Trends in Morbidity and Mortality of Extremely Preterm Multiple Gestation Newborns

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abstract

OBJECTIVES: To examine the risk of mortality and major morbidities in extremely preterm multiple gestation infants compared with singletons over time.

METHODS: This is a retrospective study of 15 402 infants born ≤27 weeks' gestation, admitted to NICUs in the Australian and New Zealand Neonatal Network from 1995 to 2009. Mortality and major morbidities were compared between singletons and multiples across three 5-year epochs.

RESULTS: Extreme preterm multiples were more likely to have lower birth weight; higher maternal age; and higher rates of assisted conception, antenatal steroid use, and cesarean delivery compared with singletons. The mortality rate was significantly higher in multiples compared with singletons even as there was a trend of decreasing gestational-age stratified mortality in multiples over the time period investigated. The rates of major morbidities or composite adverse outcomes were not different between multiples and singletons across all epochs. The adjusted odds ratio (AOR) for mortality in multiples was significantly higher in multiples compared with singletons (AOR 1.20, 95% confidence interval [CI] 1.08–1.34). There were no differences in the adjusted odds for poor outcomes in multiples compared with singletons in the most recent epoch: mortality (AOR 1.00, 95% CI 0.84–1.19), major morbidity (0.95, 95% CI 0.81–1.10), and composite adverse outcome (0.96, 95% CI 0.83–1.11).

CONCLUSIONS: Over the 15-year period, the odds for mortality in extremely preterm NICU infants of multiple gestation was significantly higher compared with singletons. The adjusted odds of poor outcomes in multiples were not significantly different from that of singletons in the most recent epoch.

WHAT’S KNOWN ON THIS SUBJECT: Studies on the risk of mortality and morbidities of extremely preterm infants of multiple gestation births have shown inconsistent results. Perinatal antecedents, admission status and severity of illness after birth can adversely affect outcomes of the extremely premature infants.

WHAT THIS STUDY ADDS: Preterm multiple gestation infants have increased risk of mortality but similar risk of major morbidities compared with singletons. Outcomes improved over time and all adverse outcomes, including mortality, were comparable between multiples and singletons in the most recent 5-year epoch.
Admission of multiple gestation infants (multiples) to NICUs in Australia and New Zealand has increased steadily over the past 2 decades. This trend has paralleled increases in multiple gestation births as a result of increased use of fertility drugs, increased access to assisted reproductive technology (ART) and increased maternal childbearing age. In 2009, there were an estimated 4605 and 908 multiple gestation pregnancies in Australia and New Zealand respectively, accounting for 1.5% and 1.6% of all pregnancies in both countries. Available data in Australia and New Zealand indicate that ~1006 (18.2%) of all multiple gestation pregnancies in 2009 were a result of ART.

Multiple gestation pregnancies are associated with increased risk of preterm delivery and increased risk of poor outcomes as a result. It is estimated that 1 in 10 twins are born before 32 weeks compared with 1 in 100 singleton births. This is thought to account for the increased likelihood of admission of multiples to the NICU. Multiple gestation pregnancies have also been associated with increased risks of antenatal complications and congenital anomalies, which have important implications on the outcome for both mother and child. Even so, the risk of poor outcomes in extremely preterm multiples compared with their singleton counterpart has not been well characterized.

Several recent prospective cohort and single-center studies have reported conflicting results on the risk of death in twins compared with singletons. Several studies have also highlighted the effect of birth weight as a potential confounder in assessing the risk of mortality in multiples. Additionally, there has been a smaller number of reports with some conflicting results on the effects of plurality on the risk of major morbidities such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and necrotizing enterocolitis (NEC) in extremely preterm infants.

The current study aimed to determine the trends in hospital mortality and major morbidities of extremely preterm infants of multiple gestations compared with singletons. In this study, we tested the hypothesis that extremely preterm multiples have a higher risk of mortality and major morbidity compared with singletons. We also determined the trends in mortality and major morbidity in this population over time.

