.9) (aRR, 0.65; 95% CI, 0.57–0.74). The risk of LGA was lower...
for cycles performed at clinics in the Northeast (aRR, 0.93; 95% CI, 0.89–0.97) and West (aRR, 0.88; 95% CI, 0.84–0.93) regions of the United States than in the Midwest and for cycles in 2018 (aRR, 0.95; 95% CI, 0.92–0.99) than in 2016.

**DISCUSSION**

Our population-based study using the NASS data found that from 2004–2018, the proportion of FET cycles increased from 20%–74% of all transfers performed, whereas the rate of LGA singletons born after FET decreased from 18%–9%. The rate of LGA singletons after fresh embryo transfer also decreased from 11%–9% during this period. In a subanalysis limited to FET cycles during 2016–2018 that resulted in singleton infants, the factors associated with the increased risk of LGA included increasing maternal BMI and parity of ≥1. In contrast, the cycle characteristics associated with the lower risk of LGA included low maternal BMI (<18.5 kg/m²) and cycles involving NH Asian, Native Hawaiian, or Pacific Islander; NH Black; or Hispanic ART patients.

Our study confirmed previous findings that maternal BMI is an independent risk factor for having an LGA infant after FET-associated conceptions, with the risk increasing directly with increasing BMI (21). Although weight loss before FET...
| Characteristic                              | LGA   | 12.8% | Non-LGA | 87.2% | P value |
|--------------------------------------------|-------|-------|---------|-------|---------|
| Patient age at cycle start (y)             |       |       |         |       |         |
| 16–24                                      | 97    | 0.6%  | 801     | 0.7%  | <.0001  |
| 25–29                                      | 1,483 | 9.1%  | 10,350  | 9.3%  |         |
| 30–34                                      | 5,631 | 34.4% | 37,815  | 34.0% |         |
| 35–39                                      | 6,165 | 37.7% | 40,109  | 36.1% |         |
| 40–44                                      | 2,353 | 14.4% | 16,628  | 15.0% |         |
| ≥45                                        | 645   | 3.9%  | 5,448   | 4.9%  |         |
| Patient race and ethnicity<sup>a</sup>     |       |       |         |       | <.0001  |
| Hispanic                                   | 600   | 3.7%  | 4,206   | 3.8%  |         |
| NH American Indian or Alaska Native        | 32    | 0.2%  | 173     | 0.2%  |         |
| NH Asian, Native Hawaiian, Pacific Islander| 950   | 5.8%  | 12,183  | 11.0% |         |
| NH Black                                   | 393   | 2.4%  | 3,392   | 3.1%  |         |
| NH White                                   | 7,365 | 45.0% | 42,201  | 38.0% |         |
| Missing                                     | 7,034 | 43.0% | 48,996  | 44.1% |         |
| Maternal body mass index (kg/m<sup>2</sup>)<sup>a</sup> |       |       |         |       | <.0001  |
| <18.5                                      | 207   | 1.3%  | 2,874   | 2.6%  |         |
| 18.5–24.9                                  | 6,396 | 39.1% | 52,812  | 47.5% |         |
| 25.0–29.9                                  | 3,784 | 23.1% | 22,597  | 20.3% |         |
| 30.0–34.9                                  | 1,864 | 11.4% | 9,533   | 8.4%  |         |
| ≥35.0                                      | 1,457 | 8.9%  | 6,286   | 5.7%  |         |
| Missing                                     | 2,666 | 16.3% | 17,049  | 15.3% |         |
