Increased incidence of gestational hypertension and preeclampsia following assisted reproductive technology treatment

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Author's roles

YAW and AAC was involved in the study design, methods investigation, data analysis and preparing the manuscript. CMF, WP, and KL were involved in revision of the manuscript. EAS was involved in the study design, methods investigation and revision of the manuscript. All authors have contributed to the conducting of this study. The manuscript has been seen and approved by all authors; the order of authorship was agreed by all authors.

Conflict of interest

None

Running title: Gestational hypertension following ART

Capsule (summary of the abstract)

Mothers following assisted reproductive technology (ART) had 17% increased likelihood of gestational hypertension and preeclampsia than non-ART mothers. The increased likelihood is likely associated with multiple pregnancies among ART mothers.

Abstract

Objectives: To determine the association between assisted reproductive technology (ART) treatment and the rate of combined gestational hypertension (GH), preeclampsia (PE).

Design: A retrospective population study.

Setting: Victoria, Queensland, Western Australia, Tasmania and the Australian Capital Territory.

Participants: 596520 mothers (3.6% ART mothers) who gave birth between 2007 and 2011.

Intervention: None

Main Outcome Measures: The rate of GH/PE for ART and non-ART mothers was compared. Odds ratio (OR), adjusted odds ratio (AOR), and 95% confidence intervals (CIs) were used to assess the association between ART and GH/PE.

Results: The overall rate of GH/PE was 4.3%, with 6.4% for ART mothers and 4.3% for non-ART mothers. The rate of GH/PE was higher for mothers of twins than singletons (12.4% vs. 5.7% for ART mothers; 8.6% vs. 4.2% for non-ART mothers). ART mothers had 17% increased odds of GH/PE compared with non-ART mothers (AOR 1.17; 95% CI 1.10-1.24). After stratification by plurality, the difference in GH/PE rates between ART and non-ART mothers was not significant, with AOR 1.05 (95% CI 0.98-1.12) for mothers of singletons and AOR 1.10 (95% CI 0.94-1.30) for mothers of twins.

Conclusion: The changes in AORs after stratification indicated that multiple pregnancies following ART is the single most likely explanation for the increased rate of GH/PE among ART mothers. The lower rate of GH/PE among mothers of singletons compared with mothers of twins suggests that a policy to minimise multiple pregnancies following ART may reduce the excess risk of GH/PE due to ART treatment.

Key words: assisted reproductive technology, gestational hypertension, preeclampsia

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INTRODUCTION

Hypertensive disorders are the most common medical problem encountered in pregnancy with an estimated rate between 5% and 11% of pregnancies (1, 2). There are three types of hypertensive disorders: chronic hypertension, gestational hypertension (GH), preeclampsia (PE) including PE superimposed on chronic hypertension (3, 4) . Of these disorders, GH and PE occur during pregnancy and are leading causes of perinatal and maternal morbidity and mortality (5).

Pregnant women with GH and PE are more likely to develop placental abruption, disseminated intravascular coagulation, cerebral haemorrhage, hepatic and renal failure (National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy 2000). Preeclampsia in particular accounts for a significant number of preterm deliveries and subsequent neonatal and longer term morbidity (6-8). In the longer term, women experiencing PE appear to be at increased risk of high blood pressure, cardiovascular complications, kidney disease, diabetes mellitus, thromboembolism, thyroid disease and impaired memory (9-11). The offspring of these pregnancies, particularly if born small for gestational age, also appear to be at increased risk of cardiovascular disease (10).

A number of demographic factors and conditions such as advanced maternal age (12), high pre-pregnancy body mass index (BMI) (13), primiparity, pre-existing diabetes mellitus and gestational diabetes (14) have been associated with GH and PE. Assisted reproductive technology (ART) treatment, especially with multiple gestational pregnancies, has been associated with significantly higher rate of GH and PE in some but not all studies (15). The inter-dependent effects between ART treatment and advanced maternal age, multiple gestations, pre-existing diabetes and gestational diabetes may contribute to the higher rate of GH and PE among ART pregnancies (16-19). It remains unclear whether ART itself, the underlying subfertility or other co-existing risk factors independently predict GH and PE.

