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The Impact of ART on Live Birth Outcomes: Differing Experiences across Three States

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Abstract

Background: Research has shown an association between assisted reproductive technology (ART) and adverse birth outcomes. We identified whether birth outcomes of ART-conceived pregnancies vary across states with different maternal characteristics, insurance coverage for ART services, and type of ART services provided.

Methods: CDC's National ART Surveillance System data were linked to Massachusetts, Florida, and Michigan vital records from 2000 through 2006. Maternal characteristics in ART- and non-ART-conceived live births were compared between states using chi-square tests. We performed multivariable logistic regression analyses and calculated adjusted odds ratios (aOR) to assess associations between ART use and singleton preterm delivery (<32 weeks, <37 weeks), singleton small for gestational age (SGA) (<5th and <10th percentiles) and multiple birth.

Results: ART use in Massachusetts was associated with significantly lower odds of twins as well as triplets and higher order births compared to Florida and Michigan (aOR 22.6 vs. 30.0 and 26.3, and aOR 37.6 vs. 92.8 and 99.2, respectively; $P_{interaction} < 0.001$). ART use was associated with increased odds of SGA in Michigan only, and with preterm delivery (<32 and <37 weeks) in all states (aOR range: 1.60, 1.87).

Conclusions: ART use was associated with an increased risk of preterm delivery among singletons that showed little variability between states. The number of twins, triplets and higher order gestations per cycle was lower in Massachusetts, which may be due to the availability of insurance coverage for ART in Massachusetts.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

Keywords

Assisted Reproductive Technology; preterm birth; small-for-gestational age; multiple birth; population-based

The use of assisted reproductive technology (ART) has steadily increased since first being introduced in 1978.[1,2] Although the majority of ART-conceived children are healthy, questions remain about the potential risks associated with its use. Current evidence shows an association between ART and preterm delivery, multiples and small for gestational age (SGA) infants.[3,4] It is widely accepted that ART-related risks are due in part to the increased frequency of multiple pregnancies.[5] However, singleton infants born through ART also have a higher prevalence of adverse outcomes.[6,7] It remains unclear whether these outcomes are due to ART procedures and/or underlying subfertility factors.[4,8-10]

Several studies have shown that sub-fertile women who conceive spontaneously exhibit some of the same adverse obstetric and perinatal outcomes as those who conceive through ART. In addition, sub-fertile women who conceive spontaneously have higher risks of adverse outcomes compared to fertile women and the general population.[10-15]

Nevertheless, current evidence indicates that commonly used ART procedures, such as intracytoplasmic sperm injection (ICSI), gamete intrafallopian transfer (GIFT), and fresh-embryo transfer may contribute to poorer birth outcomes.[1,3,16] In a population-based cohort study, birthweights were lower in both singletons and twins conceived through GIFT, ICSI and fresh-embryo transfer compared to frozen-embryo transfer (FET).[12] Preterm delivery rates have also been found to be higher in singletons conceived through fresh-embryo transfer compared to frozen-embryo transfer and ICSI.[16] It has been suggested that frozen embryos result in better outcomes because the use of ovarian stimulation, which may negatively impact the endometrial environment, is not required.[17]

Research has shown that the costs associated with ART treatment predict the degree of access and number of embryos transferred.[18,19] Insurance mandates for ART coverage vary widely between states. To date, 15 states require private insurance to cover costs associated with infertility treatments.[20] There is variability in the types of treatments covered with some states covering the costs for four oocyte retrievals, others stipulating that coverage is dependent on the type of insurer, and some providing coverage only for treatments other than ART. Massachusetts has the most comprehensive mandate that requires insurers to cover ART in the instance that treatment is deemed a medical necessity. There is no limit on the number of cycles covered and no dollar lifetime cap, however, insurers may use patient medical histories to set limits.[21,22] The majority of states do not currently have state mandates to cover ART.

Although the contribution of ART to birth outcomes has been estimated for each state, this association has not been explored in the context of varying population characteristics between states.[1] We seek to identify whether birth outcomes of ART-conceived pregnancies vary between three states (Massachusetts, Michigan and Florida) with different maternal characteristics, insurance coverage for ART services, and type of ART services provided.

