

Explaining “Unexplained Infertility” and It’s Treatment

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“Unexplained Infertility” has been described as “a misfortune due to laws of chance or limitations of our knowledge.” It is a diagnosis of exclusion, meaning the diagnosis is made after a standard evaluation of a couple fails to provide an explanation for their infertility. Most experts believe a standard evaluation for the female partner includes a history, exam, and tests to assess ovulation and the pelvis. For the male partner evaluation usually includes a history, exam, and semen analysis. About 15% of young couples with infertility of at least one-year duration will have all normal findings after a standard evaluation. By definition, these couples have unexplained infertility.

Why is infertility unexplained in these couples?

The simple answer is there are limitations to our ability to evaluate human fertility. It is helpful to divide the factors affecting fertility into categories of Ovulation, Pelvis, Sperm, Time, and Age. The assessment of each has limitations and can provide clues to why infertility is often unexplained. ([For images, see the PDF Article “Reproductive Overview.”](#))

- **Ovulation/Egg:**

To become pregnant a woman must develop and release a mature, healthy egg. Assessment of ovulation often involves ultrasound visualization of follicle growth, collapse, and evaluation of the progesterone producing ability of the corpus luteum. (A follicle is the balloon like structure that contains an egg. As it expands by filling with fluid, it matures an egg, ultimately popping and releasing or ovulating the egg. The popped follicle is called a corpus luteum. The corpus luteum makes the hormone progesterone. The presence of progesterone is unequivocal proof of ovulation.) However the egg that we hope is released with the popping and collapsing of the follicle is only 0.1 mm in diameter; it cannot be visualized by ultrasound. Unless pregnancy occurs or eggs are actually extracted, as with IVF (in vitro fertilization), it must be

assumed that an egg is released and that it is a healthy, mature egg. Ovulation assessed by history (regular periods), temperature charting, urine LH testing, or even serial ultrasounds and progesterone levels provide only indirect evidence of egg release and very little information about egg quality.

- **Pelvis:**

Two common ways to examine the Pelvic factor are HSG & Laparoscopy, each has its limitations.

Hysterosalpingogram (HSG) is a X-ray study in which dye is injected into the cervix in order to visualize the uterine cavity and tubes. When the HSG is normal it indicates the uterine cavity is without filling defects (adhesions, polyps, fibroids, or congenital abnormalities) and that the tubes are open (able to fill with and spill dye). However, the HSG is usually unable to detect filmy adhesions (scar tissue) involving the outside of the tubes and ovaries or endometriosis, which can significantly impact a woman's fertility.

Laparoscopy (surgical visualization of the pelvis by placement of a narrow scope into the abdomen) can detect and treat these problems. Yet, even a normal laparoscopic exam does not guarantee normal function of the fallopian tubes. In fact, even the tubes of a fertile woman are not thought to pick up every egg that is released. Furthermore, capturing the egg is only one of many critical functions of the tube. The tube must also facilitate the transport of the egg and sperm to near its end where fertilization must then occur. Finally, the tube must transport and nurture the developing preembryo to the uterine cavity where implantation will occur. It is necessary for the tube to perform all of these functions successfully in a natural conception cycle; however our ability to evaluate these critical functions is imperfect. Typically, if the tube appears normal, it is assumed to function normally.

- **Sperm:**

Semen analysis evaluates numbers, movement, and the appearance of the sperm. But the real question is, can the sperm work? Are there functioning sperm that are able to

make the journey to the end of the tube and penetrate and fertilize an egg? Tests used to assess sperm function include the hamster egg penetration test and Kruger strict morphology. Although helpful, these tests have limitations – analogous to the assessment of Ovulation/Egg, and the functionality of the Pelvis/Tubes, unless conception occurs or one performs IVF (where fertilization can be documented in the lab), the functionality of sperm is an assumption. Besides function, tests are available to assess the integrity of the DNA carried by the sperm; these tests (e.g. the SCSA test) have yet to be proven to be relevant (3).

- **Time:**

With all the things that must go right for conception to occur, it is easy to understand why there is a critical element of time (chance) to achieve a conception. However unlike flipping a coin, the chance of conception is not constant. Studies have estimated that a young couple has about a 25% chance of conceiving per month for the first 3 months of trying. This decreases to about 10% if conception has not occurred by months 9-12. Early on, couples with unexplained infertility may experience spontaneous conceptions. However, couples with unexplained infertility of greater than 2 years duration have a spontaneous conception rate of only 3% per month.

