Relation between the Number and Size of Follicles in Ovulation Induction and the Rate of Pregnancy

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Abstract

Objective: The aim of this study was to investigate the relation between number and size of preovulatory follicles and the outcome of controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI) in cases of unexplained infertility.

Subjects and methods: This prospective study included 200 couples with unexplained infertility. They were submitted to COH with clomiphene citrate and hMG followed by hcg when at least one growing follicle reaches the size of ≥18mm follicular monitoring started on the 10th day of the cycle until at least one follicle reaches 18mm or more. We recorded the highest follicular count of different diameters in the two ovaries during the days preceding hCG injection. Growth of more than one follicle with a diameter of ≥18mm is considered multifollicular growth. IUI was performed with fresh sperm 24 to 36 hours after hCG administration to a maximum of three cycles. The primary outcome measure was achieving pregnancy confirmed by rising hCG levels.

Results: Eighteen couples were excluded from the study. Clinical pregnancy occurred in 42 cases (23.1%). Significantly higher pregnancy rates were achieved in younger females (73.8%) and in those with duration of infertility <5 years (28.6%).Pregnancy rate increases significantly with more follicles ≥12mm or ≥15mm,but not with number of follicles ≥18mm. Pregnancy rate was significantly higher in cases with multifollicular growth.

Conclusion: In couples with unexplained infertility treated with IUI, pregnancy rate was positively associated with multifollicular growth and higher number of ≥12mm or ≥ 15mm

Key Words: Infertility – Number and size of follicles – Ovu-lation – Induction

Introduction

INTRAUTERINE insemination (IUI) is well-recognized as an empirical treatment in unexplained infertility [1]. Controlled ovarian hyperstimulation (COH) using gonadotrophins with IUI has been

shown to be a more effective treatment of infertility than IUI in natural cycles[2]. This is presumably owing to increasing the number of oocytes available for fertilization and the number of spermatozoa that reach the oocyte [3].

Pregnancy rates following IUI range between 8% and 26% [4]. Higher pregnancy rates were associated with some factors such as sperm count [5] and follicle development [6] whereas high cycle number and higher female age have been negatively associated with pregnancy rates [4,7]. Other prog-nostic variables predictive of pregnancy in IUI include history of prior pregnancy, duration of infertility, endometrial thickness, and progressive sperm motility and number of follicles $\geq$ 15 or 18mm [8-12].

In this prospective study we aimed to investigate the relation between number of follicles of different sizes and the outcome of controlled ovarian hyper-stimulation and intrauterine insemination for treat-ment of unexplained infertility.

Subjects and Methods

This prospective study includes 200 patients attending infertility private clinic Al-Haboby Teaching Hospital, Bent-Al-Huda, University between August 2012 and August 2015. All couples enrolled suffered from unexplained infertility with regular cycles, patent tubes, normal hormonal milieu and normal parameters of semen analysis according to the WHO.

Treatment protocol:

All patients were submitted to controlled ova-rian hyperstimulation with clomiphene citrate (CC), 100mg for 5 days starting from the second day of menstrual cycle followed by human menopausal gonadotrophin (hMG) 75 to 150mIU for 3 or more days. When at least one growing follicle reaches the size of $\geq$18mm, a dose of 10000 IU of human chorionic gonadotrophin (hCG) was injected.

Follicular monitoring was done using transvaginal ultrasonography (Toshiba Medical Systems 7.5MHz probe) daily starting on the 10th day of the cycle until at least one follicle reaches 18mm or more. We calculated follicular diameter (in millimeters) as the average of two perpendicular dimensions, measured from the outer wall of one side of the follicle to the inner wall of the other, in the most rounded configuration. The growth of one or more follicles to a diameter of $\geq$12mm is a

prerequisite to complete the study protocol. Growth of more than one follicle with a diameter of $\geq$ 18mm is considered multifollicular growth. We recorded the highest follicular count in the two ovaries during the days preceding hCG injection.

A single intrauterine insemination (IUI) was performed with fresh sperm 24 to 36 hours after hCG administration. Sperms were processed by wash, swim up, or swim-down methods. Each couple tried a maximum of three cycles of IUI.

The primary outcome measure was achieving pregnancy confirmed by rising hCG levels. A transvaginal ultrasound examination was performed when hCG exceeded 2000 mIU, to confirm intrau-terine implantation and to determine the number of gestational sacs. The secondary outcome was biochemical pregnancy (initial hCG level of 25 mIU and rising without a gestational sac) and ectopic pregnancy. Normal pregnancies were fol-lowed up by ultrasound examination until 6 weeks' gestation.

Results

Eighteen couples were excluded from the study, 13 did not show on follow up and 5 females failed to reach 12mm follicles on hyperstimulation. HCG injection and IUI were done in all remaining cases (n=182) to a maximum of three cycles. Here we show the results of the last cycle for all couples. The mean age of the females was 29.3±2.5 years (range 26-34 years). Females more than 30 years old represented about 43% of cases (Table 1). Couples with infertility duration <5 years were 118 patients (64.8%) while patients with duration more than 5 years were 64 patients (35.2%).

Multifollicular growth was rather common in this studied group; it was seen in 103 women (56.6%), while 79 patients (43.4%) developed one mature follicle $\geq$18mm in diameter (Table 2).

We observed clinical pregnancy in 42 cases (23.1%). First cycle succeeded in 12 couples (6.6%). The majority of the pregnancies (73.8%) were achieved in younger females (<30 years old). Patients with duration infertility <5 years showed significantly higher pregnancy rates (34/119, 28.6%) compared to those with 5 years duration of infertility or more. Pregnancy rate increases significantly with more follicles $\geq$12mm or $\geq$15mm, but not with number of follicles $\geq$18mm. However, pregnancy rate was significantly higher in cases with multifollicular growth (Table 3).

