



## Research Article

# Success of Controlled Ovarian Hyperstimulation and Intrauterine Insemination in couple with Unexplained Infertility

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**Received:** 05 April 2020; **Accepted:** 18 April 2020; **Published:** 23 April 2020

**Citation:** Nazdar Raouf, Roj Hikmat, Aveen Munib, Maida Shamdeen, Ramadhan Salahaldeen, Hameed Abdullah.

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Journal of Women's Health and Development 3 (2020): 077-091.

## Abstract

**Background:** Management of unexplained infertility remains largely empirical, the therapeutic approach should be individualized taking into account patient age and duration of infertility, treatments include expectant observation with timed intercourse and lifestyle changes, controlled ovarian hyperstimulation with intrauterine insemination, and in vitro fertilization. The aim of this study was to assess the pregnancy rate and outcome of couples with unexplained infertility treated with intrauterine insemination after controlled ovarian hyperstimulation and to evaluate the effect of various prognostic factors.

**Results:** In this study 198 cycles of controlled ovarian stimulated intrauterine insemination were analyzed for 110 couples with unexplained infertility. The overall pregnancy rate in our study was 30.9%.

**Conclusion:** Ovarian stimulation combined with intrauterine insemination is a cost-effective treatment for couple with unexplained infertility before jumping into in vitro fertilization, but recommend that couples be informed of all information about the chances of success as well as the costs and complications of this treatment.

**Keywords:** Unexplained Infertility; Intrauterine Insemination; Pregnancy rate

## Background

The problem of infertility in the world is continuing to grow among women of reproductive age [1]. Infertility or sub-fertility is defined as no pregnancy after one year in women less than 35 years of age and in women more than 35 years old after six months of regular intercourse without the use of contraception [2]. Fecundability is the probability of achieving a pregnancy in one menstrual cycle [3].

There are different causes of infertility, one population-based study reported 28 percent is due to unexplained infertility, which is defined as a couple does not conceive after unprotected vaginal sexual intercourse with basic infertility evaluation shows no obvious abnormality in women less than 35 years old of age after one year of attempting conception or after six months in women 35 years and older [2,4]. Investigations require to meet the definition includes (normal ovulatory function, normal semen analysis as well as sperm function tests, at least one patent fallopian, uterus assessed by transvaginal ultrasound, hysterosalpingography as well as hysteroscopy, assessment of peritoneal factor by laparoscopy and lastly adequate ovarian reserve) [5,6].

The management of unexplained infertility creates some complexity mainly because of the lack of a specific treatable abnormality. The treatment is generally empirical, it depends on the availability of resources, patients age, duration of infertility, balance the effectiveness against the cost and side effects.

The standard protocol is to Progress from simple as lifestyle changes or timed intercourse then move to complex treatment as controlled ovarian hyperstimulation plus intrauterine insemination then progression to assisted reproductive technique, if after three cycles of a specific fertility treatment does not result in pregnancy, alternative treatments should be considered [7,8,9].

Approximately 1 percent of couples with unexplained infertility will become pregnant per cycle with no intervention. Expectant management is an option for female partner of less than 32 years of age as an ovarian reserve decrease after the age of 37 years. Lifestyle change such as discontinuing cigarette smoking and achieving a normal body weight may increase fertility in women with unexplained infertility [10].

Initial active treatment of unexplained infertility is start with three to four cycles of clomiphene citrate plus controlled ovarian hyperstimulation with intrauterine insemination rather than gonadotropin injections because of the high pregnancy rate, low rate of multiple pregnancies, low cost, orally administer, no need for monitoring. Clomiphene citrate it enhances fertility by correcting a subtle defect in ovarian function, either follicular development or luteal phase defect as well as it increases the number of follicles that develop and consequently oocyte that is released [11].

During intrauterine insemination procedure, the processed and concentrated motile sperm is deposited as close to the oocyte as possible. The cervical mucus barrier is bypassed and there is an additional psychological benefit that the infertility is being treated. The requirements for performing the procedure are controlled ovarian hyper stimulation, patency of at least one fallopian tube, and absence of genital organ infection. Effectiveness of intrauterine insemination in the treatment of unexplained infertility 12-22% [12].

