Assisted Reproductive Technology and Early Intervention Program Enrollment

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abstract

OBJECTIVES: We examined the prevalence of Early Intervention (EI) enrollment in Massachusetts comparing singleton children conceived via assisted reproductive technology (ART), children born to mothers with indicators of subfertility but no ART (Subfertile), and children born to mothers who had no indicators of subfertility and conceived naturally (Fertile). We assessed the natural direct effect (NDE), the natural indirect effect (NIE) through preterm birth, and the total effect of ART and subfertility on EI enrollment.

METHODS: We examined maternal and infant characteristics among singleton ART (n = 6447), Subfertile (n = 5515), and Fertile (n = 306 343) groups and characteristics associated with EI enrollment includingpreterm birth using χ^2 statistics ($\alpha = 0.05$). We estimated the NDE and NIE of the ART–EI enrollment relationship by fitting a model for enrollment, conditional on ART, preterm and the ART-preterm delivery interaction, and covariates. Similar analyses were conducted by using Subfertile as the exposure.

RESULTS: The NDE indicated that the odds of EI enrollment were 27% higher among the ART group (odds ratio$_{NDE}$ = 1.27; 95% confidence interval (CI): 1.19–1.36) and 20% higher among the Subfertilegroup (odds ratio$_{NDE}$ = 1.20; 95% CI: 1.12–1.29) compared with the Fertile group, even if the rate of preterm birth is held constant.

CONCLUSIONS: Singleton children conceived through ART and children of subfertile mothers both have elevated risks of EI enrollment. These findings have implications for clinical providers as they counsel women about child health outcomes associated with ART or subfertility.

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Dr Diop conceptualized and designed the study; interpreted the findings; drafted, reviewed, and wrote the final version of the manuscript; and directed the project overall; Ms Gopal participated in the planning of the study, had full access to all of the data, performed statistical programming and carried out the analyses, contributed to data interpretation, and reviewed the manuscript; Dr Cabral participated in the planning of the study, performed initial statistical programming, and contributed to data interpretation; Drs Belanoff, Declercq, Kotelchuck, Luke, and Stern participated in the planning of the study, contributed to data interpretation, and reviewed the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: The association of assisted reproductive technology (ART) and risks of adverse perinatal outcomes among singleton children is well established. The risk of Early Intervention enrollment among children conceived through the use of ART and children born to subfertile mothers remains unknown.

WHAT THIS STUDY ADDS: Early Intervention enrollment among children born to ART and subfertile mothers is mainly due to the direct effect of ART and subfertility; preterm birth is not the primary contributor through which ART and subfertility are associated with enrollment.

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In 2011, Massachusetts had 7502 assisted reproductive technology (ART) procedures performed per 1 million women aged 15 to 44 years, >3 times the US national average of 2401.[1]Based on2010 data from the 14th European IVF–Monitoring Consortium, only 2 European countries, Denmark and Slovenia, had higher proportions of births from ART (5.9% and 5.1%, respectively) than Massachusetts (4.5%).[1,2] In the United States, states such as Massachusetts with ART-coverage insurance mandates have reported higher ART utilization rates.[3]

Previous research described associations between ART, subfertility, and risks of adverse perinatal outcomes, including multiple birth, preterm birth, low birth weight, small for gestational age, and long-term disability.[4–12] Children with these adverse outcomes are at increased risk of poor developmental and behavioral outcomes and are specifically in need of Early Intervention (EI) programs.[13–16] Cognitive, behavioral, and social outcomes can be improved if developmental/behavioral interventions are initiated early in life.[15,17,18] These beneficial and long-lasting services can be provided through EI programs to children with developmental delays or at risk for such delays at no cost. As the number of children born from ART increases, it is important to understand the health and developmental needs of these children.

The likelihood of EI enrollment among children conceived through the use of ART remains unknown. Given that ART is associated with preterm birth[19] and that preterm birth is associated with EI enrollment,[13] we assumed that preterm birth may contribute to the ART/subfertility–EI enrollment relationship. In this study, we tested the hypothesis that EI enrollment among ART children and children born to subfertile mothers is partially explained by preterm status using the single-mediator model.[20] This approach is used when a factor is on the causal pathway between the exposure and the outcome, and as such should not be adjusted for in the analysis of the total effect.

