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
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; Kolvurova 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, zygozity, 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 each 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
assumption (Lazar did not have access to fetal death certificates for this study, a previous 
these are cases in which one twin was a fetal death. Although we 
the plurality variable indicated the infant was a twin. We assumed 
(2%), only one live born infant was included in the files, although 
live births were reported for 4098 (98%); for the remaining 77 
described above for logistic regression with dichotomous outcomes. 
with adverse outcomes) rather than a lower category. Models were 
denote the probability of being in a higher category (i.e. both infants 
adverse outcomes. This model calculates cumulative ORs that 
twin infants, we used ordinal logistic regression to calculate adjusted 
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 
twins, we used ordinal logistic regression to calculate adjusted 
cumulative ORs and 95% CIs for the relationship between the afore-
mentioned 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 deliv-
eries 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 Massa-
chusetts 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 con-
ceived 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 propor-
tions 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 
ot 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
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.

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

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

<table>
<thead>
<tr>
<th>Birth plurality</th>
<th>All births in selected study population</th>
<th>Twin births in selected study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth plurality</td>
<td>ART (%)(N = 4745)</td>
<td>No ART (%)(N = 179478)</td>
</tr>
<tr>
<td>Birth plurality</td>
<td>ART (%)(N = 1446)</td>
<td>No ART (%)(N = 2729)</td>
</tr>
<tr>
<td>Birth plurality</td>
<td>Singleton</td>
<td>66.11b 98.44</td>
</tr>
<tr>
<td>Birth plurality</td>
<td>Twin</td>
<td>30.47 1.52</td>
</tr>
<tr>
<td>Birth plurality</td>
<td>Triplet/+</td>
<td>3.41 0.04</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>&lt; 35</td>
<td>43.44b 74.35</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>≥ 35</td>
<td>56.56 25.65</td>
</tr>
<tr>
<td>Parity</td>
<td>1</td>
<td>67.76b 42.45</td>
</tr>
<tr>
<td>Parity</td>
<td>&gt; 1</td>
<td>32.24 57.55</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Non-Hispanic white</td>
<td>91.78b 88.22</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Non-Hispanic black</td>
<td>2.32 2.84</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Hispanic</td>
<td>1.98 3.08</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Asian, American Indian, other</td>
<td>3.92 3.86</td>
</tr>
<tr>
<td>Maternal education</td>
<td>High school</td>
<td>14.67b 18.86</td>
</tr>
<tr>
<td>Maternal education</td>
<td>Some college/college graduate</td>
<td>85.33 81.14</td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td>Yes</td>
<td>2.17b 5.15</td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td>No</td>
<td>97.83 94.85</td>
</tr>
<tr>
<td>Trimester prenatal care initiation</td>
<td>1</td>
<td>94.31 94.34</td>
</tr>
<tr>
<td>Trimester prenatal care initiation</td>
<td>2</td>
<td>5.69 5.66</td>
</tr>
<tr>
<td>Kotelchuck index prenatal care</td>
<td>Intermediate/adequate</td>
<td>42.23b 64.38</td>
</tr>
<tr>
<td>Kotelchuck index prenatal care</td>
<td>Adequate plus (110–149%)</td>
<td>29.08 27.56</td>
</tr>
<tr>
<td>Kotelchuck index prenatal care</td>
<td>Adequate plus (150–199%)</td>
<td>16.31 6.20</td>
</tr>
<tr>
<td>Kotelchuck index prenatal care</td>
<td>Adequate plus (≥ 200%)</td>
<td>12.37 1.87</td>
</tr>
<tr>
<td>Hospital delivery of care level</td>
<td>1 and 2</td>
<td>41.92b 64.55</td>
</tr>
<tr>
<td>Hospital delivery of care level</td>
<td>3</td>
<td>58.08 35.45</td>
</tr>
</tbody>
</table>

*aBirths 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.

bP < 0.01 for chi-square test of distribution of variable in ART group versus distribution in non-ART group.

cP < 0.05 for chi-square test of distribution of variable in ART group versus distribution in non-ART group.
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’.
deaths in ART twins versus 24 in naturally conceived twin cohort study, Fitzsimmons
ings of lower rates for infant death among ART twins are meta-analysis conducted by McDonald
reported a relative risk of 0.58 (0.44–0.77) for perinatal mor-
very preterm delivery (data not shown).

A closer assessment of the current sample by all potential confounders indicated that 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 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

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 primi-

### 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.

<table>
<thead>
<tr>
<th>Distribution of deliveries with an infant death</th>
<th>ART (%)</th>
<th>No ART (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two live born infants reported, two infants died</td>
<td>8.1%</td>
<td>34.45%</td>
</tr>
<tr>
<td>Two live born infants reported, one infant died</td>
<td>42.8%</td>
<td>21.01%</td>
</tr>
<tr>
<td>One live born infant reported that died, one presumed a fetal death</td>
<td>8.1%</td>
<td>13.45%</td>
</tr>
<tr>
<td>One live born infant reported (alive at 1 year), one presumed a fetal death</td>
<td>40.82%</td>
<td>31.09%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analyses of live born infants that died</th>
<th>N = 33</th>
<th>N = 124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of infant death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 1 day</td>
<td>57.58%</td>
<td>77.42%</td>
</tr>
<tr>
<td>2–6 days</td>
<td>9.09%</td>
<td>10.48%</td>
</tr>
<tr>
<td>7–27 days</td>
<td>24.24%</td>
<td>4.63%</td>
</tr>
<tr>
<td>28 days–1 year</td>
<td>9.09%</td>
<td>8.06%</td>
</tr>
<tr>
<td>Birthweight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1500 g</td>
<td>84.85%</td>
<td>89.17%</td>
</tr>
<tr>
<td>1500–2499 g</td>
<td>9.09%</td>
<td>5.83%</td>
</tr>
<tr>
<td>2500–5000 g</td>
<td>6.06%</td>
<td>5.00%</td>
</tr>
<tr>
<td>Gestational age at delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;32 weeks</td>
<td>78.79%</td>
<td>91.06%</td>
</tr>
<tr>
<td>32–36 weeks</td>
<td>12.12%</td>
<td>4.88%</td>
</tr>
<tr>
<td>≥37 weeks</td>
<td>9.09%</td>
<td>4.07%</td>
</tr>
</tbody>
</table>

*P < 0.01 for Fisher’s exact test.

Number of deaths was <5.
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.

**Acknowledgement**

The authors acknowledge the member clinics of the Massachusetts Consortium of Assisted Reproductive Technology Epidemiologic Research (MCARTER) for their support and assistance with data collection for this linkage project. These clinics include Baystate Reproductive Medicine, Boston IVF, Brigham and Women’s Hospital ART Center, Fertility Center of New England, Massachusetts General Hospital, New England Fertility and Endocrinology Associates, Reproductive Science Center, and Women and Infants Division of Reproductive Medicine and Infertility. The original ART surveillance system data used for this study were collected by the Society for Assisted Reproductive Technology (SART). The listed authors were solely responsible for the study design, data analysis, and writing of this manuscript. The findings and conclusions in this report are those of the listed authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, nor the ART clinics comprising MCARTER.

**Funding**

This research was supported in part by an appointment to the Research Participation Program at the National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and CDC.

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