

# Research Paper: Evaluation of the Appropriate Size of Follicles on Success Rate in Patient Undergoing Controlled Ovarian Stimulation and Intrauterine Insemination Cycles



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## ABSTRACT

**Objectives:** Intra-Uterine Insemination (IUI) is one of the methods for infertility treatments. The size of the follicles and endometrial thickness are two important factors in pregnancy rate of patients undergoing controlled ovarian stimulation and intrauterine insemination cycles (COH-IUI). The aim of this study was to investigate the success rate of IUI and follicular size and other associated factors in infertile couples.

**Materials & Methods:** The study group was the patients who were undergoing COH-IUI. BMI of all women recorded and ovulation induction was propelled and when there was appropriate endometrial thickness and at least one dominant follicle in trans-vaginal ultrasonography. 36 hours after HCG injection, IUI was performed. Then pregnancy rate between patients who had follicle size fewer than 20 mm and higher than 20 mm was assumed.

**Results:** 159 cases of IUI were performed and pregnancy happened in 22(14.1 %). In non-pregnant group (134 cases), 78 cases had under 20 mm follicles and 47 cases had higher than 20 mm follicles. In pregnant group (22 cases) 10 cases had fewer than 20 mm follicles and 12 cases had higher than 20 mm follicles in the time of HCG injection. Endometrial thickness was  $8.01 \pm 1.42$  mm in patients with follicles more than 20 mm.

**Conclusion:** The success rate in controlled ovarian stimulation and intrauterine insemination cycles closely related to obtaining of optimal size of follicles and endometrial thickness.

## 1. Introduction

A

ccording to the World Health Organization infertility definition is when a couple one year without using any contraceptive have complete sexual intercourse and preg-

nancy does not occur [1]. The prevalence of infertility is about 10-15% of the population of reproductive age and several factors are infertility causes such as the maternal age and quality of the oocytes, sperm quality, infections in women [2]. Today assisted reproductive mechanism is helpful for treatment of infertility. Intra-Uterine Insemi-

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nation (IUI) is an intermediate stage and easier than other methods of infertility treatment such as In Vitro Fertilization (IVF) and Intra Cytoplasmic Sperm Injection (ICSI). IUI is one of the method for treatment of infertility created by cervical factor, anovulation, endometriosis, immunological factor and unknown cause [3].

Success rate of IUI was influenced by different factors. In various studies has been done chance of pregnancy in infertile couples with ovulation induction and IUI had a significant increase [4, 5]. Clinical pregnancy rate in IUI cycles when using clomiphene citrate or another gonadotropin for ovulation induction is about 12% but in patients less than 30 years old and duration of infertility is about 4 years, Pregnancy rate increased to 22% [6].

The use of human Chorionic Gonadotropin (hCG) for ovulation triggering is important. Jarvela and colleagues in the study between 2008 and 2010 reported that if HCG injection for patient 3 to 5 minutes after the IUI, pregnancy rates progresses [7]. This hCG timing is essential because early management of hCG actions similar an early LH surge and can causes atresia in follicles [8]. Diameter of follicles in ART cycles is important. Researchers reported best follicular size before triggering is between 16-18 mm [9].

In 2012 Anna Palatnik studied to determine the best size of the follicle after ovulation induction with clomiphene or letrozole. In this study, 800 infertile women were treated with clomiphene or letrozole. They reported follicular size 24 mm and endometrial thickness 9 mm in IUI cycles are effective for treatment [10]. Several studies is done to examine the optimal size and number of dominant follicles and timing of gonadotropin injection in IUI cycles. All of these studies have controversies regarding on the appropriate size of the follicles and gonadotropin injection time [10, 11]. The aim of our study was to evaluate the appropriate and optimal size of follicles before HCG injection in COH-IUI cycles and comparison of pregnancy rate in patients with different follicle size.

## 2. Materials and Methods

### Study subjects

In this randomized prospective, observational study, 156 infertile patients referred to Yazd Research and clinical center for infertility, from April 2012 to May 2014, randomly selected. (Figure 1). Our study was approved by the ethical committee of the Yazd, Shahid Sadoughi University of Medical Sciences.

