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# Perinatal outcomes of twin births conceived using assisted reproduction technology: a population-based study†

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**BACKGROUND: Approximately 18% of multiple births in the USA result from assisted reproduction technology (ART). Although many studies comparing ART and naturally conceived twins report no difference in risks for perinatal outcomes, others report slight to moderate positive or protective associations. METHODS: We selected twin deliveries with and without indication of ART from Massachusetts live birth–infant death records from 1997 to 2000 linked to the US ART surveillance system. The sample was restricted to deliveries by mothers with increased socioeconomic status, private health insurance and intermediate/plus prenatal care use. Our final sample included 1446 and 2729 ART and non-ART twin deliveries, respectively. Odds ratios (OR) for associations between ART and perinatal outcomes were adjusted for maternal demographic factors, smoking, prenatal care and hospital care level. RESULTS: ART twin deliveries were less likely than non-ART to be very preterm (adjusted OR 0.75; 95% confidence interval 0.58–0.97) or include a very low birthweight (<1500 g) infant (0.75; 0.58–0.95) or infant death (0.55; 0.35–0.88). In stratified analyses, these findings were observed among primiparous deliveries, but there were no risk differences among multiparous ART and non-ART twin deliveries. CONCLUSIONS: ART treatment was not a risk factor for adverse perinatal outcome, and risks for several outcomes were somewhat lower among ART twin deliveries. Nonetheless, ART is strongly associated with twinning and twins remain a high-risk group, relative to singletons. Promoting singleton gestation in assisted conception is an important strategy for reducing adverse outcomes.**

*Keywords:* assisted reproduction technology; infant; low birthweight; premature birth

## Introduction

Since its introduction in 1981, there has been a marked increase in the USA in the use of assisted reproduction technology (ART, defined as infertility treatments in which both oocytes and sperm are manipulated). The total ART use increased 98% from 1996 to 2004 with concomitant increases in ART-associated live birth rates (CDC and American Society for Reproductive Medicine, 2006; Wright *et al*., 2007). ART currently accounts for slightly >1% of all births in the USA and 18% of multiple births (CDC and American Society for Reproductive Medicine, 2006; Wright *et al*., 2007). In 2004, ART procedures in the USA resulted in the birth of 49 458 infants, 45% of which were twins (Wright *et al*., 2007). The recent decline in the proportion of ART procedures involving three or more embryos transferred (Reynolds and Schieve, 2006) has resulted in a notable decline in ART-associated triplet and higher order births in the USA (Wright *et al*., 2006). However, most of the downward shift in embryos transferred was from ≥3 to 2 embryos, with little increase in single embryo transfer. Thus, the contribution of ART to twin birth rates continues to rise (Reynolds *et al*., 2003; Wright *et al*., 2006).

Past studies that document associations between ART and increased risks for adverse maternal and perinatal outcomes in singleton pregnancies (Schieve, Meikle *et al*., 2002; Schieve, Cohen *et al*., 2007; Jackson, Gibson *et al*., 2004) raised the question of whether there are similar associations among twin pregnancies. However, twin pregnancies and births are at substantially higher risks than singletons for many adverse outcomes including obstetric complications, preterm delivery, low birthweight (LBW), congenital malformations and perinatal mortality; thus any added risks posed by ART and/or a woman's

