Original Research

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Medically Assisted Reproduction Treatment Types and Birth Outcomes

A Between-Family and Within-Family Analysis

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OBJECTIVE: To compare risks of adverse birth outcomes among pregnancies conceived with and without medically assisted reproduction treatments.

METHODS: Birth certificates were used to study birth outcomes of all neonates born in Utah from 2009 through 2017. Of the 469,919 deliveries, 52.8% (N=248,013) were included in the sample, with 5.2% of the neonates conceived through medically assisted reproduction. The outcome measures included birth weight, gestational age, low birth weight (LBW, less than 2,500 g), preterm birth (less than 37 weeks of gestation), and small for gestational age (SGA, birth weight less than the 10th percentile). Linear models were estimated for the continuous outcomes (birth weight, gestational age), and linear probability models were used for the binary outcomes (LBW, preterm birth, SGA). First, we compared the birth outcomes of neonates born after medically assisted reproduction and natural conception in the overall sample (between-family analyses), before and after adjustment for parental background and neonatal characteristics. Second, we employed family fixed effect models to investigate whether the birth outcomes of neonates conceived through medically assisted reproduction differed from those of their naturally conceived siblings (within-family comparisons).

RESULTS: Neonates conceived through medically assisted reproduction weighed less, were born earlier, and were more likely to be LBW, preterm, and SGA than neonates conceived naturally. More invasive treatments (assisted reproductive technology [ART] and artificial insemination [AI] or intrauterine insemination) were associated with worse birth outcomes; for example, the proportion of LBW and preterm birth was 6.1% and 7.9% among neonates conceived naturally and 25.5% and 29.8% among neonates conceived through ART, respectively. After adjustments for various neonatal and parental characteristics, the differences in birth outcomes between neonates conceived through medically assisted reproduction and naturally were attenuated yet remained statistically significant; for example, neonates conceived through ART were at 3.2 percentage points higher risk for LBW (95% CI 2.4–4.1) and 4.8 percentage points higher risk for preterm birth (95% CI 3.9–5.7). Among siblings, the differences in the frequency of adverse outcomes between neonates conceived through medically assisted reproduction and neonates conceived naturally were small and statistically insignificant for all types of treatments.

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CONCLUSION: Medically assisted reproduction treatments are associated with adverse birth outcomes; however, those risks are unlikely to be associated with the infertility treatments itself.

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Existing studies suggest that neonates born after medically assisted reproduction are more likely to have adverse perinatal outcomes than neonates conceived naturally.[1–6] The causes behind these negative associations are multifactorial and interrelated, for example, parental subfertility, treatment procedure, multiple births.[5–9] A few studies have attempted to isolate the effects of medically assisted reproduction treatments from other characteristics by applying a sibling design to large-scale population register data.[10–15] These studies found a decrease in the magnitude of the negative effects of medically assisted reproduction but none of them could isolate the effects of the various types of medically assisted reproduction treatments. The utilization of specific medically assisted reproduction treatments such as ovulation induction, artificial insemination (AI), intrauterine insemination (IUI), or assisted reproductive technology (ART) depends on many factors including the length and causes of infertility and as well as access and cost of treatment.[16–19] In this study, we aim to compare risks of adverse birth outcomes by mode of conception and type of medically assisted reproduction treatments. Based on previous evidence,[7,20,21] we expect that more invasive treatments are likely to be associated with worse outcomes. In the sibling comparisons, we expect the association between medically assisted reproduction and birth outcomes to attenuate; however, it is unclear whether there are any differences by type of treatments.

This study has two key elements. First, we analyzed birth outcomes of neonates conceived through medically assisted reproduction using Utah birth certificates from 2009 to 2017 with a specific emphasis on the influence of the type of treatment distinguishing between fertility-enhancing drugs, AI or IUI, and ART. Utah represents a unique pronatalistic context with longstanding emphases on marriage and larger families and has one of the highest proportion of neonates conceived through medically assisted reproduction of all U.S. states (approximately 5%).[22] Second, we performed a within-family analysis by focusing on a subset of families who conceived both naturally and through medically assisted reproduction. This method has an advantage of accounting for unobserved characteristics shared by siblings (eg, parental subfertility) and therefore helps us to isolate the effects of some unobserved factors from those of the medically assisted reproduction treatments per se.

METHODS

This study employed population-based data from the Utah Population Database, which holds data derived from all Utah birth certificates. This study was approved by the Institutional Review Board of the University of Utah and by the Utah Resource for Genetic and Epidemiologic Research, an administrated board that oversees access to the Utah Population Database. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies were followed. From 2009 to the present, Utah birth certificates contain information related to infertility treatments used to achieve pregnancies. Through these questions we identified neonates conceived through specific medically assisted reproduction treatments–fertility-enhancing drugs, AI or IUI, or ART. We considered women who reported other treatments such as progesterone, metformin, and surgery for endometriosis in the natural conception group (n=1,236), unless they reported undergoing these treatments together with one of the medically assisted reproduction treatments (n=3,338).

