

Timed Intercourse versus Intrauterine Insemination with Mild Ovarian Stimulation for Unexplained Infertility

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Abstract

Background: Infertility is unexplained in about 22% - 28% of infertile couples. Spontaneous pregnancy may occur in them. If did not happen, Expectant management will be via clomiphene citrate (CC) administration, intrauterine insemination (IUI), and IVF & ICSI. **Aim:** to assess the effectiveness of intrauterine insemination with mild controlled ovarian stimulation compared with expectant management in couples with unexplained infertility more than one year. **Methods:** 160 couples with unexplained infertility were selected, The couples were randomly divided into two groups: Group (A) “80 couples”: Intrauterine insemination (IUI) with mild controlled ovarian stimulation (combination of CC + hMG) using prepared semen and was performed 36 hours after hCG injection, Group (B) “80 couples”: Couples had no ovulation induction. They encouraged for timed intercourse in the most fertile days of female cycle guided by folliculometry for 6 months. Data were collected quantitatively, coded and analyzed using SPSS. The power of study is 80% and 95% confidence interval. **Result:** The pregnancy rate was calculated in both groups: In group (A) (IUI/COS): OPR (Ongoing pregnancy rates) was 27.5% and PR (pregnancy rates)/cycle was 8.6%. In group (B) (Expectant management): OPR was 25% and PR/cycle was 5.3%. **Conclusion:** Mild controlled ovarian stimulation CC + hMG with IUI offers no statistical significance in terms of pregnancy outcomes over expectant management in this study however significance in the response to stimulation.

Keywords

Intrauterine Insemination, Ovarian Stimulation, Unexplained Infertility

1. Introduction

Failure to conceive after having frequent, unprotected sex for at least a year is considered infertility. In 30% - 40% of couples having routine reproductive studies, the cause of infertility is unknown or poorly understood, and treatments range from expectant care through IUI, IVF, and ICSI [1].

Infertility is currently successfully treated with assisted reproductive technology (ART) in a wide range of clinical conditions. It encompasses a variety of procedures, the most prominent of which are “intrauterine insemination (IUI), *in vitro* fertilisation (IVF), and intracytoplasmic sperm injection (ICSI)” [2]. Contrary to IVF and ICSI, IUI is simple, affordable, and offers a number of benefits, including the need for little to no special equipment, ease of learning, and a lower psychological burden on couples [3].

Increasing the gamete density at the site of fertilisation is the goal of intrauterine insemination (IUI). There is still debate concerning the efficacy of artificial insemination using husband’s semen despite the wealth of literature on the subject, particularly in regards to IVF and ICSI [4].

Numerous studies indicate that IUI with ovarian stimulation increases the likelihood of conception in couples with unexplained infertility; however, the effectiveness of the agent employed for stimulation is the main area of concern [5].

The UK national guidelines on infertility propose that a couple attempting to conceive a baby try naturally for 12 months before any serious testing or intervention if there is no reason to suspect underlying infertility. Over the course of this 12-month span, 84% of couples will become pregnant. The other 16% of couples undergo testing throughout the ensuing year for common underlying causes of infertility, at which time half of them will become pregnant (for a total pregnancy rate of 92%). Those whose infertility has a known cause are placed onto the proper treatment pathway, while those whose infertility is “unexplained” are urged to “keep trying” for a third year [6].

Aim of the work

The aim of this study was to assess the effectiveness of intrauterine insemination with mild controlled ovarian stimulation compared with expectant management in couples with unexplained infertility more than one year.

2. Patients and Methods

This study was Randomized controlled trial, included 160 couples of unexplained infertility during the period between November, 2020 and October, 2021 at Boy and Girl Centre.

Inclusion criteria: Age is between 18 - 30 years, Normal semen parameters according to WHO parameters, Normal ovulatory cycles and Patent both tubes (normal salpingography).

Exclusion criteria: Cases with failed previous 3 IUI trials.