Table (1): Demographic and clinical characteristics of the studied group (n=182).

Variable	Value
Age (years, mean ± SD)	29.3±2.5
Age groups (<30/³30 years)	104/78
Weight (kg)	68.3±9.3
Body mass index (kg/m2)	23.8±1.4
Primary infertility [n (%)]	154 (84.6%)
Duration of infertility [years, median (range)]	3 (2-7)
Days of ovarian stimulation (mean ± SD)	8.1±2.3
Days of hMG injection (mean ± SD)	3.1±1.4

Table (2): Clinical outcome of ovarian stimulation if IUI.

Variable	Value
Overall clinical Pregnancy rate	42(23.1%)
Monofollicular growth [n (%)]	79(43.4%)
Multifollicular growth [n (%)]	103 (56.6%)
2 follicles [n (%)]	48(26.4%)
3 follicles [n (%)]	34(18.7%)
>3 follicles [n (%)]	22(11.5%)

Discussion

This prospective study aimed to assess the relation between number and size follicles and likelihood of pregnancy. In this study, clinical pregnancy was achieved in 42 cases (23.1%). Younger age and shorter duration of infertility were associated with higher pregnancy rates [OR (95% CI), 2.6 (1.2-5.6), 2.8 (1.2-6.4)]. Pregnancy rate was significantly higher in cases with multi-follicular growth (OR, 95% CI: 2.7, 1.2-5.7). In addition, pregnancy rate

increases significantly with more follicles ≥12mm or ³15mm, but not with number of follicles ≥ 18mm.

Table (3): Patient and follicular factors in relation to clinical pregnancy in the studied group (n=182).

	Clinical pregnancy		p-value	OR (95% CI)
	+ve (n=42)	-ve (n=140)		
Age Group: <30 yrs (n=104) □30 yrs (n=78)	31 (29.8%) 11 (14.1%)	73 (70.2%) 67 (85.9%)	0.013	2.6 (1.2-5.6)
Duration of infertility: <5 yrs (n=119) ≥5 yrs (n=63)	34 (28.6%) 8 (12.7%)	85 (71.4%) 55 (87.3%)	0.016	2.8 (1.2-6.4)
Follicular Growth: Multifollicular (n=103) Monofollicular (n=79)	31 (30.1%) 11 (13.9%)	72 (69.9%) 68 (86.1%)	0.010	2.7 (1.2-5.7)
No. of follicles≥12mm: Mean±SD >3 (n=141) □3 (n=41)	4.9±1.9 40 (28.4%) 2 (4.9%)	3.8±1.2 101 (71.6%) 39 (95.1%)	<0.001 0.002	7.7 (1.8-33.5)
No. of follicles≥15mm: Mean±SD >3 (n=76) □3 (n=106)	5.0±1.4 36 (47.4%) 6 (5.7%)	3.0±0.8 40 (52.6%) 100 (94.3%)	<0.001 <0.001	15.0 (5.9-38.4)
No. of follicles≥18mm Mean±SD >2 (n=48) □2 (n=134)	2.3±1.2 14 (29.2%) 28 (20.9%)	1.9±1.1 34 (70.8%) 106 (79.1%)	0.073 0.243	1.6 (0.7-3.3)

The effect of age on fertility potential has been demonstrated in the general population and in infertile women whether undergoing treatment or not. This effect usually overrides the effect of other variables that may affect pregnancy. Our results of higher likelihood of pregnancy in younger age have been previously determined in other studies [8-10,13-15]. Duration of infertility has been considered to be a predictor of pregnancy in previous fertility studies [4,11,14]. We found that duration of infertility less than 5 years had a change of

success 2.8 times as couples with infertility duration of five years or more.

Multifollicular growth is the rationale of adding controlled ovarian hyperstimulation to IUI cycles aiming to increase the pregnancy rate [16]. Nevertheless, the drawback of multifollicular growth in these cases is the risk of multiple pregnancies which may increase the risk of pregnancy complications, as preterm delivery, growth retardation and pre-ecclampsia [17,18].

Several previous studies reported contradictory results regarding the relation

between the number of preovulatory follicles and pregnancy rates in ovarian stimulation with IUI. The majority of the studies reported a positive association between the number of follicles and pregnancy rate [3,4,6,9,19]. On the other hand, others did not find such a positive association [20,21]. Moreover, two other studies reported high pregnancy rates of in couples where over 60% of the cycles were monofollicular [22,23].

In the current study, multifollicular growth was positively associated with pregnancy rate (OR, 95% CI: 2.7, 1.2-5.7). A meta-analysis reporting on 11599 cycles of IUI with COH in 7489 couples from 14 studied, the pooled OR for pregnancy after two follicles as compared with monofollicular growth was 1.6 (99% CI 1.3-2.0), whereas for three and four follicles as compared with monofollicular growth this was 2.0 (99% CI 1.6-2.5) and 2.0 (99% CI 1.5-2.7), respectively [21]. A recent retrospective evaluation of 255 IUI cycles in 232 women, preg-nancy rate was 3.1 % for 1 preovulatory follicle, 9.3% for 2 follicles, 16.9% for 3 and 23.1% for 4 [24].

We can conclude that in couples with unex-plained infertility treated with IUI, pregnancy rate was positively associated with multifollicular growth and higher number of $\geq$ 12mm or $\geq$ 15mm.