

Intrauterine Insemination after Controlled Ovarian Stimulation in Unexplained Infertility

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Abstract

Introduction: Unexplained infertility is an inconvenient situation for some couples who failed to conceive as no authoritative or comprehensible cause for this failure. Actual line of management is difficult to be designed.

Aim: Aim of the study was to prove that Controlled ovarian stimulation (COS) with intrauterine insemination (IUI) is a wise option to be practically tried before proceeding to *in vitro* fertilization (IVF) as a last option.

Materials and Methods: 70 females of unexplained infertility with 272 IUI cycles were assessed. Controlled ovarian stimulation was done by means of orally letrozole (Femara, Novartis, East Hanover, NJ), 2.5 mg two time/day, from day 3 of the menstrual cycle and for 5 days then intramuscular injection of urofollitropin (Fostimon HP; IBSA) 75 IU/ml. I.M 1 ampoule per day and the dose would be changed in proportion to the response of follicular growth perceived by Transvaginal ultrasounds Intrauterine insemination (IUI) was planned 36 hours later from HCG injection.

Results: The age, body mass index, the type of infertility, duration of infertility and endometrial thickness on the day of eliciting the ovulation had no statistically significance in relation to pregnancy rate. Number of follicles with (p value 0.01) and number of IUI cycles were with (p value 0.05) were significantly affect the outcome of IUI. From 41 pregnancies 33 (80.5%) were single, 4 (4.9%) were twin, one (2.4%) triple, 4 had first-trimester abortion and one (2.4%) was ectopic.

Conclusion: IUI can be achieved to the patients with unexplained infertility to offer them some time they need for a respectable chance of pregnancy before moving on to IVF procedure.

Keywords: Unexplained Infertility; Intrauterine Insemination; Gonadotropin; Letrozole

Introduction

Causes of Unexplained infertility remain unknown even after full work up, The current rate of unexplained infertility is about 50% for couples with a female partner below age 35 ys, and concerning 80% by age 40 ys [1]. In the majority of cases, IUI is frequently the realistic management before stirring on to IVF as its Success rate with controlled ovarian stimulation (COS) varies between 8 and 22% also less invasive and less costly process; it is based on the belief of "increasing the number of gametes (sperms and oocytes) at the accurate place at the correct time" [2]. Intrauterine insemination (IUI) is a procedure where the semen is prepared into extremely concerted motile sperm followed by injection into the uterus throughout the cervix using a fine catheter [3]. As it is the least price, least invasive and most effective method, so; It is the initial line of assisted conception in many cases of unexplained infertility like; unilateral tubal block, low sperm

quality, cervical factors, ovulatory dysfunction and endometriosis [4,5]. In general, pregnancy rate of IUI fluctuates from 5% to 70%. Many researchers have not correlated definite variables with the success of IUI management [6].

Aim of the Study

The aim of the current study is; to find the results of undergoing COS with IUI in cases of unexplained infertility and if there are prognostic factors.

Material and Methods

This study was prospective, observational study performed at cytogenic unit of Obstetrics and Gynecology department at Zagazig University Hospital, Egypt from January 2016 to March 2017. The ethics committee approved the study protocol. 70 females of unexplained infertility were included in this work. Unexplained infertility was described when the essential workup of infertility showed; ovulatory cycles established by hormonal profile in third day of the menstrual cycle (F.S.H, L.H, Prolactin and T.S.H) and midluteal progesterone level more than 5 ng/ml, no abnormality in uterine cavity, established one patent tube at least on hysterosalpingographic image or through laparoscopy, and normal semen parameters according to WHO 2010 criteria [7].

Their age ranged from 19 - 39 years, they were unable to conceive for one year or more in spite of normal marital life, no intrauterine insemination (IUI) was done before and had 3 follicles or less on the day of promote the ovulation.

All participants were subjected to full history taking, clinical examination and then, transvaginal ultrasounds examination was performed on cycle day 3 to exclude any ovarian cyst and to measure endometrial thickness to be 5 mm or less.

