Hypertensive pregnancy complications in poor and normal responders after in vitro fertilization

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Objective: To investigate whether women pregnant after a poor response in IVF have pregnancy-induced hypertension and preeclampsia more frequently than women with pregnancies after a normal response in IVF. Poor response to ovarian stimulation for IVF reflects advanced ovarian aging, which may be associated with early vascular aging. This may become apparent in an increased incidence of hypertensive pregnancy complications in pregnancies achieved after poor response in IVF.
Design: Patient-control study.
Setting: Tertiary Fertility Center.
Patient(s): One hundred fifty poor (three oocytes or fewer) and 150 normal responders (8–12 oocytes) pregnant after IVF–intracytoplasmic sperm injection (ICSI), matched for age, type of infertility, dose of recombinant FSH, singleton or twin pregnancy, and IVF or ICSI treatment.
Intervention(s): None.
Main Outcome Measure(s): Primary end points were birth weight of the neonate and the incidence of pregnancy-related hypertensive disorders. Secondary end points were duration of pregnancy, type of delivery, and live birth of the neonate.
Result(s): Poor and normal responders did not have significantly different incidences in pregnancy-related hypertensive disorders, nor did their neonates differ significantly in birth weight. Moreover, duration of pregnancy, type of delivery, and live birth ratios were similar in both poor and normal responders.
Conclusion(s): From this matched control study we were unable to confirm our hypothesis, that women pregnant after a poor response in IVF have pregnancy-induced hypertension and preeclampsia more frequently than women with pregnancies after a normal response in IVF. These results do not support a vascular etiology of poor response. (Fertil Steril® 2010;93:652–7. ©2010 by American Society for Reproductive Medicine.)

Key Words: In vitro fertilization, response to gonadotropins, preeclampsia, pregnancy-induced hypertension

As compared with pregnancies in the general population, IVF pregnancies are associated with a 2.7-fold increased risk of preeclampsia and with an increased incidence of hypertensive pregnancy complications in general (1–3). In these studies the incidence of pregnancy-induced hypertension in IVF pregnancies ranged from 6.4% to 21% and for spontaneous conceptions from 4.0% to 5.2%. For preeclampsia, incidences were 2.4% in spontaneously conceived pregnancies and 4.7% in IVF–intracytoplasmic sperm injection (ICSI) pregnancies. This association can be explained partly by factors such as multiple gestation and advanced female age.

The advanced female age and associated subfertility reflect a group of women with decreased ovarian reserve, which also has been associated with cardiovascular risk (4, 5). Moreover, vascular status in poor responders to IVF stimulation (6–8) indeed has been shown to be worse compared with normal responders (9). Finally, preeclampsia occurring in pregnancies established after IVF was more common in women requiring higher doses of exogenous FSH for ovarian stimulation, reflecting decreased ovarian reserve (10). It has been described that this higher incidence of preeclampsia in women with poor ovarian reserve may be attributed to advanced vascular aging compared with age-matched controls, affecting both vascular quality and ovarian reserve (9, 11).

Additional evidence suggests that ovarian aging may be caused by vascular aging mechanisms. Cardiovascular risk factors such as hypertension, obesity, and hypercholesterolemia are associated with onset of menopause. Every year delay in onset of menopause has been shown to decrease the risk of development of cardiovascular disease by 2% (12). Cardiovascular disease risks have repeatedly been shown to be associated with a decreased age at natural menopause and vice versa (12, 13).

Because a poor response after IVF stimulation reflects a declining ovarian reserve (7, 14), we hypothesized that hypertensive pregnancy complications are more common in IVF poor responders compared with normal responders. An increased frequency of hypertensive pregnancy disorders after poor response in IVF would substantiate a possible causative relation between vascular and ovarian aging (10, 15).

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MATERIALS AND METHODS

Study Population and IVF Treatment Characteristics

From our own IVF database, we selected 150 women who became pregnant after a poor ovarian response ($\leq$3 oocytes after follicle aspiration [16]) between the years 2000 and 2004 and compared those with 150 matched control pregnancies after a normal response in IVF (8–12 oocytes after follicle aspiration) (17). Matching was done by hand with exact matching for type of infertility (primary or secondary), pregnancy multiplicity (singleton or twin), and treatment received (IVF or ICSI) and a nearest match for age at the time of the follicle aspiration and daily dose of recombinant FSH administered. There are no uniform criteria for the definition of poor ovarian response (7). In this analysis, poor response refers to insufficient oocyte yields, defined as less than four oocytes after pickup, which definition has been published earlier (18–21). Other studies regarding poor response also have included cycle cancellation and insufficient follicular growth. Because we are interested in pregnancy complications, we obviously could not include cancelled cycles and insufficient follicular growth yielding no oocytes after pickup. The upper limit of the definition for a normal response of 12 oocytes has also been reported earlier (22–24). The lower limit of our normal response group was set at eight oocytes after pickup as proposed by the International Society for Mild Approaches in Assisted Reproduction and as reported earlier (17, 25).