For couples with unexplained infertility who have failed three cycles of clomiphene citrate, gonadotropins are often administered it is less costly than an invitro fertilization cycle but less likely to result in a pregnancy and more likely to result in multiple pregnancy while, invitro fertilization results in the highest per-cycle pregnancy rate in the shortest time interval [13].

When the in vitro fertilization is NOT an option for woman with unexplained infertility, especially symptomatic, as these women may have minimal or mild endometriosis or peritubal adhesion, laproscopic treatment of endometriosis is the next step, is associated with improved fertility after that a course of clomiphene citrate plus intrauterine insemination is starte . Last treatment options include ovulation induction with letrozole, donor-egg, surrogacy, adoption, and cessation of treatment. Both bromocriptine and danazol are not effective in treating a woman with unexplained infertility [14-16].

## Methods

### Design and Setting

This study was conducted at three infertility centers and private clinics in Duhok, Iraqi Kurdistan from November 2017 to August 2019, and reviewed retrospectively. The ethical approval from the Ethics and Scientific committee of the Kurdistan board for Medical Specialties was obtained. The written informed consent of all the participants was obtained. All couples with unexplained infertility planned to have intrauterine insemination after controlled ovarian hyperstimulation.

### Measures

Full history was taken from all couples as well as clinical examination was done for all women. All women had tests for cervical smear, high vaginal swabs, and immunity against rubella. Preconception folic acid was given to all woman. The diagnosis of unexplained infertility was done through the absence of obvious causes for infertility. Inclusion criteria was maternal age less than 40 years old, normal semen analysis according to world health organization 2010, patent tubes confirmed by hysterosalpingography or laparoscopy, normal hormonal profile including day 3 FSH and LH, TSH, prolactine, anti mullerian hormone and day 21 progesterone, normal uterus evaluated by transvaginal ultrasound and

hysteroscopy.

Exclusion criteria were the couple who refuse the procedure, Couple have obvious causes for infertility, presence of any ovarian cyst detected by ultrasound and women with sensitivity to ovarian stimulation agents.

The initial management were includes advice given on lifestyle, told couples to return after three months if they have still not achieve pregnancy, avoidance of stress, vaginal sexual intercourse every 2 to 3 days, stop smoking, try to achieve normal weight, avoidance of excessive (tea, coffee and colas) intake and avoidance of tight wearing underwear.

### **Controlled ovarian hyperstimulation (COH)**

A baseline Trans vaginal ultrasound was performed on day 2 of the menstrual cycle to assess the presence of ovarian cysts. and to measure endometrial thickness to be 4 mm or less. In those cases with presence of ovarian cyst until the cyst disappear either spontaneously or after suppression with oral contraceptive pills ovarian stimulation was withholding. Counseling of couples regarding the complications and cycle cancellation if there was no response or if there were more than three follicles and advice to avoid unprotected intercourse. Each couple received 3-4 treatment cycles unless pregnancy occurred. Rest cycles were taken sometime between treatment cycles.

Controlled ovarian stimulation was done by clomiphene citrate letrozole and injectable gonadotropin. Clomiphene citrate was taken as 100 mg for five consecutive days beginning on day 2, while letrozole was taken as 5 mg/day beginning on day 3 to 7. Injectable gonadotropin was used on day 2 or day 3 of the cycle at doses of 75–300 units. For follicular development serial transvaginal ultrasound was taken to monitor the number and size of developing follicles and to time human chorionic gonadotropin (hCG) administration usually, performed every two or three days which was started from day 7.

### **Ovulatory trigger**

When at least 2 follicles have reached an average diameter of  $\geq 18$  mm and the endometrial thickness is 8 mm, hCG was used to trigger ovulation, a dose of 250 mcg of recombinant hCG or 10,000 units of urinary hCG were used.

### **Semen collection and preparation**

Fresh ejaculate was collected by masturbation after two or three days of sexual abstinence with avoiding usage of any lubricants. Sample was prepared by swim up technique with considering the woman and sperm sample for intrauterine insemination and maintain the specimen at body temperature until insemination.

