Postponement of Parenthood—The Good, the Bad, and the Ugly

As more women are choosing to enter the workforce—and often assuming leadership roles—their age at first childbirth has risen dramatically. In the U.S., that age is on average now 24.8 years, up from 22.1 in 1970.[1] Trends in Europe and Asia are similar, although the average age is older, for example 29 in Spain and 28 in Japan. Meanwhile, public awareness of fertility issues in women previously thought to be of "reproductive age" has increased.

Fertility naturally declines with age. The percentage of women not using contraception and desiring pregnancy, but remaining childless, rises steadily with age.[2] Six percent of women at age 20–24 cannot conceive, compared with 15% at age 30–34, 30% at age 35–39, and 64% at age 40–44.

These statistics reflect the natural loss of oocytes with age. When puberty begins, women have about 500,000 oocytes. Around 1,000 are recruited each month, about 20 are visible by ultrasound at the beginning of each menstrual cycle, and only one makes it to ovulation. Also, as women age, the quality of the oocytes diminishes because of the following factors:

- Damage to the oocytes during the woman's fetal life
- Aging of the supporting somatic granulosa cells, which with the oocyte forms the follicle
- Direct damage to the adult woman's oocytes (from smoking, toxins, chemotherapy, or radiation)

Rates of monthly fecundity—the ability to conceive and have an embryo successfully implant—show this natural aging. In the clinical study summarized in Figure 1, fecundity rates in women aged 30 or younger average around 25% but drop off after age 31, the result of both falling numbers and diminished quality oocytes.[3] The women in this study were considered fertile and came to infertility clinics for donor insemination. The drop in fecundity with age is not related to uterine factors, because studies with donor eggs reveal that the endometrium of women aged 50 or older responds to hormonal therapy and can support implantation and pregnancy. The rate-limiting step is the ovarian reserve—the number and quality of oocytes.

Moreover, assisted reproductive technologies, such as in vitro fertilization (IVF) or injectable gonadotropins combined with insemination (IUI), cannot correct this drop in fecundity; these patients experience the same age-related drops. By age 35, success rates are down to 30% for IVF and 15% for IUI, and by 40 they are less than 10% for both technologies.[4] Although exceptions occur—we have all heard of a 42-year-old woman getting pregnant without trying—these women are usually not first-time parents, nor are they seeking help from infertility clinics.

Predicting the age of decreased fertility in twentysomethings would help with family planning. Unfortunately, such accurate tests do not exist. Today's tests all relate to the ovarian reserve or the number of follicle cohorts recruited in each cycle. But most results do not become "abnormal" until evidence of subfertility emerges. The most commonly used markers

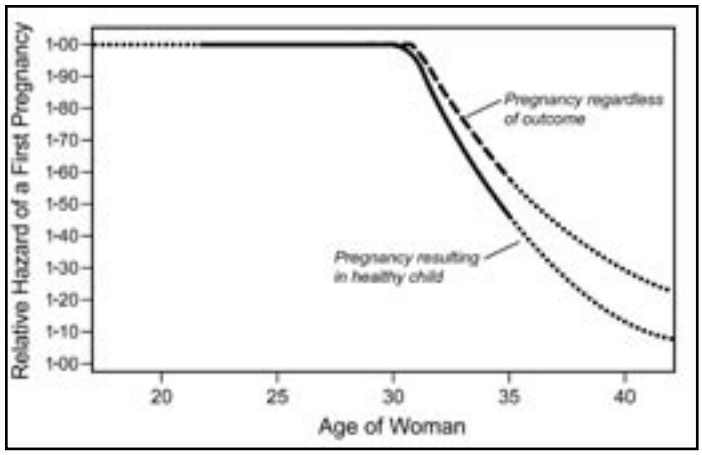

Figure 1. Rate for pregnancy by age with regard to outcome. Dashed lines: relatively fewer women in cohort, and hence a different mode of data analysis employed, but statistically significant.[3]

