Higher prevalence of gestational diabetes mellitus following assisted reproduction technology treatment

Y.A. Wang1,*, R. Nikravan1, H.C. Smith2, and E.A. Sullivan1

1National Perinatal Epidemiology and Statistics Unit, School of Women’s and Children’s Health, Medicine, The University of New South Wales, Level 2, McNevin Dickson Building, Randwick Hospitals Campus, Randwick, Randwick, NSW 2031, Australia and 2Department of Reproductive Medicine, Westmead Hospital, Westmead, NSW 2145, Australia

*Correspondence address. Tel: +61 2 9382 1014; Fax: +61 2 9382 1025; E-mail: alex.wang@unsw.edu.au

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STUDY QUESTION: Do mothers following assisted reproduction technology (ART) treatment have increased likelihood of gestational diabetes mellitus (GDM) compared with non-ART mothers after controlling for maternal factors and plurality?

SUMMARY ANSWER: ART mothers had 28% increased likelihood of GDM compared with non-ART mothers.

WHAT IS KNOWN ALREADY: Advanced maternal age and multiple pregnancies are independently associated with increased likelihood of GDM. Given the average age of mothers having ART treatment is higher than non-ART mothers and the higher multiple pregnancy rate following ART treatment, ART treatment might be expected to be associated with increased risk of GDM.

STUDY DESIGN, SIZE, DURATION: A population retrospective cohort study of 400,392 mothers who gave birth in Australia between 2007 and 2009, using the Australian National Perinatal Data Collection from five states (Australian Capital Territory, Queensland, Tasmania, Victoria and Western Australia) where a code for ART treatment is available.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The study included 13,732 ART mothers and 386,660 non-ART mothers. The prevalence of GDM was compared between ART and non-ART mothers. Logistic regressions were used to assess the association between ART treatment and GDM. Odds ratio (OR), adjusted OR (AOR) and 95% confidence interval (CI) were calculated.

MAIN RESULTS AND THE ROLE OF CHANCE: A larger proportion of ART mothers were aged ≥40 years compared with non-ART counterpart (11.7 versus 3.4%, P < 0.01). The prevalence of GDM was 7.6% for ART mothers and 5.0% for non-ART mothers (P < 0.01). Mothers who had twins had higher prevalence of GDM than those who gave births to singletons (8.8 versus 7.5%, P = 0.06 for ART mothers; and 7.3 versus 5.0%, P < 0.01 for non-ART mothers). Overall, ART mothers had a 28% increased likelihood of GDM compared with non-ART mothers (AOR 1.28, 95% CI 1.20–1.37). Of mothers who had singletons, ART mothers had higher odds of GDM than non-ART mothers (AOR 1.26, 95% CI 1.18–1.36). There was no significant difference in the likelihood of GDM among mothers who had twins between ART and non-ART (AOR 1.18, 95% CI 0.94–1.48). For mothers aged <40 years, the younger the maternal age, the higher the odds of GDM for ART singleton mothers compared with non-ART singleton mothers.

LIMITATIONS, REASONS FOR CAUTION: It was not possible to investigate which ART procedure is associated with increased risk of GDM and how the risk could have been minimized. The information on BMI and smoking during pregnancy was not stated for a large proportion of mothers. These limitations may have reduced the validity of the study.

WIDER IMPLICATIONS OF THE FINDINGS: In agreement with other studies, our data suggest that the underlying cause of subfertility and some particular ART procedures might have played an important role in the increased likelihood of GDM. Together with the public education on not delaying motherhood, minimizing multiple pregnancies by applying single embryo transfer may diminish the excess risk of GDM related to ART treatment.

STUDY FUNDING/COMPETING INTEREST(S): There is no funding for this study. Authors declare no competing interest related to this study.

Key words: gestational diabetes mellitus / assisted reproduction technology / multiple pregnancy
**Introduction**

Gestational diabetes mellitus (GDM) is one of the most frequent maternal complications during pregnancy (Sibai and Ross, 2010). It is a condition where a woman without prior diagnosed diabetes experiences high blood glucose levels during pregnancy. It occurs when a woman’s pancreatic function is not sufficient to cope with the relative insulin resistance created by the anti-insulin hormones, such as human placental lactogen, and the increased fuel consumption necessary to provide for the growing fetus (Schneider et al., 2003). It was estimated that GDM complicates 3–5% of pregnancies worldwide, and in Australia it has been reported to affect as many as 5–10% of pregnant women (Ross, 2006; Makgoba et al., 2012).

