FAQs and OPTIONS: Unexplained Infertility

Unexplained Infertility

What is unexplained infertility?

If all of your testing is normal, yet you have not conceived over the course of one year (for women under 35) or 6 months (for women over 35), your physician may diagnose you with unexplained infertility. This diagnosis encompasses any problem we cannot see or diagnose, such as; problems with egg quality, problems with fertilization of the egg and sperm, and anatomic or pelvic problems that block the egg and sperm from meeting (that we cannot see on ultrasound). Many cases of unexplained infertility or sub-fertility are probably caused by the presence of multiple factors (for example, slightly advanced female age or sperm parameters at the low end of normal) each of which on their own may not significantly reduce fertility, but can reduce the pregnancy rate when combined.

The pregnancy rate per month in couples with unexplained infertility is approximately 3%. However, many patients with "unexplained infertility" may actually suffer from "sub-fertility", meaning that many, given the opportunity over time, they may eventually conceive on their own.

What is NRM's approach to treatment for unexplained infertility?

Your provider is balancing your history and results with the efficacy, safety, and costs of various treatment options. One common approach is to start with treatments that require less intervention, cost and risk, such as oral medications and intrauterine insemination (IUI), and move to more advanced treatment solutions if this is unsuccessful. In general, if a treatment has not resulted in pregnancy after 3 cycles, alternate treatments and next steps are pursued.

Because of the effects of age and time on egg quality, studies show greater success in couples who are pro-active and enter treatment after 12 months trying if <35 or 6 months trying if >35. Many patients understandably come in with a desire to move one step at a time through treatment. Certainly our goal is to thoughtfully set you up for individualized treatment based on your needs, while staying pro-active and focused on your most cost-effective approach to success. Studies show that a common regret of individuals struggling with fertility for many years is not pursuing treatment, or not moving to more advanced treatments, sooner.

How does empiric treatment for unexplained infertility work?

The primary treatment for unexplained infertility is based on "boosting" or maximizing the opportunity to conceive in patients with sub-fertility. Essentially, we aim to have patients ovulate one or more eggs in a cycle, and place a high number of sperm in the Fallopian tubes at the time of ovulation, in hopes of increasing your chances of successful sperm-egg interaction and thus, pregnancy. This strategy is also referred to as "cycle compression" or "empiric therapy", and simultaneously treats mild abnormalities of ovulation, egg function, and sperm function. In multiple studies, empiric therapy has been shown to increase the pregnancy rate; however, it also increases the multiple pregnancy rate.

Lifestyle changes

Studies indicate that smoking, abnormal body mass index "BMI" (<19 or >27), and excessive caffeine or alcohol consumption reduce fertility in both partners. We recommend optimizing BMI to 19-27kg/m2, reducing caffeine intake to <250mg/day (about 2 cups of coffee), and reducing alcohol intake to <=4 drinks per week.

What are the options for treatment?

Treatment is typically sequential, meaning simpler, less invasive, less expensive options are tried first prior to moving to more complex, higher-tech options.

1. Clomiphene/ IUI: The first and most basic options utilizes **ovulation induction medication clomiphene combined with Intrauterine Insemination (IUI)**. The "AMIGOS" trial co-authored by NRM's Dr. Casson compared clomiphene citrate, letrozole, and gonadotropins for unexplained infertility, showed the clomiphene to be a superior first line medication for these patients, while maintaining a low multiples rate (9%).

- A follicular ultrasound is typically done to assess your response to the medication
- IUI's are typically timed either with urine LH kits (24 hours after a +) or an hCG "trigger" injections (40 hours after trigger)

2. FSH/IUI (no longer recommended): Couples often inquire about a "middle" options between basic therapy such as clomiphene and IUI, and advanced therapy such as IVF. In the past, this has involved the use of injectable gonadotropin's (FSH) combined with IUI. This approach may increase pregnancy rate by a few percentage points, but greatly increase the risk of multiples (30%), and this may include triplet (5%) or higher order gestations (1%).

- A recent randomized controlled trial to evaluate optimal treatment for unexplained infertility (FASTT) demonstrated that it is more cost-effective to "fast track" from clomiphene and IUI (option 1) to in-vitro fertilization (IVF, option 3), both in terms of time taken to establish a pregnancy and also cost of all treatment.
- This trial showed no added value overall for FSH/ IUI cycles.
- The risk of FSH/IUI cycles should not be understated; twin and other higher order multiple pregnancies pose significant risks to both the babies and the mother.

3. IVF. In Vitro Fertilization is a laboratory techniques used to control more aspects of the process, and to increase the numbers of eggs and sperm available for one cycle attempt. Fertilization happens in a petri dish, sometimes with assistance called ICSI or intra-cytoplasmic sperm injection, and the best developed embryos from the process are used to place back in the women's uterus (1-3 embryos may be transferred depending on a woman's age). For more information on this advanced therapy, speak with your provider.

What is the success rate?

The success rate for clomiphene/ IUI cycles is approximately 8-12% for a woman under the age of 35. Note this is approximately 3 times higher than the rate of conception per cycle for couples diagnosed with unexplained infertility (3%) who continue to try on their own.

The success rate for IVF greatly depends on age and varies from 50-65% per cycle for women <35, to 20-30% per cycle for women in their early 40's. Pregnancy rates with IVF decrease significantly at age 42.

What are the risks of therapy?

The risk of twins with clomiphene and IUI cycles is approximately 8-10%. The risk of twins with IVF depends on the number of embryos transferred, with a single embryo transfer the risk of twins is 2% as the embryo may split and make identical twins. The twin risk approaches 30% in younger patients who transfer two embryos; however typically one good quality embryo is transferred with IVF in young patients, thus minimizing this risk.

How many cycles of basic therapy should I attempt prior to considering more advanced treatment like IVF?

Women <40: Studies, including the FASTT and AMIGOS trials noted above, generally show similar pregnancy rates for each of the first 3 Clomid and IUI cycles in women (up to age 38-40). If you do not achieve pregnancy in the first 3 cycles, generally your provider will recommend moving to IVF.

Women 38 and older: Studies in women age 38-42 show that moving immediately to IVF may be more effective as this results in superior pregnancy rates with fewer treatment cycles. In women with infertility >38 years of age, 80-85% of all infants resulting from treatment are achieved with IVF.

The above studies leave some discretion between the ages of 38-40 as to whether it is better to start with Clomid and IUI cycles or move directly to IVF. You can discuss this with your provider, based on your history and evaluation, and your desires.

Commonly Asked Questions:

Are there other options? Can I try medication only or IUI only if I want to start with a simpler treatment that clomid and IUI?

- There is strong evidence that trying clomid or letrozole (fertility medications taken by mouth) with timed intercourse does not increase the success rate of pregnancy in women with regular menstrual cycles over their success rate trying on their own without medication.
- IUI alone is no more effective than timed intercourse for couples with unexplained infertility, at a greater cost.

- IUI alone is less effective than Clomid and IUI together, by 3-5 fold.

Where can I find more information about UEI?
You are not alone on this journey- learn from other patients' questions and other physicians across the country.
Check out this amazing podcast: **Fertility Docs Uncensored** offers perspectives from 3 REI specialists from 3 different US clinics. They discuss fertility topics each week- answering and exploring common patient questions and developments in the field. Check out the episodes about IUI and IVF, episodes about lifestyle changes, optimizing fertility, supplements, exercise, and more.

"If you want to be a parent, then one day you will be a parent, but you may need to open to the way in which that will happen. When you are finally holding that child in your arms, it will be your child, and you will be its parent, no matter how the two of you are brought to each other."