Hospital Costs of Multiple-Birth and Singleton-Birth Children During the First 5 Years of Life and the Role of Assisted Reproductive Technology

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**IMPORTANCE** The unprecedented increase in multiple births during the past 3 decades is a major public health concern and parallels the uptake of medically assisted conception. The economic implications of such births are not well understood.

**OBJECTIVES** To conduct a comprehensive economic and health services assessment of the frequency, duration, and cost of hospital admissions during the first 5 years of life for singleton, twin, and higher-order multiple (HOM) children and to examine the contribution of assisted reproductive technology (ART) to the incidence and cost of multiple births.

**DESIGN, SETTING, AND PARTICIPANTS** A retrospective population cohort study using individually linked birth, hospital, and death records among 233,850 infants born in Western Australia between October 1993 and September 2003, and followed up to September 2008.

**EXPOSURES** Multiple-gestation delivery and ART conception.

**MAIN OUTCOMES AND MEASURES** Odds of stillbirth, prematurity and low birth weight, frequency and length of hospital admissions, the mean costs by plurality, and the independent effect of prematurity on childhood costs.

**RESULTS** Of 226,624 singleton, 6941 twin, and 285 HOM infants, 1.0% of singletons, 15.4% of twins, and 34.7% of HOM children were conceived following ART. Compared with singletons, twins and HOMs were 3.4 and 9.6 times, respectively, more likely to be stillborn and were 6.4 and 36.7 times, respectively, more likely to die during the neonatal period. Twins and HOMs were 18.7 and 525.1 times, respectively, more likely to be preterm, and 3.6 and 2.8 times, respectively, more likely to be small for gestational age. The mean hospital costs of a singleton, twin, and HOM child to age 5 years were $2730, $8993, and $24,411 (in 2009-2010 US dollars), respectively, with cost differences concentrated in the neonatal period and during the first year of life. Almost 15% of inpatient costs for multiple births could have been avoided if ART twins and HOMs had been born as singletons.

**CONCLUSIONS AND RELEVANCE** Compared with singletons, multiple-birth infants consume significantly more hospital resources, particularly during the neonatal period and first year of life. A significant proportion of the clinical and economic burden associated with multiple births can be prevented through single-embryo transfer. Increasing ART use worldwide and persistently high ART multiple-birth rates in several countries highlight the need for strategies that encourage single-embryo transfer. The costs from this study can be generalized to other settings.

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The unprecedented increase in twin, triplet, and other higher-order multiple (HOM) births during the past 3 decades is a major public health concern worldwide. In 2011 in the United States, 131,269 infants were born in twin deliveries, representing a twin birth rate of 33.2 per 1000 births, a 76% increase from 1980 to 2011 according to national statistics.1 Even more striking, the rate of HOM births in the United States rose by 500% from 1980 (0.37 per 1000 births) to 1998 (1.94 per 1000 births) but has since trended downward to 1.37 per 1000 births in 2011 (5417 births).1

Similar, although less extreme, trends in multiple births have been reflected in other countries, including the United Kingdom, Canada, and Australia.2-5 The increase in twins and HOMs during the past 3 decades parallels the trend to higher maternal age, which predisposes to naturally occurring multiple births, and the increasing use of medically assisted conception.6 Medically assisted conception includes assisted reproductive technology (ART) such as in vitro fertilization and non-ART fertility treatments involving ovulatory stimulation with or without intrauterine insemination. Recent data from the United States indicate that ART accounted for 17% of twins and 32% of HOM births in 2011, while non-ART treatment accounted for 19% of twins and 45% of HOM births.7 Furthermore, it was estimated in 2006 that two-thirds of the increase in multiple births since the early 1980s was attributed to medically assisted conception.8

National registries for non-ART fertility treatment do not exist, but ART treatments are comparatively well recorded in developed countries. These ART registries highlight the continued increase in the uptake of ART treatment, with an estimated 400,000 children conceived each year worldwide.9 However, striking differences exist in clinical practice, particularly in the numbers of embryos transferred. This leads to significant variation in ART multiple-birth rates worldwide, ranging from less than 10% of deliveries in most Nordic countries and Australia and New Zealand10,11 to consistently more than 30% in the United States12 and even higher rates in a number of Asian and European countries.10,13

It is well established that multiple-birth infants are at increased risk of poorer health outcomes than singleton infants, but few investigations have quantified these risks in terms of health care service use and costs.14 It is also well established that ART singletons are at a small increased risk of poorer perinatal health outcomes, including congenital abnormalities, than spontaneously conceived singletons and that such differences are reflected in health care resource use and costs.15-17 The literature indicates that a significant proportion of iatrogenic multiple births can be avoided through a policy of single-embryo transfer.17-20 Therefore, an understanding of the clinical and economic burden of ART multiple births is needed to inform ART policy and health care resource planning.14

The objective of this study was to use a large population data set to conduct a comprehensive economic and health services assessment of the frequency, duration, and cost of hospital admissions during the first 5 years of life for singleton, twin, and HOM children. The study also examined the contribution of ART to the incidence and cost of multiple births.

