Delayed Childbearing: Impacts on Fecundity and Treatment

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As more women are choosing to delay childbearing secondary to educational opportunities, career advancement, and other social factors, there is a gradual increase in the absolute number of births among women in their 30 and 40s [1]. Although the number of births has increased, fecundity, which is defined as the ability to conceive, decreases substantially as maternal age is considered to be the most important factor affecting it. Large population studies demonstrated an initial decline in fecundity when women are in their mid-20s and significantly decreases after the age of 35 [2]. Unfortunately, many women are not entirely cognizant of this age-associated decline in fecundity [3]. Even in cases where women are aware of this decline, they tend to find comfort on assisted reproductive technologies (ART) as a potential means of treatment, but not adequately informed of ART limitations.

The process of reproductive aging begins before birth and continues until menopause. During fetal development, germ cells divide until 20 weeks of gestation to produce a finite follicular pool of approximately 20 million oogonia [4]. Thereafter, the process of oocyte atresia begins resulting in 1 million, 300,000, and 1000 remaining oocytes at birth, puberty, and menopause, respectively [5]. The follicular pool continues to decrease even when women are anovulatory, on birth control, or pregnant [6]. As the quantity of the oocytes decreases with age, the quality of the oocytes also diminishes secondary to an increased rate of meiotic errors resulting in a higher rate of miscarriages in women over the age of 35 [7]. Based on population studies, women age 35-39 have a 25% risk of spontaneous abortion, while women age 40-44 have a 51% risk [8]. Interestingly, even young women are thought to have a high rate of embryo aneuploidy. It has been noted that <40% of embryos are genetically normal in women less than 38 years old based on pre-implantation genetic screening (PGS) studies [9]. Thus, age has the biggest impact on oocyte quality. In addition, older women have a higher incidence of fibroids, tubal disease, endometrial polyps, and endometriosis that can all negatively affect fecundity. Given the elusive clinical signs of reproductive senescence, most women are unaware of their progressive decline in fecundity and oocyte quality until it may be too late for any intervention.

With an increased rate of women choosing to delay childbearing, there is a concurrent rise in the number of women of advanced maternal age seeking infertility evaluation and treatment. Non-invasive markers of ovarian reserve such as serum anti-mullerian hormone (AMH) and day 2-3 follicle stimulating hormone (FSH) are often used to assess a woman’s reproductive potential either for reassurance or referral for fertility treatment. FSH, which is often elevated in older women or those with decreased ovarian reserve (DOR), is not an ideal marker due to its lack of specificity and sensitivity, partly due to its fluctuation during a menstrual cycle [10]. Serum AMH, although largely secreted by the granulosa cells of early antral follicles, directly correlates with the number of remaining primordial follicles and is considered to be a more reliable marker of ovarian reserve as it doesn’t fluctuate [11]. Alternatively, antral follicle count (AFC), defined as fluid-filled structures in the ovaries measuring 2-10 mm in diameter noted by transvaginal ultrasound, is considered to be an ideal marker of ovarian reserve as it also directly correlates with the number of remaining primordial follicles in the ovaries just like AMH [12]. Similar to AMH, AFC does not fluctuate with menstrual cycle. While AMH and AFC have been described as ideal markers of ovarian reserve and good predictors of response to treatments using assisted reproductive technology (ART), it is important to recognize that they are neither absolute markers of fecundity or oocyte quality and should not be the only criteria used to determine if a patient will be able to conceive.

Although infertility is defined as failure to conceive after 12 months, it is generally recommended that fertility evaluation should be initiated after 6 or 3 months in women at 35 or 40 years of age or older, respectively. Basic tests should include a marker of ovarian reserve (FSH, AMH, or AFC), semen analysis, and hysterosalpingogram (HSG). Additional tests may need to be performed as infertility work-up is individualized to each patient. Referral to an infertility specialist is highly recommended with any abnormal results. Patients with abnormal semen analyses or HSG are often treated with specific modalities to address those abnormalities. In contrast, patients with isolated elevated FSH or low AMH are often diagnosed with DOR. There is a wide range of treatment options for women with DOR or age associated decline in fecundity [13]. Common initial treatment includes controlled ovarian stimulation (COS) with either clomiphene citrate or letrozole and intrauterine insemination (IUI). Alternative, COS with exogenous gonadotropins could also be attempted in older women as this type of ovarian stimulation will often produce more

oocytes in comparison. However, the rate of multiple gestations concurrently increases with more aggressive treatment. The effectiveness of COS and IUI depends on the age of the patients and their overall ovarian responses with medications.