Our objectives were as follows: (1) to examine the prevalence of, and characteristics associated with, EI enrollment among singletons in Massachusetts comparing 3 groups (children conceived via ART, children born to women with indicators of subfertility but no ART [Subfertile], and children born to women with neither ART nor indicators of subfertility [Fertile]); (2) describe the most frequent reasons for EI enrollment; and (3) assess the direct, indirect (through preterm birth), and total effects of ART and subfertility on EI enrollment among singletons using a mediation model.

METHODS

Data Sources

This study linked 3 population-based data systems: the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS), the Massachusetts Pregnancy to Early Life Longitudinal data system (PELL), and the EI program participation data. SART CORS contains ART treatment records collected in compliance with the Fertility Clinic Success Rate and Certification Act of 1992.[21] All ART clinics in Massachusetts during our study period contributed data to SART CORS, which includes data on patient demographic characteristics, medical history, infertility diagnoses, ART treatments, and pregnancy outcomes.[1] SART CORS has been described elsewhere.[22,23]

PELL is a population-based database of mothers and children, which links delivery records to their corresponding hospital discharge records for the delivery and non–birth-related inpatient admissions, observational stays, and emergency department visits over time and deaths of mothers and children. More than 99% of all deliveries in Massachusetts from 1998 to 2012 have been linked in PELL. The PELL linkage allows children born to the same mother to be identified as siblings and multiple hospitalization records belonging to the same women or children to be attributed as such.[15]

EI program participation data are collected by the Massachusetts Department of Public Health (MDPH) under part C of the Individuals with Disabilities Education Act (IDEA 97). EI programs provide services at no cost to infants/children aged 0 to 3 years at risk of or with established developmental delays due to birth, social/emotional, and environmental factors. There are 4 categories of eligibility: (1) established conditions, (2) established developmental delays, (3) at risk of developmental delays, and (4) clinical judgment. Many of these risk factors are recognizable at the time of birth and recorded on birth or delivery hospitalization records.[14,15] Eligibility is determined by using an approved tool, the Battelle Developmental Inventory, Second Edition, or informed clinical opinion if the child does not meet the current definition of established condition or developmental delay when qualitative concerns can be documented. The most commonly used EI services include developmental specialists, occupational therapists, and speech and language pathologists.[13] When children are determined to be eligible for EI services, an Individualized Family Service Plan (IFSP) is developed by EI providers and parents. The EI data system contains information on all EI participants, including demographic characteristics, reasons for referral, referral date, and types of EI services provided. Each child in the data system has a unique ID.[16]

Data Linkage and Study Sample

We constructed the Massachusetts Outcomes Study of Assisted Reproductive Technology (MOSART) database by linking PELL and SART CORS usingmother's first and last name, father's last name, andmother's and infant's dates of birth. The 5-phase linkage algorithm used to construct MOSART has been previously described.[24] All linkages and analyses were performed by using SAS version 9.2 (SAS Institute, Cary, NC) and Link Pro(InfoSoft, Inc, Winnipeg, Manitoba, Canada).

We used a previously described algorithm to identify subfertile deliveries in the MOSART database.[25] Briefly, a delivery was classified as subfertile if it met any of the following conditions from the data sources included in the MOSART database: (1) at least 1 of the 2 fertility-treatment questions on the Massachusetts birth certificate was answered "yes" for an index delivery or on a delivery record to the same woman within the 5 years before the index delivery, (2) a hospital encounter for a condition specifically related to infertility was associated with an index delivery or occurred in the 5 years before an index pregnancy, and (3) an ART cycle before the index delivery was found in SART CORS. We then removed those cases where a mother received ART for the index delivery, and the remaining deliveries were classified as subfertile.

We linked 334 152 state-resident deliveries in PELL occurring in Massachusetts between July 1, 2004, and December 31, 2008, to 42 649 eligible ART treatment cycles between January 1, 2004, and December 31, 2008, derived from SART CORS, with an overall linkage rate of 89.7% and a 95.0% linkage rate among Massachusetts-resident women receiving ART treatment in Massachusetts clinics. These linkage rates were previously published.[24] The resulting database contained 342 035 live births and fetal deaths associated with the 334 152 deliveries.

