Ovarian synchrony factor: a new ultrasound parameter in the prognosis of follicular rupture

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The present study was carried out to present a new ultrasound parameter used in stimulated cycles and called the ovarian synchrony factor (OSF), which reflects the response of the total follicular cohort. It is calculated from the formula: OSF = (total no. of follicles ≥16 mm)/(total no. of follicles ≥10 mm). OSF was determined on the day of human chorionic gonadotrophin (HCG) administration (indicated when at least one follicle was ≥16 mm) by measuring the widest follicular diameters with an ATL ultrasound apparatus model Ultramark 4, with a 5.0 MHz vaginal transducer, in a total of 221 cycles stimulated for non-invasive assisted reproduction techniques (i.e. no oocyte retrieval). A new ultrasound examination was performed 56–60 h after HCG administration to determine the possible presence of follicular rupture indicated by the disappearance of the follicular image and/or a >5 mm decrease in the widest follicular diameter. The mean OSF in the group of patients with rupture of at least one follicle (195 cycles) was mean ±SD, 0.57 ± 0.25, as opposed to a mean ±SD of 0.39 ± 0.25 for the group without follicular rupture (26 cycles). The Mann–Whitney test showed that the OSF of the group with follicular rupture was significantly higher than that detected in the group without follicular rupture ($P < 0.01$). This information suggests that ovarian stimulation protocols should produce a synchronous follicular response (an OSF as close as possible to 1), i.e. that the follicular lots developing in both ovaries should not vary widely in size. This follicular homogeneity should facilitate the follicular rupture process.

Key words: follicular rupture/ovarian synchrony factor/ultrasound

Introduction

Ultrasound is currently used as a basic parameter to monitor the ovarian stimulation process (Marrs *et al.*, 1983; Grinsted *et al.*, 1989). In natural cycles, only one dominant follicle is usually present immediately before follicular rupture, a fact that facilitates the use of serial ultrasonography for the determination of the daily growth of this follicle (Hackeloer *et al.*, 1979). However, in stimulated cycles it is difficult to precisely characterize the process of follicular maturation since several follicles become dominant, and oestradiol concentrations in blood are not always correlated with the total number of growing follicles. Thus the basic data (ultrasonographic and hormonal) signalling the ideal time for the administration of human chorionic gonadotrophin (HCG) are imprecise.

From the ultrasonographic point of view, the simple rule of using HCG to induce the process of follicular rupture when the leading follicle reaches a diameter 16–18 (Check *et al.*, 1992; Silverberg *et al.*, 1992) may overlook important data related to ovarian response, especially the development of the remaining follicular cohort.

Since ultrasonographic ovulation detection was first introduced, many authors have speculated about the value of this technique for the prediction of ovulation throughout spontaneous cycles (Hamilton *et al.*, 1987). However, there are no reports of ultrasound-based studies to predict follicular rupture alone in stimulated cycles, by ultrasound data obtained before HCG administration. The objective of this study was to present a new ultrasound parameter, called the ovarian synchrony factor (OSF), and to test its ability to predict the follicular rupture phenomenon during ovarian stimulation cycles.

Materials and methods

A group of 110 patients (mean age ±SD, 29 ± 4.21 years, mean duration of infertility ±SD, 5.10 ± 2.67 years) were submitted to routine tests for investigation of the female factor (post-coital test, mid-luteal phase progesterone, pelvic sonography, hysterosalpingography) and all were found to have at least one patent tube. The patients were admitted to a programme of ovarian stimulation for correction of ovulation disorders or in order to induce multiple ovulation prior to the use of a non-invasive (no oocyte retrieval) assisted reproduction technique, i.e. intra-uterine or intra-tubal insemination.

Ovarian stimulation was achieved using clomiphene citrate (Clomid; Merrell Dow, Brazil), 100 mg twice daily on days 5–9 of the cycle, and/or human menopausal gonadotrophin [HMG: follicle stimulating hormone (FSH) = 150 IU and luteinizing hormone (LH) = 150 IU per day; Pergonal; Serono, Brazil], which was administered on alternate days (minimum four ampoules) starting on the third day of the menstrual cycle until the criterion of administration of 10 000 UI of HCG was fulfilled, i.e. the presence of at least one follicle of diameter ≥16 mm.

