

# Increased risk of pregnancy-induced hypertension and operative delivery after conception induced by in vitro fertilization/intracytoplasmic sperm injection in women aged 40 years and older

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**Objective:** To clarify the association between preconception fertility status and obstetric outcomes in women aged 40 years and older.

**Design:** Retrospective study by reviewing medical records.

**Setting:** Tertiary perinatal center in a university hospital.

**Patient(s):** 330 women aged 40 years and older who delivered a singleton from 2006 to 2010, and 450 women aged 30 to 34 years who delivered at the same facility as controls.

**Intervention(s):** None.

**Main Outcome Measure(s):** Incidence of pregnancy-induced hypertension, gestational diabetes mellitus, preterm birth, low birth weight, and mode of delivery assessed based on the mode of conception; spontaneous conception (SC) and in vitro fertilization/intracytoplasmic sperm injection conception (IVF-ICSI).

**Result(s):** The incidence of pregnancy-induced hypertension was statistically significantly higher in IVF-ICSI group than the SC group. This gap was commonly observed in both the women aged 40 years and older and those in the 30 to 34 age group. No statistically significant difference was observed in the frequency of gestational diabetes mellitus, preterm birth, or low birth weight. As a characteristic of nulliparous women of advanced age, the rate of operative delivery, which includes emergency cesarean section and instrumental delivery, was statistically significantly higher in IVF-ICSI group than in the SC group. Detailed investigation into the medical indications for operative delivery revealed that the difference was attributable to the elevated incidence of labor protraction and arrest.

**Conclusion(s):** Preconception fertility status can be a predicting factor of the incidence of pregnancy-induced hypertension and labor outcome, especially for women aged 40 years and older. (*Fertil Steril*® 2014;102:1065–70.

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**Key Words:** Advanced maternal age, assisted reproduction technology, labor abnormality, preconception fertility status, pregnancy-induced hypertension

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In the last few decades, drastic changes in modern society and culture have affected women's lifestyle. In the area of reproduction, the mean age of women at first childbirth has been rising rapidly in many countries (1–3). The cause is probably multifaceted: longer time in school,

higher career goals, later age of marriage, and advances in assisted reproductive technology (ART). This trend is noticeable in Japan, especially in Tokyo, a representative city. According to the Tokyo metropolitan government's 2012 statistics, the percentage of women over age 35 giving birth has reached 33.2% (4). Further, at our facility located in central Tokyo, the proportion of women over age 35 exceeded 50% of all delivery cases in 2012. Although advanced maternal age has been defined as age 35 or over, the proportion of pregnancies that belong in that age category has been increasing in modern obstetrics.

It is generally acknowledged that women's reproductive capacity declines with age (5). With the emerging social tendency to delay childbirth, more and more women are benefiting from ART to overcome age-related infertility. Although a consensus is lacking, an increasing number of studies have suggested an adverse impact from in vitro fertilization with or without intracytoplasmic sperm injection (IVF-ICSI), on obstetric outcomes. These include preterm birth, low birth weight (LBW), hypertensive disorders, and congenital malformation (6, 7). The majority of these previous studies evaluated the data without categorizing the women into age groups. Reflecting the current increase of IVF-ICSI conceptions among advanced age women, it is important clinically to gain knowledge about obstetric outcomes in advanced age women who require IVF-ICSI.

Our study clarified the correlation of perinatal outcomes with the mode of conception, focusing on woman aged 40 and older (advanced age group). In addition, we conducted a comparison with a younger control group, aged 30 to 34 years, to confirm the age-specific influence.

## MATERIALS AND METHODS

Under the approval of the institutional review board of the University of Tokyo, a retrospective analysis of pregnancies managed at the University of Tokyo Hospital (Tokyo, Japan) from January 2006 to December 2010 was performed. Clinical data were extracted by reviewing obstetric records. All the pregnant women aged 40 and older who delivered a singleton without fetal anomalies after 22 weeks of gestation during the study period (330 women) were classified into two categories based on the mode of conception: a group of spontaneous conception (SC) and a group of conception through IVF-ICSI procedures. All of the embryos transferred were autologous, as gamete donation is not approved in Japan. All the women aged 30 to 34 who delivered a singleton without fetal anomalies after 22 weeks of gestation at our facility from January 2009 to December 2010 (450 women) were set up as a control population to elucidate the age-associated impact.

In the analysis of obstetric complications, the incidence of pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), preterm birth (defined as delivery at <37 weeks of gestation), LBW (defined as birth weight <2,500 g), and umbilical artery pH were examined. We diagnosed PIH based on the clinical criteria set by the Japan Society for the Study of Hypertension in Pregnancy: systolic pressure >140 mm Hg or diastolic pressure >90 mm Hg after

20 weeks of gestation. We diagnosed GDM with a 75-g oral glucose tolerance test, which was interpreted as positive when the results met two of the following criteria:  $\geq 100$  mg/dL in fasting,  $\geq 180$  mg/dL at 1 hour after load, or  $\geq 150$  mg/dL at 2 hours.

In the analysis of delivery outcomes, the mode of delivery was evaluated by excluding women who received epidural analgesia because this can negatively affect the spontaneous vaginal delivery rate. In the assessment of delivery outcomes, total cases were separated into a group undergoing elective cesarean section and a group who tried vaginal delivery. The group who tried vaginal delivery was divided into women who completed a spontaneous vaginal delivery and those who received operative intervention by forceps/vacuum or emergency cesarean section. In all analyses, pregnancies with fetal major congenital abnormalities or chromosomal abnormalities were excluded because they affect obstetric management.

Statistical analysis was performed using JMP 9 software (SAS Institute). The incidences of obstetric complications and delivery outcomes were analyzed by chi-square test.  $P < .05$  was considered statistically significant. Odds ratios (ORs) with 95% confidence intervals were calculated.

## RESULTS

During the targeted study period, 330 women in the advanced age group and 450 women in the younger control group were found to meet the inclusion criteria described in *Materials and Methods*. Maternal characteristics in each age group are summarized separately based on the mode of conception in [Table 1](#). In the advanced age group, 242 cases (73.3%) were conceived spontaneously and 88 cases (26.7%) by IVF-ICSI. In the younger control group, 422 cases (93.8%) were conceived spontaneously and 28 cases (6.2%) by IVF-ICSI. As expected, IVF-ICSI was more prevalent in the advanced age group than the younger control group. This reflects the generally-acknowledged impact age has on women's fertility. The mean age, prepregnancy body mass index (BMI), weight gain during pregnancy, and medical complications of women with SC and women with IVF-ICSI conception were comparable between both groups (see [Table 1](#)).

The incidences of the obstetric complications were analyzed, targeting total cases from each age group, as shown in [Table 2](#) (analysis 1 in [Supplemental Fig. 1](#), available online). A statistically significant increase in the incidence of PIH was confirmed in pregnancies conceived by IVF-ICSI in both groups ( $P = .002$  advanced age group, and  $P = .010$  younger control group). When the two groups were compared, PIH occurred more frequently in the advanced age group regardless of mode of conception, with statistical significance in the SC group ( $P = .002$ ) ([Fig. 1A](#)). No statistically significant differences that depended on the mode of conception were observed in the incidence of GDM, preterm birth, or LBW (see [Table 2](#)).

The relevance of prepregnancy fertility status to mode of delivery was examined. There were 53 cases (23.9%) of elective cesarean sections in SC group and 28 cases (34.6%) in the IVF-ICSI group among the advanced age group. There were 76 cases (18.6%) and 5 cases (19.2%), respectively, in the younger

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