### **Technique of intrauterine insemination**

A single intrauterine insemination was planned 36 hours after hCG injection. Equipment were used during the procedure (disposable Speculum, 1ml sterile syringe and disposable soft polyethylene insemination catheter).

A woman lie on bed in dorsal lithotomy position, those with an anteverted uterus maintain a full bladder to facilitate straightening of the uterus, 1ml syringe was opened and draw up approximately 0.5 mL of air, then the processed sperm and its suspension media aspirated into the syringe. The sperm is suspended in a small volume of media, no more than 0.5 mL, to prevent uterine contractions and expulsion of fluid after it is inseminated into the uterus, attach the syringe to insemination catheter with an external flexible sheath.

Speculum was inserted, use of a tenaculum and touching the end of the catheter were avoided, the catheter was inserted through the cervical os to the endocervical canal, and into the uterus to a depth of approximately 6 cm and touch the fundus was avoided, as this will cause pain and bleeding which is toxic to embryo. The sperm was injected then slowly withdraw the catheter.

Woman was rest in supine position for 10-15 minutes following the procedure. Sometime for psychologically reassurance this time was extended for 30 minutes.

#### **Post procedure care**

Instructions were given to woman about, increase wetness, spotting, and for pelvic pain acetaminophen was prescribed. Woman return to normal activities and Patients may have intercourse after IUI if they wish to do so. Vaginal progesterone 400 mg daily for 15 days was prescribed to support the luteal phase with folic acid and continued till 12 weeks if pregnancy became positive.

A urinary or serum pregnancy test is performed two weeks after IUI. If the value exceeded 10 mIU per milliliter, the measurement was repeated at 48 hours. Pregnancy was indicated by an increase in the serum  $\beta$ -human chorionic gonadotropin. Ultrasonography was done at 6 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).

Outcomes studied were clinical pregnancy rate, recorded parameters of maternal age, paternal age, duration of subfertility, type of subfertility (primary or secondary), number of dominant follicles, measured diameter of dominant follicles on the day of hCG, endometrial thickness, number of the total motile sperm, progressive motile sperm, and total sperm count all were used to determine the prediction value. Subsequently also recorded the outcome and complications of this intervention such as live birth, miscarriage, ectopic pregnancy, multiple pregnancy and ovarian hyperstimulation syndrome.

#### **Statistical analysis**

The data were collected and statistically analyzed using a software package, current versions IBM (SPSS) Statistic, descriptive statistics for nominal variables were interpreted as number and percentage (%), while quantitative variables were expressed as mean  $\pm$  standard deviation. 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

During the study period, from November 2017 to August 2019 there were 110 couples with unexplained infertility and planned to have intrauterine insemination after controlled ovarian stimulation. Initially they were 121 couples, but 11 couples were excluded from the study after they achieved pregnancy spontaneously during a period of 1 to 3 months of expectant management. In this study 198 cycles of controlled ovarian stimulated intrauterine insemination were analyzed. There were 34 cases achieved pregnancy and 39 baby were a product of this study, all newborns were examined by a neonatologists . The overall pregnancy rate in our study was 30.9%, cases of multiple pregnancies was reported , no case of ectopic pregnancy and ovarian hyperstimulation syndrome were recorded in this study.

### Couples characteristics

The characteristics of couples with unexplained infertility selected for the controlled ovarian stimulation(COH) and intrauterine insemination (IUI) are summarized in Table1.The mean age of females in a positive pregnancy group was  $23.8 \pm 4.3$ , while for females in a negative pregnancy group was  $26.2 \pm 2.2$  years. The mean age of males in a positive pregnancy group was  $26.4 \pm 2.7$ , while for males in a negative pregnancy group was  $28.1 \pm 4.6$  years.