The OSF was determined in a total of 221 stimulated cycles by measuring the largest follicular diameters (Kerin *et al.*, 1981; Bryce *et al.*, 1982) on the morning of the day of exogenous HCG administration. Measurements were made with an ATL ultra-

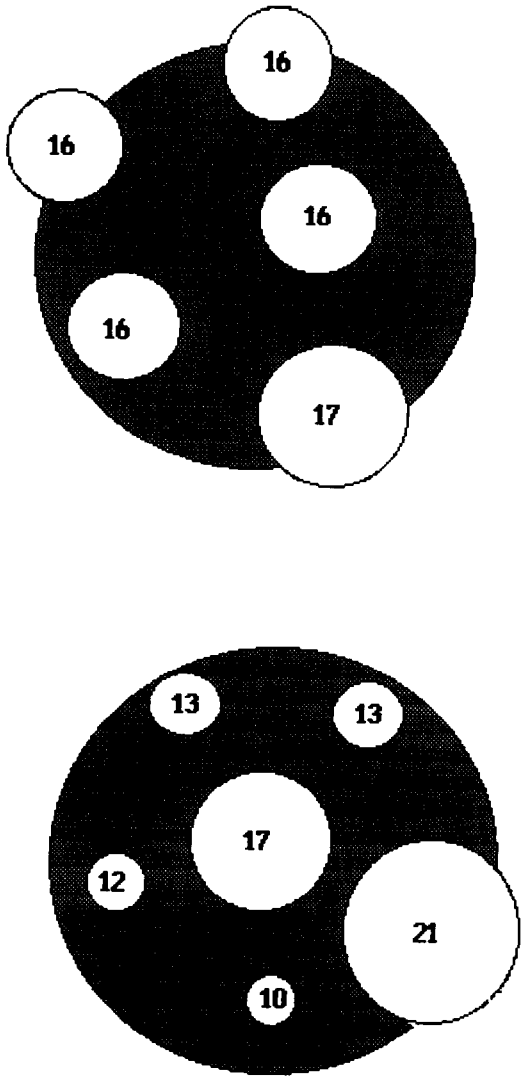

Fig. 1. Ovarian synchrony factor (OSF) according to the synchronous (**upper**; OSF = 1) or asynchronous (**lower**; OSF = 0.33) response to ovarian stimulation.

sound apparatus, Ultramark 4 model, equipped with a 5.0 MHz vaginal transducer. The OSF was defined by the following quotient:

$$\text{OSF} = \frac{\text{total no. of follicles} \geq 16 \text{ mm}}{\text{total no. of follicles} \geq 10 \text{ mm}}$$

and its effect is depicted in Figure 1.

The patients were submitted to ultrasound examination 56–60 h after HCG administration to determine the possible presence of follicular rupture by follicle disappearance and/or a >5 mm decrease in the largest follicular diameters (Check *et al.*, 1990). The largest follicular diameters and the OSF values for the groups with and without follicular rupture were compared by the Mann–Whitney test.

Results

The pregnancy rate per cycle was significantly higher ($P < 0.05$, using Fisher's exact test) in the patients with follicular rupture when compared with a non-rupture group (Table I). The mean

Table I. Pregnancy rates after the use of non-invasive assisted reproduction techniques in the presence or absence of follicular rupture evaluated by ultrasound

Follicular rupture	No. of patients	No. pregnant	Pregnancy rate (%)
Presence	195	42	21.5
Absence	26	1	3.8

$P = 0.043$.