METHODS

Data Source

The data for this study was sourced from the Australian and New Zealand Neonatal Network (ANZNN) database that began in January 1995. ANZNN is a collaborative network of all 29 tertiary-level NICUs in the region. The network monitors the care of high-risk newborns by pooling data of all infants admitted to tertiary-level NICUs during the neonatal period (≤28 days) for any of the following indications: completed gestational age of <32 weeks, birth weight less ≤1500 g, need for assisted ventilation (mechanical ventilator or continuous positive airway pressure device) for ≥4 hours and major surgery. The care of extremely preterm infants has been regionalized since the early 1990s, where extremely preterm infants who are offered intensive care will be cared for in a tertiary level NICU. As such, the ANZNN contains 99% of all live births <29 weeks in both countries. Neonatal, maternal, and perinatal data are collected from each NICU and compiled into a central ANZNN database located at the University of New South Wales, Australia. Each NICU has an audit officer who collects and checks the data before submission into the central database. The accuracy of the data collection is validated by random data cross-checking by ANZNN coordinators.

Study Population

For this study, infants born ≤27 weeks’ gestation admitted to a collaborating NICU during the period of 1995–2009 were included. The study population was grouped by plurality (singletons, multiples) and by three 5-year epochs (epoch 1: 1995–1999, epoch 2: 2000–2004, epoch 3: 2005–2009). Analysis was limited to infants who were born alive and survived to admission in the NICU.

Outcome Variables and Definitions

Variables were defined according to the ANZNN data dictionary (http://www.npesu.unsw.edu.au/anznn-data-dictionaries-registration-criteria). Gestational age is defined as the best obstetric estimate of completed weeks based on obstetric history, clinical examination, and prenatal ultrasound. Assisted conception is classified as the use of fertility treatments including hormonal therapy, artificial insemination, or any methods of in-vitro fertilization. An infant is classified as small for gestational age (SGA) if the birth weight is less than third percentile according to published norms for Australian infants. “Outborn” refers to newborns who were delivered in a non-tertiary-level NICU before transfer to a tertiary-level unit. Clinical Risk Index for Babies II (CRIB II) scores were calculated on the basis of the 5-variable algorithm as previously defined. Mortality and major morbidity is limited to those occurring before discharge from the NICU. For multiples, each infant was considered separately for purposes of analysis.
Major morbidities examined included the presence of BPD, grade 3 or grade 4 IVH, PVL, medically or surgically treated NEC, and grade 3 or grade 4 ROP. BPD is defined as oxygen requirement or respiratory support for a chronic pulmonary disorder at 36 weeks' postmenstrual age. Classification of IVH grade is that defined by Papille and colleagues. PVL is defined as the presence of typical changes in the periventricular white matter of the brain parenchyma as detected by head ultrasound by 6 weeks of life. The classification of NEC is by diagnosis at surgery/postmortem or radiologic diagnosis (pneumatosis intestinalis or portal vein gas or persistent dilated bowel loop on serial x-rays) with a consistent clinical history or a clinical diagnosis (abdominal wall cellulitis and palpable abdominal mass) with a consistent clinical history. ROP is classified according to the staging by International Classification for Retinopathy of Prematurity. A composite adverse outcome variable was also used to identify infants who died or survived with ≥1 of the major morbidities as described earlier.

**Statistical Analysis**

We compared the variables of interest between singletons and multiples using the $\chi^2$ test for proportions and $t$ test for means, as appropriate. Analysis was performed for the whole study population and also for subgroups from 23 to 27 weeks’ gestation. We developed multivariate logistic regression models to estimate the adjusted odds ratio (AOR) of the outcomes of interest including death, major morbidities, and composite adverse outcome. The following clinical variables were included in the final model to investigate the effects of plurality on outcomes of interest: gender, gestational age, SGA status, receipt of antenatal steroids, outborn status, and the presence of congenital malformations. Odds ratio (OR) and AOR were expressed with 95% confidence intervals (95% CI). A level of significance of $\alpha < .05$ using a 2-tailed comparison was used in this study. Statistical analyses were performed by using IBM SPSS Statistics version 22.0. (IBM Corp., Armonk, NY).

