

Early Marriage: a Policy for Infertility Prevention

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Abstract

Female fertility begins to decline many years prior to the onset of menopause despite continued regular ovulatory cycles. Age related infertility is due to oocyte abnormalities and decreased ovarian reserve. Treatment of infertility when the cause is limited to decreased ovarian reserve is empirical at present except for oocyte donation.

This mini review of the literature covers all available English biomedical journals that have been published from 1995 to 2008. The search based on combination of the words age, fertility, infertility, and oocyte abnormalities. The important findings from this search strategy are summarized and presented in the sub headings including female age and fertility, miscarriage and in vitro fertilization. Regarding infertility prevention, this mini review suggested that early marriage is a primordial, effective, inexpensive and easy way to prevent infertility.

Key words: Aging, Fertility, Infertility, Oocyte abnormalities

Introduction

Perhaps the greatest threat to woman's fertility is advancing age. Many women are now choosing to delay marriage until they are much older and consequently, many are attempting pregnancy in their mid to late 30s and early 40s. Unfortunately, the biological clock has not changed to coincide with the evolution of our societal values and fertility for women is greatest in the late teens and early 20s. There is no treatment that can "turn back the clock" on a woman's ovaries (1, 2). A large part of this population will be infertile by the time they consider to conceive, mainly because of a decreasing ovarian reserve and low oocyte quality resulting from age. Aging oocytes have been widely suggested to be the

major cause for the decline in fertility (3).

Many physicians use fertility medications to increase the chance of pregnancy. Fertility medications increase the number of ova that develop in a given month, and enhance the chance that at least one of them might be fertilized and develop into a pregnancy. Although fertility medications seem to offer some hope, the pregnancy rates are generally poor.

Female age and fertility

Women are born with a lifetime supply of oocytes and during each month of a natural cycle one oocyte develops in the dominant follicle, and undergoes ovulation. This development is initiated and supported by follicle stimulating hormone (FSH). At the same time, a group of smaller unselected follicles become atretic and are no longer capable of reaching ovulation. As women age, the number of remaining eggs declines, furthermore, those that are available may demonstrate a decrease in egg quality. Aging of the ovary is characterized by a reduction in the number of primordial

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follicles from 1-2 million at birth to only 250 000 at menarche and very few by the time of the menopause. The size of the original pool and the rate of loss are genetically determined with a strong familial tendency transmitted through the familial line. The rate of loss accelerates from the age of approximately 37 years and precedes the true menopause by 10-12 years (4, 5).

Female age is very important in consideration of probability for achieving pregnancy. The real issue is egg quantity and quality, which translates to embryo quality after fertilization. Increased infertility with ageing is a well documented problem and very apparent in modern society. As women wait longer to have children, a higher percentage of couples have fertility problems because of the quality of the oocytes, and other issues that affect fertility. As women increasingly delay childbearing, our society has done a very poor job of educating people about the decline in female fertility with increasing age (6). Too many couples learn about the impact of age when it could already be too late for them. If they had tried to have a baby sooner, they could have built the family. The American Society for Reproduction Medicine said it well: "As women delay childbearing there is now an unrealistic expectation that medical science can undo the effects of aging" (7).

Many people are not aware of the decline in fertility as the age of the female partner increases: There is a slow decline in pregnancy rates in the early 30's. This decline is more substantial in the late 30's and early 40.

A study published in 1957 examined the relationship between the age of the female partner and fertility. This study found that:

- By age 30, 7% of couples were infertile
- By age 35, 11% of couples were infertile
- By age 40 and 45, 33% and 87% of couples were infertile, respectively (8).

For several reasons, infertility rates are even higher in the general population in the U.S. today than for the population studied by Tietze in the 1950s. The available evidence indicates that the age related decline in female fertility can be attributed to progressive follicular depletion and a high incidence of abnormalities in aging oocytes such as aneuploidy resulting from disordered regulatory mechanisms governing meiotic spindle formation and function (9-12).

Ageing does not appear to have any significant adverse effect on the uterus. Although the prevalence

of benign uterine pathologies (leiomyomas, endometrial polyps, adenomyosis) increases with aging (13-15), evidence exists to indicate it has much overall impact on fertility in women (16-19). Age also does not appear to adversely affect endometrial development or function in response to steroid stimulation (20).

Perhaps the strongest evidence comes from comparing outcomes in non donor and donor egg IVF cycles. Whereas earlier studies suggested that donor egg IVF pregnancy and delivery rates decreased modestly with the increasing age of the recipient (21-23) more recent data clearly refute those conclusions (24-26). Live birth rates declined progressively with increasing age for nondonor egg cycles. In contrast, live birth per transfer rate in donor egg IVF cycles averaged 43% overall, and did not vary significantly with age of the recipient. Live birth rates in donor egg IVF cycles relate to the age of the donor, rather than the recipient (27).

