

A study on outcome of controlled ovarian hyperstimulation and intrauterine insemination (husband) in a medical college in Kolkata



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ABSTRACT

Background: A combination of controlled ovarian hyperstimulation and intrauterine insemination (IUI) remains an important treatment option for couple having infertility. Success rate of IUI with ovulation induction ranges from 8-20% depending on many factors. **Aims and Objectives:** To assess the factors affecting the success rate of IUI and to evaluate the success of ovulation induction by different methods of controlled stimulation protocol. **Materials and Methods:** It is a duration-based prospective cross-sectional study where total of 67 couples were included by inclusion and exclusion criteria. They underwent 90 cycles of IUI with each couple having a maximum of three cycles. Ovulation induction was done by clomiphene citrate or letrozole or gonadotrophins. Semen preparation was done by density gradient method. The outcome was measured by positive urine pregnancy test. Range, percentage, confidence interval, mean with standard deviation, median, range, and P-value were calculated. $P < 0.05$ was taken as statistically significant. **Results:** Out of 90 IUI cycles 8 were successful resulting in a success rate of 8.8% per cycle and 11.9% per couple. Factors that had a positive impact were follicle size > 21 sqmm, endometrial thickness > 9 mm, post wash count > 15 million/ml, > 2 cycles of IUI and on the number of follicles 2 or more on the day of trigger. **Conclusion:** The study concluded that IUI after ovulation induction can be a simple and safe cost-effective procedure in selected group of infertile couple. **Clinical Significance:** IUI following ovulation induction can be a successful approach for specific indications in a low-resource setting where options for other ART interventions are absent or limited.

Key words: Intrauterine insemination; Ovulation induction; Clomiphene; Success rate; Letrozole; Gonadotrophin; Controlled ovarian hyperstimulation

INTRODUCTION

Infertility is the inability to conceive within 12 months of regular unprotected intercourse. Epidemiological data shows the prevalence to be 8–32%.^{1,2} Causes can be broadly divided into three groups: Female factors, Male factors, and unexplained infertility. Female factors include ovulation disorder, tubal disease, endometriosis, and all together accounts for 40 percent of total infertility. Male factors account for 30 % and unexplained infertility 10%. Rest 20% include both male and female factors.³

A combination of controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI) remains an important treatment option available to an infertility specialist and is widely used treatment modality for a broad range of indications. Common indications are cervical factor, anovulation, mild male factor, mild endometriosis, and unexplained infertility. The reported pregnancy rates per cycle range from 8 to 22%.² Commonly clomiphene is used as the drug of choice for ovulation induction, but nowadays letrozole is on the verge of replacing clomiphene as the first-line drug of choice for ovulation induction.

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Gonadotrophin is usually used in resistant cases and requires more strict monitoring of follicular growth. After ovulation induction, the processed semen from either husband or donor is put into the uterine cavity through the cervix via an insemination cannula. The pregnancy rates per cycle are quite variable in the literature due to differences in the cause and duration of infertility, sperm preparation technique, treatment cycles, and number of IUI performed during a cycle. The cumulative pregnancy rates for COH with IUI vary according to the indications. The reported success rate with clomiphene is 8.3%, whereas that of gonadotrophin is 17.3% however IUI without any ovulation induction has a success rate of only 3.8%.⁴ IUI is a simple low-cost procedure without any significant side effects. It is more suitable in patients with poor sperm count and reduced total motility. Furthermore, in unexplained infertility, it is a first-line cost-effective approach in developing countries rather than going for ART. Studies have shown that post wash counts >5 million/ml have a higher chance of success for IUI. Success rate in case of anovulation and unexplained infertility varies between 15 and 20% and that of mild male factor infertility is 10–12%.⁵

Aims and objectives

To assess the factors affecting the success rate of IUI and to evaluate the success of ovulation Induction by different methods of controlled stimulation protocol.

