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ORIGINAL ARTICLE

Does detection of follicle rupture affect success in intrauterine insemination cycles? A tertiary center experience

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ABSTRACT

Objective: The aim of this study is to investigate the effect of intrauterine insemination (IUI) performed simultaneously with ultrasound detected follicular rupture during biological reproduction window on pregnancy rates in patients with unexplained infertility undergoing ovulation induction (OI) cycles with gonadotropins.

Material and Methods: Three-hundred and twenty-five patients with unexplained infertility were included in this prospective cohort study, who received recombinant follicular stimulating hormone (75–150 IU/day) or Human Menopausal Gonadotropin starting from the 2nd to 3rd days of the cycle. IUI was carried out with ultrasonographic monitoring of the follicles. The presence of free fluid within the Douglas pouch, detection of corpus luteum, and/or loss of the dominant follicle was interpreted as follicular rupture. Pregnancy rates with or without follicular rupture were compared after 14 days.

Results: Among those with follicular rupture, the time between administration of recombinant hCG and IUI was significantly longer as compared to those without follicular rupture (p<0.001). β hCG was positive at 14 days after IUI in 19.01% (31/163) and 13.92% (22/158) of the cases with or without follicular rupture, respectively. The difference in pregnancy rates was not significant (p=0.219).

Conclusion: IUI simultaneously performed with ultrasound-detected follicular rupture in OI cycles with gonadotropins does not increase pregnancy rate.

Keywords: Follicle rupture, infertility, intrauterine insemination, ovulation induction.

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INTRODUCTION

According to the International Committee for Monitoring Assisted Reproductive Technologies, unexplained infertility is defined as infertility in couples with apparently normal fallopian tubes, cervical and uterine anatomy, ovulatory function, testicular function, ejaculate, and adequate coital frequency.[1] The general prevalence of unexplained infertility ranges between 22% and 28%,[2,3] with reported prevalence rates of 21% and 26% in those under and over 35 years of age, respectively.[4]

Predictors of successful intrauterine insemination (IUI) include the etiology and duration of infertility, patient age, number of preovulatory follicles, total sperm motility, and the permeability of the fallopian tubes. It is widely accepted that IUI increases pregnancy outcomes following ovulation induction (OI) with oral agents or gonadotropins with unexplained infertility patients.[5–8] In a recent randomized, controlled study by Farquhar et al.[9] involving patients with unexplained infertility, three cycles of OI/IUI were compared with 3 months of expectant management, and the number of live-births was found to be three-fold higher in those undergoing OI/IUI cycles, as compared to natural conception.

In patients with unexplained infertility, OI with gonadotropins and IUI generally represent the most frequent strategy prior to *in vitro* fertilization. Allowing multi follicular development, increasing the likelihood of fertilization, and accurate timing of IUI form the rationale of this approach. According to 2009 ESHRE (European Society of Human Reproduction and Embryology) Capri Workshop Group, pregnancy rates per cycle are 7% with clomiphene citrate (CC)/IUI versus 12% with (OI with gonadotrophins)/IUI.[5]

Recent areas of discussion include the number of IUIs per cycle,[10] the timing of IUI,[11] and identification of the follicle rupture (FR) during IUI.[12] Concerning the optimal timing of IUI, ESHRE Capri Workshop Group recommended a 32–36-h interval after administration of human chorionic gonadotropin (hCG) in stimulated cycles.[5] Some investigators have further extended this interval to 38 h. The scientific rationale for the 32–38-h time interval is based on ultrasound and hormone studies showing follicular rupture in 68% of the cases with spontaneous cycles and 81% of the cases with stimulated cycles, following hCG administration.[13–15]

Until now, only few studies have evaluated the timing of IUI concerning FR. The aim of this study was to examine the effect of IUI carried out simultaneously with ultrasound-detected FR during the biological fertility window in cycles induced by gonadotropin OI on the success of getting pregnant among patients with unexplained infertility.

MATERIAL AND METHODS

Patient Population

Patients diagnosed with unexplained infertility in the Infertility Clinic of a tertiary center hospital between August 2016 and January 2017 was included in this prospective cohort study. The study was conducted in accordance with the Declaration of Helsinki. Approval for this study was obtained from the Institutional Review Board (165/2016). Written informed consent was obtained from all participants.

A total of 325 women with unexplained infertility were included. Eligible subjects were between 20 and 40 years of age, had at most two dominant follicles, had no systemic comorbidity, had regular menstrual cycles (21–35 days), and had no pathology in the fallopian tubes or uterus as documented by hysterosalpingography (HSG) and ultrasound examination, in addition to a post-wash total progressively motile sperm count of ≥ 5×106 in the partner.

