

Intra uterine insemination

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Abstract

Intrauterine insemination is a simple, non-invasive and safe initial treatment option, especially in low resource settings for selected group of patients before initiating assisted reproduction technology treatment. A wise selection of patients and timing are key to its success. Detailed assessment of the infertile couple, controlled ovarian stimulation with follicular development monitoring, appropriate processing the seminal fluid, trigger with hCG at a correct time, single IUI in strict aseptic condition followed by 10-15 minutes of immobilization are currently considered vital elements of Intrauterine insemination to improve its outcome. Intrauterine insemination can be considered as a bridge between basic and advanced fertility treatment for selected infertile couples especially in countries with limited resources for assisted reproductive technologies.

Key words: intrauterine insemination, ovarian stimulation, follicular tracking, processed sperm, trigger with hCG.

Introduction

Intrauterine insemination (IUI) is an assisted conception technique that involves the deposition of processed semen sample by a fine catheter (IUI Catheter) in the upper uterine cavity in order to increase sperm density at or closer to the site of fertilization^{1,2}. However, assisted reproductive technology (ART) does not include assisted insemination by sperm from either a woman's partner or a donor. ART includes in-vitro fertilization and embryo transfer, intrafallopian gamete

transfer, zygote intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy^{3,4}. IUI is a simple technique performed without expensive infrastructure and technology and it can be provided as a safe and simple treatment with minimal risks with appropriate monitoring⁵.

In 1962, the first scientific paper titled intrauterine insemination (IUI) was published by Cohen MR et al⁶.

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Insemination of semen in humans was initially developed to help heterosexual couples to become pregnant and in severe male factor infertility due to physical or psychological nature. However currently insemination with homologous semen is most commonly used for unexplained and mild male factor infertility. Later donor insemination (DI) was used primarily for male infertility caused by azoospermia, severe oligospermia and inherited genetic diseases such as Y linked chromosomal diseases. Currently DI is commonly used for individual women who desire a pregnancy⁷.

Types of sperm insemination

The sperm suspension can be deposited in the cervix, uterus, or fallopian tube. Accordingly, it can be classified as intra cervical insemination (ICI), intrauterine insemination (IUI), and intrafallopian insemination / fallopian tube sperm perfusion (FSP).

ICI is performed with processed or non-processed semen directly introduced into the cervix by a needleless syringe. IUI is performed as an aseptic procedure by introducing 0.2-1 ml of processed sperm into the uterus with a small IUI catheter and usually without imaging guidance. Intrauterine insemination showed a 2-fold rise in pregnancy rate than ICI and has a better outcome with frozen semen^{8,9}. In fallopian tube sperm perfusion (FSP), a larger volume (approximately 4 ml) of processed semen is used to inseminate into the female genital tract. The rationale behind FSP is to flush the processed semen into tubes to place motile spermatozoa closer to the eggs. Several randomized control studies and meta-analyses suggested that FSP is more efficient than standard IUI. However, due to technical difficulties, pain during insemination and potential risk of ascending infections it has not replaced the standard IUI¹⁰.

Indications

IUI is the first-line therapy for selected couples, who have functionally normal tubes with infertility due to a male-factor, unexplained factors, cervical factor, immunological factor and ejaculatory disorders with clinical pregnancy rates per cycle ranging from 10 to 20%¹.

IUI with or without ovarian stimulation is considered and recommended for a broad range of conditions. The most common indication is male infertility and especially where donor sperm is required. IUI had shown superior results than timed intercourse (TI) for

male subfertility⁹. IUI is indicated for all categories of unexplained infertility and couples with minimal and mild endometriosis and is considered slightly superior to TI/ ICI for unexplained subfertility¹¹. Couples with a cervical factor diagnosed by a post-coital test with normal semen parameters have reported higher pregnancy rates following IUI than expectant management^{12,13}.

In addition, IUI with ovarian stimulation, particularly with low-dose gonadotropins, may be considered while awaiting ART or in women who can't afford ART with patent tubes and has been shown to be beneficial in terms of success rate and pregnancy outcomes compared with timed intercourse alone^{14,15}. Therefore, IUI is widely used in low resource countries for infertility treatment beyond the evidence-based indications.

