Original Articles

Reproductive Biology Section

Improved pregnancy outcome for women with decreased ovarian oocyte reserve and advanced reproductive age by performing in vitro fertilization-embryo transfer

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Summary

Objective: To compare the pregnancy rates with IVF-ET vs non-assisted reproductive technology in women of more advanced reproductive age with decreased egg reserve as manifested by elevated day 3 serum FSH. *Methods:* A retrospective evaluation was made in women aged ≥ 38 with a day 3 serum FSH of ≥ 15 mIU/ml with ≥ 1 year of infertility. Another inclusion criterion was three cycles (unless a pregnancy occurred before that time) of either IVF-ET or non-assisted reproductive therapy which as a minimum included luteal phase support with progesterone. *Results:* The clinical pregnancy rates in three cycles for non-IVF were 11.7% vs 27.2% for IVF. Delivery rates were 2.9% vs 15.1%. For ages 40-42 the clinical pregnancy rates were 37.5% vs 0.0% (p = .02). *Conclusions:* Live deliveries are possible in women ≥ age 38 with marked decreased egg reserve. In vitro fertilization is more effective than non-IVF when follicle stimulation with gonadotropins is mild.

Key words: Diminished egg reserve; In vitro fertilization; Minimal stimulation, FSH.

Introduction

Many factors affect fertility in the general population. Two factors limiting fertility include advanced maternal age and poor ovarian reserve, as shown by elevated day 2 or 3 serum follicle stimulating hormone (FSH) levels. There is a decline in fecundity that accelerates between 35 and 40 years of age and approaches zero by age 45 [1]. As one ages, or as menopause approaches, there is a paucity of ovarian follicles [2]. In aging women, a natural selection process has occurred at each previous cycle, whereby the oocytes recruited during each cycle were the ones with the best quality. The remaining follicles are of lower caliber – having extra chromosomes and defective cytoplasmic mitochondria [3]. Some studies have concluded that an elevated FSH level at any age decreases pregnancy rates in assisted reproductive technologies (ART) [4]. However, in the younger patient with elevated serum FSH levels, it has not been determined whether the oocytes undergo an accelerated atretic process or another indiscriminatory destructive process in which both the "best" and "worst" immature oocytes are destroyed [5]. Regardless of the mechanism, elevated serum FSH levels and advanced age provide a 'double hit' to fertility.

Despite the above discouraging assessments, several case reports have established precedents that pregnancy remains possible given advanced age and imminent ovarian failure [6-11]. Early studies of euestrogenic women with elevated serum FSH levels have shown that without in vitro fertilization (IVF) or gamete intrafallopian transfer (GIFT), pregnancy rates varied based on age [5]. Previous studies have also found a much worse prognosis for women with elevated day 3 serum FSH levels in the age range of 38-45 in both IVF cycles and non-IVF cycles compared to younger women with elevated FSH [5, 12]. Thus one might conclude that the combination of advanced age and elevated day 3 FSH levels leads to low pregnancy outcomes. Incorrectly, donor egg programs are recommended to these women as the only means of achieving pregnancy. Recent data have shown that pregnancy rates per embryo transfer (ET) vary from 21.7% in women aged 40-42 and up to 30.8% in women aged 36-39 [13] following single ET despite decreased oocyte reserve [13]. Thus, pregnancy with one's own eggs remains a viable option for older women experiencing ovarian failure.

Women older than age 40 elect either IVF or non-IVF to achieve a pregnancy. In vitro fertilization is often chosen if there are tubal factors and/or severe male factor. Women with patent fallopian tubes and/or mild male factor problems have the option of using either IVF or non-IVF. However, one of the pitfalls of IVF is the decline in success rate with increasing maternal age. One study showed that in older patients, GIFT has a higher success rate than IVF [14]. Several studies have alluded to the role of the fallopian tube in improving fertilization and embryo development [15].

