INTRODUCTION

Artificial insemination is an assisted conception method that can be used to alleviate infertility in selected couples. The rationale behind the use of artificial insemination is to increase the gamete density near the site of fertilization. The effectiveness of artificial insemination has been clearly established in specific subsets of infertile patients such as those with idiopathic infertility, infertility related to a cervical factor, or a mild male factor infertility (Table 36-1). An accepted advantage of artificial insemination is that it is generally less expensive and invasive than other assisted reproductive technology (ART) procedures.

This chapter provides a comprehensive description of indications for artificial insemination, issues to consider before donor insemination, complications associated with intrauterine insemination (IUI), factors affecting the success of artificial insemination, and the current evidence available on effectiveness of artificial insemination for different indications.

HISTORY

Artificial insemination has been used in clinical medicine for more than 200 years for the treatment of infertile couples. In 1785 John Hunter, a Scottish surgeon from London, advised a man with hypospadias to collect his semen and have his wife inject it into her vagina. This was the first documented case of successful artificial insemination in a human.

In the second half of the nineteenth century, numerous reports were published of human artificial insemination in France, England, Germany, and the United States. In 1909, the first account of successful donor artificial insemination was published in the United States. By 1949, improved methods of freezing and thawing sperm were being reported.

Today, artificial insemination is frequently used in the treatment of couples with various causes of infertility, including ovulatory dysfunction, cervical factor infertility, and unexplained infertility as well as those with infertility caused by endometriosis, male, and immunologic factors. Artificial insemination with donor semen has become a well-accepted method of conception.

GENERAL CONSIDERATIONS

Semen Sources

The source of semen for artificial insemination can be either from the woman’s male partner or from a donor, who usually remains anonymous. When donor insemination first became widely available, the terms homologous artificial insemination and heterologous artificial insemination were used to differentiate these two alternative sources. However, the use of these biomedical terms in this manner is at variance with their scientific meaning, where they denote different species or organisms (as in, e.g., homologous and heterologous tissue grafts).

In the latter half of the 20th century, the terms artificial insemination, donor (AID) and artificial insemination, husband (AIH) found common use. However, the widespread use of the acronym AIDS for acquired immunodeficiency syndrome resulted in the replacement of AID with therapeutic donor insemination (TDI). An analogous alternative term for AIH has not evolved, probably in part because of the increasingly common situation where the woman’s partner is not her legal husband. In this chapter, artificial insemination using these two standard sperm sources will be designated simply as partner and donor insemination.

Techniques

Several different techniques have been used for artificial insemination. The original technique used for over a century was intravaginal insemination, where an unprocessed semen sample is placed high in the vagina.

In the latter half of the 20th century, the cervical cap was developed to maintain the highest concentration of semen at the external os of the cervix. It was soon discovered that placing the semen sample into the endocervix (intracervical insemination) resulted in pregnancy rates similar to that obtainable using a cervical cap and superior to those seen with high vaginal insemination.

Intrauterine Versus Intracervical Insemination

A major breakthrough came in the 1960s when methods were developed for extracting enriched samples of motile sperm from semen. These purified samples were free of proteins and prostaglandins, and thus could be placed within the uterus using a technique designated intravaginal insemination (IUI).
Male subfertility is significantly increased when the antisperm antibody level is greater than 50%. Antisperm antibodies interfere with sperm–zona pellucida binding and prevent embryo cleavage and early development.

**Complete Evaluation**

In the presence of persistently abnormal results on semen analysis, a complete history, physical examination, and laboratory evaluation is performed to find and treat any potentially reversible abnormalities (see Chapter 35).

**Female Evaluation**

The female partner should undergo a basic infertility evaluation so that any correctable factors can be identified and treated before artificial insemination (see Chapter 34). In addition to a detailed history and physical examination, each woman considering partner or donor insemination should be evaluated with an imaging technique, usually a hysterosalpingogram, to document patent tubes. Unless oral or injectable medications are used to induce superovulation, ovulatory function should be evaluated with a urinary luteinizing hormone (LH) detection kit and mid-luteal serum progesterone level. Further evaluation is required in the event of detection of any clinical or laboratory abnormalities.