MATERIALS AND METHODS

The above study was a prospective cross-sectional study done between a period of March 2018 to July 2019 in ESI-PGIMSR & MC, Joka in the Department of Gynecology and Pathology. A total of 67 couples who were attending Gynecology OPD of obstetrics and gynecology department of ESIC Joka were identified. A total of 90 cycles of IUI were done in the above mentioned time. The study was pre-approved by the Institutional Ethics Committee of ESIC, Joka for the final permission.

Inclusion criteria included females with unexplained infertility, endometriosis with at least one patent tube, and only peritoneal spots <5 mm depth found in laparoscopy (Mild endometriosis), anovulation diagnosed by ultrasonography, and mild male factor infertility (sperm count 5–15 million/ml).

Exclusion criteria were women with bilateral tubal block as seen by HSG followed by diagnostic laparoscopy and hysteroscopy, severe endometriosis (endometriosis with bilateral tubal block or bilateral ovarian involvement), unexplained genital bleeding. Furthermore, male with severe male factor infertility (sperm count <5 million/ml),

post-wash sperm count <5million/ml were excluded from the study.

Methodology

- Infertile couples were selected as per inclusion and exclusion criteria from OPD after taking their informed consent
- A detailed history of both the partners was taken followed by general physical examination
- Different hormonal tests such as LH, FSH, thyroid function test, and prolactin were carried out
- Baseline antral follicle count, follicular growth was monitored in unstimulated cycles to assess ovulation.

Once timed induction or hyperstimulation was decided the women were subjected to undergo COH by either clomiphene citrate or purified FSH/HMG or letrozole in titrating doses from day 2 of the menstrual cycle.

- After the hyperstimulation the patients were monitored by trans vaginal sonography for follicular development from day 10 of the menstrual cycle onwards
- If one or more follicle sizes reaches >18 sq mm and endometrial thickness reaches more than 7 mm and if there are no features of ovarian hyperstimulation syndrome (abdominal swelling, pain, vomiting, and ascites) then the patient will be triggered with HCG injection 5000u or 10000u through intramuscular route for ovulation
- The male partner was asked to attend within 36–42 h later for supplying the semen sample which was then processed by DENSITY GRADIENT METHOD. The semen sample was obtained by masturbation after 72 h of abstinence. At first, a Pre-wash count was taken with the help of Neubers chamber and microscope. The media was preheated to 37°C in a thermal bath for 2 h before the procedure starts. Then 1 ml of 90% (v/v) media was taken in a conical tube (Falcon tube) with a sterile pipette. It was gently overlaid with 1 ml of 45% (v/v) gradient media. The whole semen was then placed on top of two layers. It was centrifuged at 1500 rpm for 15 min. The supernatant was discarded leaving the pellet with as little of 90% solution as possible. In another test tube, 5 ml of sperm wash media was taken and the pellet was transferred via pipette. It was then centrifuged at 1500 rpm for 10 min. The supernatant was discarded and pellet with 0.5–1 ml solution was prepared. A small amount of (0.2 microliter) of this sample was put under microscope with Neubers chamber. Under ×10 focal length the number of motile sperms were counted in the middle counting chamber of neubers chamber and if the post-wash count was more than 5 million/ml then the sample was taken for further steps. The final processed sample was used for insemination through insemination cannula

- Urine pregnancy test was done after 14 days, and a transabdominal ultrasound was done after 6 weeks
- Positive urine pregnancy test and Ultrasonic evidence of pregnancy were taken as successful outcome
- All the expenses were carried out by the Department of Obstetrics and Gynecology, ESIC JOKA
- The study has been cleared by the ethical clearance committee of ESIC JOKA.

Statistical analysis

The statistical analysis with these three determining groups was done by using the P-value (<0.05) with 95% confidence interval. Data were entered in Microsoft Excel 2013 and Statistical Package for Social Sciences Version 22.0 software was used for data entry and analysis. Descriptive analysis was done by calculating percentages, confidence interval, mean with SD, median, and range. Appropriate statistical test was applied as per the need of study. P<0.05 was taken as significant.

RESULTS

Total 90 IUI had been done and out of them, eight were successful.

Total 67 couples had IUI.

