Intrauterine Insemination

Kaylen M. SIlverberg
Medical Director
Texas Fertility Center
Austin, TX

Intrauterine insemination (IUI) is one of the most commonly employed therapeutic modalities in infertility practice today. It was initially described in the mid-1770s, and, in the modern era, was originally advocated as a treatment for male factor and cervical factor infertility. Over the past several years, its indications have rapidly expanded, and it is now used to treat a variety of types of infertility. Specifically, IUI is used as a treatment for male factor infertility (especially low sperm counts or poor motility). It is also used for cervical factor infertility (ie. abnormal or absent cervical mucous production), and for cases of immunologic infertility (ie. when antibodies to sperm are produced by either the man or the woman). Many programs also treat couples with unexplained infertility or recently treated endometriosis with IUI. Frequently, IUI is used in conjunction with clomiphene citrate (Serophene or Clomid) or gonadotropin (Pergonal or Metrodin) therapy in these latter instances. In this article, I will attempt to address some of the most commonly asked questions about IUI.

How do I know if I need IUI?

The post-coital test (PCT) is frequently used as a screening test for cervical factor and immunologic factor infertility. In this test, the couple is asked to have intercourse mid-cycle. Between 2-12 hours after intercourse, a small sample of cervical mucous is removed from the woman's cervix during a routine pelvic examination. The mucous sample is then examined for several parameters. First, mid-cycle mucous should be present in an abundant amount (ie. greater than 0.3 cc). Second, the mucous should be watery and clear. Due to hormonal changes that occur mid-cycle, the mucous should be very thin and stretchy (a concept known as Spinnbarkeit). Specifically mucous should stretch to a distance of at least 8 cm. When examined under a 40X objective microscope lens, one should be able to see moving sperm. There is no concensus as to the exact number of viable sperm that should be present in a PCT in order for it to be considered "normal". In fact, in one of the best known studies about the PCT, performed by John Collins, there was no difference in fertility rates over a 2 year period - regardless of whether or not any sperm were present at all on the microscope slide!(1) Despite this, most physicians like to see at least 2 motile sperm per high power microscope field in order to declare the test "normal".

In light of the controversy about the PCT, one might ask why perform the test at all? We perform the PCT for very specific indications. First, up to 40% of women who take clomiphene citrate may experience a marked adverse effect on their cervical mucous production due to the clomiphene. They may have thick mucous, a markedly diminished quantity of mucous, or no mucous production at all. In these cases, we suggest proceeding to IUI rather than encouraging the couple to have intercourse mid-cycle. Second, women who have undergone cervical surgery (cone biopsies, laser ablation, etc.) frequently will have diminished or absent mucous production. We recommend IUI for these patients.

Third, we use the PCT to rule out cervical infection. If we see white blood cells under the microscope, we treat the couple with antibiotics and repeat the PCT after the antibiotics are completed. Fourth, we frequently use the PCT as a screening test for the presence of anti-sperm antibodies. If we see sperm shaking in place on the PCT - or no sperm despite a normal semen analysis, we proceed with both a direct and an indirect antibody test. If the male is making antibodies to his own sperm, then we suggest IUI following sperm collection in a special media to reduce the number of sperm bound by antibodies. If the woman has antibodies in her mucous, then we recommend IUI in order to bypass the cervical mucous. If the woman has a high concentration of antibodies in her blood, then we offer her treatment with steroids or in vitro fertilization.

In addition to absent mucous production or an abnormal PCT, several studies have suggested that gonadotropin therapy is another indication for IUI. In these studies, pregnancy rates were significantly higher for gonadotropin therapy combined with IUI than for gonadotropin therapy combined with intercourse. (2,3)

Should a hysterosalpingogram (HSG) be performed before IUI therapy is begun?