All of the women who were 18-40-year-old included in this study, and hysteron-salpingography were done for diagnosis and Confirmed of Openness of fallopian tubes. Patient with tubal factor, severe endometriosis, endocrine factor and hypothalamic amenorrhea and severe male factor (sperm count lower than 5 million per ml based on WHO 2012 classification) excluded from this study. After completing an informed consent by the couples, age, Body Mass Index (BMI) of female, sperm analysis and duration of infertility were recorded.

### Ovulation stimulation protocol

All the patients were on IUI cycle. Standard protocol for all of patient were done, the protocol was that all women received 100 mg clomiphene citrate daily from the third to the seventh day of her menstrual cycle, on days 8, 9 and 10, 150 IU Gonol-F (Serono Company 75 IU) were injected subcutaneously.

Then, the patients underwent vaginal sonography on the 11th day and follicular count and size were recorded. In this step patients were divided into two groups. The first group that follicle size less than 20 mm and second group more than 20 mm. Continuous treatment with gonadotropin was adjusted according to the count and size of follicle. The daily administration of gonadotropin was at least increase a 2 mm in the follicle size. After this stage both groups were given 10000 IU HCG and 34-36 hours after injection, IUI was performed for patients.

A chemical pregnancy test ( $\beta$ -HCG) was given 2 weeks after the IUI procedure. On the determination of approving a clinical pregnancy in the women with positive results, transvaginal sonography was done in the seventh week of the gestational age. A gestational sac with a fetus and fetal heart beats were considered as the checking facts. Finally chemical and clinical pregnancy rate and abortion rate compared between tow study groups.

### Statistical analysis

After collecting the necessary information required in this study, data were recorded in the computer system and then using SPSS-17 by using the Chi-Square test and student t-test and correlation data were analyzed.  $P < 0.05$  was considered statistically significant. All procedures performed in studies involving human participants were in accordance with the Ethics Committee of the Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, and with the 1964 Helsinki declaration and its later amendments or compa-

able ethical standards. Informed consent was obtained from all individual participants included in the study.

### 3. Results

Our study showed 97 patients (62.2%) were in the group I and 59 (37.8%) in group II. The mean age of patients were  $28.10 \pm 3.84$ , range between 19 and 37 years. The patients' characteristics are listed in Table 1. Mean age, BMI and duration of infertility were similar in both groups. (Table 1, Figure 1). In the division of the causes of infertility patients alienated in the five categories. Male factor (Men who had one of the sperm parameters was below the normal range (sperm concentration= $20 \times 10^6$ , motility=50%), PCO, Unexplained, Mild Endometriosis, Mixed) 72 patients (46.2%) were in the unexplained infertility group (Table 1).

Endometrial thickness on HCG injection by vaginal ultrasound measurements and showed that the average thickness was 7.82 mm. Endometrial thickness was significantly higher in group by follicles over than 20 mm ( $7.42 \pm 1.73$  vs.  $8.01 \pm 1.42$  mm;  $P=0.03$ ) (Table 2). There was no significant difference in the number follicles, duration of IUI cycles between two studied groups ( $P>0.05$ ) (Table 2). There was no significant difference in clinical pregnancy rate between two groups ( $P>0.05$ ) (Table 3).

### 4. Discussion

Two important factors in IUI cycles are including the size of the follicles and endometrial thickness [12]. Ovulation usually occurs when follicles size are about 21 to 23 mm, although ovulation may occur in the size of 17 mm to 26 mm [13].

The chance of ovulation increases with follicular diameter. The ultrasonography examination after HCG injection showed ovulation in follicles with 14 mm in size and smaller rarely may occur, but ovulation occur in about 40% of 15 to 16 mm follicles in size, 70% of 17 to 18 mm, and up to 80% in 19 to 20 and larger than 20 mm, follicles in size [14].

In this study, 156 patient treated by COH-IUI cycles and pregnancy rate was about 14.1% and our result was similar to Pursley et al. and Esmaeilzadeh and colleagues. They have reported about 15% pregnancy rate in IUI cycles [15, 16].

