In fertility and recurrent pregnancy loss

Chapter 36

Artificial Insemination

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 causal 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 intratruine 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 hypoplasia 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, infertility, and immunologic factors. Artificial insemination with donor semen has become a well-accepted method of conception.

GENERAL CONSIDERATIONS

Semnen 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 AID 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 of obtainable using a cervical cap and superior to those seen with high vaginal insemination.

Intratruine 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 intratruine insemination (IUI). This...
Male subfertility is significantly increased when the antisperm antibodies are present in large titers. Antisperm antibodies interfere with sperm–gonadotropin 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 injectable or oral 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 perivulvar cervical mucus, using what is termed a postcoital test. This test had many false-positive results because of the variable 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 is only 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 procedure appears to be good with partner insemination. Theoretically, increasing the number of 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 marked abnormal parameters on routine semen analysis often reflect a sperm defect that decreases the ability to fertilize eggs. This type of defect is usually born to overcome by increasing the number of sperm to the egg which is exposed at the site of fertilization. In patients with severely abnormal parameters on semen analysis and those undergoing assisted hysterosalpingogram with the use of 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 exist 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. However, even women with normal cervical secretion and a correctable cervix appears to be the limiting factor in sperm reaching from the site of fertilization in the tube.

Donor Insemination
In the past, the only available options for couples with severe male factor infertility (e.g., 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 using ICSI is unsuccessful. Alternatively, many candidates for IVF/ICSI initially choose donor insemination because they are uncertain whether they might be able to conceive in the future. In other cases, a subfertility defect might exist that is manifested by increasing the absolute number of sperm reaching the egg.
In an effort to further improve pregnancy rates, techniques were developed to place washed sperm samples directly into the tubes via intratubal insemination (intratubal insemination) or into the peritubal cavity via a needle placed through the posterior cul-de-sac (intraperitoneal insemination). Another technique developed to increase pregnancy rates is retrograde ejaculation. This technique involves pressure injection of a large volume (4 mL) of washed sperm sample while the cervix is sealed to prevent reflux of the sample. This technique is used to provide a higher pregnancy rate than IUI in couples with unexplained infertility. The remainder of these technically difficult approaches have never been shown to result in better pregnancy rates than IUI. One prospective, randomized study found that simultaneous intratubal insemination actually decreased the pregnancy rates associated with IUI.5 In modern clinical practice in the United States, IUI is the predominant technique used for artificial insemination.

EVALUATION

Male Evaluation

Semen Analysis

The male partner is initially evaluated by obtaining a complete semen analysis and screens for sperm antibodies. A minimum of two samples provided over 1 to 2 months is analyzed. A third sample is recommended if there is a discrepancy between the initial samples. All samples should be provided after 48 to 72 hours of sexual abstinence. Samples should be analyzed within 2 hours of collection.

Antisperm Antibodies

Male antisperm antibodies are found in approximately 10% of semen samples from infertile couples. Men with antisperm antibodies attached to their sperm are classified as having immunologic infertility. These antibodies are believed to decrease fertility by inducing agglutination or immobilization of the sperm. Studies have identified multiple antisperm antibodies that correspond to a variety of sperm components.5

There are multiple risk factors for the development of male antisperm antibodies. Vasectomy results in the development of antisperm antibodies in the majority of men. After successful vasovasostomy, more than half of these men will have detectable sperm-bound antibodies. The pregnancy rates will depend on many factors, including the titer and quantity of gross agglutination. Obstructive azospermia from any cause (e.g., congenital absence of the vas deferens, cystic fibrosis, infant hernia repair) increases the risk of antisperm antibodies. Reproductive infections (e.g., epididymitis, prostatitis, or orchitis) are also associated with antisperm antibodies.

Antisperm antibody tests are performed as a routine part of a complete semen analysis during the initial infertility evaluation. The most commonly used test in clinical practice is probably the immunofluorescence assay.7 The test involves incubating sperm sample and indicates percent bound, antibody isotype, and binding location. For routine screening, some andrology laboratories are commercially available rapid antiglobulin reaction assay (SpermMAR).
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has no viable sperm (i.e., azoospermia) or when IVF/ICSI fails to achieve fertilization. Finally, even 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. 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
- HIV
- human transmissible spongiform encephalopathy (including Creutzfeldt-Jakob disease)
- syphilis
- 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 reviewed and quarantised for 6 months. Before a donor sample is used for insemination, the donor is retested and determined if eligible.