In the past, a great deal of time was spent investigating the possibility of cervical factor infertility by evaluating the character and sperm survivability in periovulatory cervical mucus, using what is termed a postcoital test. This test had many false-positive results, because it depended more on timing in the cycle and hormonal status than on static cervical characteristics. Except for exclusion of cervicitis during pelvic examination, timed evaluation of cervical mucus and sperm interaction is infrequently included in a fertility examination. This is because partner IUI is used as a basic fertility enhancement method for the majority of couples who have otherwise been unable to conceive regardless of diagnosis.

**INDICATIONS**

**Partner Insemination**

Partner insemination was originally developed as a treatment for male factor infertility. With the advent of IUI, partner insemination has been found to be an excellent treatment for a range of diagnoses, including cervical factor infertility, unexplained infertility, and subfertility, on the basis of other diagnoses or therapeutic measures (Table 36-2). This ability of partner insemination to increase pregnancy rates regardless of diagnosis has made this technique one of the fundamental approaches to infertility treatment today.

**Male Factor Infertility**

Partner insemination appears to be of clear benefit when the couple’s infertility is the result of any condition that makes it difficult to place semen high in the vagina during coitus. Male conditions resulting in this situation are termed ejaculatory failure. The most common causes of ejaculatory failure are impotence, severe hypospadias, and retrograde ejaculation. A unique condition that has been found to be treatable with artificial insemination is impotence secondary to spinal cord injury.
Partner insemination is also commonly used as a treatment for male factor infertility documented by repeated abnormal results on semen analysis. In couples where there is mild male factor infertility, defined as a progressive sperm motility of at least 20% to 30%, the prognosis appears to be good with partner insemination. Theoretically, increasing the number of motile sperm reaching the egg should improve fertility whenever decreased numbers and motility of normally functioning sperm is the primary problem.

Unfortunately, the pregnancy rates after partner IUI for the treatment of severe male factor infertility have been disappointing. This is probably because markedly abnormal parameters on routine semen analysis often reflect a sperm defect that decreases the ability to fertilize eggs. This type of defect is unlikely to be overcome by increasing the number of sperm to which the egg is exposed at the site of fertilization. In patients with severely abnormal parameters on semen analysis and those with male factor infertility not amenable to partner insemination, more effective treatment will be either donor insemination or in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI).

**Female Factor Infertility**

Female reproductive conditions can also make it difficult to place semen high in the vagina during coitus. Such conditions that can benefit from partner insemination include severe vaginismus and other psychological problems, and less common anatomic conditions. Little data exists documenting the success of partner insemination for these conditions.

Women with cervical factor infertility will benefit from IUI, because this approach bypasses the cervical abnormalities that decrease fertility. This includes women with abnormal cervical mucus secondary to noninfectious chronic cervicitis and women with scant mucus or cervical stenosis, usually the result of cervical surgery. However, even women with a normal cervix and mucus appear to benefit from IUI, because the cervix appears to be the limiting factor in sperm reaching the site of fertilization in the tube.

**An Adjunct to Other Infertility Treatments**

Partner IUI appears to be of value for increasing per cycle fecundity when inducing ovulation in women with ovulatory dysfunction. After ovulation induction with clomiphene citrate, partner IUI might work by overcoming the decreased cervical mucus associated with the use of clomiphene. With gonadotropins, partner IUI might compensate for subtle changes in sperm transport within the uterus or tubes related to marked alterations in circulating estrogen and progesterone levels associated with their use.

Partner IUI also appears to be of some benefit when women with mild and minimal endometriosis are trying to achieve pregnancy. After appropriate surgical treatment, the monthly improvement in fecundity with partner IUI appears to be similar to that seen in patients with idiopathic infertility.

Women with severe endometriosis or tubal disease have a far lower fecundity rate and often an increased rate of ectopic pregnancies. For this reason, these patients appear to benefit more from IVF than from partner IUI combined with superovulation.

**Unexplained Infertility**

Unexplained (i.e., idiopathic) infertility is diagnosed after all known etiologies of infertility have been excluded. In these cases, semen analyses are normal and there is no evidence of any female causes of infertility, such as ovulation defects, tubal factor, endometriosis, and cervical factor. The average incidence of unexplained infertility is approximately 15% among infertile couples.