Controlled ovarian stimulation was done by means of orally letrozole (Femara, Novartis, East Hanover, NJ), 2.5 mg two time/day, from day 3 of the menstrual cycle and for 5 days then intramuscular injection of urofollitropin (Fostimon HP; IBSA) 75 IU/ml. I.M 1 ampoule per day and the dose would be changed in proportion to the response of follicular growth perceived by Transvaginal ultrasounds examination which was started from day 7 and then every other day until the day of planned ovulation trigger. When one follicle measured ≥ 18 mm in diameter, trigger of ovulation was done using injection Human chorionic gonadotropin (Choriomon; IBSA, Switzerland) (10.000 IU/I.M) intramuscularly. If the follicles were more than 3 (15 - 18) mml, HCG injection was concealed [8].

Intrauterine insemination (IUI) was planned 36 hours later from HCG injection. Instructions were given to husband to provide the semen sample after abstinence of 2 - 4 days by masturbation in a sterile container.

Sample was prepared by swim up technique [9].

After liquefaction directly, a drop of the well-mixed specimen was put on a clean, warmed glass slide at 37°C then covered with a cover slide. Parameters were lettered down to be balanced with the values after processing. The standard swim-up technique was used for gathering of motile and active sperms. The sperm sample was centrifuged after mixing it with media Ham's F-10 (Sigma Chemical, St. Louis, MO) (double volume of semen sample) at 400g for 15 minutes. The supernatant was discarded; the pellet was suspended in pre-warmed 2.5 ml of Ham's F-10 culture medium supplement with human serum albumin then centrifuged one time more. After removing the supernatant the pellet was gently over-layered with medium in the tube which was sealed, inclined at 45°C and kept at 37°C for 60 - 90 minutes in 5% CO₂. A sterile Pasteur pipette was used to remove the supernatant containing actively motile sperms. Before dispatching the prepared sample, a drop was examined under light microscope. Motility and morphology were proofed and the specimen was maintained at 37°C till dispatched to be inseminated. Under transabdominal ultrasonography guidance, IUI was done with full bladder using Wallace soft IUI catheter. Patient was requested to lie down with head in low position slightly for 30 minutes. Micronized progesterone vaginal suppository 400 mg daily for 15 days was prescribed to support the luteal phase. On day 15, Serum beta hCG was done to estimate the

pregnancy rate. It was considered positive if values were above 100 mIU/mL. Ultrasonography was done at 5 weeks after last menstrual period to determine the clinical pregnancy rate (CPR) then to confirm the presence of fetal cardiac activity and followed up till delivery to determine the live birth rate (LBR). Not more than 4 cycles of IUI were done.

The data was collected, tabulated and statistically analyzed using statistical package for social science (SPSS) version 12 (SPSS Inc. USA). Data were articulated as number and percentage for qualitative variable while they were expressed as mean ± SD for quantitative variables.

Student’s t-test was applied to difference of mean of quantitative variables. Chi-square test was applied to study the difference of frequency. For interpretation of results, p value < 0.05 was considered significant.

Results

70 couples with 272 IUI cycles were analyzed in this study. 212 were primary infertility and 60 were secondary infertility. The type of infertility had no significant difference in the pregnancy rate. It was (14.1% p value 0.5) in primary and (18.3% with p value 0.6) in secondary infertility (Table 1). The average female age was 24.3 ± 4.24, 26.1 ± 3.02 years for positive and negative pregnancy respectively. The average male age 36.7 ± 3.8 and 37.9 ± 3.7 years for positive and negative pregnancy respectively. The age, body mass index and duration of infertility had no statistically significance in relation to pregnancy rate (Table 1). On the day of eliciting the ovulation, Endometrial thickness (p value 0.9) and size of follicles (p value 0.7) were similar in both the groups (positive or negative pregnancy) with no significant difference (Table 2). Number of follicles (p value 0.01) and number of IUI cycles were (p value 0.05) significantly affect the outcome of IUI (Table 2).

| Parameter | Pregnancy | | P value |
|-----------------------------------|--------------|--------------|---------|
| | Positive | Negative | |
| Age (female partner) (years) | 24.3 ± 4.24 | 26.1 ± 3.02 | 0.3 |
| Age (male partner) (years) | 36.7 ± 3.8 | 37.9 ± 3.7 | 0.5 |
| BMI of female partner (mean ± SD) | 27.53 ± 0.79 | 27.49 ± 1.12 | 0.7 |
| Duration of infertility (years) | 5.6 ± 1.68 | 6.5 ± 3.14 | 0.6 |
| Primary infertility | 30 (14.1%) | 182 | 0.5 |
| Secondary infertility | 11 (18.3%) | 49 | 0.6 |

Table 1: Demographic distribution.