Both GH and PE have significant impacts for women, their babies and public resourcing. Attempts to stratify women into risk categories to determine their mode of antenatal care are

increasingly being introduced (20). Therefore, accurate data regarding the rates of GH and PE in women undergoing ART is an important factor in such planning. The current population study which included mothers who gave birth in Australia during 2007 to 2011, aimed to determine the association between ART treatment and the rate of combined GH and PE (GH/PE), taking into account other potential confounding factors.

MATERIAL AND METHODS

Data

A population cohort study used data and definitions from the National Perinatal Data Collection (NPDC). The NPDC is a national population-based data collection of all mothers who gave birth (live births and stillbirths of ≥ 20 weeks gestation or ≥ 400 grams birthweight) in Australia. This study included 596520 mothers (including 3.6% who had ART treatment) from Victoria, Queensland, Western Australia, Tasmania and the Australian Capital Territory (ACT) between 2007 and 2011 where information about the use of ART was available. Data were not complete for all items with some jurisdictions not supplying voluntary data items for the NPDC.

Study factors

ART treatment referred to all types of ART treatment including in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI) or gamete intra-fallopian transfer (GIFT). However, the type of ART treatment was not specified in the NPDC. Maternal age was categorised into four groups (< 30 years, 30–34 years, 35–39 years and ≥ 40 years). Parity was grouped as primiparity and multiparity. BMI was divided into four groups (< 20, 20–24.9, 25–29.9 and ≥ 30). Smoking during pregnancy, pre-existing diabetes mellitus, essential hypertension and gestational diabetes mellitus were coded as ‘yes’, ‘no’ or ‘not stated’.

Smoking during pregnancy and BMI are not minimum data items in the NPDC. Of the above five jurisdictions where ART data were available, none reported BMI data for five years and only one jurisdiction reported BMI data for four years. Remaining jurisdictions reported BMI

data for 1 to 3 years. Smoking during pregnancy was reported by two jurisdictions for all five years of the study period and remaining jurisdictions reported smoking data for 2 to 4 years. BMI data were available for 249,091 (41.8%) of mothers and smoking during pregnancy data were available for 450,677 (75.6%) of mothers.

Main outcome measures

The primary outcome was presence of GH/PE. GH is defined by the International Society for the Study of Hypertension in Pregnancy criteria as a blood pressure recording of more than 140/90 mmHg on at least two occasions more than six hours apart without evidence of chronic hypertension after 20 weeks' gestation. PE is defined by presence of hypertension with proteinuria, maternal organ dysfunction or uteroplacental dysfunction (21-23).

Statistical analysis

The rate of GH/PE for ART and non-ART mothers was compared. Student t-test and Chi-square test were used for continuous variables and categorical variables respectively. Univariate and multivariate binary logistic regressions was used to assess the association between ART and GH/PE. Odds ratio (OR), adjusted odds ratio (AOR), adjusted for maternal age, parity, BMI, smoking status during pregnancy and pre-existing diabetes mellitus, and gestational diabetes mellitus), and 95% confidence intervals (CIs) were calculated. A sub-analysis to investigate the association between ART and GH/PE was conducted for mothers where data on BMI and smoking during pregnancy were available. Stratifications by parity and plurality were used to assess the changes in OR and AOR of GH/PE in ART mothers compared with non-ART mothers. Data were analysed using Statistical Package for Social Sciences (SPSS) software, version 22 (SPSS, Inc., Chicago, IL, USA).