| Patient smoking history<sup>b</sup>        |       |       |         |       | .27     |
| Yes (within 3 mo of cycle start)           | 253   | 1.6%  | 1,542   | 1.4%  |         |
| No                                         | 14,419| 88.1% | 97,964  | 88.1% |         |
| Missing                                     | 1,702 | 10.4% | 11,645  | 10.5% |         |
| Patient maximum FSH level<sup>b</sup> (mIU/mL) |       |       |         |       | <.0001  |
| <4.0                                       | 340   | 2.1%  | 2,680   | 2.4%  |         |
| 4.0–9.9                                    | 8,189 | 50.0% | 54,309  | 48.9% |         |
| ≥10                                        | 1,933 | 11.8% | 14,936  | 13.4% |         |
| Missing                                     | 5,912 | 36.1% | 39,226  | 35.3% |         |
| Parity                                     |       |       |         |       | <.0001  |
| 0                                          | 8,376 | 51.2% | 68,189  | 61.3% |         |
| 1                                          | 5,980 | 36.5% | 32,209  | 29.0% |         |
| ≥2                                         | 1,746 | 10.7% | 9,196   | 8.3%  |         |
| Missing                                     | 272   | 1.7%  | 1,557   | 1.4%  |         |
| Gravidity                                  |       |       |         |       | <.0001  |
| 0                                          | 4,839 | 29.6% | 39,087  | 35.8% |         |
| 1                                          | 4,941 | 30.2% | 31,748  | 28.6% |         |
| ≥2                                         | 6,322 | 38.6% | 38,039  | 34.2% |         |
| Missing                                     | 272   | 1.7%  | 1,557   | 1.4%  |         |
| Reason(s) for ART<sup>b</sup>              |       |       |         |       | .01     |
| Diminished ovarian reserve                  | 3,415 | 20.9% | 25,903  | 23.3% |         |
| History of endometriosis                   | 1,226 | 7.5%  | 7,890   | 7.1%  | .07     |
| Male factor infertility                    | 5,565 | 34.0% | 35,642  | 32.1% | <.0001  |
| Polycystic ovary syndrome                   | 2,608 | 15.9% | 16,537  | 14.9% | .0005   |
| Tubal factor                               | 1,736 | 10.6% | 11,840  | 10.7% | .86     |
| Uterine factor                             | 932   | 5.7%  | 6,894   | 6.2%  | .01     |
| Recurrent pregnancy loss                   | 604   | 3.7%  | 4,091   | 3.7%  | .95     |
| Other factors                              | 3,862 | 23.6% | 27,929  | 24.6% | .01     |
| Unexplained                                 | 2,125 | 13.0% | 14,721  | 13.2% | .35     |
| Year of FET cycle start                    |       |       |         |       | <.0001  |
| 2016                                       | 4,621 | 28.2% | 30,812  | 27.7% | .0003   |
| 2017                                       | 5,596 | 34.2% | 36,737  | 33.1% |         |
| 2018                                       | 6,157 | 37.6% | 43,602  | 39.2% |         |
| Clinic region                              |       |       |         |       | .01     |
| Northeast                                  | 4,430 | 27.1% | 30,572  | 27.5% | <.0001  |
| Midwest                                    | 2,898 | 17.7% | 16,761  | 15.1% |         |
| South (including Puerto Rico)              | 4,899 | 29.5% | 31,052  | 27.9% |         |
| West                                       | 4,154 | 25.4% | 32,766  | 29.5% |         |

