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Original Research Article

Randomized Controlled Trial on Effect of Vaginal Misoprostol as an Adjuvant after Intra Uterine Insemination

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ABSTRACT

One year prospective randomized controlled trial was conducted to evaluate the efficacy of misoprostol in enhancing pregnancy rate after Intra Uterine Insemination.600 ovulation induced cycles for IUI were randomized into study group (200µg vaginal misoprostol) and control group (without misoprostol) , 300 subjects in each group. Demographic data, causes of infertility and pregnancy rates in relation to various causes of infertility were comparable between the two groups. There was no significant difference in pregnancy rates among three different strategies of ovarian stimulation between the two groups. Subjective side effects were also comparable in both groups. Pregnancy rate results did not demonstrate superiority of the misoprostol group over the control groups (8.4% v/s 9.6%).
***Keywords**:* IUI, Misoprostol, prostaglandins.

INTRODUCTION

Infertility, though does not claim an individual's life, inflicts devastating emotional trauma on the individual for being unable to fulfill the biological role of parenthood. It has been estimated that in India between 10-15% of the couples are infertile. Assisted reproductive techniques (ART) have made women conceive in certain situations. However, many of these require enormous technical expertise and infrastructure and have a success rate of below 30% under the best of circumstances. [1]

Intrauterine insemination (IUI) is frequently used in the treatment of infertility. The overall success rate of IUI is variable and ranges from 5% to 70% per patient. However, a 10-20% clinical pregnancy per cycle is acceptable range for all etiologies. [2] Because, complication occur following intrauterine injection of seminal fluid, only washed sperm is injected in to uterus in IUI. Therefore, the supportive effects of PGs like increasing myometrial contractility, isthmic tubal relaxation, luteal maintenance, immuno suppression and enhancing spermatozoa oocyte binding effects are limited. [3] The aim of this study was to determine the rate of fertility using misoprostol after IUI.

METHODOLOGY

After taking ethical clearance from the institute, Prospective randomized controlled trial was conducted. All infertile

women attending assisted reproduction centre (ARC) over a period of one year were offered study entry. Women with known history of kidney or liver disorder were excluded. Six hundred IUI cycles meeting the inclusion criteria have been recruited after obtaining informed voluntary consent and randomized into two groups based on computer generated randomization technique. Various causes of infertility were documented (Table 1). [4] Stimulating protocol and decision for IUI was made by attending physician. (Table 2) They were monitored by serial transvaginal ultrasonography. Inj. human chorionic gonadotropin (HCG) 5000 IU intra muscular was given at the time of appearance of dominant follicle and endometrial thickness was noted. [5] After 36 hours rupture of follicle was checked before insemination. If ruptured, single IUI was done, otherwise IUI was repeated after 24 hours. Prior to speculum removal after IUI, an opaque white misoprostol (200 µg) pessary was kept in the vagina for all women in the study group and not in the control group. Subjects were contacted by telephone for follow up data concerning side effects - vaginal bleeding and pelvic pain. Severity of pain was assessed using verbal pain score. Pregnancy confirmation was made by urinary HCG test after 16 days of IUI if there is no menstruation. Positive tests were further followed by transvaginal ultrasonography at 4-6 weeks from insemination. Those with gestational sacs with cardiac activity were defined as clinical pregnancies.

Table 1: Etiology of infertility

Etiology	Criteria
Poly Cystic Ovarian Syndrome (PCOS)	Based on Rotterdam criteria. [11]
Male factor	Oligospermia , asthenozoospermia, azoospermia.
Endometriosis	Confirmed by laparoscopic visualization.
Tubal factor	At least one abnormal fallopian tube on hysterosalphingography (HSG) or laparoscopy.
Uterine disease	Hysteroscopic confirmation and correction of abnormalities.
Unexplained infertility	All other causes excluded.

Table 2: Stimulation Protocols

Tab.Clomiphene citrate (CC)	50 to 150 mg. FromD3 to D7 or D5 to 9
Tab. CC + Inj Human menopausal gonadotropin (HMG)	CC (50 to 150 mg) daily from D3 to 7 or D5 to D9 + Inj HMG (75 IU) alternate day or daily from D3 or D5, 3 or 4 doses.
Letrozole	2.5 – 5 mg daily from D5 to 9

Statistical Analysis

For different quantitative variable mean and standard deviation were calculated. Means were compared using Student's unpaired't' test. The frequencies belonging to different categories of the two groups were counted and percentages were calculated. The respective percentages (proportions) were compared using the test of proportion.