Though IUI is not absolutely contraindicated in most infertile couples it is relatively contraindicated in women with cervical atresia due to technical difficulty, cervicitis, endometritis and lower genital tract infections and bilateral tubal obstruction. Meanwhile, it may also be relatively contraindicated in women with sperm-immobilizing antibodies secreted by the female reproductive tract, which might reduce the sperm passage, inhibit fertilization, and impair post-fertilization processes¹⁶.

Complications

Though IUI is a simple, non-invasive and safe technique it is associated with pelvic infections or abscess due to ascending infections, ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies due to ovarian stimulation.

The potential risk of infections is due to uterine catheterization and injection of the semen especially in the case of non-processed semen¹⁸. But this risk has been reported to be only 0.01-0.2%¹⁷. Couples and individuals, including donors who are undergoing IUI, should be screened for infectious agents based on local, regional and national standards and regulations to minimize the risk of infection⁵.

According to the WHO laboratory manual, leukocytes in semen may indicate infections and can be associated with poor sperm quality. With regards to HIV infection no seroconversions of female partners were reported after inseminations with washed sperm from HIV-positive men. However, couples should be informed that sperm preparation techniques do not guarantee

that HIV is 100% removed from the post-processed or washed sperm sample of HIV-positive men¹⁹.

Strict patient selection criteria and individualized stimulation protocols designed according to the patient's age, ovarian reserve and aetiology with a strict cycle cancellation policy will help to reduce complications and eventually increase the outcome¹. Aiming for a maximum of two dominant follicles during the IUI cycle has been shown to minimize high-order multiple pregnancies with optimal pregnancy outcomes²⁰.

Ovarian stimulation (OS) and monitoring follicle and endometrium

The basis behind the OS is to achieve multiple follicular growths. Ovarian stimulation should be mild with a low dose of clomiphene citrate (50-100 mg per day for five days) and it remains a first-choice of ovulation induction drug. However, it might have a negative effect on the endometrium due to anti osteogenic effect. Clomiphene citrate is readily available, easy to use and less costly compared to gonadotropins. In addition to clomiphene citrate, a low dose (50-75 IU per day) of recombinant FSH can be used to archive optimal follicular growth with minimal complications such as OHSS and multiple pregnancies^{21,22}.

It had been shown that multiple follicular growths resulted in significantly higher pregnancy rates compared to mono follicular growth (15% versus 8.4%), and compared to one dominant follicle, pregnancy rates increased further when two or more dominant follicles were present at the time of trigger²³. In a randomized controlled trial conducted in couples with male infertility to compare IUI with or without OS, couples with a (Total Motile Sperm Count) TMSC less than 10 million, OS did not enhance pregnancy rates. On the other hand, it improved in couples with a TMSC of more than 10 million²⁴. For unexplained infertility, the Cochrane systematic review showed that IUI without OS does not positively influence pregnancy outcomes, but OS with IUI significantly increases live birth rates²⁵. IUI following ovulation induction with clomiphene citrate was randomly compared to expectant management in couples with unexplained infertility. It showed that OS with clomiphene citrate significantly increased cumulative live birth rates compared to expectant management²⁶. A meta-analysis reported a significant improvement in fecundity using IUI following OS with follicle-stimulating hormone (FSH) compared to IUI or FSH treatment alone²⁷.

Appropriate and strict ultrasound monitoring for each OS cycle is mandatory to minimize complications such as multiple pregnancies and OHSS. In literature, different criteria were explained to cancel IUI following OS to prevent such complications. One should aim at two dominant follicles larger than 15 mm, but all follicles larger than 10 mm should be considered to define cancellation criteria^{28,29}. Recommended secondary preventive measures are either cancellation of the cycle or the aspiration of supernumerary follicles and proceed to IVF; however, the evidences are lacking^{30,31}.

Endometrial thickness (EMT) before IUI and trigger time was analyzed in several studies and concluded as it is not related to treatment outcome. Differences in EMT between women who get pregnant and who do not get pregnant are too small to be helpful as a tool to guide treatment or to make a recommendation. Therefore, cancelling IUI cycles due to thin endometrial lining with expected poor outcome is currently not recommended³¹.

Sperm preparation and quality

Processing seminal fluid is essential before IUI to remove debris, dead or immobile sperms, and prevent prostaglandin-induced uterine contraction. It can be achieved by relatively simple procedures. The most frequently used methods are centrifuging spermatozoa through culture medium or density gradients followed by re-suspension in suitable culture media.