Methods

Western Australian Linked Data Set

The study was approved by the human research ethics committees of The University of New South Wales and the Western Australian Department of Health, as well as the Western Australian Reproductive Technology Council. Informed consent was not required.

This population-based cohort study uses data on the Western Australian population obtained through the Western Australian Data Linkage System (www.datalinkage-wa.org.au). Western Australia occupies the western third of the Australian continent, although most of its area is sparsely populated except for the southwest corner and coastal settlements to the north. The state has a population of 2.4 million people, with low levels of migration out of the state by international standards (2.8% per annum). Six private fertility clinics operate in the state, all of which are located in the capital city of Perth, where more than three-quarters of the state’s population reside.21 Similarly, all tertiary neonatal intensive care units are located in Perth.

We obtained deidentified data from 4 data sets of the Western Australian Data Linkage System. First, the Midwives Notification System is a statutory data collection of demographic and clinical information on all births (live or stillborn) delivered in Western Australia with a birth weight of at least 400 g or with at least 20 weeks’ gestation, including home births. Second, the Reproductive Technology Register is a statutory database containing information about all ART procedures (in vitro fertilization and intracytoplasmic sperm injection) undertaken in Western Australia. Third, death registrations are collected by the Registrar General. Fourth, the Hospital Morbidity Data System collects data on all inpatient hospital admissions in public and private hospitals in Western Australia.

Record linkage between the data sets was performed by the Western Australian Department of Health. Validation investigations indicate that the Western Australian Data Linkage System has a low level of missing data and a 0.3% false-positive linkage rate.22 The linkage between the Reproductive Technology Register and the Midwives Notification System was 100% complete for births in Western Australia.

The linked data set included all births in Western Australia between October 1993 and September 2003 and all hospital admissions and death notifications until September 2008. This provided a 10-year birth cohort with linkage to the Hospital Morbidity Data System and death registrations to age 5 years.

Outcome Measures

Clinical Outcomes

Perinatal outcomes included measures of preterm birth, low birth weight, and small for gestational age (<10th percentile of birth weight). Death outcomes included rates of fetal death (stillbirth), neonatal deaths (death within 28 days of birth), and postneonatal deaths (death between age 28 days and age 5 years) per 1000 children.

Hospital Use

The odds of being readmitted to hospital after the birth admission were calculated for each period of interest (ie, after...
the birth admission to the end of the infant’s first year and during the second year to the fifth year) using the number of infants alive at the start of each respective period. Hospital episodes that resulted in a transfer were merged with the previous episodes of care to calculate the length of stay (LOS) and the risk of readmission. If an admission spanned 2 periods, it was allocated to the later period. The LOS of an admission was calculated as the LOS of all episodes of care, including transfers, minus days on leave. The mean LOS for each period of interest was calculated by dividing the total LOS by the number of children with at least 1 admission during the period of interest. If a child was admitted and discharged on the same day, an LOS of 1 day was assigned.

Hospital Cost Analysis
The inpatient hospital cost for each episode of care was assigned based on the Australian Refined Diagnosis Related Group (AR-DRG) code recorded in the Hospital Morbidity Data System record. Costs were assigned to each episode using the AR-DRG–specific mean national public hospital costs reported in the National Hospital Cost Data Collection Round pertaining to the year in which the episode of care occurred (ranging from 1993-1994 AR-DRG version 3.1 to 2008-2009 AR-DRG version 5.1). The AR-DRG costs capture the mean direct and overhead costs associated with each episode of care, including medical, nursing and allied health staff, pharmaceuticals, operating and diagnostics procedures, critical care, supplies, capital, and depreciation. All amounts were adjusted to 2009-2010 Australian dollars using the Australian Institute of Health and Welfare government final consumption expenditure in hospital and nursing homes price index. Australian dollars were converted to US dollars using the mean quarterly interbank 1994 to 2009 exchange rate of 0.7011.