The function of the fallopian tube includes: ovum pickup, sperm transport, ovum and sperm capacitation, ovum fertilization, zygote development and transfer [15]. One other function of the fallopian tube is to allow hatch-

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ing of the embryo out of the embryo membrane by providing certain enzymes [16, 17]. Though there are data that provide information on assisted embryo hatching with acidic Tyrode's solution or laser drilling showing improved success rates in older women having fresh ET or women of all ages having frozen ET, the possibility exists that the efficiency of these artificial procedures is inferior to natural hatching as the embryo traverses the fallopian tubes [16, 17].

To date there have only been retrospective studies comparing efficacy of IVF with GIFT [18]. It has not yet been established whether one technique is superior to the other, and under what conditions. Cost considerations suggest that non-IVF treatments should be used initially if possible (patent fallopian tubes and adequate sperm). Early comparative studies of GIFT vs IVF found that possibly the former may be superior to the latter for the older reproductive group [18]. Thus, the possibility exists that maybe for this advanced age group, who with decreased egg reserve will not produce very many embryos with IVF, the advantage of the embryos traversing the fallopian tube if non-IVF methods are employed could obviate the usual advantage of IVF of multiple embryos and provide equal or even superior pregnancy rates.

The study presented herein attempts to determine if IVF-ET results in a higher pregnancy rate in this older group with elevated day 3 serum FSH vs correcting follicular maturation, sperm-mucus interaction problems, and correcting luteal phase defects without IVF.

Materials and Methods

Female patients who presented during a seven year period, from 1996 to 2003, who met the following criteria were included in the study: FSH ≥ 15 mIU/ml, age ≥ 38, and infertility (primary or secondary) > 1 year. Each woman was evaluated as to pregnancy outcome (clinical or ongoing/delivered pregnancy past the first trimester). The pregnancy outcome was determined for the first three cycles of treatment.

A total of 67 female subjects were included in the study. The women were stratified into two groups depending on whether IVF-ET was performed or not.

All patients were treated in the luteal phase with at least 200 mg progesterone vaginal suppositories twice daily to compensate for the greater uterine need for progesterone at an older age. The dosage of progesterone was increased by IM injection if the woman did not attain a homogeneous hyperechogenic pattern in the mid-luteal phase. A non-homogeneous hyperechogenic pattern on ultrasound indicates lower fertility potential [19, 20].

Follicular maturation issues were resolved by using minimal stimulation with gonadotropins. Non-IVF cases were not given any follicle maturation if they attained a mature follicle ≥ 17 mm by sonography with a serum estradiol (E2) level of at least 175 pg/ml. Failing to achieve a mature follicle resulted in the minimal use of gonadotropins, usually 75 IU once the serum E2 was ≥ 100 pg/ml.

For IVF cases no more than 75-150 IU of gonadotropins were used from the earliest day 3. They were never given while the serum FSH was increased ≥ 11 mIU/ml. Frequently they were only given when a follicle advanced far enough to secrete sufficient estradiol to lower the FSH. The various follicular stimulation methods have been previously described in detail [21].

Table 1. — *Clinical pregnancy and delivery rates following non-IVF and IVF treatment.*

	Non-IVF Group	IVF Group
Number	34	33
Average age	41.0 ± 2.3	40.7 ± 2.0
Average serum FSH (mIU/ml)	29.6 ± 13.0	22.6 ± 7.4
No. of clinical pregnancies	4	9
No. of deliveries	1	5
Delivery rate/patient	2.9% (1/34)	15.1% (5/33)
Clinical pregnancy rate per patient	11.7% (4/34)	27.2% (9/33)

Table 2. — *Clinical pregnancy rates after three cycles of treatment for patients aged 38-39, 40-42 and 43-45.*

	Age 38-39 years	Age 40-42 years	Age 43-45 years
IVF (n = 33)	30% (3/10)	37.5% (6/16)	0.0% (0/7)
Non-IVF (n = 34)	9.1% (1/11)	0.0% (0/13)	0.0% (0/10)
p-value, Fisher's exact test	0.311	0.02	

Cases with male factor not using IVF were treated with intrauterine insemination (IUI). Intracytoplasmic sperm injection (ICSI) was performed for male factor when IVF was performed. For patients undergoing IVF, embryos were transferred on day 3 and assisted hatching was performed prior to transfer. If the egg of a woman intending to do IVF released before retrieval, an IUI would be performed. However once designated as IVF, the cycle would not count as a non-IVF cycle but not be included as an IVF cycle either.

