

## Intrauterine insemination with husband semen: an evaluation of pregnancy rate and factors affecting outcome

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Received: 12 May 2008 / Accepted: 17 October 2008 / Published online: 22 November 2008  
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### Abstract

**Purpose** The aim was to determine pregnancy rate following intrauterine insemination (IUI) and its associated factors in a university assisted reproductive technique center in Tehran, Iran.

**Methods** A retrospective analysis of 350 IUI cycles with ovarian stimulation by clomiphene citrate and/or gonadotropins was performed.

**Results** The overall pregnancy rate was 22% (77/350). Of the 77 pregnancies, 88.3% resulted in live birth, 7.8% in spontaneous abortion, 2.6% in blighted ovum and 1.3% were ectopic. Logistic regression analysis revealed three predictive variables as regards pregnancy: number of the treatment cycle (OR:3.5 CI:1.9 – 6.4  $p=0.006$ ), duration of infertility (OR:2.1 CI:1.2 – 3.7  $p=0.001$ ) and age (OR:2.15 CI:1.1 – 4.4  $p=0.04$ ). Pregnancy rate did not have any

independent relation to sperm count, type of infertility, number and size of follicle and side of ovulatory ovary.

**Conclusion** Our results indicate that clomiphene citrate and/or gonadotropins IUI is a convenient and useful treatment option in women with younger age (<30 years) and fewer treatment cycles and fewer infertility duration (4 years).

**Keywords** Clomiphene citrate · Human menopausal gonadotropin · Infertility · Intrauterine insemination · Pregnancy rate · Prognostic factors

### Introduction

Intrauterine insemination (IUI), together with ovarian stimulation, is a less expensive and invasive treatment in comparison with other assisted reproductive techniques (ART) [1], and has been widely used for the treatment of infertile couples with a variety of indications, such as non-severe male factor infertility, unexplained infertility, cervical mucus hostility and ovulatory disturbances [2].

The overall success of IUI varies, with pregnancy rates ranging from as low as 2.7% to as high as 66% [3–5]. Variance in pregnancy rate achieved may be due to the small size of the study populations, variability in characteristics of subjects and ovarian stimulation and treatment protocols, including maternal age [6], timing and frequency of insemination [7, 8], number of treatment cycles [6], use of ovarian stimulation regime [9], etiology and duration of infertility [6] and total number of motile sperm inseminated [10]. Although results may appear concordant for some of these factors, a lack of consistency is still evident for some others, such as female age, size of follicles and ovulatory ovarian side [2].

**Capsule** Best results for intrauterine insemination with ovarian stimulation is obtained in women with younger age, fewer treatment cycles and fewer infertility duration. This study was conducted in Human Reproduction Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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In this retrospective study we have attempted to evaluate the results of IUI with ovarian stimulation and identify the variables that contribute to the success of treatment. These data would be valuable in planning subfertility treatment and predicting the success rate of IUI therapy in individual couples.

## Materials and methods

### Subjects

In the present study we have evaluated a total of 350 IUI cycles in which a clomiphene citrate and/or gonadotropins stimulation protocol and a standard IUI technique with partner's spermatozoa were used. This study was based on data collected from the records of infertile couples who underwent IUI cycles in Mahdieh infertility research center in the period 2001–2005.

The study couples had at least 1 year of infertility, and had undergone extensive infertility evaluation prior to IUI consisting of at least two semen analyses, monitoring of ovulation by ultrasound and mid-luteal progesterone, prolactin and thyroid hormone concentrations, a post-coital test performed in the pre-ovulatory phase and hysterosalpingography. Couples with an abnormal post-coital test according to WHO criteria [11], due to either a male or a cervical factor, were candidates for IUI. Male factor was defined as a sperm count  $<1 \times 10^6/\text{ml}$ ; normal forms  $<30\%$ ; or progressive motility (grade A+B)  $<40\%$  before sperm preparation [11]. Couples with husband's progressively motile sperm count after preparation  $<1 \times 10^6/\text{ml}$  in the basic infertility evaluation, were not enrolled in IUI treatment. Women had at least one patent tube, documented by laparoscopy or hysterosalpingography.