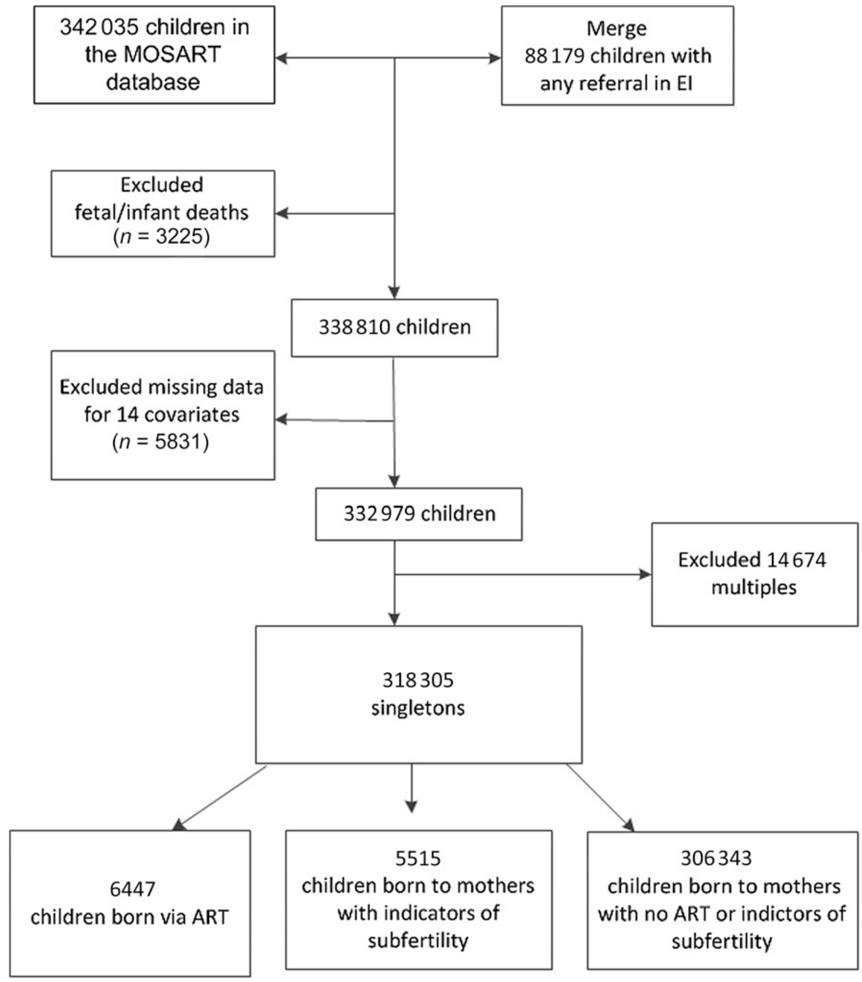

FIGURE 1
Flow diagram of study sample with inclusion and exclusion criteria.

We then linked EI program data with PELL using the PELL unique child ID. The EI linkage algorithm to PELL has been previously described.[26] The 342 035 live births were subsequently merged with 88 179 children who had any referral to EI between July 1, 2004, and December 31, 2011, to capture all potential enrollments from birth to age 3 (Fig 1). Almost 86% of EI enrollees linked to a PELL birth certificate. We excluded all multiple births from this study because of the high rate of plurality among ART-conceived pregnancies; and more importantly, after preliminary analysis, we found that multiple births did not meet the criteria for mediation analysis as described below.[27] There is also a well-established association of plurality with adverse outcomes including low birth weight, perinatal mortality, and preterm birth.[4,28] After excluding fetal and infant deaths (3225), records missing covariates (5831), and multiples (14 674), our final study sample included 318 305 children (ART, n = 6447; Subfertile, n = 5515; and Fertile, n = 306 343).

Dependent Variable

Our dependent variable was EI enrollment, defined here as having a signed IFSPin the EI database.