†*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.*

underlying infertility might be negligible in comparison (Luke and Keith, 1992; Hansen *et al*., 2005; Pharoah, 2006). Although most studies based on clinic- or hospital-based samples report no association between ART and preterm delivery, LBW, and/or perinatal or neonatal mortality (Tan *et al*., 1992; Olivennes *et al*., 1996; Agustsson *et al*., 1997; Isaksson *et al*., 2002; Koivurova *et al*., 2002; Zadori *et al*., 2003; Zaib-un-Nisa *et al*., 2003; Luke *et al*., 2004; Huang *et al*., 2006), many were limited by fairly small samples. Moreover, some clinic-based studies reported positive associations between ART and preterm and/or LBW (Tallo *et al*., 1995; Moise *et al*., 1998; Daniel *et al*., 2000; Koudstaal *et al*., 2000; Zuppa *et al*., 2001; Nassar *et al*., 2003; Adler-Levy, *et al*., 2007) and others reported protective associations or a trend toward a protective association with reduced birthweight and/or perinatal mortality (Fitzsimmons *et al*., 1998; Minakami *et al*., 1998; Kozinszky *et al*., 2003). Larger population-based studies have also been reported that considered a range of potential confounding factors such as maternal age and parity, birth year, infant sex, zygosity, geographic residence and maternal education. Even among these studies, results were not completely consistent. Although several reported no association with preterm and LBW and/or perinatal mortality (Bergh *et al*., 1999; Dhont *et al*., 1999; Westergaard *et al*., 1999; Pinborg *et al*., 2004a), two studies reported slight increases in preterm and LBW among ART twins (Klemetti *et al*., 2002; Verstraelen *et al*., 2005). Lambalk and van Hooff (2001) reported significantly lower mean gestational age and birthweight and a 50% increase in mortality among dizygotic ART twins, and, in contrast, Dhont *et al*. (1999) reported a non-significant trend toward a decreased mortality risk among ART twins. In one of the largest studies to date, Pinborg *et al*. (2004a) report no associations with preterm, LBW or perinatal mortality after adjustment for maternal age and parity and restriction to opposite-sex pairs; however, ART twins in all subgroups were more likely to be admitted to the neonatal intensive care unit and, although perinatal mortality rates were not statistically different, infant mortality rates were significantly higher among ART twins than controls. In sum, although the data overall suggest generally comparable risks for adverse perinatal outcome among ART and naturally conceived twins, inconsistencies in some studies are not easily explained by methodological differences. Indeed, two meta-analyses that included many of the above studies also present conflicting findings for preterm delivery and mortality (Helmerhorst *et al*., 2004; McDonald *et al*., 2005).

In our previous population-based analysis of ART twins in the USA, we reported similar LBW risks for ART twins and twins in the general population (Schieve *et al*., 2002). Although we adjusted for maternal age and parity differences, the analysis was conducted on two unlinked data sets, and thus we were unable to account for many likely differences between ART and other twin pregnancies in maternal socioeconomic status and access and level of care received. We since created a population-based data set, by linking data from the US ART surveillance system to the Massachusetts birth–infant death files (Sunderam *et al*., 2006). These data allowed us to compare a range of obstetric complications, birth outcomes and mortality among twins conceived by ART and non-ART twins with more comprehensive consideration of many potential confounding factors. This is the first population-based assessment of US twins in which ART infants are directly compared with non-ART twins.

## Materials and Methods

The data for this analysis were derived from the 1997–2000 Massachusetts ART linked data file. Details of the data linkage methods and results have been described elsewhere (Sunderam *et al*., 2006). The data file includes births to Massachusetts residents in 1997–2000 that occurred in Massachusetts, Rhode Island, New Hampshire or Connecticut; these states together accounted for 99.9% of all live births to Massachusetts-resident mothers. ART clinic records data for Massachusetts-resident births included in the National ART Surveillance System maintained by the Centers for Disease Control and Prevention were linked to their corresponding birth records based on maternal and infant dates of birth. Maternal names were used to confirm a sample of records that were matched by birth dates, to resolve duplicate matches and to link unmatched records. More than 85% of the selected ART births were successfully linked. Further, separate analyses that adjusted the linkage rate for estimates of out-of-state residents receiving ART in Massachusetts clinics and in-state residents migrating out of state before birth indicated the 'true' linkage rate might exceed 95%.

For the current analysis, we selected all linked ART twin births and all twin births not linked to an ART record or indicated to be likely conceived with a non-ART treatment. Non-ART fertility treatments—assisted insemination and/or infertility medications—were reported on the Massachusetts birth record but were excluded because a separate analysis indicated incomplete and possibly biased reporting for birth certificate infertility treatment variables; the excluded births accounted for ~5% of the total twins.

For this analysis, the twin delivery was our unit of observation (i.e. twin pairs were linked and counted as a single birth event). Our initial sample included 1575 ART twin deliveries and 4368 non-ART twin deliveries. Because previous analyses of the same data set indicated that no or rare ART births occurred in certain demographic subgroups (Schieve *et al*., 2007), we restricted our sample by excluding records in these subsets: maternal age <20 years, <high school education, unmarried marital status, public or no health insurance for prenatal care, public or no health insurance for labor and delivery, no or inadequate prenatal care (based on Kotelchuck index; Kotelchuck, 1994) or third trimester prenatal care initiation. Our final sample included 1446 and 2729 ART and non-ART twin deliveries, respectively.

