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Does the FSH/LH Ratio in the Serum on the Third Day of the Cycle Predict ICSI Success?

Siklusun 3.Günü Normal FSH Değeri Olan Kadınlarda FSH/LH Oranı ICSI Başarısını Öngörebilir mi?

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Abstract

Objective: To determine whether the follicule stimulating hormone (FSH)/ luteinizing hormone (LH) ratios on the third day of the cycle predict intracytoplasmic sperm injection (ICSI) outcomes in women with normal day 3 FSH levels.

Patients and Methods: A retrospective cohort analysis of one hundred and ninety-nine consecutive women undergoing ICSI treatment with long-down regulation and recombinant follicular stimulating hormone injections was carried out in a University hospital. Four groups were compared in terms of in vitro fertilization (IVF) outcomes. Groups A, B, C and D consisted of women with FSH/LH ratios of <1; ≥1 and <1.5; ≥1.5 and ≤2 and >2, respectively. The clinical pregnancy and implantation rates per transfer were compared.

Results: There was no significant difference between the groups regarding the clinical pregnancy or implantation rates per transfer.

Conclusion: It appears that the basal FSH/LH ratio does not predict the cycle outcome in ICSI cycles in women with normal day 3 FSH levels. *(Marmara Medical Journal 2012;25:69-73)*

Key Words: FSH/LH ratio, Pregnancy, ICSI, Cancellation

Özet

Amaç: Siklusun 3.günü normal FSH değeri olan kadınlarda follikül stimule edici hormon (FSH)/luteinize edici hormon (LH) oranının sitoplazma içi sperm enjeksiyonu (ICSI) başarısının öngörülebilirliğini araştırmak.

Hastalar ve Yöntem: Uzun protokol ve rekombinant folikül stimüle edici hormon kullanılarak ICSI tedavisi alan ardışık yüz doksan dokuz infertil kadın retrospektif olarak analiz edildi. Grup A, B, C ve D sırasıyla FSH/LH oranları <1; ≥1 ile <1.5 arası; ≥1.5 ile ≤2 arası ve >2 olan kadınlardan oluşturuldu. Transfer başına klinik gebelik ve implantasyon oranları karşılaştırıldı.

Bulgular: Transfer başına klinik gebelik ve implantasyon oranları gruplar arasında benzer idi.

Sonuç: Siklusun 3.günü FSH/LH oranı ICSI sikluslarında tedavi sonuçlarını normal 3. gün FSH seviyesi olan kadınlarda öngöremez. *(Marmara Üniversitesi Tıp Fakültesi Dergisi 2012;25:69-73)*

Anahtar Kelimeler: FSH/LH oranı, Gebelik, ICSI, İptal

Introduction

In vitro fertilization (IVF) is a stressful and expensive procedure for patients who are hoping to get pregnant. Markers of ovarian reserve were investigated in order to help predict a patient's prognosis, including the likelihood of cycle cancellation, the required dose of medication, number of oocytes and embryos generated, as well as the prognosis for pregnancy. Ovarian reserve has been used to predict prognosis in IVF treatments[1]. Clinical markers of ovarian reserve include basal (day 3) levels of FSH, inhibin, and anti-mullerian hormone; antral follicle counts (AFC) and ovarian volumes[2]. The day 3 FSH level which is the most widely used clinical parameter has a limited[3] or lower predictive value[4]. Women with normal FSH levels on cycle day 3 can require higher

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than average doses of medication where disappointing cycle outcomes can be expected . Better markers of poor prognosis are needed to identify these patients, to aid in planning their IVF cycles, and to counsel them as to the likelihood of success.

Poor ovarian responsiveness and low pregnancy rates (i.e. diminished ovarian reserve) can be predicted in patients undergoing one of the assisted reproduction treatments[1] on the basis of several parameters, including: elevated day 3 FSH values[5], abnormal clomiphene citrate challenge tests[6], abnormal GnRH-agonist stimulation tests[7], abnormal exogenous FSH ovarian reserve tests[8] or elevated day 3 oestradiol concentrations[9] A number of hormonal parameters are currently thought to be predictive of poor ovarian responsiveness to stimulation and low pregnancy rates in patients undergoing one of the assisted reproduction treatments[1]. None of these tests, however, was found to be sufficiently accurate for predicting the ovarian response[3,4].