Ethics

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

RESULTS

Supplemental Table 1 sets out the different demographics of ART and non-ART mothers. ART mothers were older compared to the non-ART mothers. A larger proportion (11.7%) of ART mothers was aged 40 years or older, compared with the non-ART mothers (3.4%) ($p<0.01$). Approximately 60% of ART mothers were primiparous, which was significantly higher than non-ART mothers (40.6%) ($p<0.01$). A lower proportion of smoking during pregnancy was reported for ART mothers than for non-ART mothers (2.5% and 13.3% respectively, $p<0.01$). Of ART mothers, 11.0% had multiple pregnancies, significantly higher than non-ART mothers (1.3%) ($p>0.01$).

Supplemental table 1

The rate of GH/PE was 6.4% (95% CI 6.1-6.7) for ART mothers and 4.3% (95% CI 4.1-4.3) for non-ART mothers. The rate of GH/PE doubled for mothers who gave births to twins compared with those who had singletons (12.4% vs. 5.7% for ART mothers; 8.6% vs. 4.2% for non-ART mothers) (Supplemental figure I).

Supplemental figure 1

A comparison of the rates of GH/PE for ART and non-ART mothers is shown in Table 1. For both ART and non-ART mothers, the rates of GH/PE were higher in primiparous mothers and in mothers with BMI ≥ 30. A significant linear trend was observed for an increase in GH/PE rates and an increase in BMI regardless of ART treatment and parity. Mothers who smoked during pregnancy had a lower rate of GH/PE in the ART group, but had high rate of GH/PE in non-ART group. The GH/PE rate doubled for mothers with pre-existing diabetes mellitus compared with those without pre-existing diabetes mellitus.

Table 1

Factors independently associated with increased odds of GH/PE are presented in Table 2. Overall, ART mothers had a 17% increased likelihood of presenting with GH/PE compared with non-ART mothers (AOR 1.17; 95% CI 1.10-1.24). Primiparity, high BMI and presence of diabetes mellitus were strongly associated with increased odds of GH/PE.

Table 2

The plurality stratified analysis shows that the AOR decreased to 1.05 (95% CI 0.98-1.12) for ART mothers who had singletons compared with non-ART singleton mothers (AOR 1.10, 95% CI 0.94-1.30) (Table 3). For mothers who had BMI or smoking data available, a similar pattern of decrease in AOR was observed for ART singletons mother compared with non-ART singletons mothers. Parity stratified analysis is given in Table 4. Primiparous ART mothers had a 16% increased likelihood of presenting with GH/PE compared with non-ART mothers (AOR 1.16, 95% CI 1.08-1.24), while the likelihood of multiparous ART mothers presenting with GH/PE increased by 30% (AOR 1.30, 95% CI 1.16-1.46).

Tables 3 and 4

DISCUSSION

In this study, there was a 17% increased likelihood of mothers presenting with GH/PE who conceived following ART compared with non-ART mothers after controlling for co-existing risk factors. The decrease in the AOR from 1.17 (95% CI 1.103-1.24) to 1.05 (95% CI 0.98-1.12) for mothers who had singletons and to 1.10 (95% CI 0.94-1.30) for mothers who had twins, indicates that multiple pregnancies confounded the association between ART and GH/PE. Almost 11% of the ART mothers gave births to multiples, which is significantly higher than the 1.3% for non-ART mothers. The disproportion of multiple pregnancy and high risk of GH/PE among ART mothers suggests that minimising the incidence of multiple pregnancies would reduce the risk of GH/PE among ART mothers.

Some historical studies as well as a recent systematic review have shown an association between GH/PE and ART treatment (16-19). However our results are in accordance with a large retrospective cohort study in the United States and Canada (24). Hernandez-Diaz and colleagues found the overall rates of GH in women with and without infertility treatments were 15.8% and 8.9% respectively (RR 1.6, 95% CI 1.1 to 2.1). Like our study, stratified by plurality, there was no difference by presence of infertility treatments (RR 1.3 95% CI 0.9 to 1.9 for singletons; and RR 1.1 95% CI 0.4 to 3.1 for twins) (24). Similarly studies restricted to singleton or twin pregnancies reported compared rate of GH between ART and non-ART pregnancies (25, 26).