*Roshong. Factors associated with LGA after FET. Fertil Steril Rep 2022.*
| Characteristic                        | LGA N = 16,374 | LGA 12.8% | Non-LGA N = 111,151 | Non-LGA 87.2% | P value |
|--------------------------------------|----------------|-----------|---------------------|---------------|---------|
| No. of thawed embryos transferred    |                |          |                     |               |         |
| 1                                    | 13,032         | 79.6%    | 88,593              | 79.7%         | .9389   |
| 2                                    | 3,208          | 19.6%    | 21,646              | 19.5%         |         |
| ≥3                                   | 134            | 0.8%     | 912                 | 0.8%          |         |
| Oocyte source                        |                |          |                     |               |         |
| Patient                              | 14,487         | 88.5%    | 96,674              | 87.0%         | <.0001  |
| Donor                                | 1,887          | 11.5%    | 14,477              | 13.0%         |         |
| Gestational carrier                  |                |          |                     |               |         |
| Yes                                  | 1,022          | 6.2%     | 6,469               | 5.8%          | .03     |
| No                                   | 15,352         | 93.8%    | 104,682             | 94.2%         |         |
| Assisted hatching                    |                |          |                     |               |         |
| Yes                                  | 16,048         | 98.0%    | 108,527             | 97.6%         |         |
| No                                   | 294            | 1.8%     | 2,356               | 2.1%          |         |
| Missing                              | 32             | 0.2%     | 268                 | 0.2%          |         |
| Intracytoplasmic sperm injectiona    |                |          |                     |               | <.0001  |
| Yes                                  | 12,026         | 73.4%    | 84,513              | 76.0%         |         |
| No                                   | 1,982          | 12.1%    | 13,334              | 12.0%         |         |
| Missing                              | 2,366          | 14.4%    | 13,304              | 12.0%         |         |
| Preimplantation genetic testinga     |                |          |                     |               | <.0001  |
| Yes                                  | 8,414          | 51.4%    | 61,278              | 55.1%         |         |
| No                                   | 7,926          | 48.4%    | 49,661              | 44.7%         |         |
| Missing                              | 34             | 0.2%     | 212                 | 0.2%          |         |
| Stimulation protocolc                |                |          |                     |               |         |
| No GnRH protocol                     | 931            | 5.7%     | 7,747               | 7.0%          | <.0001  |
| GnRH agonist suppression             | 1,030          | 6.3%     | 6,901               | 6.2%          |         |
| GnRH agonist flare                   | 598            | 3.7%     | 4,472               | 4.0%          |         |
| GnRH antagonist suppression          | 8,559          | 52.3%    | 62,145              | 55.9%         |         |
| Missing                              | 5,256          | 32.1%    | 29,886              | 26.9%         |         |
| No. of oocytes retrievedc            |                |          |                     |               |         |
| 0–4                                  | 394            | 2.4%     | 3,441               | 3.1%          | <.0001  |
| 5–9                                  | 1,602          | 9.8%     | 12,674              | 11.4%         |         |
| 10–19                                | 4,868          | 29.7%    | 34,874              | 31.4%         |         |
| 20–29                                | 2,805          | 17.1%    | 19,919              | 17.9%         |         |
| ≥30                                  | 1,481          | 9.0%     | 10,632              | 9.6%          |         |
| Missing                              | 5,224          | 31.9%    | 29,611              | 26.6%         |         |
| Sperm sourcec                        |                |          |                     |               | <.0001  |
| Partner                              | 10,133         | 61.9%    | 75,381              | 67.8%         |         |
| Donor/male patient/mixed             | 959            | 5.9%     | 5,736               | 5.2%          |         |
| Missing                              | 5,282          | 32.3%    | 30,034              | 27.0%         |         |
| Semen collection methodc             |                |          |                     |               | <.0001  |
| Ejaculation                          | 10,702         | 65.4%    | 78,244              | 70.4%         |         |
| Other                                | 395            | 2.4%     | 2,904               | 2.6%          |         |
| Missing                              | 5,277          | 32.2%    | 30,003              | 27.0%         |         |
| Embryo qualitya                      |                |          |                     |               | .09     |
| Good                                 | 9,992          | 61.0%    | 68,698              | 61.8%         |         |
| Fair                                 | 3,019          | 18.4%    | 19,603              | 17.6%         |         |
| Poor                                 | 170            | 1.0%     | 1,171               | 1.1%          |         |
| Missing                              | 3,193          | 19.5%    | 21,679              | 19.5%         |         |
| No. of fetal heartbeats             |                |          |                     |               | <.0001  |
| 1                                    | 15,784         | 96.4%    | 106,163             | 95.5%         |         |
| ≥2                                   | 307            | 1.9%     | 2,739               | 2.5%          |         |
| Missing                              | 283            | 1.7%     | 2,249               | 2.0%          |         |
| Infant sex                           |                |          |                     |               |         |
| Male                                 | 8,551          | 52.2%    | 57,106              | 51.4%         | .04     |
| Female                               | 7,823          | 47.8%    | 54,045              | 48.6%         |         |
| Mean gestational age (wk)            | 39.0           |          | 38.8                |               | <.0001  |
| Mean infant birth weight (g)         | 4,098          |          | 3,210               |               |         |

