

AGE & FERTILITY: Effective Evaluation & Treatment

© I. LANE WONG, MD, FACOG. www.HopeFertilityCenter.com www.HopeIVF.com

Age has a profound effect on female fertility. This is common knowledge, but often misunderstood. My goal in this brief article is to provide practical information on this vast and complicated topic. One in five women in the USA are having their first child at age 35 years or older. At this age, about one third of women will have troubles conceiving. For women over 40 years of age, at least one half will have difficulty conceiving.

Why is this? The simple answer is egg quantity and quality decrease with age. Also other conditions that can affect fertility such as endometriosis, pelvic scarring, and fibroids can be more common as one ages.

It is estimated that both ovaries contain a total of about 2,000,000 follicles at birth. A follicle is a spherical collection of cells in the ovaries, each containing an egg. Women are born with a finite number of follicles and eggs. Unfortunately, the follicles are continually degenerating. At the onset of the first ovulation, at about age 13 years, it is estimated that only 400,000 follicles (eggs) remain. Furthermore, the "best" eggs are ovulated first, leading to a measurable decline in fertility in one's 30's and a profound decline in one's 40's. Physiologically, menopause ensues when no functioning follicles remain, thus ovulation ceases, as does menstruation.

Older eggs have more trouble properly separating their chromosomes (genetic material) when they are fertilized. This leads to a higher incidence of chromosomal abnormalities (for example, trisomy 21, Down's Syndrome) and infertility and miscarriages. In contrast, men constantly produce new sperm. Thus, although there is a gradual decline in fertility in men, there isn't an absolute age at which men cannot father a child.

What are ways in which Ovarian Follicular Reserve (Quantity) can be assessed?

- Day 3 FSH and Estradiol level: Near the beginning of the menstrual cycle (Day ~3), the hormones Follicle Stimulating Hormone (FSH) and Estradiol can be measured. An elevated FSH level is a sign of diminished follicular reserve (aging). As long as one is ovulating, there isn't an absolute level in which fertility is impossible. However, the combination of a high FSH and waning of ovulation can indicate pre-menopause, an interval of varying length that precedes menopause. Besides an elevated FSH level, a decreased serum Inhibin B, and a decrease in anti-Mullerian Hormone also indicates diminished follicular reserve. A variation of the Day 3 FSH test, that is even more sensitive at detecting abnormalities, is the Clomiphene Challenge Test (FSH levels are measured before [Day 3] and after [Day 10] the ovaries are stimulated with the oral medication Clomiphene). With the Clomiphene Challenge Test, an elevated Day 10 FSH is a sign of diminished follicular reserve. FSH levels provide useful but not absolute information. A normal FSH level at age 42 does not mean age is not affecting fertility. However, it does mean a much higher chance of conception naturally or with treatment compared to a 42 year old with an elevated FSH level.
- Ultrasound assessment of Antral Follicles: Ultrasound can be used to measure ovarian volume and count the number of small follicles. Usually, the higher the count the better. (Others and we have studied a subset of ovaries with high count and 'polycystic appearance.' This has subtly different implications [1].)
- Response to Ovarian Stimulation: The ability of the ovaries to develop multiple mature follicles when stimulated with medications reflects ovarian follicular reserve.

What are ways in which Egg Quality can be assessed?

- In as much, quantity (follicular reserve), is usually correlated with quality, the tests listed above can be used to indirectly suggest egg quality.
- In Vitro Fertilization (IVF): Ovaries are stimulated by FSH injections to mature multiple follicles. The eggs are extracted with a needle from each mature follicle.

The eggs are taken to the lab where quality is assessed, largely in visual terms. The eggs are fertilized in the lab ('in vitro fertilization') either by co-incubating with sperm, or by injection of a single sperm into each mature egg (ICSI – intracytoplasmic sperm injection). The resultant fertilized egg starts cleaving or dividing and is now known as an embryo (technically, a pre-embryo). The health and quality of the egg largely determines the quality of the resultant embryos. (There are however, well-documented cases in which the sperm profoundly determines embryo quality [2].) Three days after an egg has been fertilized, the best resultant 'day 3 embryos' have formed a ball of about 8 equal sized cells (blastomeres). Two days after this, the best 'day 5 embryos' are about 100 cells and have formed a ball of cells with a fluid filled cavity (blastocyst). Only the best fertilized eggs are able to become blastocysts. For most women, being able to transfer 2 high grade blastocysts into the uterus will result in a pregnancy rate of over 50%. Thus IVF allows a direct assessment of egg and embryo quality.

- Preimplantation Genetic Screening (PGS, also sometimes referred to as PGD):
Three days after an egg has been fertilized, most viable embryos are about 6-10 cells each. At this time, one of the cells (blastomere) can be removed and screened for some, but not all, chromosomal abnormalities. Typically the blastomere is screened for missing or extra chromosomes such as 13, 18, 21, X and Y. Not surprising, as one ages, chromosomal abnormalities are found at a higher rate. The results of this analysis, called Preimplantation Genetic Screening, are useful but not absolute. There are embryos that are mosaic (comprised of genetically dissimilar blastomeres) and thus a given blastomere may test normal, while the rest of the blastomeres and resultant baby may have a chromosomal abnormality. PGS does not screen for abnormalities in all 23-chromosome pairs. There also technical limitations to PGS, for example, the test may indicate a chromosome is missing when it is actually present. PGS can be taxing on an embryo, the embryo must undergo a removal of one of its cells at the 8-cell stage and then grow for 2 more days in the lab (becoming a blastocyst) while awaiting

the results of PGS. Bottom line is chromosomal abnormalities increase with advancing female reproductive age. PGS can screen for chromosomal abnormalities and can be a useful tool for some couples. PGS does have limitations however, and is best suited for couples who produce many eggs / embryos. PGS has not yet been proven to increase 'take home baby rates' for older women [6]. [For more details on PGS, see the PDF Article "Preimplantation Genetic Screening: Is it right for you?"](#)

What are useful treatments for age related fertility decline?

