

# Effect of chronic hypertension on assisted pregnancy outcomes: a population-based study in Ontario, Canada

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**Objective:** To evaluate maternal and neonatal outcomes in women with chronic hypertension who conceive using assisted reproductive technologies (ART).

**Design:** Population-based retrospective cohort study.

**Setting:** Obstetric hospitals.

**Patient(s):** Singleton pregnancies of at least 20 weeks' gestational age to women 18 years and older who delivered a live or stillborn infant between April 1, 2006, and March 31, 2012, categorized as exposed based on a diagnosis of chronic hypertension in the mother predating the index pregnancy.

**Intervention(s):** Medically assisted pregnancy including in vitro fertilization/intracytoplasmic sperm injection (IVF-ICSI), intrauterine insemination, and ovulation induction.

**Main Outcome Measure(s):** Primary outcome: placental-mediated complications of pregnancy (preeclampsia/eclampsia, stillbirth, fetal growth restriction/low birthweight [ $<10$ th percentile], or clinically significant placental abruption); secondary outcomes: cesarean delivery (planned/unplanned), prematurity ( $<37$  or  $<32$  weeks), and neonatal death.

**Result(s):** Our cohort included 807,765 singleton pregnancies. We used log binomial regression to compute the adjusted relative risks of the various outcomes in women with hypertension as compared with healthy women in ART and unassisted pregnancies. When we tested an interaction term between hypertension and ART in multivariate models, women with ART pregnancies were at higher risk of placental-mediated complications than were those with unassisted pregnancies (adjusted risk ratio 1.48; 95% confidence interval, 1.35, 1.56). The risk was even greater in hypertensive women who used ART (adjusted risk ratio 6.77; 95% confidence interval, 4.72, 9.72). Our findings persisted when assessing IVF only and when evaluating nulliparas.

**Conclusion(s):** Hypertension is more frequent in ART-treated women. Hypertension increases the risk of placental complications, which appear to be compounded in ART versus unassisted pregnancies. (Fertil Steril® 2016;105:1003–9. ©2016 by American Society for Reproductive Medicine.)

**Key Words:** ART, hypertension, placental complications of pregnancy

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**P**regnancy by assisted reproductive technology (ART) is increasingly common in Western societies (1, 2). In North America, up to 4% of pregnancies are estimated to be conceived using ART, including in many women with chronic health conditions (3). The adverse pregnancy outcomes associated with ART include preterm birth, low-birth-weight infants, and hypertensive disorders of pregnancy (4–8). Although underlying infertility and other maternal factors contribute to these adverse outcomes (9, 10), fertility therapy itself may play a role. Placental insufficiency via either hyperestrogenic effects of controlled ovarian stimulation (11) or by clomiphene-associated variations in endometrial thickness (12) are putative mechanisms for these complications in ART pregnancies.

Women who seek treatment for infertility are older and are likely to have medical conditions that increase with age such as chronic hypertension. Chronic hypertension affects approximately 5% of pregnant women in Western populations, and this prevalence is expected to rise in parallel with changing maternal demographics (13, 14). Because elevations in blood pressure are frequently only identified during pregnancy (15), prepregnancy hypertension is likely underdiagnosed, and thus under-appreciated as a significant problem in reproductive-aged women. Chronic hypertension is strongly associated with perinatal complications such as preeclampsia, placental abruption, prematurity, cesarean delivery, and neonatal mortality (13,16–19), outcomes that commonly arise due to placental insufficiency.

It is of potential concern that ART may further augment these perinatal risks in women with chronic metabolic conditions. We have recently demonstrated synergism between maternal obesity and in vitro fertilization (IVF) treatment with an estimated absolute risk of preeclampsia above 20% in obese women who conceived by IVF–intracytoplasmic sperm injection (ICSI) (20). In addition, we reported a high rate of maternal and neonatal complications in a small case series of pregnant women with heart disease who conceived with fertility therapy (21).

This population-based cohort study estimated the risk of serious placental-mediated complications among women with chronic hypertension who conceived using ART as compared with unassisted pregnancies, and we evaluated the potential for an interaction between hypertension and ART. We hypothesized that the risk of these outcomes would be substantially higher in ART pregnancies to mothers with chronic hypertension as compared to unassisted pregnancies in normotensive women, due to possible negative synergistic effects on placental implantation and development.

## MATERIALS AND METHODS

### Study Population

This retrospective analysis of all singleton pregnancies in women aged 18 years and older who delivered in hospitals in Ontario, Canada, between April 1, 2006, and March 31, 2012, used administrative health data from the Niday Perinatal Database. The Niday Perinatal Database, created by the Perinatal Partnership Program of Eastern and South-eastern Ontario and managed by Better Outcomes Registry

& Network (BORN) Ontario, is a comprehensive Internet-based system containing detailed baseline and demographic maternal information as well as interventions during pregnancy and perinatal outcomes (22). The Niday database has been estimated to capture 96% of all obstetric deliveries in the province and has undergone a quality audit to assess the completeness of these data (22).

We excluded pregnancies resulting in embryonic or fetal loss before 20 weeks as well as multifetal gestations, given the known high rate of our primary outcome among multiples (23). We further excluded women with serious medical conditions (systemic lupus erythematosus, heart disease, and human immunodeficiency virus) that might impact our outcome.

### Exposures and Covariates

We considered all assisted reproductive treatments, including IVF (with or without ICSI), intrauterine insemination, and ovulation induction to represent “exposed” pregnancies, as per the Canadian standard definition for ART (24). A diagnosis of chronic hypertension (of any cause) as coded in the patients’ obstetric chart was extracted and represented a second category of exposure. We also extracted data on common overlapping conditions such as diabetes mellitus and thyroid disease as well as smoking status and demographic and socioeconomic variables. The database lacked information on stimulation protocols, number of embryos transferred per cycle, and number of IVF cycles.

### Outcomes

Our primary outcome was a placental-mediated complication of pregnancy, which we defined as preeclampsia/eclampsia, stillbirth, small for gestational age (SGA) (<10th percentile adjusted for gestational age), or clinically significant placental abruption. Similar composite outcomes have been used previously to reflect serious placental syndromes with a shared pathophysiology (25). The maternal secondary outcome was cesarean delivery. Neonatal secondary outcomes included prematurity (<37 weeks and <32 weeks) and neonatal mortality before hospital discharge. Neonatal mortality was available for all hospitals if it occurred in the labor and delivery unit, and for all nontertiary institutions in neonatal intensive care units.

### Analysis

The characteristics of the study population were described using frequencies and proportions for categorical variables, and mean and standard deviation for continuous variables. Non-normally distributed data were transformed, and frequencies and proportions were suppressed when there were fewer than six events per category.

To estimate risk for our composite primary outcome, each of its components, and our secondary outcomes, we performed univariate and multivariate log binomial regression comparing pregnant hypertensive women who used ART with pregnant normotensive women who conceived without therapy. We considered the following discrete categories of exposure: unassisted pregnancies without hypertension

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