Assisted Reproductive Technology and Perinatal Mortality: Selected States (2006–2011)

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Abstract

Objective This study aimed to compare trends and characteristics of assisted reproductive technology (ART) and non-ART perinatal deaths and to evaluate the association of perinatal mortality and method of conception (ART vs. non-ART) among ART and non-ART deliveries in Florida, Massachusetts, and Michigan from 2006 to 2011.

Study Design Retrospective cohort study using linked ART surveillance and vital records data from Florida, Massachusetts, and Michigan.

Results During 2006 to 2011, a total of 570 ART-conceived perinatal deaths and 25,158 non-ART conceived perinatal deaths were identified from the participating states. Overall, ART perinatal mortality rates were lower than non-ART perinatal mortality rates for both singletons (7.0/1,000 births vs. 10.2/1,000 births) and multiples (22.8/1,000 births vs. 41.2/1,000 births). At <28 weeks of gestation, the risk of perinatal death among ART singletons was significantly lower than non-ART singletons (adjusted risk ratio [aRR] = 0.46, 95% confidence interval [CI]: 0.26–0.85). Similar results were observed among multiples at <28 weeks of gestation (aRR = 0.64, 95% CI: 0.45–0.89).

Conclusion Our findings suggest that ART use is associated with a decreased risk of perinatal deaths prior to 28 weeks of gestation, which may be explained by earlier detection and management of fetal and maternal conditions among ART-conceived pregnancies. These findings provide valuable information for health care providers, including infertility specialists, obstetricians, and pediatricians when counseling ART users on risk of treatment.

Keywords
- perinatal mortality
- stillbirth
- infant death
- assisted reproductive technology

Key Points

- ART use is associated with a decreased risk of perinatal deaths prior to 28 weeks of gestation.
- ART perinatal mortality rates were lower than that for non-ART perinatal mortality.
- This study used linked data to examine associations between use of ART and perinatal deaths.

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Data from 2011 to 2015 National Survey of Family Growth (NSFG) suggest that almost 7% of married women of reproductive age (15–44 years) were unable to achieve pregnancy after at least 12 consecutive months of trying to conceive, and that 12% of women of reproductive age (over 7 million) had received some type of infertility service, including testing, medical advice, or treatment to become pregnant.[1] Assisted reproductive technology (ART), defined as any procedure in which oocytes or embryos are handled in the laboratory for the purpose of establishing a pregnancy, has been increasingly used in the United States since 1981.[2] Today, ART-conceived infants account for approximately 1.8% of all infants born in the United States, with about a third being multiples (twins or higher-order).[3,4]

Although ART treatments are generally considered safe, adverse pregnancy outcomes such as low birth weight, preterm birth, birth defects, stillbirths, infant deaths, and maternal deaths may occur at a higher rate compared with spontaneously conceived pregnancies.[2,3,5] Researchers in Scandinavia found a two- to fourfold increased risk of stillbirth delivery among women who conceived using ART as compared with women who conceived naturally.[6–9] This increased risk of stillbirth delivery was particularly prominent among singleton births occurring at <28 weeks of gestation.[6] Chughtai et al[9] also found a significantly higher overall perinatal mortality rate among ART-conceived births (16.5/1,000 births) than non-ART births (11.3/1,000 births). However, the perinatal mortality rate was lower for ART births at <32 weeks of gestation compared with non-ART births. While the latest available data in the United States show that <1% of ART births resulted in stillbirth in 2016, no information is available on early infant deaths following ART.[2] The purpose of this study was to exam whether ART is associated with increased risk of perinatal mortality.

Materials and Methods

We conducted a retrospective cohort study using data from the States Monitoring Assisted Reproductive Technology (SMART) Collaborative. The SMART Collaborative database is a linked database of the Centers for Disease Control and Prevention's (CDC's) National ART Surveillance System (NASS) and standardized state vital records (including birth, fetal death, and infant death certificates) for three states (Florida, Massachusetts, and Michigan).[10–12] Briefly, the linkage was conducted by using Link Plus, a probabilistic record linkage program developed by the U.S. CDC with maternal date of birth, infant date of birth or fetal death, plurality, gravidity, and ZIP codes as linking variables.[10–12] Linkage method for live births has been previously described and validated[10–12]; a similar method was used to link fetal deaths. The SMART Collaborative database yielded linkage rates of 91% for both birth certificate and infant death certificate records and 74% for fetal death records. In compliance with the Fertility Clinic Success Rate and Certification Act, each medical center in the United States that performs ART procedures is required to report data on every ART procedure and its resultant pregnancy outcome annually to the CDC.[2,13] The NASS database contains ART cycle-specific information on patient demographics, medical history, pregnancy history, infertility diagnoses, clinical information pertaining to the ART procedure, treatment outcomes, and if applicable, pregnancy outcomes.[2] State vital records provided the information on live born infants (birth certificate data), stillborn infants (fetal death of ≥20 weeks of gestation from fetal death report data), and early neonatal deaths (death of an infant within the first 7 days of life from infant death certificate data).

