JAMA Insights | WOMEN'S HEALTH

Ovarian Aging and Fertility

David B. Seifer, MD; Eve C. Feinberg, MD; Albert L. Hsu, MD, MS

Women in their late 30s to early 40s who have difficulty conceiving are often unaware that success rates of fertility treatment decline with age, most commonly due to declining ovarian function. Counseling about the high prevalence of infertility and miscarriage may be met with surprise and sadness. Reports of children born to high-profile women older than 50 years may contribute to misconceptions, but these births highlighted in the media were likely achieved with donor oocytes from a younger woman or with oocytes or embryos that were previously cryopreserved. Consistent with declining fertility rates worldwide,[1] the fertility rate in the US has declined from 70.9 births per 1000 women in 1990 to 56.1 per 1000 in 2022.[2] Simultaneously, the 2019 US Census reported that age at first birth had risen from 27 years in 1990 to 30 years in 2019 as more women postponed first birth.

CME at jamacmelookup.com

Reasons for these trends may include lack of a partner, economic insecurity, career aspirations, and long work hours. Concerns about childbearing discrimination, including lack of pregnancy and postpartum support, and childcare challenges also likely influence decisions to delay pregnancy. Results of a questionnaire completed by 5692 US general surgery residents reported that more female than male residents delayed pregnancy because of training (46.8% vs 32.7%; $P < .001$) and experienced pregnancy/parenthood-based mistreatment (58.1% vs 30.5%; $P < .001$).[3]

Declining Oocyte Quantity

Human females have a fixed number of nongrowing follicles in the ovary, with up to 7 million at 20 weeks in utero, up to 2 million at birth, and several hundred thousand at menarche. On histology, the "bipotential gonads" start to develop into ovaries (or testicles) at 10 weeks of gestation and primordial follicles can be first visualized in the human embryo at about 16 weeks' gestation. This fixed oocyte pool is depleted through apoptosis and follicular atresia. Only 12% of prebirth ovarian nongrowing follicles remain by age 30 years and oocyte depletion accelerates in the late 20s and 30s, with a mean of 65 000 oocytes at 25 years, 16 000 by 35 years, and approximately 1000 by menopause (mean [SD] age, 49.6 [10] years).[4] Age-related decline in ovarian nongrowing follicles is irreversible and correlates with the natural decrease in female fertility with increasing age (**Figure**, A).[4] Currently, there is no effective method to grow new ovarian follicles, and few women older than 45 years achieve live birth with their own oocytes, despite optimal diet, exercise, or in vitro fertilization (IVF). Women who are unaware of the biology of ovarian aging may decide to postpone pregnancy, resulting in the unanticipated consequences of infertility and childlessness.

Advancing Age and Fertility, Live Births, and Miscarriages

According to the World Health Organization (WHO), the incidence of infertility in reproductive-aged couples is 1 in 6. Although there are many causes of infertility, including ovulatory disorders, male factors, and obstructed fallopian tubes, ovarian aging is an important and irreversible factor. In addition to lower fecundity, as women age, oocytes develop defects in mitochondrial structure and function and have meiotic spindle dysregulation that increase rates of aneuploidy and miscarriage. Rates of miscarriage are approximately 12% in women aged 20 to 29 years, 25% by 40 years, 40% by 43 years, and 65% in females 45 years and older.[5]

IVF for Infertility

IVF is an effective treatment for infertility; however, according to 2021 IVF data from the Society for Assisted Reproductive Technology, live birth rates peak at 40% per embryo transfer for women younger than 35 years and decrease to less than 5% by 43 years of age. The reduced success of IVF in older women is related to decreased levels of antimullerian hormone (AMH), which correlates with declining ovarian nongrowing follicles,[6] resulting in lower numbers of retrieved oocytes during fertility treatment[7] and reduced cumulative live birth rates.[8] Cumulative live birth rates ranged from 28.1% in women with AMH levels from 0.91 ng/mL to less than 1 ng/mL to 10.9% in women with AMH less than 0.10 ng/mL.[8] When considering both age and AMH, cumulative live birth rates ranged from 22% to 41% for women younger than 35 years to 1% to 4% for women older than 42 years.[8] Even among female physicians, the decreased success rates associated with IVF in older individuals are not widely appreciated. In a questionnaire study of 1056 female physicians published in 2023, 38.6% overestimated the likelihood of IVF success among women older than 43 years.[9]