All Patients Subjected to Complete History Taking and Clinical Examination for Both Group.

In group (A) (intervention group):

- After satisfactory basal TVS, ovarian stimulation started at 3rd day of cycle by both clomiphene citrate with highly purified gonadotrophine as a combination, (clomiphene citrate “clomid” 100 mg tablet orally/daily from day 3rd to 7th day” & highly purified gonadotrophine (merional; IBSA; Lugdno; Switzerland), in dose 75IU once daily IM injection).
- At 7th day, TVS folliculometry had been done and dose of hMG was tailored according to response.
- Follow up was done by using TVS folliculometry which had been performed every two days according to the response to stimulation.
- Ovulation triggering had been done when at least one follicle ≥ 18 mm in diameter and endometrial thickness was ≥ 8 mm. by using 10.000 IU of human chorionic Gonadotrophines (hCG) (Choriomon; IBSA; Switzerland) IM injection, 36 hour before IUI procedure.

Semen preparation for insemination:

- Intra uterine insemination had been done using fresh semen obtained from husband.
- On day of insemination, semen sample was collected in a sterile container by masturbation. Then the container had been lifted on hot stage (37°C) for 15 - 20 minutes for liquefaction.
- Assessment of count and motility was done microscopically. The semen sample was transferred into nutrient media (Ham’s medium) in 1:1 ratio (semen: media) then to uniform mixture was obtained using glass pipette (Pass-tair’s pipette).
- Tube containing the mixture was centrifuged at 1500 rpm for 10 minutes at 37°C.
- The supernatant was discarded and the pellet was re-suspended in 2 ml of media and centrifuged again for 5 minutes at 1000 rpm.
- After the 2nd wash, the supernatant was discarded and the resulted undisturbed pellet was layered by nutrient media (sperm prep) without mixing and incubated for 30 - 60 minute.
- Then the supernatant had been taken and used for intrauterine insemination.

Technique used for insemination:

- With the patient in the dorsal lithotomy position dry sterile Cusco-speculum was inserted into the vagina, the cervix was cleaned with a sterile dry cotton swab.
- An IUI catheter containing the prepared semen was gently introduced through cervical canal into uterine cavity above the isthmus then the 0.5 ml prepared semen in the syringe was slowly injected intrauterine.
- The tube was gently withdrawn after completion of insemination. Then patient discharged with allowed normal activity.
- Support for the luteal phase was provided with 200 mg vaginal progesterone suppositories (Prontogest, GMP, EPISA) twice daily beginning on the day after

insemination for two weeks. If pregnancy was confirmed, progesterone treatment was extended for an additional eight weeks.

In group (B) (control group):

- Couples had been allocated in expectant management by encouraging timed intercourse in the most fertile days of female cycle.
- No ovulation inducing drugs were used in this group.
- TVS folliculometry was started at 5th day of cycle and continued every 2 - 3 days to follow follicular growth and determine time of ovulation for encouraging timed intercourse.
- Timed intercourse (TI) instructed when follicle reached 16 mm. This counseling is repeated until occurrence of pregnancy or for 6 months.

The outcome of interest was the Pregnancy Rate (PR)

Pregnancy (clinical Pregnancy) is defined if gestational sac with fetal pole was detected by ultra sonography at 5th week.

Also “Chemical Pregnancies” which defined by detectable rising in concentrations of beta human chorionic gonadotropins (Bh CG) level in serum (≥ 5 mIU/ml) with no gestational sac was seen on ultrasound and no chorionic villi were seen in surgical specimens.

Statistical analysis: Data were collected quantitatively, coded and analyzed using SPSS. The power of study is 80% and 95% confidence interval.

