SHORT COMMUNICATION

Follicular Sensitivity Index: A Tool To Predict Successful Conception After Intra-cytoplasmic Sperm Injection

Rehana Rehman[1], Amara Zafar[2], Nida Zahid[3] and Nuruddin Mohammed[4]

[1]*Department of Biological and Biomedical sciences, The Aga Khan University, Karachi, Pakistan*
[2]*Dow Medical College (DMC), Dow University of Health Sciences, Karachi, Pakistan*
[3]*Department of Surgery, The Aga Khan University, Karachi, Pakistan*
[4]*Department of Obstetrics and Gynaecology, The Aga Khan University, Karachi, Pakistan*

ABSTRACT

Follicular sensitivity index (FSI) is used for estimation of follicular responsiveness to controlled ovarian hyperstimulation (COH) during intra-cytoplasmic sperm injection (ICSI). In a retrospective study, FSI of 1,385 females was calculated as [pre-ovulatory follicle count (PFC) × 100,000]/ [antral follicle count (AFC) × total received stimulation doses]. Females were then categorised into low, middle and high FSI groups according to FSI tertile values. FSI was 8.65 ±2.82 in non-pregnant as compared to 12.02 ±2.04 ($p < 0.01$) in pregnant cohort. FSI turned out to be a strong predictor of successful conception on the receiver operating curve with cutoff value 10.36 at 76% specificity, sensitivity of 86% and area under the curve (AUC; 0.83). Calculation of FSI can thus predict the chances of successful conception in females with different causes of infertility.

Key Words: *Follicular sensitivity index, Infertility, Intra-cytoplasmic sperm injection, Ovarian response, Follicular output rate.*

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Assisted reproductive techniques (ART) refer to different methods that are used to achieve pregnancy by artificial means. For these procedures, controlled ovarian hyperstimulation (COH) is given with variable doses of exogenous gonadotropins to initiate follicular development followed by a sequence of steps to establish a successful pregnancy.

Pre-treatment assessment of ovarian reserve (OR) is made by ovarian reserve test (ORT), which gives an idea about probable response to ovarian stimulation; and therefore, the success of ART. Ovarian responsiveness is assessed by a number of predictive tools.

Antral follicle count (AFC) is the number of antral follicles in both ovaries. It determines response of ovarian follicles to stimulation and exerts an impact on reproductive competence in terms of oocytes retrieved, embryos produced and success rates of ART procedures.[1] The predictive value of AFC can be compared with accuracy and clinical value of anti mullerian hormone (AMH) as well.[2] Pre-ovulatory follicle count (PFC) is defined as number of follicles measuring more than or equal to 16 mm. This number is calculated at the end of ovarian stimulation and depends on the availability of number of small antral follicles subjected to treatment.[1]

Correspondence to: Dr. Nuruddin Mohammed, Department of Obstetrics and Gynaecology The Aga Khan University, Stadium Road, Karachi, Pakistan
E-mail: nuruddin.mohammed@aku.edu
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Ovarian stimulation index (OSI) is calculated by the number of retrieved oocytes divided by the total dose of follicle stimulating hormone (FSH) given for COH.[3] Follicular output rate (FORT) is calculated as (PFCX100)/AFC. This index can be used as a prognostic indicator of the response to FSH and reproductive competence after *in vitro* fertilization (IVF)/ICSI.[4] It has been seen in different studies that the higher FORT values had better oocyte yield and clinical pregnancy rate in women with unexplained infertility undergoing IVF/ICSI with potentially normal ovarian response.[5] FORT and OSI had been the tools previously used to predict the outcome of ART most commonly done *via* IVF/ICSI.

More recently, follicular sensitivity index (FSI) has been introduced as a tool for assessment of follicular responsiveness to external gonadotropins and predict the outcome of ART. FSI is calculated as (PFC x 100,000) / (AFC x total received FSH doses). Hassan *et al.* introduced FSI as a tool to predict clinical pregnancy with a significant and progressive increase in clinical pregnancy from low to high FSI groups in females with unexplained infertility.[3] Based on observation from his study on subjects with unexplained infertility, the authors developed the research questions, which were:

Can calculation of FSI be used as an absolute criterion of perception of poor/good ovarian response and clinical pregnancy outcome in IVF/ICSI cycles in females with different causes of infertility?

Can this be used as a guide for IVF cycle management and direct about cycle cancellation in case of poor ovarian response assessed by FSI?

Table I: Baseline characteristics and COH data in the FSI groups.