Strategies to Address Infertility Due to Ovarian Aging

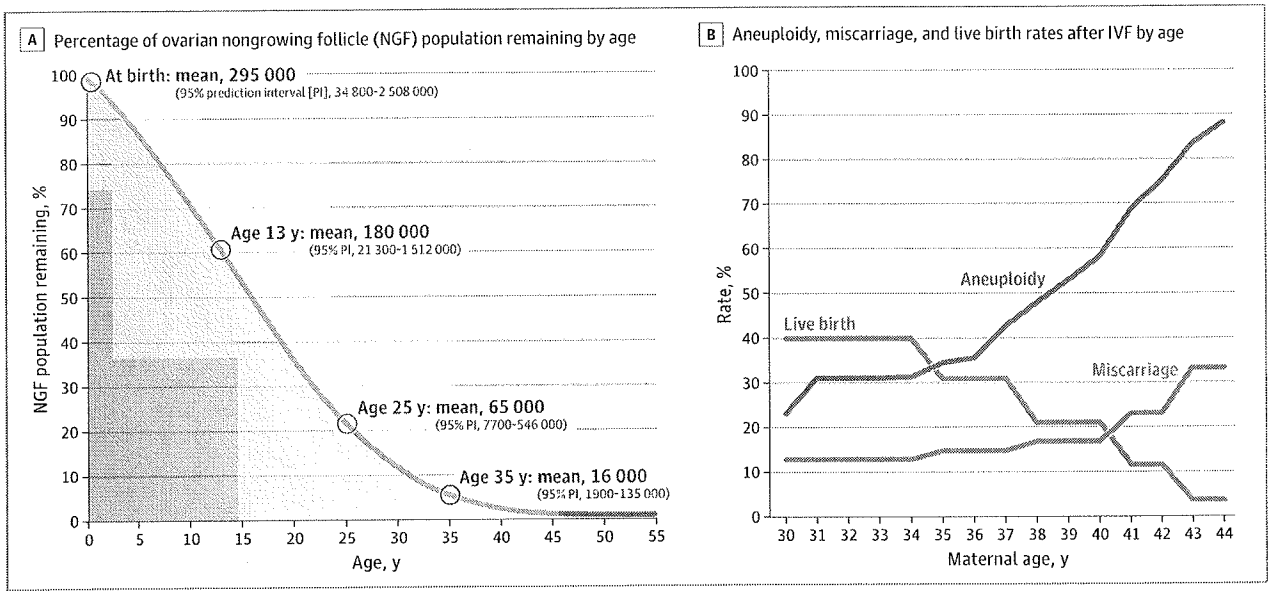
Education and Societal Support

All primary care clinicians should ask about interest in parenthood and, if appropriate, educate patients about ovarian aging and the reduced likelihood of pregnancy with advancing age. On a broader societal level, it is important to reduce the multifaceted barriers to family building in the US, including lack of universal health coverage, gender disparities in parenting and household responsibilities, insufficient maternity and family leave policies, limited availability of childcare options, and reported lack of occupational flexibility to accommodate pregnancy and parenthood.

Oocyte and Embryo Cryopreservation

Oocyte cryopreservation is an effective option that allows women to achieve pregnancy at older ages. The ovaries must first be stimulated for 8 to 14 days with injectable gonadotropins to recruit multiple mature follicles. Oocytes are then surgically retrieved by transvaginal needle-guided aspiration and rapidly cryopreserved. At a future date, the oocytes can be thawed and fertilized using IVF; the resulting embryos can either be transferred to the uterus or cryopreserved for future use. There is no known upper limit for the length of time that oocytes or embryos can remain cryopreserved. Oocyte cryopreservation is more successful at achieving pregnancy and more cost-effective for delayed childbearing compared with pursuing IVF at advanced reproductive ages without oocyte cryopreservation.[10]

Figure. Ovarian NGF Population and Rates of Aneuploidy, Miscarriage, and Live Births



Data used were from studies by (A) Wallace and Kelsey[4] and (B) Franasiak et al and the Society for Assisted Reproductive Technology. IVF indicates in vitro fertilization.

