

# INTRAUTERINE INSEMINATION: CONCEPTIONS, MISCONCEPTIONS, AND WHAT PATIENTS SHOULD KNOW

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Intrauterine insemination (IUI), the injection of sperm into the uterus by means of a catheter directed through the cervix, has been practiced for many years. The premise of this procedure is that sperm can reach and fertilize the egg more easily if placed directly into the uterine cavity.

In the early '60s, physicians were injecting small quantities of raw, untreated semen, (sperm plus the seminal plasma) directly into the uterus at the time of expected ovulation. However, when more than 0.2 ml of semen was injected in to the uterus, serious and sometimes life endangering shock-like reactions often occurred. It was subsequently identified that the reason for such reactions related to the presence of prostaglandins within the seminal plasma. This led to the practice of injecting small amounts (less than 0.2 ml) of raw semen. However, the pregnancy rates were dismal and side effects, such as severe cramping and infection were rampant.

Soon after establishing the Northern Nevada Fertility Center in Reno in 1982 (the Nation's first private in vitro fertilization (IVF program), we began to recognize the potential advantage of washing and centrifuging raw semen, so as to separate sperm from the seminal fluid, and thereby remove prostaglandins that cause most of the problems. We subsequently introduced and, thereupon, became the first to publish on intrauterine insemination (IUI) in the Journal, *Fertility and Sterility* (April 1984).

## Indications for Intrauterine Insemination (IUI)

- Artificial insemination using frozen (donor) sperm: The recognition of HIV infection as a sexually transmitted disease, coupled with the fact that the virus is present in semen months before it can be detected in the blood, mandates that all donors have their semen cryopreserved (frozen) and stored for at least six months, whereupon, they be re-tested for HIV infection. Only upon confirmation of a negative test should the cryopreserved semen specimen be thawed and used for insemination. Since cryopreservation inevitably reduces sperm motility and function, it is not adequate to simply thaw the frozen specimen and then inseminate the raw semen into the vagina. Rather, the semen specimen should be processed for IUI. Provided that the recipient is ovulating normally, there is no need to administer fertility drugs, such as Clomiphene, Pergonal, etc.
- Artificial insemination with partner's sperm: In cases of sexual dysfunction (impotence, retrograde ejaculation, etc.) or timing issues, partner's sperm may need to be collected and processed in preparation of IUI.
- Cervical mucus hostility: Sometimes the cervical mucus acts as a barrier to the activation and passage of sperm as it passes through the cervical canal. Such hostility may be due to poor physical qualities of the mucus, cervical infection, or the presence of antisperm antibodies. In all but the latter situations, IUI can readily be performed during natural cycles, unless the woman has ovulation dysfunction. However, when infertility results from the presence of antibodies in the cervical mucus, IUI will likely be ineffectual and should be replaced by in vitro fertilization (IV).

- Absent or dysfunctional ovulation: In some cases where the woman requires the use of fertility drugs to induce normal ovulation, the concomitant performance of IUI might improve pregnancy rates.

### **Selecting the Fertility Drugs for Intrauterine Insemination (IUI)**

*Clomiphene citrate (Serophene, Clomid)*: A study confirmed that normally ovulating women taking Clomiphene citrate experience a reduced chance of achieving pregnancy when compared with fertile women who are not taking Clomiphene. Furthermore, additional studies have reported very few viable Clomiphene-induced pregnancies in women over the age of 40. The reason is Clomiphene's anti-estrogen effect often leading to a poor uterine lining and reduced/abnormal cervical mucus. Moreover, in about 20% of cases, the woman develops Luteinized Unruptured Follicle Syndrome (LUFS), a condition where the hormonal changes that precede, accompany and/or follow ovulation (including an increase in blood progesterone level) occurs. This often leads to the erroneous conclusion that an egg has been released when, in fact, it remains "trapped" in the ovarian follicle.