In couples with unexplained infertility, partner IUI has been demonstrated to improve pregnancy rates when used in conjunction with superovulation. In a meta-analysis of almost 1000 superovulation cycles for unexplained infertility, partner IUI was found to almost double pregnancy rates (20%) compared to timed intercourse alone (11%).

Partner IUI appears to overcome one or more unknown fertility deficiencies that we cannot currently detect. Theoretically, this might be decreased sperm transport from the vagina to the tube secondary to either a sperm defect or an abnormality in sperm transport mechanisms in the female reproductive tract. In other cases, a subtle sperm fertilization defect might exist that is surmounted by increasing the absolute number of sperm reaching the egg.

**Donor Insemination**

In the past, the only available options for couples with severe male factor infertility (e.g., severe oligospermia, or failure to conceive using partner insemination) desiring children were either donor insemination or adoption. Since the widespread availability of IVF using ICSI, many couples with severe male factor infertility have chosen to procreate their own genetic children using these techniques. However, donor insemination remains an option when IVF/ICSI has been unsuccessful. Alternatively, many candidates for IVF/ICSI initially choose donor insemination because it is less invasive and ultimately more likely to achieve pregnancy for couples with limited resources.

Some women choose donor insemination because they are not candidates for IVF/ICSI. Perhaps the most obvious situation is a couple without male partners who seek pregnancy. The use of donor insemination is also indicated when the male partner...
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Infertility and Recurrent Pregnancy Loss

has no viable sperm (i.e., azoospermia) or when IVF/ICSI fails to achieve fertilization. Finally, men with a known genetic disorder often choose donor insemination to avoid transmission to their children.

**Donor Selection**

Couples choose a donor from profiles of nonidentifiable information. This information usually includes racial or ethnic background, blood type, physical characteristics, and certain social characteristics. Many women who become pregnant as a result of donor insemination desire to use the same donor for further pregnancies.

**Donor Evaluation**

Thorough evaluation of all potential sperm donors (other than sexually intimate partners) is necessary to avoid inadvertent transmission of sexually transmitted diseases or known genetic syndromes.\(^1\) All donors undergo a review of relevant medical records, personal and family history, and a physical examination. Determination of normal semen characteristics is extremely important. In addition, blood grouping and karyotyping is performed.

Each donor must be screened for risk factors and clinical evidence of communicable diseases, including:

- human immunodeficiency virus types 1 and 2
- human T-lymphotropic virus types I and II
- hepatitis B and C
- cytomegalovirus
- human transmissible spongiform encephalopathy (including Creutzfeldt-Jakob disease)
- Treponema pallidum
- Chlamydia trachomatis
- Neisseria gonorrhoeae

If the donor is deemed acceptable and is aware of the ethical and legal implications, semen can be collected. All donor semen samples are cryopreserved and quarantined for 6 months. Before a donor sample is used for insemination, the donor is retested and determined if eligible.

**Success Rate**

The actual per cycle fecundity rate with donor IUI is dependent on multiple factors. A meta-analysis of seven studies demonstrated that IUI yielded a higher pregnancy rate per cycle than intracervical insemination with donor frozen sperm.\(^1\) Overall, the average live birth rate per cycle of donor IUI is approximately 10%.\(^1\)

**IUI TIMING, COST, AND FREQUENCY**

**Timing**

Timing of insemination in relationship to ovulation is one of the crucial factors in the success of IUI. Although viable sperm remain in the female reproductive tract for up to 120 hours after coitus, the best pregnancy rates are obtained when IUI is performed as close as possible to ovulation.\(^1\)

In the past, IUI was performed on the estimated day of ovulation based on basal body temperature rises during previous cycles. However, to optimize fecundity, modern prospective timing strategies are based on either detection of a urinary LH surge or administration of an ultrasound-timed dose of human chorionic gonadotropin (hCG) to trigger ovulation.