The medical records, including duration of infertility (years), type of infertility (primary or secondary), number of sperms, size and number of follicles and number of IUI cycles of these couples were reviewed, then pregnancy rate and its associated factors were compared. The couples were considered eligible for this study if the necessary information was obtained from their medical records.

### Sperm preparation

Semen was obtained from male partners of couples who were undergoing IUI for treatment of infertility. The specimen was collected by masturbation into a sterile jar after 2–4 days of sexual abstinence. After liquefaction at room temperature, the semen samples were examined under a microscope to define their characteristics regarding concentration and motility.

The standard swim-up technique, employing (Hams F10 or Medi-Cult) medium supplemented with 10% human

serum albumin was used for preparation. The sperm sample was centrifuged at 500 g for 15 min. The supernatant was discarded and the pellet diluted in 2.5 ml of medium and re-centrifuged. After removing the supernatant the final pellet was gently covered with medium and incubated for 1 h at 37°C in an incubator.

### Ovarian stimulation and timing of insemination

All women in the study underwent ovarian stimulation using clomiphene citrate (Clomifen; Leiras, Tampere, Finland) and/or human menopausal gonadotropin (HMG)/human chorionic gonadotropin (HCG) (Pergonal; Serono, Aubonne, Switzerland). For clomiphene citrate-stimulated cycles, 100 mg clomiphene citrate was given between days 3 and 7. For clomiphene citrate plus gonadotropin stimulation, 100 mg clomiphene citrate was given between days 3 and 7, followed by 150 IU of gonadotropins added by day 9. For cycles managed by gonadotropins only, stimulation was started on day 3 with 75–150 IU HMG daily. Follicle maturation was monitored by serial transvaginal ultrasonography. Ovarian and endometrial responses were monitored by vaginal ultrasonography on cycle days 9 to 13 and 5000–10000 IU of HCG (Pregnyl; Organon or Profasi; Serono) was administered when at least one follicle was  $>16$  mm in mean diameter. Standard IUI was scheduled 36 h after administration of HCG [12, 13].

### Insemination procedure and detection of pregnancy

Intrauterine insemination was performed using an intrauterine catheter (Kremer Delafontaine; Prodimed, Neuilly-en-Thelle, France) with a 1- or 2-ml syringe. The catheter was gently passed through the cervical canal and the sperm suspension expelled into the uterine cavity. Insemination volumes ranged from 0.5 to 2 ml. All techniques were carried out using sterile procedure. The IUI was performed with the patient in the dorsal lithotomy position. The women remained supine for 10–15 min after IUI. After insemination, each patient received progesterone daily (400 mg vaginal or rectal suppository or 100 mg intramuscular), followed as the same dosage after pregnancy for 6–12 weeks. Plasma  $\beta$ -HCG levels were measured routinely, 2 weeks after IUI. Clinical pregnancy was defined as transvaginal ultrasonographic visualization of intrauterine gestational sac(s).

### Statistical analysis

The variables selected for the initial analysis were female age, duration and type of infertility, sperm concentration, number and size of pre-ovulatory follicles ( $>16$  mm in diameter), ovulatory ovarian side and number of treatment cycles. Differences in pregnancy rates between groups

were tested by using 2 tests. The correlation between two variables was studied with the Pearson test. Multivariate logistic regression analysis was then used to identify significant variables that contribute to the success of ovarian stimulation/IUI treatment. Only statistically significant variables were included in the final model. The chosen level of significance was  $P < 0.05$ . All the statistical analyses were conducted using SPSS software (SPSS, Chicago, IL, USA; Version 16).

**Results**

A total of 350 IUI cycles by husband spermatozoa in women aged 18 – 43 years old were analyzed. The majority of subjects experienced maximum 4 years duration of infertility (64.9%) and had primary infertility (76.9%). Pregnancy outcome is presented in Table 1. The overall pregnancy rate in the study period was 22% (77/350). Of the 77 pregnancies, 88.3% resulted in live birth, 7.8% in spontaneous abortion, 2.6% in blighted ovum and 1.3% were ectopic.

The pregnancy rates according to the female characteristics and sperm parameters after preparation are summarized in Table 2.

