CLINICAL PRACTICE

In Vitro Fertilization

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 37-year-old woman who has never been pregnant and her 40-year-old husband have been attempting to conceive a child for the past 3 years. An infertility evaluation has shown no cause for the difficulty. She is ovulating regularly, and a hysterosalpingogram shows that her reproductive tract is anatomically normal. He has a normal sperm count; he has not fathered any children. They are frustrated and want to proceed with in vitro fertilization. What should you advise?

THE CLINICAL PROBLEM

Infertility is common — approximately 10% of couples have difficulty conceiving a child. In young, healthy couples, the probability of conception in one reproductive cycle is typically 20 to 25%, and in 1 year it is approximately 90%.[1] An evaluation is commonly recommended after 1 year of unprotected intercourse without conception, the standard clinical definition of infertility.

Many infertility specialists are surprised by the number of otherwise highly educated older couples with unrealistic expectations of fertility. The negative effect of a woman's age on fertility cannot be overemphasized. As women age, fertility declines and the rate of miscarriages increases. In addition, the rate of pregnancy after treatment for infertility drops more rapidly in women who are over the age of 35 years than in younger women. Thus, some clinicians argue that an infertility evaluation should begin after six cycles of unprotected intercourse in women older than 35 years.[2]

Several societal factors may contribute to infertility related to aging in women. In the United States, there have been increases over time in the mean maternal age at first birth (25.1 years in 2002 vs. 21.4 years in 1968) and in the mean age of women delivering a child (27.3 years in 2002 vs. 24.9 years in 1968).[3] This trend toward delayed childbearing in part reflects an increasing emphasis on career and educational goals as well as a later mean age at first marriage.[4] In addition, the increased availability of effective methods of birth control makes it more likely that earlier unplanned pregnancies will be avoided.

STRATEGIES AND EVIDENCE

Regardless of the cause of infertility, the treatment that leads to the highest pregnancy rate per cycle is in vitro fertilization (IVF). Since its inception in 1978,[5] there has been a remarkable increase in the numbers of IVF cycles worldwide. Approximately 1 in 50 births in Sweden, 1 in 60 births in Australia, and 1 in 80 to 100 births in the United States now result from IVF. In 2003, more than 100,000 IVF cycles were reported from 399 clinics in the United States, resulting in the birth of more than 48,000 babies.

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The process of IVF (Fig. 1) involves ovarian stimulation, egg retrieval (see video in the Supplementary Appendix, available with the full text of this article at www.nejm.org), fertilization, embryo culture, and the transfer of embryos to the uterus. The fertilization of eggs can be achieved by culturing eggs and sperm together or by means of the newer procedure of intracytoplasmic sperm injection (Fig. 1). As compared with the rate of pregnancy associated with routine IVF, this procedure has been proved to increase the rate of pregnancy only for couples with severe male-factor infertility, but it is now used in the majority of IVF cycles.

Figure 1 (facing page). The Process of IVF.

The ovaries are stimulated by daily injections of gonadotropins to optimize follicular development, which is monitored by means of transvaginal ultrasonography. Ultrasonography of an unstimulated ovary shows a small antral follicle (Panel A, arrow). The same ovary has multiple growing follicles after gonadotropin stimulation. One follicle is shown with measurements in two dimensions (Panel B). After ovarian stimulation, eggs are retrieved by means of ultrasound-guided transvaginal aspiration of follicular fluid (Panel C). A mature human egg is recovered from the aspirated fluid (Panel D). Recovered eggs are often fertilized in vitro by culturing eggs with many motile sperm (Panel E); in this image, multiple sperm are attached to the egg's zona pellucida (arrows point to three of the sperm). Eggs can also be fertilized by means of intracytoplasmic sperm injection, a technique in which a single sperm is injected into the egg with the use of a thin glass pipette (Panel F). This technique was developed to facilitate fertilization in cases of male-factor infertility but is now used in a majority of IVF cycles. Multiple embryos are cultured, often for 3 days (an eight-cell embryo, shown in Panel G) or 5 days (a blastocyst embryo, shown in Panel H, with the inner cell mass indicated by the arrow) before selected embryos are transferred back to the uterus (Panel I). Good-quality, excess embryos are often cryopreserved.

