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OPINION

Intrauterine insemination

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ABSTRACT

Stimulated intrauterine insemination (IUI) should be the first choice treatment for mild male factor infertility, unexplained infertility or minimal to mild endometriosis. In mild male factor infertility, unexplained infertility, IUI is as effective as IVF & at 1/3 of the cost per pregnancy. In couples with the most severe semen defects, IUI in natural cycle should be the treatment of choice. In mild to moderate semen defects, mild ovarian hyperstimulation with IUI is recommended. In endometriosis, simplified ultrlong protocol with IUI gives better chances of achieving pregnancy. Ultrasonographic monitoring & human chorionic gonadotropin (hCG) induction of ovulation does not produce an increased pregnancy rate over urinary lutenising hormone (LH) monitoring of ovulation. Double IUI showed no significant benefit over single IUI. Four cycles of IUI are enough. Continued IUI is not recommended.
Key words: intrauterine insemination, infertility

INTRODUCTION

The place of intrauterine insemination (IUI), especially in relation to invitro fertilization (IVF) remains controversial. There are wide variations in indications, protocols of ovarian stimulation, semen preparation, timing, number & technique of insemination. There are divergent opinions regarding the benefits obtained from IUI. The question is often asked whether in the light of predictable success of IVF & intracytoplasmic sperm injection (ICSI) if IUI still has a place in assisted reproductive technology (ART)? The objective of this article is to review the up-to-date randomized controlled trials (RCT) concerning IUI. RCT were reviewed as regard the following: Indications of IUI, ovarian stimulation, semen preparation, insemination, improving the results, & the end point.

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INDICATIONS OF IUI

1. Unexplained infertility:

Ovulation induction & IUI is justified in couples with unexplained infertility (1,2). Ovulation induction with IUI is an effective treatment in unexplained infertility, but ovulation induction with timed intercourse (TI) has negligible impact (3). The likelihood of pregnancy is 3 times greater with IUI (4).

2. Male factor infertility:

A. Mild to moderate male infertility: IUI Vs timed intercourse in male infertility: 17 trials comparing 3775 treatment cycles were reviewed (5). IUI in natural cycles & IUI with COH significantly improved the probability of conception. IUI with COH is superior to TI with COH. IUI overcomes failure to fertilize due to impaired mucus

penetration & poor survival in the female reproductive tract (6).

B. Severe male factor infertility: Severe male factor infertility is not a candidate for IUI but ICSI (7). ICSI is more cost effective than IUI when the mean total motile sperm count is <10 million.

3. Mild male infertility or unexplained infertility

IUI Vs IVF: The pregnancy rate per started cycle was 7.4% for IUI, 8.7% for IUI with COH, 12.2% for IVF (8). These differences did not reach statistical significance. The cost (US$) per pregnancy was 4000 for IUI, 5000 for IUI with COH, 13000 for IVF. IUI is as effective as IVF at 1/3 of the cost per pregnancy (9). Stimulated IUI should be the first choice treatment for mild male factor infertility or unexplained infertility. It has the same efficacy as stimulated IVF & is more cost-effective due to its lower cost.

4. Cervical factor infertility

Cervical factor infertility was diagnosed when postcoital test after 8-12h showed no sperms with progressive forward motion. IUI in natural cycle is an effective treatment for cervical factor infertility (10)

5. Male immunological infertility

Male immunological infertility was diagnosed when mixed antiglobulin reaction to IgG was positive. IUI is significantly better than limited intercourse with prednisolone (11). IUI is an effective method, results are obtained rapidly & steroid side effects can be avoided. IUI significantly improved pregnancy rate (PR) when used as an adjuvant therapy to cyclical dose steroid therapy (12)

6. Endometriosis

A. Minimal endometriosis: Superovulation in combination with IUI is effective in treatment of minimal endometriosis (13)

B. Minimal & Mild endometriosis: Treatment with COH & IUI was associated with superior outcome both by crude live-birth rates & proportional hazard analysis (14)

OVULATION INDUCTION

A. Stimulated IUI Vs natural IUI

1. In general: The cumulative pregnancy rate per couple was 33% for IUI & COH & 18% for IUI alone (15). COH has independent positive effect on pregnancy rate when combined with IUI. In young patients without a prior pelvic surgery & with good-post-wash semen quality COH doubles IUI pregnancy rate (16).
2. In male factor infertility: In case of severe semen defect: (with more than 1 million motile sperm after semen preparation & no sperm defect): IUI in natural cycle should be the treatment of choice (5). In cases with less severe semen defects: (average total motile sperm concentration > 10 million): Mild ovarian hyperstimulation with human menopausal gonadotropin (HMG) is recommended. COH should be reserved for moderate semen defects. In couples with the most severe semen abnormalities, the largest effect of IUI was seen & the least effect of COH
3. In Unexplained infertility: Ovarian stimulation increases the PR (17,18)
4. In Endometriosis: HMG/IUI is more effective than IUI alone for the treatment of endometriosis (17)

B. Protocol of stimulation

I. In unexplained infertility & male factor infertility

1. Clomiphene citrate (CC) Vs & HMG: Clomiphene citrate is at least as effective as HMG (19). No adverse effect of CC compared to HMG as far as pregnancy rates are concerned. IUI seems to be an effective in treating cervical factor problems induced by CC (20). On other hand Karistrom et al (21) found that follicular stimulation with HMG is more effective than CC. The PR obtained with CC was half that obtained with follicle stimulating hormone (FSH) (22).

