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

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.

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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 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 40.

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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 35\(^{28-30}\) 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 it 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 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.\(^{38-41}\) 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.\(^{32-45}\) 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. 

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