Data regarding the established pregnancies were obtained from The Netherlands Perinatal Registry (26). At the time of matching, no perinatal outcome data were available yet. The inclusion period from 2000 through 2004 was chosen because our national registry (The Netherlands Perinatal Registry) provides linked data from midwives, gynecologists and neonatologists for this time period only, which provides approximately 95% coverage. We included only women <41 years of age whose pregnancies were established after fresh IVF or ICSI cycles. Women were included only once. Because data were collected retrospectively, it wasn't possible to obtain reliable and complete information regarding smoking and body mass index (BMI). We excluded women with polycystic ovary syndrome and previous ovarian surgery and those who needed <150 IU recombinant FSH per day. Previous studies by Out et al. (27) and Yong et al. (28) have shown that ovarian stimulation in women aged 33 years and over and in women aged 30 to 39 years, respectively, can be considered to be maximal when at least 150 IU/day of recombinant FSH is used.

All women were treated with a long GnRH agonist suppression protocol, details of which have been published earlier (29). The menstrual cycle was suppressed by starting leuprorelin (Lucrin; Abbott, Hoofddorp, The Netherlands) in the midluteal phase of the preceding cycle or after at least 10 days of oral contraception use. After the onset of subsequent menses or the onset of oral contraception withdrawal bleeding, ovarian hyperstimulation was started with follitropin (Puregon; Organon, Oss, The Netherlands; or Gonal-F, Serono Benelux, The Hague, The Netherlands) with a daily dose of at least 150 IU. If one or more dominant follicles of at least 18 mm diameter were observed at ultrasound examination, 10,000 IU of hCG (Pregnyl; Organon) was administered and 36 hours later transvaginal oocyte retrieval was performed. After IVF and 3 to 4 days after the follicle aspiration, two or three embryos were transferred if available; if not, a lower number of embryos was transferred. In general, women aged 38 years or older could choose to have a maximum of three embryos replaced. Women 37 years of age or younger were allowed a maximum of two embryos to be transferred. Remaining embryos were cryopreserved for transfer in a later natural cycle. The luteal phase was supported with three doses of 5,000 IU hCG (Pregnyl). Eighteen days after oocyte retrieval a pregnancy test was done. If results of this test were positive, subsequent ultrasound examinations were scheduled at a gestational age of 7 and 11 weeks.

Power Calculation

A power calculation for a two-group comparison of proportions showed we have 80% power (α 0.05) to detect a difference in the incidence of pregnancy-related hypertensive disorders of 10% with a total number of 150 subjects in both groups, assuming a 5% incidence in the normal response group.

Data Analysis

Primary end points included the birth weight of the neonate and the incidence of pregnancy-related hypertensive disorders: preeclampsia and pregnancy-induced hypertension. Pregnancy-induced hypertension was defined according to the International Society for the Study of Hypertension in Pregnancy criteria as a systolic blood pressure $\geq$140 mm Hg and/or a diastolic blood pressure $\geq$90 mm Hg after 20 weeks of gestation (30). Prepregnancy blood pressure should have been normal, and blood pressure should be normalized within 3 months after delivery. Preeclampsia was defined as pregnancy-induced hypertension with proteinuria $\geq$300 mg/24 h. Secondary end points were the duration of pregnancy, type of delivery, and live birth of the neonate. All patient information was entered into the statistical program SPSS (version 12.01; SPSS, Inc., Chicago, IL). The baseline data of the paired poor and normal responders were compared with use of McNemar tests for categorical data and Wilcoxon signed rank tests for continuous variables. A P value of .05 was considered statistically significant.

Institutional Review Board approval was not sought, because cases were collected retrospectively and anonymously. Perinatal registry data were also acquired and used anonymously.

RESULTS

We studied 1,359 poor-response cycles in women aged 41 years or younger between 2000 and 2004, which resulted in