Pregnancy complicated with GDM is associated with adverse acute and long-term consequences for both mother and infant (Sibai and Ross, 2010). Research has shown that pregnant women with GDM have significantly higher rates of pre-eclampsia and Caesarean section than similar pregnant women without GDM (Schneider et al., 2003; Tundidor et al., 2012). Infants born to mothers with GDM are at increased risk of large for gestational age (birthweight above 90th percentile for gestational age), high cord-blood serum C-peptide levels and perinatal mortality (Schneider et al., 2003; HAPO Study Cooperative Research Group et al., 2008). Furthermore, a long-term follow-up study demonstrates that most women with GDM will progress to type 2 diabetes (Schneider et al., 2003; Ross 2006). Children born to women with GDM have increased risk for obesity and type 2 diabetes later in life (Schneider et al., 2003; Boney et al., 2005).

Factors which increase the risk of GDM include advanced maternal age, high pre-pregnancy BMI, family history of diabetes, pre-existing hypertension, smoking during pregnancy, parity, multiple gestational pregnancy and assisted reproduction technology (ART) treatment (England et al., 2004; Chu et al., 2007; Hedderson and Ferrara 2008; Choi et al., 2011; Bener et al., 2011; Makgoba et al., 2012; Jones et al., 2013). Advanced maternal age is the most significant contributor to GDM. Bener et al. (2011) reported that 45% of pregnant women aged 35–45 years had GDM. An Australian study suggested that primiparous women aged ≥35 years were at 83% increased likelihood of GDM compared with their younger counterparts (Biro et al., 2012). Multiple gestational pregnancy is another important factor associated with GDM (Rauh-Hain et al., 2009; Sibai and Ross 2010). It has been reported that progress to severe complications due to GDM in multiple gestational pregnancies could be accelerated compared with singleton pregnancies (Sibai and Ross, 2010).

Given the higher proportion of older women undergoing ART treatment and the higher multiple pregnancy rate following ART treatment (Macaldowie et al., 2012; Ferraretti et al., 2012), some studies suggested that ART is associated with an increased risk of GDM (Sibai and Ross, 2010; Pandey et al., 2012; Jones et al., 2013). Jones et al. (2013) suggested that women with multiple pregnancies conceived following ART have impaired glucose tolerance compared with those who conceived spontaneously. However, Shevell et al. (2005) reported no differences in GDM between spontaneously conceived pregnancies and those conceived through ART treatment. Also, it is not clear whether singleton pregnancies following ART treatment are also at increased risk of GDM compared with non-ART singleton pregnancies. This study, using population data of women who gave birth in Australia during 2007–2009, aims to determine the association between ART treatment and the prevalence of GDM stratified by plurality.

**Materials and Methods**

**Data**

A population retrospective cohort study used data and definitions from the National Perinatal Data Collection (NPDC). The NPDC is a national population database of all mothers who gave birth (live births and stillbirths of ≥20 weeks of gestation or ≥400 g birthweight) in Australia. Data used in this study include 400 392 mothers (including 3.6% of all mothers who conceived following ART treatment) from 5 jurisdictions (Australian Capital Territory, Queensland, Tasmania, Victoria and Western Australia) between 2007 and 2009 where ART information is available.

**Study factors**

The ART treatment included IVF, ICSI or gamete intrafallopian transfer. However, details of the type of ART treatment provided for each woman were not specified in the NPDC.

Maternal age was categorized into seven groups (<20, 20–24, 25–29, 30–34, 35–39, 40–44 and ≥45 years). Parity was grouped as primiparous and multiparous. BMI was divided into five groups (<20, 20–24.9, 25–29.9, 30–34.9 and ≥35 kg/m²). Health insurance included private or public cover.

Smoking during pregnancy was grouped as yes, no or not stated. Pre-existing diabetes mellitus and essential hypertension were both coded as yes, no or not stated.