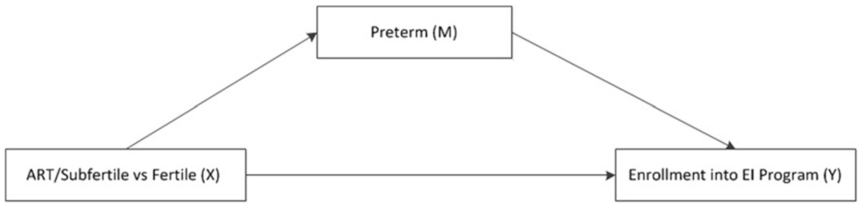

FIGURE 2
Mediation framework for assessing whether preterm birth is a mediator of ART or subfertility in EI enrollment.

Independent Variables and Mediator

Our main independent variable was fertility status of the delivery for the index child categorized as ART, Subfertile, or Fertile. We conducted 2 separate analyses comparing the association of EI enrollment among (1) ART children and children born to fertile mothers and (2) children born to subfertile and children born to fertile mothers. Our mediator was preterm birth defined as a delivery at <37 weeks' completed gestation.

Covariates

Covariates were selected on the basis of known risk factors for preterm birth, EI enrollment, and ART. These included maternal age, race and Hispanic ethnicity, education, nativity, marital status, delivery payer source, parity, prenatal care, infant gender, cigarette smoking during pregnancy, complications of labor and delivery, and abnormal conditions of the newborn.

Mediation Approach

Consistent with Ananth and VanderWeele's mediation analysis approach,[27] which involves several "no-unmeasured confounding assumptions," we presumed that adjusting for the set of covariates listed above would be sufficient to control for confounding of (1) exposure–outcome (ART–EI enrollment), (2) mediator–outcome (preterm–EI enrollment), and (3) exposure –mediator (ART–preterm). We made similar assumptions using Subfertile as the independent variable. This mediation approach allowed us to split the total effect of ART and subfertility on EI enrollment into natural direct effect (NDE) and natural indirect effect (NIE).[29,30] Figure 2 illustrates our mediation framework.

Statistical Analysis

We examined maternal and infant characteristics among singleton ART, Subfertile, and Fertile and prevalence and reasons for EI enrollment by fertility status using χ^2 statistics ($\alpha = 0.05$). We used logistic regression to estimate crude odds ratios (ORs) and adjusted ORs (aORs) and 95% confidence intervals (CIs) to assess the 3 mediation conditions defined above for ART versus Fertile and Subfertile versus Fertile. Using Ananth and VanderWeele's approach,[27] we estimated the NDE and NIE of the ART–EI enrollment relationship by fitting a model for enrollment (Y), conditional on ART (X), preterm delivery (M), and ART–preterm delivery interaction (X × M) and the covariates (C). We then fit a model for preterm delivery (M), conditional on ART (X) and the covariates (C). We conducted similar analyses using subfertility as the exposure. We ruled out the possibility of effect modification of preterm birth on the association of Subfertile and EI enrollment after we examined the interaction terms in our models. The mediation analysis was conducted using the mediation macro provided by Valerie and VanderWeele.

[29] This study was approved by the Institutional Review Board of MDPH.

RESULTS

Table 1 presents the distribution of infant and maternal characteristics of our study sample by fertility status. All *P* values were significant at <.001, except for gender. Preterm birth was significantly higher among ART and Subfertile (10.1% and 7.8%, respectively) compared with the Fertile (6.2%) group.

Table 2 shows the prevalence of EI enrollmentby fertilitystatusand infant and maternal characteristics among singleton children. All *P* values were significant at <.001. The prevalences of EI enrollment among ART, Subfertile, and Fertile groups for singleton term children were 15.9%, 15.8%, and 15.2%, respectively. Among singleton preterm children, the prevalence of EI enrollment was more than twice that of all 3 fertility groups (44.0%, 36.9%, and 36.2% among ART, Subfertile, and Fertile, respectively).

Table 3 summarizes the reasons for EI enrollment by fertility status. *P* values were significant at <.05 for most conditions, with the exception of central nervous system disorder, circulatory disorder, sensory disorder, expressive language, suspected central nervous system abnormality, and clinical judgement.