**LH Surge**

A commonly used method for timing of IUI is based on urinary LH measurement. Ovulation occurs 40 to 45 hours after the onset of the LH surge.\(^2\) Insemination is thus planned for the day after detection of a rise in urinary LH. This approach offers the simplest and most cost-effective of the indirect methods for predicting ovulation and is just as effective in achieving pregnancy as more complex ones.\(^2\)

**Ultrasound and Human Chorionic Gonadotropin**

Transvaginal ultrasonography is widely used to monitor the size of the follicles and to assess the timing of ovulation. Follicles become recognizable once they grow to 2 to 3 mm in diameter. After 8 mm, linear follicular growth occurs at a rate of approximately 2 to 3 mm per day. Ovulation occurs during a natural cycle when the lead follicle reaches 15 to 24 mm in size.

Injection of hCG can be given to induce predictable ovulation when at least one follicle diameter is between 17 and 21 mm. For optimal pregnancy rates, IUI is scheduled 24 to 36 hours after the injection.

**IUI Cost**

The cost-effectiveness of the treatment is an important consideration when deciding on the most appropriate infertility treatment option.\(^3\) The cost of insemination varies from clinic to clinic, but is presently less than $500 per IUI, including sperm preparation and injection of the prepared sample. This compares favorably with the cost of other appropriate ART approaches. Even when the cost of ovulation induction medication and monitoring are included, the cost per live birth for IUI after superovulation has been calculated to be less than half the cost of IVF treatment.\(^4\)

**IUI Frequency**

It is recommended that IUI be performed either one or two times during each cycle. Performing two inseminations per cycle is likely to be especially advantageous when timing in relationship to ovulation is less precise. Although it seems intuitive that fecundity should be increased by two inseminations per cycle, it remains inconclusive whether the increased fecundity is worth doubling the patients’ cost and inconvenience compared to one insemination per cycle.\(^5\) A recent meta-analysis of more than 1000 IUI cycles revealed a slightly higher but statistically insignificant difference between the per cycle fecundity rate for two inseminations (14.9%) compared to one insemination per cycle (11.4%).\(^6\) Accordingly, one well-timed insemination appears to offer the best balance between efficacy and cost.

**SPERM PREPARATION FOR IUI**

Sperm preparation methods are used to process semen samples such that viable sperm are separated from seminal plasma. This is necessary before IUI to avoid the consequences of intrauterine injecting of semen plasma proteins and prostaglandins.\(^7\) Although seminal plasma protects the spermatozoa from stressful...
Table 36-3
Common Techniques Used for Sperm Preparation Prior to Intrauterine Insemination

<table>
<thead>
<tr>
<th>Technique</th>
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<tbody>
<tr>
<td>Washing</td>
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<tr>
<td>Swim-up techniques</td>
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<tr>
<td>Swim-up from pellet</td>
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<tr>
<td>Swim-up from ejaculate</td>
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<tr>
<td>Swim-up from ejaculate into hyaluronic acid</td>
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<tr>
<td>Density gradient centrifugation</td>
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<tr>
<td>Glass wool filtration</td>
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<tr>
<td>Mechanical aids</td>
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conditions such as oxidative stress, it also contains factors that inhibit the fertilizing ability of the spermatozoa and reduce the induction of capacitation. Sperm preparation involves removing the seminal plasma efficiently and quickly and eliminating dead sperm, leukocytes, immature germ cells, epithelial cells, and microbial contamination. Several methods for sperm preparation are currently used (Table 36-3).

The ideal sperm preparation method recovers highly functional spermatozoa and enhances sperm quality and function without inducing damage. It is also cost-effective and allows for the processing of a large volume of the ejaculate, which in turn maximizes the number of spermatozoa that are available. The ideal sperm preparation method minimizes the risk of reactive oxygen species generation, which can adversely affect DNA integrity and sperm function in vitro. Several preparation methods incorporate methylxanthines and pentoxifyllines to increase sperm motility and improve the fertilization outcome.

The first step in sperm preparation is the performance of a semen analysis according to the World Health Organization (WHO) standards to determine the prewash quality of the sample. Throughout the semen analysis and preparation, it is important to use sterile technique and media both to minimize the risk of iatrogenic intrauterine infection and because sperm can be damaged by bacterial contamination.

Swim-up Techniques

Swim-up techniques are based on active self-migration of motile spermatozoa into the washing medium. Allowing sperm to swim up from ejaculate avoids the need for centrifugation, which can lead to oxidative damage of the sperm. However, this technique can be used only for ejaculate with a high degree of progressive motile spermatozoa, because the percentage of motile sperm recovered depends on sperm motility.