Among pregnancies, the highest rate occurred in < 30 years old women (85.7%). There was no pregnancy in women less than 20 years old and no pregnancy occurred in the limited sample of women who were > 40 years. A statistically significant, age-related decline in pregnancy rate was found ( $P < 0.05$ ). These results were more pronounced when dividing subjects into two groups: aged < 30 and  $\geq 30$  years. In the < 30 year age group, 66 pregnancies out of 265 cycles (24.9%) occurred, declining to 11 pregnancies out of 85 cycles (12.9%) in older women ( $P < 0.05$ ).

Our results showed that infertility duration less than 5 years is associated with a significantly better pregnancy rate compared with a longer duration of infertility (27.3 vs. 12.2%, respectively). In addition, most pregnancies (84.4%) were obtained within the first two treatment cycles. All of the pregnancies occurred within the first four treatment cycles and no pregnancy was achieved in the fifth, sixth and seventh cycles.

**Table 1** Pregnancy outcome of the intrauterine insemination cycles

Pregnancy outcome	No. of patients (%)
Pregnancies/cycle	77/350(22)
Live births	68 (88.3)
Miscarriages	6 (7.8)
Ectopic pregnancies	1 (1.3)
Multiple pregnancies (twins)	3 (3.9)
Blighted ovum	2 (2.6)

**Table 2** Intrauterine insemination pregnancy rate according to female characteristics and sperm parameters (after preparation)

Characteristic	Pregnancy rate (%)
Age (years)	
<30 (265)*	66 (24.9)
30–34 (49)	5 (10.2)
35–39 (28)	6/ (21.4)
>40 (8)	0 (0)
Type of infertility	
Primary (269)	64 (23.8)
Secondary (81)	13 (16.1)
Infertility duration (years)	
1–3 (155)	48 (31)
3–5 (72)	14 (19.4)
$\geq 5$ (123)	15 (12.2)
Sperm count	
$\leq 5 \times 10^6$ (15)	3 (20)
$5.1–10 \times 10^6$ (57)	12 (21.1)
$10.1–20 \times 10^6$ (114)	20 (17.5)
$20.1–30 \times 10^6$ (87)	22 (25.3)
$\geq 30 \times 10^6$ (77)	20 (26)
Size of follicle (mm)	
16–19 (246)	55 (22.4)
$\geq 20$ (104)	22 (21.2)
Follicle number	
1 (104)	16 (15.4)
2 (111)	20 (18)
3 (53)	21 (39.4)
$\geq 4$ (82)	20 (24.4)
Ovulatory ovarian side	
Left (115)	19 (16.5)
Right (81)	19 (23.5)
Both (154)	39 (25.3)
Cycle number	
1 (279)	46 (16.5)
2 (38)	19 (50)
3 (31)	10 (32.3)
4 (2)	2 (100)

\*The numbers in the parenthesis are the number of the subjects in each groups

The median number of pre-ovulatory follicles (>16 mm in diameter) was two. In cycles with a single pre-ovulatory follicle, the pregnancy rate (15.4%) was significantly lower compared to cycles with more follicles. The highest pregnancy rate (39.4%) in this regard was observed among patients with three pre-ovulatory follicles. There was no correlation between the number of follicles and multiple pregnancy rate ( $p > 0.05$ ).

Pregnancy rate did not have any relation to sperm count and there were not any significant differences in total sperm concentration among pregnant and not pregnant study population, and sperm parameters did not significantly affect the outcome of IUI treatment. In addition, the type of

infertility, size of follicle and ovulatory ovarian side were not related to treatment outcome.

Logistic regression analysis revealed three predictive variables as regards pregnancy: number of the treatment cycle (OR:3.5 CI:1.9 – 6.4  $p=0.006$ ), duration of infertility (OR:2.1 CI:1.2 – 3.7  $p=0.001$ ) and age (OR:2.15 CI:1.1 – 4.4  $p=0.04$ ). In other words, best pregnancy rates were obtained in patients with younger age and fewer cycles and years of infertility complaints. Pregnancy rate did not have any independent relation to the number of preovulatory follicles.

## Discussion

This study describes the pregnancy rates achieved by 350 cycles of ovarian stimulated IUI and its associated factors. Favorable patient characteristics for treatment success in our sample were younger age, fewer cycles and duration of infertility complaint.