Smoking during pregnancy and BMI are not required data items of the NPDC. Of the five jurisdictions in the study, only one reported BMI for the 3-year study period. Another jurisdiction reported BMI for 2008 and 2009. The other three jurisdictions did not report BMI. Smoking during pregnancy was reported by three jurisdictions for all 3 years of the study and one jurisdiction for last 2 years only. One jurisdiction did not report smoking during pregnancy. Therefore, BMI was available for 117 838 mothers and smoking during pregnancy was available for 256 726 mothers.

**Main outcome measures**

In the NPDC, GDM was recorded as yes, no or not stated. At the state level of data collection, GDM was identified using a tick box method, with data collected in a paper or electronic form, or a combination of both. Methods to diagnose GDM were recommended by the Australasian Diabetes in Pregnancy Society (ADIPS) and have been used nationally (Hoffmann et al., 1998; Moses et al., 2011). In the ADIPS guidelines, the diagnosis of GDM is made if one or more of the following values are abnormal after an oral glucose tolerance test: fasting venous plasma glucose ≥5.1 mmol/L, 1 h venous plasma glucose ≥10.0 mmol/l or 2 h venous plasma glucose ≥8.5 mmol/L.

**Statistical analysis**

The prevalence of GDM was compared between ART and non-ART mothers. Student t-test for continuous variables and χ² test for categorical variables were used to analyse the difference in means and proportions between ART and non-ART mothers. Univariate and multivariate binary logistic regression analysis was used to assess an association between ART and GDM. Odds ratio (OR) and adjusted OR (AOR, adjusted for maternal age, parity, BMI, health insurance and smoking status during pregnancy) and 95% confidence interval (CI) were calculated. Missing data were recorded as a separate group (‘not stated’) and included in the regression module. A sub-analysis to investigate the association between ART and GDM was
conducted for the 117,838 mothers where BMI was available. Data were analysed using the Statistical Package for Social Sciences (SPSS) software, version 20.0 (SPSS, Inc., Chicago, IL, USA).

Ethical approval

Ethical approval for this study was granted by the Human Research Ethics Committee of the University of New South Wales (HREC 11024), and the Australia and the Australian Institute of Health and Welfare Ethics Committee (EC 2011/1/5).

Results

Table I details the difference in the demographics between ART and non-ART mothers. More than 60% of ART mothers were primiparous, which was higher than non-ART mothers (40.5%) \( (P < 0.01) \). A lower proportion of smoking during pregnancy was reported for ART mothers than non-ART mothers (2.6 and 12.4%, respectively, \( P < 0.01 \)). A significantly lower proportion of missing data for BMI, health insurance and smoking during pregnancy was observed for ART mothers than non-ART mothers.

For mothers where BMI is available, overall more than half (50.1%) of non-ART mothers had a BMI over 25 kg/m\(^2\) compared with 47.1% of ART mothers \( (P < 0.01) \). For mothers aged 30–34 years and 35–39 years, there was a significantly higher proportion of non-ART mothers with a BMI over 25 kg/m\(^2\) than ART mothers (48.4 versus 43.3%, \( P < 0.01 \) for mothers aged 30–34 years and 51.0 versus 48.0%, \( P = 0.02 \) for mothers aged 35–39 years). For other age groups, there was no difference in the proportion with a BMI over 25 kg/m\(^2\) between non-ART and ART mothers (Fig. 1).

The overall prevalence of pre-existing diabetes mellitus was 0.6%. There was no difference in the prevalence of pre-existing diabetes mellitus between ART and non-ART mothers.

Table I  Characteristics of ART and non-ART treatment mothers.