**Ethics Approval**

Ethics approval was obtained from the South Eastern Sydney and Illawarra Area Health Service Human Research Ethics Committee.

**RESULTS**

A total of 15,402 infants ≤27 weeks’ gestation were admitted to the network centers during the study period: 4932 in epoch 1, 5282 in epoch 2, and 5188 in epoch 3. Of these, 11,278 (73.2%) were singletons, 3681 (23.9%) were twins, and 443 (2.9%) were of higher-order multiples (Fig 1A). There was an increase in the percentage of twins from Epoch 1 to Epoch 3: 21.6% to 25.6% (Fig 1B). The percentage of multiples from assisted conception increased from Epoch 1 to 2 but decreased marginally in Epoch 3. The clinical characteristics of the cohort are described in Table 1. Mean gestational age was similar in all the groups across the epochs. Multiples had lower mean birth weight but similar rates of SGA compared with singletons in the 2 recent epochs. There were also a significantly lower number of outborn multiples in the most recent epoch.

Mothers of multiples were ∼8 times more likely to have used artificial conception therapy compared with...
There was a significantly higher rate of cesarean delivery (OR 1.5, 95% CI 1.4–1.6), antenatal steroids (OR 1.4, 95% CI 1.2–1.5), and surfactant usage (OR 1.4, 95% CI 1.3–1.5) in multiples compared with singletons. Mothers with multiples had significantly lower rates of pregnancy induced hypertension and antepartum hemorrhage. The mean CRIB II score, an early indicator of neonatal disease severity within the first 12 hours after birth, was not significantly different between singletons and multiples across all epochs.

Over the 15-year period, the mortality rate for multiples was significantly higher for multiples compared with singletons (24.7% vs 21.9%, P < .01). There was an overall reduction in the mortality rate of these extremely preterm infants from epoch 1 to epoch 3 (Table 1). The NICU mortality for multiples (27.5% to 19.2%) demonstrated a greater