3. Results

There were no statistically significant differences between both groups (**Table 1**). There were no statistically significant differences between both groups regarding basal hormonal profile and semen parameters (**Table 2**). The number of dominant follicles “ ≥ 18 mm” and endometrial thickness were significantly higher in 1st group than 2nd group (**Table 3**). 256 cycles were carried out over 4 consecutive trials. 22 pregnancies were achieved in this group. This gives a pregnancy rate of 8.6% per cycle in this group. The 2nd trial gave the highest pregnancy rate per cycle (13.9%) while the lowest pregnancy rate was reported in the 4th cycle (4.1%) (**Table 4**). Pregnancy rate per cycle in the 2nd group: 276 cycles were carried out over 6 consecutive trials. 20 pregnancies were achieved in this group. This gives a pregnancy rate of 5.3% per cycle in this group. The 5th trial gave the highest pregnancy rate per cycle (12.0%) in this group. On the other hand, no pregnancies were reported in the 6th trial (**Table 5**). There is a comparison between both groups regarding pregnancy rate per cycle (PR/cycle) & over all pregnancy rate (OPR). With no significant difference in between both groups (**Table 6**).

4. Discussion

Early on in the history of assisted reproduction controlled ovarian stimulation (COS) using clomiphene citrate and intrauterine insemination (IUI) were the standard treatments for unexplained infertility [7].

Table 1. Base line characteristics of both groups.

Baseline characteristics	Group A	Group B	Test	P
	IUI Group (n = 80)	EM Group (n = 80)		
Wife's age (years)				
mean \pm SD	25.7 \pm 4.1	24.1 \pm 3.4	t = 1.98	0.05
Range	(19 - 30)	(20 - 30)		
BMI				
mean \pm SD	31.4 \pm 7.3	30.8 \pm 6.4	t = 0.47	0.69
Range	(22.5 - 35)	(23 - 34)		
Husband's age (years)				
mean \pm SD	31 \pm 4.8	28.8 \pm 4.6	t = 2.69	0.06
Range	(23 - 43)	(24 - 41)		
Husband habits (Smoking)				
n (%)	16 (20%)	20 (25%)	X ² = 1.01	0.31
Type of infertility				
- 1ry n (%)	68 (85%)	72 (90%)	X ² = 0.34	0.55
- 2ry n (%)	12 (15%)	8 (10%)		
Duration of infertility (years)				
mean \pm SD	2.8 \pm 0.4	2.5 \pm 0.6	t = 1.90	0.07
Range	(1.3 - 3)	(1.5 - 3)		

Table 2. Shows baseline investigations of both groups.

Base line Investigations	Group A	Group B	Test	P
	(n = 80) (mean \pm SD) (Range)	(n = 80) (mean \pm SD) (Range)		
Basal hormonal profile				
• FSH (day3) (mIU)	5.5 \pm 1.5 (2.6 - 8.5)	6.3 \pm 1.9 (3.2 - 10.3)	t = 1.64	0.15
• TSH (mIU)	2.5 \pm 1.6 (0.39 - 6.9)	2.7 \pm 1.9 (0.55 - 7.4)	t = 1.33	0.25
• Prolactin (ng)	9.8 (1.2 - 20.9)	10.3 (5.2 - 18.2)	t = 0.24	0.81
Semen analysis parameters				
• Sperm count (x 106)	57.7 \pm 10.9 (33 - 80)	60.4 \pm 10.2 (45 - 86)	t = 1.07	0.23
• Sperm motility (Progressive %)	37.3 \pm 5.7 (28 - 40.4)	27.7 \pm 4.3 (23 - 38)	t = 0.09	0.90
• Abnormal form (%)	70.4 \pm 10.2 (64 - 86)	76.3 \pm 8.9 (65 - 88)	t = 0.94	0.37

Table 3. Late follicular TVS data in both groups.

Late follicular TVS data	Group (A)	Group (B)	T	P
Number of Dominant follicle				
(Median)	3	1	Mann = 198.7	0.00*
(Range)	(2 - 5)	(1 - 2)		
Endometrial thickness (mm)				
(Mean + SD)	11.8 ± 0.5	8.1 ± 0.5	3.4	0.04*
(Range)	(10 - 12.5)	(7.8 - 10.5)		

Table 4. Pregnancy rate per cycle in group "A" (IUI group).