**Success Rate**

The actual cycle per cycle fecundity rate with donor IIUI 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. Overall, the average live birth rate per cycle of donor IIUI is approximately 10%.17,18

**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.

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 a ultrasonographically sized 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.21 Insemination is thus planned for the day after detection of a rise in urinary LH. This approach offers the simplest, most cost-effective of the indirect methods for predicting ovulation and is just as effective in achieving pregnancy as more complex ones.22,23

**Ultrasound and Human Chorionic Gonadotropin**

Transvaginal ultrasonography is widely used to monitor the size of the follicles and to time 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.11

**IUI Cost**

The cost-effectiveness of the treatment is an important consideration when making a decision among the most appropriate infertility treatment options.29 The cost of insemination varies from clinic to clinic, but is presently less than $5000 per IUI, including sperm preparation and insemination of the prepared sample. This compares favorably with the cost of other appropriate ART approaches.

Even when the cost of ovulation induction medication and surgery for donors are included, the cost per live birth for IUI after superovulation has been calculated to be less than half the cost of IVF treatment.25

**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 double the patients’ inconvenience and expenses.30,31

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%) compared to one insemination per cycle (11.4%).31 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 injection of seminal plasma proteins and proinflammatory cytokines.22 Although seminal plasma protects the spermatozoa from stressful conditions such as oxidative stress,32 it also contains factors that inhibit the fertilization of spermatozoa and reduce the induction of capacitation.33,34 Sperm preparation involves removing the seminal plasma efficiently and quickly 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.36 The ideal sperm preparation method minimizes the risk of reactive oxygen species generation, which can adversely affect DNA integrity and sperm function in vitro.37 Several preparation methods incorporate antioxidants and hydrogen peroxide 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 intrageneric 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 to 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 required depends on semen maturity. 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 50% motility is common. The entire procedure takes 2 hours.

**Basic Sperm Washing**

Sperm washing, the oldest and perhaps the simplest technique, involves removing 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 sample is centrifuged such that all cells aggregate in a pellet, and the seminal washout 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 seminal fluid and separates living sperm from other material after sperm has been washed. For this technique, the semen sample is 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 resulting 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.

Sperm samples that are most commonly used today are the double density gradient centrifugation and the glass wool filtration sperm washing techniques. These techniques have been shown to be effective in separating motile spermatozoa with grade A motility and with normal chromatin condensation in the prepared sample.38,39 In addition, these techniques best reduce the amount of reactive oxygen species and leukocytes in the prepared sample and provide spermatozoa with minimal chromatin 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, or centrifugation/hypotonic techniques.34 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.

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**Table 36-3**

Common Techniques Used for Sperm Preparation Prior to Intracervical Insemination

<table>
<thead>
<tr>
<th>Technique</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washing</td>
<td>Sperm nuclei first aspirated, then swim-up performed</td>
</tr>
<tr>
<td>Swim-up</td>
<td>Sperm nuclei first aspirated, then swim-up performed</td>
</tr>
<tr>
<td>Density gradient</td>
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</tr>
<tr>
<td>Glass wool filtration</td>
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- human immunodeficiency virus types 1 and 2
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- hepatitis B and C
- leprosy
- human transmissible spongiform encephalopathy (including Creutzfeldt-Jakob disease)
- pulmonary tuberculosis
- Chlamydia trachomatis
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If the donor is deemed acceptable and is aware of the ethical and legal implications, semen can be collected. All donor semen samples are screened and quarantined for 6 months. Before a donor sample is used for insemination, the donor is retested and determined if eligible.