We examined maternal and perinatal outcomes reported on the birth or linked birth–death record. These included placental abruption, Cesarean delivery, preterm delivery (<37 weeks gestation), very preterm delivery (<32 week gestation), birthweight discordance >25%, either infant with LBW (<2500 g), either infant with very LBW (<1500 g; VLBW), death of either infant within the first year of life and Apgar score for either infant <7 at 5 min. The chi-square test was used to test for significant differences in the proportion of adverse outcomes between the ART exposure groups.

For each of the above outcomes, we conducted stratified analyses to examine potential confounding and/or effect modification of the ART-outcome associations by maternal age, parity, race/ethnicity, education, smoking during pregnancy, prenatal care initiation and adequacy, and hospital level of care. Because >80% of twin deliveries in our sample had adequate plus prenatal care (using Kotelchuck index

classification; Kotelchuck, 1994), we further subdivided prenatal care adequacy into 110–149%, 150–199% and ≥200% of the expected visit ratio.

We also performed multiple logistic regression analyses to calculate the odds ratios (OR) and 95% confidence intervals (CI) for the independent associations of ART on each outcome. In addition to ART, each model included maternal age, race-ethnicity, education, parity, smoking during pregnancy, prenatal care use and hospital level of care as independent variables. The inclusion of the smoking variable in the placental abruption model caused a convergence failure (occurs when values of the outcome variable overlap or are tied at a single or only a few values of a predictor variable) because of the small number of women who used ART and smoked; thus, smoking during pregnancy was not included in the final model for that outcome only. Because in our stratified analyses we observed differential effects for several outcomes according to parity, we also ran a second set of models that included all of the above factors and additionally included an ART-parity interaction term.

Because (i) in general, perinatal mortality and morbidity are higher in monozygotic than dizygotic twins and (ii) ART and naturally-conceived twins are estimated to differ markedly in the relative distributions of monozygotic versus dizygotic twins, we separately examined a subset of known dizygotic twins—twin pairs with unlike sex infants. Although this particular subset is not a representative sample, it nonetheless provided an opportunity to examine associations between ART and adverse outcome independent of zygosity differences.

Because some of the outcomes of interest, such as LBW, VLBW, Apgar <7 and infant death, can occur in either one or both of the twin infants, we used ordinal logistic regression to calculate adjusted cumulative ORs and 95% CIs for the relationship between the aforementioned outcomes and ART. The ordinal outcomes modeled using the proportional OR model were no infant with adverse outcome, one infant with adverse outcome or both infants with adverse outcomes. This model calculates cumulative ORs that denote the probability of being in a higher category (i.e. both infants with adverse outcomes) rather than a lower category. Models were constructed to include an analogous set of independent variables as described above for logistic regression with dichotomous outcomes.

Among the 4175 twin deliveries included in our final sample, two live births were reported for 4098 (98%); for the remaining 77 (2%), only one live born infant was included in the files, although the plurality variable indicated the infant was a twin. We assumed these are cases in which one twin was a fetal death. Although we did not have access to fetal death certificates for this study, a previous analysis of fetal deaths among twins in Massachusetts supports this assumption (Lazar *et al*., 2006). The small percentage of twin deliveries with only a single live born infant reported posed an analytic challenge. Because these are assumed to be among the highest-risk twin births, we did not want to exclude them from analysis. However, including 'one live birth only' deliveries in analyses in which adverse outcomes were defined as having occurred if the outcome was reported for either infant in a twin delivery might have resulted in an underestimate of such outcomes. If fetal deaths varied according to ART status, this underestimation might potentially bias our findings. Thus, for LBW, VLBW, low Apgar score and infant death outcomes, we performed two sets of analyses. First, we only considered the live born infants reported to the natality files in defining outcomes for the twin delivery; thus, by default, we assumed the non-reported twin did not have the outcome. Second, we coded all deliveries for which only one live birth was reported in the data file as positive for each outcome; thus, we assumed all non-reported twins had the adverse outcome and at least one infant had the adverse outcome. Results from analyses using these two coding schemes were essentially the same for analyses of LBW and VLBW; we present results based on the first coding scheme only. Notable differences in risk estimates by coding scheme were observed for low Apgar score and infant death outcomes. Therefore, we present analyses based on both coding schemes for these outcomes.

The characteristics of the infant deaths were further explored by comparing the distribution of timing of death, gestational age at birth and birthweight. For these analyses, each infant who died was treated as a unique observation, even if he or she was part of the same twin birth pair. Statistically significant differences were assessed with Fisher's exact test.