Cycle No	No of cycles	No of pregnancy
1 st	80	4 (5.0%)
2 nd	72	10 (13.9%)
3 rd	60	6 (10.0%)
4 th	44	2 (4.5%)

* Dropped out cases: 4 in 2nd & 2 in 3rd & 10 in 4th trials respectively.

Table 5. Pregnancy rate per cycle in group "B" (Expectant group).

Cycle NO	No. of cycle	No. of pregnancy
1 st	80	2 (2.5%)
2 nd	76	4 (5.3%)
3 rd	70	4 (5.7%)
4 th	60	4 (6.7%)
5 th	50	6 (12.0%)
6 th	40	0 (0.00%)

* Dropped out cases: 2 in 1st & 2 in 2nd & 6 in 3rd & 6 in 4th & 6 in 5th & 4 in 6th trials respectively.

Table 6. Shows comparison of pregnancy rate (PR) between both groups.

	Group A (n = 80)	Group B (n = 80)	X ²	P
No. of cycles	256	276		
No. of pregnancies	22	20		
PR/ cycles	8.6%	5.3%	3.07	0.09
Over all pregnancy rate (OPR)	27.5%	25%	0.88	0.27

Couples went step-by-step via FSH/IUI treatment if pregnancy wasn't obtained, and then, if that didn't work, on to IVF/ICSI [7].

In this randomised controlled trial, expectant management is compared to controlled moderate ovarian stimulation and intra uterine inseminations (COS/IUI)

as therapeutic alternatives for couples experiencing unexplained infertility.

No statistically significant difference was found between the two groups as regards basic infertility investigations and baseline parameters. Therefore, variations in the outcome may be linked to variations in management protocol.

This supports the conclusions of other investigations. Steure *et al.* (2018) separated 253 couples with unexplained infertility into two groups, one with COS/IUI and the other for expectant management. The study was a randomised trial. They discovered that the pregnancy rates in the two groups (33% versus 32%) did not differ significantly [8]. Couples experiencing unexplained infertility can therefore be offered an expectant management alone.

Another study by Guzick *et al.* (2018) found that 33% of couples with unexplained infertility who utilised COS/IUI were pregnant within 6 months; however, other couples who delayed therapy for 12 months while continuing regular sex also saw a comparable pregnancy rate. They came to the conclusion that treating infertility with IUI alone help patient to conceive sooner than later [7].

Uncertain mechanisms underlie how assisted reproductive technologies conquer infertility. The likelihood that an embryo will implant is likely to increase as a direct result of ovarian stimulation, which also leads to an increase in the number of follicles and embryos [7].

Improved folliculogenesis, which in turn may remedy a minor ovulation issue, or increased progesterone production, which may enhance endometrial receptivity, are examples of potential side effects [9].

Ovarian stimulation/IUI improves the course of treatment for couples with unexplained infertility as compared to a natural cycle [10]. In a meta-analysis comparing IUI with TI in stimulated cycles with gonadotropins in a prospective randomized research, Zeyneloglu *et al.* (2015) only included cases of unexplained infertility. A significant increase in PR was observed in IUI patients across eight studies with 980 cycles (OR = 1.84; 95% CI = 1.3 - 2.62) [11].

In 119 couples with unexplained infertility, Nulsen *et al.* (2013) conducted a randomized control study contrasting IUI in natural cycle with COS/IUI. IUI/COS had a cycle fecundity rate of 2.4% but IUI/natural cycle had a rate of 19.3%. This discrepancy was quite important [12].

Additionally, IUI and TI each had stimulated cycles in the treatment of infertility with no known cause. No statistically significant difference in PR between the two was discovered in study of Isaksson and Tiitinen [13].