RESULTS

Pregnancy rate in misoprostol (Study) group was 8.4% and that in control group was 9.6%. Overall pregnancy rate achieved in 600 IUI cycles was 9% per cycle. Demographic data of both study and control group are presented in table 3. Causes of infertility and pregnancy rate in relation to it are tabulated in table 4. Different strategies of ovarian stimulation and pregnancy rate of both are shown in table 5. Subjective side effects like pain and spotting have been noted among all participants and documented in table6. None

of the participants reported with severe pelvic pain, fever or diarrhea. Outcome details were not available in 5cases (4 in the study & 1 in control group) and hence were excluded from study.

Table 3: Subject Demographic Data

Variable	Study group Mean ±SD	Control group Mean ±SD	'p' value
Age	28.62±6.1	28.32±5.45	NS
BMI	27.3±0.47	26.5±0.43	NS
Duration of infertility in years	6.06±3.43	5.72±2.92	NS
Previous number of IUI	2.41±1.74	2.57±1.87	NS
Day of IUI	14.73±1.82	14.67±1.94	NS

Table 4: Pregnancy rate (%) by infertility diagnosis

Variable	Study Group (296)	Control Group (299)	'p'
PCOS	6/15(2.03)	4/10(1.34)	NS
Male factor	7/122(2.06)	13/122(4.3)	NS
Endometriosis	2/7(0.68)	0/5	NS
Unexplained	8/140(2.7)	11/156(7.68)	NS
Uterine disease	2/9(0.68)	1/10(0.33)	NS
Tubal factor	0/3	0/6	NS
Total	25(8.4)	29(9.6)	

Values in parenthesis are percentages, PCOS = Polycystic ovarian syndrome

Table 5: Pregnancy rate (%) by treatment and cycle type

Cycle type	Study group	Control group	Total	'p' value
CC	8.07(18/223)	9.9(22/222)	8.98(40/445)	NS
CC+HMG	8.51(4/47)	8.77(5/57)	8.65(9/104)	NS
Letrozole	11.53(3/26)	10.00(2/20)	10.86(5/46)	NS
Total	8.4(25/296)	9.6(29/299)	9.1(54/595)	NS

Values in parenthesis are actual numbers

Table 6: Subjective Side effects

Variable	Study Group (296)	Control Group (299)	'p'
Spotting	26(9.4)	21(7)	NS
Pain	12(4)	9(3)	NS

Values in parenthesis are percentages

DISCUSSION

The role of decreased level of prostaglandin E in etiology of unexplained infertility was mentioned first in 1947. [6] However, the precise physiological effects of a decrease in PGE mediating infertility in these couples have never been determined. [7] Based on earlier studies, it seems that PGs especially PGE may help fertility rate , through facilitation of sperm transfer by relaxing cervical isthmus, increase retrograde uterine contraction, fallopian tube relaxation, facilitating sperm penetration in the ovum and helping suppressing female immune response to spermatozoa. [8-12] PGs are lost during the preparations of semen for IUI. Brown et al used vaginal misoprostol synthetic analogue of PGE1, 400mg mixed with inert triglyceride, administered via suppository at IUI and found that the cumulative pregnancy rate with drug was significantly greater than with placebo (17% vs 9% per cycle). A significant difference was noted in clomiphene cycles but not in clomiphene/ follicle-stimulating hormone or natural cycles. [2] In contrast, current study

did not find any benefits of 200 mg of vaginal misoprostol in the clomiphene citrate/human menopausal gonadotropin cycle; clinical pregnancy rates were 8.4% vs 9.6% in the treatment and control groups, respectively. We found increased pregnancy rate with letrozole (11.5% Vs 10%) which was not statistically significant.

Sperm was identified in the oviduct within 5 minutes from deposition into the proximal vagina and constant level was found from 15 to 45 min. [13] Sperm travel rapidly in-vivo or retrograde uterine contraction assist their passage. [13, 15] After vaginal administration of misoprostol, action begins within 15 minutes, there is a gradual rise to a maximum level at 60-120 minutes and at 240 min the level is still at 60% of peak level. Increased uterine contraction frequency at the time of IUI is associated with improved pregnancy rates. [16] In current study, administration of vaginal misoprostol after insemination might have resulted in increased uterine contraction frequency before which the sperm would have reached the fallopian tube. We speculate that this factor could have an impact on the pregnancy rate. Misoprostol was mixed with inert triglyceride base, this has caused sustained release of drug and hence side effects observed in current study are consistent with Brown et al in contrast to Zeyneloglu et al. [17]

The findings of the index study do not support the hypothesis that the use of vaginal PG is important in assisting the process of human fertilization in establishing pregnancy. However, link remains to be established and further studies are needed to determine the precise role of PG in early human reproductive events. Also, timing of misoprostol administration with respect to the insemination has to be evaluated. In conclusion, at this time, there is limited evidence to support the use of misoprostol in an IUI procedure.

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