Table 4 presents the unadjusted ORs and aORs used to establish that our 3 mediation criteria were met. ART children were more likely to be preterm (aOR: 1.45; 95% CI: 1.32–1.59) and enrolled in EI (aOR: 1.34; 95% CI: 1.26–1.44) compared with their Fertile counterparts. After controlling for ART and other covariates, children who were preterm had 2.6 times the odds of being enrolled in EI. Those in the Subfertile group had significantly higher odds of being preterm (aOR: 1.18; 95% CI: 1.06–1.31) and being enrolled in EI (aOR: 1.21; 95% CI: 1.13–1.31) compared with those in the Fertile group.

TABLE 1 Maternal and Infant Characteristics by Fertility Status: Massachusetts Singleton Births, July 1, 2004, to December 31, 2008

	Distribution of Study Sample at Birth, %		
	ART (*n* = 6447)	Subfertile (*n* = 5515)	Fertile (*n* = 306 343)
Maternal characteristics			
Age			
<30 years	7.8	11.9	48.4
30 to <35 years	30.9	33.7	30.4
35 to <40 years	40.2	39.8	17.6
40 to <45 years	18.1	13.7	3.5
≥45 years	3.0	0.9	0.1
Race/ethnicity			
White non-Hispanic	86.1	85.1	67.4
Black non-Hispanic	3.0	3.0	8.4
Asian/Pacific Islander	6.7	6.3	7.5
Hispanic	3.1	4.4	14.3
Other non-Hispanic	1.1	1.2	2.4
Marital status			
Married	96.1	94.5	66.3
Not married	3.9	5.5	33.7
Education			
Less or no HS/GED	9.4	11.9	37.7
Some college/associate degree	16.5	18.0	21.6
Bachelor/postgraduate	74.0	70.1	40.7
Nativity			
Foreign-born	17.5	17.3	27.6
US-born	82.5	82.7	72.4
Delivery payer source			
Private	96.8	92.1	58.8
Public	3.2	7.9	41.2
Cigarettes during pregnancy			
No	99.2	98.2	92.3
Yes	0.8	1.8	7.7
Prenatal care			
Inadequate/intermediate	7.4	8.9	17.2
Adequate	43.9	43.5	45.4
Adequate plus	48.7	47.6	37.4
Parity			
1	62.4	39.3	45.7
2	30.0	40.0	34.2
≥3	7.6	20.7	20.1
Complications of labor delivery and risk factors			
No	27.9	34.3	39.1
Yes	72.1	65.7	60.9
Infant characteristics			
Gender [a]			
Male	50.9	50.5	51.1
Female	49.1	49.5	48.9
Abnormal conditions of newborn			
No	68.8	72.3	73.7
Yes	31.2	27.7	26.3
Prematurity			
No	89.9	92.2	93.8
Yes	10.1	7.8	6.2

N = 318 305 singleton births. HS/GED, high school/general educational development.
[a] *P* = .69 for ART versus Fertile and 0.33 for Subfertile versus Fertile.

Table 5 shows the results of the mediation analysis. The NDE indicates that the odds of EI enrollment is 27% higher among ART (OR_{NDE}: 1.27; 95% CI: 1.19–1.36) and 20% higher among Subfertile (OR_{NDE}: 1.20; 95% CI: 1.12–1.29)compared with the Fertile group, even if the rate of preterm birth is the same across the 3 groups. Although the NIEs (odds of EI enrollment among ART group under their observed preterm rate) were statistically significant, the ORs were close to 1 (OR_{NIE} for ART versus Fertile: 1.03; 95% CI: 1.02–1.04; OR_{NIE} for Subfertile versus Fertile: 1.01; 95% CI: 1.00–1.01). The total effect, which is the product of NDE and NIE for Subfertile ($OR_{Total\ Effect}$: 1.21; 95% CI: 1.12–1.30) was equal to the aOR in Table 3. For ART, the total effect ($OR_{Total\ Effect}$: 1.31; 95% CI: 1.22–1.40)] is slightly different from the aOR due to the inclusion of the interaction term in the mediation analysis.