Then there is the strong likelihood that most normally ovulating woman who receive fertility drugs (clomiphene included) only release one egg at a time anyway. So to administer such medication to such women in the hope that they will release multiple eggs at a time and so improve the chance of conceiving defies all logic.

*The following additional factors must be considered when it comes to the use of Clomiphene:*

- 1) It is best not being prescribed for more than three consecutive months in a row to anyone and certainly not without taking a full cycle break before restarting a fourth cycle of treatment. The reason is that after the 3-4 consecutive months of clomiphene therapy, the antiestrogenic properties are compounded to the effect of virtually converting it to an anti-fertility drug. This explains why >80% of successful clomiphene pregnancies occur within the first 3 months of treatment, and why the vast majority of clomiphene pregnancies that occur after >3 consecutive (back-to-back) cycles of treatment are lost (usually due to early miscarriages).
- 2) Clomiphene should not be used in women that have diminished ovarian reserve (e.g. women with elevated FSH levels) or in women over 40 years of age. As stated, clomiphene is antiestrogenic. Thus, in women who are not taking clomiphene, even a single ovarian follicle will usually produce sufficient estrogen to result in the development of an adequate uterine lining that can support an n implanting embryo. Women on clomiphene require at least 3 sizeable follicles to accomplish the same. Older women (over age 40) and those with diminished ovarian reserve are often incapable of producing at least 3 sizeable follicles on clomiphene, and are thus much less likely to be able to produce enough estrogen to override the antiestrogenic properties of clomiphene.
- 3) Increased production of Luteinizing Hormone: Clomiphene causes the pituitary gland to produce increased amounts of FSH and LH. FSH promotes follicle growth development while excess LH causes the ovary to produce male hormones such as testosterone. While a little testosterone is indispensable to follicle and egg development, too much testosterone can have the reverse effect and harm egg development. In fact, it is often cited as an important reason why women receiving clomiphene have about a one third lower pregnancy rate per cycle than is the case using injectable fertility drugs. This effect

is even more deleterious in women with diminished ovarian reserve (elevated FSH levels) and those over 40 whose ovaries tend to produce more testosterone-like hormones.

The good news is that upon discontinuation of Clomiphene for 4-6 weeks, adverse effects disappear, leaving the slate clean.

*The real benefit of clomiphene lies in its oral route of administration, low incidence of side effects, and its low cost. The birth rate per clomiphene IUI cycle is about 5-7%.*

Letrozole(Femara): Letrozole, like clomiphene is an oral agent induces ovulation that causes the pituitary gland to release large amounts of FSH as well as LH. The advantage that Letrozole has over clomiphene is that unlike the latter, it is NOT antiestrogenic and thus does not compromise development of the uterine lining or adversely affect the production of cervical mucus. However as is the case with clomiphene, Letrozole causes increased LH release that can lead to overproduction of male hormones (e.g. testosterone) by the ovaries with potentially adverse effect on egg/embryo quality.

Thus while Letrozole does have potential advantages over clomiphene, the exaggerated LH-induced testosterone effect, especially in women over 40 years of age and/or those with evidence of diminished ovarian reserve limits its value.

Gonadotropin (Menopur, Gonal-f, Follistim and Puregon:) Women with absent or abnormal ovulation who require fertility drugs in preparation for IUI should receive gonadotropins. Granted, these agents are more expensive than clomiphene, but they have no antiestrogenic properties.

