Infertility treatment and the risk of small for gestational age births: a population-based study in the United States

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Objective: To evaluate the association between infertility treatments and small for gestational age (SGA) births.
Design: Cross-sectional study.
Setting: United States, 2015–2019.
Patient(s): Women (n = 16,836,228) who delivered nonmalformed, singleton live births (24–44 weeks' gestation).
Intervention(s): Any infertility treatment, including assisted reproductive technology (ART) and prescribed fertility-enhancing medications.
Main Outcome Measure(s): Small for gestational age birth, defined as sex-specific birth weight <10% for gestational age. Associations between SGA and infertility treatment were derived from Poisson regression with robust variance. Risk ratios (RR) and 95% confidence intervals (CI) were derived after adjusting for confounders. In a sensitivity analysis, we corrected for nondifferential exposure misclassification and unmeasured confounding biases.
Result(s): Subsequently, 1.4% (n = 231,177) of pregnancies resulted from infertility treatments (0.8% ART and 0.6% fertility-enhancing medications). Of these, SGA births occurred in 9.4% (n = 21,771) and 11.9% (n = 1,755,925) of pregnancies conceived with infertility treatment and naturally conceived pregnancies, respectively (adjusted RR, 1.07; 95% CI, 1.06, 1.08). However, after correction for misclassification bias and unmeasured confounding, infertility treatment was associated with a 27% reduced risk of SGA (bias-corrected RR, 0.73; 95% CI, 0.53, 0.85). Similar trends were seen for analyses stratified by exposure to ART and fertility-enhancing medications, as well as for SGA <5th and <3rd percentiles.
Conclusion(s): Exposure to infertility treatment is associated with a reduced risk of SGA births. These findings, which are contrary to some published reports, may reflect changes in the modern practice of infertility care, maternal lifestyle, and compliance with prenatal care within the infertile population. Until these findings are corroborated, the associations must be cautiously interpreted. (Fertil Steril Rep® 2021;2:413–20. ©2021 by American Society for Reproductive Medicine.)
Key Words: Infertility, assisted reproductive technology, small for gestational age, misclassification bias

Infertility treatments are increasingly utilized worldwide to help couples achieve pregnancy and build families. These treatments include assisted reproductive technology (ART), a term that encompasses the use of both in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), as well as other less invasive options, such as prescribed fertility-enhancing medications and intrauterine insemination (IUI). It is estimated that 12.7% of women in the United States (US) between ages 15 and 49 years used some form of fertility services to

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conceive from 2015 to 2017 (1). The National Survey of Family Growth reports that 0.6% of women have used ART, 4.3% have used fertility-enhancing medications, and 2.0% have used IUI (1). The use of these treatments is highest among women of older reproductive age who have delayed childbearing (1).

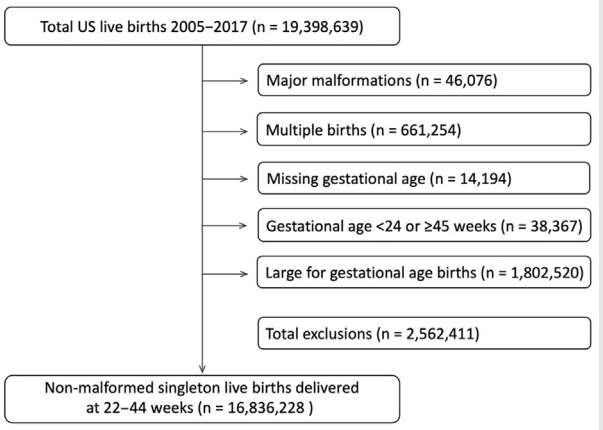
Pregnancies conceived as a result of infertility treatment may be at increased risk of small for gestational age (SGA) births, but there is conflicting data regarding the potential impact of these treatments. Compared with appropriate for gestational age births, infants that are SGA are at increased risk of perinatal morbidity and mortality, and thus, understanding this relationship is of critical clinical importance (2). In a prior population-based study that included over 2 million births, infants conceived from ART had increased rates of adverse outcomes, including a 13% increased odds of SGA births (odds ratio, 1.13; 95% confidence interval [CI], 1.10–1.15) (3). A large meta-analysis found an even greater risk of SGA in pregnancies conceived by ART (RR, 1.35; 95% CI, 1.20–1.52) (4). However, other data suggests that pregnancies conceived with ART are not at increased risk of SGA or are at only a minimally increased risk of this outcome (5). For example, in another population-based review, there was only a slightly increased risk of SGA noted in pregnancies conceived via ART compared with pregnancies conceived in the general fertile population (RR, 1.04; 95% CI, 0.97–1.12) (5).