A systematic review of sperm preparation techniques revealed that there was insufficient evidence to choose one particular method over the other. Meanwhile, in a normal semen sample, the advantages of isolating motile spermatozoa before IUI by using the whole population of spermatozoa is still unclear and has similar success rates¹⁸. Currently there is no definitive recommendations based on evidence with regards to the lower limit of semen quality at which ART would be recommended rather than IUI. Also, there is lack of robust evidence with regards to the precise lower cut-off levels of sperm parameters for success rate in IUI treatment. Anyway, the currently available evidence suggests a TMSC of more than 1 million and more than 4% normal morphology are possible positive predictive values. Below the above cut-off levels, IUI should be withheld as the success rates of conceptions are very low^{32,33,34}.

Trigger and Timing of IUI

The timing of insemination relatively around the time of ovulation plays an indispensable role in the optimal success rate in IUI. Along with timing of IUI beta hCG is considered a suitable trigger for IUI¹⁰. Normal sperm is capable of fertilizing an oocyte in the female genital tract approximately for about five days, and an oocyte is usually fertilizable for 12-24 hours after ovulation³⁵. A multicenter study was conducted by WHO and concluded that ovulation occurred between 24 and 56 hours (average 32 hours) after the onset of luteinizing hormone (LH) surge³⁶. Insemination can be done at various time points around ovulation. Most commonly insemination is done 24-36 hours following trigger (hCG) administration³⁷.

Post-procedure

Rest

Studies conducted on spermatozoa's intrauterine behavior had shown that spermatozoa would usually reach the fallopian tubes within 5 to 10 minutes following IUI³⁸. After vaginal intercourse, a large amount of the semen is lost by 'flow back', and around 1% of the spermatozoa are retained in the female reproductive tract. Thus, an assumed hypothesis of immobilization in the supine position after IUI could prevent direct loss of many spermatozoa and eventually improve fertility outcomes. Therefore, 10-15 minutes of bed rest after insemination is recommended for women undergoing IUI⁵.

Luteal phase support

There is no biological or empirical evidence that treatment with hCG or progesterone in the luteal phase is necessary to improve the pregnancy rate. However, usage of progesterone or hCG in the luteal phase exists in clinical practice with the absence of robust evidence³⁹. Studies conducted in hypophysectomized women with ovulation induction found that it was necessary to provide continuous support in the form of hCG until the mid-late luteal phase for optimal outcome. However, women undergoing ovarian stimulation during IUI cycles are not hypogonadotropic, and the half-life of hCG is relatively long. Therefore, the use of at least 5000IU hCG is biologically enough to persist for at least ten days, by which time the cytotrophoblast would have resumed secreting hCG in adequate amounts⁴⁰.

Other factors affecting the success rate

Different success rates had been shown in several studies according to factors such as the causes of infertility, number for treatment cycles, duration of infertility, age of female and the number of dominant follicles before IUI^{9,10}. Other known factors that affect the outcome of IUI are sperm quality and quantity, tubal patency, ovarian reserve and response to the ovulation induction^{41,42}.

