CLINICAL ASSISTED REPRODUCTION

An Analysis of the Effect of Age on Implantation Rates

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Purpose: To evaluate implantation rate as a function of age.

Methods: A total of 1621 consecutive cycles of IVF were evaluated for implantation as a function of age at The New York Hospital/Cornell Medical Center.

Results: An overall implantation rate of 23.3% (1328/5691) was found. The implantation rate as a function of age decreased in a nonlinear fashion. Implantation remained constant until the age of 35 and then decreased in a significantly, linear fashion by 2.77% per year ($P < 0.001$, $R^2 = 0.975$). A formula to predict implantation rates for a given age was developed: $\text{Implantation rate} = -119.352 + (9.985 \times \text{Age} - (0.164 \times \text{Age}^2))$.

Conclusions: We have demonstrated that implantation rates remain constant until the age of 35 at which time a linear decrease of 2.77% per year is observed.

KEY WORDS: Implantation; IVF-ET; maternal age.

INTRODUCTION

Success after in vitro fertilization–embryo transfer (IVF-ET) is negatively affected by advancing maternal age. Part of this decline is explained by the fact that older women undergoing controlled ovarian hyperstimulation for IVF-ET are less likely to produce as many oocytes as younger women (1–3). In addition, decreased implantation rates in older women have been demonstrated, which appear to be most profound after the age of 37 years (3). A case–control study investigating implantation after intracytoplasmic sperm injection

reported implantation rates that were over three times higher in women under 40 years compared to women over 40 years (14.3 vs. 4.5%) (1). Recently, a biphasic model was described to demonstrate the decrease in implantation rates as a function of increasing age (1). This report noted a 7% per year drop in implantation rates until the age of 37 years, at which time implantation rates fell at a rate of 20% per year. To date, no other studies have confirmed these findings in women under the age of 35 years.

In Tietze's (4) classic study, infertility did not begin to rise appreciably until the age of 35. Furthermore, it is not until the age of 37 to 38 that an acceleration of follicular loss is noted (5). At this time, subtle elevations in follicle-stimulating hormone (FSH) concentration and diminishing inhibin levels have been found. Given the above biological observations, one can question whether the purported age-related drop in implantation rates before age 37 truly exists. Thus, in this investigation, we evaluated age-specific implantation rates in a large series of women undergoing IVF.

MATERIALS AND METHODS

A retrospective study was performed on 1621 consecutive treatment cycles resulting in an embryo transfer over an 18-month period dating May 1995–October 1996 at The Center for Reproductive Medicine and Infertility, The New York Hospital/Cornell Medical Center. All cycles were reviewed for the age of the patient, the primary diagnosis of infertility, the number of embryos transferred, and the number of fetal hearts at a 7-week gestational age ultrasound examination (32 days after the ET). Patients utilizing donor oocytes or frozen embryos were not included in the analysis.

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Ovarian stimulation, timing of human chorionic gonadotropin (hCG) injection, follicular aspiration, and ET were performed as previously described (6). An implantation was considered to have occurred if a fetal heart was detected by ultrasound examination. Data and statistics were compiled by computer using a database and statistical package to calculate means, standard deviations, correlation testing, regression analysis, χ^2 , and t testing. A P value < 0.05 was considered significant.

RESULTS

A total of 1621 patients underwent embryo transfer after controlled ovarian hyperstimulation and IVF. The average age of the patient population was 36.06 ± 4.52 years. A total of 5691 embryos were replaced and a total of 1328 fetal hearts were detected, yielding an overall average implantation rate of 23.33%.

Table I demonstrates the implantation rate by primary diagnosis of infertility. Patients with immunologic infertility had the highest implantation rate, although only 26 patients were in this category. The implantation rate in patients with male factor infertility was significantly higher than in patients with tubal, diethylstilbestrol (DES)-related, endometriosis-related, anovulatory, or idiopathic infertility ($P < 0.05$).

The implantation rate as a function of age is demonstrated in Fig. 1. Analysis of the raw data revealed a nonlinear function. Implantation appears to remain constant until the age of 35, at which time a progressive decline begins. Utilizing a polynomial regression to explain implantation as a function of maternal age, a highly significant model is developed ($P < 0.001$).

The decline in the implantation rate in women over 35 years old was linear. A simple regression analysis of the implantation in women 35 years and older demonstrates a significant model with a decline in the

Table II. Implantation and Delivery Rates by Age

Age	Number	Implantation rate (%)	Delivery/transfer (%)
≤ 25	28	24.4	50.0
26	13	28.9	53.8
27	20	32.7	65.0
28	28	37.5	50.0
29	48	31.9	62.5
30	57	35.4	57.9
31	89	33.0	60.7
32	69	33.0	52.2
33	92	36.8	65.2
34	113	29.5	54.0
35	133	31.0	51.1
36	125	28.2	44.8
37	138	23.8	49.3
38	150	18.9	40.0
39	121	18.8	38.8
40	108	16.3	36.8
41	111	14.0	29.7
42	77	9.9	22.1
43	71	5.1	15.5
44	19	5.9	15.8
> 44	11	2.3	0

implantation rate of 2.77% per year ($P < 0.001$, $R^2 = 0.975$).

