Effects of in vitro fertilization and maternal characteristics on perinatal outcomes: a population-based study using siblings

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Objective: To study birthweight in consecutively born sibling singletons conceived with and without in vitro fertilization (IVF) to disentangle the effects of maternal characteristics from those of the IVF treatment itself.
Design: Population-based study.
Setting: Not applicable.
Patient(s): Firstborn and secondborn children from a 9-year birth cohort (1999–2007) comprising of 272,551 women who conceived two siblings.
Intervention(s): No intervention; children were conceived naturally or through IVF.
Main Outcome Measure(s): Birthweight.
Result(s): The study included 545,102 children born by natural conception (NC) or IVF with the data set obtained from the population-based Netherlands Perinatal Registry (PRN) containing information on pregnancies, deliveries, and neonatal outcomes. We used two approaches: [1] the intersibling approach and [2] the sibling-ship approach. In the first approach we included children born to four groups of mothers who conceived in the following order (numbers indicate birth order): NC1-NC2 (reference, n = 254,721), IVF1-NC2 (n = 1342), NC1-IVF2 (n = 471), and IVF1-IVF2 (n = 687). Several comparisons were made to interpret the effects of IVF and maternal characteristics separately. In the second approach, perinatal outcomes of IVF children (n = 1,813) were compared with those of their NC siblings (n = 1,813). The intersibling analyses suggested an association between maternal characteristics and a lower birthweight, with estimates of the maternal effect ranging from −7 g (95% CI, −40; 26) to −101 g (95% CI, −170; −32). Neither the intersibling analyses nor the sibling-ship analyses indicated an additional adverse effect of IVF treatment itself.
Conclusion(s): Maternal characteristics of subfertile women are associated with a lower birthweight. In vitro fertilization treatment itself does not additionally contribute to a lower birthweight in the offspring. (Fertil Steril® 2016;105:590–8. ©2016 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology, in vitro fertilization, perinatal outcomes, siblings, subfertility

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The number of children conceived through in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) is steadily increasing (1, 2). Yet it is well known that IVF is associated with adverse short-term outcomes, including a lower birthweight, preterm birth, and a higher prevalence of birth defects (3, 4). The underlying cause of these adverse outcomes is still under a debate: it remains unclear whether poorer perinatal outcomes are primarily caused by parental characteristics, or whether the IVF treatment itself is a contributing factor.

In the late 1980s and early 1990s it was first suggested that decreased fecundability is associated with suboptimal health outcomes in the offspring (5–7). Later studies, which used a control group of subfertile women who eventually conceived naturally or used time to pregnancy as a proxy for the severity of subfertility, also repeatedly suggested that the underlying parental subfertility is associated with obstetric problems and poorer perinatal outcomes (8–16). Furthermore, in another study the initially increased risk for congenital abnormalities after IVF attenuated after the adjustment for time to pregnancy (17), supporting the hypothesis that parental factors at least partly play a role.

On the other hand, factors related to the IVF technique itself have also been linked to worse perinatal outcomes (18, 19). Theoretically, artificial in vivo maturation of large cohorts of oocytes, early embryonic development in vitro, and the altered intrauterine environment associated with ovarian hyperstimulation could each influence developmental potential (20). Evidence for a role of the IVF treatment in causing worse perinatal outcomes can be obtained from studies using a so-called sibling-ship design in which one child is conceived naturally and the other child, from the same mother, is conceived via IVF (21). As the children share the same mother and often the same father, confounding by parental characteristics is minimized, and differences can mainly be attributed to the IVF treatment. Romundstad et al. (21) found no adverse effects of IVF on perinatal outcomes using sibling-ship analyses. Henningsen et al. (22), on the other hand, found that on average IVF children weigh 65 g less at birth than their naturally conceived siblings. A meta-analysis of both reports resulted in a pooled estimate adjusted odds ratio (aOR) of 1.27 (95% confidence interval [CI], 1.08–1.49) for preterm birth (iatrogenic and spontaneous preterm birth combined), suggesting that IVF treatment itself is associated with adverse perinatal outcomes (23).

However, the sibling-ship approach has several limitations. First, when comparing siblings conceived differently, parity should be taken into account as it is known that secondborn children have higher birthweights than firstborn children (21, 22). Other than just correcting for parity, it would be better to compare firstborn children with firstborn children, and secondborn children with secondborn children. Second, sibling-ship analyses do not provide information about the effects of parental characteristics such as subfertility.

We disentangled the effects of the IVF treatment from those of maternal characteristics on perinatal outcomes. Considering the advantages of sibling-ship analyses, we decided to use this approach. In addition, considering its disadvantages and to answer our research question, we also used a new approach: the intersibling approach. To perform intersibling analyses we included four types of mothers, each giving birth to two consecutively born singletons (the numbers 1 and 2 denote whether the child is the firstborn or the secondborn, respectively) through IVF or natural conception (NC): mothers NC1-NC2, mothers IVF1-NC2, mothers NC1-IVF2, and mothers IVF1-IVF2. By comparing the firstborn children (denoted by number 1 after the mode of conception) of mothers IVF1-NC2, NC1-IVF2, and IVF1-IVF2 with the firstborn children of control mothers NC1-NC2, and by comparing the secondborn children (denoted by number 2 after the mode of conception) of mothers IVF1-NC2, NC1-IVF2, and IVF1-IVF2 with the secondborn children of mothers NC1-NC2, effects of the IVF treatment and maternal characteristics can be studied as most maternal characteristics are constant between the different comparisons and parity is not a confounding factor.

MATERIALS AND METHODS

Participants

For this study we used a longitudinal linked data set of first and secondborn children based on a 9-year birth cohort from January 1, 1999, until December 31, 2007 (24, 25). This data set of 272,551 women was obtained from the Netherlands Perinatal Registry (PRN), a population-based registry containing information on pregnancies, deliveries, and perinatal outcomes (including readmissions) until 28 days after birth. The PRN is obtained by a validated linkage of three registries: the midwifery registry (LVR1), the obstetrics registry (LVR2), and the neonatology registry (LNR) of hospital admissions of newborns (26). Permission for record use and analysis of data for the purpose of this study was obtained from PRN (registered as data petition 14.21).

We selected all women who were pregnant with two subsequent singletons. Next, we retrieved the mode of conception of these singletons (IVF or NC) from the database as recorded by the woman's treating obstetrician or midwife. To prevent chance findings, we selected a small set of relevant outcome parameters based on the literature and with a plausible underlying pathophysiologic mechanism for the association. Birthweight was chosen as the primary outcome (22). The secondary outcome measures were gestational duration in days, spontaneous or iatrogenic preterm birth, fetal growth restriction, perinatal mortality, the presence of a congenital abnormality, and pregnancy-induced hypertensive disease (HTD).

In case of a natural conception, gestational duration was based on the date of the last menstrual period, ultrasound measurements before 20 weeks of gestation, or a combination of both. If the ultrasound measurement differed >6 days from the last menstrual period, the ultrasound measurement was considered dominant. In IVF pregnancies, gestational duration was based on the date of ovum pickup. Preterm birth (<37 weeks) was divided into spontaneous and iatrogenic preterm delivery as IVF pregnancies may more often involve an anxious patient and/or a cautious doctor, which could