

Pregnancy loss in the first in vitro fertilization cycle is not predictive of subsequent delivery in women over 40 years

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Objective: To determine if there is an association between first IVF cycle outcome and subsequent delivery rate for women over 40 years.

Design: Retrospective data analysis.

Setting: Large, private academically affiliated IVF center.

Intervention(s): Patients over 40 years of age undergoing IVF.

Main Outcome Measure(s): Delivery rate compared between patients with a pregnancy loss versus a negative β -hCG in their first cycle. Additional factors including subsequent pregnancy losses, total number of IVF cycles, and delivery rates per cycle were also analyzed.

Result(s): Among women who underwent their first IVF cycle over age 40, 8% of women had a pregnancy loss and 82% had a negative β -hCG in their initial IVF cycle. In the pregnancy loss and negative β -hCG groups, 17.9% and 21.9%, respectively, had a successful delivery in a future cycle. There were no further pregnancies leading to delivery after the fourth treatment cycle for the pregnancy loss group and the sixth treatment cycle for the negative β -hCG group. The average number of cycles and the number of subsequent pregnancy losses were similar in both groups.

Conclusion(s): Outcome of initial IVF cycle is not prognostic of future delivery for women over the age of 40 years. (Fertil Steril® 2008;89:364–7. ©2008 by American Society for Reproductive Medicine.)

Key Words: ART, advanced maternal age, delivery rates, IVF, pregnancy loss, spontaneous abortion, biochemical pregnancy, ectopic

Women over the age of 40 years face many challenges with fertility treatments, not the least of which are decreased pregnancy rates and an increased risk of spontaneous abortion. Historic studies of the Hutterites provide useful information in assessing the natural limitations of fertility in a monogamous population who seek to bear as many children as possible. Within this ideal population, the average age of the last birth was 40.9 years, 33% of Hutterite women were infertile by 40 years of age, and >87% were infertile by 45 years of age (1). Menken et al. (2) reported a similar incidence of female infertility, with 30% of women infertile by 40 years and 64% infertile by 45 years of age.

The primary determinants of age-related infertility are generally believed to be a loss of oocytes and an increased rate of aneuploidy in those oocytes that remain. Elevation of FSH and E_2 levels either in the early follicular phase or af-

ter clomiphene challenge test are associated with decreased number of oocytes and decreased IVF success rates (3). Chromosomal abnormalities as determined by preimplantation genetic diagnosis increase in older women with >50% of embryos found to be abnormal over the age of 40 (4). The risk of spontaneous abortion increases with age as a result of the more prevalent chromosomal abnormalities in the oocytes obtained from older women. Irrespective of fertility status, approximately 24%–67% of conceptions in women over 40 years result in a spontaneous abortion (5). Furthermore, this rate increases steadily with each year beyond the age of 40. Even following documentation of a clinical pregnancy (ultrasonographic identification of fetal cardiac motion), women over the age of 40 years have a fivefold increased risk of spontaneous abortion when compared with younger women (6).

IVF success rates in infertile women decrease rapidly over the age of 40 years. A large study from our IVF center recently revealed that pregnancy rates were 9.7% per cycle in infertile women over the age of 40 years compared with approximately 28% for infertile women <40 years (5). Cumulative live birth rates from IVF also decline with age. Approximately 28% of women at age 40 and only 9.6% at age 43 achieve a birth from IVF treatment. In most large studies, no deliveries were reported in women 46 years of age or greater undergoing IVF with their own oocytes.

Received September 18, 2006; revised and accepted February 21, 2007.

Conflicts of interest/financial support: none.

Presented at the ASRM meeting 2004, Philadelphia, Pennsylvania.

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Given the lower success rates observed in older women, there exists much controversy regarding the appropriate number of cycles that should be undertaken before abandoning IVF as a treatment option for infertility. For women under the age of 40 years, pregnancy in a prior cycle (even a pregnancy loss) is associated with an improved chance of pregnancy in a subsequent IVF cycle (7). Although one is tempted to apply this to women over 40, especially given the higher rates of spontaneous abortion in these women, this has not been previously studied. The present analysis was performed to determine whether a pregnancy loss in a prior IVF cycle is predictive of an improved delivery rate in subsequent cycles for women over 40 years as is the case for women under the age of 40 years.

