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SINGLE VERSUS DOUBLE INTRAUTERINE INSEMINATION IN CONTROLLED OVARIAN STIMULATION CYCLES FOR SUBFERTILE MALES

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Abstract

This study aimed to compare the efficacy of single intrauterine insemination (IUI) with double IUI in controlled ovarian hyperstimulation (COH) and IUI cycles for subfertile males. This is a prospective, nonrandomized study in hospital based outpatient infertility center.

The subfertile males were diagnosed by at least two sperm analyses. The study included ovulatory women having patent tubes and undergoing COH cycles with either single or double IUI.

Controlled ovarian hyperstimulation was induced by either clomiphene citrate (CC) with gonadotropins or only gonadotropins. Intrauterine insemination of husband's sperm was performed 36 hours after hCG administration in single IUI group. In the double IUI group, first IUI was performed 12-18 hours and second IUI 36 hours after hCG administration. The decision as to which intervention group a patient was placed in was determined by the day of hCG administration. Ovarian response to hyperstimulation was the only factor influencing the day of hCG administration. Statistical analyses was carried out by using the student's t test and chi-squared test. The main outcome measure is Clinical Pregnancy rate (CPR). Pregnancy was determined ultrasonographically by the presence of fetal cardiac activity.

A total of 191 couples underwent 216 COH-IUI cycles; 110 couples underwent 124 cycles with single IUI and 81 couples underwent 92 cycles with double IUIs. Cycle pregnancy rates were 9.2% (12/124) in the single IUI group and 8.2% (9/92) in the double IUI group, respectively (p=0.782).

It is concluded that a single IUI may be as effective as double IUI for couples undergoing COH/IUI for subfertile males.

Introduction

Intrauterine insemination (IUI) has been advocated as a treatment of infertility for several indications (e.g., male infertility, ovulatory disorders, endometriosis, tubal factor and unexplained infertility)[1-4]. IUI may have some advantages such as minimal equipment required, being less invasive and simpler to start with a reduced cost[5,6]. Controlled ovarian hyperstimulation (COH) combined with IUI may improve cycle fecundity rate compared with timed intercourse presumably due to increased number of oocytes available for fertilization[7,8]. Some factors such as sperm count[9] and number of follicles developed have been positively related to pregnancy rate, whereas advanced female age and high cycle number have been negatively associated[10].

Despite widespread use of COH-IUI cycles, limited data exist on the timing and number of IUI to optimize success rate[11,12]. Although, some different technics such as detection of LH in the urine or blood, hCG administration, monitoring of the follicles by ultrasound, GnRH agonist administration were used to detect optimal timing of IUI no difference was found among them[13]. Optimal timing for double

insemination has been reported as 12-18 to 34-60 hours in a review[14].

Although, the number of randomized trials assessing the effectiveness of IUI is limited and most of these studies have small sample sizes, several studies reported on the effectiveness of IUI in couples with male subfertility[15-19].

Regarding the value of double IUI in male subfertility, two recent meta analysis concluded that double insemination seems to be more effective for couples suffering from mild male subfertility when more dominant follicles are available[14,20]. Moreover, some of the recent trials also reported a better cycle outcome with double IUI[21-23] for male subfertility. However, one recent study reported no significant difference in pregnancy rate between double IUI and single IUI in the presence of multiple follicles in cases of mild male infertility[20].

Since there is still limited data available as to whether increasing the number of IUI per treatment cycle to improve success rate in male subfertility, we attempted to compare cycle pregnancy rates of cycles with a single IUI performed 36 hours after hCG administration and double IUIs 12 and 36 hours following hCG administration.

Patients & Methods

This study was based on the data from 216 IUI cycles of 191 couples carried out in Assisted Conception Unit of Basrah Medical College between March 2009–December 2011.

All couples who attended the center had had at least one year of infertility, and underwent basic infertility evaluation consisting of at least two semen analyses, assessment of prolactin, TSH, FSH and mid-luteal serum progesterone levels. Tubal patency was investigated by hysterosalpingography or laparoscopy prior to IUI treatment.

Inclusion criteria were women with bilateral tubal patency, age less than 43 years with normal ovulation. Women with previous IUI in other centers were also included in the study. Mild/moderate male factor was defined according to the total motile sperm count prior to IUI attempt. Male partners with a quantity of total motile sperm count between 1 $x10^6$ to 10 $x10^6$ in two different sperm analyses performed at least 6 months apart were included.