The Utah birth certificate data contains records for 469,919 children born between 2009 and 2017. We excluded women who gave birth before 2009 because information on the mode of conception before that year was not included in the birth certificates (n=220,188). We additionally excluded cases where conception involved donor gametes because it would not be possible to link biological parents' characteristics such as genetic and demographic (eg, biological mother's age) to the neonates' birth outcomes and amongst siblings (n=663). We excluded families from the sample with triplets (n=168), quadruplets and quintuplets (n=13). Sensitivity analysis confirmed that the main results persist if neonates conceived with donor gametes and higher order multiple births were included in the sample. The final sample comprised 248,013 live births, with 12,943 (5.2%) conceived through medically assisted reproduction treatments (Fig. 1).

We analyzed five main birth outcomes: birth weight and gestational age (in days, calculated from available data on full weeks of gestation) (continuous), low birth weight (LBW, less than 2,500 g), preterm birth (less than 37 weeks of gestation), and small for gestational age (SGA, birth weight less than the 10th percentile of all neonates born in Utah in 2009–2017 for the appropriate gestational week). We present

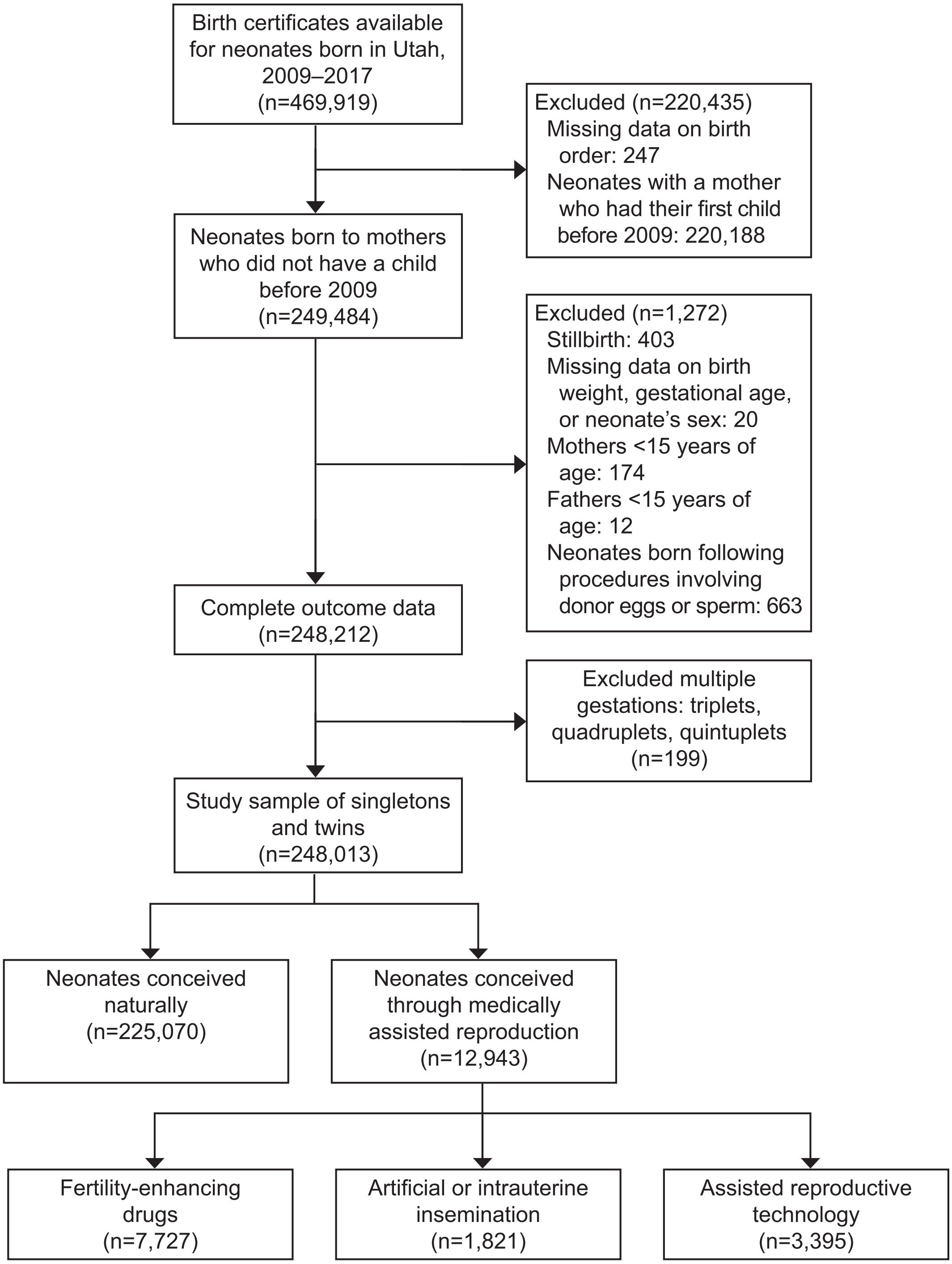

Fig. 1. Study sample flow diagram.