While all infants born in hospital in Australia are admitted patients, only “qualified” newborns are eligible for funding under the Australian Health Care Agreements. An uncomplicated or well newborn is not directly funded, but a small cost is included in the mother’s admission. A child is classified as a qualified newborn if he or she is in the hospital for more than 9 days after birth, receives any sort of special care, remains in the hospital without the mother, or is the second or subsequent live-born infant of a multiple birth. Therefore, to be in line with national health care resourcing arrangements and to more accurately quantify the relative difference in resource consumption between singletons and multiple births, only qualified newborn admissions were costed in this study. This approach is also in line with most hospital discharge classification systems that classify newborns as sick or well (uncomplicated). Statistical Analysis
All analyses were performed using statistical software (STATA 11; StataCorp LP). t Tests were used to test for differences in the means of continuous data, and the χ2 statistic was used to test for differences in proportions for categorical data. Logistic regression analysis and generalized estimating equations were used to derive odds ratios (95% CIs) to compare the relative odds of perinatal outcomes and readmission to hospital in twin and HOM children compared with singleton children.

Multivariable regression analysis was used to measure the effect of a range of covariates known to influence hospital costs (cost drivers) on the costs of the birth admission and on the remaining hospital costs to age 1 year (all children combined). Robust standard errors were used to account for possible violations of the error term that are common in health data (Huber-White sandwich estimators). Covariates considered in the regression analysis included maternal age, parity, year of birth, sex, mode of delivery, gestational age, birth weight, hospital funding source, and socioeconomic status (SES) of the mother at the time of birth of the child. The SES was based on Socio-economic Indexes for Areas codes, which are small area (statistical local areas) geographical-based scores of social disadvantage.

Results
Population Characteristics
In total, 226,624 singleton, 6941 twin, and 285 HOM infants were born in Western Australia between October 1993 and September 2003 and followed up to September 2008. Of these, 1.0% of singleton, 15.4% of twin, and 34.7% of HOM children were conceived following ART treatments (Table 1). Twins and triplets were more likely to be born to older, nulliparous women and to be born by cesarean section. Mothers who gave birth to twins or HOMs had an SES distribution similar to that of mothers who gave birth to singletons but were more likely to have hospital insurance and to be privately funded hospital patients.

Compared with singletons, the odds of being born preterm (<37 weeks’ gestation) was 18.7 times higher for twins and 525.1 times higher for HOMs, while the odds of being small for gestational age was 3.6 times higher for twins and 2.8 times higher for HOMs. Compared with singletons, twins and HOMs were 3.4 and 9.6 times, respectively, more likely to be stillborn and were 6.4 and 36.7 times, respectively, more likely to die during the neonatal period.

Health Service Use
The mean LOS of the hospital birth admission (including all hospital transfers) was 5 days for singletons, 14 days for twins, and 34 days for HOMs. Twins were 66% more likely and HOMs were 243% more likely to be readmitted to hospital during their first year and were 13% and 62%, respectively, more likely than singletons to be admitted during their second year of life. Differences in the mean LOS between singletons and multiple-birth infants were less than 1 day during years 1 and 2. Fewer differences in the odds of readmission and LOS were observed in subsequent years (Table 2).