SCREENING BEFORE IVF

Before IVF, most couples will have had a standard infertility evaluation, including a semen analysis; assessment of the female reproductive tract by means of hysterosalpingography, transvaginal ultrasonography, or both; and tests to detect ovulation. Because there is great variation in ovarian responsiveness and fertility at a given chronologic age, additional testing of ovarian reserve is commonly performed in women before they undergo IVF. A reduced ovarian reserve is manifested by a diminished ovarian response to medications for ovulation stimulation, resulting in fewer eggs retrieved, fewer embryos, and a lower pregnancy rate. Many women with unexplained infertility are found to have a reduced ovarian reserve when tested.

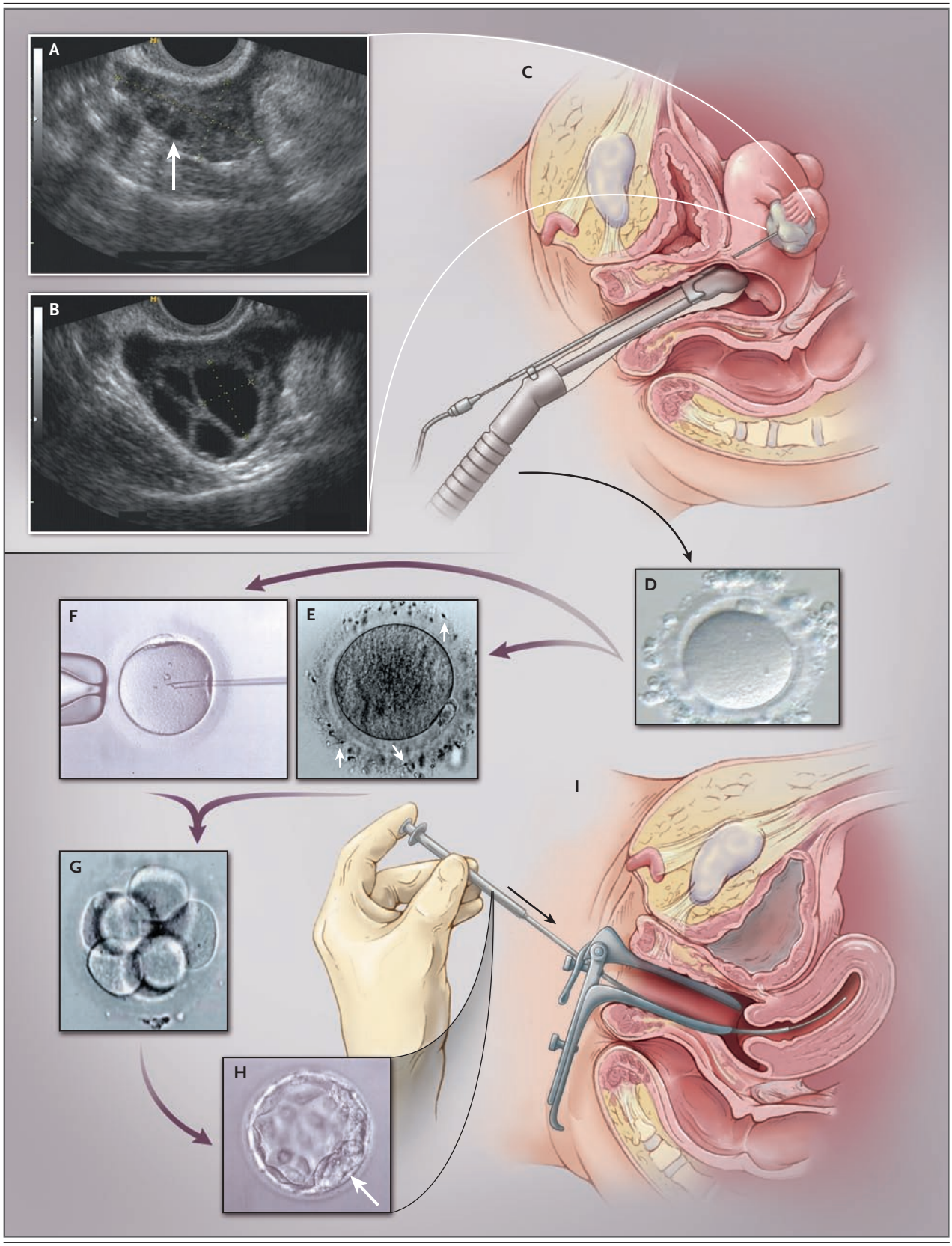
A reduced ovarian reserve is commonly diagnosed on the basis of either an elevated serum follicle-stimulating hormone level (e.g., >12 mIU per milliliter) on cycle day 3 or transvaginal ultrasonographic findings of a low ovarian volume (e.g., <3 ml per ovary) or few antral follicles (e.g., <10 antral follicles between 2 and 10 mm in diameter). These tests have less than ideal characteristics.[6,7] The positive predictive value of abnormal test results is lower among women younger than 35 years of age than among older women, and women older than 40 years of age have a poor chance of achieving pregnancy even with normal test results. All tests are better at predicting ovarian responsiveness to gonadotropins than at predicting pregnancy. Nevertheless, tests of ovarian reserve provide some prognostic information, and the results are sometimes used to select the ovarian-stimulation protocol.