Clinical practice of infertility has evolved significantly since treatments were first introduced in the early 1980s, and there are several confounding variables involving the use of these interventions that make meaningful analysis of perinatal outcomes challenging. Therefore, we performed this population-based study of live births in the United States to examine the associations between exposure to infertility treatments and SGA births adjusting for potential confounders and correcting for misclassification bias. We hypothesized that infertility treatments are not associated with an increased risk of SGA births after these adjustments.

MATERIALS AND METHODS

We utilized data from the US Vital Statistics System on natality data files, years 2015–2019 (latest year available as of January 2021). These data are assembled by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. These data are provided by every state under uniform coding specifications and transferred to the NCHS for data cleaning and compilation. Demographic variables and outcome data were obtained from the US live birth certificates based on the 2003 revision (6). Gestational age was determined by a best obstetrical estimate, which was a combination of dating based on an ultrasound estimate or clinical estimate (7). Before release, the NCHS removed all personal identifiers, so no ethics approval from our University's Institutional Review Board was necessary. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cross-sectional studies.

FIGURE 1



Flowchart describing the cohort selection.

Glatthorn. Infertility and SGA births. Fertil Steril Rep 2021.

Exposure

Pregnancies conceived with infertility treatment were considered to have the exposure. Infertility treatment was defined as ART—a term that encompasses IVF with or without ICSI—as well as fertility-enhancing medications and other methods such as IUI. Fertility-enhancing medications included injectable gonadotropins, letrozole, and clomiphene citrate, or a composite of such medications. These exposures were compared with naturally conceived pregnancies.

Outcome Measures

The primary outcome was SGA births, defined as live-born infants with birth weight for gestational age below the 10th percentile and corrected for neonatal sex, on the basis of the US singleton live births reference published by Talge et al. (8). We additionally examined the risks of SGA <5th and <3rd percentiles as the secondary outcomes.

Cohort Composition

Of the 19,398,639 total live births that occurred in the United States between 2015 and 2019, we restricted the study to nonmalformed singleton births and excluded large-for-gestational-age births (≥90th percentile). The final study population included women who delivered a nonmalformed, singleton live birth between 24 and 44 weeks' gestation (Fig. 1).

Statistical Analysis

We estimated the risks of SGA births (<10th, <5th, and <3rd percentiles) among women who received infertility treatment and compared these risks among naturally conceived pregnancies from fitting log-linear Poisson regression models with robust variance. The association between any infertility treatment and risks of SGA birth was expressed as risk ratio (RR) and 95% CI. The associations were then adjusted to

account for potential confounders, guided based on directed acyclic graphs (9). The analyses were repeated for only primiparous women to avoid potential bias by birth order and avoid combining first and recurrent SGA births within women. Since the findings were similar for the entire cohort and for primiparous subjects, the overall analysis is presented here.

