Fertility Care for Perimenopausal and Menopausal Women

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Female infertility is a common condition that affects almost 15% of couples in the general population who are trying to conceive. A significant number of these subfertile women are over the age of 40, and are often referred to as being of "advanced reproductive age." In the modern sense, they are at the threshold of "middle age." However, due to the natural history of ovarian aging, their declining reproductive potential appears to accelerate the process of reproductive aging.

As members of the baby boom generation, many women have placed great emphasis on education and careers, and on delayed childbearing. Often, patients present to their gynecologist after many months of trying to get pregnant. Fear of failure and concern over how they may be perceived by their healthcare practitioners often dissuade women from seeking subspecialty fertility care. Patients who are perimenopausal or menopausal represent the most difficult clinical cases, as the age-related decline in fertility is irreversible. As physicians, it is important to accurately advise women of the various therapeutic options that are available to improve their fertility potential. In this older population, oocyte donation has, by far, yielded the best success rates of all assisted reproductive techniques (ARTs). However, there is a limited role for traditional methods in well-selected cases.

Fertility and Advancing Age

It has long been known that fertility declines with advancing age. Fertility rates have been studied in various "natural populations," defined as populations that practice little or no contraception. Historical data from the Hutterites, a religious sect living in the Dakotas, Montana and Canada, has revealed an overall downward trend in fertility rates, with a gradual decline beginning as early as age 25, accelerating between ages 35 and 40, and reaching a nadir at the age of 45 (Figure 1).[1] These data have led to the definition of advanced reproductive age as the point when reproductive potential declines at its steepest rate, generally accepted as age 35 and older.[1]

In menopausal women and those of advanced reproductive age, the high prevalence of infertility is due in large part to diminished ovarian reserve.[2] Increasing rates of aneuploidy and mitochondrial mutations also play a role.[3] Females of the mammalian species are born with a finite number of oocyte precursors. There is a progressive loss of oocytes beginning in fetal life and continuing through menopause due to follicular atresia.[4] Females have 6- to 7-million oocytes at 20 weeks' gestational age, 1- to 2-million oocytes at birth, approximately 25,000 at the age of 37 and only a few hundred at the time of menopause[5,6] (Figure 2). The rate of oocyte loss by apoptosis accelerates from the age of 37 years and precedes true menopause by 10 to 13 years, despite the presence of regular monthly cycles.[3,5] Fertility is often markedly diminished during this time period of reproductive transition.

Age-related menstrual changes. As

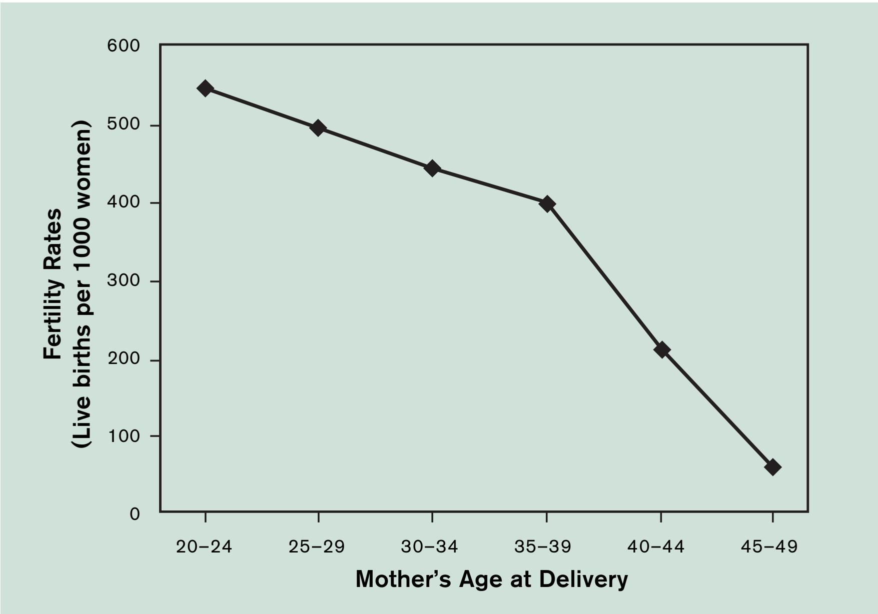

Figure 1. Fertility rates in natural population (Hutterites, US 20th century). Note a dramatic fall beginning approximately at age 30 years to almost negligible levels at age 45 years.