Female age and miscarriage

Numerous studies have documented the increased risk of miscarriage as women get older. Most of the increased risk for miscarriage in older women is due to the increase in chromosomal abnormalities in their eggs. This is also the main reason for the decline in overall fertility with increasing female age (9-12, 28-30).

The meiotic spindle is a critical component of the egg that is involved in organizing the chromosome pairs so that a proper division of the pairs can occur as the egg is developing. An abnormal spindle can predispose to development of chromosomally abnormal eggs.

In one study, 17% of the eggs from women 20-25 years old were found to have an abnormal spindle appearance and at least one chromosome displaced from proper alignment. In contrast, 79% of the eggs studied from women 40-45 years old were found to have an abnormal spindle appearance and at least one chromosome displaced from proper alignment (29). This study illustrates how chromosomally abnormal eggs (and therefore, embryos) are produced more often in older women. When the chromosomes line up properly in a straight line on the spindle apparatus in the egg, the division process would be expected to proceed normally so that the egg would end up with its proper complement of 23 chromosomes. However, with a disordered arrangement on an abnormal spindle, the division could easily be uneven – resulting in

Table1: Pregnancy loss according to maternal age

Maternal age (year)	Pregnancy loss rate
< 30	5%
30 – 34	8%
35 - 39	16%
40 - 41	30%
42 - 43	40%
44 - 46	60%

an unbalanced chromosomal situation in the egg. Therefore as women get older, the incidence of chromosomally abnormal eggs increases dramatically. This results in lower chances for getting pregnant, as well as increased risk for miscarriage (Table 1).

When mothers are 35 or older, amniocentesis is recommended because of the increased risk of a chromosomally abnormal child (e.g. Down syndrome).

Female age and IVF success rate

Many aged women are pursuing fertility treatments and are undergoing assisted reproductive techniques (ARTs). For many older women, their single best chance to achieve pregnancy is by undergoing In Vitro Fertilization (IVF) because every step along the conception pathway is maximized. Whereas, the number of remaining ovarian follicles steadily declines with increasing age, more rapidly after approximately age 38, observations in stimulated cycles suggest that aging follicles also become progressively less sensitive to gonadotropin stimulation. As age increases, the total dose and duration of treatment required to stimulate multiple follicular development increase. The rate at which estradiol levels rise and the peak concentration achieved decrease, reflecting the smaller cohort of follicles that can be recruited to respond (31). Success rates achieved with ART also decline as age increases. The number of oocytes retrieved and embryos available are lower, embryo fragmentation rates are higher, and implantation rates are lower in older women (32, 33). Although pregnancy rates have steadily increased over the past 15 years for women in all age groups, age is the single most important factor affecting the probability of success with ART. Pregnancy and live birth rates by age for ART cycles using fresh, non donor eggs or embryos vary little for women younger than age 32 but thereafter steadily decrease in an almost linear fashion as age increases. According to the 1999 ART Success Rates, live birth rates per cycles were 32.2%

in women under 35, 26.2% in women aged 35 – 37, 18.5% in women aged 38 – 40, 9.7% in women aged 41 – 42, and approximately 5% in women 43 and older (34).

Age is one issue, but the real fertility issue is egg quality and quantity and not the number in a woman's age. A woman can be 45 years old with exceptionally good quality eggs and still be fertile (which is rare at that age), or she can be 25 years old with very poor quality eggs and be infertile. These are extreme examples, but the point is that egg quality and quantity tends to decline significantly in the late 30s and faster in the early 40s, but egg quantity and quality in an individual woman can be average for her age, better than average, or worse than average. Therefore the age – related decline of the success in IVF is largely attributable to a progressive decline of ovarian oocyte quality and quantity. Woman's age is an independent factor determining the success of assisted reproductive technology treatment (35, 36).

Many infertility doctors recommend to women over 38 that are infertile should have aggressive treatment and proceed to IVF relatively quickly – before all fertility potential is lost.

In summary, the postponement of marriage and bearing the first child, the transition still underway toward nontraditional family forms and unfavorable economic and institutional factors explain a considerable part of the increase in levels of infertility so marriage in early ages is a good way to prevent infertility.

The main conclusion of the present review can be summarized below points:

- Fertility declines significantly with increasing age
- Age – related infertility is due to oocyte abnormalities
- Miscarriage rates are higher for older women.

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