Ovarian sensitivity index is a better measure of ovarian responsiveness to gonadotrophin stimulation than the number of oocytes during in-vitro fertilization treatment

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Abstract

Purpose To validate the use of the ovarian sensitivity index (OSI) as a measure of ovarian response during in-vitro fertilization (IVF) treatment.

Methods This is a retrospective study carried out in an assisted reproduction unit in a teaching hospital. We analysed data from 2,556 women undergoing the first IVF cycle between 2002 and 2009. OSI was calculated as the number of retrieved oocytes divided by total dose of FSH administered (per 1,000 IU). Its correlation to other parameters of ovarian response was compared to that of the oocyte number.

Results The correlation coefficients of OSI with age, AFC, AMH, total dose of gonadotrophin, average daily dose of gonadotrophin and duration of stimulation were significantly higher than that of oocyte number with these respective parameters. OSI demonstrated a higher intraclass correlation coefficient (ICC) than the oocyte number when comparing the two parameters across the first and second stimulated IVF cycles.

Conclusions OSI is a better measure of ovarian responsiveness to gonadotrophin stimulation than the oocyte number, and is particularly useful when different subjects are treated with different stimulation regimens which would have confounding effect on the oocyte number.

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Introduction

Ovarian stimulation is an integral part of in-vitro fertilization (IVF) treatment. The responsiveness to gonadotrophin stimulation is a factor which has important implications on treatment success [1] as well as the risk of complications such as cycle cancellation and ovarian hyperstimulation syndrome (OHSS). On one hand, a good ovarian response upon stimulation implies a higher number of oocytes and thus transferrable embryos after the same stimulation cycle, leading to an increased chance of achieving cumulative live birth, compared to situations of poor ovarian response. On the other hand, excessive ovarian response may lead to increased risk of OHSS [2] and poorer pregnancy rates in the fresh cycle [3]. Hence, ovarian responsiveness is one of the most commonly studied and reported parameters in clinical research concerning IVF treatment, so as to search for measures to optimize live birth rate while minimizing risks.

Conventionally, the number of oocytes retrieved is adopted as the main outcome measure of ovarian responsiveness to gonadotrophin stimulation. It has been suggested that around 15 oocytes on retrieval might be the optimal number to maximize treatment success while keeping a low risk of OHSS [4]. Other secondary outcome measures may include total dose of gonadotrophin, duration of stimulation, and peak serum oestradiol level.

It has been considered that both the absolute number of oocytes retrieved and the total gonadotrophin dose are important measures of ovarian responsiveness, and a ratio of them is a better representation of ovarian responsiveness rather than

either parameter on its own. This ratio, which has been termed as “ovarian sensitivity index (OSI)”, was first proposed by Biasoni et al. [5]. OSI was shown to have good correlation with anti-Müllerian hormone (AMH) and antral follicle count (AFC) [5], ovarian reserve markers which have been suggested as the best currently available predictors of ovarian responsiveness [6, 7]. The use of OSI instead of the number of retrieved oocytes as the measure of ovarian responsiveness would be more appropriate where different subjects are subjected to different daily dosages of gonadotrophin. However, there has been no formal report to validate the use of OSI as a measure of ovarian responsiveness.

This retrospective analysis was carried out to validate the use of OSI as a measure of ovarian response during IVF treatment by correlating it with other measures of ovarian response such as number of retrieved oocytes, total dose of administered gonadotrophin, duration of stimulation and peak serum oestradiol level. We also studied the variation of OSI and the oocyte number between the first and second IVF cycles. We redefined the OSI with the number of retrieved oocytes in the numerator and the total dose of administered gonadotrophin dose in the denominator.

Materials and methods

This retrospective study reviewed all women who underwent the first IVF cycle between January 2002 and December 2009 at our Centre. Clinical data were retrieved from the computerised clinical database of the Centre as well as from review of patients’ clinical records. Ethics approval was obtained from the Institutional Review Board of our institution for this retrospective study to be carried out.