For the swim-up technique, a layer of wash media is gently layered over the semen sample. The sample is incubated so that the motile sperm can swim out of the semen sample into the media. The media is then carefully removed from the semen fluid and used for IUI. If the initial semen sample has normal sperm parameters, recovery of reasonable number of sperm with at least 90% motility is common. The entire procedure takes 2 hours.

Basic Sperm Washing

Sperm washing, the oldest and perhaps the simplest technique, removes the seminal fluid with little enrichment of motile sperm. The semen sample is diluted in a sperm wash media containing antibiotics and protein supplements in a conical centrifuge tube. The specimen is centrifuged such that all cells congregate in a pellet, and the supernatant wash solution is carefully removed. The pellet is resuspended in wash media, and the centrifugation is repeated. The final pellet, from which all seminal fluid has been eliminated, is resuspended in a small volume of wash media for IUI. The entire procedure takes less than an hour.

Density Gradient Centrifugation

The density gradient method is a sperm washing method that both removes semen fluid and separates living sperm from other material, including dead sperm cells, white blood cells, and bacteria. For this method, a density gradient is prepared by layering suspensions of different concentrations of coated colloidal silica particles (e.g., Percoll) in a conical centrifuge tube, with the higher concentrations more superior. The liquefied semen sample is placed over the upper layer and the tube is centrifuged. The supernatant is removed from the pellet, and the process is repeated. The final pellet is resuspended in wash media and used for IUI. Density gradient sperm washes take approximately 1 hour.

Glass Wool Filtration

The glass wool filtration method is another method for removing seminal fluid and separating living sperm from other cellular material after sperm has been washed. For this technique, the semen samples are first diluted with wash media and centrifuged in a manner similar to sperm washing. The resulting pellet is resuspended in wash media and placed on glass wool columns, created by inserting glass wool into the barrel of a 3-mL syringe. The washed sperm solution is allowed to filter through the column by gravity, and the filtrate is collected for IUI.

Which Preparation Method is the Best?

Presently, there is no general consensus as to the best sperm preparation technique for IUI. In general, swim-up, simple sperm washing, density gradient centrifugation, and glass wool filtration methods all effectively produce adequate sperm samples. However, some preparation techniques appear better suited for particular types of samples; thus, the technique chosen should be tailored to individual samples.

The preparation techniques most commonly used today are the double density gradient centrifugation and the glass wool filtration sperm washing techniques. These techniques have been shown to improve the number of morphologic normal spermatozoa with grade A motility and with normal chromatin condensation in the prepared sample. In addition, these techniques best reduce the amount of reactive oxygen species and leukocytes in the prepared sample and provide spermatozoa with minimal chromat and nuclear DNA anomalies and high nuclear maturity rates.

For semen samples with normal or near-normal sperm parameters, one study has shown that swim-up and density gradient techniques result in higher pregnancy rates compared to the washing, swim-down, and refrigeration/heparin techniques. For poor samples, the density gradient centrifugation and glass wool filtration techniques appear to be superior. In cases of very low sperm counts, simple sperm washing will recover the highest number of sperm, both motile and nonmotile.
IUI TECHNIQUE

IUI is performed using one of several commercially available intrauterine insemination catheters connected to a 2-mL syringe (Fig. 36-1). With the fully awake patient in a dorsal lithotomy position, the cervix is visualized with a bivalve vaginal speculum. After excess vaginal secretions are wiped from the external cervical os, the tip of a thin flexible catheter is passed into the uterine cavity, and the sperm sample, suspended in less than 1 mL of wash media, is gently expelled high in the uterine cavity. Increased resistance during injection suggests that the catheter is kinked or the tip might be inadvertently lodged in the endometrium or tubal ostia. In this situation, the catheter should be withdrawn 1 cm, and injection reattempted. After IUI, the catheter is slowly removed and the patient allowed to remain supine for 10 minutes after insemination in case she experiences a vasovagal reaction.