All women in the study had transvaginal ultrasound performed on the third day of the menstrual cycle as a baseline then underwent ovarian stimulation protocols. Two types of ovarian stimulation protocols; Clomiphene citrate (CC) and recombinant FSH (CC/r-FSH) and r-FSH (Gonal F^R, Serono) alone were used. In the CC/r-FSH protocol; CC 100 mg was used between cycle day 3 to cycle day 7 then the recombinant FSH (Gonal F^R, Serono), 75 IU was started on cycle day 9 and every other day according to the response of the ovaries. As a second protocol r-FSH was used 75 IU daily starting on cycle day 2 until the dominant follicle reached to 17 mm in diameter.

Follicular development and endometrial thickness were monitored by transvaginal ultrasound, starting for group 1 on day 12, for Group 2 on day 9.

Human chorionic gonadotropin (5,000-10,000 IU) was administered when at least one follicle was more than 16 mm in mean diameter and endometrial thickness was >6mm.

The decision as to which intervention group a patient was placed in was determined by the day of hCG administration. Ovarian response to hyperstimulation was the only factor influencing day of hCG administration. Women who had hCG adminstration in the first 3 days of the week were enrolled into double IUI group and others to single IUI group.

In single IUI group, IUI was performed at approximately 34-36 hours after administration of HCG, in double IUI group first IUI was performed 12 hours and second IUI was performed 36 hours

following hCG administration. Semen was collected by masturbation into a sterile container after 2-4 days of sexual abstinence, on the same day of insemination.

After liquefaction and initial sperm analysis using World Health Organization guidelines, the standard swim up technique was used for preparation, employing Earle's balanced salt solution. The sperm sample was centrifuged at 500 g (relative centrifugal force) for 15 minutes. The supernatant was discarded and the pellet diluted in 2.5 ml of medium and recentrifuged. After removing supernatant the final pellet was gently covered with medium and incubated for one hour at 37°C. Insemination volumes were 0.8 ml in all cycles.

Catheter (Cook, Australia) was inserted gently through cervical os and prepared semen with motile spermatozoa was injected into the uterus approximately 0.5 cm below the fundus.

A serum βHCG test was performed 12 days after insemination to establish a biochemical pregnancy. Clinical pregnancy was defined as detection of gestational sac confirmed by ultrasound.

Statistical analysis was performed by using X^2 test and student's t test to analyze the association between discrete variables such as female age, duration of infertility, total motile sperm count, number of preovulatory follicles and method of ovulation stimulation. Statistical significance was assumed at $p<0.05$. The data are expressed as Mean±SD.

Results

A total of 216 completed cycles were evaluated. Of these, 124 cycles in 110 couples (Group 1) and 92 cycles in 81 couples (Group 2). Baseline characteristics of the patients are shown in Table I. The mean age of the women (29.4±3.7 and 28.9±4.1 years) and duration of infertility (4.8±3.2 and 5.3±4.3 years) were similar between Group 1 and Group 2, respectively. Regarding COH cycle characteristics; mean number of total motile spermatozoa inseminated in the first insemination (7.7±1.6 and 8.1±1.1 $x10^6$), endometrial thickness (8.8±2.1 and 9.1±1.8 mm), number of follicles >17 mm (2.8±0.8 and 2.9±1.1) were similar between Group 1 and Group 2, respectively. Regarding ovulation induction protocols; CC/r-FSH protocol was used 36.2% and 33.6% and r-FSH protocol 63.8% and 66.4% of the cycles in Group I and Group II, respectively.

Clinical pregnancy rates were 9.6% (12/124) in the single IUI group and 8.2% (9/92) in the double IUI group and the difference was not statistically significant (p=0.782), as indicated in Table II. Miscarriage rates were 8.3% (1/12) and 11% (1/9) in Group 1 and Group 2, respectively. Both miscarriages occurrred after the detection of the fetal heart beat around 7 weeks of gestation. Only one twin pregnancy was diagnosed in Group 1 and no multiple pregnancy in Group 2.

We also compared CPR with two different of ovulation induction protocols in all COH-IUI cycles. CPR seemed to be higher in r-FSH group then CC/r-FSH group (15/140, 10.7% vs. 6/76, 7.8%), although it did not reach to a statistical significance (p=0.067).

Discussion

In this study, the aim was to compare clinical pregnancy rates of single and double IUI in controlled ovarian hyperstimulation cycles for male subfertility. It can be speculated that double IUI may deliver more spermatozoa to the site of fertilization during stimulated cycles in subfertil males and improve CPR. However, this study demonstrated that double IUI is not superior to single IUI in COH cycles for mild/moderate male infertility. Disadvantages of double IUI seemed to be higher cost and burden to the couple and medical staff.