The objective of our study was to evaluate whether the FSH/LH ratio on cycle day 3 can be used to predict the ICSI-cycle outcome in women with normal day 3 FSH values.

Patients and Methods

One hundred and ninety-nine women undergoing consecutive IVF treatments at the Assisted Reproductive Techniques (ART) Unit at Marmara University Hospital in Istanbul, Turkey, were recruited in a retrospective cohort study. Exclusion criteria were: age over 39 years, cycle day 3 FSH level >12 IU/L, endometriosis (other than minimal); the presence of only one ovary or previous ovarian surgery; polycystic ovary syndrome or other endocrine disorders. In our ART unit, a detailed explanation, both verbal and written, is given to each infertile couple prior to ART treatments. Patients gave written consent to publication of any study derived from aggregate data. Ethical approval for this study was not required and has not been included as there were no interventions that are not a part of standard care. All practices and protocols conformed to the ethical requirements for assisted reproductive technology programs of the Ethics Commitee of Marmara Medical School and it conforms to the provisions of the Declaration of Helsinki.

All patients undergoing ART treatment in our institution do receive intracytoplasmic sperm injection (ICSI) no matter what the cause of infertility is. Patients were seen on day 3 of the cycle before their stimulation. On that day, serum samples were collected in the morning after a 12 h fasting. 5 ml of venous blood was collected. All patients underwent a transvaginal ultrasound documenting antral follicule count (AFC) by one examiner. All measurements were performed on one ultrasound machine (General Electric Loqic 200, 8-4 MHz, Istanbul, Turkey). AFCs measured all follicles between 2 and 8 mm on each ovary[12].

Subjects commenced down-regulation with a daily subcutenous injection of leuprolide acetate (1 mg/mL; Lucrin flacon , Abbott, Turkey) in the mid-luteal phase of the previous cycle. When adequate down regulation had been achieved (endometrial thickness <4 mm or serum estradiol <50 pg/ml), usually after at least 10 days of leuprolide acetate , controlled ovarian stimulation (COS) was started with recombinant FSH preparations, either Gonal F (Merck-Serono,Turkey) or Puregon (Schering-Plough,Turkey) at starting doses between 150 and 300 IU per day. Dose adjustments were individualized after 5 days of ovarian stimulation. Final oocyte maturation was induced by human chorionic gonadotrophin (hCG), 10,000 IU (Pregnyl, Schering-Plough, Turkey) when the two leading follicles were 18 mm in mean diameter. The analogue was continued till the day of the hCG injection.

Oocytes were retrieved 34 h after hCG administration under guided vaginal sonography, with the patient in a sedated but conversant state. An ICSI procedure was performed 3-5 h after retrieval of every oocyte. Approximately 16-19 h after the injection, normal fertilisation was checked. Selection for embryo replacement was made according to top quality embryo selection criteria. Embryos were transferred in a blastocyte medium (G2, Vitrolife, SISMED, Istanbul, Turkey). All embryos were transferred with the Wallace catheter (Smiths Medical International, UK) on the third day after ICSI. Abdominal ultrasonographic guidance was used. Luteal phase support was provided by vaginal progesterone gel 8% (Crinone, Serono, Turkey) starting on the day of ovum pick-up.

Clinical pregnancy was determined by the presence of a gestational sac during an ultrasound exam. The implantation rate was calculated as the ratio between the number of embryonal sacs diagnosed by sonography and the total number of embryos transferred into the uterus. Clinical pregnancy rates and implantation rates were calculated per embryo transfer.

All demographic information, IVF cycle information, and cycle outcomes were obtained from the patients' charts. The charts were reviewed by one investigator. Patients were placed into four groups for analysis: FSH/LH ratio <1(group A); FSH/LH ratio between ≥1 and <1.5 (group B); FSH/LH ratio between ≥1.5 and ≤2 (group C) ,and FSH/LH ratio >2 (group D) .

