

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 E₂ 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.

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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

TABLE 1**Comparison of subgroups.**

First cycle outcome	Average cycles	Average age	Average parity	Women with subsequent delivery, number (percent)
Pregnancy loss ^a N = 39	2.98	41.7	0.41	7 (18.0) ^b
Negative β -hCG N = 365	2.63	41.9	0.47	80 (21.9) ^b

Note: Similar age, average cycles, and parity were observed between negative β -hCG and pregnancy loss groups. The primary outcome of subsequent delivery did not differ significantly.
 SAB = spontaneous abortion; TAB = therapeutic abortion.
^a Includes biochemical, SAB, TAB, or ectopic pregnancies.
^b Chi-squared $P > .05$.

Sneeringer. Pregnancy loss in women over 40 years. Fertil Steril 2008.

a negative β -hCG. Pregnancy losses in the initial cycle included 35 (71.4%) spontaneous abortions, 11 (22.5%) biochemical pregnancies, 2 (4.1%) ectopic pregnancies, and 1 (2.0%) termination for developmental anomalies. One hundred seventy-five women (30.0%) had only one cycle and were therefore excluded from further analysis. Four hundred four women had no prior delivery and had at least one subsequent IVF cycle, allowing for inclusion in this study. This group was comprised of 39 women from the pregnancy loss group and 365 women from the negative β -hCG group. In summary, our study was performed on the IVF outcomes of these 404 women who underwent 1,307 cycles.

Comparison of Subgroups

The average age and parity did not differ between the two groups (Table 1). The average number of cycles was 2.98 for the pregnancy loss group and 2.63 for the negative β -hCG group. Most of the women were nulliparous in both groups, with an average parity of 0.41 in the pregnancy loss group and 0.47 in the negative β -hCG group.

Liveborn Delivery

Comparison of the pregnancy loss and negative β -hCG groups revealed no statistically significant difference in the percent of women achieving a subsequent liveborn delivery. Cumulative delivery rates per woman were 18.0% and 21.9% for pregnancy loss and negative β -hCG groups, respectively (P value was not significant). The likelihood of delivery in each cycle was also evaluated. In both groups, the overall percentage of deliveries per cycle remained relatively constant ranging from 5.9% to 15% when at least 10 women were treated. Table 2 shows the number of women in each group for each cycle and the associated number and percentage of liveborn deliveries.

The last treatment cycle that resulted in a liveborn delivery differed slightly between groups and may have been effected by the disproportionately larger negative β -hCG group with more women choosing to continue treatment after three unsuccessful IVF cycles. For the pregnancy loss and negative

β -hCG groups, the last IVF cycle resulting in a delivery was cycle 4 and 6, respectively.

Subsequent Pregnancy Losses

We also evaluated whether women with a pregnancy loss in the first cycle were more likely to have repetitive losses such as spontaneous abortions, biochemical, or ectopic pregnancies. Although the specific types of loss varied within each group, the total subsequent pregnancy losses were similar. Table 3 demonstrates the number and percentage of one or more pregnancy losses per group stratified by type of loss. Most of the women in each group had all negative subsequent cycles (no subsequent pregnancy losses or deliveries). All negative subsequent cycles were observed in 241 (66%) of

TABLE 2**Liveborn delivery rates.**

Cycle	Pregnancy loss first cycle ^a		Negative β -hCG first cycle	
	N Start	No. (%) delivery	N Start	No. (%) delivery
1	49	—	478	—
2	39	3 (7.7)	365	34 (9.3)
3	27	3 (11.1)	224	24 (10.7)
4	17	1 (5.9)	118	15 (12.7)
5	9	0 (0.0)	49	4 (8.2)
6	5	0 (0.0)	20	3 (15.0)
7	0	—	3	0 (0.0)
8	0	—	1	0 (0.0)

Note: The number and percentage of deliveries per cycle for each subgroup is presented above. When >10 patients undergo a cycle, the delivery rate remains within a range of 5.9%–15% per cycle for both groups.

SAB = spontaneous abortions; TAB = therapeutic abortion.

^a Includes biochemical, SAB, TAB, or ectopic pregnancies.

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TABLE 3**Subsequent pregnancy losses.**

First cycle outcome	Subsequent losses No. (%)				All negative β -hCG No. (%)
	SAB	TAB	Biochem	Ectopic	
Pregnancy loss group	4 (10.3)	—	5 (12.8)	1 (2.6)	23 (59.0) ^a
Negative β -hCG group	36 (9.9)	1 (0.3)	15 (4.1)	4 (1.1)	241 (66.0) ^a

Note: The total number of women in each subgroup who had a subsequent SAB, termination, biochemical pregnancy, or ectopic pregnancy is shown. Recurrent outcomes within the same woman were excluded. Comparison of women who underwent at least two cycles and had no pregnancies (all negative cycles) revealed no statistically significant difference in the risk for subsequent pregnancy losses between patients with initial negative cycle versus a pregnancy loss.

SAB = spontaneous abortion; TAB = therapeutic abortion.

^a Chi-squared $P \geq .05$.

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the negative β -hCG group and 23 (59%) of the pregnancy loss group.

DISCUSSION

For younger women, prior studies have demonstrated that a positive pregnancy test in an early IVF cycle is a predictor of subsequent success in achieving a pregnancy (7). Our study demonstrated that for women over the age of 40 years, a pregnancy loss in their first IVF cycle is not a prognostic factor for either future success or failure in subsequent IVF cycles. Furthermore, among women with either a pregnancy loss or a negative β -hCG in their first IVF cycle, the cumulative delivery rate and subsequent per cycle delivery rates were similar. The rates in both groups approximated published rates for women over age 40 years (5, 8).

Our results differed from prior studies on younger women in which any type of pregnancy in an IVF cycle was found to predict an improved likelihood of future livebirth. Possible explanations for this difference include disparate age groups, disparate infertility etiology, or disparate primary outcomes studied. We believe the most likely reason for this difference in findings is age. Both decreased baseline pregnancy and increased spontaneous abortion rates significantly impair a couple's ability to become pregnant in this older cohort. Once the age-related pregnancy rate drops to a certain level, our data suggest that there is no greater likelihood to conceive even if a couple experiences a pregnancy loss.

Disparate etiology for infertility may explain the difference in findings for young and older cohorts. Although the older age group's etiology for infertility is primarily decreased ovarian reserve, younger patients are more likely to have varied etiologies for their infertility. An improved prognosis with a proven ability to become pregnant, as with an

early pregnancy loss, may select for patients with an infertility etiology associated with a higher likelihood of future successful delivery. However, for older women, the most pronounced etiology for infertility is declining oocyte function and number consistent with diminished ovarian reserve. Thus, an early pregnancy loss does not select for a group with a more favorable prognosis in this older cohort.

In summary, among women over 40 years of age, there is no significant difference in subsequent delivery rates between women experiencing a pregnancy loss compared with women not achieving a pregnancy in their initial IVF cycle. In contrast to studies of infertile women under the age of 40 years, an early pregnancy loss is not predictive of a successful delivery in subsequent IVF cycles.

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