The confounders included maternal sociodemographic characteristics such as age (grouped in 5-year categories as <15, 15–19, 20–24, 25–29 [reference], 30–34, 35–39, 40–44, 45–49, and ≥50 years), live-born parity (parity 1 [reference], parity 2, or, parity ≥3), maternal education (below high school, high school, college, or beyond college [reference]), marital status (single or married), race/ethnicity (non-Hispanic white [reference], non-Hispanic black, Hispanic, or others), smoking 3 months before pregnancy and during pregnancy (nonsmoker, smoking before pregnancy only, or smoking before and during pregnancy), and prepregnancy body mass index (<18.5, 18.5–24.9 [reference], 25.0–29.9, 30.0–34.9, and ≥35.0, corresponding to underweight, normal weight, overweight, obese, and morbidly obese categories, respectively). In addition, we adjusted for chronic medical conditions including chronic hypertension and pregestational diabetes mellitus. All associations were additionally adjusted for year of delivery. Evaluation of confounders was based on the change in estimate criterion.

Missing Data

The exposure (infertility treatment) and a few covariates contained missing data. Operating under the assumption that the missing data patterns were "missing at random," we imputed missing data based on the multiple imputation by chained equations approach (10). Models were accomplished on the basis of the expectation-maximization algorithm (11) based on 20 imputations. Missing data were modeled based on all covariates listed earlier. Infertility data were missing as follows: any infertility treatment, ART, and fertility-enhancing medications. Details regarding missing covariate data are shown in the tables.

Sensitivity Analysis

A validation study of infertility treatments on the vital statistics data against the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) has indicated that the sensitivity and specificity of IVF-related variables were 36.5% and >99%, respectively (12). Given the low prevalence of infertility treatment in the vital statistics data suggesting misclassification and the potential for confounding by unmeasured factors of the infertility treatments and SGA births, we undertook a probabilistic bias analysis to simultaneously account for potential misclassification of the exposure (infertility treatment) and unmeasured confounding biases (13, 14). To address misclassification bias, we assumed that the misclassification was nondifferential and simulated scenarios by allowing the sensitivity and specificity parameters under a uniform distribution to vary between 0.3 and 0.9 and 0.95 and 1.00, respectively (12). To address unmeasured confounding bias, we allowed the prevalence estimate of the unmeasured confounder(s), under a uniform distribution, to vary between 0.1 and 0.3 among women with infertility treatment and 0.05 and 0.2 among women with naturally conceived pregnancies. We further ranged the RR of the unmeasured confounder(s) and SGA births to vary, under a uniform distribution, between 0.5 and 5.0. To address exposure misclassification and unmeasured confounding biases, each simulation was performed 100,000 times, and we report the median bias-corrected RR and 95% CI.

Statistical analysis was performed in SAS (version 9.4; SAS Institute, Cary, NC). The probabilistic bias analysis was performed in R, using the *episensr* package (15, 16).

RESULTS

Of the 16,532,330 pregnancies that resulted in a nonmalformed singleton live birth (2015–2019), the prevalence rate of any infertility treatment was 1.4% (n = 231,177). Demographic characteristics in relation to infertility treatment are shown in Table 1. The utilization of infertility treatment was more prevalent with advancing maternal age, particularly at 35 years or older, primiparous, more educated, and white women.

The rates of SGA births by infertility treatment are described in Table 2. Compared with naturally conceived pregnancies, the risks of SGA <10th, <5th, and <3rd percentiles were lower for infertility treatment in overall analyses and in individual analyses by ART and fertility-enhancing medications.

The associations between infertility treatment and risks of SGA births (before and after adjusting for confounders, as well as corrections for exposure misclassification and unmeasured confounding biases) are shown in Table 3. After adjustment for confounders, the risk of SGA <10th percentile birth was 7% higher (RR, 1.07; 95% CI, 1.06, 1.08) among pregnancies conceived with infertility treatment. There were similar results for SGA <5th and <3rd percentiles. However, bias-corrected RRs were protective for infertility treatment. For example, the risk of SGA <10th percentile was 27% lower (RR, 0.73; 95% CI, 0.53, 0.85) for pregnancies conceived via infertility treatment compared with that for naturally conceived pregnancies. Similar patterns of associations were seen for more severe forms of SGA.