We included all ART cycles performed during 2006 to 2011 (the most recent linked SMART Collaborative data available) that resulted in livebirths, stillbirths, or early infant deaths in a participating state and that were linked with state vital record data.[10–12] We excluded ART cycles in which gestational carriers were used and pregnancies with unknown plurality. Stillbirths and infant deaths in the state vital records were classified as non-ART perinatal deaths if they could not be linked to the NASS database. For the purpose of this study, we used definition III of perinatal deaths described by Barfield and the American Academy of Pediatrics Committee on Fetus and Newborn, which includes fetal death of ≥20 weeks of gestation and infant deaths <7 days of age to better capture deaths that occurred at early gestational age and around the time of delivery.[14] Fetus or infant was the unit of analysis for the study.

We used the Cochrane-Armitage test to assess trends in ART and non-ART perinatal mortality rates (number of perinatal deaths/1,000 live births) during 2006 to 2011 by plurality. We used Pearson's Chi-squared test to examine bivariate associations between selected characteristics (maternal sociodemographic factors, smoking status during pregnancy, parity, pre-pregnancy body mass index [BMI], gestational weight gain according to Institute of Medicine (IOM) recommendations,[15] preexisting diabetes and hypertension, and infant sex), and the method of conception (ART vs. non-ART) among all births (live births and infant deaths) and perinatal deaths by plurality. All states and territories require reporting of standard maternal demographic characteristics including pregnancy history, fetal characteristics, medical risk factors associated with pregnancy, obstetrics, and delivery information. However, pre-pregnancy BMI and gestational weight gain during pregnancy were not uniformly collected in Massachusetts during the years of study; therefore, analyses involving these variables are restricted to Florida and Michigan only.[16] For variables that were available in both NASS and vital records, we used information from vital records.

To address the impact of imperfect linked observations, we weighted the observations by the probability of successful linkage; we used weighted log-binomial regression models to calculate crude and adjusted risk ratios (cRR and aRR, respectively) with 95% confidence intervals (CIs) for the association between method of conception (ART vs. non-ART) and perinatal death, stratified by plurality (singletons vs. multiples) and gestational age (<28 and ≥28 weeks).[16] We selected a priori potential confounders associated with perinatal deaths and included in the adjusted models: state,

age, race, marital status, parity, smoking status, and preexisting conditions of diabetes and hypertension. In addition, we conducted subanalyses using data from Florida and Michigan only to determine the effects of pre-pregnancy BMI and gestational weight gain by including and excluding them from the model. We also applied weighted propensity scores using ART as the outcome and maternal characteristics (age, race, education, marital status, smoking status, alcohol use, and parity) as predictors to correct for potential population bias between the ART and non-ART groups. We used a generalized estimating equations approach to account for the correlation of infants born to the same mother. Due to high frequency of missing values (>10%) for certain variables (pre-pregnancy BMI and gestational weight gain), we used multiple imputation to estimate these data points, assuming these missing values were missing at random (MAR).

Statistical analyses were conducted by using SAS, version 9.4 (SAS Institute), SUDAAN 11.0.3 (RTI International), and all p-values <0.05 were considered statistically significant. The institutional review boards (IRB) of the CDC and the Massachusetts Department of Public Health approved this study; the Michigan Department of Health and Human Services IRB and the Florida Department of Health IRB determined that their institutions were not engaged in human subject research. Table cells with counts less than 10, and cells allowing for calculation of counts less than 10 were suppressed to protect patient confidentiality.

