Babies born after ART treatment cost more than non-ART babies: a cost analysis of inpatient birth-admission costs of singleton and multiple gestation pregnancies

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BACKGROUND: Currently, about one-third of infants born after assisted reproductive technology (ART) worldwide are twins or triplets. This study compared the inpatient birth-admission costs of singleton and multiple gestation ART deliveries to non-ART deliveries. METHODS: A cohort of 5005 mothers and 5886 infants conceived following ART treatment were compared to 245 249 mothers and 248 539 infants in the general population. Birth-admission costs were calculated using Australian Refined Diagnosis Related Groups and weighted national average costs (2003–2004 euro). RESULTS: ART infants were 4.4 times more likely to be low birthweight (LBW) compared with non-ART infants, translating into 89% higher birth-admission costs (€2832 and €1502, respectively). ART singletons were also more likely to be LBW compared with non-ART singletons, translating into 31% higher birth-admission costs (€1849 and €1215, respectively). After combining infant and maternal admission costs, the average cost of an ART singleton delivery was €4818 compared with €13 890 for ART twins and €54 294 for ART higher order multiples. Findings were not sensitive to changes in casemix. CONCLUSIONS: The poorer neonatal outcomes of ART singletons compared with non-ART singletons are significant enough to impact healthcare resource consumption. The high costs associated with ART multiple births add to the overwhelming clinical and economic evidence in support of single embryo transfer.

Keywords: assisted reproduction technology; cost analysis; multiple pregnancy; single embryo transfer

Introduction

Despite the trend over the last decade to transfer fewer, and increasingly only one, embryo during assisted reproductive technology (ART) procedures, the latest published figures indicate that, multiple births still account for 32%, 23% and 17% of all deliveries after such procedures in the US, Europe and Australia, respectively (CDC, 2006; Wang et al., 2006; ESHRE, 2007). Although the obstetric and infant risks associated with multiple births are undisputed (Elster, 2000; ESHRE Capri Workshop Group, 2000; ESHRE, 2003), the impact on healthcare resources is less understood. However, it has been estimated that the cost of care of ART multiples exceeds the cost of ART treatment itself (Collins and Graves, 2000; Collins, 2002).

In addition to the risks associated with ART multiple births, recent studies have shown that ART singleton pregnancies also have an increased risk of poorer perinatal outcomes compared with naturally conceived singleton pregnancies (Dhont et al., 1999; Koudstaal et al., 2000; Helmerhorst et al., 2004; Jackson et al., 2004; Schieve et al., 2004a,b; Wennerholm and Bergh, 2004). Whether this phenomenon is due to differences in confounding characteristics between couples seeking fertility treatment and those who spontaneously conceive, or to fertility treatment per se has not been fully elucidated (Draper et al., 1999; Basso and Baird, 2003; Gaudoin et al., 2003; Schieve et al., 2004a,b; Wang et al., 2005; Kapiteijn et al., 2006). These increased risks are also reported in infants after non-ART fertility treatment, such as ovulation induction or controlled ovarian stimulation with or without assisted insemination (Wang et al., 2002; Kapiteijn et al., 2006; Ombelet et al., 2006). Furthermore, there is also a growing body of evidence which suggests that the spontaneous
Methods and Materials
Costing model
This study utilized three national data collections to construct a costing model for ART and non-ART infant and maternal inpatient hospital birth-admissions. Infant and maternal birth-admissions were sourced from the National Hospital Morbidity Database (NHMD), which is a collection of summary records for admitted patients separated in public and private hospitals in Australia. Of women who gave birth in Australia in 2003, 99.3% were as admitted hospital patients (Laws and Sullivan, 2005). The ART study population was sourced from the Australian and New Zealand Assisted Reproductive Database (ANZARD), which records information about all ART treatment cycles conducted in Australia and New Zealand and the resulting pregnancies and birth outcomes. The reference non-ART population was sourced from the Australian National Perinatal Data Collection (NPDC), which is a cross-sectional database of all births in Australia, and includes maternal demographic factors, delivery characteristics and perinatal outcomes.

Infant and maternal records in each of the three data collections were stratified into 72 clinically and economically important cost categories. Infant admissions were stratified into 42 cost categories based on plurality (singleton, twin and HOM), sex and birthweight, or admission weight in the case of the NMHD (<750, 750–999, 1000–1249, 1250–1499, 1500–1999, 2000–2499 and >2499 g). Fetal deaths were excluded from the study because they are not recorded in the NHMD. Maternal admissions were stratified into 30 cost categories based on plurality (singleton, twin and HOM), maternal age at delivery (<25, 25–29, 30–34, 35–39 and ≥40) and mode of delivery (Caesarean deliveries and non-Caesarean deliveries).

