INFERTILITY TREATMENT IN PERIMENOPAUSAL WOMEN: ETHICAL CONSIDERATIONS

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The number of women seeking treatment for infertility continues to grow. It is estimated that approximately 1 in 136 or two million people in United States are infertile (1). These numbers are explained, in part, by an age-related decline in fertility that is well documented in the medical literature. Despite the availability of new technologies such as in vitro fertilization (IVF), this age-related loss of fertility cannot be overcome by the use of assisted reproductive technologies (ART), if donor oocytes are not used (2–10).

ART has been viewed as a panacea for perimenopausal women seeking motherhood late in their reproductive lives. According to the 2003 CDC Assisted Reproductive Technology Report (11), 20 percent of women seeking ART were of the age of forty and older. Most women in this age-group either delayed childbearing to pursue higher education and careers, or are part of the large cohort of women born during the "baby boom" (1946–1964) period. Although these women can have spontaneous pregnancies, the likelihood of pregnancy and live birth is less than 1–2 percent in those older than forty-three (11), and the time to conception can be prolonged.

Age is the most important factor affecting the chance of a live birth when a woman uses her own eggs. Among women in their twenties, pregnancy and live birth rates are relatively stable; and decline steadily from the mid-thirties onward (11). The live birth rate for infertile women is 37 percent for women younger than thirty-five years, 30 percent at ages thirty-five to thirty-seven, 20 percent at ages thirty-eight to forty, and 4 percent after age forty (11). ART success rates also differ for women who are forty and older and declines with each year of age using fresh nondonor eggs or embryos (7). The average chance for pregnancy is nearly 23 percent for women aged forty, and the live birth rate is about 16 percent. For women aged forty-three and older, the live birth rates are less than 1–2 percent (11) (Figure 72.1).

The dramatic decline in female fertility, over the age of forty, characterizes the perimenopause. It occurs approximately ten years prior to menopause despite regular menses. It is the period with variations in menstrual cycle length in a woman who has a monotropic follicle-stimulating hormone rise and ends with the final menstrual period (12). Elevations of FSH and estradiol and a decrease in inhibin B levels represent the most clinically significant hormonal alterations in perimenopausal women (4, 6, 8, 13), and represents diminished ovarian reserve and impending ovarian failure. Even when faced with the remote prospect of a live birth with ART, many women in this age-group often elect to continue their efforts to reproduce. They view ART as a realistic and viable option despite their age and medical evidence. These women often refuse to objectively consider the likelihood of achieving a live birth and are willing to accept a 1 percent chance of getting pregnant. They do not want to stop treatment, and seek alternative clinics and providers that will offer them additional IVF cycles (14). As a result, they demand utilization of reproductive technologies that is of little or no benefit to them. The difficulty for the physician lies in offering treatment to perimenopausal women knowing that the likelihood of success is low (14).

This chapter will review the literature on the effects of age on fertility in the perimenopausal woman. We will also look at the appropriateness and ethical implications of using ART to extend the reproductive lives of perimenopausal women despite their low likelihood of having a live birth. We will conclude the chapter by presenting potential clinical guidelines for age in perimenopausal women using their own oocytes.

REVIEW OF THE LITERATURE

The effect of age on female fertility is difficult to assess because of confounding variables such as coital frequency and other biological causes associated with infertility (2), the use of contraception and the social and economical constraints that limit family size (8). Cultures that prohibit the use of contraception are a useful model for examining the impact of age on fertility. Tietze (15) created fertility curves for a religious sect (Hutterites) living in the Dakotas and Montana that do not practice birth control or receive economic incentives to limit their family size. Three and a half percent of Hutterite women less than twenty-five years old were sterile, and the sterility rate increased markedly beyond ages thirty-five to forty. Eighty-seven percent of the Hutterite women older than forty were sterile, and all were sterile over the age of forty-five. Tietze also showed that with increasing age of the mother, there was a marked increase in the average duration of the interval between pregnancies.

