The association between follicular size at the time of spontaneous rupture and pregnancy rates in clomiphene citrate treated PCOS patients in coit cycles

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Abstract

Objective: To investigate the follicular size at spontaneous rupture on pregnancy rate in patients with polycystic ovary syndrome (PCOS) undergoing clomiphene citrate (CC) ovulation induction.

Design: Cross-sectional study.

Patients and methods: One hundred and four women with ovulatory cycles after use of CC followed by ultrasound to determine the follicle size at the time of rupture, which was subsequently correlated with the occurrence of pregnancy or not in coit cycles.

Results: In the group of follicular rupture at a mean diameter ≤25 mm (n = 54), pregnancy rate was 35.1% and when follicular rupture occurred at a mean diameter >25 mm (n = 50), it was 34% (p > 0.05). When different diameters at follicular rupture were randomly correlated with the pregnancy rate, there was no significant difference.

Conclusion: Our data suggest that the occurrence of pregnancy after ovulation induction with CC in women with PCOS is not associated with follicle size at the time of rupture.

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous and complex endocrine disorder characterized by ovulatory dysfunction, hyperandrogenism and morphologically polycystic ovary [1,2]. It is present in 5–12% of women at reproductive age, depending on the diagnostic criteria used. The main causes considered are hyperandrogenism and anovulation [1]. PCOS is considered an important cause of infertility due to ovulatory factor [3], which could be corrected with measures such as weight loss [4,5], improvement of metabolic disorders [2,5] and ovulation induction [5–7].

Ovulation induction by the administration of clomiphene citrate (CC) is expected to succeed in 80–85% of women with PCOS, but the pregnancy rates per therapeutic cycle are limited to 20–40% [7–9]. The delay in LH peak after using CC is recognized as a determinant factor for follicular rupture at a diameter higher than the diameter in natural cycles [7,9]. Ultrasound monitoring is not mandatory, but it is regularly performed to confirm ovarian response [7,8] and it seems useful when the dominant follicle reaches from 19 to 30 mm as a guide for sexual intercourse [9,10].

Considering the lag of follicular and endometrial development as well as the discrepancy in literature on ovulation rates resulting in pregnancy, the aim of this study is to correlate the follicular development up to spontaneous rupture in women with PCOS undergoing CC ovulation in coit cycles with pregnancy rate.

Patients and methods

This was a cross-sectional study that consecutively evaluated 104 infertile women diagnosed with PCOS, who ovulated after CC induction in coit cycles. It was held at two different fertility clinics from January to December 2011. The sample size calculation was based on the prevalence of PCOS [1], with a margin of error of 3% and confidence interval of 95%, resulting in a rough estimate of 100 patients. All couples were considered infertile after 12 months of unprotected sexual intercourse without achieving pregnancy. Our study was approved by the Ethics Committee on Research from Superior School of Health Science of Brasilia (study number 20/2010). All patients were informed about the study and, once aware and willing to participate, they signed an informed consent form.

Women who had ovulatory factor – hyperandrogenic chronic ovulation according to the criteria established by the Rotterdam Consensus [11] – as the only cause of infertility were submitted to ovulation induction with CC after confirmation of normal semen parameters by spermogram according to the guidelines of the World Health Organization [12] and tubal patency by hysterosalpingography.

The first ultrasound examination was performed before ovulation induction on the second or third day of onset of menstrual flow. After ensuring the absence of follicles greater
than 10 mm and endometrial thickness value less than or equal to 5 mm, ovulation was induced with CC at an initial dose of 50 mg from the third to the seventh day of the cycle. The dosage was increased 50 mg every month, with a maximum dose of 150 mg until ovulatory cycles with a maximum of two follicles were obtained. The second ultrasound control was performed between the 9th and 12th day and the other tests were performed according to the individual needs until follicular rupture was verified. After follicular rupture, micronized natural progesterone was administered daily (200 mg vaginally) for luteal phase support up to the moment of the pregnancy test (β-hCG), 14 d after follicular rupture, keeping this scheme until the eighth week of pregnancy.

Patients were stratified into two groups according to the follicle mean diameter at the time of spontaneous rupture: group 1, follicular diameter equal or less than 25 mm and group 2, follicular diameter greater than 25 mm.

Statistical analysis
Statistical analysis was performed using the SPSS software package (SPSS Inc., Chicago, IL). Association between variables was analyzed by the chi-square test. Comparisons were analyzed using Student’s t test or Mann–Whitney U test when appropriate. Finally, the nonparametric model of Spearman analyzed the correlation between pregnancy and follicle size. Value of less than 0.05 was considered significant.

Results
We evaluated 104 infertile women with PCOS and irregular cycles who underwent CC-induced ovulation: 54 cycles with size of follicular rupture ≤25 mm and 50 with size >25 mm. The demography and clinical characteristics of the patients are detailed in Table 1, which also shows the pregnancy rates according to the size of follicular rupture. Patient’s age, body mass index (BMI), duration of infertility and baseline serum level of FSH, estradiol, TSH and total testosterone were comparable between both groups of patients. The relationship between the groups about mono- or bi-follicular response and thickness of endometrial lining did not reveal any difference. The pregnancy rate was 35.1% in the group ≤25 mm and 34% in the >25 mm. Similarly, no significant differences were observed.

