

EFFECT OF AGE ON THE SUCCESS OF THERAPY FOR INFERTILITY

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The present study aims at evaluating the reproductive capacity of the older patient. We attempt to determine whether a treating physician would have a higher success rate in correcting infertility for women under age 35 in contrast to women over age 35. The question of age-related spontaneous abortion is also raised.

Introduction

In evaluating the reproduction capability in older women, several early studies have suggested that fecundity decreases with advancing age.¹⁻⁴ Tulandi et al. confirmed that fertility does indeed decline as age increases but stated that the most important cause of infertility was not the ovulatory factor. In fact, the most common infertility factor in women age 36-40 was the tubal factor, and in women over the age of 40, unexplained factors were most frequently present.⁵

Many of these studies raised important questions concerning the inability to control certain variables. A study from France overcame many of these variations by evaluating female fecundity as a function of age in 2,193 nulliparous women receiving artificial insemination by donor where their husbands were azoosper-

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mic.⁶ The study confirmed a decrease in cumulative success rates for women 31-35 and an even greater decrease in women over 35.

However, there are at least some researchers who question whether fecundity truly does decrease with advancing age. William James suggested that the decline in fecundity is related more to a decrease in coital frequency with advancing age and also, in some part, to unrecognized spontaneous abortions.⁷

The present study was aimed at evaluating the reproductive capacity of the older patient in a slightly different way. Taking into consideration the numerous advances in diagnostic and therapeutic capacities now available to the infertile woman as compared to the years when several of these studies were performed, we wanted to determine if the treating physician would have a higher success in correcting infertility in women under age 35 versus age 35 and older. Furthermore, we hoped to evaluate the fecundity potential of women age 40 and over if the numbers were adequate for comparison.

Materials and Methods

A total of 200 consecutive couples seeking help for infertility were enrolled in the study. A semen analysis was requested of all husbands and normal levels were based on standards established by the World Health Organization (WHO).⁸ A serum progesterone (P) was obtained one week prior to menses in women with regular cycles, with a level under 3 ng/ml considered anovulatory. The serum P was obtained weekly in patients with irregular cycles until menses unless previous information indicated anovulation, that is, monophasic basal body temperature charts.

Patients with regular menses were evaluated first by serial pelvic sonography and serum estradiol (E_2) and P measurements to determine the women's ability to produce a mature follicle.⁹⁻¹³ An average diameter of 17 mm, along with a minimum serum E_2 of 200 pg/ml, was considered normal.¹⁴ Release of the ovum from the follicle was assumed by demonstration of shrinkage of the follicle by at least 5 mm, 2-3 days from follicular maturation.^{15,16}

Luteal phase adequacy was determined by an endometrial biopsy taken 13-14 days from the serum E_2 peak. The biopsy was

considered abnormal if it dated more than two days out of phase. Patients with luteal phase deficiency (LPD) were divided into two types: pure LPD where the follicle attained maturity and LPD associated with immature follicles.^{17,18} Women with mature follicles and pure LPD were treated with supplemental progesterone only; those with immature follicles were treated with clomiphene citrate with the dosage titrated to achieve follicular maturation, or bromocriptine if hyperprolactinemia was present, or human menopausal gonadotropins (hMG) if a mucus problem existed.^{19,20}

The luteinized unruptured follicle (LUF) syndrome was treated with human chorionic gonadotropins (hCG) or hCG mixed with hMG.²¹ A large majority of the patients treated with follicle maturing drugs were given supplemental progesterone vaginal suppositories in the luteal phase.¹⁴

A cervical factor problem was diagnosed if, at the time of a mature follicle, and assuming a normal semen analysis, there were not at least 3 sperm per high powered microscopic field with progressive forward motion 6-12 h following intercourse (assuming a normal semen analysis).²² Poor cervical mucus was treated by either guaifenesin,²³ a short course of estrogen,²⁴ or estrogen and hMG.^{25,26}

If a husband had a subnormal spermiogram and if his gonadotropins were normal he was treated with clomiphene citrate, 25 mg for 25 days each month.²⁷⁻²⁹ Splitting of the ejaculate and insemination of the better portion was also used.³⁰

Some of the patients previously had a laparoscopy performed by another physician and some had a history of a previous hysterosalpingogram. Normally our policy is not to insist on repeating these procedures, but we do give the wife the option of having the procedure repeated or performed for the first time. If adhesions are present, then we try to lyse them and if endometriosis is present, the implants are then coagulated.³¹ Nevertheless, we do not insist on a laparoscopy unless there is failure to conceive after 8 corrected cycles. Since this study covered that same time period, from 8 months from a patient's initial visit, not all patients elected to have tubal studies.

The number of pregnancies achieved within an 8-month time period from the initial consultation was recorded. The patients requiring progesterone supplementation were treated during their

first trimester as previously described.¹⁴ A pelvic ultrasound confirming viability was performed at 5-6 weeks from conception and at 12 weeks from conception.

The women were divided into two groups. Group 1 (age 34 and under) and Group 2 (age 35 and over), for comparison and statistical analyses.

Results

The rate of conception was not statistically different in women over 35 (17 of 36 or 47%) versus women under 35 (91 of 164 or 55%). Chi-square analysis indicated a value of $p = .73$. Six of 8 women over 40 conceived (75%), but there were too few cases for statistical analysis.

