Follicular sensitivity index: A tool to predict successful conception after intra-cytoplasmic sperm injection

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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 \[\text{FSI} = \frac{\text{PFC} \times 100,000}{\text{AFC} \times \text{total received FSH doses}}\]. 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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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       | <0.01* |
| Pre ovulatory follicle count    | 6.47 0.99        | 7.98 1.67         | 9.04 1.91        | 0.002* |
| 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 2^ 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/m², 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. 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. We found that the embryos were better in those who successfully achieved pregnancy as compared to non-pregnant...
Follicular sensitivity index

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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