Mean values (± SD), P < 0.05 = Significant

| Parameter | Pregnancy | | P value |
|----------------------------|-------------|-------------|---------|
| | Positive | Negative | |
| Endometrial thickness (mm) | 9.1 ± 2.54 | 9.3 ± 1.91 | 0.9 |
| Number of follicles | 3.4 ± 2.67 | 2.0 ± 1.16 | 0.01 |
| Number of IUI cycles | 2.13 ± 1.11 | 3.9 ± 1.83 | 0.05 |
| Size of follicles (mm) | 19.6 ± 1.14 | 20.0 ± 6.48 | 0.7 |

Table 2: Parameters upsetting pregnancy rates in intrauterine insemination.

Mean values (± SD), P < 0.05 = Significant

From 41 pregnancies 33 (80.5%) were single, 4 (9.75%) were twin, one (2.4%) triple, 4 had 1st-trimester abortion and one (2.4%) was ectopic (Table 3).

| Pregnancy outcome | N | % |
|--------------------------|----|------|
| Singleton | 33 | 80.5 |
| Twin | 4 | 9.8 |
| Triple | 1 | 2.4 |
| First trimester abortion | 2 | 4.9 |
| Ectopic | 1 | 2.4 |

Table 3: Pregnancy outcome.

N: Number; *%:* Percentage

Discussion

As Unexplained infertility is diagnosed by exclusion when the basic infertility workup is found to be normal so, the management is often empiric in the form of either expectant treatment (planned intercourse with lifestyle changes), ovarian stimulation, intrauterine insemination, and *in vitro* fertilization [10]. Ovarian stimulation with IUI has been found to be helpful as ovarian stimulation increases the number of follicles and IUI introduces the concentrated motile sperms via prepared semen sample directly into the uterine cavity and next to the real place of fertilization (the fallopian tube) therefore exceeding any undiagnosed cervical factor increasing the chances of fertilization and thus pregnancy rate.

In spite of high pregnancy rate and live birth of IVF in management of such cases, the high cost and insidious of the procedure make the couple and physician need primary option (less expensive and more easy) [11]. Many studies found that age of the couple, especially of the female is a significant predictor in rate of pregnancy when ovarian stimulation with IUI were used in management of unexplained infertility like Montanaro Gauci, *et al.* in 2001 and AMIGOS trial in 2016 who supposed that advancing age related to decrease pregnancy rate may be due to less number and bad quality of oocytes [12,13]. Others found no association between pregnancy rate with age like Isa, *et al.* in 2014 and our result agreed with those [14]. Body mass index as a prognostic factor, has been analyzed and found that no association with success rate (p value 0.7). This was similar to the results of Wang, *et al.* [15]. According to duration of infertility as a prognostic factor, we did not find any significance associated with pregnancy rate. This agreed with, Tay, *et al.* [16] and disagreed with that of Ashrafi, *et al.* [17] and Hansen, *et al.* [13]. In the present study the number of dominant follicles/cycles was more among the patients who get pregnant (p value 0.01), this agreed with Dickey, *et al.* [18] and Ibérico, *et al.* [19]. Gregoriou, *et al.* [20] performed one randomized trial using letrozole 5 mg daily for 5 days compared to 150 IU daily of gonadotropins, beginning at day 3 of the cycle, with later adjustment based on monitoring results, and there was no difference in mature follicle number. In the present work, there was significant difference between the pregnancy rate and endometrial thickness. Quintero, *et al.* [21] and Gregoriou, *et al.* [20] reported that endometrial thickness was greater in the gonadotropin group when compared to the letrozole groups. In our study, we use both medication and so, I thought that is the reason (no difference).

Conclusion

IUI can be achieved to the patients with unexplained infertility to offer them some time they need for a respectable chance of pregnancy before moving on to IVF procedure.

Funding

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Conflict of Interest

None declared.

Ethical Approval

The study was approved by the institutional ethics committee.

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