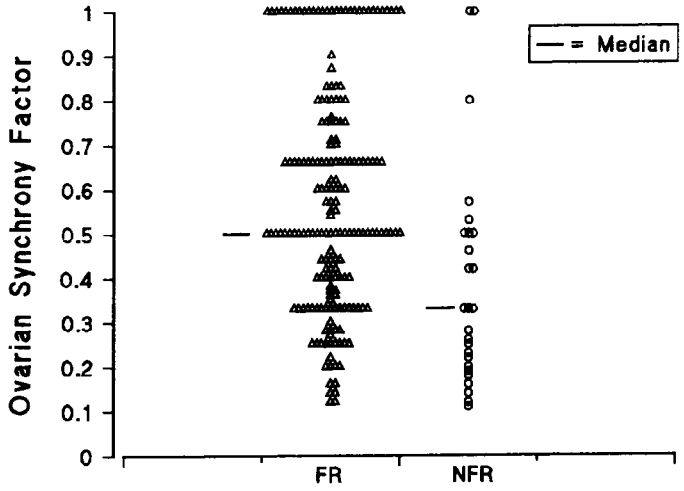

Fig. 2. Distribution of the individual values of the ovarian synchrony factor as a function of the median for the groups with (FR) and without (NFR) follicular rupture.

Table II. Distribution of ovarian synchrony factor (OSF) values as a function of the median on the day of human chorionic gonadotrophin administration according to the presence or absence of follicular rupture

Follicular rupture	OSF	
	≥0.50	<0.50
Presence	124	71
Absence	8	18

$P = 0.0023$.

OSF for the group of patients with rupture of at least one follicle (195 cycles) was 0.57 ± 0.25, as opposed to a mean value of 0.39 ± 0.25 for the group without follicular rupture (26 cycles). Statistical analysis by the Mann–Whitney test showed that the OSF of the group with follicular rupture was significantly higher than that detected in the group without follicular rupture ($P < 0.01$).

The distribution of OSF values as a function of the median (0.50) for the groups with and without follicular rupture is presented in Figure 2. Also, there were significantly higher OSF values above the median in the patients with follicular rupture versus non-rupture ($P < 0.01$) using Fisher's exact test (Table II).

Discussion

It is usually accepted with few exceptions that only one follicle is dominant in natural cycles, reaching a mean size of ≥16 mm,

with the remaining follicles reaching values of <10 mm (Hackeloer *et al.*, 1979). Thus, in natural cycles the ideal OSF would be equal to 1 at the time of endogenous LH discharge.

The ultrasonographic criterion on which HCG administration is based, i.e. when one of the dominant follicles reaches a diameter of 16–18 mm in stimulated cycles, almost always leads to a false analysis of the rest of the follicular cohort. In other words, the efficacy of the process triggering follicular rupture with the use of HCG may be increased by waiting for the maturation of other dominant follicles. Thus, a daily increase in the OSF value may reflect increasing homogeneity of the follicular cohort, with a correspondingly greater chance of follicular rupture.

This fact was quantitatively demonstrated by the study of OSF values on the day of HCG administration, which indicated significantly higher values in the group with subsequent follicular rupture than in the group without rupture. This information indicates that ovarian stimulation protocols should aim at a synchronous follicular response, i.e. the developing follicular cohorts should not present wide variability in size (follicular homogeneity), a situation that should facilitate the process of follicular rupture. However, it should be noted that sometimes an unruptured follicle cannot be distinguished from a cystic corpus luteum, a problem for which there is as yet no solution.

The accuracy of this new ultrasonographic parameter is indicated by the fact that a population with OSF values ≥ 0.50 has a significant chance of presenting follicular rupture after the use of HCG (Table II). Therefore, screening ovarian stimulation by means of ultrasound and subsequent OSF values may be a useful method to select the proper treatment. In addition, the dose should be individually planned for each patient in order to produce follicular homogeneity by daily stimulation until an ideal OSF is reached, which indeed would be the value closest to one, as is the case for the natural cycle.

In summary, analysis of OSF values on the morning of the day of HCG administration may serve to predict follicular rupture, and progressively increasing OSF values are associated with follicular homogeneity and greater chance of follicular rupture.

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Received on August 6, 1993; accepted on February 25, 1994