# Increased incidence of gestational hypertension and preeclampsia after assisted reproductive technology treatment

Yueping A. Wang, Ph.D.,[a,b] Abrar A. Chughtai, Ph.D.,[b] Cynthia M. Farquhar, M.D.,[c] Wendy Pollock, Ph.D.,[d] Kei Lui, M.D.,[b] and Elizabeth A. Sullivan, M.D.[a,b]

[a] Faculty of Health, University of Technology Sydney, Ultimo and [b] School of Women's and Children's Health, University of New South Wales, Sydney, New South Wales, Australia; [c] Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand; and [d] Mercy Hospital for Women, La Trobe University, Melbourne, Victoria, Australia

**Objective:** To determine the association between assisted reproductive technology (ART) treatment and the rate of combined gestational hypertension (GH), preeclampsia (PE).
**Design:** Retrospective population study.
**Setting:** Not applicable.
**Patient(s):** A total of 596,520 mothers (3.6% ART mothers) who gave birth between 2007 and 2011.
**Intervention(s):** Not applicable.
**Main Outcome Measure(s):** Comparison of the rate of GH/PE for ART and non-ART mothers, with odds ratio (OR), adjusted odds ratio (AOR), and 95% confidence interval (CI) used to assess the association between ART and GH/PE.
**Result(s):** 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). The ART mothers had a 17% increased odds of GH/PE compared with the 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 statistically 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(s):** The changes in AOR after stratification indicated that multiple pregnancies after ART are 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 minimize multiple pregnancies after ART may reduce the excess risk of GH/PE due to ART treatment. (Fertil Steril® 2016;105:920–6. ©2016 by American Society for Reproductive Medicine.)
**Key Words:** Assisted reproductive technology, gestational hypertension, preeclampsia

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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 hemorrhage, and hepatic and renal failure (4). 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

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Reprint requests: Yueping A. Wang, Ph.D., Faculty of Health, University of Technology Sydney, P.O. Box 123, Broadway NSW, 2007, Australia (E-mail: alex.wang@uts.edu.au).

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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 prepregnancy body mass index (BMI) (13), primiparity, preexisting 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 a statistically significantly higher rate of GH and PE in some but not all studies (15). The interdependent effects between ART treatment and advanced maternal age, multiple gestations, preexisting 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 coexisting risk factors independently predict GH and PE.

Both GH and PE have a major impact on women, their babies, and public resources. 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 are an important factor in such planning. Our current population study, which included mothers who gave birth in Australia during 2007 to 2011, is aimed at determining the association between ART treatment and the rate of combined GH and PE (GH/PE), taking into account other potential confounding factors.

## MATERIALS 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 g birthweight) in Australia. This study included 596,520 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

In our study, ART treatment referred to all types of ART treatment including in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), or gamete intrafallopian transfer (GIFT). However, the type of ART treatment was not specified in the NPDC. Maternal age was categorized into four groups (<30 years, 30–34 years, 35–39 years, and ≥40 years). Parity was grouped as primiparity and multiparity. Body mass index was divided into four groups (<20, 20–24.9, 25–29.9, and ≥30). Smoking during pregnancy, preexisting 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 5 years, and only one jurisdiction reported BMI data for 4 years. Remaining jurisdictions reported BMI data for 1 to 3 years. Smoking during pregnancy was reported by two jurisdictions for all 5 years of the study period, and the remaining jurisdictions reported smoking data for 2 to 4 years. The 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. We defined GH by the International Society for the Study of Hypertension in Pregnancy criteria as a blood pressure recording of more than 140/90 mm Hg on at least two occasions more than 6 hours apart without evidence of chronic hypertension after 20 weeks' gestation. We defined PE by the 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's *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. The odds ratio (OR), adjusted odds ratio (AOR), adjusted for maternal age, parity, BMI, smoking status during pregnancy, preexisting diabetes mellitus, and gestational diabetes mellitus), and 95% confidence interval (CI) were calculated. A subanalysis 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 analyzed using Statistical Package for Social Sciences (SPSS) software, version 22 (SPSS, Inc.). 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 (available online) sets out the different demographics of ART and non-ART mothers. The ART mothers were older compared with 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%) ($P<.01$). Approximately 60% of ART mothers were primiparous, which was statistically significantly higher than non-ART mothers (40.6%) ($P<.01$). A lower proportion of smoking during pregnancy was reported for ART mothers than for non-ART mothers (2.5% and 13.3%, respectively; $P<.01$). Of ART mothers, 11.0% had multiple pregnancies, statistically significantly higher than the non-ART mothers (1.3%) ($P<.01$).