It was suggested that multiple pregnancies following ART treatment are highly related to transfer of two or more embryos (27, 28). The multiple pregnancy rate for double embryo transfer (DET) was up to 60 times higher than for single embryo transfer (SET) (3, 29). The number of embryos transferred is one of the modifiable factors significantly associated with pregnancy and birth outcomes (30). Adopting a policy of SET has been suggested as the most effective way to minimise multiple pregnancies and complications following ART treatment (31, 32). Reproductive Technology Accreditation Committee, which is a regulative body for ART treatment in Australia and New Zealand, has advocated the implementation of an SET policy since 2005 (33). As a result, the multiple delivery rate following ART treatment in Australia and New Zealand has decreased from 11.7% in 2006 to 6.9% in 2011, corresponding with the increase in the proportion of SET from 56.9% in 2006 to 73.2% in 2011 (34). It is even lower in New Zealand where the funding for ART treament is tied to SET for women less than 36 years of age (35).

Of cycle-based studies and reports, SET significantly reduces the multiple pregnancy rate as well as live birth rate (36, 37). However,, the literature shows that the cumulative live birth rate of single embryo transfers is similar to one following fresh double embryo transfers. This supports even more the policy of SET in ART (38, 39). Unfortunately the information on the number of embryos transferred was not available in this study. While the decrease in GH/PE

for ART mothers in Australia from 8.0% in 2007 to 5.2% in 2011 correlates with the increase in SET in Australia from 63.7% in 2007 to 73.2% in 2011 (36).

The key factor differentiating ART and non-ART mothers was subfertility. The slightly higher rate of GH/PE among ART mothers who had singletons may have been related to the underlying known or unknown cause of subfertility. For example, polycystic ovarian syndrome (PCOS) is one of the most common reasons for accessing fertility treatment including ART and both essential hypertension and GH/PE are relatively more common in patients with PCOS (18, 40, 41). PCOS is also associated with high insulin resistance (42) which leads to both diabetes mellitus and gestational diabetes mellitus. Unfortunately, the detailed cause of subfertility was not available in this study.

Other notable differences in demographics between ART and non-ART mothers are maternal age and parity, which are both associated with increased risk of pregnancy-related complications including GH/PE. Advanced maternal age is strongly associated with obstetric complications, with a significantly higher risk of presenting with GH/PE after the age of 40 (43-45). In the current study, mothers aged 40 years or older had 37% increased odds of presenting with GH/PE than those aged <30 years. Primiparity had an even stronger association with GH/PE (46-48). Primiparity was associated with 2.9 times (for spontaneous conceptions) and 2.7 times (for ART conceptions) increased odds of PE compared with multiparity (47). In this study, first-time mothers had significantly high odds of presenting with GH/PE compared with those who have previously given birth. Given the higher proportion of ART mothers compared with non-ART mothers who were aged ≥ 40 years were primiparous and had presented with GH/PE, the interaction between ART treatment, advancing maternal age and lower parity is significant when drawing an association between ART treatment and GH/PE (18).

A number of studies have reported an increased risk of GH/PE in women with a high BMI (48-51). Farhi and colleagues found that for ART pregnancies, the rate of GH/PE was higher in overweight and obese women than those with normal BMI (52). The current study also

reported an increase risk of GH/PE in women with a high BMI. Interestingly, most studies found that smoking during pregnancy was associated with a low rate of GH/PE (53, 54). The current study also found that smoking during pregnancy was associated with 24% lower odds of GH/ PE. The reason for this association is unknown, but studies suggest that smokers with PE have a high rate of placental abruption and low birthweight babies (53). In the current study, only one jurisdiction reported BMI data for four years and remaining jurisdictions reported BMI data for 1 to 3 years. The data on the smoking during pregnancy was reported by two jurisdictions for all five years and remaining jurisdictions reported smoking data for 2 to 4 years. In the sub-analysis for mothers where BMI was reported, a significant linear trend of increases in the odds of GH/PE and higher BMI were observed regardless of ART treatment. The sub-analysis of BMI data also showed 18% higher odds of GH/PE in the ART group (OR 1.18; 95% CI 1.09-1.27), compared with the non-ART group. Even though the missing information on BMI is likely to be non-differential, the high proportion of mothers with missing BMI data would reduce the validity of the comparison and multivariate analysis.