DISCUSSION

In this large population-based cross-sectional study of nonmalformed singleton live births in the United States (2015–2019), we found that women who conceived pregnancies with infertility treatment, including ART and fertility-enhancing medications, had a decreased risk of SGA compared with those with naturally conceived pregnancies. Although initially adjusted analyses found a small increase in the risk of SGA births, corrections for misclassification bias and unmeasured confounding variables identified a protective effect.

Our results are unique given that prior studies that have similarly investigated ART and fertility-enhancing medications have not found these treatments to have a protective

TABLE 1

Distribution of maternal characteristics in relation to infertility treatment status among nonmalformed singleton live births: United States, 2015–2019.

Maternal characteristics	Spontaneously conceived pregnancies: number (%)	Infertility treatment: number (%)		
		Any treatment	Assisted reproductive technology	Fertility-enhancing drugs
Total pregnancies	16,532,330 (98.6)	231,177 (1.4)	132,830 (0.8)	99,540 (0.6)
Maternal age (y)				
<15	9,580 (0.1)	0 (0)	0 (0)	0 (0)
15–19	915,857 (5.4)	197 (0.1)	37 (0.0)	93 (0.1)
20–24	3,478,369 (20.7)	5,485 (2.4)	1,166 (0.9)	3,660 (3.7)
25–29	4,906,119 (29.1)	33,573 (14.5)	12,092 (9.1)	20,119 (20.2)
30–34	4,680,151 (27.8)	80,887 (35.0)	42,691 (32.1)	38,081 (38.3)
35–39	2,326,953 (13.8)	72,541 (31.4)	46,717 (35.2)	27,262 (27.4)
40–44	483,814 (2.9)	29,444 (12.7)	22,430 (16.9)	8,351 (8.4)
45–49	32,329 (0.2)	7,428 (3.2)	6,288 (4.7)	1,622 (1.6)
≥50	3,056 (0.0)	1,622 (0.1)	1,409 (1.0)	352 (0.4)
Missing		72,721	89,382	89,382
Parity (live-born)				
Parity 1	5,454,834 (32.4)	99,619 (43.1)	55,152 (41.5)	45,238 (45.5)
Parity 2	4,701,721 (27.9)	62,045 (26.8)	35,611 (26.8)	26,662 (26.8)
Parity ≥3	6,679,673 (39.7)	69,513 (30.1)	42,067 (31.7)	27,640 (27.8)
Missing		72,721	89,382	89,382
Maternal education				
Below high school	553,090 (3.3)	814 (0.36)	392 (0.3)	336 (0.3)
High school	6,016,147 (36.3)	17,697 (7.8)	8,119 (6.3)	8,714 (8.9)
College	8,040,854 (48.6)	126,457 (55.8)	68,885 (53.4)	57,562 (58.7)
Beyond college	1,951,818 (11.8)	81,539 (36.0)	51,522 (40.0)	31,533 (32.1)
Missing	2,743,19	286,160	302,700	302,700
Marital status				
Single	6,431,556 (41.1)	16,797 (7.8)	9,260 (7.7)	6,988 (7.4)
Married	9,200,046 (58.9)	198381 (92.2)	110,542 (92.3)	88,120 (92.6)
Missing	1,204,626	1,277,047	1,293,708	1,293,708
Race/ethnicity				
White	8,485,624 (50.6)	164,719 (71.3)	90,532 (68.2)	74,398 (74.7)
African American	2,493,790 (14.9)	11,142 (4.8)	6,478 (4.9)	4,424 (4.4)
Hispanic	4,007,206 (23.9)	19,331 (8.4)	10,902 (8.2)	8,601 (8.6)
Other	1,789,718 (10.7)	35,985 (15.6)	24,918 (18.8)	12,117 (12.2)
Missing	59,890	72,721	89,382	89,382
Smoking status				
Nonsmoker	15,146,675 (90.8)	226,630 (98.3)	131,050 (98.9)	97,070 (97.8)
Before pregnancy only	1,533,525 (9.2)	3,947 (1.7)	1,428 (1.1)	2,231 (2.3)
Before and during pregnancy	1,193,812 (7.2)	1,906 (0.8)	592 (0.5)	1,095 (1.1)
Missing	170,454	182,177	184,386	198,760
Prepregnancy body mass index				
Underweight	590,923 (3.6)	5,493 (2.4)	3,405 (2.6)	2,091 (2.1)
Normal weight	7,289,208 (44.6)	111,240 (48.9)	68,073 (52.1)	44,413 (45.2)
Overweight	4,271,431 (26.1)	57,223 (25.2)	33,323 (25.5)	24,486 (24.9)
Obese	2,325,382 (14.2)	29,413 (12.9)	15,419 (11.8)	13,922 (14.2)
Morbidly obese	1,871,275 (11.5)	24,095 (10.6)	10,374 (7.9)	13,264 (13.5)
Missing	488,009	498,341	514,657	514,657
Chronic hypertension				
Present	309,777 (1.9)	7,427 (3.2)	4,203 (3.2)	3,211 (3.2)
Absent	16,453,730 (98.1)	223,750 (96.8)	128,627 (96.8)	96,329 (96.8)
Missing	72,721	72,721	89,382	89,382
Pregestational diabetes				
Present	118,725 (0.7)	2,391 (1.0)	1,273 (1.0)	1,064 (1.1)
Absent	16,644,782 (99.3)	228,786 (99.0)	131,557 (99.0)	98,476 (89.9)
Missing	72,721	72,721	89,382	89,382
Gestational diabetes mellitus				
Present	977,481 (5.8)	24,111 (10.4)	13,836 (10.4)	10,377 (10.4)
Absent	15,786,026 (94.2)	207,066 (89.4)	118,994 (89.6)	89,163 (89.6)
Missing	72,721	72,721	89,382	89,382

