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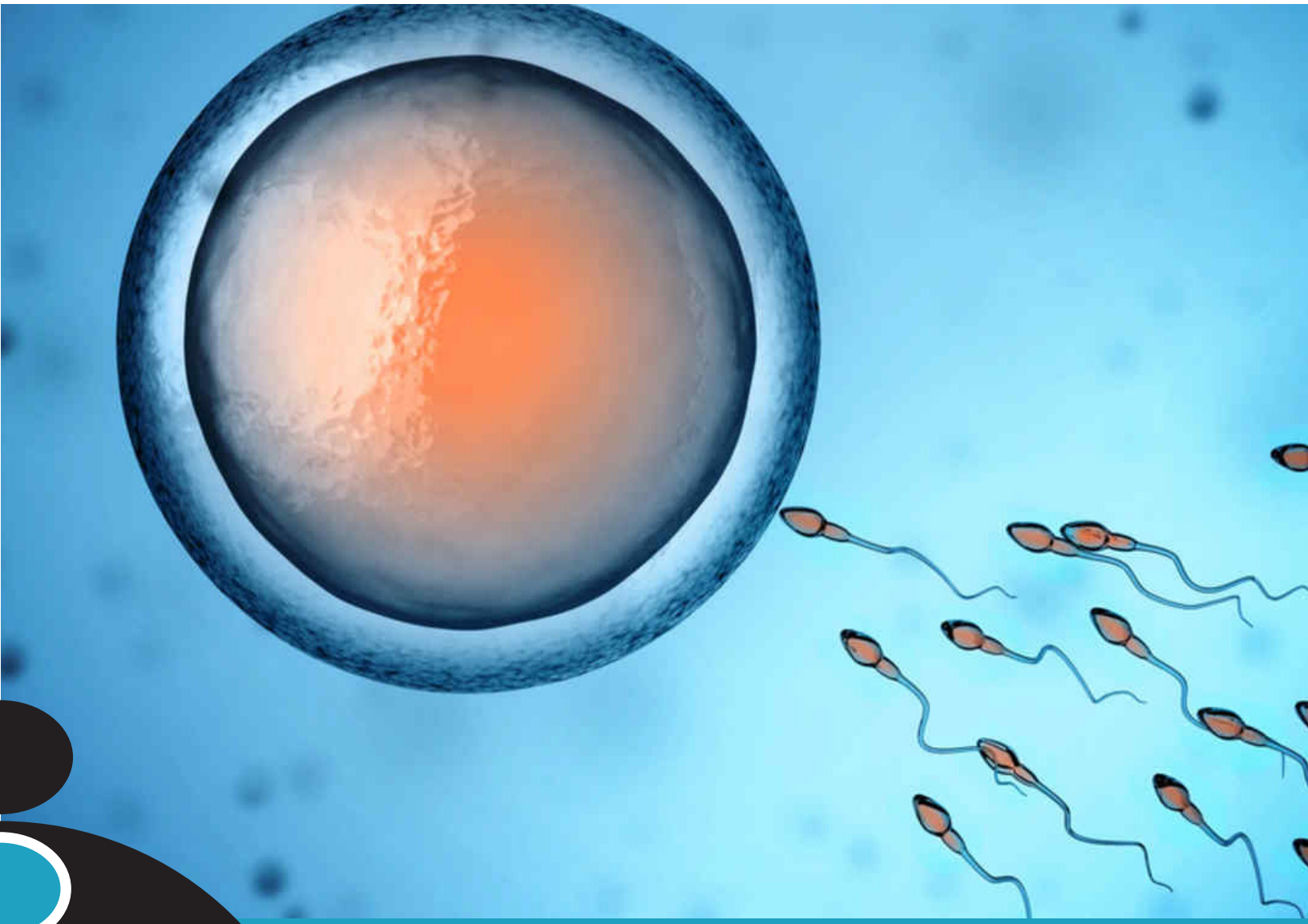


Reproductive Immunology

In terms of geographical exploration, "Space is the final frontier…" For those of us working in the innovative sectors of medicine and science, we might say, "Immunology is the final frontier." Until relatively recently the immune system was largely invisible, and it was certainly misunderstood; a system that holds more questions than answers.

