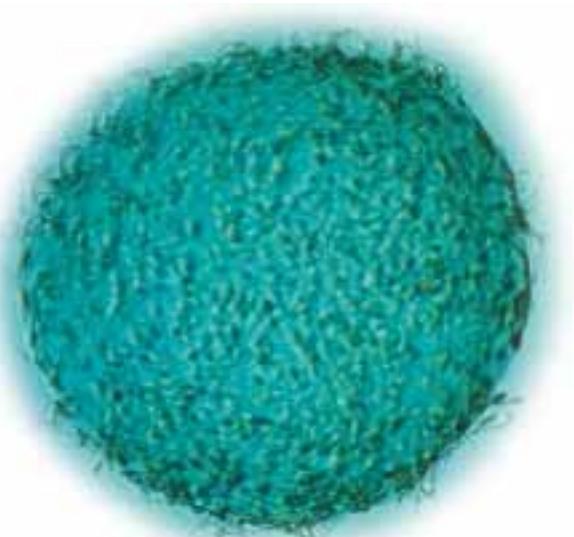


Rewinding the biological clock: oocyte donation in older women

As recently as a decade ago, oocyte donation was limited to young women with premature ovarian failure. Since then, the strategy's high success rates have been duplicated in patients over 40, making it one of the most reliable fertility methods for women in this age group.

The age-related decline in human fertility is a well-documented phenomenon. Studies in natural populations have clearly shown that as women get older, birth rates decrease—an effect that first becomes apparent at approximately 30 years of age.¹

In the United States, babies born to women over the age of 40 represent less than 1% of total live births.² By age 47, this number decreases to a mere 0.01%.³ Although it is unclear whether these low rates are due to age-related physiologic changes or merely reflect alterations in behavior, evidence suggests that a real decline in fertility accompanies female aging.^{4,5} This decline parallels an increase in chromosomal anomalies observed



in the oocytes and embryos of older women.^{6,7} What remains to be determined is whether these abnormalities reflect an inherent deficiency of the remaining oocytes within the ovary, or whether the aging cytoplasm promotes the development of aneuploidy during meiosis or subsequent mitotic divisions.^{8,9}

Neither simple nor complex fertility treatments have been able to overcome the age-related decline in fertility. Statistics generated by the Society for Assisted Reproductive Technology (SART) Registry have consistently demonstrated a live birth rate of less

■ *Dr. Paulson is professor of OBG and chief of the division of reproductive endocrinology and infertility at the University of Southern California Keck School of Medicine in Los Angeles.*

KEY POINTS

- Oocyte donation to women of advanced reproductive age is similar to donation to younger recipients, although precycle screening is more extensive.
- Although the incidence of gestational diabetes and preeclampsia appears to be increased in women over 40, neonatal outcomes are roughly equivalent to those of younger women.
- Relatively few women over 50 seek ART; to date, fewer than 300 pregnancies have been reported in this age group worldwide.

than 10% per embryo transfer in women over the age of 40. Other studies of embryo transfer using autologous oocytes have yielded similar findings in this age group.¹⁰⁻¹²

The age of the egg donor

Older women who receive donor oocytes demonstrate implantation and pregnancy rates that are essentially the same as those of younger women.¹³ Thus, the success of assisted reproductive technology seems dependent on the age of the donor, rather than the recipient.¹⁴

Although it may seem obvious now, the fact that female reproductive aging is concentrated in the oocyte was not known before oocyte donation became a common practice—nor was it necessarily anticipated. The clinical practice of oocyte donation evolved as a natural consequence of standard in vitro fertilization embryo transfer (IVF-ET). Since the gametes were collected independently and then combined in the laboratory, oocyte donation was conceptually no different from sperm donation. The key distinction was the difficulty of retrieving donated oocytes.

Initially, the problem was solved using a method known as “ovum donation,” in which the donor was inseminated with the sperm of the infertile woman’s partner. The oocyte was fertilized in vivo, then retrieved from the uterus using a flushing method. This process was relatively simple and required no anesthesia or operating room. The first pregnancy achieved in this manner was reported in 1983.¹⁵

Unfortunately, there were problems with this approach, among them the risk of sexually transmitted disease (STD) and the potential for a retained pregnancy in the donor.¹⁶ But the biggest drawback was the lack of efficiency: A viable embryo was recovered in only a small proportion of natural cycles, and attempts at superovulation were unsuccessful.¹⁶

Still, as technology advanced, success rates improved. Even though laparoscopy was still needed for oocyte retrieval, the practice of egg donation shifted toward standard IVF

methodology, with fertilization performed in vitro rather than in vivo. Trounson et al were the first to report a successful pregnancy using this method.¹⁷ Shortly thereafter, Lutjen et al reported a pregnancy in an agonadal recipient.¹⁸ Oocyte donation had become a standard part of the ART armamentarium.