The longer LOS during the birth admission and the higher rates of readmission for twins and HOMs were clearly reflected in the associated economic costs. The mean hospital costs of a singleton, twin, and HOM child to age 5 years were $2730, $8993, and $24,411, respectively. In addition to the significant differences between pluralities, differences were also
<table>
<thead>
<tr>
<th>Variable</th>
<th>Singletons (n = 226,624)</th>
<th>Twins (n = 6,941)</th>
<th>Twins vs Singletons, OR (95% CI)a</th>
<th>HOMs (n = 285)</th>
<th>HOMs vs Singletons, OR (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth status</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stillbirth, No. per 1000 births</td>
<td>1401 (6.2)</td>
<td>142 (20.5)</td>
<td>3.36 (2.70-4.16)</td>
<td>16 (56.1)</td>
<td>9.56 (4.23-21.61)</td>
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<td>Live birth, No.</td>
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<td>6799</td>
<td>1 [Reference]</td>
<td>269</td>
<td>1 [Reference]</td>
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<td>Mode of conception, No. (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ART</td>
<td>2199 (1.0)</td>
<td>1068 (15.4)</td>
<td>18.55 (17.17-20.05)</td>
<td>99 (34.7)</td>
<td>54.32 (42.41-69.57)</td>
</tr>
<tr>
<td>Non-ART</td>
<td>224,425 (99.0)</td>
<td>5873 (84.6)</td>
<td>1 [Reference]</td>
<td>186 (65.3)</td>
<td>1 [Reference]</td>
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<td>Death of live-born infants, No. per 1000 alive children</td>
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<td></td>
<td></td>
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<td></td>
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<td>0 to 27 d</td>
<td>481 (2.1)</td>
<td>89 (13.1)</td>
<td>6.43 (4.93-8.36)</td>
<td>19 (70.6)</td>
<td>36.73 (17.93-75.24)</td>
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<tr>
<td>28 d to 5 y</td>
<td>516 (2.3)</td>
<td>29 (4.3)</td>
<td>1.88 (1.29-2.74)</td>
<td>3 (11.2)</td>
<td>5.2 (1.19-22.78)</td>
</tr>
<tr>
<td>Mode of delivery, No. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cesarean</td>
<td>54,478 (24.2)</td>
<td>3743 (55.1)</td>
<td>3.82 (3.56-4.08)</td>
<td>245 (91.1)</td>
<td>28.92 (14.94-55.95)</td>
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<td>Vaginal</td>
<td>170,745 (75.8)</td>
<td>3056 (44.9)</td>
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<td>24 (8.9)</td>
<td>1 [Reference]</td>
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<td>Socioeconomic status of mother at delivery, No. (%)</td>
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<td></td>
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<tr>
<td>0% to &lt;20%, Low social disadvantage quintile</td>
<td>47,001 (20.9)</td>
<td>1310 (19.3)</td>
<td>0.98 (0.95-1.00)</td>
<td>58 (21.6)</td>
<td>1.07 (0.90-1.26)</td>
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<tr>
<td>20% to &lt;40%</td>
<td>48,094 (21.4)</td>
<td>1441 (21.2)</td>
<td>0.99 (0.89-1.10)</td>
<td>47 (17.5)</td>
<td>0.99 (0.65-1.49)</td>
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<td>40% to &lt;60%</td>
<td>45,596 (20.2)</td>
<td>1379 (20.3)</td>
<td>1.10 (1.03-1.18)</td>
<td>160 (59.5)</td>
<td>1.20 (1.08-1.32)</td>
</tr>
<tr>
<td>60% to &lt;80%</td>
<td>35,806 (15.9)</td>
<td>1021 (15.0)</td>
<td>0.99 (0.96-1.01)</td>
<td>44 (16.4)</td>
<td>1.27 (0.62-2.60)</td>
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<td>80% to 100%, High social disadvantage quintile</td>
<td>39,031 (17.3)</td>
<td>1348 (19.8)</td>
<td>1.14 (1.03-1.27)</td>
<td>51 (19.0)</td>
<td>1.07 (0.90-1.27)</td>
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<td>Missing</td>
<td>9695 (4.3)</td>
<td>300 (4.4)</td>
<td>NA</td>
<td>24 (8.9)</td>
<td>NA</td>
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<td>Funding source of delivery admission, No. (%)</td>
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<td>Public</td>
