



FERTILITY FACT SHEET

San Ramon / Orinda / San Jose

Fertility after Forty

More than 15 percent of couples in this country have difficulty conceiving a child. The recent tendency to delay childbearing in order to pursue a career has meant that more women in their late 30s and early 40s are attempting conception for the first time. Studies have demonstrated that almost 50% of women over the age of 40 will experience infertility. Because fertility in women decreases with advancing age, prompt evaluation and aggressive treatment are critical in infertile women over the age of 40. This article discusses the following topics:

- *Fertility and Age*
- *Patient Evaluation*
- *Ovarian Reserve*
- *Treatment*
- *Egg Donation*
- *Recommendations*
- *Summary*

Fertility and Age

Numerous demographic studies suggest a consistent decline in fecundity (the chance to conceive in any given month) with increasing age. The average 25 year old woman who is trying to conceive may have a 25% per month chance for pregnancy, if all fertility factors are optimal. Compare this with the 5% per month chance for conception that the average 40 year old woman has. This age associated decline in fertility (and increase in miscarriages) is largely due to abnormalities in the egg itself. The meiotic spindle (that helps the chromosomes segregate for cell division) exhibits abnormalities in chromosome alignment. High rates of abnormal chromosome distribution are a major factor that can explain a lower rate of successful pregnancies in older women.

When reviewing treatments for infertility, one must consider success ultimately, in terms of a baby being born. In addition to decreasing fecundity, older women experience an increasing incidence of miscarriage. Women over age 40 have approximately a one in three chance of having a miscarriage in any given pregnancy. In addition at age 40 one in sixty live births are genetically abnormal.

With this in mind, it seems reasonable to promptly evaluate women over 40 who are concerned about fertility. Before starting an evaluation, however, it is important to discuss with them some of the special considerations for the older woman trying to conceive. These would include general health issues, since women over 40 are more likely to have medical problems—e.g., diabetes, hypertension, heart disease—that can complicate a pregnancy. Therefore, an older woman contemplating a pregnancy should have a thorough medical evaluation, including a mammogram. Due to the increased incidence of genetic abnormalities, women over age 40 should be counseled about prenatal genetic testing such as chorionic villus sampling, nuchal translucency screening, amniocentesis or Triple marker testing.

Patient Evaluation

The usual trial period of one year of attempting conception prior to an infertility evaluation may not be appropriate for women who are forty years old. A basic infertility evaluation is indicated for any couple who have been attempting conception for six months if the woman is approaching the age of 40.

First, an infertility history should include how long the couple has been trying to conceive and the frequency of intercourse, as well as questions regarding menstrual regularity, premenstrual symptoms, and any prior pregnancies. Factors suggesting problems with the patient's fallopian tubes, such as a history of sexually transmitted diseases, IUD use, or pelvic infection, should be noted, as well as any previous cervical procedures such as cryotherapy or conization. In addition, the patient should be asked about early menopausal symptoms, and in utero exposure to diethylstilbestrol (DES).

Laboratory and other tests should include:

- *A semen analysis for the patient's partner.*
- *Evaluation of ovulation, e.g., BBT charts, a mid-luteal serum progesterone level, a urine LH test using an ovulation predictor kit, or ultrasound monitoring of follicular development.*
- *An evaluation of the patient's fallopian tubes with a hysterosalpingogram.*
- *Evaluation of Ovarian Reserve (see below)*

The basic evaluation should be performed over a period of one month in women approaching 40 years of age, rather than spreading it over a number of cycles. Any abnormalities that are uncovered in the basic evaluation should be corrected promptly.

Ovarian Reserve

A woman's chronologic age and her ovarian reserve are independent predictors of fertility. Ovarian reserve describes a woman's reproductive potential with respect to egg quantity. Perhaps the best method we have readily available to measure ovarian reserve is a cycle day 2 or 3 blood FSH (Follicle Stimulating Hormone) level. This measurement may be very important in evaluating how aggressively to treat women approaching the age of 40 and also to give that woman a realistic idea of her chance for a successful pregnancy. An Antral Follicle count is also helpful.

Risk factors for early loss of ovarian reserve include smoking, family history of early menopause, shortening menstrual cycle interval and previous ovarian surgery.