Reproductive immunology is asubset of immunology, making it a mystery within a mystery of sorts. While the topic has been studied at great length by some, as well as researched and written about (in small circles), it is largely ignored by most mainstream endocrinologists and fertility specialists. We should pay homage to the original "seeker and finder" of reproductive immunology, the late pathologist Dr. Alan E. Beer.

Dr. Beer began studying the placentas of women who had delivered stillbirths, as well as placental tissue from miscarriages. Over time, he noticed a surprising number of the tissue samples demonstrated unique immune responses. He eventually published the book, *Is Your Body Baby-Friendly*… and we highly recommend purchasing it if you embark on the reproductive immunology trail. The information found within will be extremely insightful as you learn more about the topic, and as you begin to field various test results.

Today, **the protocols for treating immunologic fertility are extremely successful**. Here in the Washington D.C. area, *Columbia Fertility Associates* is the only fertility clinic that provides immunology treatments. As such, we receive a tremendous number of referrals via other fertility clinics as well as *infertility chat rooms*. Once patients are diagnosed with immunologic infertility factors, and undergo the correct treatment protocol, their pregnancy rates are as high as 70% (assuming transferred embryos are chromosomally normal). **That is a statistic worth getting excited about!**

Reproductive immunology is in its infancy period in the field of reproductive medicine

There are several reasons why reproductive immunology and related treatments aren't more widespread. First, scientists and physicians are trained to rely on evidence-based, controlled clinical research result, and to largely ignore the physical evidence that presents itself on a regular basis – even if it presents itself day in and day out. For these experts, the lack of published evidence means the diagnosis and subsequent treatments are not worth looking into at this time. Secondly, only about 1 in 10 ART clinics focus on the topic of reproductive immunology, and this makes those of us who know about it a rare breed. Some of our colleagues may even poo-poo the idea that immunology plays a substantial role in conception, pregnancy and fertility.

Slowly but surely, emerging evidence from clinics who take on this innovative niche are gaining the evidence required to catalyze a more universal appreciation for what is proving to be an highly successful fertility treatment option.

Here at Columbia Fertility Associates, *Dr. Rafat A. Abbasi* has dedicated much of her research to the study of reproductive immunology, and has a 15-year history of successful fertility treatment for women and/or couples whose infertility issues are the result of an immune system response.

In this eBook, our goal is to frontload you with information about this incredible new world of reproductive research, as well as your treatment options.

Who is Most Likely To Have Immunologic Infertility?

You may have an immunological infertility factor if:

- ✓ You have years of repeat IVF cycles and multiple miscarriages
- ✓ You're having a hard time getting pregnant even though your first pregnancy was successful
- ✓ Repeat IVF and miscarriages don't fit your age bracket, and don't make sense given your clear pre-conception genetic screening
- ✓ You are in your 30s and hardly ever get sick or succumb to infection (the curse of a healthy immune system…)

If any of the above resonates with you, **your immune system could be the culprit**, and Dr. Abbasi and the team at CFA may have the solution.

There's a chance your immune system is working against your fertility chances

The immune system is your body's first and last armor of defense against foreign invaders. This is as true for the common cold as it is for cancer. If the body can't arm a defense against the attacker or invader (pathogens), it will eventually succumb. If the body's immune system is working effectively, it kills the invaders off and the body returns to its inherently healthy and balanced state.

Unfortunately, for some women, the immune system views the sperm, or the fertilized egg (which consists of the "invader" sperm) as a pathogenic invader, and it launches its attack to get rid of it. If this is happening in your body, you will find it impossible to get pregnant (perhaps even after a first, successful pregnancy), your pregnancies will always result in a miscarriage (typically before week 12 but not always) or you may even experience late-pregnancy miscarriages or a stillbirth.

Ultimately, in cases where the immune system causes infertility, the innate or adaptive immune response launches activated killer cells, B-cells or T-cells that eliminate the freshly fertilized egg or embryo.

That's the very short story.

There's a chance your immune system is working against your fertility chances

The longer story requires a brief introduction to immunology. Consider it a very basic version of an Immunology 101 course, which will build a bridge to the reasons why your immune system could be the cause of your infertility.

Here are some of the important immunological concepts that will come into play as you further your explorations into reproductive immunology.