- Out of this 29 couples have one cycle of IUI
- 23 couples have two cycles of IUI
- 15 couples have three cycles of IUI.

In this study, Gonadotrophin and Letrozole have success rate of 20%, which is statistically significant. Clomiphene citrate has success rate of 14.3% only (Table 1 and Figure 1). Success rate increases if IUI is done at an endometrial thickness is above 9 mm (11.11%) and it is statistically significant (Table 2 and Figure 2). There is a significant success rate in IUI if stimulation is given on follicle size above 21 square mm (11.11%) which is statistically significant (Table 3). Success rate of IUI doubles if number of follicles at the time of trigger is >2 (20%), which is statistically significant. Up to 2 follicles it is 10% and 6.66% for 1 follicle (Table 4).

The success rate is almost similar (13%) in 2 cycles of IUI. Success rate does not increase much after second cycle fails (1/15=6.6%), which is statistically significant (Table 5). Success rate doubles if post wash count is more than 15 million/ml (14.28%), a statistically significant finding. Below 15 million/ml the success rate drops down to 6.25% (Table 6) IUI success rate is 8.8% per cycle and 11.94 % per couple. Live birth rate is 6.6 % and 1 case each resulted in miscarriage and ectopic pregnancy (Table 7).

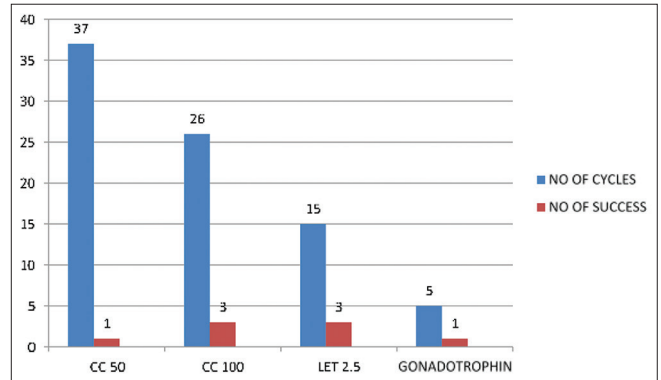


Figure 1: Success rate by type of stimulation

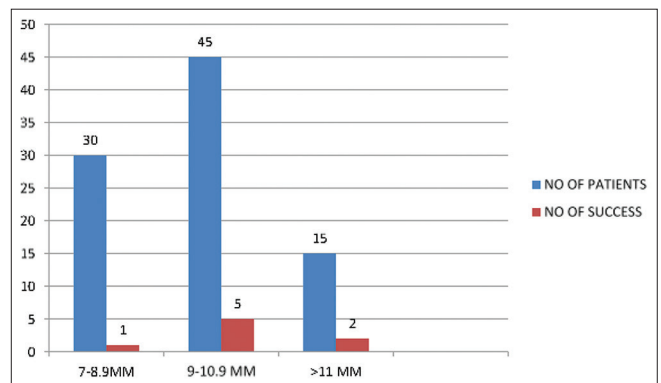


Figure 2: Endometrial thickness (x axis) (n=90 cycles)

Type of stimulation	Success rate	Percentage	P-value
Clomiphene Citrate 50 mg	1/37	2.8	
Clomiphene citrate 100 mg	3/26	11.5	
Letrozol 2.5 mg	3/15	20	0.02
Gonadotrophin (FSH)	1/5	20	0.02

Gonadotrophin and letrozol has success rate of 20%, which is statistically significant. clomiphene citrate has success rate of 14.3%

Endometrial thickness (mm)	Success rate	Percentage	P-value
7-8.9	1/30	3.33	
9-10.9	5/45	11.11	0.002
>11	2/15	13.3	

Success rate increases if IUI is done at an endometrial thickness above 9 mm and it is statistically significant

DISCUSSION

In this study clomiphene citrate (50 mg), clomiphene citrate (100 mg), letrozole (2.5 mg), and gonadotrophin (follicle-stimulating hormone) is used for ovulation induction. Success rate is 20% for both gonadotrophin and letrozole but goes down to 11.8% in clomiphene citrate (100 mg)