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effect against SGA infants. Our results are most consistent with another large epidemiologic study that utilized the Massachusetts Pregnancy to Early Life Longitudinal data system and the SART CORS to study 351,692 singleton live births between 2004 and 2010 (17). Hwang et al. (17) found a small overall decrease in the risk of SGA in pregnancies conceived

TABLE 2

Rates of small for gestational age births by infertility treatment status among nonmalformed singleton live births: United States, 2015–2019.

Small for gestational age births	Spontaneously conceived pregnancies	Infertility treatment: Any infertility treatment	Infertility treatment: Assisted reproductive technology	Infertility treatment: Fertility-enhancing drugs
Appropriate for gestational age, n	14,806,013	209,406	120,852	89,672
Small for gestational age, n (%)				
<10th percentile	1,755,925 (11.9)	21,771 (9.4)	11,978 (9.0)	9,868 (9.9)
<5th percentile	841,682 (5.7)	10,273 (4.7)	5,574 (4.4)	4,726 (5.0)
<3rd percentile	472,938 (3.2)	5,767 (2.7)	3,065 (2.5)	2,677 (2.9)

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with ART compared with those conceived naturally (adjusted odds ratio [aOR], 0.99; 95% CI, 0.91–1.07), and this effect was more pronounced among infants born at earlier gestational ages. Infants born between 28 and 33 weeks' gestation had a substantially reduced risk of SGA (aOR, 0.39; 95% CI, 0.16–0.92), and a similar effect was seen for those born between 34 and 36 weeks' gestation (aOR, 0.64; 95% CI, 0.44–0.95) and those born between 37 and 38 weeks' gestation (aOR, 0.89; 95% CI, 0.74–1.06) (17). However, they found that infants born after 39 weeks actually had a 7% increased risk of SGA (17). Another large study that also analyzed the Pregnancy to Early Life Longitudinal and SART CORS data and included 459,623 live births found only a minimal association between ART and the risk of SGA births (5). Luke et al. (5) reported a 4% increased risk (RR, 1.04; 95% CI, 0.97–1.12) for SGA births in pregnancies conceived with IVF compared with those conceived naturally. The investigators raise the possibility that the rates of SGA were underreported in their study because of the failure of the analysis to account for multiple gestations, which could have lowered the reference birth weight. However, we included only singleton births (and corrected for potential exposure misclassification) and found no increased risk of SGA infants among patients who utilized infertility treatments.