Note: ART = assisted reproductive technology; FET = frozen embryo transfer; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LGA = large-for-gestational age; NH = non-Hispanic.

* Data obtained from both transfer and retrieval cycles.

a Reasons for ART are not mutually exclusive.

b Data from retrieval cycles only, thus not available for transfer cycles that did not link to retrieval cycle.

Roshong. Factors associated with LGA after FET. Fertil Steril Rep 2022.
### TABLE 2

Relative risk of large-for-gestational-age infants conceived from frozen embryo transfer cycles resulting in singleton live births.

| Variable | Unadjusted | Adjusted<sup>a</sup> |
|----------|------------|---------------------|
|          | RR         | 95% CI              | aRR      | 95% CI              |
| **Patient age at cycle start (y)** | | | | |
| 16–24    | 0.86       | (0.70–1.04)         | 0.88     | (0.72–1.07)         |
| 25–29    | Ref.       | Ref.                | Ref.     | Ref.                |
| 30–34    | 1.04       | (0.98–1.09)         | 1.02     | (0.96–1.07)         |
| 35–39    | 1.06       | (1.01–1.12)         | 1.03     | (0.97–1.09)         |
| 40–44    | 0.99       | (0.93–1.05)         | 1.00     | (0.93–1.06)         |
| ≥45      | 0.85       | (0.78–0.93)         | 0.87     | (0.79–0.97)         |
| **Patient race and ethnicity<sup>b</sup>** | | | | |
| Hispanic | 0.84       | (0.78–0.91)         | 0.83     | (0.76–0.89)         |
| NH American Indian or Alaska Native | 1.06       | (0.77–1.46)         | 1.07     | (0.78–1.48)         |
| NH Asian, Native Hawaiian or Pacific Islander | 0.49       | (0.46–0.52)         | 0.55     | (0.51–0.59)         |
| NH Black | 0.70       | (0.64–0.77)         | 0.64     | (0.59–0.71)         |
| NH White | Ref.       | Ref.                | Ref.     | Ref.                |
| **Maternal body mass index (kg/m²)<sup>b</sup>** | | | | |
| <18.5    | 0.62       | (0.54–0.71)         | 0.65     | (0.57–0.74)         |
| 18.5–24.9| Ref.       | Ref.                | Ref.     | Ref.                |
| 25.0–29.9| 1.32       | (1.27–1.37)         | 1.31     | (1.26–1.36)         |
| 30.0–34.9| 1.51       | (1.44–1.58)         | 1.48     | (1.41–1.55)         |
| ≥35.0    | 1.74       | (1.65–1.83)         | 1.68     | (1.59–1.77)         |
| **Patient maximum FSH level (mIU/mL)<sup>b</sup>** | | | | |
| <4.0     | 0.86       | (0.78–0.96)         | 0.88     | (0.80–0.98)         |
| 4.0–9.9  | Ref.       | Ref.                | Ref.     | Ref.                |
| ≥10      | 0.87       | (0.84–0.92)         | 0.95     | (0.90–0.99)         |
| **Parity** | | | | |
| 0        | Ref.       | Ref.                | Ref.     | Ref.                |
| 1        | 1.43       | (1.39–1.47)         | 1.36     | (1.31–1.41)         |
| ≥2       | 1.45       | (1.39–1.53)         | 1.38     | (1.30–1.46)         |
| **Gravidity** | | | | |
| 0        | Ref.       | Ref.                | Ref.     | Ref.                |
| 1        | 1.24       | (1.20–1.29)         | 1.02     | (0.97–1.07)         |
| ≥2       | 1.32       | (1.27–1.36)         | 1.02     | (0.97–1.07)         |
| **Reasons for ART (yes vs. no)** | | | | |
| Diminished ovarian reserve | 0.88       | (0.85–0.91)         | 1.00     | (0.96–1.05)         |
| Male factor infertility | 1.08       | (1.05–1.11)         | 1.05     | (1.02–1.09)         |
| Polycystic ovary syndrome | 1.07       | (1.03–1.11)         | 0.99     | (0.95–1.03)         |
| Uterine factor | 0.93       | (0.87–0.98)         | 0.93     | (0.88–1.00)         |
| **Year of cycle start** | | | | |
| 2016     | Ref.       | Ref.                | Ref.     | Ref.                |
| 2017     | 1.02       | (0.98–1.06)         | 1.02     | (0.98–1.06)         |
| 2018     | 0.96       | (0.93–0.99)         | 0.95     | (0.92–0.99)         |
| **Clinic region** | | | | |
| Northeast | 0.86       | (0.82–0.90)         | 0.93     | (0.89–0.97)         |
| Midwest  | Ref.       | Ref.                | Ref.     | Ref.                |
| South    | 0.92       | (0.88–0.96)         | 0.98     | (0.94–1.03)         |
| West     | 0.76       | (0.73–0.80)         | 0.88     | (0.84–0.93)         |
| **Oocyte source** | | | | |
| Patient vs. donor | 1.13       | (1.08–1.18)         | 1.16     | (1.08–1.24)         |
| Gestational carrier (yes vs. no) | 1.07       | (1.01–1.14)         | 1.25     | (1.16–1.34)         |
| Assisted hatching used (yes vs. no) | 1.16       | (1.04–1.29)         | 1.06     | (0.95–1.18)         |
| Preimplantation genetic testing used (yes vs. no) | 0.88       | (0.85–0.90)         | 0.98     | (0.95–1.01)         |
| **Stimulation protocol<sup>c</sup>** | | | | |
| No GnRH protocol | 0.89       | (0.83–0.95)         | 0.95     | (0.89–1.02)         |
| GnRH agonist suppression | 1.08       | (1.01–1.15)         | 1.03     | (0.97–1.10)         |
| GnRH agonist flare | 0.97       | (0.90–1.05)         | 0.99     | (0.92–1.08)         |
| GnRH antagonist suppression | Ref.      | Ref.                | Ref.     | Ref.                |
| **Number of oocytes retrieved<sup>d</sup>** | | | | |
| 0–4      | 0.84       | (0.76–0.92)         | 0.91     | (0.83–1.01)         |
| 5–9      | 0.92       | (0.87–0.97)         | 0.93     | (0.89–0.99)         |
| 10–19    | Ref.       | Ref.                | Ref.     | Ref.                |
| 20–29    | 1.00       | (0.96–1.05)         | 1.01     | (0.97–1.06)         |
| ≥30      | 1.00       | (0.94–1.05)         | 1.02     | (0.96–1.08)         |
| **Sperm source<sup>e</sup>** | | | | |
| Partner | Ref.       | Ref.                | Ref.     | Ref.                |
| Other (donor, male patient, or mixed) | 1.21       | (1.14–1.29)         | 1.17     | (1.10–1.25)         |