Sucess Rate

The actual per cycle pregnancy 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.17 Overall, the average live birth rate per cycle of donor IUI is approximately 10%.18

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 in time as possible to ovulation.20

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

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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 to 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.28 The cost of insemination varies from clinic to clinic, but is presently less than $3500 per IUI, including sperm preparation and insemination of the prepared sample. This compares favorably with the cost of other appropriate ART approaches. Even when the cost of ovulation induction medication and semen processing are included, the cost per live birth for IUI after superovulation has been calculated to be less than half the cost of IVF treatment.25

IUI Frequency

It is recommended that IUI be performed either once 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 of treatment.29

Sperm preparation and insemination per cycle.29 A recent meta-analysis of more than 1000 IUI cycles revealed a slightly higher but statistically insignificant difference between the per cycle pregnancy rate for two inseminations (14.9%) compared to one insemination per cycle (11.4%).31 Accordingly, one well-timed insemination appears to offer the best balance between efficacy and cost.

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For semen samples that most commonly used today are the double density gradient centrifugation and the glass wool filtration sperm washing techniques. These techniques have been shown to effectively remove leukocytes and to separate spermatozoa with minimal chromatin 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, followed by swim-up/leukocyte techniques.39 For poor sperm 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.

Chapter 36

Artificial Insemination

Table 36-3 Common Techniques Used for Sperm Preparation Prior to Intracervical Insemination

<table>
<thead>
<tr>
<th>Washing</th>
<th>Swim-up techniques</th>
<th>Wash-out from pellet</th>
<th>Density gradient separation</th>
<th>Glass wool filtration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Swum-up from ejaculate</td>
<td>Swum-up from ejaculate into isotonic acid</td>
<td>Density gradient centrifugation</td>
<td>Mechanical aids</td>
</tr>
</tbody>
</table>
A catheter is used for intrauterine insemination (IUI) to facilitate the passage of sperm to the uterus. A second method for navigation of the endocervical canal for IUI is by using a semiretained 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), distillation 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 outcome with IUI, even with 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. Second, 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. A total sperm count of more than 5 million and normal morphology of more than 5% have been associated with a successful pregnancy. A study in patients with mild male factor infertility, a live birth rate of 15% per cycle was reported.

When prepropeparations semen analyses are characterized, the chances of pregnancy after IUI correlate best with the total sperm count and with a normal sperm morphology (Kruger) shown that when the prewashed semen specimens had more than 4% normal sperm morphology, the chances of pregnancy after IUI were significantly increased. 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 number of motile sperm after wash or swim-up. In a retrospective study of 9663 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. This analysis showed that the total motile sperm count before semen preparation was less than 1 x 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 semen analysis. Three experimental models have been proposed that 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 DFI is greater than 27% after IUI processing. TUNEL evaluates the degree of sperm DNA fragmentation and stability. In another study, lower degrees of DNA fragmentation after IUI is associated with increased pregnancy rates.

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 spermatids to increase motility. 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 resultant 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 and IVF in patients 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 are a few common female factors that are useful in predicting pregnancy rates after IUI. These factors are maternal age, duration of infertility, and female infertility factors.

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 diplopia in...
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A

Figure 36-1. Intratubal insemination catheter: A, tip of catheter is directed to a 4 to 6 cm distance from cervical os (CookSystem, Parten, Bloomington, Ind). B, C ygolyBiSysten catheter (CookBlyBiSysten, Parten).

IIU Technique

IIU 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 bivalved vaginal speculum. After excess vaginal secretion are wiped from the external vaginal 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 cervical isthmus. In this situation, the catheter should be withdrawn 1 cm, and injection reattempted. After IIU, 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 through the cervix before IIU is the total must be confirmed by careful twisting of the catheter as it is gently advanced. Resistance in any direction that 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 7 to 8 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 IIU 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 counteract resistance. Because the diameter of some of these types of catheters is usually larger in caliber (greater than 3 mm), distillation is sometimes required in the presence of cervical stenosis.

Factors That Predict Pregnancy Rates

The highest pregnancy rates with IIU are seen among those with IVF who have normal semen characteristics and with 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. Second, pregnancy rates positively correlate with the number of motile sperm recovered for IIU, and this number is often lower in men with abnormal results on semen analysis.