BENEFITS OF IVF

By law, all IVF clinics in the United States report outcomes to the Centers for Disease Control and Prevention (CDC), and national and clinic-specific outcomes are available on the CDC Web site (www.cdc.gov/ART/ART2003/index.htm). In 2003, the clinical pregnancy rate per cycle for IVF cycles with fresh, nondonor eggs was 34% in the United States. Because of subsequent miscarriages, the actual live-birth rate per cycle was 28%. Thus, although IVF is considered to be highly effective in relation to other treatments and outcomes have steadily improved over time, the majority of IVF cycles still do not result in pregnancy.

The effect of a woman's age on the outcomes of IVF with her own eggs is striking (Fig. 2).[8] The rate of live births per embryo transfer in women who are 34 years of age or younger is between 40 and 49%. Thereafter, the live-birth rate drops by 2 to 6% for each 1-year increase in chronologic age. By the time a woman is 43 years of age, the live-birth rate is only 5%. Concomitantly, the miscarriage rate increases dramatically, and by 43 years of age, 50% of pregnancies conceived with IVF result in miscarriage.

In contrast, IVF with the use of donor eggs



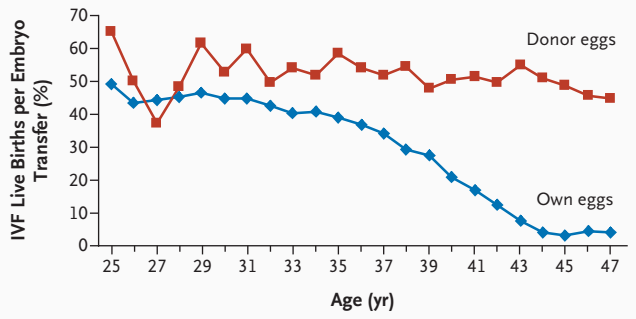


Figure 2. Effect of a Woman's Age on the Rate of Live Births per IVF Embryo Transfer.

Data are for the United States in 2003.[8]

from young women is highly successful, and the rate of pregnancy appears to vary little according to the age of the recipient (Fig. 2). The average live-birth rate per embryo transfer for donor-egg cycles is approximately 50%, indicating that the reduced rate of pregnancy associated with aging is a direct result of diminished ovarian function and egg quality and is not due to a reduction in endometrial receptivity.

