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Original Research Article

Comparison of different ovulation protocols in patients undergoing controlled ovulation hyperstimulation with intra uterine insemination

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ABSTRACT

Background: For many couples' advent of a baby is the most beautiful gift of life. Involuntary childlessness by itself does not threaten physical health but can have a strong impact on the psychological and social wellbeing of couples. The aim of the present investigation was comparison of different ovulation protocols in patients undergoing controlled ovulation hyperstimulation with Intra uterine insemination.

Methods: A Prospective observational study was conducted in the department of obstetrics and gynaecology. 200 couples who underwent 541 cycles with controlled ovarian hyperstimulation. Variables selected for analysis were female age, menstrual history, duration of infertility, number of cycles, number dominant follicle diameter, endometrial thickness.

Results: Maximum patients underwent ovulation induction with clomiphene citrate (202/541) and then with letrozole (202/541).

Conclusions: Nowadays when the costs of health care are limited, intrauterine insemination can hold its place as a low-cost method of infertility treatment. Conclusively with careful selection of subjects, appropriate controlled ovarian stimulation and intra uterine insemination, good pregnancy rates with low multiple pregnancy rates can be achieved.

Keywords: Controlled ovulation hyper stimulation, Intra uterine insemination, Ovulation protocols

INTRODUCTION

For many couples' advent of a baby is the most beautiful gift of life. Involuntary childlessness by itself does not threaten physical health but can have a strong impact on the psychological and social well-being of couples. Infertility is defined as failure of a couple to conceive after one year of unprotected intercourse. Approximately 85%-90% couple conceive within one year. Infertility therefore affects 10-15% couples.^{1,2}

Though prevalence of infertility has been stable, the demand for infertility cure has increased significantly

over the past decade. Intra uterine insemination (IUI) is the first step in the ladder of fertility management in couples with no evidence of tubal damage or severe male factor.^{3,4}

IUI with husband's sperm has been widely used for treatment of infertility with variety of indications, such as moderate male infertility, unexplained infertility, cervical mucus hostility and ovulatory disturbances.⁵ The overall success of intra uterine insemination varies, with pregnancy rates between 5 and 26% per cycle.⁶ IUI with controlled ovarian hyperstimulation is more effective than intra uterine insemination alone or intra cervical

insemination.⁷ Ovarian stimulation has been shown to significantly improve the outcome in IUI cycles by two mechanisms; by increasing the number of eggs available for fertilisation and by overcoming a subtle defect in ovulatory function in ovulatory function and luteal phase.⁸

IUI is widely used for treating infertility in couples because it is simple, inexpensive. Ejaculated semen is a mixture of spermatozoa and seminal plasma, seminal plasma is constituted by secretions of epididymis, seminal vesical and prostate, semen may also contain other components like microorganisms and leucocytes. The main objective of semen preparation techniques is to harvest the most functional sperms from this ejaculate with minimal damage. Pregnancy outcomes after IUI are determined by a number of factors, these factors include the use of ovulation induction protocols, patient age, duration of infertility and the type of infertility.^{9,10}

So, the aim of the study is to compare different ovulation protocols in patients undergoing controlled ovulation hyper stimulation with Intra uterine insemination.

METHODS

This prospective observational study was conducted at Department of Obstetrics and Gynaecology. The study was approved by Ethics Committee. This study included 200 couples who underwent 541 intra uterine insemination cycles, with controlled ovarian hyper stimulation and who fulfil the inclusion and exclusion criteria. The duration of infertility was defined by the time interval from beginning of unprotected intercourse until registration at the fertility centre.

Detailed history of the couple include age, duration of infertility, regularity of periods, duration of contraception, sexual history, previous treatments if taken, occupation, family history. After obtaining history general physical and systemic examination was carried out. Per speculum examination was performed & Pap smear taken if indicated. Per vaginal examination was done. Abnormal findings noted. Semen analysis done for male partner as per WHO criteria.⁸

Inclusion criteria

- women of age less than 40
- negative pregnancy test
- patent fallopian tubes
- normal uterine cavity
- history of Infertility >1 year
- Men age <50, history of Infertility >1 year
- normal semen analysis.

Exclusion criteria

- women with previous IVF
- previous H/O PID

- previous IVF
- Men with previous H/O of intrauterine insemination.

Couple were requested not to have inter course for 3-5 days before the day of semen collection. Semen samples were produced by masturbation and collected in sterile containers. After complete liquefaction for 30 min samples were assessed according to WHO criteria.

After analysis, standard swim up technique was employed using Hams F-10 medium. Briefly, sample was centrifuged at 500 rpm for 15 min. The supernatant discarded, and the pellet diluted in 2.5 ml of medium and recentrifuged. After removing the supernatant, the final pellet was gently covered with medium and incubated for 1 hr at 37°C in an incubator.

Different methods of ovulatory stimulation in our study. Administration of Clomiphene citrate 100 mg daily from third day of patient's cycle up to five days (d3 d4 d5 d6 d7). Administration of Letrozole 2.5 mg from third day patient's cycle up to five days. Administration of Inj recombinant FSH 75 IU intramuscular alternately on three days, starting from third day of patient's cycle (d3 d5 d7) Administration of Tab Clomiphene citrate and Inj. recombinant FSH 75IU, Tab. Clomiphene citrate 100mg was administered orally from day 3 to day 7 and Inj recombinant FSH 75IU intra muscular injection of 75 mg from day 3 to days 7 on alternate days. Administration of Letrozole and Inj recombinant FSH 75IU. Tab Letrozole 2.5 mg. orally from d3 to d7 daily for 5 days and Inj recombinant FSH 75IU IM on alternative days from day 3 to day 7.