As demonstrated in Table I, there is variation in the implantation rate by primary etiology of infertility. To remove the possible confounding variables that the

Fig. 1. Implantation rate as calculated by maternal age is demonstrated. The implantation rate appears to remain constant until the age of 35 years.

Table I. Implantation Rate by Category of Infertility

Category	Number	Age ($\pm$ SD)	Implantation rate
Tubal	315	36.84 ± 4.21	18.5
Male	745	35.06 ± 4.69	26.2
Endometriosis	251	36.07 ± 4.15	21.9
DES exposed	16	38.17 ± 4.03	15.5
Immunologic	26	36.69 ± 4.28	47.9
Anovulatory	28	36.64 ± 4.62	27.0
Idiopathic	240	37.61 ± 4.26	20.2
Total	1621	36.06 ± 4.46	23.3

etiology of infertility may have on implantation rate when evaluating its relationship with maternal age, we analyzed the 745 patients with primary male factor infertility in a separate fashion. Once again, a polynomial regression demonstrated a highly significant model to explain the variation of implantation rate as a function of age ($P < 0.01$) as demonstrated in Fig. 2.

Finally, an equation was developed to determine the prospective implantation rate based on maternal age: $\text{implantation rate} = -119.352 + (9.985 \times \text{Age} - (0.164 \times \text{Age}^2))$. Figure 3 demonstrates the actual and the calculated implantation rates based on this mathematical model.

DISCUSSION

We have demonstrated the significant effect that maternal age has on implantation rates. We found that after the age of 35 years, the implantation rate declines by 2.77% per year. These findings in women older than 35 is similar to the time frame that a significant drop in implantation was found by van Kooij *et al.* (3). A French study evaluating nulliparous women with azoospermic partners undergoing artificial insemination also reported that the conception rate per cycle as

Fig. 2. Implantation rate of patients with male factor infertility as calculated by maternal age is demonstrated. The implantation rate appears to remain constant until the age of 36 years.

Fig. 3. The actual data points for implantation rate as determined by age are demonstrated by the circles. The curved line represents the calculated implantation rates as a function of age as demonstrated by the following equation:

$$\text{Implantation Rate} = -119.352 + (9.985 \times \text{Age} - (0.164 \times \text{Age}^2))$$

a function of a woman's age did not markedly decrease until 35 years of age (7). Thus, from our study and the available evidence from the literature, it appears that after the age of 35 years a decrease in implantation rate begins.

However, in women younger than 35 years of age, controversy exists as to the effect of age on the implantation rate. In contrast to what was reported by van Kooij *et al.* (3), we did not find variation in the implantation rate in women younger than 35 years old. We found that the implantation rate in women under 35 years appears to remain constant. In an effort to remove the effect that female infertility may have on implantation, we evaluated the women with male factor infertility as the primary diagnosis and found that there also was a constant implantation rate until the age of 36 years. These findings are consistent with the work with Hutterites described by Tietze (4) and Faddy *et al.* (5). The Hutterites did not have a significant decrease in fertility until after the age of 35 years. Furthermore, it is not until the age of 37 that an increase in day 3 FSH and a decrease in inhibin is noted. These natural and biological data are consonant with our findings of a constant implantation rate until 35 years old.

Why patients after the age of 35 have a decrease in implantation is probably mostly related to the age of the female partner. After 35 years of age, there is an increase in the number of genetically abnormal embryos (8). A significant relationship between the rate of aneuploidy for chromosome 16 and age has been previously described (9). Monosomy for chromosome 16 was detected in over 70% of the embryos with aneuploidy for chromosome 16, a genetic abnormality not found in spontaneous abortions. This would indicate that monosomic aneuploidies result in implantation failures. Therefore, given that aneuploidy is significantly increased in the embryos of older women, this may partially explain the decreased implantation rate in older women.

Several authors have suggested that the successful implementation of oocyte donation in women older than 40 years suggests that the endometrium of older women retains normal receptivity (10, 11). In a report comparing pregnancy outcomes in younger IVF donors with those in their respective older recipients who shared oocytes from the same cohort there was no statistically significant difference in clinical pregnancy and delivery rates between the donors (33% and 23%, respectively) and recipients (40% and 30%, respectively) (12). This suggests that oocyte quality, rather than uterine factors, is the primary determinant of human implantation efficiency.

On the other hand, others have suggested that uterine factors play a role in the age-related decline in fecundity. It has been reported that doubling the dosage of exogenous progesterone may offset the slight reduction in the embryo implantation rate in women older than 40 years undergoing oocyte donation (13). Feldberg *et al.* (14) concluded that the ability of the uterus to sustain an implantation in older women was partially responsible for the decreased pregnancy rates in older women. Thus, although oocyte quality appears to be the major factor associated with the reduction in fecundity with advancing age, uterine factors and reduced endometrial receptivity also may play a role.

In conclusion, we have demonstrated the significant effect that age has on implantation rates. This effect is predominantly found in women over 35 years of age. Contrary to what has been previously reported, implantation in women younger than 35 years of age appears to remain constant without an age influence.

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