A high success rate

The technological advance that played the greatest role in further accelerating the refinement of oocyte donation was transvaginal follicle aspiration. Laparoscopy was no longer needed, and oocyte retrieval became an outpatient procedure that did not require anesthesia. As a result, donors could be

The high success rates associated with oocyte donation in younger women were mirrored in those over 40.

recruited with greater ease. As the relatively high degree of success of oocyte donation became apparent,¹⁹ direct comparisons of it and standard IVF became possible.²⁰ These comparisons clearly demonstrated that endometrial receptivity and oocyte quality are 2 separate entities, each of which can affect overall success.²¹

Prior to 1990, no series had explored oocyte donation to women of advanced reproductive age. This process was considered a therapy for young women with premature ovarian failure rather than a means of overcoming the age-related decline in fertility. Thus, it was serendipitous to discover that the high success rates associated with oocyte donation in younger women were mirrored in those over 40²² and that the age of the uterus does not appear to play a significant role. After a number of reports confirmed the efficacy of oocyte donation in older women,²³⁻²⁵ pregnancies were achieved even in women over 50.^{26,27}

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The 'question' of late motherhood

One of the initial concerns about oocyte donation was the risk of obstetric complications that might arise as a result of the advanced age of the mother. Existing data for this age group were scarce, since most series involved women over the age of 35²⁸⁻³⁰ and only a few included women over 40.³¹⁻³³ Essentially no data had been collected for women over the age of 50, yet now these women were not only delivering—albeit in extremely small numbers—but experiencing multiple gestations.

Regardless of age, prospective oocyte recipients typically were—and still are—screened for cardiovascular disease and other underlying medical conditions, and followed very carefully during pregnancy. In women

Some ethical concerns remain. They include the “unnaturalness” of pregnancy after physiologic menopause.

over 40, screening is more extensive, including an assessment of cardiovascular risk, a treadmill test, an electrocardiogram (EKG), a chest x-ray, and standard blood tests.^{23,26} Since routine health maintenance in the older population includes additional testing, it is reasonable to require that such testing take place prior to the initiation of fertility therapy. This includes a Pap smear, mammogram and, in women over 50, a strong recommendation for colonoscopy to rule out potential malignant or premalignant lesions in the colon.

To date, no serious complications have been associated with these pregnancies in older women. Although the incidence of gestational diabetes and preeclampsia appears to be increased in women over 40, neonatal outcomes have been similar to those of younger women.^{34,35}

All oocyte recipients—again, regardless of age—undergo a practice hormone-replacement cycle culminating in an endometrial

biopsy on the seventh day of progesterone administration. This ensures that the uterus responds appropriately to exogenous estrogen and progesterone.^{36,37} Data collected thus far suggest that the older uterus responds to steroids the same way a younger one does.³⁸ However, since the doses used in most hormone-replacement regimens are supraphysiologic, the older uterus may require higher amounts of estrogen and progesterone than the younger uterus.³⁹⁻⁴¹ Still, these levels are easily achieved through intramuscular or transvaginal progesterone administration. Orally administered estrogen is usually adequate, but may be supplemented by the vaginal route in patients whose endometrium remains thin (<7 mm) after oral administration.⁴⁰

Psychosocial consultation is recommended for all couples requesting oocyte donation. Regardless of age, they must confront the issue of unequal genetic participation in their anticipated offspring. (This also holds true for couples contemplating donor sperm insemination.) When the woman is older, this consultation also should take into account the issue of handling pregnancy at an advanced age. In addition, it is important for couples to decide before conception whether or not to disclose to the child his or her genetic background.

As oocyte donation to older women has become more commonplace, society has become increasingly accepting of this practice. However, some ethical concerns remain.⁴²⁻⁴⁵ They include the “unnaturalness” of pregnancy after physiologic menopause, the possible health risks to the mother or fetus, the wider age gap between parent and child, and the potential for the child to be orphaned at an early age. Nevertheless, the abridgment of reproductive choice is a serious matter and legislators have been reluctant to pass laws limiting older women's access to reproductive assistance. Yet relatively few women over 50 seek ART; to date, fewer than 300 pregnancies have been reported in this age group worldwide.