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additional analysis for SGA neonates born after 37 weeks of gestation (term-SGA) and those born very preterm (less than 32 weeks of gestation) in Appendix 1, available online at http://links.lww.com/AOG/C552.

We considered two sets of control variables. The first group was related to neonatal characteristics: sex, multiplicity (twins), and birth order (first- and higher-order birth), which are considered common risk factors for adverse perinatal outcomes in neonates conceived through medically assisted reproduction.[3,8,9]

The second set of variables was related to maternal health and parental socioeconomic status. We controlled for maternal age (15–24, 25–29, 30–34, 35–39, 40 years or older) and whether the mother was married, as well as couple's level of education (both below tertiary; at least one parent had tertiary level). We accounted for mother's prepregnancy body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) (underweight [lower than 18.5], normal weight [18.5–24.9], overweight [25.0–29.9], obese [30 or higher]) and chronic hypertension, because these factors were shown to affect both pregnancy outcomes and subsequent neonatal health.[23–27] We could not account for other severe maternal conditions prepregnancy, such as nongestational diabetes, because the prevalence of this condition in women who conceived through medically assisted reproduction was too low (fewer than 20 women for some treatment types). We additionally included whether the mother was known to smoke during pregnancy as an important risk-factor both for maternal and neonatal health.[28,29] We defined smoking if a woman reported smoking one or more cigarettes per day at any point during pregnancy (3.5% of all mothers). We did not include maternal race or ethnicity in the analyses due to the very low proportion of Black and Asian women who conceived through medically assisted reproduction in Utah (ie, fewer than 10 women per some race groups by treatment type) and a high prevalence of missing Hispanic origin among mothers who participated in medically assisted reproduction (18% vs 10% of Hispanic origin).

We estimated linear models for the continuous outcome (birth weight and gestational age) and linear probability models for the binary outcomes–LBW, preterm birth, and SGA. The advantage of the linear probability modelling is that model coefficients can be interpreted easily as marginal (main) effects. Conventional logistic regression models for the between-family analysis provided similar results; odds ratios can be found in Appendix 2, available online at http://links.lww.com/AOG/C552. Obtaining unconditional probabilities and marginal effects from the within-family fixed effects using logistic regression is not straightforward,[30] hence we present the comparable results from linear probability models for both between- and within-family analyses. We estimated three regression models for each of the birth outcomes. Model 1 (the baseline model) presents the unadjusted descriptive association between medically assisted reproduction and each of the outcomes. Model 2 introduces controls for the neonatal sex, multiple birth, and birth order. Model 3 (fully adjusted) adds controls for parental characteristics (maternal age, whether the mother was married, couple's level of education, maternal smoking during pregnancy, prepregnancy BMI, and chronic hypertension). Each model specification was estimated separately for neonates conceived through medically assisted reproduction as one group and by type of treatment.

Table 1. Descriptive Statistics of Birth Outcomes of Neonates Born in Utah, 2009–2017, By Mode of Conception and Type of Medically Assisted Reproduction Treatment*

	Overall Population (Between-Family Sample) (N=248,013)				
			By Type of MAR		
Outcome	NC (n=235,070)	MAR (n=12,943)	FED (n=7,727)	AI or IUI (n=1,821)	ART (n=3,395)
Birth weight (g)	3,275±525	3,096±647	3,174±603	3,099±643	2,917±706
Gestational age (d)	270±13	266±17	268±15	266±17	261±20
LBW (less than 2,500 g) (%)	6.1	15.4	11.3	13.9	25.5
Preterm birth (less than 37 wk)	7.9	17.9	13.0	16.7	29.8
SGA	11.4	14.8	13.6	14.8	17.1
Term-SGA (% SGA neonates born at more than 37 wk)	11.3	14.2	13.1	14.3	16.9
Very preterm birth (less than 32 wk)	1.0	2.6	1.9	2.6	4.0

NC, naturally conceived; MAR, medically assisted reproduction; FED, fertility-enhancing drugs; AI, artificial insemination; IUI, intrauterine insemination; ART, assisted reproductive technology; LBW, low birth weight; SGA, small for gestational age.

Data are mean±SD or %.

* Refers to all neonates who were born after any of the following procedures: AI, IUI, ART, or FED.

† Values were less than 1% (and fewer than 10 people per group) for some treatment types and could not be reported due to the data provider's restrictions.