Semen Analysis Characteristics

Semen characteristics clearly affect IIU outcome. IIU is a successful treatment for human infertility, defined as a total motile sperm count of more than 5 million and normal 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 preparation semen analyses characteristics are evaluated, the chances of pregnancy after IIU correlate best with a high sperm count and a normal morphology (Kruger) scored when the prewashed semen specimen had more than 4% normal sperm morphology; the chances of pregnancy after IVF 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 IVF is the total motile sperm count after wash or swim-up. In a retrospective study of 9663 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 322 infertile women, with a kinked or course bent tip (vasovagal wash, or cl. is withdrawn) being the indicator of pregnancy. The total motile sperm count before semen preparation was less than 1 x 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 abnormally low semen analysis. Three experimental sperm chromatin structure assays, DNA fragmentation index, and terminal deoxynucleotidyl transferase-mediated deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL).

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

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 undergo fertilization. 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 infertility 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 IVF/ICSI 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. When 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.

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 include menopause, 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, pregnancy rates 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 rate is 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 oocytes and spermatogenesis, but also on the receptivity of the endometrium. In a retrospective study, the presence of uterine abnormalities 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 ultrasonography 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 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

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Artificial Insemination

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Section 6

Infertility

Allergic antibiotics rare patients experiencing severe reactions, including anaphylaxis, can occur after UII in response to potential allergens in the wash media. Reactions have been reported to both the borne serum albumin and antibiotics (penicillins and streptomyacin) commonly used in the wash media.13

These reactions are typical of a minor IgE-mediated type IV delayed hypersensitivity reaction, similar to that seen in patients with a history of penicillin allergy. For example, one report documented a case of a patient who developed an allergic reaction to penicillin after undergoing a procedure for artificial insemination.14

Antisperm Antibodies

When UII was first introduced, there was a concern that the procedure could result in the development of serum antisperm antibodies. After 40 years of experience, it appears that exposure to the upper reproductive tract to washed spermatozoa during UII does not stimulate the appearance of clinically significant female antisperm antibodies.15

Pregnancy-Related Complications

Multiple Pregnancies

The risk of multiple pregnancies is not increased by UII. However, medications used to recruit multiple follicles before UII do increase this risk. Clomiphene citrate is associated with a risk of 3% to 10% and other higher-order multiples.

Injectable gonadotropins are associated with multiple pregnancy rates of 14% to 39%. Careful monitoring of the number of follicles and use of progesterone to prevent luteal phase defects might decrease the risk of multiple pregnancies.11,12

Women are at high risk if they are younger than age 30, have more than six preovulatory follicles, and a peak estradiol level greater than 1000 pg/mL.13

Spontaneous Abortion and Ectopic Pregnancy

The risk of spontaneous abortion appears to increase after UII as compared to the fertile population and is in the range of 20% to 25%.16 The increased risk is probably not due to direct embryotoxic factors but may be due to E2 levels altering the pregnancy 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 UII procedure.17

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 face their feelings concerning infertility, donor insemination, and other concerns. The male partner may experience a loss of self-esteem and fear that he is not the father 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 uncompromising. Support groups or professional counseling can be helpful.

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 in the insemination. If one of the partners has low sperm densities, the consent 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 cases, 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 for infertile couples.
- Infertility due to cervical and male factor (without any associated female factor) can be treated with intratracheal insemination.
- 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.

Chapter 36

Artificial Insemination

14. Visso H, Sin-Petermann T, Devon L: Clomiphene citrate and ovulation induction may have the right to obtain identifying information about the donor once they reach adulthood.
Infertility and Recurrent Pregnancy Loss

Section 6

ARTIFICIAL INSEMINATION

Infertility is a tragic event. It can be a crisis that the couple undergoes after the procedure as they know that it cannot help. Infertility can be traumatic because 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 uncompromising. Support groups or professional counseling can be helpful.

Fertilization

The process begins with a sperm's penetration of an egg. The sperm must reach the egg's outer layer, the zona pellucida, before it can fuse with the egg's plasma membrane. This fusion is mediated by a variety of membrane proteins, including integrins and cadherins. The resulting complex, called the fertilization envelope, protects the egg from further sperm penetration and promotes the formation of the embryo.