The immune system has two different responses:

Innate immune system response

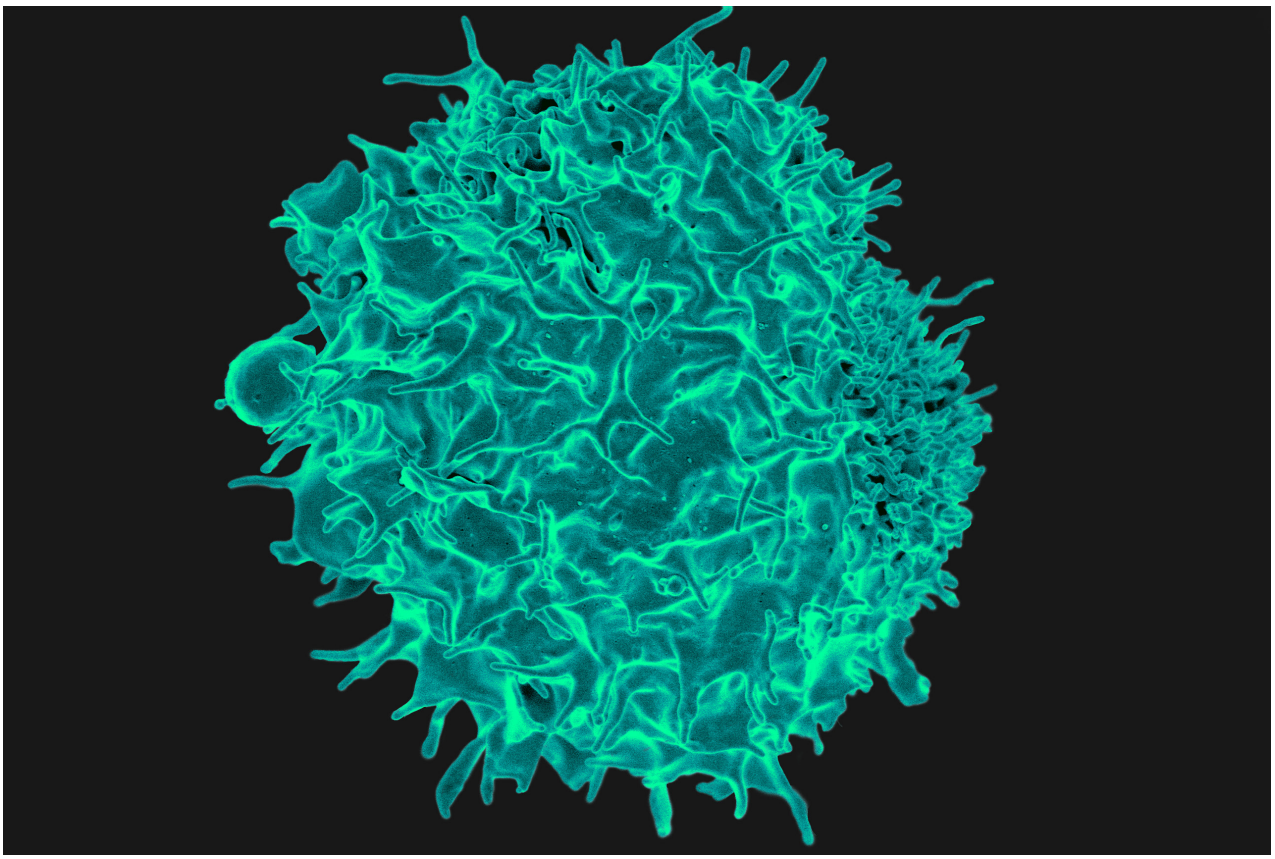
This response system is the most basic, primitive level of immune defense. The innate immune system response has been pre-programmed as the result of thousands upon thousands of years of our existence on planet earth. Human bodies are hard-wired from birth to recognize certain invaders and attack them. It does this via "natural killer cells," which are a type of lymphocyte (white blood cell.) This response happens immediately after the body recognizes a pathogen has attacked or entered its field.

Adaptive immune response.

This system is not innate. Rather, it develops over time as your immune system grows and experiences ever more invaders in the form of bacteria, viruses and even cancer cells. Through this adaptive, learned

response, the immune system "gets to know" the invader and makes a decision about which cells are the right ones to attack and eliminate it. The span of time between when the invader arrives and the adaptive immune response activates a response is called the latency period. At the end of this latency period, the adaptive immune response activates specially selected B-cells and T-cells, also lymphocytes, and these B- and T-cells produce antibodies.