- Prevention: We need to continue to spread the message of the possible problems with delayed childbearing.
- Efficient and Effective Treatment: The longer something has not happened; the less likely it will happen, unless changes are made. A young couple just trying to conceive has about a 25% chance of pregnancy per month in the beginning. After 2 years of trying, the chance of pregnancy is down to about 3% per month. ([For more details, see the PDF Article "Explaining 'Unexplained Infertility' and Its Treatment."](#))

Especially if one is in their 30's, or has obvious issues such as irregular periods (problems with ovulation), risk factors for pelvic scarring, or sperm problems, prompt professional attention is needed. The goal is to conceive in the safest and fastest means possible, time cannot be reclaimed. Depending on the specifics, common treatments include ovulation induction or superovulation, intrauterine insemination, surgery on the pelvis, and IVF with or without intracytoplasmic sperm injection (ICSI).

- The ultimate treatment for female age related fertility decline is use of eggs donated by a younger woman. We, and many others, have found if the recipient

(woman receiving the egg/embryo) is healthy, the chance of conception is usually simply determined by the age of the egg donor [3]. Since the egg donor is usually in her 20's, donor egg cycles typically have about a 70% chance of conception with the transfer of two high-grade blastocysts.

- Current Areas of Research:

- ◆ Cytoplasmic Transfer: Transferring the inner non-genetic material (cytoplasm) of eggs from a younger woman into that of eggs from an older women is an intriguing idea with bioethical controversy and undetermined efficacy [4].

- ◆ Preimplantation Genetic Screening: See above.

- ◆ Egg Freezing: Potentially, women who foresee delayed childbearing could freeze their eggs when they are younger for later use. Recently, much progress has been made worldwide with the efficiency in which a frozen egg can be thawed, fertilized and develop into an embryo and a successful pregnancy. Still the usefulness of this potentially revolutionary treatment is still being determined. Egg freezing is still in its infancy, whereas hundreds of thousands of babies have been born from frozen thawed embryos, less than 500 babies have been born from a frozen thawed egg, even though the first such birth was in 1986. The process, though improving, still remains relatively inefficient.

The main American professional fertility organization recently issued the following statement regarding egg freezing:

Oocyte cryopreservation is an experimental procedure that should not be offered or marketed as a means to defer reproductive aging, primarily because data relating to clinical outcomes are limited. Nonetheless, many women understandably have interest in this emerging technology and view oocyte cryopreservation as an elective fertility preservation strategy that may help them to realize their longer-term reproductive goals [7].

In summary, the effects of female age on fertility are potentially very profound. Although there are women with remarkable fertility up to and beyond the age of 40 [5], it is fortunate in a fertility clinic when a woman using her own eggs

delivers a healthy child after the age 45. The best treatment for age is information and then informed, appropriate, aggressive action.

[1] Wong IL, Morris RS, Lobo RA, Paulson RJ, Sauer MV. Isolated polycystic morphology in ovum donors predicts response to ovarian stimulation. *Hum Reprod.* 1995 Mar;10(3):524-8.

[2] Tesarik J, Mendoza C, Greco E. Paternal effects acting during the first cell cycle of human preimplantation development after ICSI. *Hum Reprod.* 2002 Jan;17(1):184-9.

[3] Legro RS, Wong IL, Paulson RJ, Lobo RA, Sauer MV. Recipient's age does not adversely affect pregnancy outcome after oocyte donation. *Am J Obstet Gynecol.* 1995 Jan;172(1 Pt 1):96-100.

[4] Opsahl MS, Thorsell LP, Geltinger ME, Iwazsko MA, Blauer KL, Sherins RJ. Donor oocyte cytoplasmic transfer did not enhance implantation of embryos of women with poor ovarian reserve. *J Assist Reprod Genet.* 2002 Mar;19(3):113-7.

[5] Wong IL, Legro RS, Lindheim SR, Paulson RJ, Sauer MV. Efficacy of oocytes donated by older women in an oocyte donation programme. *Hum Reprod.* 1996 Apr;11(4):820-3.

[6] Practice Committee of the Society for Assisted Reproductive Technology and the Practice Committee of the American Society for Reproductive Medicine. Preimplantation genetic testing: a Practice Committee opinion. *Fertil Steril* 2007 Dec;88(6):1497-1504.

[7] Practice Committee of the Society for Assisted Reproductive Technology and the Practice Committee of the American Society for Reproductive Medicine. Essential elements of informed consent for elective oocyte cryopreservation: a Practice Committee opinion. *Fertil Steril* 2007 Dec;88(6):1495-96.