Ovarian stimulation cycle

Details of the stimulation cycle have been previously reported [1]. Subjects were treated on either the long GnRH agonist or GnRH antagonist protocol, the latter mostly being applied to expected poor ovarian responders. All of the subjects underwent pelvic ultrasound examination to determine baseline AFC. The initial dosage of gonadotrophin (either human menopausal gonadotrophin or recombinant FSH) was determined based on baseline AFC, FSH and the women’s age. Those with AFC less than 6, or serum FSH higher than 10 IU/L, or age at or above 40 years received gonadotrophin at 300 to 450 IU daily for 2 days followed by 225 IU daily. For women below 40 years of age and serum FSH below 10 IU/L, they received gonadotrophin at 300 IU daily for 2 days followed by 150 IU daily if AFC was between 6 and 14, or at 150 IU daily if AFC was more than 14. Ultrasound tracking was carried out at appropriate intervals starting from the 7th to 9th day of stimulation, and hCG was given to trigger final oocyte

maturation when there were three or more follicles reaching at least 16 mm in mean diameter, with the leading one reaching 18 mm. Transvaginal ultrasound-guided oocyte retrieval was carried out 36 h after hCG trigger, whereby all visible follicles larger than 10 mm were aspirated. Fertilization was achieved either by conventional insemination or intracytoplasmic sperm injection depending on semen parameters.

Calculation of OSI

$$OSI(\text{oocytes per } 1,000 \text{ IU}) = \frac{\text{number of retrieved oocytes}}{\text{total dose of FSH administered}} \times 1000$$

Statistics

Correlations of OSI with patient’s age, body mass index, baseline AFC, AMH (data available only after January 2007), total dose of administered gonadotrophin, duration of stimulation, number of follicles reaching 16 mm, peak serum hCG level and number of retrieved oocytes were determined by Spearman’s test. The same were also calculated between these parameters with the oocyte number. The correlation coefficient of OSI and that of oocyte number with the respective parameters were compared using z-statistics. Among our studied subjects, 485 of them had a second stimulated IVF cycle in our Centre subsequently (data retrieved till December 2012). The inter-cycle repeatability of OSI and oocyte number across the first and second stimulated IVF cycles were determined by the intraclass correlation coefficient (ICC) with single measures using the absolute agreement definition. Statistical tests were performed by IBM SPSS Statistics (version 20, IBM Corporation, USA) and MedCalc (version 12.5, MedCalc Software, Belgium).

Results

Subject characteristics and relation to OSI

A total of 2,556 subjects fulfilled our inclusion criteria. The demographic, clinical and cycle characteristics of the subjects are listed in Table 1. The median age of the studied subjects was 35 (interquartile range: 33–37; range: 22–45) years, and the median body mass index was 21.2 (interquartile range: 19.7–23.0; range: 14.2–34.0) kg/m².

Table 2 showed the correlation between OSI and the basic demographic and clinical parameters. OSI was positively correlated with AFC and AMH, and inversely with age and BMI of the women ($p < 0.001$ for all). The correlation coefficients of OSI with age, AFC and AMH were significantly higher than that of oocyte number with these respective parameters ($p < 0.05$).

Table 1 Demographic, clinical and cycle characteristics of subjects included in this study. Values are expressed as median (interquartile range) unless otherwise stated