Exclusion criteria were FSH >10 mIU/ml, history of pelvic surgery due to endometriosis, history of ovarian surgery, presence of ovarian cysts at baseline ultrasound, anovulatory cycles, cycle cancellation due to lack of follicular development, and presence of >2 dominant follicles exceeding 17 mm in diameter.

IUI Cycles

Following a baseline ultrasound on day 2 or 3 of the menstrual cycle, hormone profile and ovarian reserve tests were performed for the infertile women. At the termination of the menstrual cycle, tubal patency was examined with HSG. OI with gonadotropins and IUI were scheduled in patients diagnosed with unexplained infertility. Doses were adjusted on an individual basis. Starting from day 2 or 3 of the cycle, daily recombinant follicular stimulating hormone (r-FSH) at a dose of 75 to 150 IU or Human Menopausal Gonadotropin (hMG) was administered. For follicle monitoring, patients were invited to the clinic on appropriate days for ultrasound examination of the follicular development starting from day 7. A GE LOGIQ 200 Pro ultrasound device was used. OI with gonadotropin was continued until a dominant follicle size of 16 to 18 mm was achieved and this was followed by subcutaneous administration of recombinant hCG (Ovitrelle, Merck Serono, Switzerland) at a dose of 250 micrograms. IUI was done 34–38 h after r-hCG. A transvaginal ultrasound (TVUSG) was carried out after IUI to examine the signs of FR. The presence of free fluid in the Douglas pouch, identification of corpus luteum, and/or disappearance of the dominant follicle was interpreted as follicular rupture. US-guide follicle monitoring and IUI were performed by two specialists. Patients with or without follicular rupture were designated into Group A and Group B, respectively. β-hCG testing was performed after 14 days to compare the two groups with respect to the occurrence of pregnancy. Women with a serum β-hCG level of >5 mIU/mL were considered pregnant.

Spermiogram

Sperm samples were collected through masturbation following 3–7 days of sexual abstinence. Sperms obtained 1–2-h before IUI and prepared using the gradient technique were introduced into the uterine cavity at body temperature using an insemination catheter. Spermiogram was assessed using the WHO 2010 criteria.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 software package (The Statistical Package for the Social Sciences, SPSS Inc., version 17; Chicago, IL, USA). Descriptive statistics were expressed with mean±standard deviation and percentage. Normal distribution of the variables was tested with visual (histogram and probability graphs) and analytic methods (Kolmogorov–Smirnov test). Pairwise group comparison of quantitative data with normal distribution was done with inde-

Table 1: Sociodemographic and clinical characteristics of patients with (group A) or without (group B) follicle rupture

	With rupture (n=163) Group A Mean±SD	Without rupture (n=158) Group B Mean±SD	p
Female age (years)[1]	30.7±4.8	29.5±4.7	0.41
Partner age (years)[2]	33.8±4.8	32.7±5.0	0.27
BMI (kg/m^2)[2]	24.5±5.4	24.1±4.8	0.75
Gravidity[2]	0.1±0.4	0.1–0.4	0.22
Abortus[2]	0.1±0.4	0.1±0.4	0.46
FSH[2]	5.8±1.8	5.7±1.7	0.83
Estradiol[2]	43.1±17.2	41.9±16.9	0.77
LH[2]	5.5±5.9	4.6±1.9	0.56
Prolactin[2]	16.3±8.3	16.4±7.3	0.92
TSH[2]	2.2±1.1	1.9±0.9	0.01*
Antral follicle count[2]	13.3±4.5	13.6±4.3	0.23
Duration of infertility (years)[2]	4.22±3.01	4.0±2.7	0.77

Statistic method: [1]Student t-testi; [2]Mann Whitney U testi; *: Statistically significant; SD: Standard deviation; BMI: Body mass index; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid-stimulating hormone.

pendent sample t-test, while Mann–Whitney U test was used for the variables without normal distribution. Qualitative data were compared with chi-square test, or when the test conditions were not met, with Fisher's Exact Chi-Square test. p<0.05 was considered significant.

RESULTS

Of the 325 patients initially included in the study, four had cycle cancellation due to abnormal ovarian response and therefore were excluded since IUI could not be done. All remaining 321 patients received OI with gonadotropins and had IUI. FR was detected with ultrasound in 163 of these 321 patients (50.8%), while no rupture could be observed in 158 (49.2%).