The current study has several limitations. As discussed above, the data on BMI and smoking status were not available for all mothers (58.2% for BMI and 24.4% for smoking during pregnancy), and both are important predictors of GH/PE. Furthermore, we were unable to control for other potential confounders such as history of preeclampsia, alcohol consumption and renal disease, or preventative treatment such as low dose aspirin, as these items were not collected in the NPDC. And most importantly, we were unable to assess the excess odds of GH/PE by type of ART procedure, for example IVF versus ICSI, and frozen versus thawed embryo transfer. A study reported more than a two-fold increase in the risk of GH/PE in pregnant women treated by ICSI procedures with surgically obtained sperm compared with those treated with IVF procedures (55).

Apart from the increased risk of GH/PE following multiple embryo transfers as discussed previously, the likelihood of GH/PE is associated with a number of other ART treatment

factors. It was reported that the rate of GH/PE following transfer of fresh embryos is higher than following transfer of frozen/thawed embryos (19). Studies explained that the change in female hormone levels during ovarian stimulation in fresh ART treatment may contribute to the increased likelihood of presenting with GH/PE (56). Some studies also suggested that recipients of donated oocytes/embryos are at increased risk of GH/PE (57) (58) (59) than those who used their own oocytes/embryos. An earlier small study by Salha and colleagues found that the incidence of GH/PE was 4-9 times higher for pregnant women who conceived using donated oocytes/embryos than those who used their own oocytes (58). A more recent summary by Younis and Laufer suggested that oocyte donation is an independent risk factor for PE among recipients in advanced age (57). The immunological pathogenesis, namely the genetic incompatibilities between recipients and donated oocytes/embryos and consequently defective placentation may have been the mechanism of PE development (57) (59). It would be worthwhile examining whether there is any difference in the rate of GH/PE after IVF versus ICSI, SET versus DET, fresh versus frozen/thawed embryo transfer, autologous versus donor treatment. More detailed data linkage studies which link the ART treatment database and perinatal data collection may help to determine which ART procedure is associated with the increased risk and how the increased risk can be minimised.

GH/PE is common pregnancy complications, representing around 4.3% of non-ART mothers and 6.4% of ART mothers in Australia. It has significant impact on the public health system, and is considered to be a leading cause of obstetric complications, and maternal and neonatal mortality and morbidity. However, from a population health perspective, some GH/PE cases are potentially preventable. In addition to public education on not delay child bearing, extra effort is needed to address modifiable risk factors such as obesity and diabetes. In the context of ART treatment, continuing the policy advocating the use of SET rather than DET may reduce the excess risk of GH/PE due to ART treatment.

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Supplemental figure 1: Rate of combined gestational hypertension and preeclampsia among ART and non-ART mothers by plurality (2007-2011)

Supplemental table 1: Characteristics of ART and non-ART mothers (2007-2011)

Table 1: Rate of gestational hypertension (GH) and preeclampsia (PE) among ART and non-ART mothers by common risk factors