<td>198,898 (88.3)</td>
<td>4437 (65.3)</td>
<td>0.24 (0.22-0.25)</td>
<td>123 (45.7)</td>
<td>0.11 (0.07-0.16)</td>
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<td>Private</td>
<td>24,361 (10.8)</td>
<td>2779 (39.5)</td>
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<td>144 (53.5)</td>
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<td>Missing</td>
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<td>83 (1.2)</td>
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<td>2 (0.7)</td>
<td>NA</td>
</tr>
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<td>Health insurance status of mother at delivery admission, No. (%)a</td>
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<td>(n = 117,365)</td>
<td>(n = 3705)</td>
<td>(n = 120)</td>
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<tr>
<td>Yes</td>
<td>35,526 (30.3)</td>
<td>1493 (40.3)</td>
<td>1.58 (1.43-1.73)</td>
<td>59 (49.2)</td>
<td>1.20 (1.03-1.40)</td>
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<td>No</td>
<td>77,589 (66.1)</td>
<td>2064 (55.7)</td>
<td>1 [Reference]</td>
<td>58 (48.3)</td>
<td>1 [Reference]</td>
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<td>148 (4.0)</td>
<td>NA</td>
<td>3 (2.3)</td>
<td>NA</td>
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<td>Sex, No. (%)</td>
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<td></td>
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<tr>
<td>Male</td>
<td>115,549 (51.3)</td>
<td>3385 (49.8)</td>
<td>0.94 (0.89-0.99)</td>
<td>136 (50.6)</td>
<td>0.97 (0.76-1.23)</td>
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<td>Female</td>
<td>109,674 (48.7)</td>
<td>3414 (50.2)</td>
<td>1 [Reference]</td>
<td>133 (49.4)</td>
<td>1 [Reference]</td>
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<tr>
<td>Gestational age, No. (%)c</td>
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<td>(n = 225,222)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;32 wk</td>
<td>1655 (0.7)</td>
<td>615 (9.0)</td>
<td>13.95 (12.33-15.78)</td>
<td>102 (37.9)</td>
<td>84.41 (55.24-128.98)</td>
</tr>
<tr>
<td>≥32 wk</td>
<td>223,567 (99.3)</td>
<td>6184 (91.0)</td>
<td>1 [Reference]</td>
<td>167 (62.1)</td>
<td>1 [Reference]</td>
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<tr>
<td>32 to 36 wk</td>
<td>10,372 (4.5)</td>
<td>2856 (42.0)</td>
<td>NA</td>
<td>159 (59.1)</td>
<td>NA</td>
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<tr>
<td>&lt;37 wk</td>
<td>12,027 (5.3)</td>
<td>3471 (51.1)</td>
<td>18.67 (17.42-20.00)</td>
<td>261 (97.0)</td>
<td>525.07 (177.85-1550.18)</td>
</tr>
<tr>
<td>≥37 wk</td>
<td>213,195 (94.7)</td>
<td>3328 (48.9)</td>
<td>1 [Reference]</td>
<td>8 (3.0)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Birth weight, No. (%)d</td>
<td></td>
<td>(n = 225,216)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;1500 g</td>
<td>1502 (0.7)</td>
<td>546 (8.0)</td>
<td>13.36 (11.81-15.10)</td>
<td>102 (37.9)</td>
<td>92.48 (63.20-135.32)</td>
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<tr>
<td>≥1500 g</td>
<td>223,714 (99.3)</td>
<td>6253 (92.0)</td>
<td>1 [Reference]</td>
<td>167 (62.1)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>&lt;2500 g</td>
<td>9709 (4.3)</td>
<td>3393 (49.9)</td>
<td>22.22 (20.89-23.63)</td>
<td>253 (94.1)</td>
<td>346.68 (172.50-696.73)</td>
</tr>
<tr>
<td>≥2500 g</td>
<td>215,507 (95.7)</td>
<td>3406 (50.1)</td>
<td>1 [Reference]</td>
<td>16 (5.9)</td>
<td>1 [Reference]</td>
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<tr>
<td>Small for gestational age, No. (%)e</td>
<td></td>
<td>(n = 225,222)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>19,688 (8.7)</td>
<td>1735 (25.5)</td>
<td>1.58 (1.35-1.80)</td>
<td>57 (21.2)</td>
<td>2.80 (1.93-4.07)</td>
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<tr>
<td>No</td>
<td>205,534 (91.3)</td>
<td>5064 (74.5)</td>
<td>1 [Reference]</td>
<td>212 (78.8)</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