Characteristics Of Couples	Positive Pregnancy Group (34)	Negative Pregnancy Group (76)	P Value
Age of female (years)	$23.8 \pm 4.3$	$26.2 \pm 2.2$	< 0.001
Age of male (years)	$26.4 \pm 2.7$	$28.1 \pm 4.6$	0.047
Duration of infertility (years)	$6.71+ \pm 2.79$	$28.51 \pm 2.22$	< 0.001
*Primary infertility	20 (18.1%)	41(37.2%)	0.046
*Secondary infertility	14(12.7%)	35(31.8%)	0.035

Data are presented as mean  $\pm$  SD \* Data are presented as number (percent), P < 0.05 = Significant, P < 0.001 highly significant

**Table 1:** Characteristics of couples with unexplained infertility selected for COH and IUI

The mean duration of infertility in a positive pregnancy group was  $6.71+ \pm 2.79$  and it was  $28.51 \pm 2.22$  in a negative pregnancy group. The type of infertility was primary infertility in 20 (18.1%) cases with a positive pregnancy group and in a negative pregnancy group was 41(37.2%) cases. In 14(12.7%) cases infertility was due to secondary type in a positive pregnancy group while in a negative pregnancy group was 35(31.8%) cases. .

There was statistically highly significant difference between the positive pregnancy group and negative pregnancy group regarding the effect of female age and the duration of infertility on pregnancy rate, type of infertility and paternal age were significantly affect the pregnancy rate.

### Sonographic evaluation

The transvaginal sonographic evaluation on the day of triggering the ovulation in couples with unexplained infertility selected for the controlled ovarian stimulation (COH) and intrauterine insemination(IUI) and are summarized in Table 2.

<b>Ultrasound Parameters</b>	<b>Positive Pregnancy Group (34)</b>	<b>Negative Pregnancy Group (76)</b>	<b>P Value</b>
Size of follicles (mm)	20.73±2.28	19.3±1.22	< 0.001
Number of follicles	3.2 ± 1.16	2.13 ± 0.71	< 0.001
Endometrial thickness (mm)	10.33±1.13	8.12±1.46	< 0.001

Data are presented as mean ± SD, P < 0.05 = Significant, P < 0.001 highly significant

**Table 2:** Sonographic evaluation in couples with unexplained infertility selected for the COH and IUI

The mean size of follicles in a positive pregnancy group was 20.73±2.28, while in a negative pregnancy group was 19.3±1.22. The mean number of follicles was 3.2 ± 1.16 in a positive pregnancy group and was 2.13 ± 0.71 in a negative pregnancy group .Thicker endometrium was noted in pregnant group10.33±1.13 than in non-pregnant group 8.12±1.46.

Pregnant women showed a highly significant number of follicles, larger follicles and thicker endometrium than non pregnant group.

### Semen parameters

The semen parameters of male selected for the IUI and are summarized in Table 3. There was a highly significant difference between the two group regarding (total sperm count, sperms with progressive motility and total motile sperms) after processing, while there was a significant difference between the two groups regarding (total sperm count and sperms with progressive motility) before processing. No statistically significant difference was observed between the two group regarding total sperm motility before processing.

### Pregnancy outcome

The pregnancy outcome and mode of delivery in couples with unexplained infertility selected for the controlled ovarian stimulation (COH) and Intrauterine insemination(IUI) and are summarized in Table 4. Among 34 pregnancies 27 (79.4%) cases were singleton pregnancy, 6(17.6 %) cases were twin pregnancy, one (2.9%) case was triple pregnancy, in another

one (2.9%) case pregnancy was ended with miscarriage and no ectopic pregnancy was recorded in our study. In 11(32.3 %) cases type and mode of delivery was spontaneous vaginal delivery, while in 23(67.6 %) cases, deliver was elective cesarean delivery due to prolonged infertility.