Even though fertility rates vary between populations, consistent age-related trends are noted. A slow decline in fertility rates become more significant through the middle of the fourth decade of life followed by a much steeper decline thereafter (8). However, some authors (8) suggest that studies of "natural populations" overestimate the effect of aging on reproductive



Figure 72.1. Pregnancy rates, live birth rates, and singleton live birth rates for ART cycles using fresh nondonor eggs or embryos among women aged forty and older, 2003.

potential because other biological causes associated with female infertility increase in frequency with age, and the frequency of coitus in older couples may decrease, thus decreasing the fecundity rate.

To control for coital frequency and the influences of male fecundity with age, Schwartz et al. (16) analyzed cumulative pregnancy rates for fertile women with azoospermic husbands undergoing insemination with donor sperm for twelve cycles. This was a prospective study of 2,193 fecund women. Women were divided into four age-groups, and the cumulative success rate after twelve cycles of insemination was 73 percent for those younger than twenty-five years, 74.1 percent for the twenty-six to thirty age-group, 61.5 percent for the thirty-one to thirty-five age-group, and 53.6 percent for the group older than thirty-five years. The curve of the cumulative success rate for women younger than twenty-five years was similar to that for women twentysix to thirty years old. However, both pregnancy curves differed from the curves for the two older groups (p < 0.001, in comparison to the age-group over thirty-five; and p < 0.03, in comparison to the age-group of thirty-one to thirty-five). This study showed that there is a slight decrease in fecundability after thirty years of age and is marked after thirty-five years.

Although fertility decreases with age, not all perimenopausal women are infertile. This is because age is just one predictor of female fecundity, albeit a very important one. As a result, we are always seeking markers of ovarian reserve and responsiveness to predict female fecundability before stimulation. Before markers were available, many women in their forties were being excluded from IVF programs (17) since there had been no practical way to identify the subset with a better prognosis. Markers of ovarian reserve provide insight into ovarian responsiveness that age does not (18).

While they may predict a lower pregnancy rate, abnormal ovarian reserve test results do not preclude the possibility of pregnancy and should not be presented to patients as absolute (19). Likewise, ovarian reserve testing alone may yield falsely reassuring results as advanced maternal age and ovarian reserve test results are independent predictors of infertility (3, 19). There is a poor negative predictive value of a normal test result in women older than forty years and emphasizes that these tests are quite specific but have limited sensitivity.

Basal FSH levels have been shown to provide more information than any other single static predictor of ovarian reserve (including age, LH, and E2) (17). Although markers of ovarian reserve are not very sensitive in predicting response, they are pretty consistent of poor fertility outcomes in older women (3, 17–18). Thus, "ovarian screening" may identify patients who should consider oocyte donation rather than traditional IVF.

Pearlstone et al. (3) conducted a prospective, observational study of 402 cycles in eighty-five infertile couples in whom the female partner was forty years or older and referred for ovulation induction therapy. Pregnancy and live birth rates were lower in this group. Women with a basal FSH less than 25 IU/L and age less than forty-four years had a clinical PR of 5.2 percent per cycle compared with a 0.0 percent per cycle in cases in which either basal FSH was 25 IU/L or higher or age was forty-four or more (p < 0.005). They concluded that basal FSH and chronological age are accurate predictors of reproductive outcomes in these couples, and both should be used in counseling patients about their chances for success.

To further substantiate the utility of FSH to predict ovarian responsiveness, Toner et al. (18) performed a prospective study of 1,478 consecutive IVF cycles to ascertain whether FSH was a better predictor of IVF performance than age. They showed that total and term pregnancy rates declined as age and FSH values increased (p < 0.0001). However, pregnancy rates (total and ongoing) per attempt steadily declined as basal FSH increased, whereby no decline in the slope of pregnancy rates with age was detected. Furthermore, there was no relationship between cancellation risk and age but with increasing FSH values. They concluded that basal day 3 FSH levels provided better predictive values for both IVF pregnancy and cancellation rates than age, but both need to be considered simultaneously for optimal prediction of ovarian reserve.

