ORIGINAL ARTICLE: EARLY PREGNANCY

# Dizygotic twin pregnancies after medically assisted reproduction and after natural conception: maternal and perinatal outcomes

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**Objective:** To compare maternal and perinatal outcomes in dizygotic twin pregnancies conceived after medically assisted reproduction (MAR) with outcomes after natural conception (NC).
**Design:** Nationwide registry based study.
**Setting:** Academic medical center.
**Patient(s):** Primiparous women who delivered opposite sex twins between January 2000 and December 2012 in the Netherlands, comprising dizygotic twin pregnancies: 6,694 women, 470 after ovulation induction (OI), 511 after intrauterine insemination with controlled ovarian hyperstimulation (IUI-COH), 2,437 after in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI), and 3,276 after NC.
**Intervention(s):** None.
**Main Outcome Measure(s):** Multivariable logistic regression and generalized linear mixed models to evaluate differences in outcomes: maternal outcomes of hypertension, preeclampsia, preterm delivery, hemorrhage, and delivery mode, perinatal outcomes including small for gestational age (SGA) with birth weight <10th percentile, birth weight <1,500 g, 5-minute Apgar score <7, admission to neonatal intensive care unit, congenital anomalies, and perinatal mortality.
**Result(s):** We found no statistically significant differences in maternal or perinatal outcomes after OI compared with NC. Women pregnant after IVF-ICSI had a lower risk for hypertension (adjusted odds ratio [aOR] 0.74; 95% confidence interval [CI], 0.66–0.83) compared with women pregnant after NC. After IUI-COH more children had Apgar scores <7 (adjusted odds ratio (aOR) 1.38; 95% confidence interval (CI) 1.05–1.81) and perinatal mortality rates were higher (aOR 1.56; 95% CI, 1.04–2.33) compared with NC. We found no differences in perinatal outcomes after IVF-ICSI compared with NC.
**Conclusion(s):** Overall, maternal and perinatal risks other than those due to multiplicity are similar for twin pregnancies conceived after MAR and after NC. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
**Key Words:** Intrauterine insemination, in vitro fertilization, natural conception, ovulation induction, twin pregnancy

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Twin pregnancies are associated with adverse maternal and perinatal complications. Women carrying multiple pregnancies are at increased risk of complications such as preeclampsia, pregnancy-related diabetes, and caesarean delivery. Perinatal complications are mostly related to

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premature delivery, causing considerable neonatal morbidity and mortality (1–4).

Since the widespread introduction of medically assisted reproduction (MAR), the incidence of multiple pregnancies has increased (5). The twinning rate after in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) is 20% to 40%, after intrauterine insemination with controlled ovarian hyperstimulation (IUI-COH) and ovulation induction (OI) it is 10% to 15% compared with approximately 1% after natural conception (NC) (6–9). Most twins due to MAR are dizygotic.

As singletons conceived after MAR have increased risks of pregnancy-related hypertension, placenta previa, hemorrhage, preterm birth, low birth weight, birth defects, and perinatal mortality compared with NC singletons, many studies have compared twin pregnancies after MAR with NC twins to assess whether their risks are also increased (10–18). The results of these studies are conflicting (12,19–21). There are three possible explanations for these conflicting results. First, the inclusion or exclusion of chorionicity or zygosity is key in predicting perinatal outcome of twin pregnancies (22–26). Second, these studies do not correct for parity or socioeconomic status (27–31). Third, in some cohorts misclassification bias has occurred because couples were allocated to the NC group while receiving ovarian stimulation (32, 33).

In view of these flaws, we evaluated maternal and perinatal outcomes of twin pregnancies after OI, IUI-COH, IVF-ICSI, and NC in a national registry-based study. We used strict controls for zygosity, parity, socioeconomic status, and conception method.

## MATERIALS AND METHODS

### Data Sources

We obtained data from the Netherlands Perinatal Registry (PRN) over the period 2000 through 2012 (34). This national database is obtained by a validated linkage of three registries: the midwifery registry, the obstetrics registry, and the neonatology registry of hospital admissions of newborn neonates (35, 36). The coverage of the registry is nearly 96% of approximately 190,000 deliveries per year at >16 completed weeks of gestation and all newborns admitted to a neonatal intensive care unit (NICU) after birth in the Netherlands. Caregivers from all three professions enter data on maternal characteristics, prenatal care, delivery, and pregnancy outcomes by standardized digital forms (37). These data are sent annually to the national registry office, where a number of range and consistency checks are conducted. False records are returned to the caregiver with ample opportunity to correct them. In earlier studies, outcome measures such as perinatal mortality in the PRN have been compared with civil registration data, and the quality of the outcome measurements was judged to be high (38, 39). Data on socioeconomic status on postal code level was obtained from the Netherlands Institute for Social Research (SCP) based on the mean household income level of the neighborhood, and determined by the recorded first four digits of the woman's postal code (40).

### Study Population

We extracted information of all primiparous women carrying twin pregnancies with children of opposite sex who delivered after 22 weeks of gestation two babies each weighing at least 500 g. We studied only opposite-sex twin pairs to ensure dizygosity. We classified the method of conception as NC, OI, IUI-COH, and IVF-ICSI. We collected possible confounders such as maternal age (as a categorical variable [<30, 30–34, 35–39, ≥40 years]) ethnicity, and socioeconomic status. We categorized ethnicity into Western (native Dutch women and women from other Western nations) and non-Western (including different ethnicities such as African, Surinamese, Creole, Hindustani, Mediterranean, and Asian). We categorized the socioeconomic status score into high, middle, and low groups based on their ranking (34, 41).

### Outcome Variables

We used the following maternal outcome variables: hypertension (diastolic blood pressure ≥90 mm Hg), preeclampsia (hypertension and proteinuria of >0.3 g in a 24-hour collection), preterm birth (<37.0 weeks' gestation), hemorrhage (blood loss >1,000 mL), and method of delivery (vaginal, instrumental vaginal delivery, or primary or secondary caesarean delivery), and whether the indication for the latter was suspected fetal distress or nonprogression of labor.

We selected the following perinatal outcome variables: gestational age; small for gestational age (SGA) (below the 10th percentile, <P10) derived from national growth curves specific for sex, parity, and race; low birth weight (<1,500 g); 5-minute Apgar score (<7); admission to a NICU within 28 days after birth; and congenital abnormalities and perinatal mortality (42, 43).

According to national guidelines, calculation of gestational age was based on the first day of the last menstrual period and verified by a first-trimester ultrasound. In cases of discrepancy between the two measurements (error margin 7 days), gestational age was determined by the results of the first-trimester ultrasound. Congenital anomalies, both minor and major, were recorded directly after the delivery. Our definition of perinatal mortality included stillbirth, intrapartum death, and mortality within 7 days after birth. These perinatal outcome variables are all reported per child.

### Statistical Analysis

We compared twins conceived by OI, IUI-COH, and IVF-ICSI with twins conceived by NC. For each outcome we calculated the odds ratio (OR) and 95% confidence interval (CI) and adjusted for potential confounders such as maternal age, ethnicity, socioeconomic status, and fetal gender. For the maternal outcomes we used multivariable logistic regression analyses to study the association with the conception method. For the perinatal outcomes we aimed to control for the fact that twins share the same mother and used hierarchical generalized linear mixed models (GLIMMIX). When GLIMMIX resulted in an unstable model, we used multivariable logistic regression instead. Analyses were performed using SAS software (version 9.3; SAS Institute). Ethics