Stata/SE 9.2 (Statacorp, Texas) was used for all analyses. For the whole group statistical evaluation, the Kruskal-Wallis test was used; $p<0.05$ was considered significant. The groups were compared with eachother by the Mann-Whitney U test. The Bonferroni adjusted level of significance was needed to obtain statistical significance, calculated as $p<0.0083$ ($0.05/6 = 0.0083$).

Multivariable logistic regression modeling was used to compute the odds ratios (ORs) of variables predictive of clinical and ongoing pregnancies after fresh ETs , and of the cycle cancellation rate. The independent variables were age, duration of stimulation, total dose of FSH administrated, AFC, day 3 FSH levels, day 3 LH levels and day 3 FSH/LH ratios.

Results

A total of 199 cycles were retropectively analysed. All women had a basal FSH value of less than 12 IU/L. Of the four groups with FSH/LH ratios of <1; ≥1 and <1.5; ≥1.5 and ≤2; and >2, group A included 65, group B 70, group C 43 and group D 21 cycles. Indications for ICSI in group A were male factor (45.3%), tubal (7.8%), or unexplained infertility (39.1%). The percentages of

distribution in group B were 58.6%, 12.9% and 14.3%, respectively. Indications for ICSI in group C were male factor (59.5%), tubal (14.3%), or unexplained infertility (14.3%). 71.4%, 5% and 9.5% of women in group D had male factor, tubal, or unexplained infertility, respectively.

The treatment cycle characteristics between the groups are given in Table I. ICSI cycle outcomes were comparable between the groups. The clinical and ongoing pregnancy rates per transfer were similar. Implantation rates per transfer did not show a significant difference between the groups (Table II).

The multivariate analysis showed that there was no association between the rate of clinical pregnancy and age, duration of stimulation, total dose of FSH administered , AFC, day 3 FSH levels, day 3 LH, or day 3 FSH/LH ratios (Table III). There was no association between the rate of ongoing pregnancy and age, duration of stimulation, total dose of FSH administered, AFC, day 3 FSH levels, day 3 LH, day 3 FSH/LH ratio (Table III). The rate of cycle cancellation was not associated with age, duration of stimulation, total dose of FSH administrated or AFC, day 3 FSH/LH ratios (Table III).

Discussion

As the age of the women increases during the reproductive years, the oocyte population declines together with endocrine changes that have an impact on reproductive outcomes.[10] A transient FSH increase in the early follicular phase is the initial response to ageing , with a normal secretion of estradiol. Cycles shorten in response to the rise in FSH concentrations and the consequent stimulation of accelarated follicular development. Later, increases of LH levels occur. Higher levels of serum FSH, increased FSH/LH ratios[11] and elevated concentrations of serum estradiol[12] have been suggested as associated with poor ovarian responses during assisted conception cycles. However, no perfect test or combination of tests has been found to predict the ovarian response to gonadotropin stimulation during ART cycles. Hence, studies are being conducted regarding this dilemma[13].

It is crucial for the infertile couples going through ART to predict their chances of conception. Thus, an acceptable predictive parameter is needed for counselling before treatment. Cycle day 3

