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 (body mass index [BMI], 25.0–29.9 kg/m^2; adjusted relative risk [aRR], 1.31; 95% confidence interval [CI], 1.26–1.36; BMI, 30.0–34.9 kg/m^2; aRR, 1.48; 95% CI, 1.41–1.55; and BMI, >35 Kg/m^2; 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/m^2) 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

The practice of frozen embryo transfer (FET) is well established in the field of assisted reproductive technology (ART) and in vitro fertilization (IVF). It has become increasingly used in recent years, over the practice of fresh embryo transfer (1, 2). The freezing of supernumerary embryos generated as a result of a single egg retrieval cycle allows ART patients the chance to transfer another embryo if the first attempt is not successful or to continue to build their family size. Furthermore, studies have demonstrated that "freeze-all" cycles reduce the risk of ovarian hyperstimulation syndrome and may increase success rates over fresh embryo transfer in some ART patients, such as those with elevated progesterone levels and polycystic ovary syndrome (3–5).

Although FET has allowed for improvements in pregnancy success rates in certain ART patients and has practical applications and advantages, numerous studies suggest that FET

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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/m^2 per that study) and LGA/macrosomia 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/macrosomic 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/macrosomia 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 χ^2 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 analysis. 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

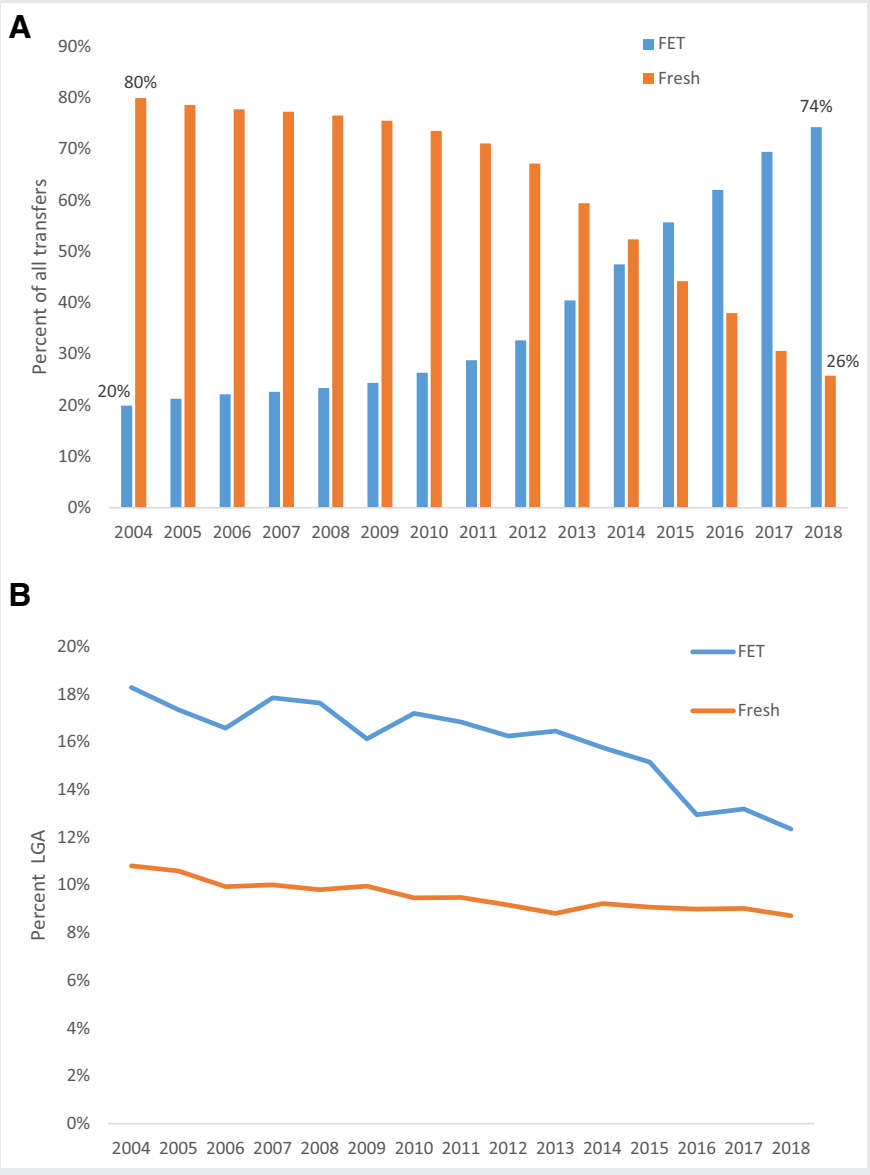
Among the 127,525 FET cycles during 2016–2018 that resulted in singleton live births, 16,374 (12.8%) cycles resulted in LGA infants and 111,151 (87.2%) cycles resulted in non-LGA infants. There were differences in the characteristics of the cycle and the ART patient with the cycle between FET cycles 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/m^2 (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/m^2; aRR of 1.48 [95% CI, 1.41–1.55] for a BMI of 30.0–34.9 kg/m^2; and aRR of 1.68 [95% CI, 1.59–1.77] for a BMI of >35.0 kg/m^2 compared with a BMI of 18.5–24.9 kg/m^2) 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

FIGURE 1



(A) Trends in the percentages of all embryo transfer cycles that used fresh vs. frozen embryos, 2004–2018. **(B)** Trends in the percentages of singleton births that were large-for-gestational-age resulting from fresh embryo transfers vs. frozen embryo transfers, 2004–2018. FET = frozen embryo transfer.