Recent research on fetal growth after infertility treatments lends further support to our findings. One retrospective cohort study compared fetal growth curves in the infertile population and found no difference between fetuses conceived with ovulation induction paired with IUI, those conceived via IVF with both fresh and frozen embryo transfers, and those conceived spontaneously after a prior diagnosis of infertility (18). Although this study did not include a fertile control group and, thus, the results are somewhat limited, its findings suggest that factors intrinsic to the infertility treatment process, such as laboratory interventions and embryo transfer, do not impact fetal growth (18).

Contrary to our results, most prior work has largely suggested that ART singleton pregnancies have an increased

TABLE 3

Risk of small for gestational age births by infertility treatment status among nonmalformed singleton live births: United States, 2015–2019.

Small for gestational age births	Risk ratio (95% confidence interval) for small for gestational age births[a]: Spontaneously conceived pregnancies (reference)	Any infertility treatment	Assisted reproductive technology	Fertility-enhancing drugs
<10th percentile				
Unadjusted RR (95% CI)	1.00	0.90 (0.89, 0.91)	0.86 (0.85, 0.88)	0.95 (0.93, 0.97)
Adjusted RR (95% CI)	1.00	1.07 (1.06, 1.08)	1.00 (0.98, 1.01)	1.16 (1.14, 1.18)
Bias-corrected RR (95% CI)[b,c]	1.00	0.73 (0.53, 0.85)	0.78 (0.56, 0.91)	0.85 (0.61, 0.99)
<5th percentile				
Unadjusted RR (95% CI)	1.00	0.88 (0.87, 0.90)	0.83 (0.81, 0.85)	0.95 (0.92, 0.97)
Adjusted RR (95% CI)	1.00	1.07 (1.05, 1.10)	0.98 (0.95, 1.00)	1.19 (1.16, 1.23)
Bias-corrected RR (95% CI)[b,c]	1.00	0.70 (0.51, 0.82)	0.61 (0.44, 0.72)	0.81 (0.55, 0.96)
<3rd percentile				
Unadjusted RR (95% CI)	1.00	0.88 (0.86, 0.90)	0.81 (0.78, 0.84)	0.95 (0.92, 0.99)
Adjusted RR (95% CI)	1.00	1.08 (1.05, 1.11)	0.96 (0.93, 1.00)	1.22 (1.17, 1.26)
Bias-corrected RR (95% CI)[b,c]	1.00	0.75 (0.54, 0.88)	0.65 (0.47, 0.77)	0.62 (0.45, 0.74)

Note: CI = confidence interval, RR = risk ratio.

[a] Risk ratios are adjusted for maternal age, parity, education, single marital status, race/ethnicity, smoking, body mass index, chronic hypertension, pregestational diabetes, and year of delivery.

[b] Unadjusted and confounder-adjusted RR and 95% CI are based on multiple imputation analysis.

[c] Bias-corrected RRs refer to multiple probabilistic bias-corrected risk ratios after simultaneous corrections for nondifferential exposure (infertility treatment) misclassification and unmeasured confounding biases.