Methods

Data sources

Data from the Centers for Disease Control and Prevention's (CDC) National ART Surveillance System (NASS) were linked to Massachusetts, Florida, and Michigan state vital records for the period of 1 January 2000 through 31 December 2006 using CDC's Link Plus software. The data were obtained through the States Monitoring Assisted Reproductive Technology (SMART) Collaborative that was established by the CDC and public health agencies of Massachusetts, Florida and Michigan. A probabilistic linkage algorithm was used to link records by maternal and infant date of birth, plurality, gravidity, and zip code.[23] The average linkage rate was 91% which includes 28 971 linked ART cycles.[24] Fetal death record linkages were not available for inclusion. NASS contains maternal demographics, infertility diagnosis, ART procedures and pregnancy success rates from fertility clinics serving women in Florida, Massachusetts and Michigan; and one Rhode Island fertility clinic serving Massachusetts residents.[23,25] The study was approved by the Institutional Review Boards of the CDC and Public Health agencies of Massachusetts, Florida and Michigan.

The study population consisted of ART and non-ART-conceived live births in Massachusetts, Florida, and Michigan from 2000 through 2006. Maternal characteristics included age, education, race/ethnicity, nativity, marital status, tobacco use, parity, gravida, labour and delivery pay source, and adequacy of prenatal care utilisation as defined by the Kotelchuck Index. Categories were bridged between older and newer versions of birth certificate. Clinical estimates were used to assign gestational age. Singleton SGA infants were identified using Alexander's method and categorised as <5th and <10th percentile.[26] Birth-weight below 300 g and >6000 g, and gestational age <24 weeks and >42 weeks were excluded from the analyses. Post-term births, occurring after 42 weeks of gestation, were excluded to prevent practice differences between states from influencing the results.

Statistical analysis

Statistical analyses were performed through the National Center for Health Statistics' (NCHS) Research Data Center (RDC).[27] Bivariate analyses were conducted to compare rates of ART-conceived multiples, singleton preterm delivery and singleton SGA births by maternal characteristics and state, and to compare ART procedures by state. Student's *t*-test and the Kolmogorov–Smirnov test were conducted to assess the distribution of multiples. Multivariable logistic regression analyses were performed to determine the associations between ART use and singleton preterm delivery (<32 weeks, <37 weeks), singleton SGA (<5th percentile and <10th percentile), and multiple births. Regression models for multiples were adjusted for maternal characteristics including age, education, nativity, race/ethnicity, tobacco use, and marital status. Regression analyses for preterm and SGA outcomes were additionally adjusted for parity, gravidity, labour and delivery pay source, chronic hypertension, and diabetes. An interaction term of ART and state was included in the regression models to compare outcomes between states. Multiples were clustered by maternal identification number. Sensitivity analyses were conducted to examine the role of

adjustment factors in the models. Statistical Analysis System (SAS) was used to conduct analyses (Version 9.3, SAS Institute, Cary, NC, USA).

Results

Maternal characteristics and plurality by ART use are presented in Table 1. Tobacco use, diabetes, eclampsia, and chronic hypertension were not reported due to small cell sizes. Massachusetts had a lower rate of ART-conceived triplets and higher order births, while ART and non-ART-conceived infants were born to older, more educated women compared to other states. The rate of ART-conceived births was higher in Massachusetts at 25.3 ART births per 1000 total births, compared to 7.3 and 6.3 per 1000 for Michigan and Florida respectively (data not shown).

Table 2 summarises the rate of multiples, singleton preterm, and singleton SGA births among ART births by state of residence and maternal characteristics. Massachusetts had lower rates of multiple births across most characteristics. The rates of ART-conceived SGA singletons were highest among foreign-born women in all three states. ART-conceived singleton preterm deliveries were highest in Florida for non-Hispanic Black women, women who did not graduate from college, and women under 30 or ≥40 years of age. In Michigan, rates of singleton preterm delivery were highest among women 35 years and older, who had not completed college, and who were classified as “other” for race/ethnicity. Results for preterm delivery <32 weeks and fifth percentile SGA were not reported because of small cell sizes and similarity to other cut points.

ART procedures and causes of infertility varied significantly by state (Table 3). A higher proportion of infants were conceived using ICSI in Florida and Michigan. Overall, 19.6% of women using ART in Massachusetts had an unexplained cause of infertility compared to 6.7% and 6.0% in Florida and Michigan respectively. The percent of women under 35 receiving more than three embryos was significantly higher in Florida (9.2%) and Michigan (25.0%) compared to Massachusetts (5.1%).