From Maroulis GB. Effect of aging on fertility and pregnancy. *Semin Reprod Endocrinol* 1991;9:165-75. Reprinted by permission.

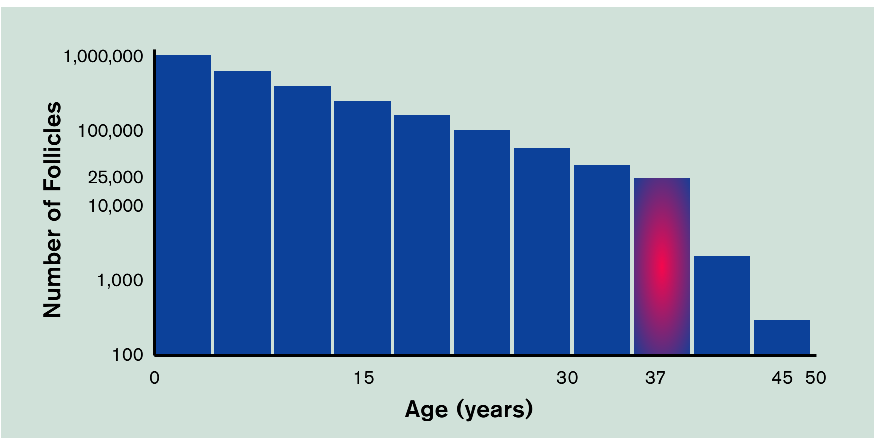

Figure 2. Decline in the number of oocytes from birth to menopause.

menopause approaches, menstrual cycles generally decrease in length as a result of oocyte loss, earlier follicular recruitment and shortening of the follicular phase.[7-9] This period is characterized by rising levels of gonadotropins and decreased production of steroid hormones and peptides secondary to depletion of the ovarian follicle pool.[1,9] The earliest endocrine change seen in the transition to menopause is a rise of follicle-stimulating hormone (FSH) in the early follicular phase, which normally occurs between ages 35 and 40 years.[10,11] This rise in FSH is caused, in part, by a decreased secretion of ovarian inhibin B, produced by the granulosa cells of the developing antral follicles, and a decrease in inhibin A, secreted by the corpus luteum.[10-14] The loss of negative feedback inhibition triggers the rise in FSH levels.[10,11,15]

In women over age 40, there generally are shorter follicular phases leading to shorter cycle lengths, elevated follicular-phase estradiols, altered corpora luteum function and higher FSH baseline levels, with an earlier start of follicular growth in the luteal phase of the preceding cycle as compared with younger women aged 22-34 years.[10,12,16] This perimenopausal period is also characterized by hypoestrogenism and decreased luteal phase progesterone production.[9]

Age-related increase in aneuploidy. Age-related changes in oocytes are clearly associated with decreased reproductive potential. Instability of the cellular mechanisms that govern meiotic spindle formation and function results in an increase in oocyte meiotic segregation errors. This increase in genetic errors accounts for the age-related increase in aneuploidy commonly found in abortuses. In donor oocyte cycles, the spontaneous abortion rate correlates with the age of the donor, suggesting that the oocyte represents the primary factor responsible for aneuploidy in the embryos of women of advanced reproductive age.[1] There is an age-related increase in chromosomal nondisjunction in oocytes.[17] Women over 40 years of age using their own eggs for in vitro fertilization (IVF) have much lower success rates than younger women. Studies performing preimplantation genetic diagnosis using fluorescence in situ hybridization in IVF embryos have documented the increase in chromosomal aneuploidies with advancing maternal age[18] (Figure 3).

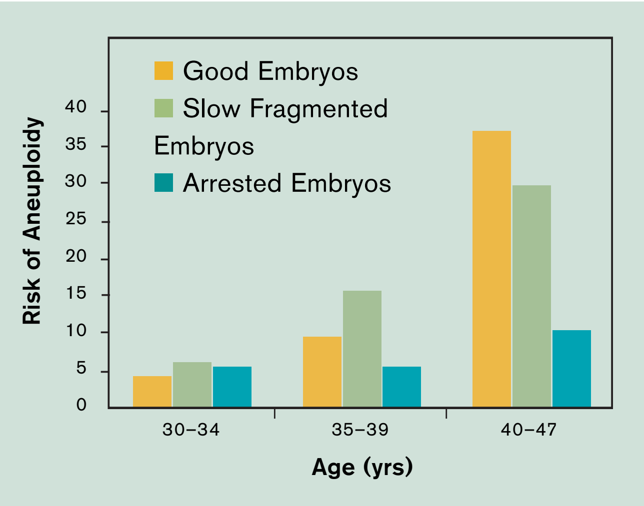

Figure 3. **Aneuploidy increases with maternal age as determined with use of fluorescence in situ hybridization assays of preimplanted embryos.**