The average national birth-admission cost for each NHMD cost category were compared to the non-ART reference group based on plurality. ART singleton infant and maternal birth-admission costs were then calculated and compared.

Sensitivity analysis
Sensitivity analysis, used to explore uncertainty around assumptions, was performed because of the right-skewed nature of the patient-level costs for ART pregnancies (infant and maternal admissions), and to compare these to a reference group of non-ART pregnancies. The ART population was defined as births resulting from in vitro fertilization techniques, and the non-ART population as all other births in the general population. We constructed an economic model utilizing clinical and administrative national data collections to compare the resource consumption of (i) ART singletons, twins and higher order multiples (HOMs) with their non-ART counterparts and (ii) ART singleton pregnancies with ART twin and ART HOM pregnancies.
admission cost data, and the assumption that the distribution of AR-DRGs within a given stratification was similar for ART and non-ART admissions. The number of admissions for the highest cost AR-DRG within each of the 42 infant and 30 maternal cost categories were collectively increased and decreased while retaining the relative proportions for the remaining admissions.

**Ethics approval**
This study was approved by the Human Research Ethics Advisory Panel I, University of New South Wales.

**Results**

**ART deliveries compared to non-ART deliveries**

**Infant characteristics and birth-admission costs**

Of ART infants, 31% resulted from multiple gestation pregnancies compared with 2.6% of non-ART infants. As a result, ART infants were 4.4 times more likely to be low birthweight (LBW) and five times more likely to be very low birthweight (VLBW) compared to non-ART infants (<2500 g, OR 4.38, CI 4.10–4.67; <1500 g, OR 5.03, CI 4.43–5.71). This translated into 89% higher infant birth-admission costs for ART infants compared to non-ART infants (£2832 and £1502, respectively).

ART singletons were also more likely to be LBW or VLBW compared with non-ART singleton infants (<2500 g, OR 1.78, CI 1.59–2.00; <1500 g, OR 2.78, CI 2.22–3.48), translating into 31% higher birth-admission costs for ART compared to non-ART singleton infants (£1849 and £1415, respectively). This difference was reduced to 25% after adjusting for maternal age (£1767 and £1415, respectively). In contrast, there was only a small (not statistically significant) increase in the incidence of LBW and VLBW twins infants in the ART cohort compared with the non-ART cohort, and therefore only a 3% higher birth-admission cost for ART twins infants (£4602 and £4477, respectively). There was a higher incidence of VLBW infants in the ART HOM cohort compared with the non-ART HOM cohort (<1500 g, OR 1.92, CI 1.07–3.47), resulting in a 26% higher infant birth-admission cost (£16429 and £13036, respectively), but this difference was almost eliminated after adjusting for maternal age. The sex distribution of the infants was similar between ART and non-ART cohorts for all pluralities (Table I).

**Maternal characteristics and birth-admission costs**

ART mothers were significantly older than non-ART mothers, with 52% of ART mothers being aged less than 35 years compared with 82% of non-ART mothers (OR 0.24, CI 0.23–0.25). After adjusting for maternal age, ART singletons and twins were more likely to be born by Caesarean section compared to their non-ART counterparts (Singletons: AOR 1.60, CI 1.58–1.61; Twins: AOR 1.56, CI 1.40–1.73). The maternal birth-admission costs for ART singletons, twins and HOMs were 11%, 6% and 8% more costly than their non-ART counterparts, respectively. The relatively small difference between the maternal admission costs for ART and non-ART deliveries, despite a significant difference in Caesarean rates, is because there is less variation and range in the costs relating to mode of delivery compared to infant admission weight AR-DRGs. However, because multiple births are more likely to be delivered by Caesarean section, there was an overall 23% higher birth-admission cost for ART mothers compared with non-ART mothers (£3321 and £2708, respectively) (Table II).