*Roshong. Factors associated with LGA after FET. Fertil Steril Rep 2022.*
cycles has been hypothesized to improve live-birth rates in certain patients [34], to our knowledge, no study has investigated the effect of patient weight loss on infant weight after FET cycles. The risk of LGA was lower after FET performed at clinics in the Northeast and West than that after FET cycles performed at clinics in the Midwest. This finding may reflect the lower prevalence of obesity in these regions [35] or other unmeasured factors. Our study found a small increased risk of LGA (aRR, 1.04; 95% CI, 1.02–1.07) in cycles involving male infants after FET. This is consistent with previous reports that suggest that male infants are more likely to be LGA than female infants regardless of IVF or spontaneous pregnancy [14, 36].

Several previous studies that assessed the LGA risk in FET cycles did not report patient race and ethnicity, often instead reporting country of origin. Most of these studies were performed in Scandinavian countries with predominantly White populations [12, 27, 37]. However, an analysis of all births in California in 2007 found that Hispanic, Asian, and Black women had a lower risk of delivering infants with macrosomia than White women [23]. Our study demonstrated that compared with cycles involving NH White ART patients, cycles involving NH Asian, Native Hawaiian, or Pacific Islander; NH Black; and Hispanic patients had a lower risk of LGA after FET. Our subanalysis only included FET cycles; therefore, it is unclear whether the relationship observed between race and ethnicity and LGA risk in our study is specific to FET-associated deliveries.