<table>
<thead>
<tr>
<th></th>
<th>Non-ART (n = 386,660)</th>
<th>ART (n = 13,732)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>29.6 (± 5.7)</td>
<td>33.9 (± 4.7)</td>
<td>&lt;0.01(^a)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>17,543 (4.5)</td>
<td>6 (0.0)</td>
<td>&lt;0.01(^b)</td>
</tr>
<tr>
<td>20–24</td>
<td>59,388 (15.4)</td>
<td>289 (2.1)</td>
<td></td>
</tr>
<tr>
<td>25–29</td>
<td>105,378 (27.3)</td>
<td>2,166 (15.8)</td>
<td></td>
</tr>
<tr>
<td>30–34</td>
<td>121,241 (31.4)</td>
<td>4,841 (35.3)</td>
<td></td>
</tr>
<tr>
<td>35–39</td>
<td>70,076 (18.1)</td>
<td>4,814 (35.1)</td>
<td></td>
</tr>
<tr>
<td>40–44</td>
<td>12,570 (3.3)</td>
<td>1,403 (10.2)</td>
<td></td>
</tr>
<tr>
<td>≥45</td>
<td>448 (0.1)</td>
<td>207 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Not stated</td>
<td>16 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primiparous</td>
<td>156,513 (40.5)</td>
<td>8,579 (62.5)</td>
<td>&lt;0.01(^b)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>230,147 (59.5)</td>
<td>5,153 (37.5)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>10,334 (2.7)</td>
<td>415 (3)</td>
<td>&lt;0.01(^b)</td>
</tr>
<tr>
<td>20–24.9</td>
<td>46,138 (11.9)</td>
<td>2,089 (15.2)</td>
<td></td>
</tr>
<tr>
<td>25–29.9</td>
<td>31,845 (8.2)</td>
<td>1,253 (9.1)</td>
<td></td>
</tr>
<tr>
<td>30–34.9</td>
<td>14,758 (3.8)</td>
<td>564 (4.1)</td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>10,030 (2.6)</td>
<td>412 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Not stated</td>
<td>273,555 (70.7)</td>
<td>8,999 (65.5)</td>
<td>&lt;0.01(^b)</td>
</tr>
<tr>
<td>Health insurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>124,839 (32.3)</td>
<td>9,990 (72.7)</td>
<td>&lt;0.01(^b)</td>
</tr>
<tr>
<td>Public</td>
<td>259,967 (67.2)</td>
<td>3,721 (27.1)</td>
<td></td>
</tr>
<tr>
<td>Not stated</td>
<td>1,854 (0.5)</td>
<td>21 (0.2)</td>
<td>&lt;0.01(^b)</td>
</tr>
<tr>
<td>Smoking during pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoked</td>
<td>47,850 (12.4)</td>
<td>354 (2.6)</td>
<td>&lt;0.01(^b)</td>
</tr>
<tr>
<td>Did not smoke</td>
<td>199,292 (51.5)</td>
<td>9,230 (67.2)</td>
<td></td>
</tr>
<tr>
<td>Not stated</td>
<td>139,518 (36.1)</td>
<td>4,148 (30.2)</td>
<td>&lt;0.01(^b)</td>
</tr>
</tbody>
</table>

\(^a\) t-test.

\(^b\) \(\chi^2\) test.
Gestational diabetes mellitus and assisted reproduction

There were 1571 (11.4%) ART mothers and 5208 (1.4%) non-ART mothers who had twins. Overall, 5.1% of the study population had GDM, with 7.6% (95% CI 7.2–8.0%) for ART mothers and 5.0% (95% CI 4.9–5.1%) for non-ART mothers. Regardless of method of conception, mothers who had twins had a higher prevalence of GDM than those who gave birth to singletons (8.8 versus 7.5%, $P = 0.06$ for ART mothers; and 7.3 versus 5.0%, $P < 0.01$ for non-ART mothers) (Table II).

The likelihood of GDM in relation to ART treatment is shown in Table II. Overall, ART mothers had 28% increased likelihood of GDM compared with non-ART mothers (AOR 1.28, 95% CI 1.20–1.37). Of mothers who had singletons, ART mothers had higher odds of GDM than non-ART mothers (AOR 1.26, 95% CI 1.18–1.36). There was no significant difference in the prevalence of GDM among mothers who had twins between ART and non-ART (AOR 1.18, 95% CI 0.94–1.48).

The sub-analysis for mothers where BMI is available shows that ART mothers had 37% increased likelihood of GDM than non-ART mothers (AOR 1.37, 95% CI 1.22–1.54). ART mother who had singletons were at 36% higher odds of GDM than non-ART mothers. There was no significant difference in the prevalence of GDM among mothers who had twins between ART and non-ART (AOR 1.29, 95% CI 0.83–2.02).