- **Age:**

Lastly there is the big factor of age as a major cause of “unexplained infertility.” One in five American women are having their first child over the age of 35. About one third of women deferring pregnancy until their mid to late 30’s will have difficulty conceiving. At least one half of women over 40 will have infertility problems. Unfortunately, even though most women still ovulate into their mid 40’s, at this age it is less common for successful conception to occur. Age is known to affect egg and therefore embryo quality. This in turn negatively affects the likelihood of fertilization, implantation, and miscarriage. Also with time, certain mechanical impediments to fertility such as endometriosis and fibroids can worsen. In addition to knowing chronological age, the effect of age on fertility is most popularly assessed by a menstrual cycle day 3 FSH and

estradiol level. A variant of this assessment is measuring these hormone levels before and after a clomiphene challenge. In one study, 38% of women with unexplained infertility had an abnormal clomiphene challenge test (1). [For more details, see the PDF Article "Age & Fertility: Effective Evaluation & Treatment."](#)

What are effective treatments for unexplained infertility?

Because these treatments are not specific to a particular cause (the infertility is "unexplained"), they are called empirical treatments. The best data on the treatment of unexplained infertility is from an analysis of 45 previous studies (2). The chance of conceiving per cycle was with:

No treatment	~3	%
IntraUterine Insemination (IUI)	~4	%
Clomiphene + IUI	~ <u>8</u>	%
Gonadotropin injections + IUI	~ <u>17</u>	%
In Vitro Fertilization (IVF)	~ <u>50</u> ⁺	%

Without treatment the monthly chance of conception was estimated to be about 3%. Treatment with intrauterine insemination (IUI) alone did not raise this conception rate significantly (4%). Treatment with Clomiphene plus IUI increases chance of conception per cycle 2-3 fold (from 3% to 8%). Treatment with Gonadotropin (FSH) injections plus IUI raises the conception rate even further to 17% per treatment cycle. Lastly, IVF conception rates for unexplained infertility are typically among a center's highest, usually at least 50% with the transfer of two blastocysts. With IVF, the chance of conception is usually simply determined by a woman's age. As noted above, besides being treatment, IVF is also a diagnostic tool. IVF allows assessment of egg, fertilization capability of the sperm, and embryo quality. (IVF can also be performed with Preimplantation Genetic Testing. [For more details, see the PDF Article "Preimplantation Genetic Testing: Is it right for you?"](#))

Why do empirical treatments work?

Fertility drugs may correct unrecognized defects of ovulation or hormone production. Intrauterine insemination places a much larger number of sperm into the upper uterine cavity so that a greater number of capable sperm may reach the egg. Clomiphene + IUI, and to a greater extent FSH injections + IUI, also help overcome issues of chance. In all women a healthy egg is not always released, the tube does not always pick up the egg, the sperm does not always fertilize the egg, and a healthy embryo is not always formed. Increasing the number of eggs released and the number of sperm reaching the end of the tube to meet the eggs enhances the likelihood everything will go right and a successful conception will occur in a given cycle.

Ultimately, if a woman's tubes never pick up an egg, IVF will be needed to achieve conception. Likewise, if a man's sperm is unable to fertilize his partner's eggs, IVF (often with intracytoplasmic sperm injection) will be needed.

IN SUMMARY, there are explanations for "Unexplained Infertility."
More importantly, there are treatments that are proven to help couples with "Unexplained Infertility" successfully conceive.

(1) Scott RT, Leonardi MR, Hofmann GE, Illions EH, Neal GS, Navot D. A prospective evaluation of clomiphene citrate challenge test screening of the general infertility population. *Obstet Gynecol* 1993 82:539-44.

(2) Guzick DS, Sullivan MW, Adamson GD, Cedars MI, Falk RJ, Peterson EP, Steinkampf MP. Efficacy of treatment for unexplained infertility. *Fertil Steril* 1998 70(2):207-13.

(3) The Practice Committee of the American Society for Reproductive Medicine The clinical utility of sperm DNA integrity testing. *Fertil Steril* 2006 86(Suppl 4):S35-37.