DISCUSSION

The proportion of singletons born via ART remains substantial in Massachusetts, yet little is known about the long-term health outcomes of these children. The likelihood of EI enrollment among ART and Subfertile groups has not been previously reported. This study presented a unique opportunity to examine child health outcomes through age 3 by using participation in EI programs as a proxy for risk of developmental delays.[13] We had hypothesized that EI enrollment among the ART and Subfertile groups could be partially explained by preterm status. However, we found that EI enrollment was mainly due to the NDE of ART and subfertility, which indicates that the ART and Subfertile groups would still have higher odds of EI enrollment, even if the preterm rates remained the same across the fertility groups.

Our findings also confirmed that ART was associated with a greater risk of preterm birth. Pooled ORs from systematic reviews with meta-analyses indicated an approximate twofold increase in singletons born at <37 weeks of gestation.[10] A recent review reported an OR of 1.5 (95% CI: 1.5–1.6) among singletons,[31] which is close to our findings (aOR: 1.45; 95% CI: 1.32–1.59). We also found that preterm birth was higher among Subfertile, but this relationship was not as strong as in the ART group (aOR: 1.18; 95% CI: 1.06–1.31). Consistent with past research, our study also found that children who were born preterm have greater needs for EI services, which have been found to have long-lasting impact on developmental and social outcomes.[13,32,33] Although we found a positive association between ART, Subfertile, and EI enrollment, our results differ from several reviews that showed no difference between naturally conceived and ART children in neurocognitive and motor development outcomes after adjusting for prematurity and other risk factors.[34–37] However, other registry-based studies have shown greater risk of developmental delays and cerebral palsy.[38–40] Given that our study used EI enrollment solely as a proxy for developmental delays, our study should be interpreted with caution. Although we report the most frequent reasons for EI enrollment, we did not assess the effect of ART on these individual developmental outcomes.

The classification of ART, Subfertile, and Fertile was made by using the gold standard, SART CORS clinical treatment data obtained directly from ART clinics and linked to delivery records. The successful linkage of 95% of eligible ART treatment records suggests that the vast majority of ART births in Massachusetts were correctly classified. However, we have no doubt that we might have underestimated the Subfertile group because many women treated in an outpatient setting may not have been included in our estimates. Although the Fertile group may contain a small proportion of women who are actually subfertile, it is unlikely that this small number is sufficient to affect the findings.

TABLE 2 EI Enrollment by Fertility Status and Infant and Maternal Characteristics: Massachusetts Singleton Births, July 1, 2004, to December 31, 2008

	Prevalence, %		
	ART (*n* = 1206 of 6447)	Subfertile (*n* = 960 of 5515)	Fertile (*n* = 50403 of 318 305)
Overall EI enrollment	18.7	17.4	16.5
Infant characteristics			
Prematurity			
No	15.9	15.8	15.2
Yes	44.0	36.9	36.2
Gender			
Male	23.3	21.0	20.6
Female	14.0	13.7	12.1
Abnormal conditions of newborn			
No	15.7	15.6	14.9
Yes	25.3	22.0	20.9
Maternal characteristics			
Age			
<30 years	16.5	14.5	17.7
30 to <35 years	17.5	17.8	14.7
35 to <40 years	19.8	17.6	15.8
40 to <45 years	18.8	17.7	17.0
≥45 years	22.2	25.5	20.7
Race/ethnicity			
Hispanic	22.2	23.7	22.2
White non-Hispanic	18.7	17.6	15.7
Black non-Hispanic	20.2	15.2	17.7
Asian/Pacific Islander	16.3	12.4	11.3
Other non-Hispanic	19.2	13.2	15.6
Marital status			
Married	18.7	17.3	14.2
Not married	19.0	19.3	20.8
Education			
Less than or no HS/GED	20.7	19.1	20.0
Some college/associate degree	20.1	19.9	16.3
Bachelor/postgraduate	18.1	16.5	13.2
Nativity			
Foreign-born	17.0	16.9	14.1
US-born	19.1	17.5	17.4
Delivery payer source			
Private	18.4	17.1	13.7
Public	27.5	20.8	20.4
Cigarettes during pregnancy			
No	18.7	17.4	15.7
Yes	21.6	19.6	25.4
Prenatal care			
Inadequate/intermediate	14.9	20.6	17.5
Adequate	16.3	15.3	14.4
Adequate plus	21.4	18.7	18.5
Parity			
1	18.2	17.4	15.8
2	20.0	17.3	16.2
≥3	18.3	17.8	18.4
Complications of labor delivery and risk factors			
No	15.3	14.8	14.2
Yes	20.0	18.8	17.9

HS/GED, high school/general educational development.