Several IVF and FET cycle factors were included in our subanalysis, including oocyte source (donor vs. patient), use of a gestational carrier, source of sperm (donor vs. partner), and number of fetal heartbeats noted on the first obstetric ultrasound. Although cycles involving gestational carriers and the use of donor sperm were associated with a statistically significant increased risk of LGA, the clinical significance of these differences is unclear. Interestingly, having >1 fetal heartbeat on the first obstetric ultrasound (which ultimately became a singleton gestation) was associated with a decreased likelihood of LGA. One possible explanation for this finding is that “vanishing twin” phenomenon is associated with smaller placentas and the increased likelihood of anatomic pathology, such as velamentous course insertion, which can contribute to fetal growth restriction [38].

Unfortunately, the NASS data did not include FET cycle protocols or regimens (i.e., natural vs. stimulated cycle, endometrial preparation regimen, and cryopreservation technique) as part of the reporting information; therefore, our study could not assess the association of these cycle characteristics on the risk of LGA. A recent retrospective cohort study conducted by Wang et al. [37] analyzed the endometrial preparation protocols in more than 9,000 singleton live births and found that singleton newborns conceived after programmed cycle (i.e., with exogenous estradiol and progesterone) FET were more likely to be LGA than those born after natural cycle FET or stimulated cycle FET. These data, coupled with earlier studies that noted associations between factors related to the freezing of embryos (cryopreservation protocols, culture media exposure, and absence of a corpus luteum), suggest that the FET protocols, along with maternal factors, influence fetal birth weight and increase the risk of LGA in FET cycles [4–6, 39].

Our analysis of the NASS data showed that the LGA rates after FET decreased from 18% in 2004 to 12% in 2018. Interestingly, a recently published retrospective cohort study from a single US fertility clinic by Shah et al. [40] demonstrated that between August 1995 and October 2019, changes in the IVF protocols coincide with the decreased rates of LGA infants after FET. This study analyzed several different time points in the evolution of IVF regimens, including vitrification at the blastocyst stage (2011), the use of benchtop incubators (2012), and single-step embryo culture media (2013). The percentage of LGA infants decreased at each time point.

Because the NASS data comprise 98% of all IVF cycles in the United States, our study represents one of the largest and most comprehensive studies to evaluate the risk factors for LGA after FET cycles. Limitations include the retrospective nature of this study, risk of selection bias using retrospective cohort design methodology, large percentages of missing data.
on BMI and race and ethnicity, and inability to link 27% of FET cycles to their preceding egg retrievals or ovarian stimulation cycles. Missing data are a large concern for studies that use large data sets and may limit generalizability of results [41]. Techniques including available case analysis, several types of data imputation, and the use of the missing data as a subvariable are used to treat these missing data [42]. We chose to use missing data as a subvariable in our analysis, and with the lack of large clinical differences in missing data between cohorts, we did not further seek specific data imputation. In addition, several important cycle variables (e.g., estradiol or progesterone levels on day of trigger) were unavailable in the NASS. The NASS data, similar to the use of data in other large databases, may also have included repeated treatment cycles by the same individual. Moreover, limiting our study to cycles that resulted in singleton deliveries may have resulted in selection bias by the predominant inclusion of good prognosis patients. Our data demonstrate that approximately 79% of all patients received a single embryo transfer, which is commonly selected for patients with a favorable prognosis for live birth [43]. However, by excluding multiple pregnancies, we aimed to minimize confounding given the known growth abnormalities associated with multiple pregnancies [44]. Studies using large databases often find significant results for variables that may have limited clinical significance [41]. Similarly, our analysis found several statistically significant associations that may or may not be clinically significant, such as differences among regions of the United States or by infant sex.

CONCLUSION

In conclusion, although the number and proportion of FET cycles dramatically increased from 2004–2018, the incidence of LGA after both fresh embryo transfer and FET decreased during the same time period. The incidence of LGA after FET was greater than the incidence after fresh embryo transfer. Among singleton infants resulting from FET in 2016–2018, the patient factors of maternal BMI, parity, and race/ethnicity were the strongest independent risk factors for LGA. Cycle factors that increased the risk of LGA were donor sperm and gestational carrier use. Because many of these factors are also known to increase the risk of LGA in non-ART pregnancies, the cause for the increased risk of LGA in FET cycles remains unclear. Focus on modifiable factors (e.g., BMI) may be helpful to reduce the risk of LGA in FET cycle patients; however, continued research is needed to uncover the pathophysiological cause of this relationship.

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