A value of $P < 0.05$ was considered significant. This study was approved by the Institutional Review Boards at CDC and the Massachusetts Department of Public Health.

## Results

Our final sample included 1446 ART and 2729 non-ART twin deliveries during the 4 year study period. Table I depicts the distribution of pregnancy and maternal characteristics for the selected study population. Approximately 30.0% of the ART deliveries were twins compared with 1.5% of the non-ART deliveries. Among twin deliveries, women who gave birth after ART were more likely than women who did not use ART to be ≥35 years of age, primiparous and non-smokers and to have some college education. Mothers of twins conceived after ART were more likely to receive intensive prenatal care and deliver in a Level 3 hospital (highest level of care).

Obstetric complications and birth outcomes among ART and non-ART twin births are described in Table II. Higher proportions of Cesarean delivery and LBW were noted among ART twins than among non-ART twins. Conversely, ART twin deliveries were less likely than non-ART twin deliveries to include an infant with a 5 min Apgar <7; this effect was not observed after sensitivity analyses in which the unreported twins of 'one live birth only' twin deliveries were assumed to have been fetal deaths and thus automatically coded as positive for having a low Apgar score. The results for known dizygotic twin deliveries were generally in the same direction as results observed for deliveries not subdivided by infant sex; however, differences between ART and non-ART twins were less pronounced and/or less precise in the dizygotic subset given the reduced sample size.

After controlling for maternal age, race and ethnicity, education, smoking during pregnancy, prenatal care use and hospital level of care, ART was associated with a lower odds of VLBW (adjusted OR 0.75; 95% CI 0.58–0.95), very preterm birth (0.75; 0.58–0.97), Apgar score <7 at 5 min (0.58; 0.43–0.80) and infant death (0.55; 0.35–0.88) (Table III). The protective associations between ART and low Apgar and infant death were observed with both coding schemes for non-reported twins; however, the magnitude of the association was less pronounced for each outcome when non-reported twins were assumed to have been fetal deaths. The odds of Cesarean delivery were 25% higher among women who used ART than women who did not, but this CI included 1.0. Addition of the ART-parity interaction term indicated statistically significant effect modifications in the

**Table I.** Distribution of pregnancy and maternal characteristics among ART and non-ART births in selected[a] study population, Massachusetts, 1997–2000.

| | All births in selected[a] study population | | Twin births in selected[a] study population | |
|---|---|---|---|---|
| | ART (%) ($N = 4745$) | No ART (%) ($N = 179\,478$) | ART (%) ($N = 1446$) | No ART (%) ($N = 2729$) |
| **Birth plurality** | | | | |
| Singleton | 66.11[b] | 98.44 | | |
| Twin | 30.47 | 1.52 | 100 | 100 |
| Triplet/+ | 3.41 | 0.04 | | |
| **Maternal age (years)** | | | | |
| <35 | 43.44[b] | 74.35 | 49.72[b] | 70.14 |
| ≥35 | 56.56 | 25.65 | 50.28 | 29.86 |
| **Parity** | | | | |
| 1 | 67.76[b] | 42.45 | 65.49[b] | 43.06 |
| >1 | 32.24 | 57.55 | 34.51 | 56.94 |
| **Race/ethnicity** | | | | |
| Non-Hispanic white | 91.78[b] | 88.22 | 90.59 | 89.85 |
| Non-Hispanic black | 2.32 | 2.84 | 2.84 | 3.23 |
| Hispanic | 1.98 | 3.08 | 2.15 | 3.04 |
| Asian, American Indian, other | 3.92 | 5.86 | 4.43 | 3.89 |
| **Maternal education** | | | | |
| High school | 14.67[b] | 18.86 | 14.18[b] | 18.61 |
| Some college/college graduate | 85.33 | 81.14 | 85.82 | 81.39 |
| **Smoking during pregnancy** | | | | |
| Yes | 2.17[b] | 5.15 | 2.28[b] | 4.22 |
| No | 97.83 | 94.85 | 97.72 | 95.78 |
| **Trimester prenatal care initiation** | | | | |
| 1 | 94.31 | 94.34 | 93.98 | 94.80 |
| 2 | 5.69 | 5.66 | 6.02 | 5.20 |
| **Kotelchuck index prenatal care** | | | | |
| Intermediate/adequate | 42.23[b] | 64.38 | 16.60[c] | 19.90 |
| Adequate plus (110–149%) | 29.08 | 27.56 | 28.63 | 30.27 |
| Adequate plus (150–199%) | 16.31 | 6.20 | 30.08 | 27.63 |
| Adequate plus (≥200%) | 12.37 | 1.87 | 24.69 | 22.21 |
| **Hospital delivery of care level** | | | | |
| 1 and 2 | 41.92[b] | 64.55 | 33.93[b] | 51.72 |
| 3 | 58.08 | 35.45 | 66.07 | 48.28 |