The use of cryopreserved embryos may be cost-effective, since ovarian stimulation is not needed.[9] In general, however, the rate of live births per embryo transfer is lower with cryopreserved embryos than with fresh embryos, indicating some detrimental effect of the cryopreservation and thawing process. In addition to their highly publicized use as a source of stem cells, residual cryopreserved embryos can be donated to other infertile couples.[10]

RISKS OF IVF

Multiple Gestations

In general, the transfer of more than one embryo results in a higher rate of pregnancy than single-embryo transfer, but it is also associated with a high risk of multiple gestations. Multiple births are the most frequent complication of IVF, contributing to a virtual epidemic of multiple gestations in the United States.[11] Of pregnancies conceived by means of IVF in 2003, 31% were twin gestations and 3% were triplet or higher-order gestations, as compared with a 1% rate of spontaneous multiple gestations.[12,13]

Multiple gestations account for 3% of all live births nationally but are linked to 23% of early preterm births (<32 weeks of gestation) and 26% of very-low-birth-weight infants (<1500 g).[14] Premature birth, in turn, is associated with long-term pulmonary and neurologic consequences.[15] Although children from triplet and higher-order multiple gestations are at greatest risk, one study showed that IVF twins were more likely than IVF singletons to be admitted to a neonatal intensive care unit, to require surgical intervention, and to have special needs and poor speech development.[16] The mothers of these IVF twins gave lower ratings for their children's general health than did the mothers of the IVF singletons, and twin births were associated with more marital stress.

As compared with women who carry one fetus, women who carry multiple fetuses have a greater need for bed rest and higher risks of premature labor, hypertension, postpartum hemorrhage, cesarean delivery, and, although rare, death. Excess hospital costs for multiple births resulting from IVF cycles have been estimated at $640 million per year in the United States.[17]

To reduce the incidence of multiple gestations associated with IVF, the number of embryos transferred is limited by law or by insurance plans in many countries, but it remains largely unregulated in the United States. The American Society of Reproductive Medicine has issued voluntary guidelines that have resulted in the transfer of fewer embryos in the United States. This reduction, in turn, has led to a lower rate of triplet and higher-order gestations; however, the rate of twin gestations remains high. The rate of monozygotic twinning (the spontaneous splitting of an embryo) is also increased with IVF (3.2%, vs. 0.4% among women in the general population).[18]

One obvious way to reduce multiple gestations is to transfer a single embryo. The transfer of a single, fresh, cleavage-stage embryo (2 or 3 days old), followed by the transfer of a single cryopreserved embryo in women who do not conceive initially, can be nearly as successful as transferring two fresh embryos in the same cycle and can markedly reduce twinning; in one study, pregnancy rates were 38.8% with the first approach and 42.9% with the second, and twinning rates were 0.8% and 33.1%, respectively.[19] Recent studies indicate that transfers of a single blastocyst (a 5-day-old embryo) may result in an even higher rate of pregnancy while lowering the rate of multiple gestations dramatically.[20,21]

Although commonly used in Europe, single-embryo transfer has not been widely adopted in

the United States, in part because patients and clinicians think that the chances of conception are lower with a single embryo than with multiple embryos. In addition, many infertile couples do not recognize the risks of multiple gestations and actually prefer twins as a way of attaining their ideal family size more quickly.[22] In the many states in which infertility treatment is not covered by insurance companies, the high costs of IVF (frequently in excess of $10,000 per cycle) may lead patients to take more risks in order to increase the likelihood of achieving pregnancy in a given cycle.[23] Couples who have insurance coverage for infertility may be more likely to choose single-embryo transfer than are couples without such coverage. This approach may ultimately be attractive to insurers, since single-embryo transfer has been shown to be more cost-effective than double-embryo transfer because of the much reduced twinning rate.[24,25]