There was a trend to lower multiple PR with CC. Each case should be considered on individual bases. CC could be a reasonable approach for young women with good prognosis, where as in the remaining cases FSH would be the preferable method.

Regimes of low dose FSH: There is no significant difference among the three regimes of low dose FSH in terms of cycle parameter (18). The three regimes are 150 IU FSH on day 4 & 75 IU FSH on days 6 & 8; 150 IU FSH on days 4, 6 & 8; & 150 IU FSH on days 4, 6, 8, & 10.

Low dose step up FSH Vs conventional FSH protocol: No significant difference in PRs, but significant reduction in the incidence of ovarian hyperstimulation syndrome (OHSS) with low dose step up FSH protocol (23)

2. CC Vs CC &HMG: CC & late pure FSH is more effective than CC alone (4% vs 13% PR). (24)

3. HMG Vs HMG & CC: Menotropin alone protocol yields significantly higher PR than CC & menotropin (25)

4. HMG Vs GnRHa/HMG: No beneficial effect of GnRHa/HMG compared to HMG alone in treatment unexplained infertility, based on PR (26)

5. Recombinant Vs urinary FSH: A standard daily dose of 100 IU of rFSH is more effective than uFSH since a more symmetric response is obtained (27,28)

II. In endometriosis

Simplified ultralong protocol (ULP) Vs long protocol (LP)

Simplified ULP (4 weeks after a single injection of 3.75 mg Dcapeptyl, daily sc 0.1 mg Decapeptyl for at least 2 w prior to ovulation stimulation) gives better chances of achieving pregnancy than LP (Daily sc 0.1 mg Decapeptyl from the mid-luteal phase & after 2 w, ovarian stimulation is started if pituitary desensitization is achieved) (29).

SEMEN PREPARATION

1. Double centrifugation, multiple tube swim up & Percol density gradient preparation yield similar cycle fecundity rates (30)

2. Sperm Prep filtration method {removal of leukocytes & seminal debris) resulted in significantly higher PR than the double sperm wash (31).

3. Swim up semen preparation with test yolk buffer incubation significantly improved the PR in unexplained infertility but not in male factor infertility (32)

4. Self-migration in sodium hyaluronate is comparable to centrifugation & swim up as regard the PR (33).

5. Wash only Vs density gradient centrifugation: The pregnancy rate for wash only was 11.6% & the rate for density gradient centrifugation (DGC) was 14.3% (34). However in samples with less than 22 million motile sperm in the inseminate, pregnancy rates were 4% for wash & 18% for DGC. So, samples with an acceptable number of motile sperm can be processed efficiently by wash only, while poor quality semen samples should be processed using DGC.

INSEMINATION

Timing

Timing of IUI with the use of a relatively expensive & time consuming method such as ultrasound monitoring of folliculgenesis & hCG induction of ovulation does not appear to produce an increased PR over urinary LH monitoring of ovulation (35). A beneficial effect arises from allowing the natural process of final follicular maturation to occur (36). PRs were 9.3% after HCG induced ovulation &
20.5% after spontaneous ovulation.

Number

Double IUI showed no significant benefit over single IUI (37).

Technique

a. Fallopian tube sperm perfusion (FSP) Vs IUI: FSP is more successful than IUI (38,39,40,41). On other hand many authors found that PR were not significantly different in both groups

(42,4344,45,46). Trout & Kemmann (47) reported that FSP significantly improve PR of patients with unexplained infertility only.
b. Intraperitoneal insemination (IPI) Vs IUI: No significant difference in PR between the IUI & IPI (48,49)
c. Intracervical insemination (ICI)Vs IUI: IUI is superior to ICI (50).

Inseminated volume

Similar PR for 0.5 ml & 3 ml of inseminated semen (51)

Type of catheter

When comparing the softer Wallace catheter to the less pliable Tomcat catheter during IUI, there was no significant difference in PR when using standard gentle technique that include no touching the top of the catheter (52)

HOW TO IMPROVE THE RESULTS

1. COH:
COH increases pregnancy rates in all indications except severe semen defect (5)
2. . Vaginal misoprostol
Use of vaginal misoprostol increases the chance of pregnancy in women having IUI (53,54)
3. Timed intercourse within 12 -18 h period.
In IUI with low number of motile sperm, TI significantly increases PR over IUI alone in infertile couple with normal semen (55)
4. Ten minutes bed rest
A 10 minutes bed rest after IUI has a positive effect on PR (56)
5. Corticosteroid treatment does not improve the results of IUI in male subfertility caused by antisperm antibodies (57).
6. Treatment of the male with FSH before IUI is not associated with increase PR (58).

CLEAR ENDPOINT

Pregnancies resulting from IUI occur during early treatment cycles. 71% of IUI pregnancies occurred in the first 2 cycles (59). 85% of IUI pregnancies occurred during the first four cycles (13). Continued IUI is not recommended (60).

CONCLUSIONS

1. Stimulated IUI should be the first choice treatment for mild male factor infertility, unexplained infertility or minimal to mild endometriosis.
2. In mild male factor infertility, unexplained infertility IUI is as effective as IVF & at 1/3 of the cost per pregnancy.
3. In couples with the most severe semen defects, IUI in natural cycle & in mild to moderate semen defects, COH with IUI.
4. In endometriosis, simplified ULP gives better chances of achieving pregnancy.
5. Ultrasonographic monitoring & hCG induction of ovulation does not produce an increased PR over urinary LH monitoring of ovulation.
6. Double IUI showed no significant benefit over single IUI.
7. Four cycles of IUI are enough. Continued IUI is not recommended

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