Parameter	Value
Age (years)	35 (33–37)
Body mass index (kg/m ²)	21.2 (19.7–23.0)
Type of subfertility	
Primary	1726 (67.5 %)
Secondary	830 (32.5 %)
Duration of subfertility (years)	4 (3–6)
Cause of subfertility	
Male	1324 (51.8 %)
Tubal	472 (18.5 %)
Endometriosis	237 (9.3 %)
Unexplained	194 (7.6 %)
Others	329 (12.9 %)
Smoking	
No	2312 (90.5 %)
Yes	217 (8.5 %)
Missing data	27 (1.1 %)
Treatment protocol	
Long GnRH agonist	2396 (93.7 %)
Short GnRH agonist	3 (0.1 %)
GnRH antagonist	156 (6.1 %)
No down-regulation ^a	1 (<0.1 %)
Type of gonadotrophin used	
HMG	1875 (73.3 %)
Recombinant FSH	681 (26.7 %)
Total dose of FSH (IU)	2025 (1650–2700)
Average daily dose of gonadotrophin (IU)	183.3 (175.0–238.6)
Duration of stimulation (days)	11 (10–12)
Peak serum oestradiol level (pmol/L)	9471 (5757–14987)
Number of follicles reaching 16 mm	6 (4–8)
Number of retrieved oocytes	9 (5–13)
OSI in the first IVF cycle (oocytes per 1,000 IU)	4.00 (2.05–6.67)
OSI in the second IVF cycle (oocytes per 1,000 IU) ^b	2.67 (1.37–5.13)
Interval between first and second IVF cycles (years) ^b	0.75 (0.48–1.56)

^a No pituitary down-regulation was used in one subject with hypogonadotrophic hypogonadism

^b Applicable to subjects who had a second IVF cycle subsequent to the index first cycle

Correlation between OSI and other parameters of ovarian response

Table 3 showed the correlation between OSI and other parameters of ovarian response. OSI showed significant inverse correlation with the total dose of gonadotrophin administered, average daily dose of gonadotrophin, and duration of stimulation, and significant positive correlation with the peak serum

oestradiol level, number of follicles reaching 16 mm, and number of retrieved oocytes ($p < 0.001$ for all). The correlation coefficients of OSI with total dose of gonadotrophin, average daily dose of gonadotrophin and duration of stimulation were significantly higher than that of oocyte number with these respective parameters ($p < 0.05$); however, that of oocyte number excelled over OSI for peak serum oestradiol level ($p < 0.05$). When stratifying the analysis between subjects treated on human menopausal gonadotrophin and recombinant FSH, the same conclusions could be drawn in both stratified groups (data not shown).

Inter-cycle repeatability of OSI and oocyte number

The single measures ICC of OSI across the first and second stimulated IVF cycles was 0.729 (95 % confidence interval 0.683–0.769), which was higher than that of oocyte number (0.560, 95 % confidence interval 0.496–0.618).

Discussion

The present study aims at providing evidence to validate the use of OSI as an outcome measure for reporting ovarian responsiveness in clinical research on IVF. Our results confirmed an excellent correlation of OSI with other measures of ovarian response, namely the duration of stimulation, total dose of gonadotrophin administered, peak serum oestradiol level, and the number of follicles reaching 16 mm, which were conventionally used as indicators of ovarian response. The correlation coefficient of OSI with most of these parameters excelled over that of oocyte number with these respective parameters, except for the peak serum oestradiol level.

The oocyte number, despite being the most widely used measure of ovarian response, can be influenced by manipulating the daily dosage of gonadotrophin. In actual practice, the latter is usually varied and individualized based on the women's characteristics such as age, baseline FSH, AFC or AMH; this would confound on the final number of oocytes actually obtained. For instance, in women with anticipated risk of excessive response based on the ovarian reserve markers, the stimulation dose is usually lowered so as to control the number of retrieved oocytes within safe limits, thus the latter would not be allowed to achieve its maximal potential. In this regard, by taking into account the total stimulation dose hence adjusting for the effect of dose manipulation, the value of OSI would still be high despite the oocyte number being not excessive. On the other hand, in expected poor ovarian responders, maximal high dose stimulation is usually adopted, although some studies have argued that increments of daily doses beyond 225 IU would not further increase the number of oocytes [8, 9]. Overzealous increase in the stimulation dose in such circumstances may thus

Table 2 Correlation between ovarian sensitivity index (OSI) and number of retrieved oocytes with basic demographic and clinical characteristics of subjects studied ($n=2,556$)