We first compared birth outcomes of neonates conceived through medically assisted reproduction to the birth outcomes of neonates conceived naturally in the overall sample (between-family analyses). We then employed family fixed effect models to investigate whether birth outcomes of neonates conceived through medically assisted reproduction differ from those of their naturally conceived siblings (within-family comparisons). These models involve comparing outcomes of neonates within families in which at least one neonate was conceived naturally and one neonate was conceived through medically assisted reproduction. The key feature of sibling fixed-effects models is that it enables us to control for all unobserved parental characteristics that are shared by siblings and do not vary over time, such as genetic traits and underlying subfertility. Time-varying observable factors that are not shared between siblings (sex, birth order, multiplicity, maternal age at birth and prepregnancy BMI) are accounted for as in standard regression analyses. Because there was almost no change in parental education, maternal smoking, chronic hypertension, and marital status between siblings, we did not adjust for these variables in the within-family analysis. One hundred ninety-four neonates had at least one sibling born to a different father; however, the sample was too small to account for any differences in the outcomes by mode of conception and type of medically assisted reproduction treatment.

RESULTS

The use of medically assisted reproduction treatments before conception was reported in 5.2% (n=12,943) of the sample. Fertility-enhancing drugs contributed up to 59.7% of all medically assisted reproduction procedures, being the most common type of treatment (n=7,727), followed by ART (26.2%, n=3,395) and AI or IUI (14.1%, n=1,821) (Table 1). The within-family sample comprised 6,536 neonates conceived naturally and their 5,551 siblings conceived through medically assisted reproduction, with a higher proportion of neonates conceived through fertility-enhancing drugs (73%), followed by ART (15%) and AI or IUI (12%) (Table 1).

In the analytical sample used for the between-family analyses, neonates conceived through medically assisted reproduction had on average lower birth weight, smaller gestational age, a higher proportion were LBW, preterm, and SGA compared with neonates conceived naturally (Table 1). Among neonates conceived through medically assisted reproduction, those conceived through ART had the highest proportion of LBW and preterm birth. For the within-family subsample, the birth outcomes of neonates conceived through medically assisted reproduction were, on average, worse compared with their naturally conceived siblings, although the differences were smaller than in the between-family sample.

The demographic profile of mothers who conceived naturally differed from those who conceived

Within-Family Sample (n=11,914)				
		By Type of MAR		
NC (n=6,416)	MAR (n=5,498)	FED (n=4,002)	AI or IUI (n=668)	ART (n=828)
3,305±534	3,157±595	3,206±574	3,168±557	2,916±662
269±12	267±15	268±14	268±15	261±18
5.7	12.3	10.1	9.6	25.7
8.9	15.3	12.0	13.6	32.1
8.6	13.2	10.7	12.4	15.9
8.3	12.8	12.6	11.9	15.6
1.1	1.6	NA†	NA†	NA†

through medically assisted reproduction (Table 2). Compared with mothers of neonates conceived naturally, mothers of neonates conceived through medically assisted reproduction were, on average, 3.5 years older, better educated, and more likely to be married. Mothers who participated in medically assisted reproduction were also more likely to experience chronic hypertension and obesity but less likely to be smoking during pregnancy. Neonates conceived through medically assisted reproductions were more likely than neonates conceived naturally to be first-born and twins.

Table 3 shows medically assisted reproduction coefficients for all birth outcomes from between- and within-family analyses. The coefficients for the control variables included in Model 2 and Model 3 are presented in Appendices 3–7, available online at http://links.lww.com/AOG/C552. The results for Model 1 (unadjusted baseline model) and Model 3 (fully adjusted for neonatal and parental characteristics) are presented in Figures 2 and 3. In Model 1, neonates conceived through medically assisted reproduction overall weighed less, had lower gestational age, and were at higher risk of being LBW, preterm, and SGA than neonates conceived naturally, but the effects varied by the type of treatment. More invasive treatments (ART and AI or IUI) were, on average, associated with worse birth outcomes. Neonates conceived through ART faced the highest risk of being LBW and preterm (25.5% and 29.8% vs 6.1% and 7.9% among neonates conceived naturally, respectively; Table 2), which could be partially explained by the higher rates of twins among neonates conceived with that method (33.6%). In Model 3, the baseline associations were attenuated by 40–70% among all types of medically assisted reproduction treatment. Nevertheless, neonates conceived through medically assisted reproduction were still more likely to have worse outcomes. For example, they were 77 g (95% CI −85 to −67) lighter and were 2.2 percentage points (95% CI 1.8–2.7) more likely to be LBW, with children conceived through ART still facing the highest risks –3.2 percentage points higher risk for LBW (95% CI 2.4–4.1) and 4.8 percentage points higher risk for preterm birth (95% CI 3.9–5.7) compared with neonates conceived naturally (Table 3 and Figs. 1 and 2).

