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Ten to 15 % of all [reproductive age couples suffer from infertility](#). As a board certified reproductive endocrinologist I spend most of my time treating both men and women, who contribute equally to this insidious disease that afflicts millions. Infertility is defined as one year of unprotected sexual relations without conception. The probability of achieving a pregnancy within one menstrual cycle, ideally each month, is on the average only 25% for normal, young, and healthy couples; thus, these couples have approximately an 85% chance of conceiving within one year and 93% in two years. Unfortunately, this probability decreases dramatically by one third to one half as women approach their mid 30's and early 40's.

Every time we watch a TV news magazine or open a print magazine we are entertained and enlightened by exposure to the latest advances in reproductive medicine, famous people revealing their difficulties, pursuits, failures and successes in having a baby, and the exceedingly rare, and thus always news-worthy occurrence of, high order multiple gestations, the "X-tuplets". Due to our present day frequent exposure and since years ago we rarely spoke or heard about people who were suffering in silence from this devastating disease, we tend to think that the rate of infertility is increasing exponentially. This is not necessarily true.

There have been a number of significant developments that have changed the practice of reproductive medicine and the public's awareness over the past quarter century. One of the most significant events was the introduction of the assisted reproductive technologies based on in vitro fertilization where eggs are removed from a woman, fertilized with sperm from a man in glassware, in vitro, and then the resultant fertilized egg (embryo) is transferred to a hormonally prepared uterus. The process is sometimes called making "test tube babies". With the birth of Louise Brown on July 25, 1978 and with assistance from the mass media, the medical community and the entire world became aware of novel and promising treatments for those suffering from the once considered shameful disease of infertility.

This publicity generated new hope for many where there was once only despair and emptiness. It also resulted in a domino effect increasing the number of researchers investigating novel diagnostic and treatment regimens, making reproductive services more widely available, successful, and affordable, and making infertility a more socially acceptable disease. This culminated in generating an immense increase in patient consults seeking fertility related care.

Another significant change that the fertility specialists have witnessed over the last 10 years was the dramatic increase in the number of women over age 35 requesting medical intervention for infertility. Approximately 20% of women in United States are having a first child after age 35. This is most likely due to a combination of older age at the time of first marriage and more significantly due to the delay of childbearing in marriage. Other attributable causes resulting in older women seeking fertility care and shortening the time interval in which they desire to reproduce genetically related children are a reflection of the current socio-economic times and morays.

Two income households are more the rule than the exception, even with dual incomes there is still financial instability and uncertainty, liberalization of abortion, effects of sexually transmitted diseases, increased worry and panic about being infertile, and increased use of various contraception options. It has become clear that what modern society is experiencing and fertility specialists are seeing is a dramatic increase in age related infertility in the baby boomer generation since they were the first group of women who could easily exercise control over their fertility.

Countless clinical trials have revealed that a woman's fertility declines significantly with increasing [age](#), yet aging only minimally effects male fertility. Another gender difference is that a man

continuously produces sperm throughout his adult life, in contrast to a woman who is born with her unique life time supply of eggs. This number continually decreases until she stops ovulating at menopause. In addition, research supports that this decline in female fertility is more likely related to the aging egg and less likely due to an aging uterus. The healthiest, most fertile eggs are ovulated when a woman is in her teens through her late 20's, a woman's time of peak fertility. When a woman reaches her mid to late 30's, the remaining eggs have substantially less potential for fertilizing and establishing a healthy pregnancy. This is mostly due to chromosomal injuries that normally occur as eggs age within the ovaries.

Advanced [egg age](#) probably accounts for the increased risk of both miscarriage and infertility in women over the age of 35 and especially by the age of 40. Because this is primarily a problem related to the chromosomes and cellular machinery of the eggs, there is little that can be done to correct or reverse this biological trend. This knowledge and clinical trials lead to the very successful treatment that employs egg donors where the entire egg cells are obtained from women usually in their 20's and fertilized with the infertile woman's husband's sperm. Nuclear transfer, where the nucleus of an infertile woman's adult cell is replaced for the nucleus in a younger woman's donor egg cell, and cytoplasmic transfer, where the cytoplasm of a fertile woman's egg is injected into the infertile woman's egg cell, have both been experimented with and pending FDA approval. The goal of both techniques is to maintain the older woman's genetics housed in the nucleus, but utilize the healthy cell replicating machinery located in the cytoplasm of the younger donor egg cell. Unfortunately, some genetic material is also found in the cytoplasm, so new questions have been raised and must be answered before these techniques become standard of care.

In women less than [35 years of age](#), the vast majority of eggs ovulated have a normal chromosomal composition. As the woman progresses beyond 35 years of age, an increasing number of her eggs are likely to be genetically abnormal, aneuploid. This is a natural process of aging. Egg quantity and quality declines at an exponential rate. Chromosomally abnormal eggs may fertilize, but will infrequently establish a healthy pregnancy. When defective genetic embryos inadvertently implant into the uterine lining, the resultant pregnancies often result in spontaneous first trimester miscarriages. This has been evidenced by an overall miscarriage rate as high as 75% in women 40 years and older. If this were not the case, there would be many more genetically defective babies born. This is also the reason why women who use their own eggs and who are 35 years or older are encouraged to undergo amniocentesis or chorionic villus sampling (CVS) to evaluate the fetus for chromosomal abnormalities. Consequently, in women of advancing age, not only is the pregnancy rate markedly lower and the miscarriage rate significantly higher, but the overall risk of chromosomal anomalies in the few babies born is also dramatically increased. After considering the above realities, you can see why there is a dismally low probability of delivering a healthy child, the ultimate goal, when using eggs from older women in natural or assisted reproduction cycles. To improve the odds, some reproductive endocrinologist advocate older patients undergoing IVF with preimplantation genetic diagnosis, PGD, where some genetic abnormalities may be identified prior to embryo transfer and thus only the "normal" embryos may be selected for transfer. Unfortunately, sampling one cell from a multi-celled embryo may not always reflect the genetics found in all the other cells and this technique does not correct for non-genetic age related defects in the egg such as defects in the meiotic spindle fibers that result in chromosomal misalignment or problems with microtubular matrix composition.