Semen Parameters	Positive Pregnancy Group (34)	Negative Pregnancy Group (76)	P-Value
Total sperm motility <b>Before</b>	<b>27.14±11.82</b>	<b>22.15±15.13</b>	<b>0.091</b>
	<b>39.64± 15.22</b>	<b>23.83± 11.34</b>	<b>&lt; 0.001</b>
Progressive motility <b>Before</b>	<b>12.67±6.82</b>	<b>10.21±5.41</b>	<b>0.044</b>
	<b>33.21± 4.41</b>	<b>22.71± 7.83</b>	<b>&lt; 0.001</b>
Total sperm number <b>Before</b>	<b>74.12±20.17</b>	<b>64.84±11.12</b>	<b>0.002</b>
	<b>60.84±20.43</b>	<b>37.89± 16.32</b>	<b>&lt; 0.001</b>

Data are presented as mean ± SD, P < 0.05 = Significant, P < 0.001 highly significant

**Table 3:** Semen parameters of male with unexplained infertility selected for intrauterine insemination

Pregnancy Outcome	Values
Singleton	27 ( 79.4%)
Twine pregnancy	6(17.6 %)
Triple pregnancy	1 (2.9%)
Miscarriage	1(2.9%)
Ectopic	0(0 %)
Vaginal delivery	11(32.3 %)
Elective cesarean	23(67.6 %)

**Table 4:** Pregnancy outcome and mode of delivery in couples with unexplained infertility selected for COH and IUI Newborn characteristics at delivery.

The characteristics of the newborn at delivery are summarized in Table 5. There were 39 baby born. The sex of the baby in 17 (43.5%) cases was male and in 22 (56.4%) cases was female. The gestational age at delivery was between (34-40weeks), in 6 (15.3%)cases was between 34-36weeks, while in 33 (84.6 %) cases was between 37-40weeks. The weight of the baby at birth was between 2.2kg-3.5kg, in 11 (28.2 %) cases was between 2.2 -2.5kg and, in 28 (71.7 %) cases was between 2.6-3.5kg.

Characteristics	Values
Numbers of newborn	39
Sex	
<b>Male</b>	<b>17 (43.5%)</b>
<b>Female</b>	<b>22 (56.4%)</b>
Gestational age	(34-40)weeks
<b>34-36 weeks</b>	<b>6 (15.3%)</b>
<b>37-40weeks</b>	<b>33 (84.6 %)</b>
Birth weight	2.2-3.5kg
<b>2.2-2.5kg</b>	<b>11 (28.2 %)</b>
<b>2.6-3.5kg</b>	<b>28 (71.7 %)</b>

**Table 5:** Newborn characteristics at delivery

## Discussion

This study outlines the pregnancy rate and outcome achieved by 198 cycles of controlled ovarian stimulated IUI and its related factors. The overall pregnancy rate in our study was 30.9%. In one study after 971 insemination cycles 47 successful pregnancies were obtained, with an overall pregnancy rate of 31 % [17]. in another study the overall pregnancy rate was 22% (77/350) [18]. In one paper presents the analysis of 901 cycles of intrauterine artificial insemination with the husband's spermatozoa (AIHIU) in 274 couples who obtained 80 pregnancies, the cumulative pregnancy rate after three cycles of AIHIU was 22% and reached 39% after six cycles [9]. In one research have been done the overall pregnancy rate was 22% in 350 IUI cycles [20].

Several studies confirmed the age of the couple, especially female age, was significant factor in successful outcome of IUI, this may be due to age related follicular depletion and bad quality of oocytes [21]. In our study a positive correlation was found between the female age and successful of IUI in the management of couples with unexplained infertility. In one study showed that The mean age in the pregnant group was significantly lower than that of the non-pregnant group [22]. In another study they found that no association between female age and successful outcome of IUI the management of couples with unexplained infertility [23].

In present study, a correlation was found between the duration of infertility in positive and negative group in couples with unexplained treated by of IUI, this disagreed with one study showed that the duration of infertility had no statistically

significance in relation to pregnancy rate [24]. while our study was agreed with another study [25].

In our study, it was revealed that pregnancy rate was higher in primary infertility than in secondary infertility . There was one study supporting this data [26]. However in one study have been reported that pregnancy rates was 7.9% in the primary infertility group, whereas the rate was 21.4% in the secondary infertility group [27]. While in two another studies revealed that infertility type (primary or secondary) did not affect pregnancy rates [28,29].