In the within-family analysis, the associations for all birth outcomes were weaker for all types of medically assisted reproduction treatments already in the baseline models compared with the between-

Table 2. Characteristics of Women Giving Birth in Utah, 2009–2017, and Their Neonates, By Mode of Conception and Type of Medically Assisted Reproduction Treatment*

	Overall Population (Between-Family Sample) (N=248,013)				
			By Type of MAR		
Covariate	NC (n=235,070)	MAR (n=12,943)	FED (n=7,727)	AI or IUI (n=1,821)	ART (n=3,395)
Multiple births	1.5	16.0	8.9	13.0	33.6
First-order birth	59.5	69.1	66.5	76.3	71.1
Neonatal sex: female	48.6	48.4	48.7	48.3	47.9
Maternal age at birth	26.3±4.8	29.8±4.7	28.4±4.1	31.0±4.6	32.2±4.7
Mother married at birth	77.1	97.6	97.3	97.4	98.4
Unknown†	0.5	0.1	NA	NA	NA
Household with tertiary education	41.7	64.2	58.6	68.5	74.6
Unknown†	1.6	0.5	0.3	0.7	0.8
Mother's BMI (kg/m^2)					
Underweight (lower than 18.5)	5.2	3.4	3.3	3.6	3.5
Normal weight (18.5–24.9)	54.7	49.9	45.6	52.6	58.2
Overweight (25.0–29.9)	21.8	22.2	22.8	21.1	21.6
Obese (30 or higher)	16.9	23.9	27.8	22.4	15.8
Unknown†	1.4	0.7	NA	NA	NA
Chronic hypertension†	0.9	2.1	2.0	2.2	2.3
Smoking during pregnancy†	3.5	0.7	NA	NA	NA

NC, naturally conceived; MAR, medically assisted reproduction; FED, fertility-enhancing drugs; AI, artificial insemination; IUI, intrauterine insemination; ART, assisted reproductive technology; BMI, body mass index.

Data are % or mean±SD.

* Refers to all neonates who were born after any of the following procedures: AI, IUI, ART, or FED.

† Values were less than 1% (and fewer than 10 people per group) for some treatment types and could not be reported due to the data provider's restrictions.

family analysis (Table 3). After adjusting for neonatal and parental characteristics, the differences in birth weight between medically assisted reproduction and neonates conceived naturally reduced to 25 g (95% CI −41 to −10) and in LBW to 0.5 percentage points (−0.4 to 1.4). Similar patterns were observed for gestational age, preterm birth, and SGA. In the analyses by type of treatments, the largest differences in birth weight from neonates conceived naturally were among neonates conceived through AI or IUI and the smallest were among neonates conceived through fertility-enhancing drugs (Fig. 1). For gestational age, LBW, preterm birth, and SGA, the differences from neonates naturally conceived were substantively small and insignificant regardless of the type of treatments (Table 3, Figs. 1 and 2). Additional analysis for term-SGA and very preterm births provided similar results (Appendix 1, http://links.lww.com/AOG/C552). The variation between different types of medically assisted reproduction treatments in the adjusted models were negligible. The results of the main analysis were highly similar if we excluded multiple births from the analytical sample (Appendix 8, available online at http://links.lww.com/AOG/C552).

DISCUSSION

Using birth certificates from Utah, we investigated whether and how types of medically assisted reproduction treatments (fertility-enhancing drugs, AI or IUI, ART) are associated with birth weight, gestational age, the risk of LBW, preterm birth, and SGA. In the adjusted between-family analyses, more invasive treatments (ART and AI or IUI) were more strongly associated with adverse birth outcomes, whereas neonates conceived using fertility-enhancing drugs were more similar to naturally conceived. In the within-family analyses, the differences between medically assisted reproduction and neonates conceived naturally were much smaller in the unadjusted models and became insignificant among all types of treatments (with an exception of small differences in birth weight), suggesting little effect of the medically assisted reproduction treatment itself.

The existing literature suggests that adverse perinatal outcomes of neonates conceived through medically assisted reproduction can be linked to several factors.[1–6] Some of them, for example, higher likelihood of multiple and first-order births can be measured and accounted for in regression analyses.

Within-Family Sample (n=11,914)				
		By Type of MAR		
NC (n=6,416)	MAR (n=5,498)	FED (n=4,002)	AI or IUI (n=668)	ART (n=828)
2.1	12.9	8.2	11.5	36.7
28.8	54.3	53.0	64.4	52.4
47.7	48.0	48.9	46.4	44.7
29.2±4.6	28.9±4.2	28.2±4.0	30.0±4.1	31.3±4.4
96.4	98.0	97.8	99.3	98.1
NA	NA	NA	NA	NA
61.2	61.9	57.9	70.4	74.5
1.5	0.4	NA	NA	NA
3.9	3.8	3.7	3.7	4.1
53.2	51.1	47.7	57.6	62.0
22.0	22.5	23.1	23.2	19.4
20.2	22.0	24.8	15.3	13.7
0.8	0.7	NA	NA	NA
1.2	1.4	NA	NA	NA
0.8	0.6	NA	NA	NA

Others, such as parental subfertility and the invasive nature of medically assisted reproduction procedures per se are harder to account for. On the one hand, we found that more invasive treatments are associated with worse birth outcomes echoing previous studies.[7,20,21] However, this could be related both to the fact couples with severe infertility problems are more likely to use AI and ART and these treatments are associated with an increased risk of multiple births. Our analysis shows that the differences in birth outcomes for all types of medically assisted reproduction treatments in the sibling comparison analyses were small and insignificant (or unlikely to be clinically important). Our findings shed light on the importance of unobserved underlying conditions and subfertility as well as of high rates of multiple births and first-births among neonates conceived through medically assisted reproduction, which might be driving these associations rather than the invasive nature of the medically assisted reproduction procedures itself.