*The birth rate with gonadotropin IUI in women under 40 years of age (in the absence of male infertility, where it is much lower) is about 10-12%. However, success is affected by, and contingent upon, the procedure being performed (1) for the correct indications, (2) avoiding the performance of IUI when contraindications exist (see below) and, (3) where the woman is ovulating normally on her own. Success rates decrease as a woman's age advances. In women over 40 years, the birth rate per cycle is under 2%, declining to less than 1% after age 43.*

### **Relative Contraindications to Intrauterine Insemination (IUI)**

Advancing age: A woman's natural ability to conceive declines with age starting after age 30. It falls more rapidly after age 35 and then, precipitously so after 40. The main reason for this is that the percentage of eggs that become chromosomally abnormal (aneuploid) through "wear and tear" increases as she gets older, such that by age 40 an ovulated egg is probably 3 times less likely to be able to propagate a viable pregnancy than at age 30. This explains the fact that under 35, the normally ovulating woman who receives injectable fertility drugs to induce ovulation has about a 10-12% chance of having a baby. In comparison, after age 40, the same woman would have about a 2% chance. For this reason alone, IUI is best suited to women under 35 and, in my opinion, should NOT be undertaken after age 40. Ages between 35 and 40 represent a "gray area."

Significant Male Infertility: Contrary to popular belief, the performance of IUI in cases of male infertility does not improve success rates over regular and well-timed intercourse alone. In vitro fertilization with intracytoplasmic sperm injection (IVF/ICSI) is the only method to optimize pregnancy rates in association with male refractory infertility.

## Tubal damage

1. Post-Pelvic Inflammatory Disease (PID): It is very important to understand that Fallopian tubes are not mere “pipes” through which sperm, egg and embryo must pass to achieve an intrauterine pregnancy. They are vital and sophisticated organs that serve intricate functions in the reproductive process. They transport sperm in the direction of the ovary, while at the same time, the *fimbriae* (petal-like extrusions at the end of the tube) apply themselves to the area of the ovary from which the egg is ovulating in order to pick up the extruding egg, and carry it back down the tube towards the uterus. About one third of the way back, the egg encounters the sperm and fertilization occurs. Thereupon, the resulting embryo is transported to the uterine cavity where it hopefully will implant.

PID, the commonest cause of damaged Fallopian tubes will, unless it is diagnosed and effectively treated very early on, inevitably and permanently disrupt the sophisticated function and continuity of the inner lining of both Fallopian tubes. In more severe cases, the intricate muscular arrangement of the tubal wall is also damaged, compromising the time-sensitive and programmed migration of sperm, egg and embryo. In advanced cases of PID, the fimbria fuse, thus compromising egg pick-up, and ultimately blocking the tube(s) completely.

PID almost always affects both Fallopian tubes. Indeed, one tube might be more damaged than the other, but both will be affected to a greater or lesser degree. That is why, even if one tube remains or is surgically rendered patent, the problem of markedly reduced fertility and the increased risk of a subsequent tubal pregnancy remains an ever present risk and reality. Thus, the use of fertility drugs to induce ovulation, or the use of microsurgery to open Fallopian tubes and free surrounding adhesions are often not curative of infertility. Furthermore, in cases where a pregnancy follows, the result is often a tubal (ectopic) gestation. This also serves to explain the fact that the intrauterine pregnancy rate following ovulation induction (with or without concomitant IUI) is likely to be at least 10 times lower in women with PID, and why, when a pregnancy does ensue, it is 10 times more likely to be a tubal (ectopic).

Thus, in women who have had PID, IVF is the only way to safely bypass the “damaged plumbing” and initiate a viable intrauterine pregnancy.

2. Post-Tubal Ligation In large part, the same holds true following successful reconnection of previously ligated (tied) Fallopian tubes. The reason is that even with successful surgical reestablishment of tubal patency, there is always a degree of shortening of the tube(s) or a degree of damage due to surgical scarring of the inner lining of the tube(s). Even when tubes are normal, the birth rate per IUI cycle is about 10%, and following any form of tubal damage (PID or surgically-induced) the success is 5-10 times lower per IUI cycle (i.e. 1%-2%). Hence, IUI can hardly be justified in such cases, and IVF becomes the only effective and viable option.