Results

We identified a total of 39,862 ART-conceived births and 2,495,710 non-ART births born to Florida, Massachusetts, and Michigan resident mothers during 2006 to 2011. After excluding cycles using gestational carrier and pregnancies with unknown plurality, there were 39,824 and 2,263,633 ART and non-ART births, respectively. During 2006 to 2011, there were 570 ART-conceived perinatal deaths and 25,158 non-ART conceived perinatal deaths in the three states. ►Fig. 1 presents ART and non-ART perinatal mortality rates by plurality and year. Overall, for both singleton and multiple deliveries, annual ART perinatal mortality rates were lower than that for non-ART perinatal mortality. Non-ART perinatal deaths among singleton gestations generally decreased over time from 10.2 in 2006 to 9.7 per 1,000 live births in 2011 ($p = 0.003$), while no significant changes were observed in other groups.

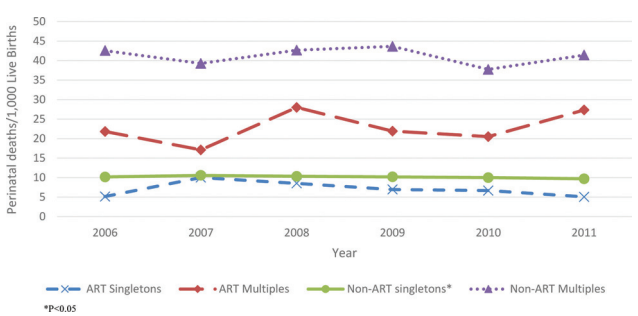

Fig. 1 Assisted reproductive technology and nonassisted reproductive technology perinatal mortality rates by plurality and year.

In general, the differences of maternal and infant characteristics by ART status for singleton deliveries were consistent whether looking at all births or perinatal deaths (►Table 1). Among singleton deliveries, most ART perinatal deaths occurred among women older than 35 years (41.7%), while most non-ART perinatal deaths occurred among women aged 35 years and younger (84.6%). The majority of ART perinatal deaths occurred among non-Hispanic white women (70.9%), while the majority of non-ART perinatal deaths occurred among women of other and unknown race/ethnicity (56.1%). Additionally, mothers who conceived using ART and who experienced perinatal deaths were less likely to smoke during pregnancy than mothers of non-ART perinatal deaths (<6 and 16.3%, respectively). Overall, the distribution of maternal education, marital status, pre-pregnancy BMI, and preexisting health conditions among multiple deliveries (data not shown) were similar to that of singleton deliveries for ART and non-ART perinatal deaths. However, among multiples, gestational weight gain was mostly above the IOM recommendations (41.4 and 39.0% for ART and non-ART, respectively).

►Table 2 presents the risk ratios for the association of perinatal death and ART use, stratified by plurality (singletons vs. multiples), and gestational age (<28 and ≥28 weeks). The crude or unadjusted risk of perinatal death was significantly lower among ART births than among non-ART births for all singleton and multiple deliveries (crude risk ratio [cRR] = 0.84, 95% CI: 0.71–0.98 and cRR = 0.68, 95% CI: 0.59–0.78, respectively), as well as for singleton births <28 weeks (cRR = 0.42, 95% CI: 0.31–0.57) and multiple births <28 weeks (cRR = 0.71, 95% CI: 0.58–0.87; ►Table 2). After adjusting for state of birth, maternal age, maternal race, parity, marital status, smoking status, and preexisting diabetes and hypertension, the risk of perinatal death remained significantly lower for singleton ART versus non-ART births <28 weeks (aRR = 0.46, 95% CI: 0.26–0.85) and for multiple births <28 weeks (aRR = 0.64, 95% CI: 0.45–0.89). When analyzing data from only Florida and Michigan, the results were similar regardless of including or excluding pre-pregnancy BMI and gestational weight gain in the adjusted model (results not shown).

Discussion

This study compared the risk of perinatal deaths between ART and non-ART conceived pregnancies in three U.S. states. Over the study period, the perinatal mortality rate was lower for ART than non-ART conceived perinatal deaths for both singleton and multiple infants. After controlling for confounders, we found a protective association between ART use and perinatal death for births occurring at a gestational age of <28 weeks regardless of plurality. Notably, there was no difference in perinatal mortality risk from 28 weeks of gestation, and later, suggesting that the protective effect seen at earlier gestational ages may be due to differences in obstetric management of ART conceived pregnancies.