	Non-ART			ART		
	Total	**GH/PE**	**GH/PE rate (%) (95% CI)**	**Total**	**GH/PE**	**GH/PE rate (%) (95% CI)**
Maternal age (years)						
<30	277,900	12,365	4.4 (4.46-4.5)	3,896	300	7.7 (6.9-8.5)
30-34	177,169	7,060	4.0 (3.9-4.1)	7,651	450	5.9 (5.4-6.4)
35-39	100,510	4,114	4.14 (4.0-4.2)	7,488	452	6.0 (5.5-6.6)
≥ 40	19,309	943	4.9 (4.6-5.2)	2,580	181	7.0 (6.0-8.0)
Parity						
Primiparous	233,241	14,838	6.4 (6.3-6.5)	13,463	1,058	7.9 (7.4-8.3)
Multiparous	341,664	9,644	2.8 (2.8-2.9)	8,152	325	4.0 (3.6-4.4)
BMI						
< 20	22,826	524	2.3 (2.1-2.5)	901	38	4.2 (2.9-5.5)
20-24.9	98,244	3,083	3.1 (3.0-3.2)	4,615	209	4.5 (3.9-5.1)
25-29.9	65,899	3,333	5.1 (4.9-5.2)	2,760	202	7.3 (6.3-8.3)
≥ 30	51,743	4,574	8.8 (8.6-9.1)	2,103	325	15.5 (13.9-17.0)
Smoking during pregnancy						
No	356,602	14,943	4.2 (4.1-4.3)	16,880	1,035	6.1 (5.8-6.5)
Yes	76,651	2,435	3.2 (3.1-3.3)	544	38	7.0 (4.8-9.1)
Diabetes mellitus						
No	565,165	23,731	4.2 (4.1-4.3)	21,203	1,344	6.3 (6.0-6.7)
Yes	3,766	429	11.4 (10.4-12.4)	144	17	11.8 (6.5-17.1)
Gestational diabetes mellitus						
No	544,036	22,678	4.2 (4.1-4.2)	19,879	1,234	6.2 (5.9-6.5)
Yes	30,869	1,804	5.8 (5.6-6.1)	1,736	149	8.6 (7.3-9.9)

Table 2: The likelihood of gestational hypertension (GH) and preeclampsia (PE) by common risk factors

	Total	GH/PE rate (%)	OR* (95% CI)	AOR** (95% CI)
Maternal age				
<30	281,796	4.5	1.00	1.00
30-34	184,820	4.1	0.90 (0.87-0.93)	1.02 (0.99-1.05)
35-39	107,998	4.2	0.94 (0.91-0.97)	1.13 (1.09-1.17)
≥ 40	21,889	5.1	1.15 (1.08-1.22)	1.37 (1.29-1.46)
Parity				
Primiparous	246,704	6.4	1.00	1.00
Multiparous	349,816	2.8	0.43 (0.42-0.44)	0.40 (0.38-0.41)
BMI				
< 20	23,727	2.4	1.00	1.00
20-24.9	102,859	3.2	1.36 (1.24-1.49)	1.38 (1.26-1.51)
25-29.9	68,659	5.1	2.24 (2.04-2.45)	2.39 (2.18-2.62)
≥ 30	53,846	9.1	4.13 (3.78-4.51)	4.67 (4.27-5.10)
Smoking during pregnancy				
No	373,482	4.3	1.00	1.00
yes	77,195	3.2	0.74 (0.71-0.77)	0.76 (0.73-0.80)
Diabetes mellitus				
No	586,368	4.3	1.00	1.00
Yes	3,910	11.4	2.88 (2.61-3.18)	2.75 (2.48-3.05)
Gestational diabetes mellitus				
No	563,915	4.2	1.00	1.00
Yes	32,605	6.0	1.44 (1.37-1.51)	1.26 (1.20-1.33)
ART				
No	574,905	4.3	1.00	1.00
Yes	21,615	6.4	1.54 (1.45-1.63)	1.17 (1.10-1.24)

* Odd ratio

**Adjusted odd ratio: Adjusted for age, parity, BMI, smoking during pregnancy, diabetes mellitus, gestational diabetes mellitus, ART.