Most infertility specialists believe that the HSG is an integral part of the routine infertility evaluation. Very few tests can give a physician so much meaningful information. First, the HSG can demonstrate tubal patency. If the tube (s) is (are) occluded, it can frequently identify the site of occlusion. Second, the HSG can evaluate the structural integrity of the endometrial cavity. For example, fibroids, polyps, and scarring inside the cavity can all be demonstrated by HSG. Third, a properly performed HSG can frequently demonstrate the mobility of the fallopian tubes. Tubal mobility can be impaired by the presence of scarring around the tubes as a result of previous infection, surgery, or endometriosis. Finally, not only is the HSG an effective diagnostic test, but there are also several studies which suggest that it is therapeutic as well. Pregnancy rates have been reported to increase for 3-6 months following the performance of an HSG. (4) For all of these reasons, I strongly believe that an HSG should be performed before considering IUI - with or without gonadotropin therapy.

How long should IUI be performed before moving on to more aggressive therapy?

Although this is one of the most important questions asked in infertility therapy, there are not yet any definitive answers. Most studies, looking at a variety of different forms of infertility therapy, suggest that the vast majority of pregnancies occur within the first 6 cycles of any specific therapy. For this reason, we advocate no more than 6 cycles of IUI before moving on to another treatment regimen. Frequently our next regimen is gonadotropin therapy combined with IUI. Although many infertility specialists will suggest empiric clomiphene citrate plus IUI as the next step for regularly ovulatory women who have not conceived with IUI alone (5), I believe that the data supports moving on to gonadotropin therapy (ie. Pergonal or Metrodin) instead.

How are sperm prepared for IUI?

There are several different methodologies used to prepare sperm for IUI. The two most-commonly employed are the swim-up technique and Percoll gradient separation. Both techniques work best on fresh semen specimens obtained in a sterile container, and delivered to the andrology laboratory within 30-60 minutes of collection.

The swim-up technique involves a natural separation of the rapidly motile, healthy sperm from dead sperm and debris. In this procedure, the semen specimen is washed and centrifuged one or two times with a sterile media in order to separate the sperm from the remainder of the semen. (A large percentage of semen is comprised of chemicals and fluid from the accessory male sex organs and is not necessary for conception. In fact, some of these chemicals can be harmful if placed into the uterus, causing intense cramping or other symptoms). Once the sperm have been separated, they are placed in the bottom of a conical shaped tube under a layer of media. The tube is tilted to a 45^0 angle and placed in an incubator for 45-90 minutes. During incubation, the healthy sperm swim to the upper layers of the media, while the dead sperm and debris stay at the bottom of the tube. The upper layer of media is then removed and the healthy sperm are then inseminated into the woman's uterus.

The Percoll technique differs from the swim-up procedure in several key aspects. After washing the semen, the sperm suspension is placed on top of several (2-3) layers of Percoll solution. The Percoll acts like tiny beads, and during centrifugation, the healthy sperm negotiate their way through the beads while dead sperm and debris gets caught in the Percoll suspension. The healthy sperm are then removed from the bottom of the conical tubes, and are inseminated into the woman's uterus. Although some believe that Percoll is the superior technique for "dirty" semen specimens (ie. those contaminated by white blood cells, debris, or other cells), no study has yet clearly demonstrated superiority of one technique over the other. Most andrology laboratories are capable of performing both methodologies.

What is the purpose of "washing" the sperm prior to insemination?

As noted above, semen contains many substances beside sperm. "Sperm washing" allows the laboratory to remove many of these substances prior to the physician inseminating the specimen into the woman's uterus. Studies have shown that if sperm are left in semen too long, that their motility and function deteriorate. By removing the healthy sperm from semen, they are not affected by the metabolic waste products of the dead or abnormal sperm.

Washing also serves another important role, ie. the initiation of the capacitation process. When sperm are ejaculated, they are not yet ready to fertilize an egg. They have to undergo two processes - capacitation and the

acrosome reaction - before they are physiologically prepared to fertilize the egg. Capacitation is a process involving the movement of chemical compounds within the surface membrane of the sperm. It is followed by the acrosome reaction, which is a process during which the inner and outer membranes of the sperm fuse, releasing enzymes which "chew" through the outer membranes of the egg. Specific egg receptors on the sperm's membrane may also be exposed during capacitation and the acrosome reaction. Ordinarily, capacitation and the acrosome reaction occur following intercourse, as the sperm pass from the vagina through the cervix and uterus, and into the fallopian tubes. Sperm washing initiates the capacitation process, so that a greater percentage of inseminated sperm will be ready to fertilize the egg shortly after insemination.