Moreover, the clomiphene citrate challenge test (CCCT) has been shown to be a better predictor of ovarian reserve than day 3 FSH. Scott et al. (20) did a prospective CCCT screening in women from the general infertility population. Approximately 10 percent of the 236 patients who were evaluated and followed for a minimum of one year had an abnormal CCCT. The incidence of an abnormal test rose with age (three percent at less than thirty years of age, 7 percent at thirty to thirty-four years, 10 percent at thirty-five to thirtynine years, and 26 percent for women older than forty years). Most importantly, the pregnancy rates in patients with diminished ovarian reserve were markedly lower (9 percent) than those with adequate reserve. Even after controlling for age, the pregnancy rates were still significantly decreased. Only seven of twenty-three patients with an abnormal test had an elevated day 3 FSH level, again suggesting that the CCCT may be more sensitive than screening with day 3 samples alone.

Even with a normal CCCT, the authors (20) showed that age is a better predictor of pregnancy outcomes in older women. Two out of ninety-two women aged forty years or more, who had a normal CCCT, became pregnant compared to 34/92 women less than thirty years of age with a normal clomiphene challenge test. This further supports the notion that age trumps current hormonal markers in predicting ovarian function in perimenopausal women.

In all, a combination of markers of ovarian reserve and age are the best modalities to predict the likelihood of success or poor outcomes in older women. The aggressive use of fertility drugs and standard assisted reproductive techniques in older patients may be of limited value, especially if they have abnormal ovarian function testing (3, 5, 17, 20). These patients may benefit from egg donation to achieve pregnancy. The ability to identify individuals with diminished reproductive potential or "ovarian reserve" is therefore of practical value (8). The predictability of a normal test, in contrast, is more limited. It seems reasonable to offer standard IVF to women (forty to forty-two years of age) without laboratory evidence of compromised ovarian reserve, because although their chances of achieving a live birth are very low, they are not nonexistent (14).

AGE-RELATED OBSTETRICAL CONCERNS

So far, our discussion has been limited to the effects of advanced age on reproductive outcomes for perimenopausal woman. What about the obstetrical complications associated with advanced maternal age? Gestational diabetes, preeclampsia, abnormal placentation, labor dystocia requiring operative deliveries, and preterm delivery are dramatically increased in women older than forty (21). The risk of spontaneous abortion also increases with female age (4, 10). According to the 2003 CDC Assisted Reproductive Technology Report (11), miscarriage rates were below 13 percent among women younger than thirty-four. The rate increased among women in their mid-tolate thirties and continued to increase with age, reaching 29 percent at age forty and 48 percent at age forty-three. The ageassociated decline in female fecundity and increased risk of spontaneous abortion are largely attributable to abnormalities in the oocyte (22–24).

EFFECTIVE ART TREATMENT FOR PERIMENOPAUSAL WOMEN

The most effective treatment for women older than forty years is oocyte donation. Although the resulting child will not be biologically related to the birth mother, oocyte donation yields the highest live birth rate of any ART treatment (19). Women older than forty have a 50 percent chance of live birth per transfer when fresh donor eggs are used (11) (Figure 72.2).

Miscarriage rates are significantly reduced from the rate normally seen in older mothers with donor eggs. The combined effect of higher implantation rates and lower miscarriage rates has made this method a more successful alternative for treating infertility in perimenopausal women.

ETHICAL CONSIDERATIONS

Infertility treatment in the perimenopausal woman raises many ethical questions. What constitutes poor prognosis or futile treatment? If a woman can afford treatment that is associated with less than 5 percent chance of success should it be offered? Does a patient's right to autonomy guarantee the right to futile or inappropriate care? Does a patient's desire and request for treatment oblige a physician to provide that care? What processes and procedures are necessary to address requests for ineffective, futile, or medically inappropriate medical care?

Turning to the first question, how do we define very poor prognosis and futility as it relates to infertility treatment, specifically IVF? Multiple authors in a variety of medical specialties



Figure 72.2. Live births per transfer for ART cycles using fresh embryos from own and donor eggs, by ART patient's age, 2003.

have defined futility, sometimes using case examples to illustrate the meaning of this term in a medical context. In one example, the family of an eighty-five-year old woman demanded medical treatment that the attending physician considered futile. The issue was further complicated by the fact that the husband was an attorney, and the funding of care was not an issue (25, 26). Many of the discussions involve treatment decisions in terminally ill patients. There are, however, several publications that address ethical issues that are germane to obstetrics and gynecology patients. In a committee opinion from the American College of Obstetricians and Gynecologists (27), one proposed definition of futile treatment required one or more of five elements:

- 1. Lethal diagnosis or prognosis of imminent death.
- 2. Suggested therapy cannot achieve its physiological goal.
- 3. Suggested therapy will not or cannot achieve the patient's or family's stated goals.
- The suggested therapy will not or cannot extend the patient's life span.
- 5. The suggested therapy will not or cannot enhance the patient's quality of life.