Table 1 Maternal and fetal characteristics of all births (live births and fetal deaths) and perinatal deaths by method of conception (ART vs. non-ART) among singleton deliveries (2006–2011)

	All births				Perinatal deaths			
	ART $n = 21,426$ (1.0%)		Non-ART $n = 2,194,493$ (99.0%)		ART $n = 151$ (0.7%)		Non-ART $n = 22,307$ (99.3%)	
State[a,b]								
Florida	7,091	(33.1)	1,167,042	(53.2)	50	(33.1)	12,058	(54.1)
Massachusetts	9,989	(46.6)	405,573	(18.5)	58	(38.4)	2,976	(13.3)
Michigan	4,346	(20.3)	621,878	(28.3)	43	(28.5)	7,273	(32.6)
Maternal age[a,b]								
<26	367	(1.7)	705,073	(32.1)	NR	NR	7,575	(34.0)
26–30	2,980	(13.9)	680,413	(31.0)	NR	NR	6,302	(28.3)
31–35	7,578	(35.4)	529,609	(24.1)	51	(33.8)	4,988	(22.4)
>35	10,501	(49.0)	279,398	(12.7)	63	(41.7)	3,442	(15.4)
Maternal race/ethnicity[a,b]								
Non-Hispanic White	16,644	(77.7)	1,245,344	(56.8)	107	(70.9)	9,783	(43.9)
Other/unknown	4,782	(22.3)	949,149	(43.3)	44	(29.1)	12,524	(56.1)
Maternal education[a,b]								
High school or less	4,139	(19.3)	1,254,078	(57.2)	NR	NR	11,383	(51.0)
College	7,009	(32.7)	563,591	(25.7)	36	(23.8)	4,996	(22.4)
More than college	10,145	(47.4)	361,230	(16.5)	82	(54.3)	3,393	(15.2)
Unknown/missing	133	(0.6)	15,594	(0.7)	NR	NR	2,535	(11.4)
Marital status[a,b]								
Married	20,279	(94.5)	1,350,791	(61.6)	138	(91.4)	10,584	(47.5)
Unmarried		NR	841,771	(38.4)	NR	NR	11,130	(49.9)
Unknown/missing	NR	NR	1,931	(0.1)	NR	NR	593	(2.7)
Smoking status during pregnancy[a,b]								
Yes	273	(1.3)	214,586	(9.8)	NR	NR	3,645	(16.3)
No	21,103	(98.5)	1,971,079	(89.8)	142	(94.0)	17,652	(79.1)
Unknown/missing	50	(0.2)	8,828	(0.4)	NR	NR	1,009	(4.5)
Parity[a,b]								
1	13,724	(64.1)	834,835	(38.0)	100	(66.2)	8,089	(36.3)
2	5,573	(26.0)	741,471	(33.8)	24	(15.9)	5,603	(25.1)
≥ 3	1,997	(9.3)	606,469	(27.6)	NR	NR	7,358	(33.0)
Unknown/missing	132	(0.6)	11,718	(0.5)	NR	NR	1,257	(5.6)
Pre-pregnancy body mass index[a,b,c]								
Underweight	331	(2.9)	63,574	(3.6)	NR	NR	552	(2.9)
Normal weight	5,582	(48.8)	720,067	(40.3)	36	(38.7)	5,999	(31.0)
Overweight	2,357	(20.6)	380,444	(21.3)	22	(23.7)	3,920	(20.3)
Obese	1,495	(13.1)	334,028	(18.7)	19	(20.4)	5,075	(26.3)
Unknown/missing	1,672	(14.6)	290,807	(16.3)	NR	NR	3,785	(19.6)
Gestational weight gain[a,c]								
Below IOM guidelines	3,690	(32.3)	586,575	(32.8)	32	(34.4)	8,192	(42.4)
Within IOM guidelines	3,203	(28.0)	440,936	(24.7)	20	(21.5)	3,392	(17.6)
Above IOM guidelines	3,973	(34.7)	665,179	(37.2)	NR	NR	4,977	(25.8)
Unknown/missing	571	(5.0)	96,230	(5.4)	NR	NR	2,770	(14.3)
Gestation weeks[b]								

Table 1 (*Continued*)