Our study has limitations. First, this study was limited to Massachusetts mothers who were residents at the time of delivery anddelivered in Massachusetts hospitals. Second, to estimate the NDEs and NIEs, the mediation analysis required an additional assumption that there

TABLE 3 Reasons for EI Enrollment by Fertility Status: Massachusetts Singleton Births, July 1, 2004 to December 31, 2008

	Distribution of Reasons for EI Enrollment[a,b]				
	ART	Subfertile	Fertile	Total	*P*
Enrolled, *n*	1206	960	50 403	52 569	
Established conditions, %	15.3	14.5	11.2	11.3	<.0001
CNS disorder	1.7	1.9	1.5	1.5	.53
Circulatory disorder	1.1	1.4	0.8	0.8	.052
Congenital torticollis	5.5	3.7	2.7	2.8	<.0001
Sensory disorder	2.0	1.8	1.3	1.3	.07
Established delays, %	85.3	86.7	83.5	83.6	<.01
Cognition	22.7	16.9	21.7	21.6	<.01
Adaptive	19.3	15.9	16.3	16.4	.02
Fine motor	59.0	60.5	59.5	59.5	.75
Gross motor	21.8	12.3	17.3	17.3	<.0001
Expressive language	32.7	25.2	22.5	22.7	<.0001
Receptive language	26.5	26.0	35.0	34.6	<.0001
Social emotional	12.0	7.5	10.1	10.1	<.01
At-risk conditions, %	38.6	34.4	49.3	48.8	<.0001
Birth weight <1200 g	3.5	1.9	2.0	2.0	<.01
Gestational age <32 weeks	7.5	4.0	3.8	3.9	<.0001
NICU admission >5 days	16.3	11.2	9.6	9.8	<.0001
Hospital stay >25 days in 6 months	7.6	5.4	4.4	4.5	<.0001
Diagnosis of IGUR or SGA	3.7	3.5	2.5	2.6	.01
Small size (weight, age, height criteria)	8.5	8.9	4.8	5.0	<.0001
Chronic feeding difficulties	11.1	10.5	8.7	8.8	<.01
Suspected CNS abnormality	4.8	4.6	5.7	5.6	.17
Parental chronic illness/disability	7.6	7.4	14.7	14.4	<.0001
Clinical judgement, %	5.0	4.3	4.0	4.0	.22

CNS, central nervous system; IGUR, intrauterine growth restriction; SGA, small for gestational age.

[a] Percentages sum to >100 because children may be enrolled in EI program for >1 reason.

[b] Not all reasons are presented; only risk factors occurring most frequently within each category are presented.

TABLE 4 Unadjusted ORs and aORs From Logistic Regression Models for Each of the Criteria for the Mediation Analysis: Massachusetts Singleton Births, July 1, 2004, to December 31, 2008

Criteria for mediation	Unadjusted OR[a] (95% CI)	*P*	aOR[b] (95% CI)	*P*
ART versus Fertile (*N* = 312 790)				
1. Relationship between ART and EI enrollment	1.17 (1.10 – 1.25)	<.001	1.34 (1.26 – 1.44)	<.001
2. Relationship between ART and preterm	1.70 (1.57 – 1.85)	<.001	1.45 (1.32 – 1.59)	<.001
3. Relationship between preterm and EI enrollment	3.21 (3.11 – 3.31)	<.001	2.60 (2.51 – 2.68)	<.001
Subfertile versus Fertile (*N* = 311 858)				
1. Relationship between Subfertile and EI enrollment	1.07 (1.00 – 1.15)	.06	1.21 (1.13 – 1.31)	<.001
2. Relationship between Subfertile and preterm	1.28 (1.16 – 1.42)	<.001	1.18 (1.06 – 1.31)	.003
3. Relationship between preterm and EI enrollment	3.18 (3.08 – 3.28)	<.001	2.57 (2.48 – 2.66)	<.001

[a] For the first 2 assumptions, the unadjusted OR is the crude OR of the association. For the third assumption, the unadjusted OR is the association of EI enrollment (outcome) and preterm (mediator), controlling only for fertility status (exposure).