Parameter	Ovarian sensitivity index		Oocyte number		P value (OSI vs oocyte number) ^a
	Correlation coefficient	P value	Correlation coefficient	P value	
Age (years)	−0.337	<0.001*	−0.278	<0.001*	0.0199*
Body mass index (kg/m ²)	−0.080	<0.001*	−0.064	0.001*	0.5745
Anti-Mullerian hormone (AMH) (ng/ml) ^b	0.708	<0.001*	0.629	<0.001*	0.0006*
Antral follicle count	0.632	<0.001*	0.530	<0.001*	<0.0001*

*Statistically significant

^a Comparing the correlation coefficient of OSI and that of oocyte number^b Data available only for treatment cycles performed in the years 2007–2009 ($n=1,147$)

exaggerate the reduction in OSI but this depends on the threshold one takes to interpret the OSI value.

Therefore, applied to the setting of research in assisted reproduction, OSI and the oocyte number can be used complementarily for reporting ovarian responsiveness in clinical studies as they refer to different sides of the mirror. OSI is a measure of the intrinsic characteristic of the woman irrespective of gonadotrophin dose manipulation, whereas the number of oocytes reflects the observed ovarian response which can reach the full potential only when stimulation is administered at or beyond the maximal.

The term OSI was first coined by Biasoni et al. [5], where it was expressed as the total administered dose of FSH per retrieved oocyte; thus a lower value represents higher ovarian sensitivity and vice versa. We redefined OSI by reversing the numerator and denominator so that it is literally and conceptually a more direct reflection of “ovarian sensitivity” rather than “ovarian resistance”. Moreover, it avoids the mathematical invalidity when the number of retrieved oocytes is zero.

Our results confirmed the previous findings [5] that OSI was strongly and significantly correlated with AMH and AFC, which were suggested in meta-analyses as the best predictors of ovarian responsiveness as defined on oocyte number [6, 7]. There was also significant correlation of OSI with age and

body mass index, the latter being not demonstrable in the previous study [5]. It conforms to the common understanding that advanced age and overweight/obesity are negative factors affecting ovarian responsiveness [10].

We further assessed the inter-cycle repeatability of OSI and oocyte number using single measures ICC, and confirmed that OSI had a higher ICC across two stimulated IVF cycles than oocyte number. This can be easily understandable since the oocyte number is subject to influence by variations in the gonadotrophin dose, whereas the OSI reflects the intrinsic ovarian responsiveness of the individual to gonadotrophin stimulation, with the different stimulation dose being corrected for.

It must be noted that the main aim of this paper is to validate the use of OSI as a measure of the intrinsic ovarian responsiveness of individual women in research studies, instead of in prediction of ovarian response after stimulation. OSI can only be derived after completion of the treatment cycle and hence not applicable on the first index stimulation cycle itself. Whether it can potentially be used to predict ovarian responsiveness in future treatment cycles is yet to be confirmed in further prospective clinical studies.

In conclusion, this study confirmed that OSI has excellent correlation with various measures of ovarian response. Both

Table 3 Correlation between ovarian sensitivity index and ovarian response parameters as well as total number of transferrable embryos ($n=2,543$)

Parameter	Ovarian sensitivity index		Oocyte number		P value (OSI vs oocyte number) ^a
	Correlation coefficient	p-value	Correlation coefficient	p-value	
Total dose of gonadotrophin (IU)	−0.723	<0.001*	−0.461	<0.001*	<0.0001*
Average daily dose of gonadotrophin (IU)	−0.533	<0.001*	−0.355	<0.001*	<0.0001*
Duration of stimulation (days)	−0.509	<0.001*	−0.312	<0.001*	<0.0001*
Peak serum oestradiol level (pmol/L)	0.692	<0.001*	0.729	<0.001*	0.0076*
Number of follicles reaching 16 mm	0.687	<0.001*	0.701	<0.001*	0.3345
Number of retrieved oocytes	0.938	<0.001*			

*Statistically significant

^a Comparing the correlation coefficient of OSI and that of oocyte number

OSI and oocyte number can be complementary to each other as measures of reporting ovarian responsiveness in research studies. OSI is particularly useful when different subjects are treated with different stimulation regimens which would have confounding manipulating effect on the oocyte number.

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