### TABLE 1 Clinical Characteristic of Singletons and Multiples by Epoch

<table>
<thead>
<tr>
<th>Epoch</th>
<th>Singleton</th>
<th>Multiples</th>
<th>Singleton</th>
<th>Multiples</th>
<th>Singleton</th>
<th>Multiples</th>
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<tr>
<td>Gestation (wk)</td>
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<td></td>
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<tr>
<td>≤23</td>
<td>272 (7.4)</td>
<td>73 (5.9)</td>
<td>236 (6.1)</td>
<td>107 (7.6)</td>
<td>173 (4.6)</td>
<td>77 (5.3)</td>
</tr>
<tr>
<td>24</td>
<td>542 (14.7)</td>
<td>178 (14.3)</td>
<td>646 (16.7)</td>
<td>217 (15.3)</td>
<td>557 (15.0)</td>
<td>246 (16.8)</td>
</tr>
<tr>
<td>25</td>
<td>771 (20.9)</td>
<td>268 (21.6)</td>
<td>791 (20.5)</td>
<td>302 (21.3)</td>
<td>776 (20.8)</td>
<td>298 (20.3)</td>
</tr>
<tr>
<td>26</td>
<td>1033 (28.0)</td>
<td>343 (27.6)</td>
<td>1001 (25.9)</td>
<td>339 (23.9)</td>
<td>1039 (27.9)</td>
<td>412 (28.1)</td>
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<tr>
<td>27</td>
<td>1072 (29.1)</td>
<td>380 (30.6)</td>
<td>1191 (30.8)</td>
<td>452 (31.9)</td>
<td>1178 (31.6)</td>
<td>432 (29.3)</td>
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<td>Mean gestational age (wk)</td>
<td>25.6</td>
<td>25.6</td>
<td>25.6</td>
<td>25.6</td>
<td>25.7</td>
<td>25.7</td>
</tr>
<tr>
<td>Male (%)</td>
<td>55.2</td>
<td>57.6</td>
<td>53.8</td>
<td>53.0</td>
<td>53.1</td>
<td>54.4</td>
</tr>
<tr>
<td>Birth weight g (SD)</td>
<td>833 (200)</td>
<td>835 (195)</td>
<td>836 (204)</td>
<td>818 (201)</td>
<td>855 (6204)</td>
<td>836 (6204)</td>
</tr>
<tr>
<td>SGA less than third percentile</td>
<td>99 (2.7)</td>
<td>19 (1.5)</td>
<td>836 (204)</td>
<td>818 (201)</td>
<td>855 (6204)</td>
<td>836 (6204)</td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>90 (14)</td>
<td>51 (4.1)</td>
<td>836 (204)</td>
<td>818 (201)</td>
<td>855 (6204)</td>
<td>836 (6204)</td>
</tr>
<tr>
<td>Maternal age (SD)</td>
<td>28.6 (6.2)</td>
<td>29.2 (5.4)</td>
<td>28.7 (6.4)</td>
<td>30.3 (5.6)</td>
<td>29.1 (6.5)</td>
<td>30.3 (6.2)</td>
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<td>Maternal ethnicity</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Aboriginal</td>
<td>4.8</td>
<td>2.7</td>
<td>7.1</td>
<td>2.9</td>
<td>5.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Caucasian</td>
<td>64.1</td>
<td>70.9</td>
<td>65.4</td>
<td>76.8</td>
<td>64.5</td>
<td>72.8</td>
</tr>
<tr>
<td>Asian</td>
<td>5.9</td>
<td>4.3</td>
<td>6.5</td>
<td>4.2</td>
<td>7.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>2.3</td>
<td>2.1</td>
<td>3.1</td>
<td>1.8</td>
<td>3.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Maori</td>
<td>5.9</td>
<td>2.9</td>
<td>6.3</td>
<td>3.4</td>
<td>6.4</td>
<td>4.5</td>
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<tr>
<td>Other</td>
<td>1.6</td>
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<td>1.3</td>
<td>1.3</td>
<td>1.8</td>
<td>1.9</td>
</tr>
<tr>
<td>PIH</td>
<td>569 (15.4)</td>
<td>72 (5.8)</td>
<td>566 (14.6)</td>
<td>86 (6.1)</td>
<td>424 (11.4)</td>
<td>60 (4.1)</td>
</tr>
<tr>
<td>Antepartum hemorrhage</td>
<td>1081 (29.3)</td>
<td>230 (18.5)</td>
<td>1150 (29.8)</td>
<td>263 (18.8)</td>
<td>1036 (27.8)</td>
<td>235 (18.0)</td>
</tr>
<tr>
<td>Assisted conception</td>
<td>134 (3.8)</td>
<td>301 (24.2)</td>
<td>171 (4.4)</td>
<td>420 (29.8)</td>
<td>222 (6.0)</td>
<td>401 (27.4)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>1659 (45)</td>
<td>629 (51.7)</td>
<td>1985 (51.7)</td>
<td>865 (61.2)</td>
<td>1847 (49.8)</td>
<td>904 (61.8)</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>2824 (78.5)</td>
<td>988 (80.4)</td>
<td>3205 (82.9)</td>
<td>123 (87.3)</td>
<td>3179 (85.4)</td>
<td>1299 (88.7)</td>
</tr>
<tr>
<td>Surfactant</td>
<td>2881 (78.3)</td>
<td>1005 (85.8)</td>
<td>3037 (78.9)</td>
<td>1183 (83.7)</td>
<td>3128 (84.6)</td>
<td>1260 (86.0)</td>
</tr>
<tr>
<td>Outborn</td>
<td>384 (10.4)</td>
<td>120 (9.7)</td>
<td>497 (12.9)</td>
<td>184 (13.0)</td>
<td>552 (14.8)</td>
<td>184 (13.0)</td>
</tr>
<tr>
<td>Mean CRIB II score (SD)</td>
<td>11.61 (5.01)</td>
<td>11.62 (5.01)</td>
<td>11.53 (2.92)</td>
<td>11.53 (5.00)</td>
<td>11.18 (2.77)</td>
<td>11.22 (2.76)</td>
</tr>
<tr>
<td>Early-onset sepsis</td>
<td>NA</td>
<td>NA</td>
<td>105 (2.7)</td>
<td>20 (1.4)</td>
<td>108 (2.9)</td>
<td>23 (1.6)</td>
</tr>
<tr>
<td>Late-onset sepsis</td>
<td>NA</td>
<td>NA</td>
<td>812 (21.0)</td>
<td>266 (18.8)</td>
<td>1132 (31.9)</td>
<td>355 (29.0)</td>
</tr>
<tr>
<td>Surgery</td>
<td>484 (13.1)</td>
<td>172 (13.8)</td>
<td>552 (14.3)</td>
<td>240 (16.9)</td>
<td>575 (15.4)</td>
<td>267 (18.2)</td>
</tr>
<tr>
<td>Death</td>
<td>904 (24.5)</td>
<td>342 (27.5)</td>
<td>861 (22.3)</td>
<td>393 (27.7)</td>
<td>705 (18.9)</td>
<td>282 (19.2)</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise specified. Infection data were not collected during first epoch. NA, not applicable; PIH, pregnancy induced hypertension.