[a]Births to women meeting the following criteria were excluded: maternal age <20 years, <high school education, unmarried, public or no health insurance for prenatal care, public or no health insurance for labor and delivery, inadequate or no prenatal care (Kotelchuck index), third trimester prenatal care initiation.
[b]$P < 0.01$ for chi-square test of distribution of variable in ART group versus distribution in non-ART group.
[c]$P < 0.05$ for chi-square test of distribution of variable in ART group versus distribution in non-ART group.

VLBW and very preterm birth models and a marginally significant effect modification in the infant death model. These models indicated ART was associated with increased odds of Cesarean delivery and decreased odds of LBW, VLBW, very preterm delivery, low Apgar and infant death among primiparous women who delivered twins but not among multiparous women.

The results of the ordinal logistic regression (data not shown) indicated that after adjusting for other covariates, the cumulative odds of LBW, VLBW, Apgar score <7 and infant death in one or both infants were significantly lower for twin deliveries to primiparous mothers who used ART compared with twin deliveries to primiparous mothers who did not use ART. No significant associations were noted among deliveries to multiparous mothers. The adjusted ORs and 95% CIs from the cumulative models are consistent with those described in Table III and are therefore not presented.

Table IV describes the distribution of deliveries with an infant death according to the number of live born infants reported and the characteristics of the live born infants that died during the first year of life. In 34% of non-ART twin deliveries with an infant death, both infants were reported as live born and both died; in contrast, this occurred among only 8% of ART twin deliveries with an infant death. ART twin deliveries were significantly more likely to be associated with a single infant death than with a double infant death. The timing of infant death also differed according to the use of ART; 77% of deaths occurred before completion of 1 day of life among non-ART twins compared with 58% of deaths among ART twins. No differences in the distribution of birthweight and gestational age were noted among deaths of ART and non-ART infants.

In a separate analysis, we assessed a sample of singletons selected from the same data file and restricted to a higher sociodemographic subset of the population with private health insurance and an intermediate or higher level of prenatal care using the same exclusion criteria as described previously for our twin sample. Within this sample, the singleton rates for preterm, very preterm, LBW and VLBW were 6.6%, 0.8%, 3.6% and 0.6%, respectively. The rates of preterm and very preterm among both ART and non-ART twins included in this study exceeded 50% and 9%, respectively. The risks of having at least one LBW twin or VLBW twin were even higher. The individual infant-based risks for ART twins (i.e. calculations in which the infant, not the delivery, was the unit of analysis) were 49.5% for LBW and 8.2% for VLBW. Likewise, the infant mortality rate for singletons in the selected high socioeconomic status subset was 0.3%; ART twin

**Table II.** Distribution of obstetric complications and birth outcomes among ART and non-ART twin births in selected[a] study population, Massachusetts, 1997–2000.

| All births | All twins | | Dizygotic twins (unlike sex) | |
|---|---|---|---|---|
| | ART (%) ($N = 1446$) | No ART (%) ($N = 2729$) | ART (%) ($N = 697$) | No ART (%) ($N = 885$) |
| **Obstetric complications** | | | | |
| Placental abruption | 1.60 | 1.48 | 1.30 | 1.02 |
| Cesarean delivery | 59.67[b] | 52.33 | 59.33[b] | 53.13 |
| **Birth outcome** | | | | |
| Low birthweight (in one or both) | 61.43[c] | 57.74 | 60.37 | 57.42 |
| Very low birthweight (in one or both) | 10.54 | 10.04 | 9.09 | 10.35 |
| Birthweight discordance ≥25% | 9.13 | 7.84 | 8.61 | 10.06 |
| Preterm | 55.36[c] | 51.58 | 53.59 | 50.45 |
| Very preterm | 10.17 | 9.57 | 9.34 | 9.50 |
| Apgar <7 at 5 minutes (in one or both) | | | | |
| *Coding based on live born infants reported* | 4.50[b] | 6.31 | 5.03 | 5.31 |
| *Coding assumes non-reported twins were deaths* | 6.44 | 7.86 | 5.75 | 5.65 |
| Infant death (in one or both) | | | | |
| *Coding based on live born infants reported* | 2.01 | 3.00 | 1.58 | 2.15 |
| *Coding assumes non-reported twins were deaths* | 3.39 | 4.36 | 1.58 | 2.15 |

