One last chance for pregnancy: a review of 2,705 in vitro fertilization cycles initiated in women age 40 years and above

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Objective: To describe live birth rates and predictors of success in 1-year age increments for women ≥40 years when initiating assisted reproductive technologies (ART).
Design: Retrospective database analysis.
Setting: A large university-affiliated infertility center.
Patient(s): One thousand two hundred sixty-three women undergoing 2,705 ART cycles at age 40 or above.
Intervention(s): Couples undergoing ART.
Main Outcome Measure(s): Pregnancy and live birth rates per cycle start were determined based on 1-year increments in women aged ≥40. Predictors of success, including number of embryos transferred, number of fetal heartbeats, availability of embryos for cryopreservation, and cycle day 3 FSH levels, were analyzed.
Result(s): The overall live birth rate per cycle start was 9.7%. Cumulative live birth rates in women ranged from 28.4% if starting ART at age 40 to 0 by age 46. The overall spontaneous abortion rate was 32.6% (range, 23.9%–66.7%). Higher pregnancy rates were predicted by the greater number of embryos available for transfer, by the availability of excess embryos for cryopreservation, and by the presence of two fetal heartbeats on ultrasound. The outcome of the first IVF cycle did not predict the outcome of subsequent cycles.
Conclusion(s): Assisted reproductive technology has a reasonable chance for success (>5%) up until the end of the forty-third year. Twins on initial ultrasound, large numbers of embryos available for transfer, and the presence of excess embryos for cryopreservation predict higher live birth rates. (Fertil Steril® 2005;84:435–45. ©2005 by American Society for Reproductive Medicine.)

Key Words: Advanced maternal age, ART, spontaneous abortion, multiple pregnancy rates

In recent years, there has been a national trend toward delaying childbirth. This is demonstrated by the fact that the number of births for women between 40 and 44 years of age nearly doubled between 1990 and 2002 (1). In 2002, the last year for which national statistics are available, over 95,000 children were born to women in this age cohort, representing 8.3 births/1,000 women. Over 20,000 of these women were having their first child between these ages (1). However, one in six women between the ages of 40 and 45 years has never had a child (1). There has also been more than a doubling of the birth rate in women aged 45–49 years, to 0.5 births/1,000 women, but the majority of these births are likely attributable to the use of donor oocytes (2).

While more women in the fifth decade of life are becoming pregnant, 50% of them will have some difficulty in their pursuit to have children (3). In fact, 19% of all women using assisted reproductive technologies (ART) are aged 40 years and above (4). The age-related drop in fecundity has long been known (5, 6). According to a study of natural fertility in Hutterites, one-third of women are infertile by 40 years of age and 87% by 45 years of age. This is an isolated community that practices early monogamy and marriage, attempts pregnancy until it is no longer possible, and shuns promiscuity, drugs, and alcohol. In this small cohort of women, the average age of last birth was 40.9 years (7).

In another society-based survey of natural fertility, it was estimated that 63.6% of women who marry between the ages of 40 and 44 years will be at risk for childlessness (8). One recent study examined a population of Israeli women in which only 0.2% spontaneously conceived and delivered on or after the age of 45 years (9). The majority of these women were members of ultraorthodox Jewish sects in Jerusalem. Like the Hutterites, this community is relatively isolated, monogamy is widely practiced, and contraception is not used as there is a strong societal pressure to reproduce for as long as possible. While ART may overcome this age-related decline to some extent, there appears to be an upper limit beyond which no pregnancies will occur using a woman's own oocytes.

Two factors that have the greatest effect on the decrease in fecundity with age are the decrease in oocyte number and the increase in aneuploidy rates (10–12). One study suggested

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that in addition to the gradual loss of germ cells that occurs with age, there may be an accelerated rate of oocyte loss that begins sometime late in the fourth decade (13). Once a woman loses a critical mass of oocytes, controlled ovarian hyperstimulation (COH) will be unable to compensate her for this decline. In addition to a reduction in fecundity, the rising percentage of aneuploid embryos is associated with an increased risk of spontaneous abortions (11).