Treatment

If the evaluation is normal, or if abnormalities have been corrected and the patient still does not conceive in a short period of time, aggressive therapy is indicated. It may be difficult to convince a couple that has been trying to conceive for only six months that a very aggressive approach such as IVF may be necessary. Similarly, use of controlled ovarian hyperstimulation with Clomiphene or gonadotropins (fertility injections) combined with intrauterine insemination (IUI) may be unacceptable to some couples. Knowledge of the patient's blood FSH level may help to convince the couple that an aggressive approach is needed.

Treatment options for age-related infertility include controlled ovarian hyperstimulation with intrauterine insemination (COH-IUI), IVF, and egg donation. COH-IUI and IVF increase the chance to conceive in any given cycle. They cannot improve egg/embryo quality. COH-IUI involves taking fertility medication to increase the number of mature eggs released in a given cycle and the placement of washed sperm into the uterine cavity at the time of ovulation. This treatment has limited success in women forty and older, with delivery rates of less than 5% per cycle. We do not advise the use of Clomiphene in women over 40 years of age due to its limited effectiveness.

For couples with tubal disease, endometriosis, or sperm abnormalities, as well as couples with unexplained infertility who want to accelerate their chance for pregnancy, IVF is an appropriate option. Pregnancy rates with IVF are higher than from COH-IUI, but do decline significantly with increasing age. Live birth rates per cycle of IVF were 19.7 % in 38-40 year old women, 10.6% in 41-42 year old women and 3.5% in women over 43 years of age. (2005 US National Fertility Clinic Report). We have recently had better success rates with IVF in women over age 40 in our center.

Treatment strategies with IVF for older women include more aggressive stimulation protocols, assisted hatching of embryos, and replacing more embryos at the time of embryo transfer. Preimplantation genetic diagnosis (PGD) may help to decrease the rate of miscarriages in this group of older patients by excluding the transfer of genetically abnormal embryos, but this treatment is still being evaluated as to how much of an impact it will actually have. Blastocyst embryo transfer (allowing embryos to develop longer outside the body before replacement) has also proven more successful in our center in older women who have more than 4 good quality day 3 embryos.

Egg Donation

Egg donation has become an accepted and successful technique to achieve pregnancy in older women. Studies show that a pregnancy rate of over 50% per cycle can be expected in recipients who are aged 40 and older. This treatment is the only treatment available to improve egg/embryo quality in older women. Egg donation involves preparing the recipient's uterus with estrogen and progesterone to create an optimal uterus for implantation. An egg donor undergoes hormonal stimulation to produce multiple eggs. The eggs are retrieved with a minor surgical procedure and fertilized with sperm from the recipient's husband. Fertilized embryos are then replaced into the recipient's uterus.

Egg donation offers couples a number of advantages over adoption. First, the sperm is obtained from the patient's husband, and therefore the child is genetically his. Second, since the pregnancy develops inside the patient herself, she has control over such factors as nutrition, smoking, and drinking during the pregnancy—control she would not have in the case of adoption. Finally, the woman experiences the positive feelings of pregnancy and delivery and is able to breast-feed—all important experiences in establishing positive feelings toward the infant. For the present, then, egg donation may be the best medical option for women over the age of 40 who have repeatedly failed other fertility therapies, as well as for women with an elevated FSH level.

Recommendations

One approach to therapy for the infertile woman aged 40 and over who has a normal evaluation and a normal CD 2-3 FSH and Estradiol is to first try one or two cycles of COH-IUI. This may give the patient a small chance of conceiving and also allows the physician to evaluate ovarian response for a future IVF cycle. In addition, it helps the patient get used to the idea of an aggressive, "high-tech" approach. For the patient who desires the highest chance for pregnancy with her own eggs, IVF is a more successful treatment.

If the patient does not conceive with COH-IUI, IVF is a next possible step. If her ovarian response is suboptimal, her embryo quality is very poor, or she does not conceive with IVF cycles using her own eggs, egg donation should be considered. For a patient with an FSH level of 10 to 12, it may be best to direct her promptly to an IVF cycle with her understanding that the chance for a successful pregnancy is reduced. Patients with a day 3 FSH greater than 14 should be offered egg donation as the best medical option.

Summary

Some women seeking to conceive after the age of 40 have little difficulty in achieving a pregnancy. For those who do, however, prompt evaluation and aggressive treatment are critical. The serum FSH level, along with the patient's comfort level with aggressive treatment can help to guide the treatment. Egg donation offers hope to women who might not achieve a pregnancy using other treatments.