Table 3: Success rate on dominant follicle size

Follicle size on triggering day (sq mm)	Success rate	Percentage	P-value
18–20.9	2/35	5.7	0.01
21–23.9	5/45	11.11	
>24	1/10	10	

There is significant success in IUI if stimulation is given on follicle size above 21 sq mm, which is statistically significant

Table 4: Success rate by number of follicle

No. of follicle	Success rate	Percentage	P-value
1 follicle	3/45	6.66	0.005
2 follicle	4/40	10	
>2 follicle	1/5	20	

Success rate of IUI doubles if number of follicles at the time of trigger is >2, which is statistically significant

Table 5: success rate by cycle of IUI (n=67 patients)

Cycles	Success rate	Percentage	P-value
1 cycle	4/29	13.79	0.005
2 cycle	3/23	13.04	
3 cycle	1/15	6.67	

Success rate is almost similar (13%) in 2 cycles of IUI. success rate does not increase much after second cycle fails (1/15=6.6%), which is statistically significant

Table 6: Success rate of IUI by post wash count in mild male factor infertility patients

Post wash count (million)	Success rate	Percentage	P-value
<15	1/16	6.25	0.005
>15	1/7	14.28	

Success rate doubles if post wash count is more than 15 million/ml, a statistically significant finding

Table 7: Pregnancy outcome of IUI (n=8)

Parameters	Outcome	Percentage
Pregnancy/cycles	8/90	8.88
Live birth/cycles	6/90	6.66
Miscarriage	1/8	12.5
Ectopic pregnancy	1/8	12.5
Multiple pregnancy	Nil	Nil

and steps further down to 2.8% in Clomiphene Citrate (50 mg). Furthermore, study done by Van rumste et al.,⁴ in 2008 showed success rate of gonadotrophin protocol to be 17.8 % which is comparable and that of clomiphene is 8.3% which is similar to this study. Rezaie et al., also showed that the success rate with gonadotrophin to be around 11 % and that of clomiphene is 7.2% which corroborates with this study. Possible explanation includes the fact that gonadotrophin induces multi follicular growth which increase the chance of success and letrozol is more effective

in patient with anovulation by preventing premature LH surge. Furthermore, induction by letrozol yields better endometrial thickness than that of clomiphene so may have a better success rate. Success rate of clomiphene is found out to be 11.8% by study done by Wadhwa et al.,⁶ in 2018 which is like our study and reiterates the fact that gonadotrophins have higher success rate. In our study clomiphene citrate is used as the first-line drug; overall estimation is that clomiphene due to its anti-estrogenic action on endometrium may lead to poor endometrial preparation and therefore poor pregnancy rate despite achieving ovulation and earlier switch over to letrozole and gonadotrophins after 2–3 failed cycles, rather than waiting for 6 cycles; may give better patient outcome.

The success rate improves with the size of the follicle. Success rate doubles with follicle size >21 mm up to 24 mm compared to follicle size 18 to 20.9 mm (11.1% vs. 5.7%). However, if follicle size >24 mm the success rate again reduces to 10% possibly because of more chances of cyst formation. American Society of Reproductive Medicine suggests >18 mm as acceptable size of the follicle for the insemination as taken in this study. Ganguly et al.,⁷ in 2016 also demonstrates the trend of increasing success rate with increase in the size of the follicle. The finding in this study is statistically significant.

The number of follicles on ovulation triggering day have always been an important factor for success rate. This study also shows that success rate is 6.6% in 1 follicle and 10% for 2 follicles but goes up to 20% for >2 follicles which is statistically significant. Study by Dickey et al.,⁵ in 2002 also shows that success rate is 17.3% in >2 follicles and therefore corroborates with our study. However higher follicular number is usually seen with gonadotrophins, and it has more chance of success but also more chances of OHSS. Nowadays as letrozol is more commonly used as first-line agent for ovulation induction and it promotes monofollicular growth hence the chance of OHSS is reduced. Therefore, this favorable factor of >2 follicles also come with an increase chance of OHSS.