After age stratification, for mothers aged $< 40$ years who had singletons, ART mothers had significantly higher odds of GDM than non-ART mothers (Table III). The younger the maternal age, the higher the odds of GDM for ART mothers compared with non-ART mothers. For mothers aged $\geq 40$ years, the likelihood of GDM was similar for ART and non-ART. For mothers where BMI is available, the likelihood of GDM showed the same direction: the younger the maternal age, the higher likelihood of GDM for ART mothers than non-ART mothers, apart for those aged $\geq 40$ years.

**Discussion**

This is the first population study in Australia to show that ART mothers had 28% increased likelihood of GDM compared with non-ART mothers after adjusting for differences in socio-demographic factors. This not only confirms the findings of other studies in the Australian context (Sibai and Ross, 2010; Pandey et al., 2012; Jones et al., 2013) but also demonstrates that for mothers who had singletons, the likelihood of GDM among ART mothers was 26% higher than non-ART mothers. This suggests that multiple pregnancies resulting from ART treatment only partially explained the association between ART treatment and GDM; and that the underlying cause of subfertility or particular ART procedure may have played an important role in the increased likelihood of GDM (Pandey et al., 2012).

However, we were unable to investigate what particular ART procedure is associated with the increased risk of GDM, and how the risk could have been minimized in this population. Detailed information on the ART procedure, such as single embryo transfer (SET) or double embryo transfer (DET), cleavage embryo or blastocyst transfer, and fresh or thawed embryo transfer was not available in the NPDC. Established evidence shows that DET significantly increases the risk of multiple gestational pregnancy, and multiple gestational pregnancy was associated with increased likelihood of GDM (Pinborg et al., 2007; Pandian et al., 2009; Sibai and Ross 2010; Rauh-Hain et al., 2009). Research has shown that blastocyst transfer is associated with a greater risk of GDM than cleavage embryo transfer (Vithala et al., 2009). A national registry study that linked national ART treatment data and the national perinatal data...
collection would provide detailed information on ART treatment, and would allow an investigation into which ART treatment and procedure are associated with the increased risk of GDM.

It was also suggested that pregnancies following fresh embryo transfer had an increased risk of maternal and obstetric complications compared with thawed embryos transfers (Maheshwari et al., 2012; Sazonova et al., 2012). It was shown that GMD is highly associated with an increased risk of having large for gestational age (LGA) baby (Boney et al., 2005; Hammoud et al., 2013; Magann et al., 2013). Interestingly, births following thawed embryo transfers had a higher rate of LGA than those following fresh embryo transfers (Pelkonen et al., 2010; Sazonova et al., 2012). Sazonova et al. (2012) reported 59% increased odds of LGA and 46% increased odds of birthweight over 4500 g for singletons from thawed embryos transfers compared with those from fresh embryo transfers. This study was unable to stratify fresh embryo transfers versus thawed embryo transfers. The contradicting correlations amongst fresh or thawed embryo transfers with GMD and birthweight need further investigations.

A limitation of this study is that the information on BMI and smoking during pregnancy was not stated for a large proportion of mothers (70.6% for BMI and 35.9% for smoking during pregnancy). This reflected that some jurisdictions did not have smoking status and or BMI in their routine data collection. The large proportion of mothers with missing data on BMI and smoking during pregnancy, and the differential missing data between ART and non-ART mothers would have reduced the validity of the comparison and multivariate analysis.

A higher BMI was reported to be associated with an increased risk of GDM in the general population (Persson et al., 2012). Within ART pregnancies, the rate of GDM was higher in overweight and obese women than those with a normal BMI (Farhi et al., 2010). In our study, a higher proportion of non-ART mothers (59.2%) did not have a normal BMI compared with 55.9% of ART mothers (P < 0.01, χ² test). Similarly,
smoking was also suggested to be associated with a 90% increase in odds of GDM (Englund et al., 2004). Of mothers who reported smoking status, 19.4% of non-ART mothers smoked during pregnancy, which was significantly higher than ART mothers (3.7%) ($P < 0.01$, $\chi^2$ test).