B-Cells. B-cells are attackers. The pathogen attacks, and very specific B-cells are activated according to the types of antibodies they produce. The specially selected B-cells multiply and attack the pathogen with the idea that there is



safety and power in numbers.

T-cells. The T-cells are specifically designed to attack pathogens with receptors that bind to things. Once the body's immune system identifies the pathogen, it activiates specific T-cells bind to the invader's receptors. The T-cells kill the invader and they also produce cytokines. Cytokines are like hormones, and they're secreted into the environment around the attacking organism.

The problem with this adaptive immune response is that sometimes T-cells are activated by the body when a fertilized egg is trying to implant into the uterus.

That's a very short and simple explanation of how the immune system works (amazing isn't it?).

One more thing worth noting: in the case of the adaptive immune response, practice often makes more perfect. The idea being that the first time a pathogen or invader attacks, the latency period is longer because the immune system is determining which types of B- and/or T-cells should be activated, and the cells themselves are learning about the invader so they can produce just-right antibodies. The second time an invader attacks, the latency period can be much quicker because the B- and T-cells know just what to do.

T-Cell Activation Can Prevent Secondary Fertility

Sometimes, our patients come to us in a state of complete shock and confusion. The first time they wanted to get pregnant, it went like clockwork. They timed conception correctly, got pregnant, and delivered a perfectly healthy baby. This time, however, it hasn't worked like that at all. They've tried and tried and can't get pregnant at all, even though their infertility tests show the sperm, eggs and anatomy are in perfect order. Or, perhaps these successful first-timers are now experiencing repeat, back-to-back miscarriages. These scenarios are often diagnosed as *secondary infertility.*

Both are signs that the immune system is activating an adaptive immune system response.

You see, the first time the couple got pregnant, the sperm (aka "the invader" in this case) fertilized the egg and it implanted. Unbeknownst to them, the mother's body activated an immune response. While this pregnancy progressed through the latency period and the baby was born alive and well, the immune system is now lying in wait – armed with the correct response for the next time they get pregnant – and the next, and the next...

In fact, this immune response will cause implantation failure or miscarriage every single time. We have found that a pregnancy-triggered immune response is the 5th most common cause of implantation failure. The body simply identifies the fertilized egg as an

invader (due to the invader sperm) and kills it before it ever has a chance to implant.

In our experience, the leading causes of implantation failure are (in order):

1. Chromosomal abnormality
2. Anatomical abnormality of the uterus (*fibroids*, septate uterus, scar tissue, etc.)
3. Hormonal issues (not enough progesterone to sustain pregnancy), or thyroid dysfunction.
4. Blood clotting factors
5. Immunological causes**

** We usually associate advanced maternal age (women 35-years and older) with low ovarian reserves and *compromised egg quality*, hence lower fertility rates. Healthy immune systems, however, can also play a role because the longer you live, the more acute your immune system becomes -and the more adept it is at killing off invaders. So, occasionally, older patients come to us with sufficient, high-quality eggs, but an immune system that is working so well, it's preventing an embryo from implanting.

When patients experience implantation failure and all other factors have been ruled out (including back to back miscarriages or failed IVF after *pre-conception screening* or PGD screenings were normal), we suspect immunological factors are at work.

The good news is that there are ways we can block the body's immunological response to your pregnancies so that the pregnancy can progress full-term.

How do you diagnose a patient for immunological causes?

After a thorough medical history has been taken, and the primary four causes of infertility have been ruled out, we begin to take a closer look at immunological factors by using a complete bloodwork panel.

This panel includes testing different populations of immune cells in the female patient, as well as taking a blood sample of the partner's blood and testing it against the female's blood for the development of the blocking antibodies.

There are two different types of antibodies that affect fertility:

- **Auto-antibodies**. These antibodies can attack your own tissue, cells or the embryo itself.
- **Allo-antibodies.**These antibodies are produced in response to foreign antigens.

The protocol of immunologic fertility treatment is selected according to which cell populations are elevated.

