

Aging and infertility in women

The Practice Committee of the American Society for Reproductive Medicine

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BACKGROUND

Female fertility begins to decline many years prior to the onset of menopause despite continued regular ovulatory cycles. Although there is no strict definition of advanced reproductive age in women, infertility becomes more pronounced after the age of 35. A classic report on the effect of female age on fertility found that the percentage of women not using contraception who remained childless rose steadily according to their age at marriage: 6% at age 20 to 24, 9% at age 25 to 29, 15% at age 30 to 34, 30% at age 35 to 39, and 64% at age 40 to 44 (1). Similarly, a sharp decline in pregnancy rate with advancing female age is noted with donor insemination studies (which control for fertility of the male partner and coital frequency) (2) and with assisted reproductive technologies (ART) including in vitro fertilization (IVF). The risk of spontaneous abortion increases with female age (3). According to the *1999 Assisted Reproductive Technology Success Rates*, the percentage of clinical pregnancies (gestational sac as imaged with sonography) that failed to result in a live birth rose according to the woman's age: 14% for patients under age 35, 19% at age 35 to 37, 25% at age 38 to 40, and 40% after age 40 (4).

A recent review of studies on the effects of male age on semen quality and fertility concluded that increasing age is associated with a decline in semen volume, sperm motility, and sperm morphology, but not sperm concentration (5). There is some decline in male fertility with age, particularly over the age of 50, but the results of many of these studies are confounded by female partner age. There is no absolute age at which men cannot father a child. Fertility is thus more related to the age of the female than the male partner.

The average age of childbearing has increased over the past three decades as more women have pursued higher education and careers and postponed marriage. Concurrently, a large cohort of women born during the "Baby Boom" (1946–1964) have reached their late reproductive years, resulting in more women in this age group seeking assistance for infertility. Not all women of advanced reproductive age who wish to conceive experience infertility. Those older women who do present to physicians for infertility may have other fertility problems (e.g., male factor) in

addition to ovaries with average to low follicle numbers and reduced quality.

PHYSIOLOGY OF REPRODUCTIVE AGING

The age at which menopause occurs reflects near complete depletion of the ovarian follicular pool (6). Subtle changes in early follicular phase serum concentrations of FSH (increase) and inhibin B (decrease) precede changes in menstrual regularity and ovarian steroid secretion. Risk factors for early loss of ovarian reserve include smoking, family history of premature ovarian failure, significant ovarian pathology, and previous ovarian surgery.

The age-associated decline in female fecundity and increased risk of spontaneous abortion are largely attributable to abnormalities in the oocyte. The meiotic spindle in the oocytes of older women frequently exhibits abnormalities in chromosome alignment and microtubular matrix composition (7). Higher rates of single chromatid abnormalities in oocytes (8), as well as aneuploidy in preimplantation embryos (9) and ongoing pregnancies, are observed in older women. The higher rate of aneuploidy is a major cause of increased spontaneous abortion and decreased live birth rates in women of advanced reproductive age.

The prevalence of uterine pathology, such as fibroids and endometrial polyps, increases with age (10), yet there is little evidence that uterine factors have a significant impact on age-related infertility. Age does not appear to have a significant effect on morphological or histological responses of the uterus to steroid stimulation (11). A recent study has not found an age-related decline in ART cycle delivery rates when oocyte donation is performed (12).

EVALUATION

Tests to evaluate infertility provide information about current fertility but do not predict when the onset of age-related infertility will occur. Although infertility is commonly defined as the inability to conceive after one year of unprotected intercourse, normal older women may take longer than one year to conceive. Therefore, earlier evaluation of infertility is warranted in women over the age of 35. The consequences of undiagnosed infertility factors can be more detrimental to women who have limited time to achieve a successful pregnancy. In addition to infertility testing, the preconception medical evaluation should also include screening for significant medical disorders such as hypertension and diabetes, which are more frequent in older women. In women 40 and older, it is advisable to perform mammography prior to attempting pregnancy.