In general, patients who failed to conceive after 3-4 rounds of COS/IUI should consider in vitro fertilization (IVF) as the next step of treatments as additional rounds of COS/IUI are unlikely to be effective [14]. Although controversial, patients with advance maternal age and/or poor ovarian reserve may consider IVF as the primary treatment option. Bypassing COS/IUI in these patients may shorten the time to pregnancy but likely at a higher cost. While ART may overcome limited ovarian reserve with more robust stimulation, it cannot overcome the age associated decline in oocyte quality resulting in aneuploidy embryos. In selected cases where there are superunumerary embryos after IVF treatment, patients may have the option of performing (PGS) on these embryos to select for euploid embryos for transfer; thus, minimizing, but not eliminating, the risk of miscarriage. Nevertheless, randomized controlled trials have not revealed a significant increase in pregnancy rates when using PGS in women of advanced maternal age undergoing IVF [15,16]. However, these studies only include PGS using fluorescent in situ hybridization screening that only evaluates for aneuploidy in 7-9 chromosomes, as opposed to the more recent technique of comparative genetic hybridization that evaluates all chromosomes. Prospective randomized control studies remain to be performed to evaluate the benefits of this new method of PGS in women of advanced maternal age. Conceiving through ovum donation is an alternative option for women with age related DOR that has failed multiple infertility treatments. Pregnancy rates of donor cycles are often >50% and is independent on the age of the recipients [17]. The use of donated oocytes may be perceived as unconventional by many patients, nevertheless it is important to discuss this option early with patients of advanced maternal age who has failed many treatments.

More recently, fertility preservation has become a promising solution for women who want to postpone childbearing. Embryo cryopreservation for later use is a viable option for couples or single women that have chosen a sperm donor to be able to conserve their ability to conceive in the future. Recent improvement in cryopreservation technique allows for the safe and reliable means of freezing oocytes. This allows women to cryopreserve their oocytes when their quality has not diminished with aging. These oocytes then can be thawed and used at a later time in the future when they are ready to start a family. This is an alternative option for women who may not have a current partner, but would like to preserve the option of having their own child in the future.

Women of advanced maternal age are at higher risk of aneuploidy, and should be offered first and second trimester prenatal screening once pregnant. Even in patients who conceived with ovum donation or known euploid embryos via PGS and ART, it is still highly recommended that they undergo first and second trimester screening to detect structural abnormalities that are still observed with euploid fetuses such as body wall, cranial, or cardiac defects [18]. Furthermore, women of advanced maternal age have an increased risk of pregnancy-related complications [19]. Chronic hypertension is more commonly seen in older pregnant women. It has been reported that there is about a 60% increased rate of pre-eclampsia in older primigravida [20]. Similarly, gestational diabetes and type II diabetes affect more women of advanced maternal age, putting them at risk for increased morbidity. There is a higher risk of preterm birth and fetal growth restriction in older pregnant patients, however the neonatal outcomes have been noted to be overall favorable [20]. Despite the overall low risk maternal mortality in the U.S., women aged 35-39 years have about a two-fold increased risk of pregnancy related death compared to women in their 20s, and it is even higher in women over 40 [21].

A women’s reproductive potential is strongly related to her age and can be significantly compromised well before the perimenopausal period. As more women are choosing to postpone child bearing, it is our duty to inform our patients of the natural decline in fecundity and the complications associated with having a child later in life. It is recommended that women over the age of 35 who are unable to conceive for more than 6 months of actively trying should promptly see an infertility specialist.

REFERENCES


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