Occasionally, there is difficulty navigating the often tortuous course of the endocervical canal with the tip of the insemination catheter. There are two common approaches to this blind procedure. Most commonly, a thin catheter (external diameter less than 2 mm) with a “memory” is used so that the tip can be bent 20 to 90 degrees thus allowing angular navigation in any direction by carefully twisting the catheter as it is gently advanced. Resistance in any direction requires that the catheter tip be withdrawn a matter of millimeters, twisted such that the curved tip is directed in a new course and re-advanced. This procedure is continued until the catheter can be advanced without resistance approximately 5 to 6 cm into the uterine cavity. Rarely, a cervical tenaculum is required to apply downward traction on the cervix to “straighten” an exceptionally tortuous canal.

A second method for navigation of the endocervical canal for IUI is by using a semirigid yet flexible catheter that has no memory. Pressure is used to force the catheter to follow the course of the canal. This technique often requires the use of a cervical tenaculum to apply countertraction. Because the diameter of some of these types of catheters is usually larger in caliber (greater than 3 mm), dilatation is sometimes required in the presence of cervical stenosis.

FACTORS THAT PREDICT PREGNANCY RATES

The highest pregnancy rates with IUI are seen within three to four cycles. The average live birth rate per cycle is approximately 10%. Cumulative pregnancy rates depend on the characteristics of the couples being treated. In most reports, the cumulative pregnancy rate reaches plateau after three to six cycles.

It is difficult to predict with certainty whether pregnancy will occur. Several models have been proposed but have not been validated.

Male Factors That Predict IUI Success

Men who have normal seminal characteristics have a higher chance of initiating a successful pregnancy as a result of IUI than those with abnormal results on semen analysis. This association is probably related to two associated factors. First, an abnormal semen analysis is often associated with an impaired fertilization capacity. Secondly, pregnancy rates positively correlate with the total number of motile sperm recovered for IUI, and this number is often lower in men with abnormal results on semen analysis.

Semen Analysis Characteristics

Semen characteristics clearly affect IUI outcome. IUI is a successful treatment for mild male factor infertility, defined as a total motile sperm count of more than 5 million and Kruger morphology of more than 5%. In a study in patients with mild male factor infertility, a live birth rate of 19% per cycle was reported.

When prepreparation semen analyses characteristics are evaluated, the chances of pregnancy after IUI correlate best with morphology. A meta-analysis of six studies using strict morphology criteria (Kruger) showed that when the prewashed semen specimen had more than 4% normal sperm morphology, the chances of pregnancy after IUI were significantly increased.

If the WHO standards were used to evaluate sperm morphology, the presence of more than 30% abnormal sperm in the ejaculate adversely influenced the pregnancy rate.

Total Motile Sperm Count

The sperm variable most clearly associated with pregnancy rates after IUI is the total motile sperm count after sperm wash or swim-up. In a retrospective study of 9963 IUI cycles, the likelihood of subsequent pregnancy was maximized when the IUI sample contained more than 4 million motile sperm numbers...
and sperm motility was greater than 60%. Total motile sperm count was reported to affect IUI outcome in 1115 cycles in 332 infertile couples. No pregnancy occurred in cases where the total motile sperm count before semen preparation was less than $1 \times 10^6$.

**Sperm DNA Damage Tests**

Efforts have been made to find objective assessments of sperm quality that will predict pregnancy outcomes in men with abnormal results on semen analysis. Three experimental assessments are the sperm chromatin structure assay, DNA fragmentation index, and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-nick end labeling (TUNEL).

The sperm chromatin structure assay provides an objective assessment of sperm chromatin integrity and can be useful as a fertility marker. In a recent study, DNA damage as measured using this test was found to predict the outcome of IUI.

The DNA fragmentation index (DFI) has been shown to be negatively correlated with the overall pregnancy rate in women undergoing IUI, IVF, or ICSI. The chances of achieving pregnancy are significantly lower when the sperm DFI is greater than 27% after IUI processing.

TUNEL evaluates the degree of sperm DNA fragmentation and stability. In one study, lower degrees of DNA fragmentation after IUI sperm preparation correlated with higher pregnancy rates, and no pregnancy occurred when more than 12% of sperm in an IUI specimen were TUNEL-positive.