[a]Births to women meeting the following criteria were excluded: maternal age <20 years, <high school education, unmarried, public or no health insurance for prenatal care, public or no health insurance for labor and delivery, inadequate or no prenatal care (Kotelchuck index), third trimester prenatal care initiation.
[b]$P < 0.01$ for chi-square test of distribution of variable in ART group versus distribution in non-ART group.
[c]$P < 0.05$ for chi-square test of distribution of variable in ART group versus distribution in non-ART group.

**Table III.** Adjusted OR for associations between ART and obstetric complications and birth outcomes among twin births, Massachusetts, 1997–2000.

| | Models without interaction terms | | Models with ART-parity interaction term included | | | | *P*-value of ART*parity interaction |
|---|---|---|---|---|---|---|---|
| | Total sample | | Parity = 1 | | Parity > 1 | | |
| | Adjusted OR[a] | 95% CI | Adjusted OR[a] | 95% CI | Adjusted OR[a] | 95% CI | |
| Obstetric complications | | | | | | | |
| Placental abruption | 1.02 | (0.58–1.79) | 1.10 | (0.53–2.30) | 0.93 | (0.40–2.14) | 0.76 |
| Cesarean delivery | 1.25 | (1.08–1.43) | 1.35 | (1.12–1.62) | 1.12 | (0.91–1.38) | 0.19 |
| Birth outcome | | | | | | | |
| Low birthweight | 0.89 | (0.77–1.04) | 0.79 | (0.65–0.96) | 1.05 | (0.84–1.31) | 0.06 |
| Very low birthweight | 0.75 | (0.58–0.95) | 0.60 | (0.45–0.81) | 1.18 | (0.78–1.76) | 0.008 |
| Preterm | 0.93 | (0.80–1.09) | 0.89 | (0.72–1.09) | 1.00 | (0.79–1.27) | 0.43 |
| Very preterm | 0.75 | (0.58–0.97) | 0.59 | (0.44–0.80) | 1.27 | (0.83–1.93) | 0.003 |
| Birthweight discordance ≥25% | 0.99 | (0.77–1.27) | 1.07 | (0.79–1.44) | 0.96 | (0.64–1.44) | 0.59 |
| Apgar <7 at 5 min (in one or both) | | | | | | | |
| *Coding based on live born infants reported* | 0.58 | (0.43–0.80) | 0.55 | (0.38–0.80) | 0.67 | (0.38–1.16) | 0.57 |
| *Coding assumes non-reported twins were deaths* | 0.72 | (0.55–0.95) | 0.71 | (0.51–0.99) | 0.75 | (0.47–1.18) | 0.87 |
| Infant death (in one or both) | | | | | | | |
| *Coding based on live born infants reported* | 0.55 | (0.35–0.88) | 0.42 | (0.24–0.74) | 0.99 | (0.47–2.09) | 0.07 |
| *Coding assumes non-reported twins were deaths* | 0.70 | (0.49-1.01) | 0.63 | (0.40-1.00) | 0.85 | (0.47–1.52) | 0.43 |

[a]Final models for all outcomes models other than placental abruption included the following as independent variables: ART, maternal age, race/ethnicity, education, parity, smoking during pregnancy, prenatal care use and hospital level of care. The model for placental abruption included all of the same variables except maternal smoking.

deliveries had a 10-fold higher risk of including at least one infant death, and ART twin infants individually each had a 6-fold higher risk of infant death than singletons.

## Discussion

The findings of this US population-based study suggest twin deliveries conceived after ART are generally comparable with non-ART twin deliveries of similar socioeconomic status (and thus comparable maternal access to prenatal care). In fact, after stratification on parity and adjustment for other factors, we noted some protective associations between ART and certain adverse birth outcomes. However, it is important to note that the risk of adverse outcomes among ART twin births remained substantially higher than those of singleton births. Thus, the protective effects reported for ART twins cannot be considered entirely 'good news'.