In our study pregnancy rate in group by dominant follicle over 20 mm was higher than group dominant follicle below 20 mm, but this variance was not significant. Our results also were consistent with the results of Trout and colleagues. In their study on 544 patients with clomiphene citrate, HCG were undergoing IUI, showed that the pregnancy rate in patients with larger dominant follicle (follicle  $\geq 20$  mm in size) was higher than who have smaller dominant follicle (follicle  $\leq 20$  mm in size)

**Table 1.** Basal variables of patients in two study groups

Study Variables		Group I Follicle Size <20 mm n=97	Group II Follicle Size >20 mm n=59	P
Age years old	Mean±SD	27.62±3.83	28.88±3.76	0.27
Infertility duration (years)	Mean±SD	5.78±6.09	5.08±3.12	0.68
Etiology of infertility	Male factor	10(10.3%)	8(13.6%)	
	PCO	30(30.9%)	17(28.8%)	
	Unexplained	43(44.3%)	29(49.2%)	
	Mild Endometriosis	7(7.2%)	3(5.1%)	
	Mixed	7(7.2%)	2(3.4%)	0.23
BMI (Kg/m <sup>2</sup> )	Mean±SD	26.08±4.07	26.72±4.43	0.12

Student's t-test were used for statistical analysis.

Data presented by Mean±SD.

BMI=Body Mass Index; PCOS: Polycystic Ovary Syndrome

$P \leq 0.05$  was considered statistically significant.

**Table 2.** IUI cycle characteristics in both study groups

Study Variables		Group I Follicle Size <20 mm n=97	Group II follicle Size >20 mm n=59	P
Endometrial thickness (mm)	Mean±SD	7.42±1.73	8.01±1.42	0.03*
Number of follicles	Mean±SD	2.06±1.12	2.38±1.23	0.46
Duration of cycle (days)	Mean±SD	11.38±1.27	11.43±1.62	0.52

Parameters expressed as mean±SD. Chi-square and Student’s t-test were used. P<0.05 was considered statistically significant.

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**Table 3.** Outcome of IUI treatment cycles in two groups

	Group I Follicle size <20 mm n=97	Group II Follicle size >20 mm n=59	P
Clinical pregnancy(%)	10(10.3%)	12(20.3%)	0.09

Chi-square test was use. P .0.05 was considered statistically significant

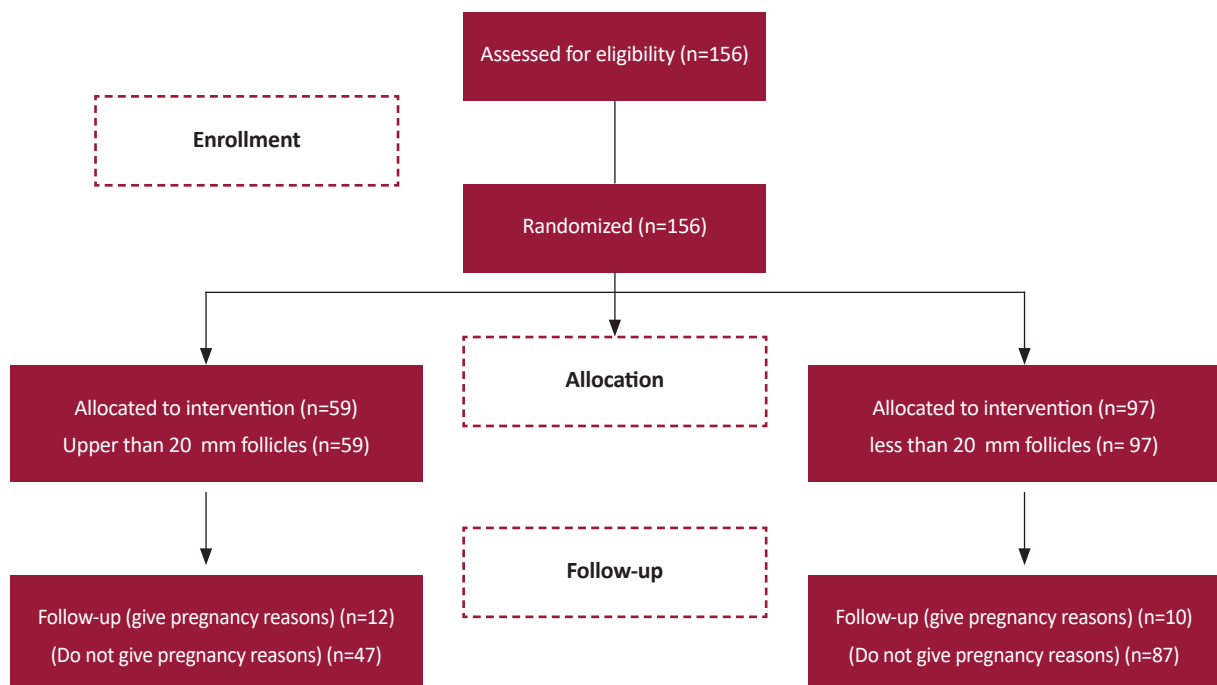
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[17], and in our study we find patients who have higher chances of pregnancy have larger than 20 mm follicles in size. Although 12 out of 22 pregnancies reported in our study among patients who their follicles size was more than 20 mm, and the number of pregnancies in patients with follicles less than 20 mm in size were 10 patients, although this difference was not statistically significant.