**Hypo-osmotic Swelling Test**

The hypo-osmotic swelling test evaluates the membrane integrity of the sperm tail, detects the differences on the sperm surface, and detects subtle damage in membrane properties, which reduces the ability of spermatozoa to induce a viable embryo. A sample "passes" the hypo-osmotic swelling test when at least 50% of sperm in an IUI sample swell. Sperm specimens that fail the hypo-osmotic swelling test appear to have decreased fertilizing ability, and thus pregnancy rates after IUI are lower. The miscarriage rate was also higher when result of hypo-osmotic swelling test was less than 50%.

**Antisperm Antibodies**

Both IUI and IVF appear to be effective in treating subfertility in men with antisperm antibodies, although IVF/ICSI appears to have higher pregnancy rates per cycle than IUI. However, to date no large prospective, randomized, controlled trial has compared IUI to IVF/ICSI in men with antisperm antibodies. In severe cases of antisperm antibodies, especially when the sperm head is involved, IVF/ICSI will often be required to achieve pregnancy.

**Female Factors That Predict IUI Success**

Many studies have examined the different variables affecting pregnancy rates after IUI. The influence of lifestyle habits (e.g., smoking, caffeine consumption, and weight) is unclear but is most probably significant. There appear to be several important female factors that are useful in predicting pregnancy rates after IUI. These factors are maternal age, duration of infertility, and female infertility factors.

**Maternal Age**

A woman's age is an indirect indicator for oocyte quality, and it has a significant effect on the pregnancy rates. An age-related decline in female fecundity has been documented in women undergoing IUI. Successful pregnancy rates decrease after age 35 and reduce dramatically after age 40. However, pregnancies can occur at relatively advanced maternal ages, and satisfactory pregnancy rates can be obtained with IUI among women age 40 to 42.

**Duration of Infertility**

The longer the duration of infertility, the lower the pregnancy rates are after IUI. Although the precise limits of infertility duration for recommending IUI have not been clearly established, the pregnancy rate may be seriously compromised when infertility has lasted 3 or more years.

**Female Fertility Factors**

The success of artificial insemination depends not only on the quality of the oocytes and spermatozoa, but also on the receptivity of the endometrium. In a retrospective study, the presence of uterine anomalies negatively affected the success of IUI.

Endometrial thickness and pattern is also predictive of IUI success. In a study on women undergoing controlled ovarian hyperstimulation and IUI, a trilaminar endometrium on the day of IUI provided a favorable prediction of pregnancy. However, endometrial thickness and Doppler surveys of the spiral and uterine arteries and dominant follicle gave no useful predictive value. A study evaluated the role of endometrial volume measurement in predicting the pregnancy rate in women receiving controlled ovarian hyperstimulation and IUI. An endometrial volume of less than 2 mL on three-dimensional ultrasound on the day of insemination was associated with a poor likelihood of pregnancy.

Pregnancy rates after IUI are dependent on ovum pickup and transport. It follows that pregnancy rates after IUI are decreased by other causes of female infertility, including tubal factor and endometriosis.

**RISKS AND COMPLICATIONS**

Complications associated with IUI are extremely uncommon. Most of the complications that occur are related to the medications used to recruit multiple follicles before IUI.

**Pelvic Infections**

Limited cramping during or after an IUI procedure from the catheter or cervical tenaculum is common. These symptoms are self-limiting and should resolve within hours of the procedure. Continued discomfort can be an indication of a developing pelvic infection, which has been estimated to occur in less than 2 per 1000 IUI procedures. Early diagnosis and treatment are essential in these rare cases to minimize the risk to the patient, particularly that of subsequent decreased fertility.

**Vasovagal Reaction**

Vasovagal reactions can occur as a result of manipulation of the cervix. The resulting vasodilation and decreased heart rate can lead to hypotension, most commonly manifest by diaphoresis in
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a supine patient. Sitting or standing increases the risk of syncope, which is unlikely to occur supine. Persistent symptomatic vaso-vagal reactions in a supine patient will often respond to the patient crossing her legs. More severe cases might require treatment with intramuscular atropine injection (0.5 mg).