For women desiring a last chance at becoming pregnant by IVF at age 40 and beyond, several critical questions are presently being debated: [1] at what ages are such attempts reasonable and feasible and [2] at these ages, what predictors can be used to identify those who have a reasonable chance for pregnancy. For many years, the upper limits for allowing IVF attempts were arbitrarily chosen (usually age 41 or 42 years) and strictly enforced. These age restrictions were based on a limited number of IVF cycles performed at a time when overall success rates were much lower than they are today. They were also based on the presumption that IVF success rates would likely improve in the younger aged women, but not in women nearing the end of their reproductive lifespan.

The purpose of the present study is to delineate the age-based chance of achieving a live birth with ART using a woman's own oocytes at a time when overall IVF success rates are improved, and to identify factors associated with success in women seeking fertility treatments at age 40 years and beyond. Furthermore, we seek to determine whether success rates in this group of women may continue to improve, or have plateaued, as previously thought. Because fertility decreases much more rapidly from year to year in women over 40 than in younger women, we felt that a year-by-year analysis would be most helpful to the clinician when counseling patients about the risks, benefits, and likelihood of success when embarking on infertility therapy beyond the age of 40 years.

The Massachusetts state insurance mandate requires insurance coverage for all couples meeting criteria that would predict a reasonable chance for success. Such a mandate maximizes the number of women over 40 years of age who have access to ART. Given that Boston IVF is the largest U.S. ART program and performs a large number of IVF cycles in women aged 40 years and older, we felt that a retrospective review of our experience would provide the best opportunity to understand predictors of success. The expense and age-related limited success of IVF for these couples would make a similar sized study through a randomized clinical trial nearly impossible.

MATERIALS AND METHODS

For this study, the Boston IVF database kept for annual Centers for Disease Control reporting was used and two individual analyses were performed. The first analysis included a retrospective review of all 2,705 IVF and intracytoplasmic sperm injection (ICSI) cycles performed in women ages 40 years or older (n=1,263 women) present in the Boston IVF database between January 1999 and June 2002. Only fresh nondonor IVF and ICSI cycles were included in this analysis, as only 153 (5.7%) cycles in this age group had excess embryos that were cryopreserved. Some of these women (n=433) underwent IVF cycles before their fortieth birthday; cycles that occurred before age 40 were excluded from the analysis. Age at cycle start was categorized into 1-year increments, and data were compared among these groups.

A second analysis was performed for a subset of 830 women whose *first* IVF or ICSI cycle was initiated after the fortieth birthday and during this same 42-month time period. For these women, a total of 1,915 fresh cycles using their own oocytes were included. For both groups, the abstracted data included procedure type, age at cycle start, indication for ART, cycle day 3 FSH, gravidity, parity, number of oocytes retrieved, number of embryos transferred, presence and number of embryos frozen, number of gestational sacs and fetal heart beats on initial ultrasound, and pregnancy outcome. Information regarding spontaneous and selective reduction was also obtained.

Virtually all women under age 44 years and many women 44 years and older had insurance coverage for infertility under the state insurance mandate. Each insurance company has separate, but similar, FSH and E_2 criteria for allowing the initiation of IVF treatment. In addition, each insurance company has separate, but similar, criteria for continuing IVF after the first cycle, including number of oocytes retrieved and fertilized and embryo quality.

All patients had basal follicle-stimulating hormone (FSH) screening on cycle days 1–3 during their initial infertility evaluation. Serum FSH concentrations were determined by a solid-phase two-site chemiluminescent immunometric assay (sensitivity 0.1 mIU/mL; intra- and interassay variation below 12; normal range, 1.9–10 mIU/mL). One of three protocols was used for controlled ovarian hyperstimulation (COH), based on physician preference, patient age, infertility diagnosis, and previous response to gonadotropins, when available. These protocols included a long lupron (leuprolide acetate; TAP Pharmaceuticals, Lake Forest, IL) regimen with or without a pretreatment oral contraceptive, an oral contraceptive/microdose leuprolide flare, and an antagonist protocol (Cetrotide; Serono, Rockland, MA; Antagon; Organon USA, Roseland, NJ) in which the GnRH antagonist was initiated when the lead dominant follicle measured ≥14 mm. Human menopausal gonadotropins (Pergonal, Serono; Humegon, Organon USA; Repronex, Ferring Pharmaceuticals, Tarrytown, NY), and recombinant FSH (Follistim, Organon; Gonal-F, Serono) were used in these cycles, alone or in combination.

Serum E_2 was measured, and ultrasound monitoring was begun between days 6 and 8 of gonadotropin stimulation. The decision to cancel a cycle was based on a combination