Abbreviations: ART, assisted reproductive technology; HOMs, higher-order multiples; NA, not applicable; OR, odds ratio.

a Odds ratios were calculated using logistic regression analysis with generalized estimating equations.

b Health insurance status of mother was available for births from July 1998 onward.

c One singleton had missing gestational age data.

dSeven singletons had missing birth weight.

eSmall for gestational age was based on the lowest 10% of the Australian population.
Table 2. Inpatient Hospital Use to Age 5 Years, Western Australia October 1993 to September 2003a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Singletons</th>
<th>Twins</th>
<th>HOMs</th>
<th>Singletons</th>
<th>Twins</th>
<th>HOMs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alive Child</td>
<td>Readmitted, No. (%)</td>
<td>LOS, Mean (SD), d</td>
<td>Readmitted, No. (%)</td>
<td>LOS, Mean (SD), d</td>
<td>Readmitted, No. (%)</td>
</tr>
<tr>
<td>Birth admission</td>
<td>222 752</td>
<td>NA</td>
<td>4.9 (6.7)</td>
<td>6682</td>
<td>NA</td>
<td>14.3 (17.5)</td>
</tr>
<tr>
<td>Birth admission</td>
<td>222 310</td>
<td>44.839 (20.2)</td>
<td>2.6 (4.0)</td>
<td>6593</td>
<td>1949 (29.6)</td>
<td>1.7 (1.6-1.8)</td>
</tr>
<tr>
<td>to 1 y</td>
<td>222 009</td>
<td>34.678 (15.6)</td>
<td>1.9 (2.5)</td>
<td>6574</td>
<td>1138 (17.3)</td>
<td>1.1 (1.1-1.2)</td>
</tr>
<tr>
<td>Second year</td>
<td>221 904</td>
<td>26.310 (11.9)</td>
<td>1.7 (2.7)</td>
<td>6572</td>
<td>871 (13.3)</td>
<td>1.1 (1.1-1.2)</td>
</tr>
<tr>
<td>Third year</td>
<td>221 847</td>
<td>24.006 (10.8)</td>
<td>1.6 (1.8)</td>
<td>6568</td>
<td>761 (11.6)</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Fourth year</td>
<td>221 816</td>
<td>22.752 (10.3)</td>
<td>1.5 (1.6)</td>
<td>6568</td>
<td>712 (10.8)</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Fifth year</td>
<td>221 752</td>
<td>101.606 (45.6)</td>
<td>3.4 (3.1)</td>
<td>6682</td>
<td>3437 (51.4)</td>
<td>1.3 (1.2-1.4)</td>
</tr>
<tr>
<td>0 to 5 y</td>
<td>222 752</td>
<td>2730</td>
<td>6682</td>
<td>8993</td>
<td>6263</td>
<td>0.02 .54</td>
</tr>
</tbody>
</table>

Abbreviations: HOMs, higher-order multiples; LOS, length of stay; NA, not applicable; OR, odds ratio.

a Alive Children are the number at the beginning of the period. The values in the Difference columns are not true differences because of rounding.
b Three HOM children had LOS for a single admission exceeding 330 days.

Table 3. Inpatient Hospital Costs to Age 5 Years by Plurality, Western Australia October 1993 to September 2003a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Singletons</th>
<th>Twins</th>
<th>HOMs</th>
<th>Singletons</th>
<th>Twins</th>
<th>HOMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth admission</td>
<td>222 752</td>
<td>1026</td>
<td>6682</td>
<td>6721</td>
<td>5695</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Birth admission</td>
<td>222 310</td>
<td>602</td>
<td>6593</td>
<td>1050</td>
<td>448</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>to 1 y</td>
<td>222 009</td>
<td>367</td>
<td>6574</td>
<td>434</td>
<td>67</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Second year</td>
<td>221 904</td>
<td>265</td>
<td>6572</td>
<td>305</td>
<td>40</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Third year</td>
<td>221 847</td>
<td>237</td>
<td>6568</td>
<td>264</td>
<td>27</td>
<td>.14</td>
</tr>
<tr>
<td>Fourth year</td>
<td>221 816</td>
<td>236</td>
<td>6568</td>
<td>252</td>
<td>16</td>
<td>.43</td>
</tr>
<tr>
<td>Fifth year</td>
<td>221 752</td>
<td>2730</td>
<td>6682</td>
<td>8993</td>
<td>6263</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: HOMs, higher-order multiples.
a Alive Children are the number at the beginning of the period. P values are by t test for difference.
b Three HOM children incurred significantly higher inpatient costs in their fourth year.

observed in the distribution of cost, with 37.6% of costs incurred during the birth admission for singletons compared with 74.7% for twins and 86.1% for HOMs, indicating that beyond the perinatal period smaller cost differences occur between pluralities (Table 3).

Predictors of Hospital Costs

Table 4 summarizes the ordinary least squares regression analysis predicting the hospital costs for admissions during the first year of life. This model narrows the explanatory variables to only infant characteristics at birth because maternal age, parity, mode of delivery, and hospital funding source of the delivery are less likely to influence longer-term outcomes. This model shows that preterm infants continue to incur additional costs to age 1 year of $408 (preterm) and $878 (very preterm), as do infants born with low birth weight of $506 (low birth weight) and $1286 (very low birth weight). Also, a consistent trend was observed for hospital expenditure in children from lower SES groups and for male sex.

Copyright 2014 American Medical Association. All rights reserved.
This study found that the increased risks of preterm birth and low birth weight are reflected in the substantially higher inpatient hospital use and costs during the first year of life, but we observed that hospital use and cost tend to be similar to those of singletons in later years. The costs of a twin child and an HOM child were almost 5 times and 13 times, respectively, higher than those of a singleton up to age 1 year, with the excess cost concentrated during the initial birth admission. These findings are similar to those of an economic study of multiple-birth children undertaken from the United Kingdom National Health Service perspective and to the results of other studies restricted to the perinatal period. While several ART registries exist internationally, this is the first cost analysis comparing the total population costs of singletons and multiple births during childhood.