**Birth episode admission costs (infant plus maternal admissions)**

After combining infant and maternal birth-admissions, the average cost of an ART singleton birth episode was 18% higher than for a non-ART singleton birth episode (£4818 and £4098, respectively). After adjusting for maternal age, this difference was reduced to 13% (£4624 and £4098, respectively). The overall cost of all ART birth episodes, regardless of

| Table I. Infant characteristics and average inpatient birth-admission costs by plurality; ART versus non-ART live born deliveries, Australia 2003 (2003–2004 euro). |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Singletons      | Twins           | HOMs            | All pluralities |
|                | ART             | Non-ART         | ART             | Non-ART         | ART             | Non-ART         | ART             | Non-ART         |
| Live born infants (n) |                  |                  |                  |                  |                  |                  |                  |                  |
| Gender          |                  |                  |                  |                  |                  |                  |                  |                  |
| Males (%)       |                  |                  |                  |                  |                  |                  |                  |                  |
| OR (95% CI)     |                  |                  |                  |                  |                  |                  |                  |                  |
| Birthweight <2500 g |                  |                  |                  |                  |                  |                  |                  |                  |
| Crude (%)       |                  |                  |                  |                  |                  |                  |                  |                  |
| OR (95% CI)     |                  |                  |                  |                  |                  |                  |                  |                  |
| Maternal age-adjusted (%) |      |                  |                  |                  |                  |                  |                  |                  |
| AOR (95% CI)    |                  |                  |                  |                  |                  |                  |                  |                  |
| Birthweight <1500 g |                  |                  |                  |                  |                  |                  |                  |                  |
| Crude (%)       |                  |                  |                  |                  |                  |                  |                  |                  |
| OR (95% CI)     |                  |                  |                  |                  |                  |                  |                  |                  |
| Maternal age-adjusted (%) |              |                  |                  |                  |                  |                  |                  |                  |
| AOR (95% CI)    |                  |                  |                  |                  |                  |                  |                  |                  |
| Mean birth-admission cost |            |                  |                  |                  |                  |                  |                  |                  |
| Crude (£)       |                  |                  |                  |                  |                  |                  |                  |                  |
| Maternal age-adjusted (£) |       |                  |                  |                  |                  |                  |                  |                  |
|                  | 1849            | 1415            | 4602            | 4477            | 16429           | 13036           | 2832            | 1502            |
plurality, was 57% higher than for non-ART birth episodes (€6652 and €4230, respectively) (Table III).

**ART singleton deliveries versus ART multiple gestation deliveries**

The combined infant and maternal birth-admission costs of ART twin (€13 890) and HOM (€54 294) birth episodes were almost 3 and 11 times higher than for ART singleton birth episodes (€4818). This difference did not alter significantly after adjusting for maternal age (Table III).

The total admission costs for all ART birth episodes was €33.3 million compared with €1037.3 million for all non-ART birth episodes. About €19.7 million were consumed by ART singleton births, €12.5 million by ART twin births and €1.1 million by ART HOMs. An estimated €9.2 million could be saved in birth-admission costs alone if all ART multiples had been singleton births. The 3294 multiple gestation non-ART deliveries consumed 3.4 times more inpatient resources than the 918 multiple gestation ART deliveries (€45.8 and €13.6 million, respectively).

**Transferred infant birth-admissions**

By definition, transferred admissions incur additional inpatient costs at the second and subsequent facility. An analysis of the cost of birth-admissions that were transferred to another facility indicates that such admissions have significantly higher birth-admission costs. For example, transferred twins had an average cost of €8917 compared with €4571 for all twins (Table IV). Furthermore, HOMs and twins infants are more likely to be transferred than singletons infants (singletons: 4.6%, twins: 18% and HOMs: 48.3%). Given that 31% of ART infants were from multiple gestation pregnancies, it is fair to conclude that our costs are an underestimate of the true cost of the birth-admission episode in particular for multiple births.

**Sensitivity analysis**

Given the indirect way in which ART infant and maternal admissions were identified within the NHMD, the key assumption of this study was that the distribution of AR-DRGs within the 72 cost categories were similar for ART and non-ART birth-admissions. Sensitivity analysis demonstrated that the change in the distribution of AR-DRGs caused by altering the number of admissions in the highest cost AR-DRGs within the cost categories did not largely affect the cost differential between the ART and non-ART birth-admissions. For example, as illustrated in Fig. 1, a 10% change in the volume of admissions assigned the highest cost AR-DRG within each cost category resulted in a ±1.1% change in the difference in costs between ART and non-ART singletons (Figs 1–3).