All patients were followed using vaginal ultrasound with Siemens sonoline Siena Ultra sound imaging system using 7.5 MHz vaginal probe. Folliculate diameters were calculated as a mean of the largest diameter and its perpendicular value. When they had at least one dominant follicle (>18 mm) 5000 units of human chorionic gonadotropin was injected intramuscularly and after 36 hrs, intra uterine insemination was done. Intra uterine insemination procedure. Patient is given lithotomy position. Vagina is cleaned with saline and cervical mucus is removed. Cervix is exposed using bivalve speculum.

IUI was performed using intra uterine insemination catheter with 2 ml syringe. The catheter was gently passed through cervical canal and the sperm suspension expelled into the uterine cavity. Insemination volumes ranged from 0.5ml to 1ml injected slowly over 1-2 minutes. Avoid any trauma to cervix or endometrium. The women remained supine for 10-15 minutes. Clinical pregnancy was defined as transvaginal ultrasonographic visualisation of intrauterine gestational sacs.

Data from 200 patients who attended the infertility clinic were included in this study. Variables selected for analysis were female age, menstrual history, duration of

infertility, number of cycles, number dominant follicle diameter, endometrial thickness.

Statistical analysis

All the continuous variables were represented by mean with standard deviation and it was analyzed by independent sample t-test. Categorical variables were presented by frequency and percentages; it was analyzed by Chi-square and Fisher exact test. Logistic regression analysis was used for multiple variable comparisons to pregnancy rate. All the analysis was done by using SPSS 14.0 version. A p value less than 0.05 was considered as significant.

RESULTS

A total of 541 IUI cycles in 200 women resulted in 65 pregnancies. The number of treatment cycles varied from 1 to 8 with a mean of 2.06 ± 1.49 per couple. The average clinical pregnancy rate was 12% per cycle and the pregnancy rate was higher in first treatment cycle (66.77%) and decreased from second cycle onwards. The overall pregnancy rate was 33% per patient. The age range varied from 19-38 years and the average age was 29.08 ± 4.19 years. The pregnancy rate in the age group <30 years was 33.04% in comparison to 31.76 in the age group more than 30 years ($p=0.849$), therefore the pregnancy rate and age of women are not statistically significant.

The pregnancy rate was 9.5% when one follicle was produced, whereas with more than 1 follicle, the rate increased to 18.1%. The pregnancy rate increased with the number of mature follicles upto 3, being significantly higher if more than one mature follicle developed and its statistically significant ($p<0.001$). The mean number of follicles was 1.42 ± 0.64 .

In present study the size of the follicle is not a significant variable. This might be because most of the follicles are above 1.5cm. Insemination between day 10 and 14 resulted in a pregnancy rate of 9.9% compared to 20.4% if insemination was carried out between day 16 and 25 and it is statistically significant ($p=0.003$).

Among the different ovulation induction protocols maximum number of patients underwent ovulation induction with clomiphene citrate, clomiphene citrate when combined with r FSH gives maximum pregnancy rate 38.5% and it is statistically significant as compared to other drugs ($p= <0.001$).

Multivariate analysis of the variable shows that number of follicles, endometrial thickness. Ovulation induction with clomiphene citrate and r FSH, number of cycles and insemination after 15th day are significant variables for better pregnancy rates.

Table 1: Number of cycles with respect to different ovulation induction protocols.

Drugs	No. of cycles	Percent
Clomiphene citrate	237	43.8
Letrozole	202	37.3
r FSH	38	7.0
Clomiphene citrate+ r FSH	13	2.4
Letrozole+ r FSH	51	9.4
Total	541	100

Maximum patients underwent ovulation induction with clomiphene citrate (202/541) and then with letrozole (202/541).

DISCUSSION

A total of 541 IUI cycles in 200 women resulted in 65 pregnancies. The number of treatment cycles varied from 1 to 8 with a mean of 2.06 ± 1.49 per couple. The average clinical pregnancy rate was 12% per cycle and the pregnancy rate was higher in first treatment cycle (66.77%) and decreased from second cycle onwards. The overall pregnancy rate was 33% per patient. The age range varied from 19-38 years and the average age was 29.08 ± 4.19 years. The pregnancy rate in the age group <30 years was 33.04% in comparison to 31.76 in the age group more than 30 years ($p=0.849$), therefore the pregnancy rate and age of women are not statistically significant.

Clomiphene citrate is considered as the drug of first choice in oligo and anovulatory patients.^{11,12} Various studies obtained rates from 9 to 12 % Present study the rate is 8.4 %. Present study is in accordance with most of the studies and showed that Clomiphene citrate is the drug of first choice as well as it is cost effective.¹³⁻¹⁵

Letrozole is in accordance with most of the studies which has exceptionally very high pregnancy rates of 3 to 14% with Letrozole.¹⁶⁻¹⁸ For Letrozole and recombinant FSH various studies gave pregnancy rate of between 17 to 19%. Present study showed a pregnancy rate of 18.2%.^{19,20}

Clomiphene citrate and Recombinant FSH. This regimen shows a significantly higher results in accordance with other studies.²¹⁻²³ In present study ovulation induction drug is a significant prognostic variable with Clomiphene citrate and Recombinant FSH regimen showing the best results.

The average pregnancy rate was 12% per cycle and 33% per couple. Multiple pregnancy rate was 7.6% mostly associated with Clomiphene Citrate. Stimulation with sequential Clomiphene citrate and recombinant FSH resulted in best pregnancy rates with low multiple pregnancy rates. Nowadays when the costs of health care are limited, intrauterine insemination can hold its place as a low-cost method of infertility treatment.

CONCLUSION

Conclusively with careful selection of subjects, appropriate controlled ovarian stimulation and intra uterine insemination, good pregnancy rates with low multiple pregnancy rates can be achieved.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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