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risk of SGA births (4, 19, 20). Zhu et al. (20) analyzed the Danish National Birth Cohort, which included over 50,000 singleton births (1997–2003), and found an increased risk of SGA <5th percentile (aOR, 1.40; 95% CI, 1.23–1.60) among couples who underwent infertility treatment. Several meta-analyses similarly concluded that infertility treatment increases the risk of SGA (4, 19), although the degree of increased risk reported varies between these studies. Qin et al. (4) found an increased risk of SGA (RR, 1.35; 95% CI, 1.20–1.52), as did Jackson et al. (19) (RR, 1.6; 95% CI, 1.3–2.0). A retrospective cohort study including 948 women reported a further increased risk of SGA in patients undergoing IVF or ICSI (aOR, 2.6) as well as a similar risk among those undergoing ovulation induction (aOR, 2.7) compared with fertile controls (21). We believe that our results, which are based on live births from the last 5 years, more accurately reflect the scope of contemporary infertility treatment practices in the United States and are, therefore, more appropriate to study the relationship to SGA births.

Infertility treatment is known to be underreported on birth certificates, and correction for potential misclassification was deemed necessary. By correcting for misclassification bias, we were able to account for women who underwent infertility treatment but did not report it at the time of delivery and were, therefore, incorrectly placed in the naturally conceived pregnancy group. In this study, where exposure misclassification is prevalent, the bias-corrected RRs are more reliable (12). The sensitivity analysis for misclassification bias is considered a valid epidemiologic tool to improve interpretation of data when there is a known discrepancy between the true size of the exposure group and that that is reported (22). Additionally, couples who seek fertility care and treatments are different with respect to sociodemographic characteristics compared with those who conceive spontaneously. This is likely to introduce bias due to unmeasured factors (e.g., socioeconomic status, income); thus, by adjusting for unmeasured confounding variables, we were able to account for those unknown factors as well.

The crux of the interpretation of the results of this study lies in the plausibility of a protective effect, rather than a deleterious effect, of infertility treatment. Recent shifts in clinical practice patterns may have contributed to our results. It has been suggested that variations in the IVF process, such as fresh versus frozen embryo transfer, can also affect the rates of SGA infants (23–26). In a population-based retrospective cohort study analyzing births in 3 states of the United States, Dunietz et al. (24) concluded that frozen embryo transfers are less likely to result in SGA infants than fresh embryo transfers when compared with naturally conceived pregnancies. Imudia et al. (27) performed a smaller retrospective cohort study of several hundred births and found that supraphysiologic levels of estradiol at the time of embryo transfer—which is typically avoided in a frozen cycle—causes an increased risk of SGA infants. They concluded that elevated peak serum estradiol levels at the time of transfer confer 9 times the risk of SGA compared with naturally conceived pregnancies (27). These findings have since been supported by other work (26, 28–30). In recent years, freeze-all cycles have been increasingly utilized for a variety of reasons, such as to minimize the risk of ovarian hyperstimulation syndrome, to allow for preimplantation genetic testing, or as the sole option for individuals undergoing fertility preservation (31). This shift in practice may have had a role in inadvertently decreasing the risk of SGA infants in those undergoing infertility treatments. Other recent research supports this concept; it has been reported that frozen embryo cycles are actually associated with large-for-gestational-age infants (23).

There may be a methodological explanation in play as well. Prior studies on this topic have largely investigated SGA <10th percentile without examining more severe forms of growth restriction. We compared infants that were SGA <5th and <3rd percentiles and found a further reduced risk of SGA infants in pregnancies conceived with infertility treatments compared with those conceived naturally. Although it is unknown why this may be the case, one possible contributing factor not previously discussed here is that patients who undergo time-intensive, expensive, and invasive procedures such as IVF to achieve strongly desired pregnancies may be more compliant with prenatal care. These patients may also better manage medical comorbidities that could contribute to worsened neonatal outcomes. It has been reported that patients with infertility have high levels of compliance and medication adherence during ovarian stimulation (32). One finding from our analysis that further supports this theory is the higher prevalence of smokers in women with naturally conceived pregnancies compared with those undergoing infertility treatment. Smoking is a known risk factor for SGA infants; although this confounding variable was adjusted in our analysis, other similar maternal lifestyle factors may have contributed to our findings (33).