Offspring

In many species, offspring development continues after the sperm has entered the egg. The resulting embryo undergoes a series of rapid cell divisions and differentiates into different tissues and organs. The development of the embryo is controlled by genes and environmental factors, including nutrient availability, temperature, and oxygen levels. The embryo continues to develop inside the mother's body, where it is nourished and protected until it is ready to be born. After birth, the offspring develops further and learns to function independently.
Section 6
Infertility and Recurrent Pregnancy Loss

Introduction

Induction of ovulation, or stimulation of ovarian follicular development, is applied in several different clinical situations. These include restoration of ovulation in anovulatory women, ovarian superovulation (stimulating more than one mature follicle) in ovulatory women, and controlled ovarian hyperstimulation (stimulating the development of several mature follicles) for assisted reproduction.

This chapter reviews the underlying scientific basis and clinical guidelines regarding the use of different medications for induction of ovulation. It focuses on a discussion of oral agents, including clomiphene citrate, insulin sensitizers, and aromatase inhibitors. Other drugs for ovulation stimulation used for assisted reproductive technology (ART), including premenstrual medications (injectable gonadotropins and gonadotropin-releasing hormone [GnRH] analogs), and specific agents applied for particular medical disorders, such as prolactin-lowering agents in cases of hyperprolactinemic anovulation, are discussed in Chapters 22 and 38.

Physiological Basis of Follicular Development and Ovulation

An understanding of normal physiology is an important basis for understanding ovulation induction. Ovulation is comprehensively discussed in Chapter 3. A brief description relevant to induction of ovulation is presented here.

Folliculogenesis

Ovarian folliculogenesis is regulated by both endocrine and intracellular mechanisms that coordinate the processes of cell proliferation, differentiation, and maturation. The main follicular component of the ovarian cortex is the primordial follicle, consisting of an oocyte arrested at the diplotene stage of the first meiotic division, surrounded by a few flattened cells that will develop into the granulosa cells.1 Also, FSH activates granulosa cell proliferation and differentiation and reduces the number of atretic follicles grown in vitro.2 Such mitogenic action is facilitated by locally produced growth factors; the production or action of these factors may be modified by FSH.3

Extrapolating from hypogonadal mice in which oocytes grow to normal size and can acquire developmental competence, gonadotropins may not be necessary for oocyte development per se. However, gonadotropins are believed to play a general role in supporting oocyte maturation by supporting follicular development and preventing degeneration.4

Early Follicular Development

During the early stage of follicular development, the oocyte and the granulosa cells proliferate to form a preantral follicle. At the preantral stage, theca cells begin to differentiate from the surrounding stroma, and once the follicle reaches a species-specific size, it forms a fluid-filled space called an antrum within the granulosa cell layers.5 Antral follicles become acutely dependent on gonadotropins for further growth and development. Follicular growth (from preantral to follicular growth stage) is continuous. However, less than 1% of preantral follicles present at the time of birth will ever proceed to ovulation, with the majority of follicles degenerating by estrus.6

During the later part of the luteal phase, when estrogen levels fall following the involution of the corpus luteum, gonadotropin levels increase.7 The beginning of development of a limited cohort of follicles. Subsequent development of this cohort during the follicular phase depends on continued stimulation by gonadotropins.

FSH Threshold

FSH concentrations must exceed a certain level before follicular development will proceed. When this FSH threshold is surpassed in the normal cycle, the growth of a cohort of small antral follicles is stimulated and ensures ongoing preovulatory follicular development.8 When this threshold is exceeded (the FSH window) is limited in the normal cycle by a decrease in FSH, which occurs in the early to mid-follicular phase because of negative feedback from rising estrogen levels.9

Extending this window would allow the continuous development of more follicles. In the normal cycle, one follicle (the leading follicle) will proceed in follicular development because it has the highest level of FSH not being able to form a blastocyst, FSH excess in follicular development.10 Extending this window would allow the development of more follicles. In the normal cycle, one follicle (the leading follicle) will undergo in follicular development because it has the highest level of FSH not being able to form a blastocyst, FSH excess in follicular development.10 Extending this window would allow the continuous development of more follicles. In the normal cycle, one follicle (the leading follicle) will undergo in follicular development because it has the highest level of FSH not being able to form a blastocyst, FSH excess in follicular development.