Verhulst *et al.* (2012) conducted a recent Cochran review in randomized controlled trials (RCTS). Couples with unexplained infertility were enrolled in the study, and the following treatments were compared: IUI versus TI both during the natural cycle and IUI versus TI both during the stimulated cycle, as well as IUI during the natural cycle versus IUI during the stimulated cycle. In addition, they found that treatment with IUI was more likely to result in pregnancy when compared to TI in stimulated cycles, and that there was no difference between expectant management and IUI in natural cycles. They concluded that IUI with COS increases live birth rate when compared to IUI alone [13].

In the current study, intervention group (A) had a higher number of dominant follicles and endometrial thickness than control group (B), and this difference was statistically significant. This importance might be explained by the intervention group's controlled ovarian stimulation protocol. The COS procedure in this study was carried out in the intervention group utilizing CC with hMG, which produces positive results in terms of follicle count and endometrial thickness. Hzargoon *et al.* (2013) conducted a prospective randomized research in which they evaluated the identical treatment (CC plus hmG) vs CC plus rFSH utilised in our study during IUI cycles in couples with unexplained infertility. They came to the conclusion that CC (clomiphene citrate) with hMG is more cost-effective [14].

Furthermore a meta-analysis of seven studies by Cantieu *et al.*, (2018) on IUI showed that there was a significantly higher pregnancy rate for treatment with gonadotropins as compared to treatment with CC alone. This suggests that ovarian stimulation method is an important component for the success of IUI [15].

At the present study inspite of higher number of follicle and endometrial thickness in the intervention group (COS/IUI) than control group, there was no statistical significant difference in pregnancy rate between both groups. This may be attributed to the fact that supra physiological level of estrogen may adversely affect endometrial receptivity

The optimum numbers of COS/IUI treatment cycles are controversial. Some authors suggested range of numbers three to six cycles. Sahakyan *et al.*, (2013) demonstrated a definite age-related drop in fecundity associated with COS/IUI and recommended limiting the number of IUI trials to four [16].

In our study and in the same cycle single insemination for couples of intervention group was performed, as this was recommended over double insemination in several studies. Polyzos *et al.*, (2013) in six randomized trials involving 829 women, 54 (13.6%) clinical pregnancies were recorded for treatment with double IUI and 62 (14.4%) for treatment with single IUI. They reported that there was no statistical significant difference was detected, and concluded that double IUI offer no clear benefit in overall pregnancy rate in couples with unexplained infertility [17].

5. Conclusion

Controlled ovarian stimulation using clomiphene citrate + hMG with intra uterine insemination offers no statistical significant in term of management of unexplained infertility outcome.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Balen, A. (2014) Infertility in Practice. 4th Edition, CRC Press, London, 321-322.