Innoculation

If we look at a woman's blood sample and see a problem with the blocking antibody, we can actually inoculate the female with the male's white blood cells. This protocol works like a TB vaccination. We draw blood from the husband, the blood is prepared and the white blood cells are extracted. These are then injected into the mother's arm and there should be evidence of a wheel and a flare.

Two weeks later, we draw the mother's blood and we should see evidence of blocking antibodies.

Once these are present, couples can *begin timing conception at home again* or proceeding with IVF treatments. If immunological factors were at play before – the blocking antibodies should now allow the fertilized egg/embryo to implant and develop normally.

The problem with this treatment is that it is no longer available in the U.S. It was banned by the FDA. Thus, if patients are interested in trying innoculation, we recommend they travel to Canada, Mexico, Australia, Japan, the UK or any other countries that still offer the treatment.
Of course, not everybody is able or willing to do that so, fortunately, there are other options.

We can suppress the immune system's killer cells without making the blocking antibody

There are other medical conditions that rely on immune suppressing treatments to block killer cells from attacking the wrong invader. These same treatments can be used on women diagnosed with immunologic infertility.

Intravenous treatments of Immunoglobulin G (IVIG)

Your body has two types of immunoglobulin: immunoglobulin M (memory) is part of the innate immune response. Immunoglobulin G is an antibody created by a previous encounter with an invader. We can administer Immunoglobulin G using an IV infusion. This treatment commonly used to boost immune systems of patients with a condition called hypogammaglobulinanemia and HIV. It can also suppress the killer cells in women with immunologic infertility.

There are a few problems with IVIG treatment:

1. It's very expensive. It costs about $3,000 per dose and it must be administered repeatedly throughout the pregnancy.
2. It's made by immunoglobulin from pooled donors. Although the samples are carefully screened, there's a slight risk of being exposed to a serious blood-borne pathogen, as in a blood transfusion.
3. IVIG isn't always available

because sometimes the demand outpaces the supply, in which case it's not available and patients with medically life threatening problems are always the top priority.

4. There are a few, serious side effects to IVIG that are rare, but still posea potential risk, like aseptic meningitis and blood transfusion type reactions.

Intralipid infusions

There is a form of nutrition called parenteral nutrition (PN) used to feed patients who aren't able to digest food on their own. In these cases, the parenteral nutrition is administered directly to the veins using an IV. Intralipids, a specialized mix of nutritional fats, are part of the PN treatment. Over time medical experts began to notice that patients who received intralipids had better functioning immune systems and their natural killer cells were suppressed.

After multiple trials and testing, we've figured out that it works as a natural killer cell suppressant for pregnant women as well. In clinical trials, researchers have compared pregnancy rates between fertility patients using IVIG withthose using intralipid infusions and the pregnant success rates arestatistically the same.