Women in Cell Biology

Dinner Meet-Up

At the ASCB Annual Meeting by yourself? Tired of eating alone or grabbing a sandwich at Starbucks? Drop by the Meet-Up poster in the Grand Foyer (lobby) of the Washington Convention Center at 6:00 pm each evening to find potential dining companions. A list of interesting restaurants will be posted; you figure out with whom and where to go. *(Sponsored by the Women in Cell Biology Committee)* ■

at IVF centers for predicting successful pregnancies are baseline levels of follicle-stimulating hormone (FSH) in the blood. (These are measured on day three of the menstrual cycle along with estradiol levels.) Because FSH levels rise quickly early in the cycle, elevated levels indicate that the pituitary is working overtime to induce follicle formation. Unfortunately, by the time this level rises to about 12 mIU/mL, most women will not respond to therapy treatments, and the chances of successful pregnancies with artificial reproductive technologies are low. The FSH assay cannot predict subfertility; it can only confirm it.

Measuring total antral follicle counts by ultrasound examination on day one or two of the menstrual cycle is routine today. Although scores of 11–14 are considered fertile, the test is inconsistent and subjective. Total ovarian volume is another ultrasonographic marker, with 14 mL representing normal fertility. Again, measurements can vary and this technique has also been criticized. Some studies suggest that anti-Müllerian hormone (normal level is 8 ng/mL) and inhibin B (should be ~84 pg/mL) are the best serum markers because both are produced and released by antral follicles directly, unlike FSH. However, most insurance plans do not cover the antral follicle count test, and clinical labs do not commonly measure either serum marker. Also, no large-scale clinical studies validating these tests for predicting subfertility have been undertaken.

In one study, patients with premature ovarian failure had microdeletions in genes for oogenesis and folliculogenesis.[5] This work and others have identified patterns of structural variation and complex deletions, primarily on the X chromosome.[6] These findings are consistent with the premature ovarian failure or insufficiency that patients with Turner syndrome (X-chromosome monosomy) experience. Genetic screening tests to gauge predisposition to early ovarian depletion of oocytes may become available.

So far, we have no blood tests that can predict reduced reproductive life span when intervention might still be an option. Research efforts are investigating genetic testing options, but infertility and shortening of the reproductive life span are probably complex traits. Current clinical strategies to predict reproductive life span include combinations of ovarian imaging and hormonal markers.

Oocyte and ovarian cryopreservation have gained attention recently as options to preserve fertility, but both techniques are flawed and risky. Although removing ovarian tissue and freezing it at the time of staging surgery for cancer has been used extensively, the method has produced only two live births worldwide. Optimizing the freezing and, more critically, the thawing of the ovarian cortex is an area of active investigation in humans and animals. Freezing fertilized embryos is common practice in most of the world's IVF centers, and related pregnancy rates are comparable to those involving fresh embryo transfers. Oocyte cryopreservation, however, has not been nearly as successful. Immature oocytes retrieved without conventional IVF protocols, such as ovulation induction and in vivo maturation, do not survive thawing, most likely because of problems with the critical processes of spindle formation and resuming meiosis. Mature oocytes obtained by inducing ovulation and through in vivo maturation have improved freeze–thaw morphology and maturation, but intracytoplasmic sperm injection, a micromanipulation technique, is required to achieve fertilization. Pregnancy rates for this procedure range from 10% to 17%—less than half the normal IVF rates. Also, the high concentrations of cryoprotectants used (e.g., 1,2-propanediol, dimethyl sulfoxide, and ethylene glycol)—and their short- and long-term effects on the oocyte—have raised concerns.

We need genetic markers correlated with abnormalities in folliculogenesis and oocyte quality, coupled with longitudinal data, to predict time from detecting elevated biomarkers to

menopause. Ideally, research either will identify genetic markers to predict premature depletion of the egg supply or will establish serum markers to diagnose dwindling follicle numbers or oocyte quality earlier in the ovarian life cycle. In time, tests could accurately predict individual spans of reproductive competence. However, to repeat, such tests are currently not available. ■

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Coming next month: Ursula Goodenough comments on the obvious disconnect between these findings and present-day science career timetables.

Share Your Family Photos

You can have a family *and* a career in cell biology. That's the message of the Women in Cell Biology Photo Montage, available at http://ascb.org/wicb/index.html.

ASCB members interested in participating should share a family photograph for possible inclusion by sending a jpeg or tif file to wicb@ascb.org. ■

Photos, top: WICB Chair Ursula Goodenough and family; middle: Kyunghee Choi and daughter; and Jodi Nunnari and family