- <https://doi.org/10.1201/b16081>
- [2] ESHRE Capri Workshop Group (2019) Intrauterine Insemination. *Human Reproduction Update*, **15**, 265-277. <https://doi.org/10.1093/humupd/dmp003>
 - [3] Abdelkader, A.M. and Yeh, J. (2019) The Potential Uses of Intrauterine Insemination as a Basic Option for Infertility: A Review for Technology-Limited Medical Settings. *Obstetrics and Gynecology International*, **2009**, Article ID: 584837. <https://doi.org/10.1155/2009/584837>
 - [4] Allahbadia, G.N. and Merchant, R. (2012) Intrauterine Insemination. In: Nagy, Z., Varghese, A. and Agarwal, A., Eds., *Practical Manual of in Vitro Fertilization*, Springer, New York, 281-296. https://doi.org/10.1007/978-1-4419-1780-5_31
 - [5] NICE Fertility Guidance (2019) Evidence on Infertility Problem; Clinical Guidelines, CG 22-Issued: March 2019.
 - [6] Alviggi, C., Humaidan, P. and Ezcurra, D. (2012) Hormonal Functional and Genetic Biomarkers in Controlled Ovarian Stimulation: Tools for Matching Patients and Protocols. *Reproductive Biology and Endocrinology*, **10**, Article No. 9. <https://doi.org/10.1186/1477-7827-10-9>
 - [7] Guzick, D.S., Sullivan, M.W., Adamson, G.D., *et al.* (2018) Efficacy of Treatment for Unexplained Infertility. *Fertility and Sterility*, **70**, 207-213. [https://doi.org/10.1016/S0015-0282\(98\)00177-0](https://doi.org/10.1016/S0015-0282(98)00177-0)
 - [8] Steure, P., Van der Steeg, J.W., Hompes, P.G., *et al.* (2018) Effectiveness of Intrauterine Insemination in Subfertile Couples with an Isolated Cervical Factor: A Randomized Clinical Trial. *Fertility and Sterility*, **88**, 1692-1696. <https://doi.org/10.1016/j.fertnstert.2007.01.124>
 - [9] Welner, S., De Cherney, A.H. and Polan, M.L. (2008) Human Menopausal Gonadotrophins: A Justifiable Therapy in Ovulatory Women with Long-Standing Idiopathic Infertility. *American Journal of Obstetrics and Gynecology*, **158**, 111-117. [https://doi.org/10.1016/0002-9378\(88\)90789-2](https://doi.org/10.1016/0002-9378(88)90789-2)
 - [10] Cohlen, B.J., Vandekerckhove, P., Te Velde, E.R. and Habbema, J.D. (2009) Timed Intercourse versus Inter-Uterine Insemination with or without Ovarian Hyperstimulation for Subfertility in Men. *Cochrane Database of Systematic Reviews*, **2000**, CD000360.
 - [11] Zeyneloglu, H.B., Arici, A., Olive, D.L., *et al.* (2015) Comparison of Intrauterine Insemination with Timed Intercourse in Superovulated Cycles with Gonadotropins: A Meta Analysis. *Fertility and Sterility*, **69**, 486-491. [https://doi.org/10.1016/S0015-0282\(97\)00552-9](https://doi.org/10.1016/S0015-0282(97)00552-9)
 - [12] Nulsen, J.C., Walsh, S., Dumez, S. and Metzger, D.A. (2013) A Randomized and Longitudinal Study of Human Menopausal Gonadotropin with Intrauterine Insemination in the Treatment of Infertility. *Obstetrics and Gynecology*, **82**, 780-786.
 - [13] Veltman-Verhulst, S.M., Cohlen, B.J., Asseler, J.F. and Ayeleke, R.O. (2020) Intra-Uterine Insemination for Unexplained Subfertility. *Cochrane Database of Systematic Reviews*, **2020**, CD001838.
 - [14] Hatasaka, H. (2011) New Perspectives for Unexplained Infertility. *Clinical Obstetrics and Gynecology*, **54**, 727-733. <https://doi.org/10.1097/GRF.0b013e3182353e54>
 - [15] Cantineau, A.E.P., Cohlen, B.J. and Heineman, M.J. (2018) Ovarian Stimulation Protocols (Anti-Oestrogens, Gonadotrophin with and without GnRH Agonists/Antagonists) for Intrauterine Insemination (IUI) in Women with Subfertility. *Cochrane Database of Systematic Reviews*, **18**, CD005356.
 - [16] Sahakyan, M., Harlow, B.L. and Hornstein, M.D. (2019) Influence of Age, Diagno-

sis, and Cycle Number on Pregnancy Rates with Gonadotropin-Induced Controlled Ovarian Hyperstimulation and Intrauterine Insemination. *Fertility and Sterility*, **72**, 500-504. [https://doi.org/10.1016/S0015-0282\(99\)00300-3](https://doi.org/10.1016/S0015-0282(99)00300-3)

- [17] Pepperell, R.J. and McBain, J.C. (1985) Unexplained Infertility: A View. *BJOG: An International Journal of Obstetrics & Gynaecology*, **92**, 569-580. <https://doi.org/10.1111/j.1471-0528.1985.tb01394.x>