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

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%–12%. 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/m^2) 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

TABLE 1

Assisted reproductive technology patient, cycle, and infant characteristics of frozen embryo transfer cycles resulting in LGA vs. non-LGA singleton infants, NASS, 2016–2018.

	LGA		Non-LGA		
	N = 16,374	12.8%	N = 111,151	87.2%	
Characteristic	**No.**	**%**	**No.**	**%**	***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[a]					
Hispanic	600	3.7%	4,206	3.8%	<.0001
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^2)[a]					
<18.5	207	1.3%	2,874	2.6%	<.0001
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	8.6%	
≥35.0	1,457	8.9%	6,286	5.7%	
Missing	2,666	16.3%	17,049	15.3%	
Patient smoking history[a]					
Yes (within 3 mo of cycle start)	253	1.6%	1,542	1.4%	.27
No	14,419	88.1%	97,964	88.1%	
Missing	1,702	10.4%	11,645	10.5%	
Patient maximum FSH level[a] (mIU/mL)					
<4.0	340	2.1%	2,680	2.4%	<.0001
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					
0	8,376	51.2%	68,189	61.3%	<.0001
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					
0	4,839	29.6%	39,807	35.8%	<.0001
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[b]					
Diminished ovarian reserve	3,415	20.9%	25,903	23.3%	<.0001
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%	27,290	24.6%	.01
Unexplained	2,125	13.0%	14,721	13.2%	.35
Year of FET cycle start					
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					
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	29.9%	31,052	27.9%	
West	4,154	25.4%	32,766	29.5%	

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TABLE 1

Continued.

	LGA		Non-LGA		
	N = 16,374	12.8%	N = 111,151	87.2%	
Characteristic	**No.**	**%**	**No.**	**%**	***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					.03
Yes	1,022	6.2%	6,469	5.8%	
No	15,352	93.8%	104,682	94.2%	
Assisted hatching					.006
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 injection[a]					<.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 testing[a]					<.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 protocol[c]					
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 retrieved[c]					
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 source[c]					
Partner	10,133	61.9%	75,381	67.8%	<.0001
Donor/male patient/mixed	959	5.9%	5,736	5.2%	
Missing	5,282	32.3%	30,034	27.0%	
Semen collection method[c]					
Ejaculation	10,702	65.4%	78,244	70.4%	<.0001
Other	395	2.4%	2,904	2.6%	
Missing	5,277	32.2%	30,003	27.0%	
Embryo quality[a]					.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.

[a] Data obtained from both transfer and retrieval cycles.

[b] Reasons for ART are not mutually exclusive.

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

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TABLE 2

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

	Unadjusted		Adjusted[a]	
Variable	**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.	
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[b]				
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.	
Maternal body mass index (kg/m^2) [b]				
<18.5	0.62	(0.54–0.71)	0.65	(0.57–0.74)
18.5–24.9	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)[b]				
<4.0	0.86	(0.78–0.96)	0.88	(0.80–0.98)
4.0–9.9	Ref.		Ref.	
≥10	0.87	(0.84–0.92)	0.95	(0.90–0.99)
Parity				
0	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.	
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.	
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.	
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[c]				
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.	
Number of oocytes retrieved[c]				
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.	
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[c]				
Partner	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.

TABLE 2

Continued.

Variable	Unadjusted RR	Unadjusted 95% CI	Adjusted[a] aRR	Adjusted[a] 95% CI
Semen collection method[c]				
Ejaculation	Ref.		Ref.	
Other	1.00	(0.91–1.10)	0.96	(0.88–1.06)
Number of fetal heartbeats				
1	Ref.		Ref.	
≥2	0.78	(0.70–0.86)	0.76	(0.68–0.84)
Infant sex				
Male	1.03	(1.00–1.06)	1.04	(1.02–1.07)
Female	Ref.		Ref.	

Note: ARR = adjusted relative risk; ART = assisted reproductive technology; CI = confidence interval; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; NH = non-Hispanic; Ref. = referent; RR = relative risk.

[a] The multivariate model included age, race and ethnicity, body mass index, maximum FSH, parity, gravidity, reason for ART, year of cycle start, clinic region, oocyte source, use of a gestational carrier, assisted hatching, preimplantation genetic testing, stimulation protocol, number of oocytes retrieved, sperm source, semen collection method, number of fetal heartbeats, and infant sex.

[b] Data obtained from both transfer and retrieval cycles.

[c] Information obtained from retrieval cycles only, thus not available for transfer cycles that did not link to prior retrieval cycle.

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.

CONLUSION

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 pathophysiologic cause of this relationship.

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