Conclusion

Oocyte donation has been successful in overcoming the age-related decline in fertility in women of advanced reproductive age. It has given us great insight into the process of embryo implantation and the relative contributions of oocyte quality and endometrial receptivity. As technology advances, oocyte donation likely will be superseded by methods that allow women to become pregnant with their own genetic children. Even so, future technology will depend on the lessons learned during oocyte donation, including the principles of endometrial preparation and embryo-endometrial synchronization and the concept of oocyte quality. As life expectancy increases and health issues recede, pregnancy in women of advanced reproductive age will become less controversial. ■

REFERENCES

1. Maroulis GB. Effect of aging on fertility and pregnancy. *Semin Reprod Endocrinol.* 1991;9:165-175.
2. National Center for Health Statistics. Advance report of final natality statistics, 1981. *Monthly Vital Stat Rep.* 1983;32(suppl 9):1-40.
3. Hansen JP. Older maternal age and pregnancy outcome: a review of the literature. *Obstet Gynecol Surv.* 1986;41:726-742.
4. Menken J, Trussell J, Larsen U. Age and infertility. *Science.* 1986;233:1389-1394.
5. Federation CECOS, Schwartz D, Mayaux MJ. Female fecundity as a function of age: results of artificial insemination in 2,193 nulliparous women with azoospermic husbands. *N Engl J Med.* 1982;306:404-406.
6. Plachot M, Veiga A, Montagut J, et al. Are clinical and biological IVF parameters correlated with chromosomal disorders in early life: a multicentric study. *Hum Reprod.* 1988;3:627-635.
7. Munné S, Alikani M, Tomkin G, Grifo J, Cohen J. Embryo morphology, developmental rates, and maternal age are correlated with chromosome abnormalities. *Fertil Steril.* 1995;64:382-391.
8. Cohen J, Scott R, Alikani M, et al. Ooplasmic transfer in mature human oocytes. *Mol Hum Reprod.* 1998;4:269-280.
9. Zhang J, Wang C-W, Krey L, et al. In vitro maturation of human preovulatory oocytes reconstructed by germinal vesicle transfer. *Fertil Steril.* 1999;71:726-731.
10. Piette C, de Mouzon J, Bachelot A, Spira A. In-vitro fertilization: influence of women's age on pregnancy rates. *Hum Reprod.* 1990;5(1):56-59.
11. Dickier D, Goldman JA, Ashkenazi J, Feldberg D, Shelef M, Levy T. Age and pregnancy rates in in vitro fertilization. *J In Vitro Fert Embryo Transf.* 1991;8(3):141-144.
12. Edwards RG, Fishel SB, Cohen J, et al. Factors influencing the success of in vitro fertilization for alleviating human infertility. *J In Vitro Fert Embryo Transf.* 1984;1:3-23.
13. Paulson RJ, Hatch IE, Lobo RA, Sauer MV. Cumulative conception and live birth rates after oocyte donation: implications regarding endometrial receptivity. *Hum Reprod.* 1997;12:835-839.
14. Stolwijk AM, Zielhuis GA, Sauer MV, Hamilton CJCM, Paulson RJ. The impact of the woman's age on the success of standard and donor in vitro fertilization. *Fertil Steril.* 1997;67:702-710.
15. Buster JE, Bustillo M, Thornycroft IH, et al. Non-surgical transfer of in vivo fertilized donated ova to five infertile women: report of two pregnancies. *Lancet.* 1983;2:223-224.
16. Sauer MV, Anderson RE, Paulson RJ. A trial of superovulation in ovum donors undergoing uterine lavage. *Fertil Steril.* 1989;51:131-134.
17. Trounson A, Leeton J, Besanko M, Wood C, Conti A. Pregnancy established in an infertile patient after transfer of a donated embryo fertilised in vitro. *Br Med J.* 1983;286:835-838.
18. Lutjen P, Trounson A, Leeton J, Findlay J, Wood C, Renou P. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. *Nature.* 1984;307:174-175.
19. Sauer MV, Paulson RJ, Macaso TM, Francis-Hernandez M, Lobo RA. Establishment of a nonanonymous donor oocyte program: preliminary experience at the University of Southern California. *Fertil Steril.* 1989;52:433-436.
20. Paulson RJ, Sauer MV, Lobo RA. Embryo implantation after human in vitro fertilization: importance of endometrial receptivity. *Fertil Steril.* 1990;53:870-874.