\( a \) P < .05 chi-squared test comparison between singleton and multiples.

\( b \) P < .05 t-test comparison between singleton and multiples.
For singletons, there was a noted difference in mortality and morbidity from that of twins across all epochs. To better assess the risk for poor outcomes, a composite adverse outcome variable was used, indicating the presence of mortality or any major morbidity. Composite adverse outcomes for singletons and multiples have decreased significantly over the 3 epochs (Table 3), and no significant differences were noted in the rates between the 2 groups.

When adjusted for potential confounders including male gender, gestational age, SGA status, receipt of antenatal steroids, outborn status, and presence of congenital malformations, multiples had significantly higher odds of mortality than singletons (Table 4). When stratified by epoch, there was a notable trend toward decreasing odds of mortality from epoch 1 (OR 1.29, 95% CI 0.99–1.66) to epoch 3 (OR 1.00, 95% CI 0.84–1.19) for multiples compared with singletons (Fig 3). A similar trend was noted when stratification was done by gestational age. While controlling for similar confounders, the AOR for the presence of any of the major morbidities (BPD, severe IVH, PVL, severe ROP, NEC) in multiples was not significantly different from singletons over time, from epoch 1 (OR 1.08, 95% CI 0.83–1.40) to epoch 3 (OR 0.95, 95% CI 0.81–1.10; Supplemental Table 5). Comparisons for individual morbidity also did not reveal any differences between the 2 groups.

Controlling for confounders, there was no detectable difference for the composite adverse outcome between singletons and multiples, with a trend of reduction of AOR from epoch 1 (OR 1.09, 95% CI 0.85–1.40) to epoch 3 (OR 0.96, 95% CI 0.83–1.11).

## DISCUSSION

In this population-based cohort study, we found an overall increased risk of in-hospital mortality for extremely preterm multiples compared with singletons admitted from 1995 to 2009. There was no significant difference in the risk of major morbidities between the 2 groups during the time period investigated. There were comparable adjusted odds of death or major morbidity in multiples compared with singletons in the most recent epoch. Despite the higher risk of preterm birth of multiples compared with singletons, there are indications that the outcomes of such infants may approach that of singletons born at the same gestation in recent times.