The sub-analysis of mothers where BMI was available shows that the higher the BMI, the higher the odds of GDM. For all mothers who had singletons, the AOR of GDM was 1.26 (95% CI 1.18–1.36) for ART mothers compared with non-ART mothers. For singleton mothers where BMI was available, the AOR of GDM increased to 1.36 (95% CI 1.20–1.54) for ART mothers compared with non-ART mothers. The change in AORs confirmed that ART treatment or the underlying cause of subfertility was independently associated with the increased likelihood of GDM.

Accompanied with ART treatment, advancing maternal age and high parity were reported as other independent risks for GDM (Savvidou et al., 2010; Bener et al., 2011; Biro et al., 2012; Koo et al., 2012). A significant linear trend between advancing maternal age and GDM was observed for all mothers. The rate of GDM increased from 1.5% for mothers aged <20 years to 13.9% for mothers aged ≥45 years ($P < 0.01$, $\chi^2$ test for linear-by-linear association). Furthermore, compared with primiparous mothers, higher rates of GDM (4.7 versus 5.3%, $P < 0.01$, $\chi^2$ test) were observed among multiparous mothers. Given the higher proportion of ART mothers aged ≥40 years, the higher proportion of primiparous ART mothers than non-ART mothers and higher rate of GDM for ART mothers than non-ART mothers, the interaction between ART treatment, advancing maternal age and high parity remains a significant contribution towards the higher prevalence of GDM among ART mothers (Savvidou et al., 2010; Bener et al., 2011).

The results stratified for maternal age showed that for singleton mothers aged <40 years, ART mothers had significantly higher odds of GDM than non-ART mothers. Also, with advancing maternal age, the AOR of GDM decreased accordingly. For mothers aged ≥40 years, there was no significant difference in the odds of GDM between ART and non-ART mothers. However, singleton ART mothers had an overall 26% increased likelihood of GDM than non-ART singleton mothers. The change in AORs suggested that maternal age differentially modified the observed effects of ART treatment on GDM.

The exact mechanism of how ART treatment can influence GDM remains unclear. Our findings suggested that maternal age and BMI did not confound the relationship between ART treatment and GDM. The higher prevalent GDM among ART mothers may have been related to the underlying infertility, such as ovariatic discord, polycystic ovaries syndrome (PCOS) or unknown infertility in some cases (Burghen et al., 1980; Shoupe et al., 1983; Maman et al., 1998). A high insulin resistance was found among patients with PCOS related to hyperandrogenism (Burghen et al., 1980; Chang et al., 1983). The change in hormone levels, including estrogen, progesterone and insulin growth factor, during ovarian stimulation in ART treatment may have contributed to the increased likelihood of GDM among ART mothers (Maman et al., 1998; Shouvell et al., 2003; Adler-Levy et al., 2007). The impact of ovarian stimulation was demonstrated by a higher fasting glucose level in the first trimester than in the second and third trimester (Szymanska et al., 2011). A more appropriate comparison among ART pregnancies following fresh embryo transfers, as well as pregnancies following frozen thawed embryo transfer and non-ART pregnancies is needed to further assess the impact of ovarian stimulation on GDM.

Pre-existing essential hypertension is another risk factor for GDM (Kjerulf et al., 2011). The present study found a significant difference in the rates of pre-existing essential hypertension between ART and non-ART mothers (1.2 versus 0.9%, respectively), probably related to the higher proportion of ART mothers of advanced maternal age, a risk factor for essential hypertension (Luke and Brown, 2007). It may also be linked with the underlying subfertility of many ART mothers with conditions such as PCOS, which is correlated with essential hypertension (Holte et al., 1996; Davies et al., 2011). Unfortunately, detailed information on the cause of subfertility is not available in the NPDC. In spite of this, as confirmed by other studies, pre-existing essential hypertension remained significant in the multivariate analysis regardless of the mode of conception (Hedderon and Ferrara, 2008; Savvidou et al., 2010).