P=0.005. Reprinted from *Fertility and Sterility*, vol. 64, Munné S, Alikani M, Tomkin G, et al., Embryo morphology, developmental rates, and maternal age are correlated with chromosome abnormalties, pp. 382-91, ©1995, with permission from American Society for Reproductive Medicine.

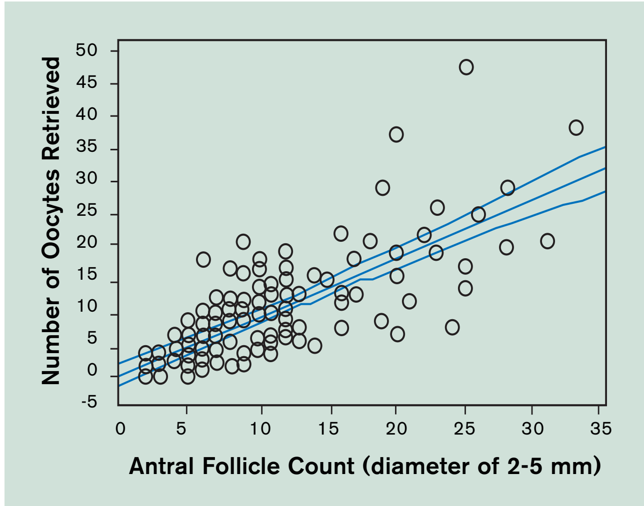

Figure 4. **Scattergram with 95% confidence bands for correlation analysis of number of oocytes retrieved and antral follicle count detected at the beginning of treatment cycles in women who underwent ARTs.**

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Assessing Reproductive Status

The assessment of fertility status in women of advanced reproductive age has focused on the hormonal milieu of the perimenopausal period. Determining which women have diminished ovarian reserve, defined as the quantity and quality of the remaining follicle pool, is of practical value as some women of advanced reproductive age will respond to standard ARTs.[1] Elevations in early follicular phase FSH and estradiol, and decreases in inhibin-B levels are common findings in women over age 40.[19] The pregnancy rates of women enrolled in assisted reproduction are much lower if FSH levels are abnormal compared with women having values in the normal range. Even if FSH levels return to a normal range, women with previously elevated levels in prior cycles continue to have a reduced chance of pregnancy.[20]

Another method used to measure ovarian reserve involves ultrasound determination of the number of antral follicles, or developing oocytes, in the early follicular phase. A detectable decline in follicle count precedes the aforementioned changes in hormone levels. Sonographic studies confirm that the antral follicle count declines with chronological age, likely a result of a diminution in the primordial follicle reserve.[21,22] Antral follicles in the ovary can be visualized by transvaginal ultrasound at a size of 2 to 10 mm. Measurements are taken in the early follicular phase (cycle days 2, 3 or 4).[22] Below the age of 30, the number of antral follicles is much greater than after 40, with women over age 40 usually revealing fewer than 10 antral follicles.[21,22] The rate of decline of antral follicle counts rapidly increases after the age of 37, reflecting the diminution of the remaining primordial follicle pool.[22] Antral follicle counts have been shown to be reproducible over multiple cycles, and correlate with age and response to ovarian stimulation during IVF (Figure 4). Therefore, some consider it to be the best marker of ovarian reserve.[23]

The clomiphene citrate challenge test (CCCT) is a provocative means to measure ovarian reserve. If basal FSH and estradiol levels are normal on cycle day 3, 100 mg of clomiphene citrate is administered on cycle days 5 to 9, followed by a second test of FSH level on day 10. The CCCT is considered abnormal if either the day 3 or day 10 FSH value is significantly elevated. Patients with decreased ovarian reserve have a poorer response to clomiphene, produce lower levels of inhibin and estradiol (E_2), and thus have less feedback of FSH.[1] This test has been shown to be of value in unmasking poor responders to controlled ovarian hyperstimulation who may have normal basal FSH screening tests.[24] However, this test is not standard in all centers because there is disagreement among clinicians as to its diagnostic superiority above routine early follicular FSH testing.