In our study the number of dominant follicles/cycles was more among positive pregnancy group this agreed with one study [30]. In the meta-analysis containing 11599 cycles, reported that the development of two follicles increased the pregnancy rate more than that with one follicle development [31]. In another study reported that multi-follicular development in IUI did not improve the chances of pregnancy, but rather increased only the number of multiple gestation possibilities [32].

In our study the diameter of the dominant follicle was larger in pregnant group than in non- pregnant group this agreed with one study reported that the success rate in controlled ovarian stimulation and intrauterine insemination cycles closely related to obtaining of optimal size of follicles [33]. While another study reported that the diameter of the dominant follicle did affect the pregnancy rate [31].

In the present study there was significant difference between the pregnancy rate and endometrial thickness. In one study reported that endometrial thickness was greater in the gonadotropin group when compared to the letrozole groups [34]. Another study reported that, a non significant increase in endometrial thickness on the day of hCG administration was observed in the letrozole group [35].

There is a lack of agreement exists about the best semen parameters to predicate pregnancy rate after IUI [36]. Several studies reported the effect of semen parameters on IUI success [37,38]. In a retrospective cohort study failed to indicate such a relationship [39]. In our study, There were a significant difference between the two group regarding (total sperm count, sperms with progressive motility) before and after processing and also there was a significant difference between the two groups regarding total motile sperms ) after processing, while no significant difference was found between the two group regarding total sperm motility before processing.

In a systematic review, they observed that total motile sperm count was an important factor for predicting pregnancy rate [40]. Several studies have shown that progressive motility was considered important factor for pregnancy rate after sperm processing [41]. In our results showed that with the increase of progressive motile sperm increase the pregnancy rate similar with the results of some articles [42,43]. Several studies found no significant relationship between total sperm count and IUI success (pre and post semen processing) [44,45].

In our study seven cases of multiple pregnancies were recorded. Previous reports in the literature indicated high rate of multiple pregnancies in stimulated IUI [46,47]. No case of ectopic pregnancy was reported in our study, in one study

reported that rate of ectopic pregnancy was 8% [48]. No cases of ovarian hyperstimulation ovarian syndrome was reported in our study this is may be due to the absence of a defect in ovulation in unexplained infertility, which is believed to be the most important predisposing factor for ovarian hyperstimulation syndrome [49]. In our study rate of miscarriage was very low this rate is lower than rates reported by in vitro fertilization [50]. In our study no case of infection was reported , as the risk of infection with the use of modern methods of semen preparation is negligible [51].

There are three major limitations in this study that must be considered. The first, small sample size. Second, the study was reviewed retrospectively, no document was available about body mass index. The third limitation of this study was that LH surge was not used for ovulation trigger. The major strength of our study was, approximately most of the associated factors for predicting pregnancy rate in couple treated with controlled ovarian hyperstimulation and IUI were studied.

## Conclusion

Infertile couple with absence major reasons for infertility and normal test results are considered to have unexplained infertility, but it certainly diagnostic testing available cannot identify all the reasons, so active treatment should be applied after three months of failed expectant management and not just wait and see especially in older woman however, couple should be involved in the final decision about which treatment method to use. Ovarian stimulation combined with IUI can be offered to the couples with unexplained infertility as a safe and cost-effective treatment before jumping into in vitro fertilization and, should be limited to a maximum of three cycles, but recommend that couples be informed of all information about the chances of success as well as the costs and complications of this treatment .Further accurate and well formulated various factors would help in future for decision making regarding treatment of couple with unexplained infertility.

## Declarations

### Ethics approval and consent to participate

The ethical approval from the Ethics and Scientific committee at the Kurdistan board for Medical Specialties was obtained. The ethics committee reference numbers was 32/0845 .The written informed consent of all the participants was obtained

### Competing interests

There are no conflicts of interests to declare

### Funding

There was no source of funding for this research.

### Acknowledgements

We would like to thank the medical and technical teams from the three infertility centers for their help .We would also like to thank all for providing assistance with the manuscript preparation. We also thank everyone involved in the

collection and interpretation of data.

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