Committee Opinion

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The infertility evaluation in women of advanced reproductive age should include an assessment of ovarian reserve. The term ovarian reserve describes a woman's reproductive potential with respect to ovarian follicle number and oocyte quality. The measurement of serum basal FSH and estradiol on day 3 of the menstrual cycle is often used to test for ovarian reserve. FSH and estradiol should be measured in the early follicular phase because accelerated follicular development may be associated with reproductive aging. Elevated FSH and estradiol levels are independent predictors of poor prognosis in older women (14–16). Common criteria for normal ovarian reserve are an early follicular phase FSH level of <10 mIU/mL and an estradiol level of <80 pg/mL. Higher cutoff values for FSH have been reported (as high as 20 to 25 mIU/mL for FSH) because of the use of different FSH assay reference standards (13). The normal range for FSH ideally should be determined in a normal fertile population by each laboratory. In the event that such data are not available, the laboratory's stated upper limit for the follicular phase can be used as an arbitrary and imperfect cutoff to define abnormal.

The clomiphene citrate challenge test (CCCT), which is another test of ovarian reserve, is performed by measuring a day 3 FSH, administering clomiphene citrate 100 mg orally on cycle days 5 to 9, and then measuring FSH on cycle day 10 (17–19). The test is considered to be abnormal if either the day 3 or the day 10 FSH is above the threshold value for the laboratory.

Women with abnormal basal FSH, estradiol, or CCCT have lower live birth rates with ovulation induction and intrauterine insemination (17, 19, 20). Women with diminished ovarian reserve also experience decreased responses to ovulation induction, require higher doses of gonadotropin, have higher IVF cycle cancellation rates, and experience lower pregnancy rates through IVF (18, 21). In a general infertility population, an abnormal CCCT predicts that a successful pregnancy will be achieved about 5% of the time (22). A single elevated day 3 FSH value connotes a poor prognosis, even when values in subsequent cycles are normal (23, 24).

Other tests of ovarian reserve under study include circulating inhibin B levels, the gonadotropin-releasing hormone agonist test, and small antral follicle count by ultrasound. Women with decreased ovarian responsiveness to gonadotropin may have decreased serum inhibin B levels even when FSH levels are normal (25). This finding suggests that inhibin B may be a more sensitive marker of ovarian reserve than FSH. However, routine testing for serum inhibin B levels is not recommended at this time due to limited availability of reliable assays and conflicting data regarding its prognostic value (26). The gonadotropin-releasing hormone agonist challenge test is not recommended for routine clinical use because of limited data on its prognostic value. The number of small antral follicles visible on transvaginal ultrasound appears to correlate directly with ovarian response

to gonadotropins (27, 28). In the future, transvaginal ultrasound may be an effective way of estimating ovarian reserve.

Currently it seems reasonable to test ovarian reserve by using day 3 FSH and estradiol or the CCCT in all infertile women age 35 and older who desire pregnancy. Ovarian reserve testing may be considered in patients under age 35 with a solitary ovary, history of ovarian surgery, poor response to exogenous gonadotropins, exposure to chemotherapeutic agents or ionizing radiation, and unexplained infertility.

COUNSELING

Preconception counseling should include a discussion of the increased risks of aneuploidy, spontaneous abortion, and obstetric complications such as delivery by cesarean section, hypertension, and gestational diabetes (29) associated with increasing maternal age. The rate of all clinically significant cytogenetic abnormalities in live births increases from about 1/500 for women under 30 to 1/270 at age 30, 1/80 at age 35, 1/60 at age 40, and 1/20 at age 45 (30).

Counseling after ovarian reserve testing should include a discussion of the results. 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. Likewise, ovarian reserve testing alone may yield falsely reassuring results, as advanced maternal age and ovarian reserve test results are independent predictors of infertility. Both should be used when counseling couples regarding their chances for conception (22).

TREATMENT

Treatment options for age-related infertility include controlled ovarian hyperstimulation with intrauterine insemination (COH/IUI), IVF, and oocyte donation. Except for oocyte donation, these treatments are intended to accelerate the time to conception rather than directly affect oocyte or embryo quality. Expectant management, which should be reserved for couples who do not desire medical intervention, is also considered a treatment option but is less likely to result in pregnancy in women of advanced reproductive age (39). COH/IUI consists of gonadotropins administered to initiate growth and ovulation of multiple follicles in conjunction with the placement of washed sperm in the uterine cavity.

COH/IUI has limited efficacy for women over 40 with otherwise unexplained infertility, yielding a per cycle delivery rate of 5% or less (range 1.4% to 5.2%) (31–36). This compares with a live birth rate per cycle of 17% to 22% for women under 35 and 8% to 10% for women aged 35 to 40 (33, 37, 38). There have been no studies comparing COH/IUI with IVF. Unfortunately, most reports have been retrospective case series or cohort studies that would be expected to overestimate treatment effectiveness.