Specifically, for those desiring 1 child, planned oocyte cryopreservation at 33 years of age (with oocyte thawing at 43 years) decreased the mean total cost per patient from $62 308 to $30 333 and increased the likelihood of live birth from 50% to 73% compared with no oocyte cryopreservation with up to 3 cycles of IVF (with preimplantation genetic testing for aneuploidy) at 43 years of age.[10] Out-of-pocket costs for oocyte cryopreservation range from $8000 to $12 000 per cycle, with annual storage fees of $300 to $1000. More US employers are offering limited benefits for oocyte cryopreservation with either a maximum dollar amount or covered number of cycles. Women who cryopreserve oocytes or embryos do require IVF to achieve pregnancy; rates of pregnancy and live birth rates with cryopreserved oocytes or embryos decline with older patient age (Figure, B).

Conclusions

Ovarian aging is an important cause of infertility in women older than 35 years. Primary care clinicians (including obstetricians and gynecologists) should inform patients interested in pregnancy about the biology of ovarian aging so they can make informed choices about balancing family, education, and work to help reduce the incidence of unintended childlessness.

ARTICLE INFORMATION

Author Affiliations: Yale School of Medicine, New Haven, Connecticut (Seifer); Northwestern University Feinberg School of Medicine, Chicago, Illinois (Feinberg); University of Cincinnati, Cincinnati, Ohio (Hsu).

Corresponding Author: Albert L. Hsu, MD, MS, PO Box 9156, Cincinnati, OH 45209 (alhsu@alum.mit.edu).

Published Online: October 29, 2024. doi:10.1001/jama.2024.18207

Conflict of Interest Disclosures: Dr Seifer reported receiving patent royalties from an agreement between Rutgers/MGH and Beckman Coulter for AMH in determining ovarian reserve. Dr Feinberg reported receiving grants from American Society for Reproductive Medicine and consulting for Ferring Pharmaceuticals. No other disclosures were reported.

Submissions: The Women's Health editors welcome proposals for features in the section. Submit yours to linda.brubaker@jamanetwork.org.

REFERENCES

1. Fauser BCJM, Adamson GD, Boivin J, et al. Declining global fertility rates and the implications for family planning and family building. *Hum Reprod Update*. 2024;30(2):153-173.

2. Centers for Disease Control and Prevention. US fertility rate drops to another historic low. Accessed July 4, 2024. https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2024/20240525.htm

3. Li RD, Janczewski LM, Eng JS, et al. Pregnancy and parenthood among US surgical residents. *JAMA Surg*. 2024;159(10):1127-1137. doi:10.1001/jamasurg.2024.2399

4. Wallace WH, Kelsey TW. Human ovarian reserve from conception to the menopause. *PLoS One*. 2010;5(1):e8772. doi:10.1371/journal.pone.0008772

5. Quenby S, Gallos ID, Dhillon-Smith RK, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet*. 2021;397(10285):1658-1667.

6. Freeman EW, Sammel MD, Lin H, Boorman DW, Gracia CR. Contribution of the rate of change of antimüllerian hormone in estimating time to menopause for late reproductive-age women. *Fertil Steril*. 2012;98(5):1254-1259.

7. Seifer DB, MacLaughlin DT, Christian BP, et al. Early follicular serum müllerian-inhibiting substance levels are associated with ovarian response during assisted reproductive technology cycles. *Fertil Steril*. 2002;77(3):468-471.

8. Tal R, Seifer DB, Tal R, Grainger E, Wantman E, Tal O. AMH highly correlates with assisted reproduction cumulative live birth rate in women with diminished ovarian reserve independent of age. *J Clin Endocrinol Metab*. 2021;106:2754-2766.

9. Bakkensen JB, Smith KS, Cheung EO, et al. Childbearing, infertility, and career trajectories among women in medicine. *JAMA Netw Open*. 2023;6(7):e2326192.

10. Bakkensen JB, Flannagan KSJ, Mumford SL, et al. A SART data cost-effectiveness analysis of planned oocyte cryopreservation versus in vitro fertilization with preimplantation genetic testing for aneuploidy considering ideal family size. *Fertil Steril*. 2022;118(5):875-884.