21. Paulson RJ, Sauer MV, Lobo RA. Factors affecting embryo implantation after human in vitro fertilization: a hypothesis. *Am J Obstet Gynecol.* 1990;163:2020-2023.
22. Sauer MV, Paulson RJ, Lobo RA. A preliminary report on oocyte donation extending reproductive potential to women over 40. *N Engl J Med.* 1990;323:1157-1160.
23. Sauer MV, Paulson RJ, Lobo RA. Reversing the natural decline in human fertility: an extended clinical trial of oocyte donation to women of advanced reproductive age. *JAMA.* 1992;268:1275-1279.
24. Pantos K, Meimeti-Damianaki T, Vaxevanoglou T, Kapetanakis E. Oocyte donation in menopausal women aged over 40 years. *Hum Reprod.* 1993;8:488-491.
25. Serhal PF, Craft IL. Oocyte donation in 61 patients. *Lancet.* 1989;1:1185-1197.
26. Sauer MV, Paulson RJ, Lobo RA. Pregnancy after age of 50: application of oocyte donation to women after natural menopause. *Lancet.* 1993;341:321-323.
27. Antinori S, Versaci C, Gholami GH, Panci C, Caffa B. Oocyte donation in menopausal women. *Hum Reprod.* 1993;8:1487-1490.
28. Buehler JW, Kaunitz AM, Hogue CJ, Hughes JM, Smith JC, Rochat RW. Maternal mortality in women aged 35 years or older: United States. *JAMA.* 1986;255:53-57.
29. Grimes DA, Gross GK. Pregnancy outcomes in black women aged 35 and older. *Obstet Gynecol.* 1981;58:614-620.
30. Kirz DS, Dorchester W, Freeman RK. Advanced maternal age: the mature gravida. *Am J Obstet Gynecol.* 1985;152:7-12.
31. Rochat RW, Koonin LM, Atrash HK, Jewett JF. Maternal mortality in the United States: report from the Maternal Mortality Collaborative. *Obstet Gynecol.* 1988;72:91-97.
32. Berkowitz GS, Skovron ML, Lapinski RH, Berkowitz RL. Delayed childbearing and the outcome of pregnancy. *N Engl J Med.* 1990;322:659-664.
33. Friede A, Baldwin W, Rhodes PH, Buehler JW, Strauss LT. Older maternal age and infant mortality in the United States. *Obstet Gynecol.* 1988;72:152-157.
34. Sauer MV, Paulson RJ, Lobo RA. Oocyte donation to women of advanced reproductive age: pregnancy results and obstetrical outcomes in patients 45 years and older. *Hum Reprod.* 1996;11:2540-2543.
35. Boostanfar R, Sorensen L, Ambroggio J, et al. Pregnancy outcome in women 50 or more years of age: a decade of experience. *Fertil Steril.* 2001;75(Supplement 1):1S-19S.
36. Sauer MV, Paulson RJ, Moyer DL. Assessing the importance of endometrial biopsy prior to oocyte donation. *J Assist Reprod Genet.* 1997;14:125-127.
37. Sauer MV, Stein AL, Paulson RJ, Moyer DL. Endometrial responses to various hormone replacement regimens in ovarian failure patients preparing for embryo donation. *Int J Gynecol Obstet.* 1991;35:61-68.
38. Sauer MV, Miles RA, Dahmouh L, Paulson RJ, Press M, Moyer D. Evaluating the effect of age on endometrial responsiveness to hormone replacement therapy: a histologic ultrasonographic, and tissue receptor analysis. *J Assist Reprod Genet.* 1993;10(1):47-52.
39. Meldrum DR. Female reproductive aging—ovarian and uterine factors. *Fertil Steril.* 1993;59:1-5.
40. Tourgeman DE, Slater CC, Stanczyk FZ, Paulson RJ. Endocrine and clinical effects of micronized estradiol administered vaginally or orally. *Fertil Steril.* 2001;75:200-202.
41. Tourgeman DE, Boostanfar R, Chang L, Lu J, Stanczyk FZ, Paulson RJ. Is there evidence for preferential delivery of ovarian estradiol to the endometrium? *Fertil Steril.* 2001;75(6):1156-1158.
42. Edwards RG. Pregnancies are acceptable in postmenopausal women. *Hum Reprod.* 1993;8:1542-1544.
43. Flamigni C. Egg donation to women over 40 years of age. *Hum Reprod.* 1993;8:1343-1344.
44. Paulson RJ, Sauer MV. Pregnancies in post-menopausal women. Oocyte donation to women of advanced reproductive age: 'how old is too old?' *Hum Reprod.* 1994;9:571-572.
45. Paulson RJ, Sauer MV. Regulation of oocyte donation to women over the age of 50: a question of reproductive choice. *J Assist Reprod Genet.* 1994;11:177-182.

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