The presence of male factor, tubal disease, endometriosis, or pelvic adhesions would argue for proceeding directly to

IVF in women of advanced reproductive age. Pregnancy rates from IVF are generally higher than from COH/IUI but also decline significantly with age. According to the 1999 *Assisted Reproductive Technology Success Rates*, live birth rates per cycle were 32.2% in women under 35, 26.2% in women aged 35 to 37, 18.5% in women aged 38 to 40, 9.7% in women aged 41 to 42, and approximately 5% in women 43 and older (Fig. 1) (4).

In a recent multicenter review of 431 initiated IVF cycles in women ≥ 41 years, there were no clinical pregnancies in women ≥ 45 years and no deliveries in women ≥ 44 years of age (40). This age-related decline in IVF success is related to decreased ovarian responsiveness to gonadotropins and, more importantly, to a marked decline in embryo implantation rates (Table 1). Embryonic aneuploidy is likely the major reason for implantation failure in older women (41).

The following alternative approaches have been described for IVF treatment in women with decreased ovarian reserve:

1. Microdose GnRH agonist flare protocol or other flare (43, 44).
2. Use of a GnRH antagonist with gonadotropins.
3. Low-dose GnRH agonist suppression before gonadotropin stimulation.
4. Assisted hatching of embryos.
5. Use of estrogen or oral contraceptives in the cycle prior to gonadotropin stimulation.

TABLE 1

Embryo implantation rates as a function of female age (42).

Age	Implantation rate
25–29	18.2%
30–34	16.1%
35–39	15.3%
40–44	6.1%

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Source: Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, RESOLVE. 1999 Assisted Reproductive Technology Success Rates. Atlanta, GA. Centers for Disease Control and Prevention; 2001 (4).

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Unfortunately, there are no randomized trials to compare the relative efficacy of these approaches. Exclusion of aneuploid embryos with preimplantation genetic diagnosis (PGD) may lower the spontaneous abortion rate in IVF cycles (45). However, the technique is expensive and is not yet widely available. Its role in the treatment of age-related infertility has yet to be defined.

Nuclear (germinal vesicle) transfer is an experimental technique in which the nucleus from the oocyte of an older woman is transferred to the enucleated oocyte of a younger woman. The safety and efficacy of this technique is currently unknown (46).

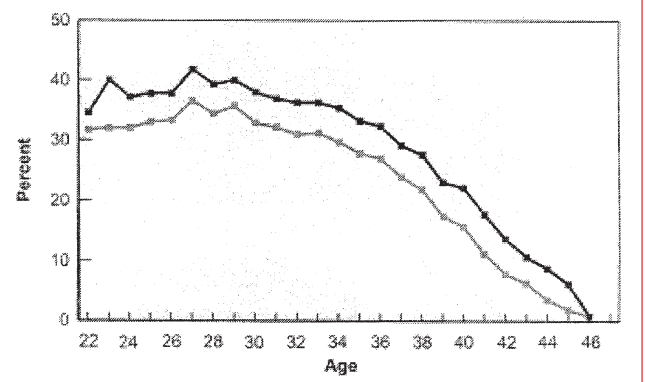
No treatment other than oocyte donation has been shown to be effective for women over 40 and for those with compromised ovarian reserve. Although the resulting child will not be biologically related to the birth mother, oocyte donation yields the highest live birth rate of any ART treatment. It is the treatment of choice for age-related infertility not successfully addressed by other methods. Pregnancy rates with oocyte donation are dependent on the age of the donor rather than the recipient.

SUMMARY

- A relatively large group of women is experiencing age-related infertility due to social trends that lead to deferred childbearing and to the current age of the “Baby Boom” generation.
- Age-related infertility is due to oocyte abnormalities and decreased ovarian reserve.
- Clinical tests to estimate ovarian reserve include FSH and estradiol levels in the early follicular phase (e.g., day 3) or a clomiphene citrate challenge test.

FIGURE 1

Pregnancy and live birth rates for ART cycles using fresh, nondonor eggs or embryos, by female age, 1999. Data from reference 4. Gray line = live birth rate; solid line = pregnancy rate. ASRM. Aging and infertility in women. Fertil Steril 2002. Source: Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, RESOLVE. 1999 Assisted reproductive technology success rates. Atlanta, GA: Centers for Disease Control and Prevention, 2001.



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- Evaluation and treatment of infertility should not be delayed in women 35 years and older.
- Treatment of infertility when the cause is limited to decreased ovarian reserve is empirical at present except for oocyte donation.

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