Our study has several strengths, including the use of a high-quality population-based vital records to study birth outcomes of medically assisted reproduction and neonates conceived naturally. Such data have an advantage of full population coverage with no nonresponse bias as opposed to survey data. The percentage of incomplete and missing data was exceedingly low and thus unlikely to affect our results.

Table 3. Between- and Within-Family Models of Birth Outcomes of Neonates Born in Utah, 2009–2017, Medically Assisted Reproduction* Compared With Natural Conception

	Between-Family Analysis		
	Model 1 (Baseline)	Model 2 (Birth Order+Multiple Birth+Neonatal Sex)	Model 3 (Model 2+Maternal Age, Marital Status, Education, Smoking, BMI, Chronic Hypertension)
Birth weight (g)†			
MAR as 1 category	−179 (−188 to −170)	−38 (−47 to −29)	−77 (−85 to −67)
By type of treatment			
FED	−101 (−113 to −89)	−27 (−39 to −16)	−68 (−80 to −57)
AI or IUI	−176 (−201 to −152)	−57 (−81 to −33)	−94 (−117 to −70)
ART	−358 (−376 to −340)	−54 (−72 to −36)	−85 (−103 to −67)
Gestational age (d)†			
MAR as 1 category	−4.6 (−4.9 to −4.4)	−1.4 (−1.7 to −1.2)	−1.8 (−2.0 to −1.5)
By type of treatment			
FED	−2.5 (−2.8 to −2.2)	−0.9 (−1.2 to −0.6)	−1.2 (−1.5 to −1.0)
AI or IUI	−4.4 (−5.0 to −3.8)	−2.0 (−2.6 to −1.4)	−2.4 (−2.9 to −1.8)
ART	−9.6 (−10.0 to −9.2)	−2.4 (−2.8 to −1.9)	−2.8 (−3.2 to −2.3)
LBW‡			
MAR as 1 category	9.3 (8.8–9.7)	1.8 (1.4–2.2)	2.2 (1.8–2.7)
By type of treatment			
FED	5.7 (4.7–5.8)	1.3 (0.8–1.9)	1.9 (1.4–2.5)
AI or IUI	7.7 (6.6–8.9)	1.6 (0.5–2.7)	1.9 (0.8–3.0)
ART	19.3 (18.6–20.2)	3.0 (2.2–3.8)	3.2 (2.4–4.1)
Preterm birth‡			
MAR as 1 category	10.1 (9.6–10.5)	2.1 (1.7–2.6)	2.4 (1.9–2.9)
By type of treatment			
FED	5.1 (4.5–5.7)	1.1 (0.5–1.7)	1.4 (0.8–2.0)
AI or IUI	8.8 (7.6–10.1)	2.5 (1.3–3.7)	2.7 (1.5–3.9)
ART	22.0 (21.0–22.9)	4.6 (3.7–5.5)	4.8 (3.9–5.7)
SGA‡			
MAR as 1 category	3.3 (2.8–3.9)	0.7 (0.2–1.3)	2.0 (1.4–2.5)
By type of treatment			
FED	2.2 (1.6–3.0)	0.8 (0.1–1.5)	2.2 (1.5–3.0)
AI or IUI	3.4 (2.0–4.9)	0.9 (−0.6 to 2.4)	1.9 (0.5–3.4)
ART	5.8 (4.7–6.9)	0.5 (−0.6 to 1.6)	1.3 (0.1–2.4)

BMI, body mass index; MAR, medically assisted reproduction; FED, fertility-enhancing drugs; AI, artificial insemination; IUI, intrauterine insemination; ART, assisted reproductive technology; LBW, low birth weight; SGA, small for gestational age.
Data are % or mean±SD.
* Refers to all neonates who were born after any of the following procedures: AI, IUI, ART, or FED.
† Linear models.
‡ Linear probability models (percentage change in the predicted probability).