Given that care for preterm births beyond the neonatal period is more likely to be provided in an outpatient setting or by family members, these costs are an underestimate of the true economic burden associated with multiple births. A review by the US Institute of Medicine conservatively estimated that the annual cost of prematurity in the United States, of which being a multiple-birth infant is a significant risk, is more than $26 billion (in 2005 US dollars) and that the excess cost of a preterm birth infant is $51,500.

While it is unlikely that eliminating all ART multiple births is possible, we theoretically estimate that almost 15% of the inpatient care costs for multiple births could have been avoided if the 15.4% of twins and 34.7% of HOMs resulting from ART fertility treatment in our study had been born as ART singletons. Given that ART multiple births constitute a similar proportion of all multiple births in the US population, similar savings would be expected by reducing the ART multiple-birth rate in the United States. Further savings would be achieved by reducing multiple-birth rates that result from non-ART fertility treatments.

During the past decade, the number of embryos transferred during ART treatment has declined worldwide because the risks associated with iatrogenic multiple births have

### Table 4. Clinical and Demographic Factors Predicting Inpatient Costs of the Birth Admission (Including Hospital Transfers), Western Australia October 1993 to September 2003, Among 219,877 Infants ($R^2 = 0.58$)*

<table>
<thead>
<tr>
<th>Categorical Group</th>
<th>Coefficient, US $</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 (Base)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>25 to &lt;35</td>
<td>-26</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>35 to &lt;40</td>
<td>-25</td>
<td>.39</td>
</tr>
<tr>
<td>≥40</td>
<td>77</td>
<td>.38</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous (base)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Parous</td>
<td>6</td>
<td>.72</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal (base)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Elective cesarean</td>
<td>118</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Emergency cesarean</td>
<td>505</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (base)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Female</td>
<td>-117</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥37 (Base)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>32 to 36</td>
<td>1438</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;32</td>
<td>12,438</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2500 (Base)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1500 to 2499</td>
<td>3091</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;1500</td>
<td>30,251</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Socioeconomic status of mother at delivery, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;20 (Base, high social disadvantage quintile)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>20 to &lt;40</td>
<td>33</td>
<td>.17</td>
</tr>
<tr>
<td>40 to &lt;60</td>
<td>46</td>
<td>.06</td>
</tr>
<tr>
<td>60 to &lt;80</td>
<td>16</td>
<td>.53</td>
</tr>
<tr>
<td>80 to 100 (Low social disadvantage quintile)</td>
<td>-53</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Funding source of delivery admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public (base)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Private</td>
<td>844</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

* The analysis excludes stillborn infants, infants not born in the hospital, and infants with a missing birth admission discharge code. Hospital costs are for qualified infants only. For costs, the denominator is the number of children alive at the start of the period. Dummy variables for each year of birth were included to account for cohort effects.

### Table 5. Clinical and Demographic Factors Predicting Inpatient Costs of Readmission to Age 1 Year, Western Australia October 1993 to September 2003, Among 219,106 Infants ($R^2 = 0.02$)*

<table>
<thead>
<tr>
<th>Categorical Group</th>
<th>Coefficient, US $</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (base)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Female</td>
<td>-242</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥37 (Base)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>32 to 36</td>
<td>408</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;32</td>
<td>878</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2500 (Base)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1500 to 2499</td>
<td>506</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;1500</td>
<td>1286</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Socioeconomic status of mother at delivery, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;20 (Base, high social disadvantage quintile)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>20 to &lt;40</td>
<td>-34</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>40 to &lt;60</td>
<td>-37</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>60 to &lt;80</td>
<td>-118</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>80 to 100 (Low social disadvantage quintile)</td>
<td>-125</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

* The analysis excludes stillborn infants, infants not born in the hospital, and infants with a missing birth admission discharge code. Hospital costs are for qualified infants only. For costs, the denominator is the number of children alive at the start of the period. Dummy variables for each year of birth were included to account for cohort effects.

### Discussion

This study found that the increased risks of preterm birth and low birth weight are reflected in the substantially higher inpatient hospital use and costs during the first year of life, but we observed that hospital use and cost tend to be similar to those of singletons in later years. The costs of a twin child and an HOM child were almost 5 times and 13 times, respectively, higher than those of a singleton up to age 1 year, with the excess cost concentrated during the initial birth admission. These findings are similar to those of an economic study of multiple-birth children undertaken from the United Kingdom National Health Service perspective and to the results of other studies restricted to the perinatal period. While several ART registries exist internationally, this is the first cost analysis to date comparing the total population costs of singletons and multiple births during childhood.