The problems of advancing age on eggs and subsequently on embryo quality occur independently of a woman's proximity to the menopause. The eggs of a younger woman who is destined to undergo premature ovarian failure, let's say in her late 20's, are just as capable of producing a healthy baby as the eggs of a woman of the same age who will enter the menopause in her late 50's. The converse is also true, that a woman in her 40's who has entered the perimenopause, a time period of 5-10 years prior to menopause and marks the advent of the accelerated decline in ovarian function, will have a relatively high percentage of chromosomally

defective eggs. Thus, growing older has a unique, irreversible, and devastatingly negative effect on female fertility.

I always remind younger patients suffering from infertility that there is no abrupt change in fertility for any given woman at age 40, and therefore, this decline in fertility may occur in younger women, although much less often, even those in their late teens. This rate of decline is on a continuum, from early and subtle changes of hormone markers (FSH or inhibin B) to noticeable impaired fertility to menopause, complete depletion of eggs.

Other factors that contribute to age related female infertility are the total number of eggs that a woman is born with and her rate of loss of these eggs. Both are genetically and uniquely predetermined. The rate of egg loss can not be slowed or stopped; but, smoking, medications, and surgery can accelerate it. In another words, the number of eggs available for possible ovulation or medical intervention per menstrual cycle is directly proportional to the unique number a woman is born with, her age, and her proximity to menopause. Although uterine pathology also increases with age, it has little impact in comparison to the effect of aging eggs.

Over the last 15 years reproductive endocrinologists have gained experience using various dynamic tests in order to predict a woman's potential for pregnancy in both natural and assisted reproduction. Qualitative "gestimations" of fertility potential at a specific time in a woman's life can be estimated through the performance of the clomiphene citrate challenge test. This test of "ovarian reserve" and possibly egg quality consists of simple blood tests measuring a woman's blood levels of follicle stimulating hormone (FSH) produced in the pituitary and estrogen, produced in the ovaries from the developing eggs before and after taking oral fertility medication, clomiphene citrate. The clomiphene citrate challenge test (CCCT) is performed by measuring day 3 FSH and estradiol, administering clomiphene citrate 100mgs daily from cycle days 5-9, and then measuring FSH on cycle day 10. The test is considered abnormal if either FSH value is above the laboratory's upper limit for the follicular phase or the cycle day 3 estradiol is greater than 80 pg/ml.

The literature strongly suggests that women who have an abnormal clomiphene citrate challenge test, regardless of their chronological age, experience decreased response to higher doses of gonadotropins, have higher cycle cancellation rates, and suffer from poor reproductive performance when using their own eggs, i.e., have a poor probability of conception and delivery of a live born baby with or without fertility treatments, around 5% per cycle. Thus, this provocative test predicts the lack of success. A single elevated cycle day 3 FSH value predicts a poor prognosis, even when normal values are obtained during future cycle. However, if the test is normal, it does not guarantee a woman's certainty of conceiving or delivering a healthy baby, especially in older women. The likelihood of an abnormal result increases with increasing age. Patients are always cautioned that no one test in medicine is 100% predictive of any outcome, positive or negative. The rule of thumb is that age is a better predictor of egg quality, and FSH level is a better predictor of egg number. I also stress to patients there is little if any literature related to an abnormal clomiphene challenge test and the age of onset of the menopause. Women still worry. The CCCT is recommended for all unexplained infertile couples, women > 34 years of age, and women < 35 with one ovary, history of ovarian surgery, and exposure to chemotherapy or radiation therapy.

Other tests of ovarian reserve under investigation that are not the standard of care due to conflicting data regarding prognostic value include inhibin B levels, gonadotropin-releasing hormone agonist test, and small antral follicle count by transvaginal ultrasound.

The most realistic options for women with an abnormal result, especially women greater than 34 years of age, are in vitro fertilization and embryo transfer using donor egg, IVF with their own eggs possibly with assisted hatching and PGD, controlled ovulation with gonadotropins and IUI, (in decreasing order of success), adoption, or to not expand their family. Of course most couples

are dismayed with these choices at first. Eventually some couples take comfort in the fact that their prior diagnosis of "unexplained infertility" has been given a more definitive and impressive name, that of diminished ovarian reserve, with an evolutionary and biological explanation. Others are angered and frustrated by yet another effect of time, the limitations of reproductive science, and the misinformation preached to them by the preceding generation.

The baby boomer generation took their lead from their parents, older friends and colleagues, and worldly teachers who advised them to be responsible and learn from their years of wisdom. This meant completing at least a college education, obtaining a financially rewarding career, finding a soul-mate to make and share a life, and once thought to be emotionally and financially secure, to embark on having children, their own genetic offspring, in order to continue the life cycle of another generation. Unfortunately, these well meaning mentors, trying to better our lives from their hard-learned lessons never carefully thought about evolution in regards to reproduction and tested the female biological clock. Now it is our responsibility to bestow on to the next generation conceived in the laboratory with love our newfound enlightenment.