Only women having three treatment cycles (IVF or non-IVF) were included unless a pregnancy occurred first (only one pregnancy was allowed even if it was a miscarriage). Fisher's exact test was used to compare delivered pregnancy rates between non-IVF and IVF groups.

Results

There were 34 non-IVF patients with an average age of 41.0 ± 2.3 years versus 33 IVF patients with an average age of 40.7 ± 2.0 years. Using the highest baseline FSH recorded the mean serum FSH was 29.6+13.0 mIU/ml for non-IVF cases and 22.6 ± 7.4 for IVF cases.

A comparison between hypergonadotropic females treated without or with IVF-ET is shown in Table 1. There were four clinical pregnancies (11.7%) in the non-IVF group versus nine (27.2%) in the IVF group. The delivery rates per cycle were 2.9% (1/34) for non-IVF versus 15.1% (5/33) for IVF. The difference in delivered pregnancies did not quite reach significance (p = .092, Fisher's exact test). Three of four non-IVF pregnancies miscarried. The IVF group had three miscarriages and one ectopic pregnancy.

Analysis of the data based on different age ranges of 38-39, 40-42 and 43-45 is shown in Table 2. Fisher's exact test p value was significant for women aged 40-42 years. In vitro fertilization treatment for these women resulted in a 37.5% clinical pregnancy rate compared to 0% for the non-IVF treatment in three treatment cycles.

Discussion

These data provide information on pregnancy outcome in the largest series to date of women of advanced reproductive age and hypergonadotropism. The 2.9% viable

pregnancy rate in three cycles in this group of women was similar to previous findings of 5.5% in six cycles [5]. Thus live deliveries with and without IVF are possible in women with decreased egg reserve as manifested by day 3 serum FSH, levels > 15 mIU/ml even in women aged ≥ 40. In vitro fertilization with embryo transfer seems to improve the likelihood of success in this most difficult group.

A previous study has shown reasonable pregnancy rates for women aged 40-42 years old and elevated serum FSH with a delivery rate per transfer of 21.7%, and 0% for women aged > 43 years old [13]. In this study when women were stratified based on age, there was a significant difference in pregnancy rates between the two treatment modalities. It is possible that the pregnancy rates of both the non-IVF and IVF group were skewed by the inclusion of women > 43 years old (Table 2). In fact by eliminating the 43-45 age group the clinical pregnancy rate per three cycles was 9/26 (34.2%) with IVF vs 3/24 (12.5%) with non-IVF ($p < .05$, Fisher's exact test). The viable delivery rate for women aged 38 to 42 years was 5/26 (19.2%) with IVF vs 1/24 (4.2%) with non-IVF. The chances of completing a viable pregnancy and delivery increase five-fold with the use of IVF. Although there was no statistically significant difference between IVF and non-IVF, a five-fold raw increase in viable pregnancies may be further delineated with a larger sample size.

Several other methods have been proposed to increase the pregnancy rates among older women with elevated FSH levels. The use of donor oocytes would increase the pregnancy success rate of infertile couples, however such an option may not be a consideration in couples who for religious, financial and personal reasons would never consider the donor oocyte program.

The aim of this report was to assess how successful IVF procedures are in securing a live birth in older women with decreased ovarian reserve. Statistical significance was reached with the Fisher exact test ($p = 0.02$) when comparing women aged 38-39 versus women aged 40-42. The study reinforces the need for aggressive treatment in older women with decreased ovarian reserve. Non-IVF treatments, while often preferred in the younger patient, would serve to only prolong infertility among women with advanced reproductive age. Such data grant a couple more information to provide a basis for either choosing to proceed with infertility treatments using their own eggs or deciding to use donor eggs. In vitro fertilization-embryo transfer provides a higher pregnancy rate per cycle but obviously at an increased expense. However, one does not have to be concerned with the biggest risk of IVF which is ovarian hyperstimulation.

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