**Allergic Reaction**

Allergic reactions, including anaphylaxis, can occur after IUI in response to potential allergens in the wash media. Reactions have been reported to both the bovine serum albumin and antibiotics (penicillin and streptomycin) commonly used in the wash media. Of these, penicillin allergies are the most common in the general population. Allergic reactions after IUI can range from a mild skin rash to life-threatening anaphylaxis with laryngeal edema, bronchospasm, and hypotension. For the rare patient experiencing an allergic reaction after IUI, the use of wash media free of albumin and antibiotics is advised.

**Antisperm Antibodies**

When IUI was first introduced, there was a concern that the procedure could result in the development of serum antisperm antibodies. Fortunately, after 40 years of experience, it appears that exposure of the upper reproductive tract to washed spermatozoa during IUI does not stimulate the appearance of clinically significant female antisperm antibodies.

**Pregnancy-Related Complications**

**Multiple Pregnancies**

The risk of multiple pregnancies is not increased by IUI. However, medications used to recruit multiple follicles before IUI do increase this risk. Clomiphene citrate is associated with a twin risk of 5% to 10% and rare higher-order multiples. Injectable gonadotropins are associated with multiple pregnancy rates of 14% to 39%. Careful monitoring of the number of periovulatory follicles and peak estradiol levels might decrease the rate of multiple pregnancies. In general, women are at high risk if they are younger than age 30, have more than six preovulatory follicles, and a peak serum estradiol level greater than 1000 pg/mL.

**Spontaneous Abortion and Ectopic Pregnancy**

The risk of spontaneous abortion appears to be increased after IUI compared to the fertile population and is in the range of 20% to 25%. The increased risk is probably not directly attributed to IUI but is most likely due to the underlying infertility problem. Likewise, ectopic pregnancy rates depend largely on the presence of predisposing factors such as tubal disease and do not appear to be attributed to the IUI procedure.

**PSYCHOLOGICAL, ETHICAL, AND LEGAL ISSUES OF DONOR INSEMINATION**

**Parents**

Donor insemination has more psychological implications than partner insemination. Before donor insemination, several issues should be discussed in detail, including the couple’s desire or need to start a family, the alternatives that the male partner has to procreate his own genetic children, and financial factors.

It is recommended that the couple undergo counseling before the procedure so that they can both face their feelings concerning infertility, donor insemination, and other concerns. The male partner may experience a loss of self-esteem and fear losing his partner because of infertility. Both partners may feel guilty or angry toward each other for having an infertility problem. Infertility tends to separate the couple, especially when one side is uncooperative. Support groups or professional counseling can be helpful.

**Offspring**

There are expert opinions both for and against disclosing to the child that he or she is the product of donor insemination. Before undergoing donor IUI, the couple should decide if they plan to disclose the nature of the procedure and the biologic implications to their friends, relatives and, ultimately, their child. If knowledge of the procedure is shared with friends and relatives, there is always the risk that the truth will be disclosed to the child by someone other than the parents. These sometimes-underappreciated issues can cause unnecessary grief if not adequately addressed prior to therapy.

**Legal Issues**

It is imperative that both partners understand the legal issues concerning donor insemination. Before donor insemination, both partners should sign an informed consent that clearly states the rights and obligations of the parties involved and those of the child. Although laws vary from state to state, when sperm is obtained from a sperm bank, the donor universally has no legal access to the couple’s identity. In cases where couples elect to use a donor known to them, an attorney should be obtained to draft the appropriate papers to terminate any parental rights of the donor and give the couple full custody of any subsequent child. In some states, the child conceived from donor sperm may have the right to obtain identifying information about the donor once they reach adulthood.

**PEARLS**

- Artificial insemination is a useful and cost-effective treatment option in selected groups of infertile couples.
- Infertility due to cervical factor and mild male factor (without any associated female factor) can be treated with intrauterine insemination without ovarian stimulation.
- Artificial insemination appears to be more cost-effective and simple compared to the IVF/ICSI if the couples are selected appropriately.
- In spite of extensive research, we are still not able to predict the success of artificial insemination in a specific couple.
- Duration of the infertility negatively impacts the artificial insemination success.
- Couples with unexplained infertility have better success with artificial insemination than natural intercourse.
- Couples with unexplained infertility should use controlled ovarian hyperstimulation along with the artificial insemination.
REFERENCES

Infertility and Recurrent Pregnancy Loss