	All births				Perinatal deaths			
<28	194	(0.9)	19,874	(0.9)	62	(41.1)	11,501	(51.6)
≥28	21,173	(98.8)	2,169,883	(98.9)	89	(58.9)	10,655	(47.8)
Unknown/missing	59	(0.3)	4,736	(0.2)	0	0	116	(0.7)
Gender								
Male	11,057	(51.6)	1,124,321	(51.2)	76	(50.3)	11,852	(53.1)
Female	10,369	(48.4)	1,069,901	(48.8)	75	(49.7)	10,198	(45.7)
Unknown/Missing	0	0	271	<0.1	0	0	257	(1.2)
Preexisting hypertension[a]								
Yes	420	(2.0)	31,456	(1.4)	NR	NR	983	(4.4)
No	20,882	(97.5)	2,151,510	(98.0)	147	(97.4)	20,667	(92.7)
Unknown/missing	124	(0.6)	11,527	(0.5)	NR	NR	657	(3.0)
Preexisting diabetes[a]								
Yes	1,625	(7.6)	117,496	(5.4)	NR	NR	1,353	(6.1)
No	19,677	(91.8)	2,065,473	(94.1)	144	(95.4)	20,297	(91.0)
Unknown/missing	124	(0.6)	11,524	(0.5)	NR	NR	401	(3.0)

Abbreviation: ART, assisted reproductive technology; IOM, Institute of Medicine; NR, not reported to protect patient confidentiality.
[a]Statistically significant with $p < 0.05$ for all births.
[b]Statistically significant with $p < 0.05$ for perinatal deaths.
[c]Limited to Florida and Michigan only, information not available in Massachusetts.
Note: Analysis excludes maternal age <20 or >60 years, and unknown gestation type (singletons vs. multiples).

Table 2 Association between perinatal deaths and ART use, by plurality and gestational age (in weeks) among all births in Florida, Massachusetts, and Michigan (2006–2011)

	ART births *n*	ART perinatal deaths *n* (%)	Non-ART births *n*	Non-ART perinatal deaths *n* (%)	cRR (95% CI)	aRR[a] (95% CI)
Singletons	21,367	151 (0.71)	2,189,757	22,307 (1.01)	0.84 (0.71–0.98)	1.27 (0.90–1.78)
<28 wk	194	62 (31.96)	19,874	11,501 (57.87)	0.42 (0.31–0.57)	0.46 (0.26–0.85)
≥28 wk	21,173	89 (0.42)	2,169,883	10,655 (0.49)	1.02 (0.82–1.25)	1.29 (0.80–2.06)
Multiples	18,348	420 (2.29)	68,543	2,851 (4.16)	0.68 (0.59–0.78)	0.90 (0.72–1.12)
<28 wk	856	293 (34.23)	4,380	2,132 (48.68)	0.71 (0.58–0.87)	0.64 (0.45–0.89)
≥28 wk	17,492	127 (0.72)	64,613	705 (1.09)	0.82 (0.67–1.00)	1.15 (0.77–1.72)

Abbreviations: aRR, adjusted risk ratio; ART, assisted reproductive technology; CI, confidence interval; cRR, crude risk ratio.
[a]Model was adjusted for state, age, race, marital status, parity, smoking status, and preexisting conditions of diabetes and hypertension and excluded perinatal deaths with unknown gestational age.

Our findings are similar to the study conducted by Chughtai et al, which showed a lower perinatal mortality rate among ART births compared with non-ART births for preterm births (<32 weeks of gestation) from a population-based cohort in Australia.[9] However, studies conducted in the Nordic countries had different findings, showing ART use to be associated with an increased risk of perinatal death and stillbirth (particularly among singleton deliveries).[6–8] This lack of consistency may be due to the use of different definitions for perinatal death, different ART practices for different study years, differences in health care system or obstetric care, and variations in the study populations, such as demographic characteristics, ART treatment characteristics, and utilization of prenatal care. For example, we used definition III of perinatal deaths by Barfield et al, which includes fetal deaths ≥20 weeks and infant deaths <7 days after birth, while Committee on Nordic ART and Safety used fetal deaths ≥20 weeks to infant deaths 27 days after birth.[6,7,14] This difference in definition could also explain the higher perinatal mortality rate in the non-ART group than that of the national average in the three participating states.[17] Although study populations vary, the differences of certain maternal characteristics, such as maternal age, race, education, marital status, smoking status, and parity, were consistent between ART and non-ART perinatal deaths.[18–20] ART practice varies by country due to differences in health care access, health insurance coverage, age limitations, procedure limitations, laboratory protocols, and in some cases, limitations on the number of embryos that can be

transferred. Thus, ART pregnancy outcomes can vary accordingly.[2,21–23] Also, differences in infertility diagnosis, severity of diagnosis, and the presence of other preexisting medical conditions among mothers can result in different pregnancy outcomes. Wisborg et al concluded that the increased risk of stillbirth after IVF may be due to the infertility treatment or other factors associated with subfertility.[7]