Table 1 shows the sociodemographic and clinical characteristics of patients with (Group A) or without (Group B) FR. The two study groups were comparable with respect to female age, partner age, Body Mass index, gravidity, abortus, and duration of infertility (p>0.05). Furthermore, hormone levels and ultrasound findings at baseline were similar across the two groups. However, TSH was statistically higher in Group A (2.2±1.1 mU/L) than in Group B (1.9±0.9 mU/L) (p=0.01), this difference was not considered to have clinical significance.

Table 2 shows the rates of follicular rupture in patients diagnosed with primary or secondary infertility, with no significant differences (p=0.245).

Table 2: The rates of follicular rupture in patients diagnosed with primary or secondary infertility

	With follicle rupture (n=163)		Without follicle rupture (n=158)		p
	n	%	n	%	
Primary infertility	148	90.8	137	86.7	0.245
Secondary infertility	15	9.2	21	13.3	

Statistic method: Chi-square test.

Table 3 depicts the cycle and ultrasound characteristics of the study subjects during OI treatment. Patients with or without FR during OI therapy were not significantly different in terms of the initial gonadotropin dose (IU), total gonadotropin dose (IU), duration of treatment (days), number of follicles >10 mm, number of follicles >16 mm, greatest follicular diameter (mm), endometrial thickness (mm), and endometrial imaging findings on TVUSG (homogenous, triple). On the other hand, the time from recombinant hCG to IUI was significantly longer among those with FR than among those without follicular rupture (p<0.001).

β hCG positivity rates 14 days after IUI were 19.01% (31/163) versus 13.92% (22/158) in those with or without follicular rupture, respectively. The difference in pregnancy rates was not significantly different between these two groups (p=0.219).

DISCUSSION

Determinants of effective IUI include the use of accurate indications for the procedure, use of appropriate techniques for sperm preparation, accurate timing of IUI, prevention of premature luteinizing hormone surge, and support strategies for the luteal phase.[16,17] In addition to these fundamental strategies, some other procedures have been used in an attempt to increase the likelihood of pregnancy, including increasing the number of IUIs or the use of double-IUI in the same cycle.

Well-established determinants of a successful OI/IUI include female age, duration of infertility, number of follicles developing, sperm concentration, and sperm motility.[18,19] To minimize the impact of other factors that might affect the outcome of OI/IUI, a homogenous group of patients with unexplained infertility was included in this study. In contrast, in a previous study by Küçük et al.,[12] patients with male infertility were also included as well as unexplained infertility. In another similar study, Ghanem et al.[20] also included anovulatory patients as well as those with male infertility, in addition to those with unexplained infertility.

In the previous study by Küçük et al.,[12] a significantly higher rate of clinical pregnancy was reported in patients in whom FR was detected using TVUSG. Based on their results, the authors recommended delaying IUI until the detection of follicular rupture. Conversely, we did not observe a positive effect of the detection of the FR by TVUSG

Table 3: The cycle and ultrasound characteristics of the study subjects during ovulation induction treatment

	With follicle rupture (n=163)		Without follicle rupture (n=158)		p
	Median (25–75%)	Mean±SD	Median (25–75%)	Mean±SD	
Initial gonadotropin dose (IU)	75 (75–75)	72.6±9.9	75 (75–75)	75.1±10.2	0.902
Total gonadotropin dose (IU)	525 (450–750)	656.3±315.8	575 (450–750)	657.7±276.4	0.523
Duration of treatment (days)	8 (6–11)	8.7±3.2	8 (7–10)	8.6±2.9	0.421
Number of follicles >10 mm	2 (1–2))	1.9±1.1	2 (1–3)	2.2±1.4	0.121
Number of follicles >16 mm	1 (1–1)	1.0±0.1	1 (1–1)	1.0±0.9	0.424
Greatest follicle diameter (mm)	17.5 (16.9–19.9)	17.8±1.5	17 (17–18)	17.6±1.2	0.409
Duration between hCG and IUI (hours)	38 (36–38)	37.1±1.2	35 (35–37)	35.8±1.4	0.000*
Endometrial thickness (mm)	9.1 (7.6–11.5)	9.6±2.6	9 (7.6–14)	9.2±2.1	0.566
Endometrial imaging findings on ultrasound[3]					0.939
Homojen	87 (53.4%)	85 (53.8%)			
Tripple	76 (46.6%)	73 (46.2%)			
B hCG pozitivity rates	31 (19%)	22 (13.9%)	0.219		

Statistic method: Mann–Whitney U test; 3: Chi-square test; *: Statistically significant; SD: Standard deviation.

at the time of IUI on pregnancy rates. In the most recent study on this topic, Giugliano et al.[21] evaluated only cases of unexplained infertility and concluded that IUI performed simultaneously with follicular rupture could not be associated with higher rates of pregnancy. In that same study, a logistic regression analysis showed that neither the confirmation of the follicular rupture nor other variables had an impact on pregnancy rates.

