

Consider: The Ramification of Female Age on Reproductive Health

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Short Communication

Female-factor infertility is an emotional, physical, social and financial stress on couples as they try to conceive children. One cause of female infertility, and one seen more commonly, is age-related decreased fertility. Clinicians within and outside the specialty of Obstetrics and Gynecology can provide a vested discussion with patients who are delaying childbearing for social or ethical reasons to consider fertility preservation. The medical profession is obligated to consider their patients' health status, age and treatments in counseling for future reproductive health and satisfaction. With the advent of ART many advances are available such as social freezing of oocytes, fertility preservation in patients undergoing treatments that can alter oocyte quality, Intrauterine Insemination (IUI) and the extreme end of management with In vitro fertilization (IVF). Unfortunately, those patients who present with diminished ovarian reserve or premature ovarian failure may not be ideal candidates for these services, but we can offer hope. The focus of the evaluation is to determine the goal of each patient, whether having a biological child, experiencing pregnancy, or the nurturing capacity of parenting. Through Reproductive Endocrinology and Infertility specialists, hope is provided for patients who may have neglected or overlooked the aging effects on oocyte quantity and, even more importantly, quality. Nevertheless, the future is optimistic and the goal is to provide women with the best care which starts through educating on reproductive health.

The process of reproductive aging

The process of reproductive aging in a woman is determined by both the quantity and quality of her oocytes. When a female fetus is developing in the uterus before birth the oocytes that she will have available throughout her life are stored in the ovaries as primordial follicles arrested in Meiosis I. At 20 weeks gestation, the number of oocytes in the ovary peaks at 7 million. By birth, this number drops to 2 million followed by slow declination via programmed mechanisms of apoptosis. Thus, by puberty the number of oocyte levels are at 250,000-400,000. During reproductive years number of oocytes continues to decline despite pregnancies, use of hormonal contraception anovulation. In fact, every month approximately 1500 eggs are destined to disintegrate with increase to 2500 after 37 years of age. Menopause occurs when, the number of primordial follicles dramatically falls below 1000 [1]. Peak age of fertility is well known to occur in the early 20's, when both health and ovarian reserve are high. Evidence supports that female fertility begins to decline in the early 3rd decade, and on average ends in the early 4th decade but with

significant variation, and precedes menopause typically by 10 years [2]. This pattern follows the decline in oocyte number and quality [3].

Delayed parenting comes with the cost that women may become subfertile/infertile and will require ART to create their families. The most significant effect of Advance Maternal Age (AMA) in women 35 year and older is the rate of aneuploidy and genetic defects that plague oocytes [4,5]. One known cause of decreased quality of oocytes comes from increased meiotic nondisjunction, resulting in aneuploidy. In the prime of reproductive age, pregnancy rate with trisomy is about 2%; however, by 40 years of age, that rate nears 35% [6] with 40-50% of all embryos being abnormal. As women age, their oocytes do as well. This decrease in oocyte quality contributes significantly to age-related decreased fertility. Together the oocyte quality and number decline, and acquired uterine and health problems in aging women contribute significantly to the increase rate of spontaneous abortion. In context of untested autologous embryo transfer in IVF the pregnancy and life birth results are inversely proportional to female age [7].

Modern methods of detecting embryo aneuploidy by preimplantation genetic screening prior to embryo transfer significantly increase the chance of successful pregnancy and commonly require only single embryo transfer, reducing risks associated with multiple gestation of untested embryo transfers. Furthermore, utilization of donor eggs for women in their 40's with diminished ovarian reserves drastically increase chance of live birth. While we can determine the quality of an oocyte after retrieval with ART, we do not currently have tools to improve or evaluate the quality of oocytes inside the ovary. Pre-genetic Diagnosis and Screening has helped and the CRISPR-Cas9 technology offer hope, but the basic workup to assess for quantity of remaining follicles, or ovarian reserve, in the aging female population is based on Anti-Müllerian Hormone (AMH). This endocrine marker has been used since 2002 as an indicator of reserve and can strongly predict poor response to ovarian stimulation [8,9]. Other assessment such as Antral Follicle count and Day 3 Follicular Stimulating Hormone (FSH) have been used to characterize ovarian reserve. These assessments are useful in evaluation of women who have delayed childbearing, approaching the end of fertility or who have had early infertility problems, and care should be used in the general practitioner practice to identify and evaluate these women.

In addition to the effects of age, studies have proven the adverse effects of smoking, autoimmune and metabolic diseases, and obesity on fertility [10-12]. As such, primary providers are encouraged to identify AMA women, and younger women with associated risks such as: smoking, autoimmune disorders (i.e. Thyroid disease, Diabetes), obesity, Irregular menstrual cycles, history of sexually transmitted disease, family history of heritable cancer, personal history of cancer, recurrent pregnancy loss, premature menopause, history of fibroids or

endometriosis, prior surgery on the uterus tubes or ovaries, and history of any surgical procedure on the cervix that may further decrease fertility. Physicians should also be aware of women who are delaying reproduction for social or career reasons, and are encouraged to consider their reproductive health, given the recommendation that the optimal and most cost-effective time for fertility preservation is between 32-34 years [13]. Recommendation and timely referral to reproductive endocrinologist and infertility specialist is the window for successful fertility treatments or fertility preservation and highly depends on female age.

Conclusion

Despite only 11.9% of all women having subfertility near half women in advance maternal age struggle to achieve a life birth in whom a timely access to care is a paramount limitation. As 57% are women are in the labor force in the US commonly postponing their reproductive needs due to the career choices, we as medical professionals must recognize this trend and provide women with information on age effects on fertility and possible options to assist with fertility preservation or treatments. As medicine, research and technology continue to merge, the future of competing against the racing biological clock for redemption of time in Reproductive aging of oocytes is advancing. Together with the patient we can form a partnership that bridges the discussion of aging and reproductive future that provides the tools for women to make an informed decision on their chances of a live birth.

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