In another study in patients who became pregnant through IUI, showed that the pregnancy rate among those who had a large dominant follicle were three times

higher than who have small dominant follicle [18], and in another study the pregnancy rate in the group that was more and larger number of follicles was higher than another group [19], which is coordinating these studies with our study.

Although our focus in this study was on optimal neither size nor number of dominant follicle, but in several studies discusses on number of dominant follicle in IUI cycles. In a study reported that the pregnancy rate in patients with 3 or more dominant follicle at the time of



**Figure 1.** Allocation and follow-up flowchart of the study

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ovulation was higher than patients who were less than dominant follicles [20].

In ovulation induction cycles with gonadotropins ultrasound measurements of endometrial thickness is important [21]. Fertility per cycle increased with endometrial thickness and is coordination with concentrations of serum estradiol. The probability of pregnancy is low in cycle that the endometrial thickness is lower than 7 mm [22]. In a study on the role of endometrial thickness on pregnancy rate in IUI cycles was concluded a direct relationship between endometrial thickness and pregnancy rate. In this study pregnancy rate was, only about 11.1% in the patients with endometrial thickness of less than 8 mm [23].

In another study to evaluate the endometrial thickness on pregnancy rate in IUI cycles was found that the direct relation between pregnancy rate and endometrial thickness in IUI. They reported in patients who endometrial thickness was  $10.1 \pm 3.5$  mm pregnancy rate was significantly higher [16].

On the role of endometrial thickness in pregnancy rate in our study showed that endometrial thickness in patients with follicles more than 20 mm is higher than patients who had follicles less than 20 mm. The mean of thickness in several studies showed significant statistical difference between positive and negative pregnancy. Pregnancy rate in the group with endometrial thickness more than 7 mm is significantly higher than the group who had endometrial thickness less than 7 mm [24, 25].

Studies about infertility cause showed pregnancy rate is lower in women with endometriosis compared to women with unknown or PCO infertility. In our study in patients with endometriosis pregnancy rate was zero, which is much lower than reports from other researchers [26]. Negative effects of endometriosis on pregnancy rate in IUI cycles have been reported in several studies [24, 27, 28]. Factors that decrease fertility in endometriosis are still unknown. Endometriosis effect on the follicle environment [29], the quality of the oocytes [30], and the implantation rate [31].

It seems in unexplained infertility, ovulation induction and IUI cycles is an effective way [25]. Peterson and his colleagues showed that the pregnancy rate in unexplained infertility is about 18% [32], that is reliable with our results.

Our study showed that the BMI on pregnancy rate is very effective, so that the pregnancy rate in our patients who had a body mass index less than 25 was higher than patients who had BMI more than 25 and 30. We don't

see any fertility in patients who are BMI over 30 and difference was statistically significant. Many studies have investigated the effects of obesity on reproductive quality and their result was parallel to our finding [33, 34].

Based on the results of studies it is establish that the estrogen and progesterone disorders in obese women can decrease their fertility [35, 36], and probably hormonal fluctuations that occur in patients enrolled in IUI cycles that will have a lower oocyte quality and pregnancy rate [37].

## 5. Conclusion

In conclusion, based on this study for IUI cycles optimal size of follicles is when follicles are more than 20 mm, so that the endometrial thickness and pregnancy rate will be better in COH-IUI cycle.

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## Conflict of Interest

The authors have no financial or nonfinancial conflicts of interest.

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