There have been concerns about underreporting of ART treatments on birth certificates in some U.S. states because the data are self-reported.[31–33] Thoma et al[34] systematically compared data from the 2011 National ART Surveillance System, which collects data from fertility clinics around the country, with birth certificates across the United States. Reassuringly, the authors found no significant differences in the percentage of births resulting from ART procedures in Utah based on both sources. Second, we were able to distinguish between different types of medically assisted reproduction treatments both in the general population as well as in the within-family analysis, which allowed us to investigate whether and how birth outcomes are associated with the type of treatments using two complementary perspectives. We found comparable prevalence of the specific type of medically assisted reproduction treatments on Utah birth certificates to the estimates published from the PRAMS survey (Pregnancy Risk Assessment Monitoring System).[22] Altogether, this provides further reassurance towards using Utah birth certificates for medically assisted reproduction–related research in the future.

We acknowledge some limitations of the study. Although we could identify the three major types of medically assisted reproduction procedures, we could not distinguish between various types and protocols of

Within-Family Analysis		
Model 1 (Baseline)	Model 2 (Birth Order+Multiple Birth+Neonatal Sex)	Model 3 (Model 2+Maternal Age, BMI)
−111 (−127 to −95)	−22 (−38 to −7)	−25 (−41 to −10)
−77 (−96 to −58)	−16 (−33 to 2)	−18 (−36 to 1)
−140 (−185 to −94)	−52 (−94 to −11)	−56 (−97 to −15)
−277 (−321 to −233)	−38 (−80 to 3)	−43 (−84 to −1)
−1.1 (−1.5 to −0.7)	0.3 (−0.1 to 0.7)	0.2 (−0.2 to 0.6)
−0.4 (−0.9 to 0.1)	0.4 (−0.1 to 0.8)	0.3 (−0.1 to 0.8)
−0.5 (−1.7 to 0.6)	0.3 (−0.8 to 1.3)	0.2 (−0.9 to 1.2)
−5.8 (−7.0 to −4.7)	−0.5 (−1.5 to 0.6)	−0.6 (−1.7 to 0.5)
4.8 (3.9–5.8)	0.4 (−0.5 to 1.3)	0.5 (−0.4 to 1.4)
3.5 (2.4–4.6)	−0.5 (−0.5 to 1.5)	0.6 (−0.4 to 1.6)
2.2 (−0.4 to 4.8)	−2.0 (−4.4 to 0.5)	−1.8 (−4.2 to 0.6)
15.1 (12.6–17.6)	2.1 (−0.3 to 4.6)	2.4 (−0.1 to 4.8)
4.3 (3.3–5.4)	−0.6 (−1.6 to 0.3)	−0.5 (−1.5 to 0.5)
2.4 (1.2–3.6)	−0.8 (−1.9 to 0.3)	−0.7 (−1.8 to 0.4)
3.3 (0.5–6.2)	−1.0 (−3.6 to 1.6)	−0.7 (−3.3 to 1.9)
16.2 (13.5–18.9)	0.8 (−1.8 to 3.4)	1.1 (−1.5 to 3.8)
3.7 (2.7–4.7)	1.6 (0.5–2.6)	1.7 (0.6–2.8)
3.3 (2.1–4.6)	1.6 (0.4–2.9)	1.8 (0.6–3.0)
4.8 (1.9–7.6)	2.1 (−0.8 to 5.0)	2.2 (−0.7 to 5.1)
4.9 (2.1–7.7)	0.3 (−2.5 to 3.2)	0.4 (−2.5 to 3.3)

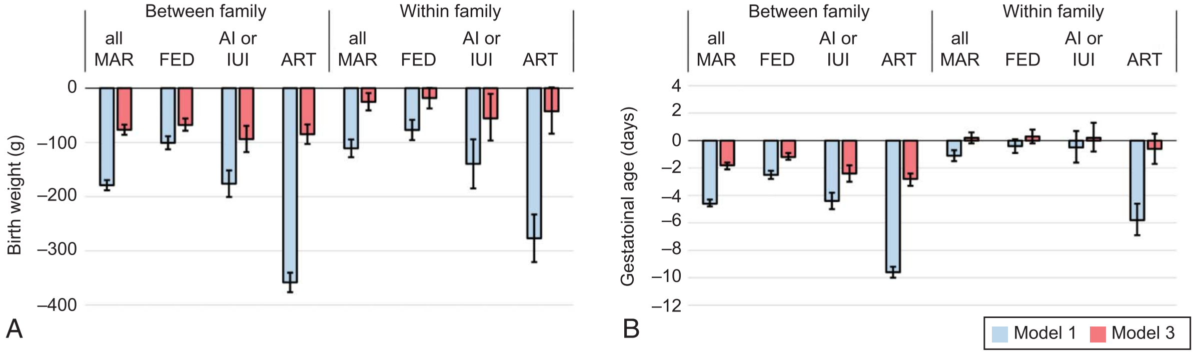

Fig. 2. Difference in mean birth weight and gestational age (95% CI) of neonates conceived through medically assisted reproduction (MAR) (reference: neonates conceived naturally) by type of treatment from between- and within-family models. Model 1 presents the unadjusted descriptive association between MAR and birth weight (g) **(A)** and gestational age (days) **(B)**. Model 3 is controlled for neonatal sex, multiple birth, birth order, maternal age, family structure, couple's level of education, prepregnancy body mass index, and chronic hypertension. *Error bars* show the 95% CI (Table 3). FED, fertility-enhancing drugs; AI, artificial insemination; IUI, intrauterine insemination; ART, assisted reproductive technology.