Endometrial thickness is another very important and well-recognized factor for the success of IUI as thick endometrium helps in implantation. This study shows success rate to be 3.33% in 7–8.9 mm of ET but jumps to 11.1% when ET is 9–10.9 mm and further increase to 13.3% in ET >11 mm. so success rate triple if ET >9 mm, this is statistically significant. One study by Jayakrishnan et al.,⁸ in 2016 shows the success rate is 41.5% in ET of 9-10.9 mm. Acceptable standard for IUI includes insemination above 7 mm and studies such as Merviel et al.,⁹ in 2010 have also shown that success rate drops below 7 mm and improves when the endometrial thickness is more.

Out of 23 patients with mild male factor infertility who had semen processing done by density gradient method, 16 patients had post-wash count <15 million/ml and 7 patients had post-wash count >15 million/ml. The success rate more than doubles (14.28% vs. 6.25%) when the post-wash count is >15 million/ml. Study by Merviel et al.,⁹ in 2010 shows the success rate 17% if post-wash count >15 million/ml which corroborates with this study. Also, study by Mohan S Kamath et al.,¹⁰ in 2010 shows success rate is 18.29% in post-wash count of 10–20 million/ml which is double of that in <10 million/ml. Despite the consensus that IUI should be done when post-wash count >5 million/ml, this study along with previous studies show that success rate improves when post-wash count reaches the WHO standard of normal sperm count.

In this study success rate after 1 cycle of IUI is 13.79% and after 2 cycles of IUI it is 13.04%. But it drops down to 6.67% on the 3rd cycle which is statistically significant. Rezaie et al.,¹¹ in 2006 found the overall success rate to be 6.8%. Ganguly et al.,⁷ in 2016 found the success rate to be 15.75% on the 1st cycle which is comparable to our finding, but it drops down to 5.88% in the 2nd cycle. Although consensus is that the cumulative effect of IUI should increase success rate in successive cycles but in this case, improper abstinence before the day of IUI or inadequate sample may be a possible explanation. As a result of this year-long study total of eight patients conceived out of 67 couples having a total of 90 cycles of IUI. Success rate per cycle was 8.88%. Six patients have uneventful antenatal period resulting in live baby. One patient had a miscarriage and one patient had ectopic pregnancy. Success rate per couple is 11.94%. Kamath et al.,¹⁰ in 2010 found the success rate to be 8.75% per cycle. Rezaie et al.,¹¹ in 2006 had a success rate of 6.8% per cycle which is comparable with this study, but it was 19.5% per couple which is more than this study. This finding is possibly due to many couples not getting the 2nd cycle because of limited time duration.

Limitations of the study

Sample size was small due to resource and time constraints. Also due to 1 year time frame all the 67 couples could not complete the three cycles of IUI. Moreover, six cycles of IUI would have given more success rate.

CONCLUSION

Success rate of IUI improves with the follicle size of more than 21 mm and endometrial thickness of more than 9 mm on the day of trigger. Two or more follicles on the day of trigger and post-wash count >15 million/ml will have a higher probability of success rate. The rate improves with

the number of cycles. The study also indicates that after 2–3 failed cycles with clomiphene despite achieving ovulation; switching over to letrozole or gonadotrophin will yield better results. However, further studies are required with larger sample sizes to validate the findings of this study.

CLINICAL SIGNIFICANCE

The study shows that IUI is an effective and alternative procedure for low-resource settings rather than IVF and other methods of ART. In limited resources, it is effective for anovulation, mild male factor infertility, minimal to mild endometriosis, and unexplained infertility. The results can be a guide for successful outcome in the patients.

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The study has been approved by the ethical clearance committee of ESIC Joka.

MANUFACTURER

IUI set with insemination cannula- Krischo medical products PVT limited. Bengaluru, Karnataka.

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Authors' Contributions:

RR- Concept and contribution of overall study, Review of literature, Critical revision of manuscript; **AS-** Design of the study, preparation of first draft, Manuscript preparation; **BSD-** Statistical analysis and interpretation, review of literature.

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