Number of IUI

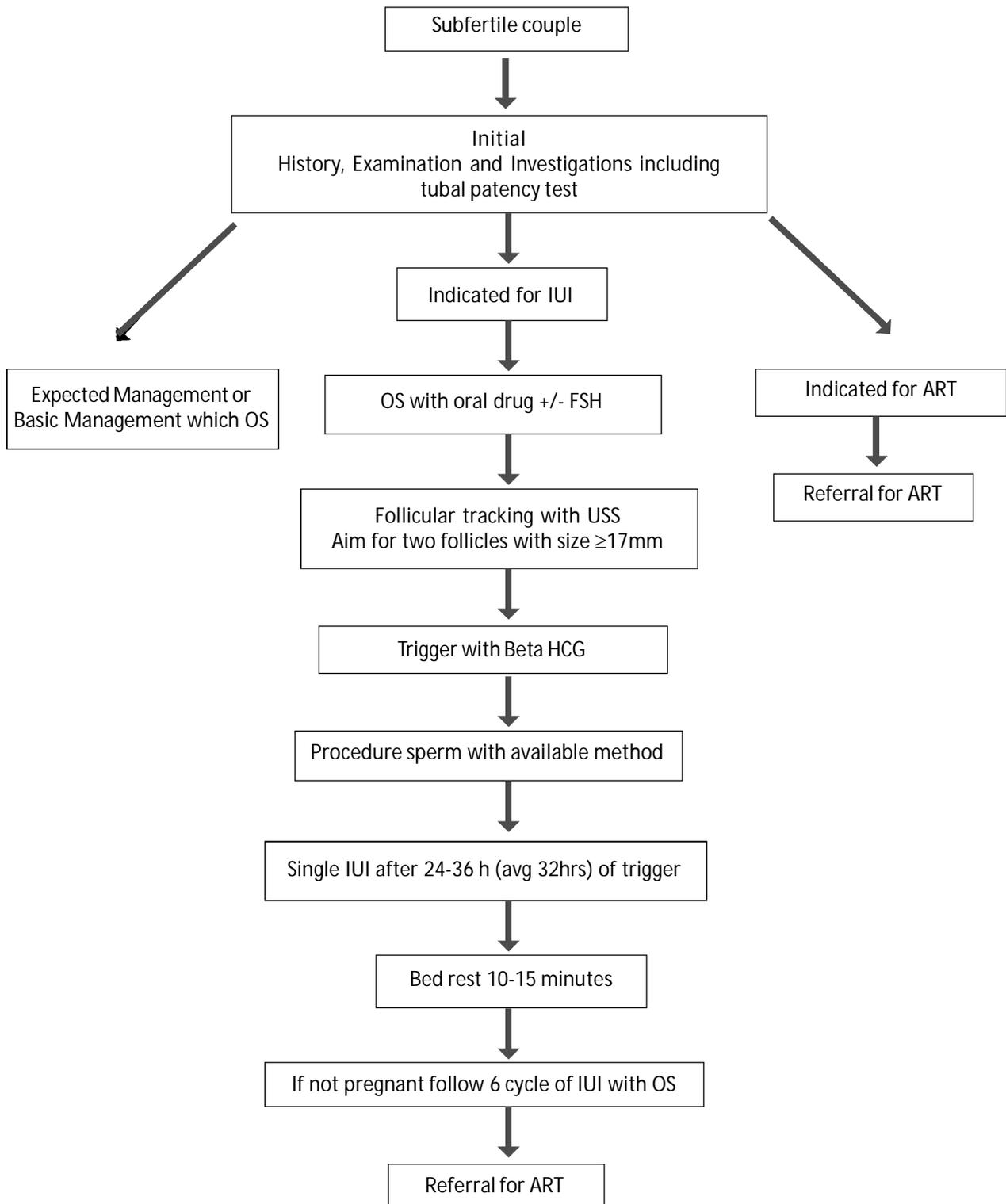
It is essential to discuss with the patient the number of IUI cycles before starting IUI treatment, especially in a low resource country with limited ART facilities. It is important to consider and the advantages between the additional IUI, its cost and the success rate. Three to six cycles of IUI has become common practice worldwide and showed that six cycles of IUI with the optimal OS is still cost-effective compared to ART in patients with unexplained and mild male infertility⁴³. Evidence suggests performing a minimum of three IUI treatment cycles and a maximum of six IUI treatment cycles in a technology-limited setting for ART⁴⁴. Studies also concluded with robust evidence that there is no significant difference in the pregnancy rate with two inseminations in a single cycle compared with one⁴⁵.

Conclusion

Intrauterine insemination remains a valuable initial treatment option, especially in low resource settings for selected group of patients before embarking on a more invasive and expensive assisted reproduction technology treatment. It is a simple, non-invasive and relatively cost-effective technique that can be performed without sophisticated technology and infrastructure.

Detailed assessment of the infertile couple and identifying the indication for IUI, controlled ovarian stimulation with intense monitoring of follicular development with a target of two dominant follicles, processing the seminal fluid with a method to improve the TMCS for insemination, provide trigger with hCG, plan IUI in the correct time according to the trigger, perform a single IUI in a strict aseptic condition followed by 10-15 minutes of immobilization are currently considered vital elements of this treatment process that will significantly improve the outcome.

Pathway of IUI treatment



Given its cost-effectiveness, simplicity and availability, intrauterine insemination can be considered as a bridge

between basic and advanced fertility treatment with a realistic success rate for selected infertile couples.

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