Perhaps the most relevant answer to the question of fertility treatments in women older than forty years old comes from the Ethics Committee of the American Society for Reproductive Medicine (14). Futility was defined as a 0 or 1 percent or less chance of achieving a live birth, while "very poor prognosis" was used to describe very low but not nonexistent odds of achieving a live birth (>1 percent but about < 5 percent per cycle).

Moreover, if a patient can afford ineffective care, should it be offered? Ironically, the women who can best afford infertility treatment are often those women who have a poorer prognosis as a result of their age (28). This question was debated within both the hospital and the court system in the case of a patient receiving respirator support in spite of a dismal prognosis. It is clear that we cannot afford a universal health care system based on the desires and demands of every patient. In contrast, should financial resources enable a wealthy elderly dialysis patient with a poor prognosis and limited life expectancy to be able to "purchase" a kidney, while more appropriate candidates remain on a waiting list? In this and similar cases, it would appear that the principle of "ethical stewardship" should be considered. Physicians must exercise appropriate stewardship in their counseling of patients and their refusal to deny inappropriate and ineffectual treatment (25, 29, 30). This is true even when the treatment has minimal risk to the patient, as in the case of IVF.

In recent years, patient autonomy has also become an increasingly important consideration. However, respect for the patient's right to autonomy does not require physicians to provide treatment that is futile. At the same time, physicians should retain some flexibility in developing policies for initiating or continuing fertility treatments in patients with poor prognoses keeping in mind circumstances or emotional needs of individual patients (14).

Most physicians would not be reticent to offer fertility treatment to older women if they knew that the outcome would be successful. The difficulty for the physician lies in offering treatment to patients knowing that the likelihood of success is low or futile. For the patient, it is knowing when to stop seeking further treatment or to look for alternatives to obtain an end to a means. But how do we counsel women who are willing to accept that less than 1 percent chance of getting pregnant?

Furthermore, what should be done to create a happy medium for both the physician, who does not want to dispense futile reproductive treatments to perimenopausal women, and the patient, who views it as her reproductive right to bear children with assistance despite age? One way to address this ethical dilemma is to establish clinical guidelines for treatment of perimenopausal women using their own eggs (14). This would allow for consistency in practice, establish evidence-based policies, and enable us to better counsel our patients. This would prove to be a win-win situation for both the physician and patient. Physicians would be guided by evidence-based data enabling them to avoid futile treatment efforts and maintain their professional integrity. While the patient with a very low prognosis of having a live birth may still have a reasonable chance of achieving a pregnancy that results in a live birth with reproductive assistance.

The ASRM ethics committee (14) has issued such guidelines. In cases of very poor prognosis, the ethics committee stated that that it is ethical to treat, if the patient is fully informed of the prognosis and still wants to proceed. However, physicians may ethically refuse to accept or provide further treatment to patients with very poor prognoses provided that they follow evidence-based policies and the rules of their fertility centers, and avoid arbitrary decisions. All fertility centers should establish guidelines based on the literature and their success rates to appropriately counsel patients about the likelihood of live birth based on age. These policies should be discussed at the initial visit, and should guide decisions about initiating or stopping treatment.

KEY POINTS FOR CLINICAL PRACTICE

In conclusion, no fertility treatment, with the exception of oocyte donation, has been associated with a live birth rate of more than 15 percent in perimenopausal women. However, when older women decide to pursue ART with their own eggs, the decision making of proceeding with treatment for the physician and patient becomes difficult. The concepts of futility and very poor prognosis of treatment must be entertained in every case, before a decision to treat is made while respecting patient autonomy. By establishing evidence-based guidelines using data in the literature and generated by each center, we are better able to counsel patients about the futility of treatment and when to consider seeking alternatives to achieve their goal of a live birth. These guidelines would also allow both the physician and the patient to justify treatment in those cases when the odds of success are low but are not nonexistent.

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