Available studies on outcomes of extremely preterm multiples have reported conflicting results on the risk for mortality and major morbidity. Many of these studies were of smaller cohorts, included infants of higher gestation, and some were uncontrolled for potential confounders.16–22,29 Large cohort studies of neonatal networks from the United States (1991–1994), Israel (1995–1999), and Europe (2003) have reported similar risks of mortality when comparing extremely preterm singletons and twins,8,21,24 although these studies are of earlier time periods. Two other cohort studies of extremely preterm multiples at 23 to 25 weeks gestational age have shown a notable trend toward decreasing mortality and morbidity over the 3 epochs.23–27

The initial difference in mortality and morbidity across the 3 epochs for singletons and multiples from 26 to 27 weeks gestational age disappeared by epoch 3.

### TABLE 2 Distribution of Major Morbidity Between Singletons and Multiples by Gestational Age and Epoch

<table>
<thead>
<tr>
<th>Age (wk)</th>
<th>Epoch 1, n (%)</th>
<th>Epoch 2, n (%)</th>
<th>Epoch 3, n (%)</th>
</tr>
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<tbody>
<tr>
<td>BPD</td>
<td></td>
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<tr>
<td>23–25</td>
<td>403 (40.7)</td>
<td>120 (38.6)</td>
<td>842 (50.5)</td>
</tr>
<tr>
<td>26–27</td>
<td>451 (34.9)</td>
<td>162 (38.1)</td>
<td>874 (40.0)</td>
</tr>
<tr>
<td>All</td>
<td>854 (37.5)</td>
<td>282 (38.3)</td>
<td>1716 (44.5)</td>
</tr>
<tr>
<td>ROP</td>
<td></td>
<td></td>
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<tr>
<td>23–25</td>
<td>218 (22.1)</td>
<td>75 (25.3)</td>
<td>263 (23.3)</td>
</tr>
<tr>
<td>26–27</td>
<td>101 (6.0)</td>
<td>50 (8.6)</td>
<td>151 (7.5)</td>
</tr>
<tr>
<td>All</td>
<td>319 (12.0)</td>
<td>125 (14.2)</td>
<td>386 (12.8)</td>
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<tr>
<td>IVH/PVL</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>23–25</td>
<td>330 (25.2)</td>
<td>117 (25.4)</td>
<td>325 (20.9)</td>
</tr>
<tr>
<td>26–27</td>
<td>284 (14.0)</td>
<td>93 (13.5)</td>
<td>237 (11.1)</td>
</tr>
<tr>
<td>All</td>
<td>614 (17.8)</td>
<td>210 (18.3)</td>
<td>560 (15.2)</td>
</tr>
<tr>
<td>NEC</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>23–25</td>
<td>124 (7.9)</td>
<td>63 (12.2)</td>
<td>139 (8.3)</td>
</tr>
<tr>
<td>26–27</td>
<td>117 (5.6)</td>
<td>38 (5.3)</td>
<td>146 (6.7)</td>
</tr>
<tr>
<td>All</td>
<td>38 (5.3)</td>
<td>101 (8.1)</td>
<td>285 (7.4)</td>
</tr>
<tr>
<td>Any major morbidity</td>
<td>23–25</td>
<td>450 (75.4)</td>
<td>133 (76.9)</td>
</tr>
<tr>
<td></td>
<td>26–27</td>
<td>522 (50.4)</td>
<td>181 (51.9)</td>
</tr>
<tr>
<td>All</td>
<td>972 (59.6)</td>
<td>314 (60.2)</td>
<td>1880 (62.8)</td>
</tr>
</tbody>
</table>

BPD, oxygen requirement at 36 wk postmenstrual age; ROP, grade 3–4; severe IVH/PVL, grade 3 or 4 IVH or presence of PVL.