Adverse Perinatal Outcomes

Recent data suggest that even singleton IVF pregnancies are associated with a significantly higher risk of adverse outcomes than are spontaneous singleton pregnancies, after adjusment for maternal age and other confounding variables. The risk of such outcomes, which include perinatal death, preterm delivery, low or very low birth weight, and delivery of small-for-gestational-age infants, is approximately twice that associated with spontaneously conceived singletons.[26] Additional risks include gestational diabetes, placenta previa, preeclampsia, and stillbirth. The causes of these adverse perinatal outcomes remain poorly understood.

Birth Defects

The majority of IVF-conceived infants do not have birth defects. However, some studies have suggested that assisted reproductive technology is associated with an increased risk of birth defects.[27] In the largest U.S. study, which used data from a statewide registry of birth defects,[28] 6.2% of IVF-conceived children had major defects, as compared with 4.4% of naturally conceived children matched for maternal age and other factors (odds ratio, 1.3; 95% confidence interval, 1.00 to 1.67). Specific birth defects that were increased in the IVF population included cardiovascular and musculoskeletal defects and certain birth-defect syndromes. The use of intracytoplasmic sperm injection does not appear to confer any risk of birth defects over and above that associated with IVF.[29,30]

The cause of the increased rate of birth defects after IVF with or without intracytoplasmic sperm injection is unclear. The reported increase may reflect ascertainment bias (due to more careful scrutiny of IVF-conceived babies) or problems inherent in the infertile couple (e.g., epigenetic errors). However, it also may result from the IVF process. For example, several syndromes caused by imprinting defects (including the Beckwith–Wiedemann syndrome and Angelman's syndrome) have been reported to be more prevalent among children born after IVF.[31] Some have speculated that prolonged exposure of the embryo to culture medium may confer a predisposition to imprinting defects, although the number of infants affected is very small; further studies are needed to clarify this issue. Further research is also needed to determine whether IVF has any adverse effects on neurodevelopmental outcomes and the long-term health of children, including their reproductive health in adulthood.

Maternal Health Risks

The ovarian hyperstimulation syndrome is a short-term consequence of gonadotropin stimulation and early pregnancy. This syndrome, which occurs in less than 5% of IVF cycles, consists of ovarian swelling, pelvic pain, and hemodynamic fluid shifts, often accompanied by ascites. The disorder almost always resolves after several weeks, although in rare cases, death due to thromboembolism has been reported.

There are no definite, long-term adverse effects of IVF on a woman's health. The high estradiol and progesterone levels resulting from ovarian stimulation have raised concern about the possible increased risks of breast and gynecologic cancers. Epidemiologic studies to date have been limited in many cases by small samples and by the fact that most women who have undergone IVF have not yet reached the age of peak cancer incidence; nevertheless, these studies have generally been reassuring.[32] For example, in an Australian study involving more than 20,000 women exposed to fertility drugs,[33] the overall incidence of ovarian, breast, and uterine cancer was no greater than that expected on the basis of age-standardized population rates. Although the rates of breast and uterine cancer were higher than expected in the first 12 months after expo-

sure, this increase might have been due to ascertainment bias.

AREAS OF UNCERTAINTY

ALTERNATIVES TO IVF

The optimal strategy for treating infertile couples is not always clear. The rate of spontaneous conception among infertile couples referred for IVF is between 2 and 12% per year.[34,35] Treatments appropriate for a couple with unexplained infertility include intrauterine insemination and ovulation induction, either alone or in combination. For intrauterine insemination, a treatment timed to coincide with ovulation, freshly ejaculated semen is processed and concentrated in the laboratory and then injected through the cervix into the uterus. These treatments are less expensive and more cost-effective than IVF[36-39]; however, the pregnancy rates associated with these methods (typically between 5 and 15% per cycle) are well below those achieved with IVF.

