

OVARIAN AGING AND INFERTILITY

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The decrease in female fecundity beginning after the age of 30 and exaggerated after 40, is a well documented finding. This age-related decline in fertility is the result of several factors that contribute to overall reproductive failure. Women over 35 require a longer period to achieve conception than younger individuals, and a higher percentage of older than younger women will never achieve pregnancy. In addition, the rate of early pregnancy wastage increases substantially during the 30s, and is over 50% percent after age 40.



With the aging of the baby boom generation and social trends to delay childbearing, the treatment of women ≥ 40 years of age who desire fertility has become a major challenge of today's fertility specialists. For many women, the option to exercise other choices while deferring their reproduction, has resulted in the need to use new reproductive technologies while treating their infertility. These technologies include controlled ovarian hyperstimulation (COH), intrauterine insemination (IUI), and assisted reproductive techniques (ART).

LITERATURE REVIEW

Over the past 15 years, there has been a surge in the assisted reproductive technologies available to treat infertility. Given such a vast array of treatments, clinicians are faced with uncertainty about the optimal technique for an individual patient with functional fallopian tubes. The optimal choice depends on the pregnancy rates per cycle (cycle fecundity) and costs, as well as the degree of invasiveness associated with each of these procedures. Recently, some authors have suggested superovulation with HMG, combined with IUI as an alternative treatment for couples with nontubal causes of infertility.

A review of the literature dealing with IUI by Allen et.al. evaluated the results in 18 studies with a 28% mean pregnancy rate (range 3.4% - 62%) in 714 patients. Confounding variables including specifics of sperm preparation, reason for IUI,

insemination timing, and number of attempts per cycle and few studies reported on the efficacy of IUI with respect to age of the patient. Further studies by Dodson et.al. showed that the mean serum estradiol concentration per follicle is inversely proportional to age, and that the woman's age is inversely proportional to cycle fecundity with IUI. My results show there is a very poor live birth rate (1.4%) per cycle in infertile couples in which the female partner is ≥ 40 years of age and treated with COH/IUI. This study seriously questions the indication of OH and IUI in women ≥ 40 -years-old. (See Table 1).

SPONTANEOUS ABORTION RATE

Even when an older woman does conceive, the aging process affects the viability of her embryo. With increasing menstrual age there is an increased risk for spontaneous abortion, implantation failure, and cleavage failure. Spontaneous abortion rates increase from 10% in women who are under 30, to 34% in woman in their early 40s.

Cytogenetic studies have shown that in 40% of all first trimester miscarriages, there is evidence of chromosomal abnormalities, and the majority of these anomalies are autosomal trisomic defects. Among recognized conceptions there is an exponential rise in the frequency of trisomies of almost every human chromosome with advancing maternal age.

IN VITRO FERTILIZATION

The early use of IVF in the treatment of women over 40 was influenced by the experience of Steptoe and Edwards, who reported a pregnancy rate less than half of that for women over 40 along with a spontaneous abortion rate that was almost 60%, yielding a live birth rate of only 3%.

The most recently published data from the US IVF-ET registry mimics the early Bourne Hall experience. The result of 115,392 IVF cycles from 391 clinics in 2002 where a delivered pregnancy rate for women 40 or older was 10% compared with 35% for all age groups. The older women also suffered a 36% spontaneous abortion rate. Older women undergoing IVF have high cancellation rates, most often because of insufficient follicular development, but the pregnancy rate declines with increasing age regardless of the number of embryos transferred.

LEADING FACTORS

Biological data suggests at least three factors undergo change at age 37, the uterus becomes increasingly unreceptive to maintaining pregnancy; oocyte abnormalities, most commonly expressed as chromosomal trisomies, finally become clinically dominant and compose half of all conceptions after 45: and altered patterns of gonadotropin release, marked by rising basal FSH levels

increase incidence of irregular menstrual function, which finally expresses itself as the inability to conceive.

It is biologic or ovarian age and not chronologic age that most likely determines the end point of fertility. Women who conceive late in life generally have a late menopause – the number of years from the loss of fertility to menopause appears to be about ten years. As there is no accurate way to predict the onset a decade in advance, perhaps women have been right all along when they say they hear the ticking of their biologic clocks.

ASSESSING OVARIAN RESERVE

Of the few good tests for ovarian reserve, an abnormal result can predict poor reproductive performance, but normal results are less reliable. The most commonly used test are basal FSH with estradiol, and the clomiphene citrate challenge test (CCCT). FSH and estradiol are drawn on day three of the menstrual cycle. Clomiphene citrate 100 mg is given on day five through nine of the cycle and day ten FSH is re-drawn. An elevation of either FSH level (greater than 10 IU/L), and an estradiol over 80 pg/ml are considered abnormal, indicating a diminished ovarian reserve. Women older than 40 who have a normal FSH level are still less likely to conceive than younger women due to the reduced quality of their oocytes.

IMPACT OF OOCYTE DONATION

Oocyte donation dramatically alters the fertility of women over 40. Success rates are independent of age. Most series reports now demonstrate live birth rates above 50% per embryo transfer in patients up to 55. Life table analysis indicates that more than half of perimenopausal women will be successful within three attempts of oocyte donation, and more than 85% by the fifth try. Furthermore, miscarriage rates reflect that of the donor who is usually under 35. Thus, losses are experienced typically in fewer than 15% of conditions.

Maternal age decreases live born rates after assisted reproductive technology (ART). These data are from 115,392 fresh ART cycles with patients' own oocytes reported to the Society for Assisted Reproductive Technology and the Centers for Disease Control and Prevention for the year 2002. Advancing maternal age adversely affects live birth rates following ART. When fresh donor ART cycles are plotted, pregnancy rates do not decrease even into the 40s. (Figure 1).

Results of oocyte donation suggests that although the uterus is less receptive in women over 40, it is the ability of the aging oocyte that is the most important factor in the decreasing fertility of older women. Patients have indicated satisfaction after having made the decision to proceed with oocyte donation. Only time will tell if this trend becomes the accepted norm.

OOCYTE PRESERVATION (EGG FREEZING)

Until recently, the ability to freeze an egg was an unrealistic dream due to the delicate structure of the unfertilized egg. Fortunately, a number of advances in our knowledge of oocyte physiology and laboratory techniques are changing this dream into a reality. Women concerned with their "biological clock" could store oocytes for use later in life. At Huntington Reproductive Center, we have started a number of studies that are helping oocyte preservation become a viable option for women to preserve their reproductive options.

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