Optimal timing and number of IUI is still a matter of debate to improve CPR in COH-IUI cycles. Insemination is usually performed 32-36 hours following hCG injection[11]. It was also reported that inseminating sperm 24 hours post-hCG had given similar results[21-25]. The optimal timing for double insemination has been reported as 12-18 to 34-60 hours following hCG administration[14]. Thus, we performed double IUIs at 12 and 36 hours and single IUI 36 hours after hCG.

Several studies provided conflicting results regarding the value of double IUI in different etiologies of infertility[1,20,21,25,26]. In a recent meta analysis, two different approaches were compared only in unexplained infertility patients and no difference was found between single and double IUI groups[27].

Moreover, there is a limited data on the value of double insemination in male subfertility[15-19]. Recently published prospective studies reported higher pregnancy rates with double IUI in male infertility patients[21-23]. Besides, two meta analysis regarding the value of double IUI compared to single IUI seemed to demonstrate an increased probability of pregnancy with double IUI in male infertility[14,20]. However one recent randomized trial comparing double IUI with single IUI in multifollicular ovarian hyperstimulation cycles in unexplained and mild male infertility found no difference[25]. We applied strict criteria for subfertile men to include in our study. This might be the reason of lower pregnancy rate (9.6 % for single IUI and 8.2% for double IUI) then some other studies published previously[21-23]. As a result, the value of IUI in these couples prior to IVF seems limited.

In one study, a marked decrease in the number of motile sperm was observed in the second IUI attempt of the double IUIs[28]. We did not find a significant decrease in the total motil sperm count in the second IUI attempt in double IUI group. Low total motile sperm count might not have been affected significantly in the second attempt.

The outcome of COH-IUI cycles may be effected by many parameters such as, age, duration of infertility, dose of medication and the number of mature follicles[9,10]. In our study, there was no significant difference between the groups regarding these variables.

Two different ovarian hyperstimulation regimens were used in our study. Average number of follicles were 2.1±0.8 and 2.9±1.1 in CC-r-FSH and only r-FSH cycles, respectively. CPR seemed to be higher in r-FSH then CC/r-FSH cycles (10.7% vs. 7.8%), although it was statistically insignificant. In one study, double IUI was found to increase pregnancy rate in CC or CC/gonadotrophin stimulated cycles. It was assumed that if fewer oocytes present in these mild stimulation regimens exposed to higher amount of sperm, pregnancy rate might increase[14]. It was also suggested that the success of multi-follicular cycles could be related to better ovarian reserve and perhaps better oocyte quality, rather than the number of follicles[29].

Although we observed higher follicle numbers in r-FSH group, CPR did not differ significantly between cc/r-FSH and r-FSH cycles. Thus, higher number of follicles seems to affect pregnancy rate positively according to our findings.

Multiple pregnancy rate in IUI cycles was reported as 12.3% per cycle[30,31]. We observed only one multiple pregnancy (twins; 8.3%) in single IUI group and none in double IUI group. Since we had limited number of pregnancies comparison on multiple pregnancy rates is not possible.

In conclusion, although cycle pregnancy rate is limited, single IUI may be as effective as double IUI in couples undergoing COH/IUI for subfertile males.

Table I: Cycle characteristics of the two groups

	Group 1(n=124)	Group 2(n=92)
Female age	29.4 ± 3.7	28.9 ± 4.1
Duration of infertility	4.8 ± 3.2	5.3 ± 4.3
Total motile spermatozoa ($x10^6$) inseminated		
First IUI	7.7 ± 1.6	8.1 ± 1.1
Second IUI		6.9 ± 1.5
CC/ r-FSH protocol (%)	36.2	33.6
r-FSH protocol (%)	63.8	66.4
Number of follicles >17 mm	2.1± 0.8	2.9 ± 1.1
Endometrial thickness	8.8 ± 2.1	9.1 ± 1.8

Gr. 1, Single IUI group. Gr. 2, Double IUI group. Values are mean±SD. No significant difference between groups.

Table II: Clinical pregnancy rates(CPR) in both groups

	Group 1 (n=124)	Group 2 (n=92)
No. of pregnancies	12	9
CPR per cycle (%)	9.6	8.2
Miscarriages (%)	1 (8.3)	1 (11)
Multiple pregnancies	1	-------

Gr.1, Single IUI group. Gr.2, Double IUI gp. No significant difference between groups.

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