Table 3: The likelihood of gestational hypertension (GH) and preeclampsia (PE) for ART mothers compared with non-ART mothers by plurality

	Non-ART		ART			
	Total	**GH/PE rate (%)**	**Total**	**GH/PE rate (%)**	**OR* (95% CI)**	**AOR** (95% CI)**
All mothers						
Singleton	567,282	4.2	19,240	5.7	1.38 (1.30-1.47)	1.05 (0.98-1.12)
Multiple	7,623	8.6	2,375	12.0	1.45 (1.25-1.68)	1.10 (0.94-1.30)
All	574,905	4.3	21,615	6.4	1.54 (1.45-1.63)	1.17 (1.10-1.24)
Mothers with BMI available						
Singleton	235,718	4.8	9,260	6.9	1.48 (1.37-1.61)	1.10 (1.01-1.20)
Multiple	2,994	10.0	1,119	12.1	1.24 (1.00-1.54)	0.91 (0.72-1.17)
All	238,712	4.8	1,0379	7.5	1.59 (1.47-1.71)	1.18 (1.09-1.27)
Mothers with smoking during pregnancy available						
Singleton	427,632	4.0	15,599	5.5	1.42 (1.33-1.53)	1.07 (0.99-1.15)
Multiple	5,621	8.3	1,825	11.5	1.43 (1.20-1.70)	1.07 (0.88-1.30)
All	433,253	4.0	17,424	6.2	1.57 (1.47-1.67)	1.17 (1.10-1.26)

* Odd ratio

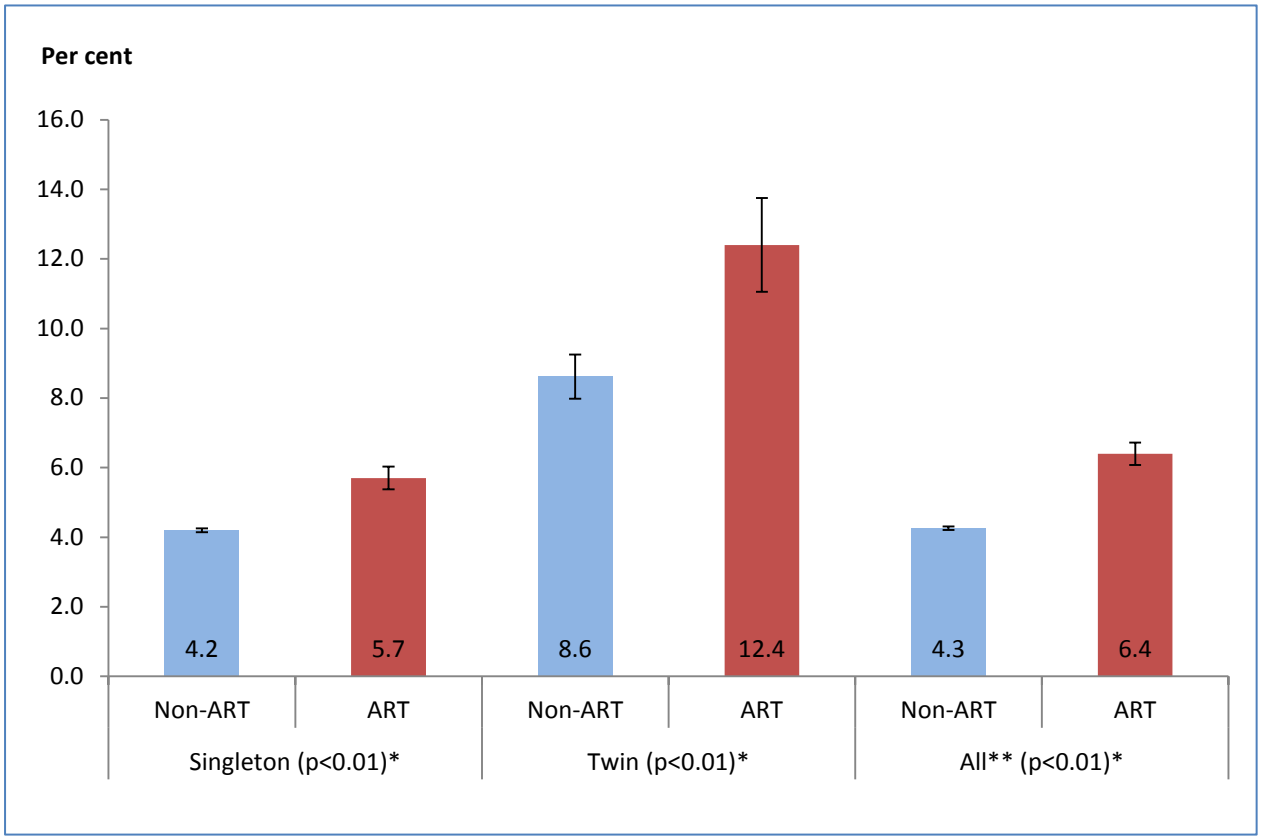
**Adjusted odd ratio: Adjusted for age, parity, BMI, smoking, diabetes mellitus and gestational diabetes mellitus.