In the study by Ghanem et al.,[20] simultaneous IUI was performed in patients who had rupture confirmed by TVUSG, and patients without rupture were also randomized for a second IUI after 24 h. It was concluded that in patients without a male factor for infertility, a single scheduled IUI following ovulation was superior to a single pre-ovulatory IUI, although double pre-ovulatory IUI was better than a single IUI in achieving clinical pregnancy in those cases involving male factor infertility.

In our prospective cohort study, we used r-FSH and HMG preparations for OI, and r-hCG for hCG triggering, with scheduled IUI 34–38 h after hCG administration. In Küçük et al.'s[12] retrospective study, stimulation was performed with r-FSH, and hCG trigger was performed with urinary hCG (u-hCG); IUI was done 36–38 h after hCG administration. In Giugliano et al.'s[21] study, stimulation was carried out with r-FSH and HMG, and r-hCG was preferred for hCG trigger; IUI was done 36–38 h after hCG. In contrast, in Ghanem et al.'s[20] study, anovulatory patients were also included, and stimulation was performed using CC, CC+HMG, and HMG preparations. Furthermore, u-hCG was preferred for hCG trigger, followed by IUI 34–38 h later. We may ask whether the use of u-hCG in these studies by Küçük[12] and Ghanem,[20] as opposed to our and Giugliano's[21] studies, had an effect on the pregnancy results. However, in two prospective randomized studies from Cochrane database, no significant differences in pregnancy results were reported between r-hCG and u-hCG use in OI/IUI cycles.[22]

Furthermore, the optimal timing for IUI, for which the clinical practice ranges in a large time window between 12 and 40 h, has been subject to considerable research in terms of its association with pregnancy rates, with no consensus. In a systematic review by Cantineau, the optimum time from hCG injection to IUI was examined for time windows ranging between 24 and 48 h, and no differences in pregnancy rates were found.[22]

The rationale for double IUI, on the other hand, is based on the demonstration of the variability in rupture timing following hCG administration,[12] which represents the theoretical basis for ensuring the continuous presence of sperm cells in the genital tract throughout the biological reproduction window. However, if this theory held true, then it would be possible to see higher success rates in all double IUI cycles as compared to single cycles. There is no consensus in the published literature regarding superiority of double IUI, with some studies reporting better results with double IUI,[11,23] while others showing no difference at all.[24–26] If IUI simultaneously performed with follicular rupture was associated with higher pregnancy rates, as reported by Küçük et al.,[12] these results would be corroborated with a consensus in the literature. Therefore, we consider the retrospective nature of the study by Küçük et al.[12] as a limitation.

In our study, the average time from hCG to IUI was 38 h and 35 h for patients in whom FR was or was not detected, respectively. This was one of the two parameters with the statistically significant difference in our study. Andersen et al.,[27] investigating the time interval between hCG and IUI, started hourly follicular rupture examinations from 32 h after hCG injection using TVUSG and observed an average duration of 38 h between hCG administration and first follicular rupture in their patients scheduled for IUI. While pregnancy rates were not reported by Andersen et al.,[27] differences in this time interval did not appear to have an impact on pregnancy in our study. In

another study, Claman et al.,[28] again examined the effect of this time interval on pregnancy rates and found no significant differences between short (33 h) and long (39 h) interval groups (21% vs. 15%, respectively; odds ratio=0.673, 95% confidence interval: 0.297–1.51).

In summary, we believe that IUI simultaneously performed with follicular rupture as detected by TVUSG in OI cycles does not contribute to better pregnancy rates. It should be noted that the previous studies at odds with our observations were retrospectively designed or used u-hCG for final oocyte maturation, which could affect the pregnancy results.[12,20] Supportive of this notion is the fact that better pregnancy rates were found for r-hCG in studies comparing different hCG types.[29,30]

CONCLUSION

Evidence to determine efficacy differences between IUI performed with follicular rupture based on TVUSG and IUI performed directly is insufficient. Further randomized and controlled studies are required to shed light on this controversy.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 25.11.2016, number: 164).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – BD, EÇ; Design – BD, ÇAY, NP; Supervision – NP, EÇ; Resource – PK; Materials – PK, BD, ÇAY; Data Collection and/or Processing – PK, BD, ÇAY; Analysis and/or Interpretation – PK, BD, EÇ; Literature Search – EÇ, NP, BD; Writing – BD, EÇ, NP; Critical Reviews – ÇAY, BD, NP, EÇ, PK.

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