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During the past decade, the number of embryos transferred during ART treatment has declined worldwide because the risks associated with iatrogenic multiple births have
become widely condemned, and success rates from strategies have been shown to be equivalent to those of multiple-embryo transfer strategies when additional treatment cycles are counted.33,34 However, a proportion of physicians and patients view twin births following double-embryo transfer as a desirable outcome of fertility treatment. This perspective is based on reduced per-cycle pregnancy rates with single-embryo transfer, shorter times to achieving the birth of 2 children, and potentially lower overall ART treatment costs.35-36

Striking international differences exist in the use of ART treatment and embryo transfer practices, reflecting differences in funding, regulatory environments, and sociocultural norms.37 While the United States is the largest user of ART in terms of ART cycles undertaken annually, its ART utilization rates and single-embryo transfer rates (15% of fresh embryo transfer cycles) are some of the lowest in the world.38 In contrast, the Nordic countries combined perform 2½ times more ART cycles per women of reproductive age than the United States and perform single-embryo transfer in 57% of fresh embryo treatment cycles.10,39 One obvious difference between these fertility markets is that most European health care systems provide some level of public funding for ART, while the United States has no public funding, and insurance mandates to cover ART treatments exist in only 5 states. In states without insurance mandates to cover ART treatment, a single ART cycle is estimated to cost $13,000, representing 51% of the mean annual disposable income, equating to the most expensive ART treatment in the world.40 This situation prevents many couples in the United States from receiving treatment and creates a financial incentive to transfer multiple embryos to maximize the chance of pregnancy.36,41-44 Several national reproductive medicine societies have clinical practice guidelines and education campaigns emphasizing the important role of single-embryo transfer. Moreover, several jurisdictions such as Belgium, Turkey, and Quebec will only fund ART if such guidelines are followed, which has led to a significant reduction in multiple-birth rates in these jurisdictions.45-47 However, Australia, Finland, and Japan have also been able to achieve multiple-birth rates of less than 10% through supportive public funding and patient and physician education.48,49

Prevention of multiple births resulting from non-ART fertility treatments that use ovarian stimulation is more difficult because of unpredictable follicular maturation and less control over how many embryos implant.50,51 The limited data available on non-ART fertility treatments suggest that they have an equally important role and may pose an even higher risk of HOMs than ART treatment and deserve equal attention from researchers, policy makers, and physicians to reduce intragenic multiple births.7,14,50

A limitation of this study is that the hospital utilization and the absolute monetary value of hospital care are likely to be different in other countries and settings because of differences in models of care, input costs of goods and services, and pricing frameworks. However, relative health outcomes are similar for singletons, twins, and HOMs among industrialized countries, making the relative differences in costs between singletons and multiple births more important than the absolute costs and suggest broad generalizability of this study’s findings. A future limitation is that no information was available on the underlying types of infertility or the length of infertility for this study. Increasing evidence indicates that underlying infertility is associated with increased perinatal risks and probably hospitalization and that ART treatment seems to further increase these risks.52,53 However, the risks associated with being born as a multiple-birth infant seem to be magnitudes higher than those associated with ART treatment per se.

Conclusions

In conclusion, the greater morbidity and mortality associated with multiple births are reflected in the substantially higher inpatient hospital costs during the neonatal period and during the first year of life. While inpatient hospital costs in later years tended to be similar to those of singletons, it is clear from other studies44,54-55 that the risk of long-term adverse health outcomes and excess societal costs is ongoing. Given the increasing use of ART worldwide and the growing body of evidence38,42 indicating that subsidized fertility treatment (either through public or private insurance) encourages safe embryo transfer practices, economic studies such as this should be used to inform funding policies and clinical practice. The application of this knowledge alongside clinical and patient education programs is important to ensure clinically responsible fertility treatments that result in the best possible outcomes for fertility patients and their children.

ARTICLE INFORMATION

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Author Contributions: Dr Chambers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Chambers, Hoang, Lee, Sullivan, Chapman. Acquisition, analysis, or interpretation of data: Chambers, Hoang. Drafting of the manuscript: Chambers. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Chambers, Hoang, Lee, Hansen.

Administrative, technical, or material support: Chambers, Sullivan. Study supervision: Chambers, Sullivan, Bower, Chapman.

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