Table 4 summarises the aORs between ART use and multiples, singleton preterm and SGA births. Although the odds of having an ART-conceived multiple birth was significantly higher in all three states compared to spontaneously conceived births, this association varied across states ($P < 0.0001$). ART use in Massachusetts was associated with a 22.6 (95% confidence interval (CI): 21.6, 23.7) increased odds of twin delivery and a 37.6 (95% CI: 31.1, 45.4) increased odds of triplet+ delivery. ART use resulted in a 30.0 (95% CI: 28.5, 31.6) increased odds of having twins and a 92.8 (95% CI: 78.4, 109.9) increased odds of having triplets in Florida, and a 26.3 (95% CI: 24.7, 28.1) increased odds of twins and 99.2 (95% CI: 82.3, 119.6) increased odds of triplets in Michigan. The aOR for singleton preterm delivery (<32 and <37 weeks gestation) and ART ranged from 1.60 to 1.87. A significant association between ART and fifth percentile singleton SGA was only observed for Massachusetts (aOR 1.14 (95% CI: 1.02, 1.27)); while ART and tenth percentile SGA singleton births was significant for Michigan (aOR 1.20 (95% CI: 1.02, 1.42)), but not for Florida and Massachusetts.

Comment

In this study, differences were seen between outcomes of ART- and spontaneously conceived infants. Variability in singleton preterm deliveries by maternal characteristics was observed among states for ART-conceived births. In Massachusetts, a higher percentage of ART-conceived births were singletons compared to the other two states. Regression results indicated that the main effect of state was significant for preterm delivery, multiples, and fifth percentile SGA in the absence of ART. These findings demonstrate the influences of variability in maternal characteristics and treatment-related factors on infant outcomes between states.

The weaker association observed in Massachusetts and higher prevalence of unexplained infertility might be attributable to the presence of an ART insurance mandate. Medical justification for investigating causes of infertility may be dependent on insurance coverage. Further examination of this finding is warranted, however, the current surveillance system does not provide substantial information on this issue. Another potential impact of coverage is the significantly lower rate of multiple embryo transfers in Massachusetts among women younger than 35. The higher magnitude of association between ART and multiple births, especially triplets+, in Florida and Michigan, is consistent with previous research that higher rates of multiple births occur in states lacking insurance mandates for ART.[28] When patients must pay per cycle, there may be heightened interest on both the part of the patient and physician to optimise pregnancy success as ART is often times cost prohibitive. The affordability of ART is an important determinant of utilisation, treatment choices, number of embryos transferred and multiple birth rates.[28] Insurance coverage for multiple cycles of IVF nation-wide could lead to increased use of elective single embryo transfer (eSET). It is estimated that the cost of caring for ART-conceived multiples exceeds the cost of ART treatment itself, and can extend well beyond the perinatal period.[29-32]

The definition of a successful ART cycle should be characterised by the delivery of a normal birthweight singleton term live birth.[33] Prior to embarking on a treatment regimen, patients should be informed about the risks associated with the number of embryos transferred. While eSET should be encouraged among patients, the high out-of-pocket costs of ART will continue to motivate patients to request the transfer of more embryos regardless of the increased risks.

This study is not without limitations. First, ART is an intricate series of procedures, which may either individually or collectively affect the quality of gamete(s), embryos, and health of the woman undergoing the procedure. We were unable to control for important confounders such as success of previous ART procedures, embryo stage and quality, length of period of infertility, aetiology of infertility, and behavioural factors. Second, the gestational age calculation is based on clinical and obstetric estimates which may lead to misclassification bias in preterm delivery and SGA categorisation.[34,35] Also, diminished ovarian reserve may have been reported differently in Massachusetts leading to misclassification. Third, there may be some definitional differences in variables because of changes in birth certificate versions over time. The data used in our study extend only through 2006 as this was the timeframe available for analysis. Finally, questions remain as to

whether it is methodologically appropriate to compare sub-fertile women who use ART with fertile women who do not.[10] In our study, women in the non-ART group included sub-fertile women as data were not available to identify them separately.

Future research is needed to compare sub-fertile women using non-ART treatments as the referent group and to compare medically indicated and spontaneous preterm deliveries. Patients undergoing ART need to be aware of the differences in pregnancy outcomes. It is also important that states recognise the long-term implications of these findings on costs associated with caring for multiples and the role of insurance mandates in mitigating these costs.

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Table 1.