**Table IV.** Distribution of deliveries with an infant death among ART and non-ART twins and distribution of ART and non-ART live born infants that died in the first year of life, Massachusetts, 1997–2000.

| | ART (%) | No ART (%) |
|---|---|---|
| **Distribution of deliveries with an infant death** | $N = 49$ | $N = 119$ |
| Two live born infants reported, two infants died | 8.16[a] | 34.45 |
| Two live born infants reported, one infant died | 42.86 | 21.01 |
| One live born infant reported that died, one presumed a fetal death | 8.16 | 13.45 |
| One live born infant reported (alive at 1 year), one presumed a fetal death | 40.82 | 31.09 |
| *Analyses of live born infants that died* | $N = 33$ | $N = 124$ |
| **Timing of infant death** | | |
| Within 1 day | 57.58[a] | 77.42 |
| 2–6 days | 9.09[b] | 10.48 |
| 7–27 days | 24.24 | 4.03[b] |
| 28 days–1 year | 9.09[b] | 8.06 |
| **Birthweight** | | |
| <1500 g | 84.85 | 89.17 |
| 1500–2499 g | 9.09[b] | 5.83 |
| 2500–5000 g | 6.06[b] | 5.00 |
| **Gestational age at delivery** | | |
| <32 weeks | 78.79 | 91.06 |
| 32–36 weeks | 12.12[b] | 4.88 |
| ≥37 weeks | 9.09[b] | 4.07[b] |

[a] $P < 0.01$ for Fisher's exact test.
[b] Number of deaths was ≤5.

Our finding of an increased rate of Cesarean delivery among ART twins is consistent with other European population-based studies (Agustsson *et al*., 1997; Dhont *et al*., 1999). Our findings of lower rates for infant death among ART twins are also supported by previous studies. In a matched retrospective cohort study, Fitzsimmons *et al*. (1998) observed 2 perinatal deaths in ART twins versus 24 in naturally conceived twin births. Helmerhorst *et al*. (2004) conducted a systematic review of controlled studies published during 1985–2002 and reported a relative risk of 0.58 (0.44–0.77) for perinatal mortality in matched studies of twin gestations. However, in a meta-analysis conducted by McDonald *et al*. (2005) with more restrictive inclusion criteria, perinatal death was not found to differ by ART status.

A closer assessment of the current sample by all potential confounders indicated that Cesarean delivery and perinatal and infant risks were divergent only between ART and non-ART primiparous mothers. One interpretation of this finding is that because, in general, primiparous women have higher risks for the perinatal outcomes examined, the effect of being primiparous was somewhat attenuated among ART mothers carrying twins. For example, although the rate of VLBW (11.5%) among twin deliveries to primiparous ART mothers was lower than that for non-ART primiparous mothers (14.5%), it was still much higher than the VLBW rates observed for multiparous mothers who delivered twins (8.8% and 6.6% for the second or later ART and non-ART twin deliveries, respectively). Thus, whatever advantage that might be potentially associated with ART conception is negligible compared with the advantage conferred by mulitparity. This same pattern was observed with very preterm delivery (data not shown).

A specific ART treatment effect that reduces perinatal risk among twins seems unlikely, especially given the established associations between ART and increased perinatal risk among singletons (Dhont *et al*., 1999; Helmerhorst *et al*., 2004; Schieve *et al*., 2002, 2007). A more likely reason for the attenuated risks among some ART twin deliveries is enhanced monitoring and prenatal and perinatal care. We restricted our sample so that ART and non-ART mother–infant pairs were comparable on many sociodemographic, health insurance and prenatal care factors; thus, differential 'access' to prenatal care does not appear to explain these results. We also evaluated the impact of numerous other potential confounders including those related to the level of care received prenatally and during labor and delivery, and included these factors in our final adjusted models. Nonetheless, various unmeasured differences in provider care for ART and non-ART pregnancies and births might remain. The hypothesis that enhanced care for ART mothers explains some of the differences in adverse outcomes between ART and non-ART twin deliveries is indirectly supported by our data and that of others. Of all the perinatal and infant outcomes studied in this analysis, ART was most strongly associated with a reduced odds of the most serious outcomes: VLBW, very preterm and infant mortality. The differential US secular trends in LBW and infant mortality clearly indicate that mortality is the outcome affected most through enhanced care (MacDorman *et al*., 2005).