Higher proportions of adequate prenatal care among ART-conceived pregnancies may have led to earlier detection and management of fetal and maternal conditions, and could explain the lower rates of early perinatal deaths observed in this study.[18–20] Although NASS captures approximately 98% of all ART cycles performed in the United States, NASS does not collect information on maternal characteristics such as pre-pregnancy BMI, weight gain during pregnancy, or preexisting medical conditions.[2] By linking NASS with vital records, we were able to control for these possible confounding factors. Additionally, using multiple imputation for missing values, we were able to conduct the analysis without reducing our sample size.

Our findings are subject to several limitations. The adoption of the 2003 standard by the states in the study was not uniform across the study period. This limited the analysis to vital statistics variables, which were collected uniformly by the three states for the full study period with exceptions as noted in methods, such as pre-pregnancy BMI and gestational weight gain. The validity and quality of fetal death records in the United States are inconsistent because there are no standard reporting requirements.[11,12,14,24,25] Fetal deaths can be misclassified as spontaneous abortion or vice versa, particularly for loss that occur during early pregnancy (20–27 weeks); similarly, misclassification between stillbirth, and infant deaths can occur among births of late gestational age (≥28 weeks). The study excludes pregnancies reaching 20 weeks, which can introduce selection bias if ART pregnancies are more likely to miscarry in early pregnancy.[26] However, previous data show no difference in miscarriage rates for ART versus non-ART births, suggesting that the bias may be minimal but cannot be discounted.[2]

Due to missing or inconsistent information in vital records, the use of a probability linkage algorithm can result in possible mismatches and lower linkage rates.[11] Certain variables on the fetal death reports or infant death certificates have consistently high levels of missing data, such as maternal BMI, pregnancy weight gain, and utilization of prenatal care, as some of these variables are self-reported and parents may be reluctant to share demographic or pregnancy information following a fetal death.[11,27,28] While there is no clear evidence that ART-conceived pregnancies are more likely to deliver before 28 weeks than spontaneously conceived pregnancies, stratifying by gestational age may have resulted in collider bias.[29] As such, the stratified estimates should be interpreted with caution, and causation should not be inferred. Information on cause of death, placentation, or chorionicity for multiple gestations; prenatally diagnosed birth defects; and subfertility factors, although not available for the current analysis, could potentially explain the differences of perinatal death rates by gestational age (<28 vs. ≥28 weeks) and use of ART. We are also unable to determine the effects of non-IVF fertility treatments that women may have received, as these data are not contained in the SMART linked database. Today, there is no scientific way to differentiate the absolute exposure and effects of ART treatments among the pregnant population at a certain time; residual effects from previous fertility treatments for previous pregnancies, births, or failed attempts at pregnancy are also possible.[30] Due to limited sample size, we were unable to compare rates of perinatal mortality stratified by shorter intervals of gestational age; however, we have no reason to suspect our findings are inaccurate. Likewise, due to the small numbers of perinatal deaths among triplets and higher order gestations, we analyzed a combined population of twins and higher order gestations. Nevertheless, the results remained unchanged when we restricted the study population to either twin (results not shown). Some nonresident patients were likely included in our dataset, but such numbers are thought to be small as the participating states provided birth certificate data only from mother's resident state for majority of the study period. In addition, numbers without known state of residence were very small and therefore not likely to bias our results. Finally, SMART Collaborative data, because it only encompasses three states, may not be generalizable to the national population.

Perinatal death is an important public health concern.[18,19] This study used linked surveillance and vital records data to examine associations between use of ART and perinatal deaths at the population level. Our findings suggest that ART use may be associated with a decreased risk of perinatal deaths prior to 28 weeks of gestation, which may be explained by earlier detection and management of fetal and maternal conditions among ART-conceived pregnancies. This information adds to the growing body of research on ART-associated perinatal outcomes and can inform patient counseling on treatment risks.

Note

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Conflict of Interest

None declared.

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