Maternal characteristics by ART across states from 2000 to 2006[c]

Maternal characteristics	All ART births[a]			All non-ART births[a]		
	Florida (*n* = 8991) (%)	Massachusetts (*n* = 13 204) (%)	Michigan (*n* = 5730) (%)	Florida (*n* = 1 410 412) (%)	Massachusetts (*n* = 508 310) (%)	Michigan (*n* = 782 073) (%)
Maternal age (years)						
<30	11.4	7.9	15.2	63.3	45.9	62.3
30–34	34.8	33.8	38.4	22.6	32.4	24.7
35–39	35.8	39.1	31.2	11.5	17.9	10.9
≥40	18.1	19.3	15.2	2.6	3.7	2.1
Education						
Did not attend college	15.2	12.1	17.3	52.8	36.7	48.8
Some college	24.1	19.1	22.2	24.1	22.5	23.2
College graduate	35.7	40.3	31.7	14.9	26.2	15.7
Postgraduate	24.5	28.5	27.1	7.3	14.5	10.2
Race/Ethnicity						
Non-Hispanic white	70.8	88.9	92.9	48.0	70.4	77.8
Non-Hispanic black	5.5	2.6	2.9	21.4	7.7	17.8
Hispanic	18.7	2.7	_*b*	26.7	12.9	_*b*
Other	4.7	5.7	3.7	3.6	8.9	4.0
Non-US nativity	23.7	14.6	11.2	28.2	24.8	11.4
Single marital status	3.7	4.2	1.9	39.9	29.4	35.4
Prenatal care (Kotelchuck)						
<Adequate	9.4	6.0	7.4	24.5	16.0	19.4
Adequate	30.0	36.2	33.5	40.7	46.9	44.5
Adequate+	52.6	57.3	54.7	28.6	36.5	32.3
Plurality						
Twins	31.2	28.3	30.0	1.3	1.5	1.5
Triplet+	3.2	1.7	4.2	0.03	0.05	0.04

[a] *P*-value<0.001 for all comparisons between states for maternal characteristics within ART and non-ART groups.

[b]Masked due to small cell size.

[c]Cells may not add up to 100% as missing values were not deleted.

Table 2.

The rate of multiples, singleton preterm births (<37 weeks) and singleton SGA births (<10th percentile) among ART users by state of residence and maternal characteristics for 2000 to 2006[b]

	ART multiples				ART singleton preterm				ART singleton SGA			
Maternal characteristics	**Florida (*n* = 3093) (%)**	**Massachusetts (*n* = 3969) (%)**	**Michigan (*n* = 1962) (%)**	***P*-value**	**Florida (*n* = 808) (%)**	**Massachusetts (*n* = 936) (%)**	**Michigan (*n* = 483) (%)**	***P*-value**	**Florida (*n* = 492) (%)**	**Massachusetts (*n* = 761) (%)**	**Michigan (*n* = 311) (%)**	***P*-value**
Maternal age (years)												
<30	41.3	35.6	37.1	0.026	14.0	11.8	12.3	0.476	7.8	9.4	8.4	0.594
30–34	36.5	33.1	36.7	0.001	13.5	9.9	11.3	<0.001	8.3	7.9	7.1	0.455
35–39	31.9	28.9	32.1	0.003	12.5	9.9	14.2	<0.001	8.9	8.3	8.8	0.700
≥40	31.1	25.0	29.4	<0.001	16.4	10.5	14.0	<0.001	7.8	8.2	9.6	0.414
Education												
No college	35.1	29.2	33.9	0.002	14.8	11.8	13.4	0.143	8.7	9.0	8.2	0.841
Some college	34.6	31.9	33.9	0.130	15.8	9.3	13.3	<0.001	8.0	8.4	8.0	0.903
College degree	33.7	30.4	35.1	<0.001	12.4	10.1	11.9	0.014	8.0	7.6	8.0	0.783
Postgraduate	34.9	28.7	33.9	<0.001	12.7	10.1	13.4	0.005	8.7	8.7	8.7	0.997
Race/Ethnicity												
NH white	34.5	30.2	34.5	<0.001	12.9	9.7	12.6	<0.001	7.4	7.8	7.9	0.654
NH black	37.0	31.6	30.9	0.172	24.0	19.8	13.2	0.045	15.4	10.1	14.9	0.171
Hispanic	33.3	29.4	_[a]	14.4	10.6	_[a]	9.4	8.6	_[a]			
Other	34.7	27.2	29.6	0.027	11.4	12.2	17.3	0.178	10.3	13.7	10.7	0.305
Nativity												
US	34.3	30.1	34.3	<0.001	13.8	10.0	12.8	<0.001	7.8	7.6	7.9	0.798
Non-US	34.8	29.6	33.5	0.002	13.3	11.2	13.1	0.220	10.1	12.1	11.0	0.266
Marital Status												
Married	34.4	30.2	34.3	<0.001	13.6	10.2	12.8	<0.001	8.3	8.2	8.2	0.954
Single	35.4	26.2	30.8	0.015	15.4	8.4	14.9	0.019	8.4	9.1	9.5	0.938
Prenatal care (Kotelchuck)												
<Adequate	16.0	16.0	17.0	0.885	7.4	8.7	10.8	0.180	8.3	6.8	6.3	0.393
Adequate	16.8	10.9	12.7	<0.001	6.6	2.5	5.6	<0.001	7.8	7.1	6.7	0.382
Adequate+	47.7	43.5	49.2	<0.001	20.9	17.8	20.9	0.002	9.0	9.6	10.4	0.342