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New Markers for Assessing Reproductive Status

Recently, promising new markers for assessing reproductive potential have emerged. Serum inhibin levels reflect the biological activity of the follicular pool. In vitro studies of cultured luteinized granulosa cells have shown that in patients with low basal FSH values (≤6 IU/L), inhibin secretion is two-fold higher than in patients with high basal FSH levels (> 10 IU/L).[25] FSH levels, therefore, reflect an indirect assessment of granulosa cell inhibin production.

Anti-Mullerian hormone, also called Mullerian Inhibitory Substance (AMH or MIS), is secreted by granulosa cells within the early developing follicles. Serum MIS levels on cycle day 3 decrease progressively with age and become undetectable after menopause.[26] During IVF cycles, higher day 3 serum MIS values are associated with a greater number of retrieved oocytes.[27] In a study at one center of 56 women with normal day 3 FSH levels, patients with a poor response to IVF (<6 oocytes retrieved) had significantly lower follicular and luteal phase MIS compared with high responders (≥20 oocytes retrieved).[28] As MIS levels represent the primordial pool of nongrowing FSH-independent follicles that may respond to exogenous gonadotropins, measuring MIS levels could help to predict ovarian response in assisted reproduction cycles.[27]

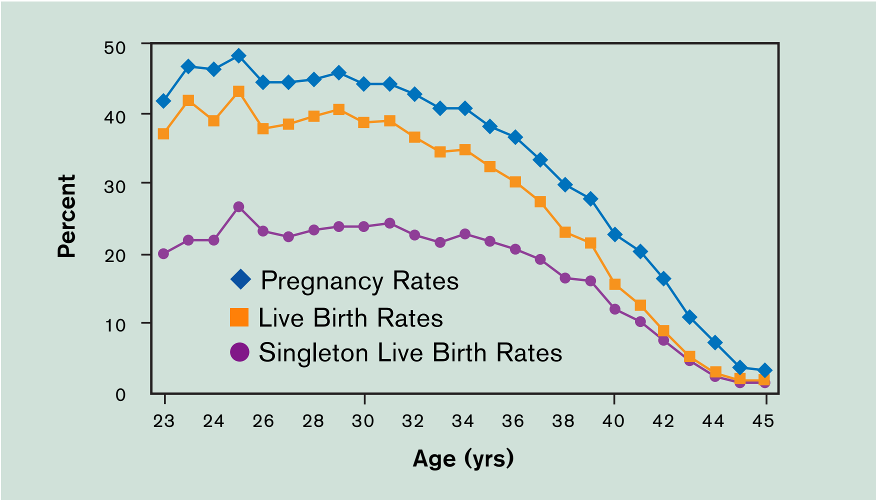

Figure 5. Pregnancy rates, live birth rates, and Singleton live birth rates for women of different ages who had ART procedures using fresh nondonor eggs or embryos in 2003.[43]

IVF in Perimenopausal Women

Poor response to ovarian hyperstimulation and IVF has been well documented in older women (Figure 5). Numerous studies have demonstrated a decline in IVF success with advancing age, especially above age 40.[29] With advancing age, the number of oocytes retrieved, embryos obtained, implantation and viable pregnancy rates rapidly decline. The response to ovarian stimulation is diminished, requiring large dosages of gonadotropins and yielding high cycle cancellation rates.[30] Often, poor response to stimulation with gonadotropins is the earliest sign of ovarian aging and is seen prior to any hormonal alterations or menstrual cycle changes.[31-33] When pregnancy does occur, women over 40 years of age are more likely to miscarry.[30]