Furthermore, low birth weight (LBW) is frequently cited in the literature as a poor obstetric outcome that is associated with ART (34–41). However, consideration of this outcome is clouded by its heterogeneous etiology due to combining both preterm delivery and SGA births. Thus, we examined SGA births to reduce the influence of preterm births on our findings. Given that LBW is widely associated with ART and our finding that infertility treatment is actually protective against SGA, it seems likely that preterm delivery may play a significant role in adverse perinatal outcomes seen among infants conceived via infertility treatments (34, 35). We suspect that preterm delivery is responsible for the increased morbidity and mortality seen in LBW infants rather than placental or hormonally mediated factors that may cause impaired fetal growth leading to SGA births. Although prior studies have found associations between infertility, infertility treatments, and preterm delivery (34–36, 42), further study is warranted to elicit the mediation versus interaction effects of preterm birth on the infertility treatment (exposure)–adverse perinatal outcome paradigm.

One of the major strengths of our study is its use of a very large database that includes all births in the United States over a recent 5-year period. This allows for identification of specific nuances in the data that may not be seen with a smaller study population. Our results are also generalizable, as our dataset included births from every US state and within every demographic group. Our analysis of SGA rather than LBW is also a strength, as this provides more specific information

about fetal growth independent of preterm delivery. Finally, the statistical analysis adjusted for unknown confounders and misclassification bias, which strengthened the study's principal findings.

Our study also has several limitations, the most significant of which is that all information collected on infertility treatment relies on self-reporting by patients and accurate recording by hospital staff at the time of delivery. A validation study comparing birth certificate reporting with the SART CORS database, which includes more than 95% of all IVF cycles performed in the United States, demonstrated that the US Vital Statistics System underreports information related to patients' infertility treatment (12). They found that only 36.5% of births of IVF children were identified on birth certificates (12). Although national statistics state that approximately 12.7% of US women aged 15–49 years use fertility services to conceive, only 1.4% of women in our study reported that they received any infertility treatment (1). We attempted to account for this discrepancy via the misclassification bias correction performed in our analysis, as discussed previously. However, the rates of infertility treatments and their subsequent birth outcomes are almost certainly underreported in our study, which may have affected our final results.

Additionally, SGA is an outcome with a broad range of contributing causes, which makes it difficult to link definitively with a single variable such as infertility treatment. We included a wide range of maternal health characteristics and pregnancy complications in our analysis to account for other known causes of SGA infants and, thereby, correct for these confounding variables.

Lastly, we are unable to analyze specific infertility treatment interventions that were not recorded in the database and, therefore, cannot determine the impact they may have on neonatal outcomes. We are unable to determine the influence of IUI specifically, as this intervention was not documented in the registry and, therefore, no subgroup analysis could be performed. However, IUI is most commonly combined with prescribed ovulation induction agents and relatively rarely used as a solitary intervention. It is likely that several IUI treatments are included in the fertility-enhancing medications subgroup because of the symbiotic nature of those 2 interventions, but this cannot be confirmed given the information available to us. It has been reported that the use of ovulation induction medications in conjunction with IUI is associated with increased rates of SGA infants (43, 44). Some have proposed that this finding is due to underlying hormonal physiology and the patient's subfertile state rather than the use of the medications themselves (26, 43, 45). However, we found that fertility-enhancing medications are associated with a reduced risk of SGA, which does not support that result.

In conclusion, we examined over 16 million subjects who delivered singleton live births in the United States from 2015 to 2019 to examine the current association between exposure to infertility treatment and the risk of SGA births. Although adjustments for potential confounders found that infertility treatment is associated with a small increased risk of SGA births among pregnancies conceived with infertility treatment compared with naturally conceived pregnancies, sophisticated statistical analyses that adjusted for misclassification and unmeasured confounding biases found that infertility treatment had a protective effect. Until large population-based studies corroborate these associations, the findings in our study should be cautiously interpreted. Our findings, which are contrary to older published data, likely reflect changes in modern practice patterns in the United States.

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