What is the best way to time insemination?

This is a very controversial issue, as there is no definitive answer. In a natural cycle, several methods have been proposed. These include timing in relation to the basal body temperature (BBT) nadir, an LH surge as detected by a urine ovulation prediction kit, follicular size as determined by transvaginal ultrasound, or following an hCG injection. If one assumes that timing is important, ie. that it is best to perform the insemination around the actual time of ovulation, then LH detection kits appear to be superior to BBT charts. Several studies have demonstrated that 80-90% of women ovulate within 24 hours of an LH surge. The time of ovulation in relation to the BBT nadir appears to be much more variable.

Although ultrasound affords us significantly more information, it too is not perfect due to the relatively large range of follicular size associated with ovulation. From ultrasound studies, it appears that the window of ovulation in a natural cycle for most women appears to be a follicular size of 17-25 mm. (6) It would, therefore, be inappropriate to inseminate all women when their largest follicle reached a mean diameter of 18 or even 21 mm. This would be too early for some, and possibly too late for others. Although hCG administration might help alleviate this problem - as we know that most women ovulate between 36-40 hours following an hCG injection, when should the injection be given? Should it be given at 18mm, 20mm, 22mm...?

For all of the above reasons, most physicians time insemination based on the LH surge. Their reasoning is that the LH surge is a physiologic phenomenon, ie. it is triggered when the developing oocyte signals the brain that it is ready to ovulate. Therefore, using the LH surge allows each woman to ovulate at the follicular size appropriate for her. Although this serves as a good general rule, there are certainly exceptions - for example women who develop follicles but do not ovulate without hCG.

Are two inseminations better than one?

This is a question that has interested me for a long time. In natural cycles, with insemination timed by LH detection kits, the data do not suggest a clear

answer. At the University of Texas Health Science Center at San Antonio, we developed a study protocol looking at three different treatment groups for normally ovulatory women with normal fallopian tubes, undergoing insemination with frozen donor sperm. Group A patients received a single insemination on the day of their LH surge. Group B patients received a single insemination on the day after the surge, and Group C patients received one insemination on the day of the surge, and one on the day after the surge. Although this study is still ongoing, the data have been analyzed at several different time points, and there do not appear to be any differences in pregnancy rates between the 3 groups. It may be that these findings do not apply to fresh sperm, however, if anything, one would assume that insemination timing for frozen sperm would be more critical than that for fresh due to frozen sperms' shorter survival time and lessened motility.

In gonadotropin cycles, we published a prospective, randomized study comparing a single insemination performed 34 hours after hCG administration (Group 1) to inseminations performed 18 and 42 hours after hCG administration (Group 2). (7) The inseminations were scheduled for Group 2 patients such that the first insemination would be performed prior to ovulation and the second following ovulation. In this study, we reported a clinical pregnancy rate of 8.7% per cycle for the single insemination group compared to 52.2% for the double insemination group. Since that study, we have changed to double inseminations for all of our Pergonal and Metrodin patients, and the pregnancy rate has stabilized at 30-35% per cycle for the past several years.

Summary

In summary, IUI is a very effective therapeutic modality. It is indicated in the treatment of a variety of infertility disorders. Prior to proceeding with IUI, the patient should undergo an HSG in order to ensure tubal patency. Therapy with IUI should be continued for approximately 6 cycles before moving on to another form of therapy. Insemination should be timed either in relation to the LH surge (in a natural cycle), or in relation to the time of the hCG injection (in a gonadotropin-stimulated cycle). Although inseminations on two consecutive days appears to markedly improve the pregnancy rate in gonadotropin-stimulated cycles, there are no definitive data regarding 1 vs. 2 inseminations in natural cycles.

Bibliography

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