Ovulation Induction in Perimenopausal Women

Ovulation induction with nonsteroidal selective estrogen receptor modulators such as clomiphene citrate, and aromatase inhibitors such as letrozole, is often used as a first-line treatment for unexplained and anovulatory infertility in young women. Few studies have demonstrated any improvements in pregnancy rates using these agents in older women as compared with younger women. Pregnancy rates are increased with the addition of intrauterine insemination to ovulation induction agents; again, however, there are few studies looking at pregnancy rates distributed by age.[34,35] Certain studies have shown some success (clinical pregnancy rates of 9-10%) using low-dose clomiphene citrate in poor responders who have failed controlled ovarian hyperstimulation (COH) trials in the past.[36] Additionally in these patients, adjuvant treatment with aromatase inhibitors can improve ovarian response to exogenous gonadotropins and decrease the dose required for COH.[37,38] Variations in the length and timing of gonadotropin-releasing hormone (GnRH) agonists, the use of GnRH antagonists and, finally, the occasional use of natural IVF cycles have also been studied in an effort to increase pregnancy rates in older women. The specifics of these protocols are beyond the scope of this review; however, none of these interventions has proven to yield pregnancy rates that are nearly as good as those achieved using oocyte donation.

Oocyte Donation

Donor egg and embryo transfer provides the most reasonable reproductive option for older women who are either perimenopausal or menopausal, and remains the best treatment of choice for patients of advanced reproductive age. Oocyte donation from young donors overcomes the problems of diminished ovarian reserve and increased aneuploidy risk that accompanies advancing age, and results in significantly higher pregnancy rates than standard IVF regimens (Figure 6). Women over 45 years of age, even as old as 55, may achieve pregnancy rates on par with young women using their own eggs.[39-41] Recipient age does not adversely affect cycle outcome when donor oocytes are used, with fertilization rates, embryo implantation rates and ongoing pregnancy rates similar to that in younger cohorts.[42] Donor IVF remains the most successful method of assisted reproductive treatment.

In 2003, 14,323 of the 112,872 total ART cycles reported to the US Centers for Disease Control and Prevention were either fresh or frozen donor egg derived, comprising almost 12% of the total number of IVF cycles performed in the United States.[43] Few women younger than age 39 used donor eggs; however, above the age of 39, the number rose sharply, with almost 80% of women older than 45 using donor eggs.[43] Success rates for women who used ART with donor eggs were dramatically higher than for those women who used their own eggs, with the average live birth per transfer equal to 50% in donor cycles, versus 0-10% in women over 40 using their own eggs.[43] Studies of obstetric outcome in postmenopausal women participating in donor cycles have shown excellent outcomes. In a study of 1,288 recipient cycles in one center, a majority of pregnancies resulted in live births of healthy babies, with the oldest patient delivering at the age of 63.[44]

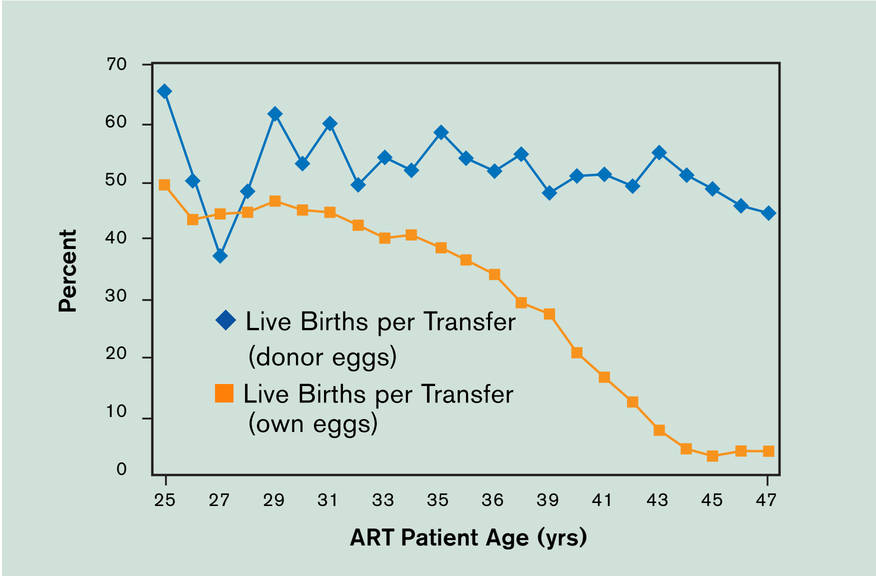

Figure 6. Live birth rates for ART cycles using fresh embryos from donor eggs versus ART cycles using a woman's own eggs among women of different ages.[43]

As oocyte and embryo quality is maximized during donor cycles since oocytes are derived from young healthy women, pregnancy and delivery rates are a function of endometrial receptivity of the recipient.[45] The fact that pregnancy rates remain constant over a wide range of ages and with consecutive cycles suggests that endometrial receptivity remains fairly constant with advancing age, making donor IVF an attractive option for women with diminished ovarian reserve.[45]