Table 4: The likelihood of gestational hypertension (GH) and preeclampsia (PE) for ART mothers compared with non-ART mothers by parity

	Non-ART		ART			
	Total	**GH/PE rate (%)**	**Total**	**GH/PE rate (%)**	**OR* (95% CI)**	**AOR* (95% CI)**
All mothers						
Primiparous	233,241	6.4	13,463	7.9	1.26 (1.18-1.34)	1.16 (1.08-1.24)
Multiparous	341,664	2.8	8,152	4.0	1.43 (1.28-1.60)	1.30 (1.16-1.46)
All	574,905	4.3	21,615	6.4	1.54 (1.45-1.63)	1.17 (1.10-1.24)
Mothers with BMI available						
Primiparous	95,717	7.2	6,388	9.1	1.29 (1.18-1.40)	1.17 (1.06-1.28)
Multiparous	142,995	3.2	3,991	4.8	1.52 (1.31-1.77)	1.38 (1.19-1.60)
All	238,712	4.8	1,0379	7.5	1.59 (1.47-1.71)	1.18 (1.09-1.27)
Mothers with smoking during pregnancy available						
Primiparous	173,007	6.0	10,688	7.6	1.28 (1.19-1.38)	1.19 (1.09-1.27)
Multiparous	260,246	2.7	6,736	3.9	1.48 (1.30-1.67)	1.31 (1.15-1.49)
All	433,253	4.0	17,424	6.2	1.57 (1.47-1.67)	1.18 (1.09-1.26)

* Odd ratio

**Adjusted odd ratio: Adjusted for age, BMI, smoking, diabetes mellitus and gestational diabetes mellitus.



* Chi-square test, ART mothers compared to non-ART mothers

** Includes higher order multiples

Supplemental table 1: Characteristics of ART and non-ART mothers (2007-2011)

	Non-ART (n=574,905)		ART (n=21,615)	
	Number	%	Number	%
Age (years)				
<30	277,900	48.3	3,896	18.0
30-34	177,169	30.8	7,651	35.4
35-39	100,510	17.5	7,488	34.6
≥ 40	19,309	3.4	2,580	11.9
Not stated	17	0.0	0	0.0
Parity				
Primiparous	233,241	40.6	13,463	62.3
Multiparous	341,664	59.4	8,152	37.7
BMI				
< 20	22,826	4.0	901	4.2
20-24.9	98,244	17.1	4,615	21.4
25-29.9	65,899	11.5	2,760	12.8
≥ 30	51,743	9.0	2,103	9.7
Not stated	336,193	58.5	11,236	52.0
Smoking during pregnancy*	76,651	13.3	544	2.5
Diabetes mellitus**	3,766	0.7	144	0.7
Essential hypertension***	5,101	0.9	265	1.2
Gestational diabetes mellitus	30,869	5.4	1,736	8.0
Plurality				
Singleton	567,282	98.7	19,240	89.0
Twin	7,541	1.3	2,290	10.6
Higher order multiple	82	0.0	85	0.4

* Smoking during pregnancy was not reported for 24.4% of mothers

** Diabetes mellitus data was not available for 1% of mothers

*** Essential hypertension data was not available for 1% of mothers