MATERIALS AND METHODS

Design

A retrospective analysis of IVF outcomes for women who underwent their first IVF cycle at the age of 40 years or greater was performed. Institutional review board approval was obtained before initiating this analysis. Data were collected for a 6-year period (between January 1st of 1995 and December 31st of 2000) for all eligible women who underwent their first cycle at Boston IVF. Women were divided into two groups based on their first cycle outcome as follows: pregnancy loss group (positive β -hCG) and negative β -hCG group.

Definitions

A positive β -hCG was defined as a peak value >100 IU/L. Any cycles with a β -hCG value between 5 IU/L and 99 IU/L were included in the negative pregnancy group. A spontaneous abortion was defined as the loss of a pregnancy following ultrasound evidence of a gestational sac. Biochemical pregnancy was defined as a β -hCG >100 IU/L in the absence of a gestational sac. Diagnosis of an ectopic pregnancy was based on the usual clinical parameters including serial β -hCG measurements, absence of an intrauterine pregnancy on ultrasound, and exam findings. Delivery rates reflect liveborn deliveries.

Inclusions/Exclusions

All women who underwent their first IVF cycle over the age of 40 years were identified. Women who had only one cycle were excluded from analysis of subsequent pregnancy outcome (175 of 584, 30%, women initially identified). Women who had a delivery in the first cycle were also excluded. The remaining 404 women underwent a total of 1,307 eligible cycles. Only cycles using the patient's own oocytes for embryo transfer were included. Eligible cycles were predominantly fresh IVF cycles (1,179 cycles, 90.2%), although 59 thaw transfer cycles (5.28%) and 69 gamete intrafallopian fertilization transfers (4.5%) were also included. The vast majority of patients were required by insurance companies to undergo intrauterine inseminations with ovarian hyperstimulation for

several cycles before being approved for IVF unless there was an obvious tubal or male factor.

IVF Protocol

Regimens included a long lupron (leuprolide acetate; TAP Pharmaceuticals, Lake Forest IL) protocol with or without a pretreatment oral contraceptive pills and an oral contraceptive pills/microdose flare. An antagonist protocol was also used, and involved the addition of a GnRH antagonist (Cetrotide; Serono, Rockland, MA; Antagon; Organon USA, Roseland, NJ) to the standard protocol when a lead dominant follicle measured ≥ 14 mm. Finally, an agonist/antagonist cycle combined a microdose agonist flare and the antagonist protocol. The dosage of gonadotropins varied according to the patient's ovarian response, and ranged from 150 IU to 750 IU per day. The gonadotropins that were used included human menopausal gonadotropins (Pergonal; Serono; Hume-gon; Organon USA; Repronex; Ferring Pharmaceuticals, Tarrytown, NY) purified urinary FSH (Fertinex; Serono), or recombinant FSH (Follistim; Organon; Gonal-F; Serono).

Monitoring during each cycle included measuring serum estradiol levels and follicular assessment by transvaginal ultrasonography beginning on treatment days 6–8. When a sufficient response was noted (at least three follicles between 15 and 20 mm), 250 μ g of choriogonadotropin (Ovidrel; Serono) or 10,000 units of subcutaneous urinary hCG was administered. Oocyte retrieval was performed under ultrasound guidance 35–36 hours after hCG, except in the rare gamete intrafallopian fertilization transfers procedures in which laparoscopic retrieval and oocyte transfer into the fallopian tubes were performed. Embryos were routinely transferred 3 days after retrieval. The number of embryos transferred was based on ASRM and institutional guidelines. The luteal phase was supported by vaginal micronized progesterone (Crinone; Serono).

Outcomes

The primary outcome was the rate of subsequent liveborn delivery after an initial IVF cycle for which a patient either did not become pregnant or had a pregnancy loss. Secondary outcomes included the rate of subsequent pregnancy loss, the cycle of last delivery, and the average number of cycles attempted.

Statistical Analysis

A chi-squared test was performed to evaluate statistical significance for subsequent delivery rate and recurrent pregnancy loss. A *P* value of $<.05$ was considered significant.

RESULTS

Compilation of Subgroups

Five hundred eighty-four women who had an initial IVF cycle over the age of 40 years were identified. Among these women, the outcomes of the first cycle were as follows: 57 (9.8%) delivered (excluded from further analysis), 49 (8.4%) had a pregnancy loss, and 478 (81.8%) had

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