Variables	FSI						p-value
	Low ≤8.36 (n=461)		Middle 8.37-11.36 (n=463)		High 11.36 (n=461)		
	Mean	SD	Mean	SD	Mean	SD	
Female age	31.82	4.84	32.15	4.4	32.32	4.74	0.25
BMI	24.5	3.77	24.64	3.39	23.7	3.84	<0.01*
Duration of infertility	6.74	3.78	7.15	4.08	7.26	3.85	0.103
Day of egg collection	14.47	0.99	14.27	0.95	14.29	0.98	0.002*
Pre ovulatory follicle count	6.47	0.99	7.98	1.67	9.04	1.91	<0.01*
Antral follicle count	16.62	1.66	14.21	2.91	13.23	2.57	<0.01*
Follicular sensitivity index	6.4	1.29	10.04	0.82	13.22	1.38	<0.01*
No. of oocytes retrieved	6.45	0.97	7.85	1.51	8.84	1.59	<0.01*
No. of oocytes metaphase II	5.54	1.74	7.43	1.52	8.47	1.33	<0.01*
No. of oocytes fertilized	4.71	1.43	6.21	1.26	6.97	0.98	<0.01*
No. of cleaved embryos	4.67	1.41	6.15	1.29	6.8	0.89	<0.01*
Ovarian stimulation Index	1.52	0.32	2	0.44	2.45	0.52	<0.01*
Number of puregons in one day	4.37	0.85	3.98	0.5	3.66	0.42	<0.01*
Good quality embryos	0.86	0.57	1.53	0.74	2.06	0.83	<0.01*
Endometrial thickness	6.97	3.13	8.26	3.33	10.65	2.65	<0.01*
No of transferred embryos	1.63	0.55	1.68	0.63	1.59	0.57	<0.01*
Follicular output rate	39.34	7.45	56.66	7.16	68.25	4.96	<0.01*
Day 2nd FSH	7.37	1.32	6.55	0.86	6.11	0.5	<0.01*
FSH dose	6285.81	1164.97	5653.67	613.78	5200.18	466.88	<0.01*
Cause of infertility	**n**	**%**	**n**	**%**	**n**	**%**	**p-value**
Male infertility	222	48.2	287	62	341	74	<0.01**
Female infertility	132	28.6	121	26.1	105	22.8	
Unexplained	107	23.2	55	11.9	15	3.3	

**p<0.05 was considered significant using one-way ANOVA. **significance using Pearson Chi-square test.*
Column wise percentage representing distribution of subjects in respective FSI groups.

A retrospective study was conducted in which data was collected from May 2010 till August 2017 after approval from Ethical Review Board of the Infertility Clinic and The Aga Khan University. The study aimed to evaluate the role of FSI for estimation of follicular responsiveness to COH and relate it to successful conception after ICSI in women with male, female and unexplained causes of infertility. Females within the age range of 20- 42 years, who were infertile for more than 2 years (all causes of male, female and unexplained infertility), had both ovaries, regular cycle of 25 ±7 days, BMI of 18–35 kg/m^2, serum FSH and basal estradiol levels less than 8 IU/ ml and 50 pg/ml, respectively, were included. Females with abnormalities of uterine cavity, short agonist or antagonist protocol, diagnosed as polycystic ovarian syndrome (PCOS) and uterine fibroids were excluded from the study. Successful conception after ICSI was confirmed by the existence of an intrauterine gestational sac with cardiac activity on transvaginal scan (5 weeks after the embryo transfer).

To interpret the possible relationship between follicle responsiveness to COH and successful conception after ICSI, study population (1,385 females) was stratified into three distinct FSI groups based on FSI tertile values; low (461), medium (463), and high (461). We observed an inverse relationship of FSI with female causes of infertility. As FSI increased from low to high in FSI group females as well as unexplained causes of infertility were seen to decrease; while, male causes of infertility were seen to increase with male factor infertility, occupying three quarters of the high FSI group.

Table I showed that female age and duration of infertility did not give any significant mean differences across the three groups of FSI. On the other hand, PFC, AFC, number of oocytes retrieved, oocytes metaphase II, oocytes fertilised, cleaved embryos, OSI, number of rFSH (Puregon), good quality embryos, endometrial thickness, number of transferred embryos and FORT, gave significant mean differences across the FSI groups. We observed the decrease in AFC with increasing FSI in our study which was contrary to that reported by Hassan *et al*. where it increased with increasing FSI, but was not found to be significant.[3] With high FSI values, the data showed a significantly higher oocyte yield, fertilisation and successful conception rates.

Similar to this work, the number of good quality embryos increased progressively with FSI in the study by Hassan *et al*.[3] We found that the embryos were better in those who successfully achieved pregnancy as compared to non-pregnant cohorts. The significant increase in the number of good quality embryos and endometrial thickness in high FSI group of

females, support its impact in acquiring successful conception after ICSI.

FSI was found to be a better predictor of successful conception than AFC, PFC, number of FSH doses, FORT and OSI on the receiver operating curves (ROC). The FSI cut-off value 10.36 at 76% specificity for predicting positive pregnancy conception was established using ROC analysis with an associated sensitivity of 86%. It had the highest area under the curve (AUC) which was very closely followed by FORT (0.83 and 0.81, respectively). OSI ranked the third with AUC being 0.68. All the parameters were, however, significant as the predictors of successful conception after ICSI.

To conclude, calculation of FSI can be one of the predictors of successful conception after ICSI using gonadotropin agonist protocol in women experiencing infertility. High FSI values (irrespective of the cause of infertility), can lead to better oocyte yield, fertilisation potential, embryo quality and clinical pregnancy rates. The gauge can thus be used to predict ovarian responsiveness, guide cycle cancellation, monitor dose adjustments in the subsequent cycles, and counsel couples for the expected outcome.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
RR: Conceived the research idea.
AZ: Collected the data.
NZ: Performed statistical analysis.
NM: Study designed.
All authors contributed towards the intellectual content of the manuscript including scientific writing, critical review and final approval.

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