Table I. Treatment cycle characteristics between groups

FSH / LH ratio Number of cycles	< 1 65	≥1 and <1.5 70	≥1.5 and ≤2 43	>2 21
Mean FSH (mIU/ml)	5.66±1.66[a,b]	6.17±1.34[c]	7.24±2.67[a,d]	9.39±3.84[b,c,d]
Mean LH (mIU/ml)	7.80±2.85[e]	4.98±1.26[e]	4 .35±1.70[e]	3.56±1.72[e]
Age (years)	29.12 ±3.83	29.17±3,63	29.65±2.99	29.48±4.08
Antral Follicule Count (#)	9.23 ± 3.61	8.45 ± 3.55	6.68 ± 2.65	8.07 ± 2.02
Total gonadotropin dose (IU)	2249± 864.2	2580.8±672.3	2332.9±842.4	2503±965.6
Mean duration of COH (days)	8.44±1.67	8.47±1.1.32	8.33±1.31	7.89±1.49
Mean number of oocytes collected (#)	13.45±6,62[f]	11.93±6.08	11.43±6.5	7.2±3.71[f]
Metaphase II oocytes (#)	10.60±5.20[g]	9.4±4.55[h]	9.34 ±5.39	5.26±2.81[g,h]
Number of fertilized oocytes (#)	7.33±3.74[i]	7.02±3.35[j]	6.33±4.08	3.58±2.19[i,j]
Percentage of embryos with >6 cells on day 3 (#)	75.42±0,36	61.94±0.4	59,26±0.39	56.86±0.47
Number of embyos transferred on day 3 (#)	2.86±0.43	2.95±0.34[k]	2.78±0.53	2.53±0.84[k]

Values shown are mean ± standard deviation (mean ± SD), COH=controlled ovarian hyperstimulation
p value <0.0083 is statistically significant.
a,j p=0.002; b,c,e,g p=0.0001; d,f,i p=0.001; h p=0.008; k p=0.006

Table II. ICSI cycle outcomes of patients

FSH / LH ratio Number of cycles	< 1 65	≥1 and <1.5 70	≥1.5 and ≤2 43	>2 21
Cancellation rate (%)	9.23±0.29	11.43±0.32	11.63±0.32	13.63±0.35
Transfer rate (%)	90.77±0.29	88.57±0.32	88.37±0.32	86.36±0.35
Clinical pregnancy rate per transfer (%)	42.37±0.5	37.1±0.49	28.95±0.46	52.63±0.51
Ongoing pregnancy rate per embryo transfer (%)	30.51±0.46	27.42±0.45	21.05±0.41	31.58±0.48
Implantation rate per embryo transfer (%)	18.96±0.29	13.98±0.25	10.53±0.22	14.91±0.27

Values shown are mean ± standard deviation (mean ± SD)
For all comparisons p value >0.0083

Table III . Multivariate analysis

	Odds Ratio	P value	95% confidence interval
Clinical pregnancy rate			
Age	0.88	0.07	0.77-1.01
AFC	1.09	0.29	0.93-1.27
Duration of stimulation	1.30	0.19	0.88-1.95
Total dose of FSH used	0.99	0.58	0.99-1.00
Number of oocytes collected	0.93	0.48	0.76-1.14
Day 3 FSH	0.70	0.06	0.49-1.02
Day 3 LH	1.14	0.22	0.92-1.42
Day 3 FSH/ LH ratio	1.81	0.066	0.96-3.41
	Odds Ratio	**P value**	**95% confidence interval**
Ongoing pregnancy rate			
Age	0.97	0.68	0.86-1.11
AFC	1.08	0.34	0.92-1.27
Duration of stimulation	1.51	0.06	0.98-2.35
Total dose of FSH used	0.99	0.37	0.99-1.00
Number of oocytes collected	0.98	0.83	0.81-1.18
Day 3 FSH	0.81	0.23	0.57-1.14
Day 3 LH	1.08	0.44	0.88-1.32
Day 3 FSH/ LH ratio	0.93	0.84	0.44-1.94
	Odds Ratio	**P value**	**95% confidence interval**
Cycle cancellation rate			
Age	1.03	0.75	0.86-1.24
AFC	0.79	0.055	0.62-1.01
Duration of stimulation	1.17	0.74	0.45-3.03
Total dose of FSH used	1.00	0.71	0.99-1.00
Number of oocytes collected	1.45	0.27	0.76-2.76
Day 3 FSH/ LH ratio	0.75	0.59	0.27-2.11

AFC: antral follicule count

FSH levels have been proposed for this purpose[14,15]. FSH concentration is the result of the feedback effects at the pituitary in response to the concentrations of inhibin B and estradiol produced by the follicular cohort[16]. Since basal FSH concentration is an indirect marker of ovarian reserve, it has been used to predict the cancellation rate in ART[17].