Endometriosis: While the exact cause of endometriosis remains an enigma, it is now apparent that immunologic dysfunction is a significant feature of this disease, and that a toxic environment exists in the pelvis (surrounding the tubes and ovaries) in patients with this condition. As a consequence, ovulation - whether spontaneous or induced by fertility drugs - commits the egg to pass through a toxic pelvic environment in order to reach the sperm waiting in the fallopian tube. This significantly reduces the egg's fertilization potential. Furthermore, once the fertilized egg

reaches the uterus, immunologic factors associated with endometriosis increase the risk of the embryo being rejected before pregnancy can be diagnosed. Such women may experience repeated “mini-miscarriages.”

In spite of these anti-fertility influences, many women with mild endometriosis do in fact conceive on their own, or following ovarian stimulation with fertility drugs. However, for reasons already referred to, the chances of conception are significantly reduced. And if they are ovulating normally on their own, the addition of fertility drugs will afford no additional benefit. Simply put, women in their late 20's to early 30's who have the time can anticipate about a 40% chance of conceiving on their own within two or three years (contingent upon their ovulating normally and having a fertile male partner). The occurrence of pregnancy in the latter cases occurs in spite of, rather than due to, such treatment. Such women may consider deferring any invasive treatments in favor of a “wait-and-see” approach. Conversely, women over the age of 35 whose egg quality is inevitably on the decline, IVF offers the only rational approach.

### **Fertility Drugs and Multiple Births**

Normally ovulating women usually develop a number of follicles (fluid filled spaces within the ovary (ies) that contain eggs and produce estrogen) during the first week of the menstrual cycle. All but one (and sometimes two) of the follicles fail to develop to the point of being eligible for ovulation. The process is known as *Selection*. It is important to recognize that in all normally ovulating women, the one or two follicles selected to ovulate will inevitably be larger than the remaining follicles, regardless of whether the woman is receiving fertility agents such as Clomiphene or Pergonal, etc. Simply put, one or two follicles will always show enhanced development over the others, and as soon as these selected follicles ovulate, all the remaining follicles are rendered incapable of following suit. As a result, normally ovulating women do not have a greater incidence of high order multiple pregnancies. In contrast, women who **do not** ovulate at all, and those who ovulate irregularly or dysfunctionally do not have the ability to select one or two dominant follicles for ovulation. As such, following the administration of fertility drugs for ovarian stimulation, numerous follicles may develop at the same rate, and several eggs can be ovulated simultaneously. This translates into a greater chance of pregnancy, but also a greater chance of multiple pregnancies. It is interesting that almost all reported cases of high order multiple pregnancies (greater than twins) following the use of fertility drugs have occurred in women who do not ovulate normally on their own.

It follows that only those women with absent or abnormal ovulation are at-risk for high order multiple pregnancies. They, therefore, need to be counseled regarding the consequences of premature birth and the availability of selective pregnancy reduction towards the end of the third month of pregnancy. Another alternative is to avoid the issue completely by choosing in vitro fertilization (IVF), where the number of potential babies can be limited by the number of embryos transferred to the uterus.

*It is indeed unfortunate that fertility treatment has become so regimented that most patients find themselves being ushered through a scripted treatment process. As an example, clomiphene, though favored for its convenience and low cost, does NOT yield the same success as IUI with gonadotropin stimulation. In fact the per-cycle success rate of IUI using clomiphene is about 30% less. Also, women with endometriosis (regardless of severity) have much lower success with IUI (see above). Women over age 40 have such a low success with IUI that they cannot afford the time wasted in the process. Such women need IVF.*

*For the majority of couples who require an individualized strategic plan of action at an early stage, such an approach is emotionally, physically, and financially draining, leaving them both suspicious and critical of the intent of the medical profession.*

**The introduction of inexpensive Micro-IVF changes the landscape. In fact, the success rate is three times higher than with IUI. Moreover at <\$5,000 per cycle, the cost of Micro-IVF is comparable to that of gonadotropin IUI. More significantly, when measured in terms of the cost per baby, the cost is much lower for Micro-IVF than for IUI.**