**Discussion**

The main finding from this study was that ART infant birth-admissions were 89% more costly than non-ART infant birth-admissions. ART twins and HOMs were 3 and 11 times more costly than ART singletons and were therefore a substantial contribution to these costs; however, ART singleton birth-admissions were also 31% more costly than non-ART singletons. These substantial differences in average inpatient costs...
are primarily attributed to differences in birthweight and maternal age distributions between the ART and non-ART cohorts (Ettner et al., 1997; Montan, 2007); however, other factors in the ART cohort may be involved, such as the physiological causes of subfertility and the fertility treatment.

The difference in costs for ART singletons compared with non-ART singletons was attributed to the significantly higher incidence of LBW and VLBW infants in the ART cohort. This is in-line with previous studies that have concluded that, even after adjusting for known confounders, such as maternal age, parity and subfertility, ART singletons have poorer perinatal outcomes than naturally conceived singletons (Dhont et al., 1999; Koudstaal et al., 2000; Helmerhorst et al., 2004; Jackson et al., 2004; Schieve et al., 2004a,b; Wennerholm and Bergh, 2004). A growing body of evidence suggests that ART treatment per se may contribute to this phenomena either through the effect of ovarian stimulation or the technique itself (Wang et al., 2002; Kapiteijn et al., 2006). A number of studies have found that the spontaneous reduction of at least 10% of ART twin pregnancies to viable singleton pregnancies increases the risk of surviving twins having poorer outcomes than true singleton infants (Dickey et al., 2002; Pinborg et al., 2005; Chasen et al., 2006). This finding adds to the impetus to transfer a single embryo during ART procedures. However, at least one recent study found no significant difference between the outcomes of singletons resulting from single embryo transfer and vanishing twin survivors from double embryo transfers (Poikkeus et al., 2007). The fact that we found such a significant cost differential between ART versus non-ART singletons indicates that the differences in clinical outcomes between these two cohorts are substantial enough to have an impact on healthcare resource consumption. These findings support a smaller Finnish study (Koivurova et al., 2004). How much this difference is due to patient characteristics or the ART treatment itself (either through ovarian stimulation or the procedure) needs to be further elucidated.

In contrast with the findings relating to ART singletons, we did not find any statistically significant difference between the incidence of LBW or VLBW infants between ART and non-ART twins. This finding is also in-line with a number of previous studies relating to the perinatal outcome of ART twins (Helmerhorst et al., 2004; Wennerholm and Bergh, 2004). The higher rates of monozygosity and, therefore a higher risk of adverse perinatal outcomes, among naturally conceived twins compared with ART twins may temper the impact of confounders, such as subfertility, evident in the singleton results. Because all twins are at much higher risk

### Table IV

<table>
<thead>
<tr>
<th>Plurality</th>
<th>% of birth-admissions discharged to another medical facility</th>
<th>Average cost of transferred birth-admissions (€)</th>
<th>Average cost of all birth-admissions (all separation modes) (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singletons</td>
<td>4.6</td>
<td>3558</td>
<td>1432</td>
</tr>
<tr>
<td>Twins</td>
<td>18.0</td>
<td>8917</td>
<td>4571</td>
</tr>
<tr>
<td>HOMs</td>
<td>48.3</td>
<td>13 870</td>
<td>12 903</td>
</tr>
<tr>
<td>All pluralities</td>
<td>5.0</td>
<td>4258</td>
<td>1543</td>
</tr>
</tbody>
</table>

Source: NHMD.

Figure 1: Sensitivity analysis—singleton deliveries: effect of changing the AR-DRG distribution of maternal and infant birth-admissions in the ART population

Figure 2: Sensitivity analysis—twin deliveries: effect of changing the AR-DRG distribution of maternal and infant birth-admissions in the ART population

Figure 3: Sensitivity analysis—HOM deliveries: effect of changing the AR-DRG distribution of maternal and infant birth-admissions in the ART population
than singletons of perinatal morbidity and mortality, the continued emphasis on reducing the twinning rate through either voluntary or legislative single embryo transfer is well placed (ESHRE, 2003; HFEA, 2006).