Another potential explanation that we were able to partially examine is the higher frequency of monozygotic twinning in naturally conceived twins. Approximately one-third of naturally conceived twins will be higher-risk monozygotic twins, whereas the proportion of monozygotic twins associated with ART twins is estimated to be much lower, as the major risk factor for twinning in ART pregnancies is multiple embryo transfer (Reynolds and Schieve, 2006; Wright *et al*., 2006). The results of this study and others that controlled for zygosity through restriction to twins of unlike sex suggest that the reduced mortality associated with ART remained evident, although less pronounced in dizygotic twins (Moise *et al*., 1998; Dhont *et al*., 1999). However, the generalizability of findings from this highly restricted subset of dizygotic twins to all dizygotic twin deliveries is unknown.

The limitations of this study include the finite set of risk factors that were available on the population-based data set for analysis. We lacked data on several risk factors known to be associated with both preterm delivery and infertility such as maternal stress, subclinical pelvic infection, micronutrient deficiencies and environmental exposures (Baird *et al*., 1999). Although we were able to assess placental abruption in this study, we lacked data on many conditions that may underlie pregnancy complications and result in less overt pathological placental effects. In addition, misclassification and/or miscoding of vital record data have been noted for gestational age and placental abruption (DiGiuseppe *et al*., 2002). It is possible that the accuracy of gestational age data is higher for ART than for non-ART deliveries; this difference could conceivably bias the ART preterm and very preterm associations toward a protective effect because data errors in

gestational age tend to bias toward finding an increased risk for preterm delivery (Kramer *et al*., 1988). However, our results for preterm and very preterm delivery were consistent with results for LBW, VLBW and infant mortality, outcomes for which reporting and data validity should not be influenced by ART use and that have been shown to be highly accurate for all births (Gould, 1999). It is also possible that some women included in the non-ART comparison group had actually used fertility medications, but remained in the final sample because of incomplete recording of fertility medication use in birth certificate data. However, the multiple-birth rate among non-ART births in our study population (1.56%) is consistent with the expected rate for naturally conceived multiple births (ESHRE, 2000). Our findings are also limited by our inability to completely assess heterogeneity within groups of dizygotic and monozygotic twins. Finally, we lacked data on fetal deaths and could not definitively classify those deliveries reported to be twins but with only one live birth reported to the natality files. We examined both extremes in our sensitivity analyses and were able to provide a probable range of risk ratios for low Apgar and infant mortality outcomes. Furthermore, the data were not linked to fetal death certificates, so we were to assess twin gestation in which both outcomes were a fetal death of $>20$ weeks gestation. Owing to lag time associated with data linkage and validation, the data used for this analysis represent a slightly earlier time period than reports based on the unlinked ART surveillance system or Massachusetts birth files.

Our study also has many strengths. Although other investigations have evaluated the relationship between twin birth outcomes and use of ART, to our knowledge, the role of parity as an effect modifier has not been described previously. Because the sample size for this analysis was larger than nearly all previous studies of this issue, we were able to assess the impact of numerous confounders and effect modifiers. In addition, this analysis included covariates that were not routinely assessed in previous studies such as maternal race/ethnicity, maternal education, prenatal care utilization and smoking. Furthermore, by using a restricted subset of controls that were more similar to the study group on a number of sociodemographic factors than general population controls, we may have been able to further reduce residual confounding.

Although the association between multiple gestation and adverse perinatal outcomes is well established, most women in the USA who use ART opt for multiple embryo transfer (Wright *et al*., 2006). This decision may be motivated by a number of factors, including the relatively high cost of ART procedures, which may not be covered by health insurance, and the desire to optimize the chance for pregnancy during a single treatment (Little *et al*., 2006). Also, a multiple pregnancy may be the preferred outcome for some women with infertility; a recent survey of fertility clinic patients in the USA indicated that 20% desired a multiple gestation over a singleton (Ryan *et al*., 2004).

This population-based study provides further information on the risk of adverse outcomes among twin births conceived with ART and indicates that parity may be an effect modifier in twin birth outcomes. Relative to singleton pregnancies, twin pregnancies face significantly higher risks of perinatal and infant morbidity and mortality, regardless of ART use (Warner *et al*., 2000). Recent studies demonstrate increasing empirical evidence that, for a subgroup of patients undergoing ART, single embryo transfer may be a viable treatment option (Gerris, 2005). Thus, the development of strategies aimed at reducing ART-associated multiple births may present the best opportunity to reduce adverse health outcomes among infants conceived by ART.

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