Of mothers who had twins, even though the prevalence of GDM was 8.8% for ART mothers compared with 7.3% for non-ART mothers, the multivariate analysis did not show a significant difference (AOR 1.18, 95% CI 0.94–1.48). Several studies have shown that twin pregnancies following ART treatment had similar or lower rates of pregnancy complications and adverse perinatal outcomes compared with non-ART twin pregnancies (Pinborg et al., 2004; Szymusik et al., 2012; Jauniaux et al., 2013). A well-accepted explanation is that the proportion of monozygotic twin pregnancies following ART treatment was lower than non-ART twin pregnancies (Schachter et al., 2001; Pinborg et al., 2004). Early data showed fewer than 1% of monozygotic twin pregnancies following ART treatment compared with 30% among non-ART twin pregnancies (Schachter et al., 2001; Sperling & Tabor, 2001). Both morbidity and mortality are known to be higher in monozygotic twin pregnancies than dizygotic twin pregnancies (Loos et al., 1998). The increased placental mass in monozygotic twin pregnancies may influence diabetogenic hormones, and hence increase the likelihood of GDM (Ben-Haroush et al., 2004). Furthermore, previous studies showed that dizygotic ART twin pregnancies had similar risks of pregnancy complications as dizygotic non-ART twin pregnancies (Joy et al., 2008; Szymusik et al., 2012). Therefore, it is hypothesized that the prevalence of GDM in ART twin pregnancies would be similar or lower compared with non-ART twin pregnancies. However, we were not able to test this hypothesis.

Consistent with findings by Sibai and Ross (2010), regardless of the method of conception, mothers who had twins had higher rate of GDM than mothers who had singletons. The rate of GDM was 1.5 times higher for non-ART mothers who had twins than those who had singletons (7.3 versus 5.0%). In contrast, the rate of GDM was 1.2 times higher for ART mothers who had twins than those who had singletons (8.8 versus 7.5%). However, ART mothers had a disproportionally higher rate of twins than non-ART mothers (11.5 versus 1.3%). It is well documented that multiple births following ART treatment is directly associated with transfer of multiple embryos (Pandian et al., 2005; Pinborg et al., 2007). The multiple pregnancy rate was up to 60 times higher for DET than for SET (Pandian et al., 2005). Reducing the number of embryos per transfer was suggested as the most effective way to minimize the maternal complications of multiple pregnancy (Pinborg et al., 2004; Nygren, 2007).

The regulatory body of ART treatment in Australia and New Zealand has advocated a policy of SET since 2005 (RTAC, 2005). As a result, the multiple delivery rate following ART treatment in Australia and New Zealand decreased from 14.1% in 2005 to 8.2% in 2009, corresponding...
to the increase in the proportion of SET from 48.3% in 2005 to 69.7% in 2009 (Wang et al., 2011). Even though the information on number of embryos transferred is not available in the NPDC data. The decrease in the proportion of ART mothers having multiple births from 13.8% in 2007 to 10.3% in 2009 during the study period indirectly reflects the benefits of the SET policy. We hypothesize that the overall reduction in multiple pregnancies for ART has in turn reduced the rates of GDM for ART mothers from 8.1% in 2007 to 7.7% in 2009.

GDM is common, occurring in more than 5% of women who gave birth in Australia. Couples planning a pregnancy should be aware of the morbidity affecting both mother and child with GDM and of its major risk factors, i.e. maternal age and obesity. A significant proportion of women requesting ART treatment have these risk factors. However, these data indicate that the increased risk of GDM in women conceiving with ART treatment is not entirely explained by their higher maternal age, BMI and multiple pregnancy rates. Other factors not identified in the NPDC may also contribute to their risk of GDM, including family history and the cause of their subfertility. Every woman planning ART treatment should be assessed for her risks of GDM and managed appropriately prior to commencing fertility treatment. Advocacy of the benefit of minimizing multiple pregnancies through a policy of SET may further reduce the excess risk of GDM associated with ART pregnancies in Australia and internationally.

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**Authors’ roles**

All authors have contributed for the conduction of this study. The manuscript has been seen and approved by all authors. The order of authorship was agreed by all authors. Y.A.W. was involved in study design, method investigation, data analysis and preparing the manuscript. R.N. was involved in method investigation, data analysis and preparing the manuscript. H.C.S. was involved in study design, review and editing of the manuscript. E.A.S. was involved in study design, method investigation and review of the manuscript.

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**Conflict of interest**

No conflict of interest in relation to this work.

**References**