[a]Masked due to small cell sizes.

[b]Cells may not add up to 100% as missing values were not deleted.

Table 3.

ART procedures performed and causes of infertility for all ART conceived births by state from 2000 to 2006

ART procedure and causes of infertility	Florida (%)	Massachusetts (%)	Michigan (%)	*P*-value
Type of ART procedure				
IVF[a]	99.5	99.7	91.0	<0.001
ICSI[a]	54.4	36.3	71.6	<0.001
Unstimulated[b]				
Yes	5.7	6.2	7.4	<0.001
Missing	14.4	9.0	13.1	
Type of cycle (Mutually exclusive)				
Fresh embryos/Nondonor eggs	76.7	82.5	73.3	<0.001
Fresh embryos/Donor eggs	12.6	7.1	10.9	
Frozen embryos/Donor eggs	1.8	1.9	2.2	
Frozen embryos/Nondonor eggs	9.0	8.5	13.6	
Number of embryos transferred by maternal age				
<35 years				
1	3.0	6.4	2.2	<0.001
2	56.8	63.5	30.0	
3	31.0	25.0	42.9	
>3	9.2	5.1	25.0	
≥35 years				
1	3.6	5.7	3.0	<0.001
2	40.9	36.1	20.5	
3	35.4	32.7	36.4	
>3	20.1	25.5	40.2	
Causes of infertility				
Tubal factor	26.3	16.8	25.0	<0.001
Ovulatory dysfunction	15.3	10.6	15.9	<0.001
Diminished ovarian reserve	17.9	5.3	17.8	<0.001
Endometriosis	18.4	11.4	18.3	<0.001
Uterine factor	4.1	3.2	3.6	0.003

ART procedure and causes of infertility	Florida (%)	Massachusetts (%)	Michigan (%)	*P*-value
Men factor	41.3	31.4	43.6	<0.001
Unexplained infertility	6.7	19.6	6.0	<0.001

[a] Fresh non-donor cycles only.

[b] This information is not available for donor cycles resulting in a high percentage of missing values.

Table 4.

Adjusted odds ratios for multiples, singleton preterm infants, and singleton SGA by ART use in Florida, Michigan and Massachusetts

State and ART use	Adjusted models, OR (95% CI)	
	Twins[a]	Triplets+[a]
Florida (ART vs. Non-ART)	30.0 (28.5, 31.6)	92.8 (78.4, 109.9)
Massachusetts (ART vs. Non-ART)	22.6 (21.6, 23.7)	37.6 (31.1, 45.4)
Michigan (ART vs. Non-ART)	26.3 (24.7, 28.1)	99.2 (82.3, 119.6)
	Singleton preterm delivery <32 weeks [b]	**Singleton preterm delivery <37 weeks** [b]
Florida (ART vs. Non-ART)	1.70 (1.43–2.04)	1.70 (1.58–1.84)
Massachusetts (ART vs. Non-ART)	1.87 (1.59–2.20)	1.63 (1.52–1.75)
Michigan (ART vs. Non-ART)	1.60 (1.22–2.10)	1.73 (1.55–1.92)
	Singleton SGA (<5 percentile)[b]	**Singleton SGA (<10 percentile)**[b]
Florida (ART vs. Non-ART)	1.06 (0.92–1.22)	1.10 (0.98–1.25)
Massachusetts (ART vs. Non-ART)	1.14 (1.02–1.27)	1.06 (0.96–1.18)
Michigan (ART vs. Non-ART)	1.21 (1.00–1.45)	1.20 (1.02–1.42)

[a] Adjusted for age, education, nativity, race/ethnicity, tobacco, marital status.

[b] Adjusted for age, education, nativity, race/ethnicity, tobacco, marital status, gravidity, parity, pay source, hypertension, diabetes.