PREIMPLANTATION GENETIC DIAGNOSIS

As compared with sperm, eggs have a very protracted meiosis, entering prophase 1 of the first meiotic division in fetal life and remaining in that phase until the time of ovulation. With aging in women, there is a reduction in egg quality resulting from abnormalities in chromosome spindle formation and alignment when meiosis resumes many years later, leading to aneuploidy.[40] Results of early-embryo biopsy and preimplantation genetic diagnosis (Fig. 3) indicate a rate of early-embryo aneuploidy after IVF of almost 60%.[41,42]

Because aneuploidy is thought to play a large role in the declining quality of eggs and embryos with aging, one might expect preimplantation genetic diagnosis, which permits the identification and transfer of normal euploid embryos, to improve pregnancy rates after IVF. Early results have not confirmed this hypothesis.[43,44] However, in a retrospective cohort study, the use of preimplantation genetic diagnosis was associated with significantly reduced rates of pregnancy loss before 20 weeks' gestation, particularly among women older than 40 years of age.[45] One limitation of preimplantation genetic diagnosis is that not all chromosomes can be assessed. In addition, this process may be inaccurate, in part because embryo mosaicism (which occurs in up to 50% of embryos in some studies) can lead to misdiagnoses, especially if only a single cell is analyzed.[44] Finally, embryo biopsy may damage the embryo, impairing its ability to become implanted and survive. If these issues are resolved, preimplantation genetic diagnosis may improve IVF outcomes.

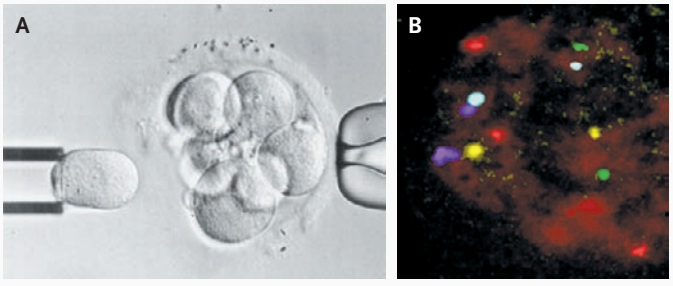


Figure 3. Biopsy and Preimplantation Genetic Diagnosis of a 3-Day-Old (Eight-Cell) Embryo.

One or two blastomeres are removed from the embryo, as shown in Panel A, for preimplantation genetic diagnosis. Fluorescence in situ hybridization (FISH) is used to identify and count individual chromosomes. Panel B shows a blastomere with trisomy 21 detected by means of FISH (red probe). With current techniques, up to 10 chromosomes in a single cell can be evaluated, although techniques that allow more comprehensive evaluation are being developed.

GUIDELINES

General policy statements, minimum standards, and practice guidelines have been issued by the American Society for Reproductive Medicine for many aspects of the practice of IVF, including recommendations regarding the number of embryos to transfer.[46]

CONCLUSIONS AND RECOMMENDATIONS

The couple described in the vignette should be counseled about the effects of age on fertility. In our clinic, my colleagues and I would first offer treatments that are more cost-effective than IVF, although, given the patient's age, we would proceed to IVF rapidly if these other treatments were unsuccessful. If the couple preferred more aggressive treatment, immediate IVF might also be performed. Ovarian-reserve testing offers additional prognostic information, although abnormal results should not preclude attempts at ovarian stimulation. Although strategies vary among clinics, I would transfer one or two blastocysts on day 5 or two or three embryos on day 3, depending on the number and quality of embryos produced;

these approaches are consistent with the American Society for Reproductive Medicine guidelines. Embryos of good quality that were not transferred would be cryopreserved. On the basis of recent national statistics, this patient could anticipate approximately a 28% chance of delivering at least one child from this procedure, which could be repeated if she did not conceive.

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A video clip showing ultrasound-guided oocyte retrieval is available with the full text of this article at www.nejm.org.

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