The overall pregnancy rate in our center was 22%. The reported pregnancy rates achieved by IUI have usually varied between 8% and 22%, but very low (2.7%) and high (66%) rates have also been published [3–5]. We obtained a rate of evolutive pregnancy of 88.3% (pregnancies which did not miscarry), which is comparable with that obtained by Mathieu et al. [14].

However, several other studies have detected lower rates of evolutive pregnancy, 68% [15], 54% [16], and 50% [17]. Due to differences on the methods of semen preparation and ovarian stimulation, it is not easy to determine a cause to account for such a high number of miscarriages.

In our study the success rate of IUI with partner's semen decreased with increasing age, which is in agreement with the results of earlier studies [2, 18], and no pregnancy occurred in women aged >40 years. The reported live birth rates following IUI in women aged 40 years are low, varying from 1.4% to 5.2% [19, 20]. The age-related decline in female fecundity has been well documented in every aspect of natural and artificial reproduction [21], and probably results from a combination of progressive follicular depletion, decline in granulosa function, poor oocyte quality [22] and reduced endometrial receptivity [23]. Put together, all these results indicate that IUI is a poor treatment option for women over 40 years.

We found that the pregnancy rate decreased with increasing infertility duration, which was the same conclusion as some [14], but not all studies [19]. Although there is not any precise limits of the duration of infertility, after which IUI success has been shown to decrease, IUI cannot be recommended to patients with a long-standing duration of infertility.

Cycle fecundity has been reported to be relatively constant for the first three to seven cycles in accordance

with infertility etiology, but decreasing pregnancy rates with an increased number of treatment cycles have also been shown [24]. However, pregnancies are recorded even after the 18th cycle [25], thus for a woman who desired to conceive by as simple intervention as possible, or could not afford a more sophisticated medical procedure, such as in vitro fertilization (IVF), treatment continuation is a relevant option. Accordingly, most of pregnancies (84.4%) in this study were obtained within the first two treatment cycles. However, since we had a low number of observations in groups with more than two cycles of treatment we cannot make definitive conclusions based on our observation.

Most of pregnancies in our patients were seen in cycles with three or more pre-ovulatory follicles, remarkably higher than in cycles with only one follicle, but the number of pre-ovulatory follicles was not significantly predictive of IUI success in our study. The poor outcome in cycles with only one pre-ovulatory follicle has confirmed in other studies [2], and it is stated that existence of at least two mature follicles is necessary for IUI therapy [26]. This indicates the necessity of using ovarian stimulation in combination with IUI. Multifollicular development may result in an increased number of fertilizable oocytes and a better quality endometrium and luteal phase, thereby improving fertilization and implantation rates.

Multiple pregnancy is an important aspect that needs to be taken into account when an ART is evaluated, with a reported incidence of 6.5–25% [27, 28]. We found an overall multiple pregnancy rates of 3.9% in our study. Multiple gestations seem to be much less frequent after IUI compared with that generally reported in IVF and intracytoplasmic sperm injection (ICSI) (25–30%) [28].

In agreement with the results published by Sinikka et al. [6], and in contrast to Kang and Wu [21] who described a slight though statistically significant higher pregnancy rate in relation to the number of motile sperm inseminated, in our study there was no evidence of a significant correlation between number of sperm and pregnancy rate. Others have also failed to find differences [27]. This is obviously due to pre-treatment sperm screening and exclusion of couples with a progressively motile sperm count after preparation of  $<1 \times 10^6/\text{ml}$ .

In conclusion, clomiphene citrate/HMG/HCG IUI as a convenient procedure for subfertility has more success rates in patients with younger age, less duration of infertility and limited cycles of treatment. Our findings highlights the importance of the younger age and fewer duration of infertility as determinants of the success of IUI treatment, indicating that the negative impact of them can only be partly overcome by ART. It seems reasonable to limit the number of IUI treatment cycles performed in older patients especially with longer duration of infertility and advice them to consider a more aggressive treatment.

**Acknowledgments** The authors are grateful for assistance from staff in Mahdieh infertility research center. We are especially grateful to our patients for consenting to participate in the study. The authors are indebted to Farzan Institute for Research and Technology for technical assistance.

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