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ART treatments, which might affect birth outcomes.[15,35–42] We acknowledge that our analyses are limited by the availability of data on potential confounders and the risk of residual confounding is still present in the analysis. For example, we did not have full information on the history of previous treatments or length of infertility preceding the conception, which did not allow us to investigate in detail the effects of subfertility on birth outcomes in the general-population analysis. The results from the within-family analyses are based on a subset of families with medically assisted reproduction and neonates conceived naturally, which, as shown by the descriptive analyses, differ from families without neonates conceived naturally. Additional between-family analysis on a sample of medically assisted reproduction families without neonates conceived naturally (available on request) confirmed similar associations between the type of medically assisted reproduction treatment and birth outcomes. This suggests that our within-family results are unlikely to be entirely driven by the selected characteristics of the medically assisted reproduction subsample with neonates conceived naturally.

This study contributes to the existing knowledge on the effects of medically assisted reproduction treatments on birth outcomes in multiple ways. First, we looked at birth outcomes of neonates conceived

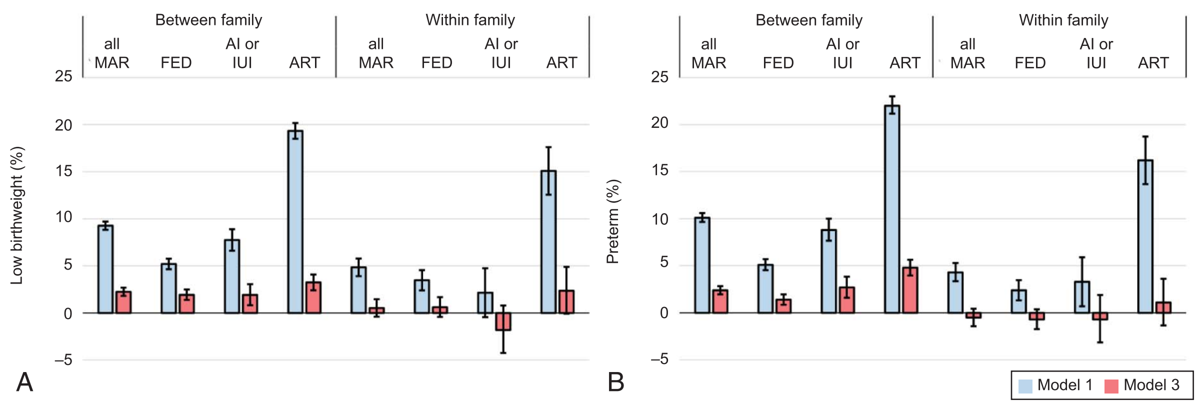

Fig. 3. Percentage change in the probability (95% CI) of low birth weight and preterm birth for neonates conceived through medically assisted reproduction (MAR) (reference: neonates conceived naturally) by type of treatment from between- and within-family models. Model 1 presents the unadjusted descriptive association between MAR and low birth weight **(A)** and preterm birth **(B)**. Model 3 is controlled for neonatal sex, multiple birth, birth order, maternal age, family structure, couple's level of education, prepregnancy body mass index, and chronic hypertension. *Error bars* show the 95% CI (Table 3). FED, fertility-enhancing drugs; AI, artificial insemination; IUI, intrauterine insemination; ART, assisted reproductive technology.

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through medically assisted reproduction in the strong pronatalist context of Utah with high utilization of medically assisted reproduction treatments but a much lower mean age at first birth compared with the Nordic countries from which most evidence comes.[43] A younger profile of couples undergoing infertility treatments helps to eliminate some of the confounding effect of age-related subfertility and health issues on birth outcomes. Second, we could distinguish between various type of treatments and have shown that in comparison with more invasive medically assisted reproduction treatments (ART and AI or IUI) birth outcomes related to fertility-enhancing drugs are more similar to those of neonates conceived naturally. Third, the within-family analyses enabled us to control for all stable observed and unobserved parental characteristics that are shared between siblings and to advance our understanding of whether the relationship between medically assisted reproduction treatments and birth outcomes is more likely to be causal. We found limited evidence of the effects of medically assisted reproduction on birth outcomes in the sibling comparison analysis, which is in line with existing studies from the Nordic countries that have also adopted a sibling-comparison design.[10,14] Obtaining similar results in highly diverse contexts (in terms of demographics, fertility rates and access to the medically assisted reproduction treatments) strengthens the argument that adverse perinatal outcomes among neonates conceived through medically assisted reproduction are unlikely to be driven by the reproductive technology itself.

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