Donor-recipient treatment protocol. In most IVF centers, donors and recipients undergo complete medical and psychological screening prior to beginning an IVF cycle. Oocyte donors are typically aged <35 years with normal baseline day 3 FSH levels (<10 mIU/mL). Tests currently required for oocyte donors are HIV-1, HIV-2, hepatitis B, hepatitis C, *Treponema pallidum* (the agent for syphilis), *Chlamydia trachomatis* and *Neisseria gonorrhea*. The screening process involves a review of medical history and test results, a physical examination, and a patient interview in which an evaluation of risk factors (including high-risk social behaviors) is made. A potential donor is deemed ineligible to donate if either the testing or screening indicates the presence of a communicable disease or risk factor. In a known donation the recipient should be prepared to sign a legal waiver acknowledging informed consent, and accepting all responsibility for the pregnancy and care of the child.

Donors are required to sign legal waivers relinquishing responsibility for any progeny conceived through egg donation.

Donors and recipients follow a standard synchronization regimen, with donors undergoing ovarian down-regulation using leuprolide acetate followed by gonadotropins. Recipients are treated with oral micronized E_2 for several days before donor-initiated gonadotropin therapy. If recipients have residual gonadal function, they undergo leuprolide acetate down-regulation prior to starting E_2 to achieve a medically castrated state. Recipients begin taking progesterone on the morning of the day before the donor's egg retrieval and continue progesterone until after the pregnancy is established. Embryo transfers occurs 72 hours post-retrieval, or 5 days post-retrieval in the case of a blastocyst transfer. E_2 and progesterone are continued until either a negative pregnancy test results or until the fetus is of 10-14 weeks of gestational age (program-dependent) in women achieving pregnancy.[46,47] Other formulations of estradiol and progesterone supplementation, including transdermal estradiol and intramuscular and vaginal progesterone, have been utilized with equal efficacy to oral regimens. The decision to proceed with donor IVF can be a tough one, especially in a woman who has pursued and failed previous IVF cycles using her own eggs. For this reason, all IVF patients, especially donors and recipients, are offered psychological support and social work services to cope with the emotional issues surrounding this process.

Obstetric risks with donor IVF. Several studies have concluded that the outcomes of pregnancies following oocyte donation are favorable. However, as donor IVF becomes more widespread, potential obstetric risks associated with this procedure have emerged. Multiple births, which are associated with adverse fetal and maternal outcomes, are related to the increasing use of IVF. Using donor eggs from young women in older recipients negates the age-related increase in aneuploidy found in older women, and therefore recipient cycles are at high risk for multiple births.[48] In a study of the reproductive and obstetric outcomes of 36 menopausal women aged 50-59 undergoing oocyte donation, 45 oocyte aspirations resulted in an implantation rate of 20.6% and a pregnancy rate of 48.9%, with nearly a 40% live-birth rate. There was a 53% multiple gestation rate, with one triplet gestation that delivered at 32 weeks. Antenatal complications occurred in eight patients, with the majority being gestational hypertension.[40] This study showed oocyte donation in menopausal women over 50 results in pregnancy rates similar to those of younger women who undergo oocyte donation. However, the incidence of antenatal complications is higher and careful obstetric surveillance is necessary, in addition to careful medical screening of recipients prior to starting a donor IVF cycle.

Conclusions

Despite the well-known success of donor egg and embryo transfer, many patients remain hesitant to embrace this treatment, perhaps due to the fact that the resulting child will not be genetically related to the mother. Future prospects involving egg donation may include the use of enucleated donor oocytes, which would allow recipients to use their own genetic nuclear material.[47] As a preventive measure, women who choose to delay childbearing may soon be able to cryopreserve their eggs for later use.[4] Recent evidence in mice points to the possibility of germ cell progenitors in the bone marrow, which challenges the tenet that females are born with a finite number of unreplenishable eggs.[49] Stem cell research may some day allow progenitor cells to replace the aging oocyte pool and markedly extend reproductive lifespan. Such possibilities to address the age-related decline in female fertility are exciting, but for now egg and embryo donation provides the most successful option for older women to experience the happiness of childbearing.

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Dr. Vardhana reports no potential conflicts related to the content of this article.

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