The basal FSH concentration has been used as a prognostic criterion before an ovarian stimulation is started. Dose adjustments of gonadotropins and preferences for certain protocols have been planned under the influence of basal FSH concentrations from a pretreatment cycle. Variations of FSH values between cycles have been reported[18] especially in women with low ovarian reserve due to their age or to low ovarian responses to ovulation induction. However, Penarrubia et al[19] have reported no significant inter-cycle variations in three consecutive cycles. The extent to which inter-cycle variability might affect patients' prognosis during ART cycles has been questioned. Scott et al.[20] and Martin et al.[21] advised that such variability had minimal relevance for the clinical decision.

Several earlier studies have investigated ovarian response to ovulation induction in patients with elevated FSH/LH ratios. Mukherjee et al.[22] reported decreased ovarian responses and lower pregnancy rates in 14 patients with a FSH/LH ratio >3.6. Barroso et al.[23] reported similar results in 28 patients with a FSH/LH ratio >3. Shrim et al.[24] chose the cut-off ratio as 3 and found lower pregnancy rates in 41 patients with an elevated FSH/LH ratio. In contrast to these previous studies our study included only 6 women out of 199 with a FSH/LH ratio >3. The reason for the differences of the outcomes between our study and previous studies is probably that women with basal FSH values lower than 12 IU/dl were included. This value has been set as our clinic's upper FSH level for expecting good ovarian response to controlled ovarian stimulation. Comparable pregnancy rates were found for all the groups with 0.5 ratio increments starting from 1.

Mukherjee et al.[22] suggested that the poor response to ovarian stimulation could be due to low day 3 LH concentrations since there were no differences in day 3 FSH values between the two groups. Nocci et al.[25] and Mukherjee et al.[26] argued that a decreased day 3 LH concentration (which could be reflected as an elevated FSH/LH ratio) is predictive of a reduced ovarian response. They speculated that there might be reduced activity of one or more of the known ovarian regulators when the early follicular LH concentration was low, and that this could influence follicular growth. Alternatively, a low LH concentration could simply be a marker of impaired balance between the gonad and the pituitary gland. Similarly, the mean day 3 LH concentrations decreased in our study as the FSH/LH ratio increased. The mean day 3 LH concentration in the highest ratio group was significantly lower than in the other groups. However, the mean LH concentrations in all of our groups were higher than 3 mIU/ml; thus our patients had higher basal LH values in contrast to those reported by Mukherjee. Our study group D had the lowest mean day 3 LH concentration and the lowest number of total oocytes and metaphase II oocytes were collected, which supports Noci's speculation[25] that there could be reduced activity of one or more of the known ovarian regulators when the early follicular LH concentration is low. The difference in mean LH levels between our study groups did not reflect on pregnancy rates between the groups. In group D of our study, 8 women out of 21 had LH concentration lower than 3 IU/ml, the percentage being higher than for the previous three groups (2/65; 4/70 and 5/43 in groups A, B and C; respectively).

Our study population had cycle day 3 serum FSH levels within normal limits. The increase in FSH/LH ratio is the result of both the decrease in LH and the elevated FSH values. Although lower LH values had been previously[23,24] reported as the cause of the high FSH/LH ratio, no association between follicular phase serum LH levels and IVF pregnancy outcomes were confirmed[27,28]. We could not obtain the results suggested by Liu and Greenblatt[29]. Our group with the lowest mean serum LH value had the least number of fertilized oocytes. Since a comparable number of embryos were transferred, similar pregnancy outcomes with the other groups with higher serum LH levels but lower FSH/LH ratios could be achieved.

Conclusion

Elevated FSH/LH ratio[22,23] or low day 3 LH levels in the presence of normal baseline FSH[24-26] were associated with an inferior IVF outcome. On the basis of our findings, it seems that the FSH/LH ratio cannot be used to predict the ICSI success in women with normal baseline FSH levels as long as a comparable number of good quality embryos are transferred on day 3.

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The authors declare that they have no conflict of interest.

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