[b] Models adjusted for maternal demographic characteristics (maternal age, race, education, marital status, nativity), insurance, smoking, prenatal care, parity, gender, labor and delivery complications, and abnormal conditions of the newborn.

TABLE 5 Estimates of NDE, NIE, and Total Effect of the Association Between ART and Subfertility and EI Enrollment Mediated Through Preterm Birth: Massachusetts Singleton Births, July 1, 2004, to December 31, 2008

	NDE		NIE		Total Effect	
	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*	OR (95% CI)	*P*
ART versus Fertile	1.27 (1.19 – 1.36)	<.001	1.03 (1.02 – 1.04)	<.001	1.31 (1.22 – 1.40)	<.001
Subfertile versus Fertile	1.20 (1.12 – 1.29)	<.001	1.01 (1.00 – 1.01)	<.01	1.21 (1.12 – 1.30)	<.001

[a]Models adjusted for maternal age, race, education, marital status, nativity, delivery payer source, smoking, prenatal care, parity, gender, labor and delivery complications, and abnormal conditions of the newborn. An interaction term was included for the ART versus Fertile comparison.

was no unmeasured confounding of the preterm birth and EI enrollment relationship by factors due to ART or subfertility. Sensitivity analyses can be used to mimic how findings might be affected by specific unmeasured confounders.[41] Although we did not conduct these sensitivity analyses, we did adjust for ART and subfertility to account for the effect of unmeasured factors associated with ART and subfertility. Third, we did not examine EI enrollment for each gestational age <37 weeks to assess the effect of earlier gestational age on enrollment. The risk of EI enrollment increasing with decreasing gestational age has been previously reported.[13] Last, this study can only be generalized to singletons born in Massachusetts.

Despite these limitations, our study has several strengths. MOSART is a large, population-based database that includes detailed ART treatment,postbirth hospital utilization, and public health program data.[24] Most ART studies in the United States have relied on the national database and clinic-based data, which do not allow investigators to follow children postbirth, nor do they allow them to link with program participation data.[24]

Our study is unique because it treated preterm birth as a mediator rather than a confounder, which allowed us to parse the total effect of ART and subfertility on EI enrollment into NDEs and NIEs.[27] The NIE allowed us to show the extent to which intervening on preterm could better estimate EI enrollment among ART/Subfertile groups, whereas the NDE showed that, regardless of preterm, ART and Subfertile groups still had higher rates of EI enrollment (27% and 20%, respectively). The results from our study suggest that preterm birth is not the primary contributor through which ART and subfertility are associated with EI enrollment.

Our findings have implications for clinical providers, mainly obstetricians as they counsel women about child health outcomes associated with ART or subfertility. These findings can also help pediatricians and neonatologists as they develop discharge plans for these children to include referrals to EI programs and to educate families about the lasting benefit of EI services on children's health. Finally, given that knowledge of long-term health outcomes among ART children and children born to subfertile mothers has been limited by the lack of longitudinal studies,[24,42] our study showing that both ART and being subfertile increase EI enrollment represents a significant step forward. Yet, further research and long-term follow-up are needed to fully understand the health implications and risks on children and their families later in life.

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ABBREVIATIONS

aOR: adjusted odd ratio
ART: assisted reproductive technology
CI: confidence interval
EI: Early Intervention
MOSART: Massachusetts Outcomes Study of Assisted Reproductive Technology
NDE: natural direct effect
NIE: natural indirect effect
OR: odds ratio
PELL: Pregnancy to Early Life Longitudinal
SART CORS: Society for Assisted Reproductive Technology Clinic Outcome Reporting System

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