The incidence of spontaneous abortion was not statistically different (13 of 91 or 14% for Group 1 and 3 of 17 or 18% for Group 2). However, 2 of the 3 abortions occurred in the Group 40 and over. Thus, in actuality, 33% aborted in the 40 and older group compared to 14% of patients under 40, but because of the small numbers in the 40 and over group, this difference is not statistically significant.

Ovulation defects were divided into categories of: (1) normal ovulation; (2) pure LPD in which a late luteal phase endometrial biopsy dated more than 2 days out of phase, but where the follicle attained an average diameter of at least 17 mm and the serum estradiol (E_2) was over 200 pg/ml while the serum P level was under 1.5 ng/ml; (3) LPD associated with immature follicles where either the follicle did not reach the right diameter, or, more likely, the serum E_2 level did not rise adequately; (4) the LUF syndrome where the follicle attained the right maturity but collapse of the follicle (as evidenced by shrinkage of at least 5 mm by sonography 2-3 days after follicular maturation was achieved) did not occur; and (5) anovulation where at no time during the cycle did the serum P level increase above 5 ng/ml. The results are listed in Table 1. In comparing women 34 and younger to those 35 and older, no significant differences were noted in any of the categories.

There were no significant differences in the type of ovulation

TABLE 1 Types of Ovulation Disorders according to Age

	Group 1 (<i>n</i> = 164)* (women age 34 and under)	Group 2 (<i>n</i> = 36)* (women age 35 and over)
Normal ovulation	20 (12%)	3 (8%)
Pure luteal phase defect	42 (26%)	10 (28%)
Immature follicle and luteal phase defect	83 (50%)	16 (44%)
Luteinized unruptured follicle	14 (9%)	4 (11%)
Anovulation	5 (3%)	3 (8%)

**p* > .05 (not significant).

inducing drugs required as seen in Table 2. Of Group 1, 58% required an ovulation inducing drug, versus 61% of Group 2 patients.

The dosages of progesterone vaginal suppositories needed to correct the endometrial biopsies are seen in Table 3. There was no statistical difference in the amounts used or the percent requiring progesterone supplementation.

Laparoscopies were performed on 111 of Group 1 patients (111/164 or 68%) and 38 (38/111 or 34%) were found to have endometriosis. Twenty-four of 36 (67%) Group 2 patients were laparoscoped and 8 (8/24 or 33%) had endometriosis (see Table 4). Thus, the incidence of this condition in the two age groups was almost identical.

The data demonstrated some other interesting findings. Re-

TABLE 2 Ovulation Inducing Drugs Employed

	Group 1 (<i>n</i> = 164)* (women age 34 and under)	Group 2 (<i>n</i> = 36)* (women age 35 and over)
Clomiphene citrate	41 (25%)	6 (17%)
Human menopausal gonadotropins	51 (31%)	16 (44%)
Bromocriptine	4 (2%)	0 (0%)
Total	96 (58%)	22 (61%)

**p* > .05 (not significant).

TABLE 3 Dosages of Progesterone Vaginal Suppositories Needed to Correct the Endometrial Biopsy

	Group 1 (<i>n</i> = 164)* (women age 34 and under)	Group 2 (<i>n</i> = 36)* (women age 35 and over)
0 mg	51 (31%)	12 (33%)
75 mg	35 (21%)	7 (19%)
100 mg	12 (7%)	4 (11%)
150 mg	2 (1%)	1 (3%)
200 mg	2 (1%)	
300 mg	2 (1%)	
Total	104 (63%)	24 (67%)

**p* > .05 (not significant).

ardless of age, women not requiring ovulation drugs were no more successful (58%) than those needing ovulation drugs (50%). Endometriosis when seen laparoscopically was coagulated as best as possible and there was no difference in the rate of conception in patients.

DISCUSSION

Previous data has demonstrated that fecundity decreases with age. The present study evaluates the effect of age in an alternative manner by trying to determine, in a group of infertility patients, whether a successful outcome is more difficult to achieve in the older woman. Also, the study was designed to determine whether the etiology of infertility, especially ovulation disorders, differs in the older age group. The data suggest that there is no greater

TABLE 4 Tubal, Cervical, and Male Factor

	Group 1 (<i>n</i> = 164)*	Group 2 (<i>n</i> = 36)*
Tubal factor	9 (5%)	1 (3%)
Cervical factor	42 (26%)	8 (22%)
Male factor	21 (13%)	8 (22%)

**p* > .05 (not significant).

difficulty in correcting infertility in patients over 35 than in those under this age. Although the group was few in number, it was encouraging to see that 6 of 8 patients 40 or older were also able to conceive.

There was no difference in the rate of spontaneous abortion in the two age groups, though we suspect that, had the percentage of the older group been composed of a higher percentage of women age 40 or more, a statistical difference would have been found.

The fact that the types of ovulating disorders were similar suggests that infertile older women are no more prone to more severe ovulatory defects than younger women. Furthermore, there does not appear to be a greater tendency for an endometrial resistance factor with increasing age since the incidence of LPD and the amount of progesterone required to correct the endometrial biopsy was similar in both age groups.

Thus, the data suggests that the treating physician should be just as aggressive in management of the older infertile woman as in the younger patient.

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