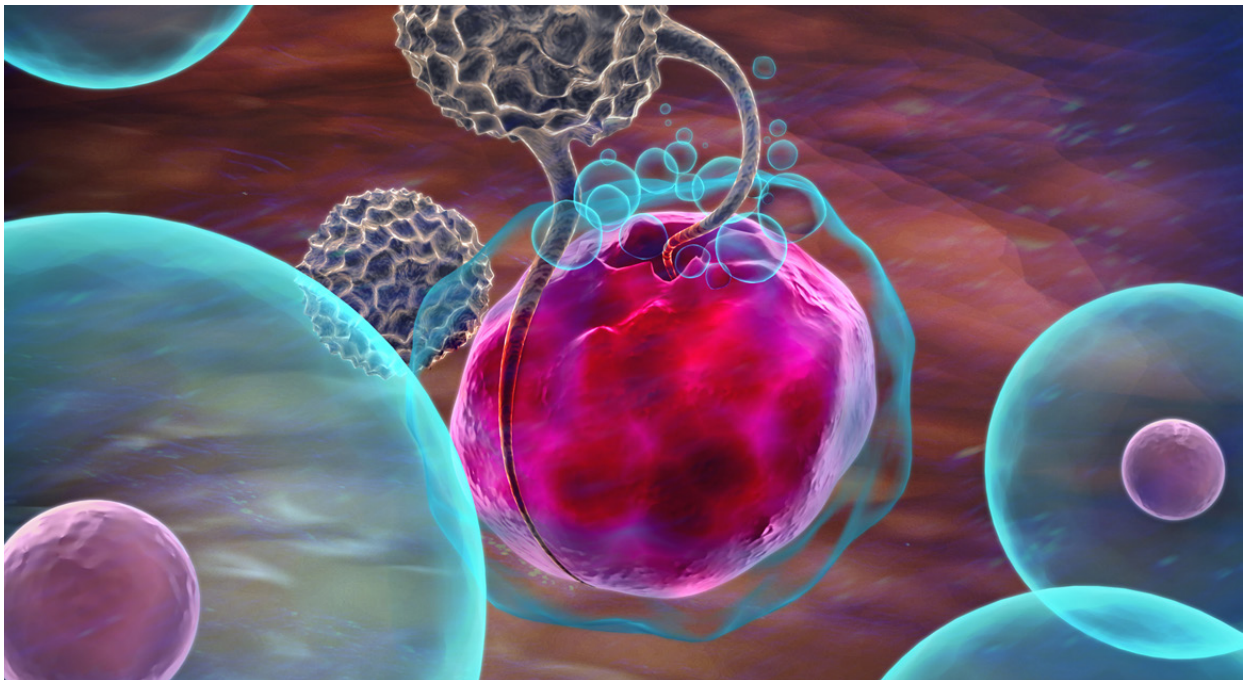
Intralipid costs less than IVIG (roughly $600 per infusion) and it's readily available so supply is never an issue. It also has very few side effects. The downside to intralipid is that it doesn't always suppress cytokines (the factors secreted by the T-cells). **If your blood panels show unnaturally high cytokine levels, intralipid probably won't be the drug of choice for you**. However, it works well against natural killer cells as well as elevated levels of B- or T-cells. If your cytokine

levels are highly elevated, you're probably better off using IVIG or Neupogen.

Neupogen

This is a granulocyte colony stimulating factor (GCSF). Granulocytes are the white cells. Neupogen has been on the market for about five years now and works by stimulating bone marrow to produce white blood cells. These white cells are important in fighting off infection. Injections are administered subcutaneously, by the patient, on a daily basis during the treatment period and throughout the pregnancy – depending on her blood work results.The Neupogen treatment option is less expensive than IVIG.

There are several negative side effects associated with Neupogen. Normal white blood cell counts are between 12,000 and 15,000; with Neupogen, they can go as high as 40,000 to 50,000.



Steroid treatments

Steroids are method of suppressing the immune system. We use steroids with most treatment protocols, either alone or in conjunction with other treatments. In cases of immunologic infertility, steroids are rarely sufficient alone without one of the aforementioned treatments.
If a patient doesn't want to do the Neupogen injections, we can pair steroids (typically prednisone, taken twice a day) and intralipid with good results. This is a common solution for women who can't afford IVIG or Neupogen or don't want to risk the side effects. In most cases, the combination of prednisone and intralipid effective enough to suppress the killer cells.

We monitor the patient's blood every three weeks or so. If, for example, we see that cytokine levels are creeping up or seem too high, we might suggest a single infusion of IVIG to get those levels back down. So the treatment protocol is always created, tweaked and amended according to the patient's test results.

How Long Do the Immune Treatments Last?

We treat patients during the cycle of conception with IVF (typically between Day 6 and 10), again the day before an IVF embryo transfer, and we do it again after she has a positive pregnancy. After that, we monitor blood levels every three weeks. The cytokine, killer cell, B- and T-cell counts determine whether or not patients have another infusion.

For a cycle with IUI (intrauterine insemination), medications usually start after ovulation.

We continue to monitor blood levels until week 32, at which point the baby will be developed enough to survive on its own if the mother goes into labor.

Will I Get Sick More Often Since My Immune System is Manually Suppressed?

No. These treatments are highly targeted to a particular population of cells that are located in the uterus and will not affect any other cells or tissues in the body. Therefore, your immune system will be just fine in terms of colds, flus and other potential “invader-related” conditions.

Contact Dr. Abbasi at Columbia Fertility Associates to Learn More

Would you like to learn more about reproductive immunology? Do you suspect that your infertility might have an immunologic link? Honor your instincts and get in touch with Dr. Rafat Abbasi and the team here at *Columbia Fertility Associates*. We firmly believe that the work we do here in regards to reproductive immunology will increase pregnancy rates and infertility rates for women around the world.

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