It was not possible in this study to distinguish deliveries in the non-ART reference population that resulted from non-ART fertility treatment. Recent data conclude that singletons and multiple gestation infants born after such treatment are also at increased risk of poorer perinatal outcomes (Wang et al., 2002; Kapiteijn et al., 2006; Ombelet et al., 2006). The use of non-ART fertility treatment is generally accepted as a first-line treatment for unexplained, ovulatory and moderate male factor subfertility, yet surveillance of such treatment is far less comprehensive than for ART treatment worldwide. Because of this, accurate estimates of the impact of non-ART fertility treatment on the incidence of multiple births is not well understood and may well vary worldwide depending on country specific funding and provision of fertility treatment. An analysis of deliveries in Flanders, Belgium found that non-ART fertility treatment was responsible for 33% of all multiple births involving ovarian stimulation (Ombelet et al., 2005). A recent study of maternity units undertaken in the UK found this figure to be 22%, and that 5% of all non-ART multiple deliveries were as a result of non-ART fertility treatment (Bardis et al., 2005). Furthermore, whereas HOM births resulting from ART treatment continue to decline with the trend to transferring fewer embryos, non-ART fertility treatment continues to contribute to an unacceptable number of HOMs pregnancies (CDC, 2000; Tur et al., 2001). The reduction of multiple births by close monitoring of follicular development and a conservative threshold for withholding treatment in non-ART fertility treatment will further reduce the perinatal morbidity and healthcare costs associated with fertility treatment.

The strength of this study is that it used a national dataset of all ART pregnancies (ANZARD) and compared it to all non-ART pregnancies extracted from a national pregnancy and births database (NPDC). The study also used a recognized costing methodology, capturing all direct and overhead costs relating to inpatient hospital stays. However, even though the costs of ART twin and HOM birth-admissions were 3 and 11 times higher than for ART singletons, these costs only represent the initial birth episode and do not account for transfers or re-admissions to other medical facilities, which were 4 and 11 times more likely in twin and HOM births.

Previous studies on the cost of singleton versus multiple pregnancies have used a number of different methodologies, time frames and definitions of costs, making direct comparisons between studies difficult (Callahan et al., 1994; Goldfarb et al., 1996; Etter et al., 1997; Koivurova et al., 2004; Lukassen et al., 2004; Ledger et al., 2006). Moreover, perinatal and infant healthcare costs only serve as an indication of the relative difference in longer-term costs of caring for singleton, twin and HOM infants. A recent modelling exercise by Ledger estimated the total cost to the UK National Health System from pregnancy until the end of the first year of life per family (maternal plus infant/s) was £3313 (2002, €5273) for ART singletons, £9122 (2002, €14 519) for ART twins and £32 354 (2002, €51 496) for ART triplets ( Ledger et al., 2006). Similarly, a study of multiple births by Henderson estimated the cost of hospital admissions in the first 5 years of life was £1532 (1998–1999, €2273) for singletons, £3826 (1998–1999, €5677) for twins, and £8156 (1998–1999, €12 101) for HOMs (Henderson et al., 2004). A systematic review performed by Petrou also highlighted the immense ongoing burden on health, education, social services and families arising from pre-term birth and LBW infants of which multiple gestation is a significant risk factor (Petrou et al., 2001). For example, even LBW children without a disability use healthcare resources 4.7 times more to the age of 8–9 years compared with control children (Stevenson et al., 1996).

ART treatment accounted for only 0.2% of Australia’s private and public healthcare expenditure in 2002–2003 (Chambers et al., 2006), but the hidden cost of fertility treatment is the continuing high incidence of multiple births. Savings to the healthcare sector by reducing multiple births through elective single embryo transfer procedures could be used to fund additional ART treatment cycles. Ledger estimated that 10 124 treatment cycles per year could be publicly funded in the UK by eliminating multiple births (Ledger et al., 2006). This was the argument used by Belgium opinion leaders in reproductive medicine with regard the public re-imbursement of ART treatments; savings from a reduction in multiple births [which are around 7% of births (HFEA, 2006)], through restricted embryo transfer policies, now provide funding for ART treatment to those who need it while ensuring better perinatal outcomes (Gerris, 2004; Ombelet et al., 2005). A number of studies have demonstrated that a policy of elective single embryo transfer in women at risk of twinning, augmented by effective cryopreservation programs, is both clinically and cost-effective (Wolner-Hanssen and Rydhstroem, 1998; De Sutter et al., 2002; Gerris et al., 2002; Tiitinen et al., 2003; Gerris et al., 2004; Thurin et al., 2004; Thurin Kjellberg et al., 2006; Heijn en al., 2007).

The clinical and economic evidence overwhelmingly supports strategies to reduce the unacceptable number of multiple births following ART treatment. The seemingly simple solution of single embryo transfer in good prognosis patients must be supported by funding, surveillance and reporting mechanisms that allow each child conceived through fertility treatment to have the best possible start in life.

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