* P < .01 for χ² test between singleton versus multiples for infants ≤27 weeks stratified by epoch.
Our study is among the largest population-based cohorts to examine the recent trends of mortality and morbidity for extremely preterm multiples. Conflicting reports with regard to outcomes could reflect differences in study designs and population characteristics. Variation in NICU practices and case mix across NICUs may also influence the outcomes of infants as reported. However, the regionalization of neonatal care in Australia and New Zealand makes this a good representation of the extremely preterm population. The standardized definitions of risk factors and antenatal complications including lower pregnancy-induced hypertension,1,8,24 antepartum hemorrhage,8,24 and prolonged rupture of membranes,24 We believe the improvement in outcomes among multiples over time may be partly due to closer perinatal monitoring. This would account for the higher rates of antenatal steroids, higher likelihood of being born in a tertiary care center, and also higher usage of surfactant in this group. We investigated the potential differences in neonatal condition after birth by comparing the CRIB II scores in singletons and multiples. There was no significant difference in the mean CRIB II scores between the 2 groups and the distribution of scores was fairly similar across the epochs (Supplemental Fig 1). This is an indication that infant’s condition after birth were comparable between the 2 groups, and it is likely that the reduction in risk of adverse outcomes can also be partly attributable to improvements in clinical practice over the time period studied. The higher incidence of congenital malformations among multiples in our study is consistent with several studies that have reported incidence of congenital malformations.1,24 This finding is in line with previous reports of increased risk of congenital malformations in multiple gestation infants in comparison with singletons.1,15,30

Our study is among the largest population-based cohorts to examine the recent trends of mortality and morbidity for extremely preterm multiples. Conflicting reports with regard to outcomes could reflect differences in study designs and population characteristics. Variation in NICU practices and case mix across NICUs may also influence the outcomes of infants as reported. However, the regionalization of neonatal care in Australia and New Zealand makes this a good representation of the extremely preterm population. The standardized definitions of risk factors and
outcomes, combined with rigorous data cross-checking by ANZNN, ensures completeness and validity of the data obtained. The system for the provision of obstetric care in Australia and New Zealand makes gestational age known for most pregnancies. This allows us to analyze the potential effect of growth independent of maturity in our regression model to better ascertain the true effect of plurality on outcomes in these very preterm infants.

This study does not include stillbirths, infants who did not survive to NICU admission, or early pregnancy losses. This may lead to ascertainment bias in our study population. The effect of zygosity and chorionicity was not examined because of the lack of data in this regard. Both zygosity and chorionicity have been suggested to affect outcomes of multiple gestations. Monozygosity have been related to higher rates of congenital anomalies, and chorionicity is known to affect the risk of growth discordance and growth restriction. The effect of ART on outcomes as it pertains to plurality also could not be investigated because of the insufficient data on artificial conception methods. ART has been reported to affect mortality and perinatal outcomes in the extremely low gestational age infants. Twins born as a result of ART have been reported to have lower risk of perinatal death compared with naturally conceived twins. The number of embryo transferred may also influence perinatal outcomes. Available evidence indicates that multiples as a result of single embryo transfer have an increased risk of mortality compared with infants of multiple embryo, likely reflecting the increased risk of mortality associated with monozygotic twinning. Although we did not detect a difference in the outcomes of our cohort when stratified by assisted conception status, there was insufficient data on artificial conception method or zygosity to analyze this further. The effects of these factors remain to be understood in the extremely preterm population, especially in light of the increased adoption of single embryo transfer in women undergoing ART.

CONCLUSIONS

The findings of this study suggest that although extremely preterm NICU infants of multiple gestation births are at increased risk of mortality compared with singletons, there is an indication that this difference may be diminishing. This has important implications in the risk assessment of outcomes in extremely preterm infants and the antenatal counseling of parents with multiple gestation pregnancies. Further studies are needed to determine the impact of multiple gestation and ART on long-term neurodevelopmental outcomes.

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ABBREVIATIONS

ANZNN: Australian and New Zealand Neonatal Network
AOR: adjusted odds ratio
ART: assisted reproductive technology
BPD: bronchopulmonary dysplasia
CI: confidence interval
CRIB II: clinical risk index for babies II
IVH: intraventricular hemorrhage
NEC: necrotizing enterocolitis
OR: odds ratio
PVL: periventricular leukomalacia
ROP: retinopathy of prematurity
SGA: small for gestational age

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