Considering that the value cut-off of 25 mm for the follicle size at the time of rupture after stimulation with CC was not correlated with the pregnancy rate, a nonparametric correlation test (Spearman) was performed between the follicle size at the time of rupture and the occurrence of pregnancy to determine a possible correlation (Figure 1). The relationship between the leading follicle size at the time of rupture and the probability of chemical pregnancy showed no correlation and is best understood

Table 1. The clinical characteristics and pregnancy rate according to follicle size at the time of spontaneous rupture (≤25 and >25 mm).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>≤25 Group</th>
<th>&gt;25 Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycles</td>
<td>N = 54</td>
<td>N = 50</td>
<td></td>
</tr>
<tr>
<td>Patients’ age (years)*</td>
<td>32.3 ± 2.8</td>
<td>31.3 ± 3.3</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>26.8 ± 1.7</td>
<td>27.1 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of infertility (years)*</td>
<td>1.1 ± 1.7</td>
<td>1.2 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>FSH basal (IU/L)*</td>
<td>4.8 ± 0.7</td>
<td>5.3 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol basal (pg/mL)*</td>
<td>31.2 ± 2.4</td>
<td>28.1 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>TSH (mU/mL)*</td>
<td>2.2 ± 1.2</td>
<td>2.1 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Total testosterone (ng/dL)</td>
<td>55.5 ± 6.5</td>
<td>58.1 ± 5.1</td>
<td>NS</td>
</tr>
<tr>
<td>Endometrial thickness on day</td>
<td>10.5 ± 2.2</td>
<td>10.4 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>at the time of follicle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rupture (mm)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono-follicular cycles (%)</td>
<td>70.3 (38/54)</td>
<td>70 (35/50)</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy rate (%)</td>
<td>35.1 (19/54)</td>
<td>34.0 (17/50)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Mean ± SD.

Figure 1. Correlation between follicle size at the time of spontaneous rupture (mm) and pregnancy rate.
Correlation coefficient = 0.004; p = 0.965
Figure 2. Distribution of the total number of patients by pregnancy and no pregnancy according to follicle size. Probability of pregnancy according to follicle size at the time of spontaneous rupture (mm).

from Figure 2. However, Figure 2 shows bimodal distribution containing the highest probability of pregnancy from 18 to 26 mm and above 28 mm, however, not statistically significant.

Discussion

In this study, we have examined follicle size at the time of spontaneous rupture in women with PCOS treated with CC to yield the highest pregnancy rates in coit cycles. Potential predictors of cycle success in achieving pregnancy such as age of patient, BMI, duration of infertility, mono- or bi-follicular cycles were not different in the groups studied (<25 or >25 mm).

On the one hand, based on a prospective study by Opsahl et al. [10], the American Society for Reproductive Medicine stated that the average peak diameter in CC cycles ranges between 19 and 30 mm (with median size of 25 mm) and it seems useful as a guide for sexual intercourse [6,9]. On the other hand, this study did not consider the relationship between follicle size at the time of spontaneous rupture after induced – CC in coit cycles and pregnancy rate. However, we believe it to be important in order to identify if there is optimal follicular size to pregnancy with the purpose of helping to decide on the need to add hCG and when to use it. The results of our study showed no significant difference between the pregnancy rates in the groups. This result was similar when establishing 25 mm as the cut-off and when making a random correlation of all sizes. Thus, it seems unnecessary to add hCG to trigger follicle rupture when its size reaches 19–24 mm in coit cycles. The pregnancy rates found in this study are in agreement with literature, between 32% and 34% [8,9,13,14]. The follicular development was monitored by ultrasound, which is not mandatory, but it is regularly performed to confirm ovarian response [8]. Our study differs from the other recent studies, which investigated the optimal size of the leading follicle before hCG administration to program an intrauterine insemination in couples with unexplained infertility [15,16].

Treatment with CC is well established with studies identifying significant pregnancy rates if the administration of this substance occurs early in the cycle, between the second and fifth day [13,14]. CC is an effective and low-cost medication with few side effects and simple administration, it remains the drug of choice for ovulation induction in patients with PCOS [8]. The growth of follicles after stimulation with CC is variable, being monitored more for their size than for their competence [8,17]. Hence, administration of hCG, mimicking the endogenous LH peak, is the event that determines the follicular maturation and development of its competence [17].

According to Rosen et al., the use of hCG is based on the assumption that the follicle size is predictive of the oocyte developmental competence, and this assumption is based on limited studies by using different models of nonstimulated cycles for animal models of in vitro maturation [17]. Also, the correlation between oocyte competence and follicle size after controlled ovarian stimulation is well characterized. Although evidence suggests that follicle size can influence the results, the true relationship has not yet been established.
Finding the relationship between follicle size and the best pregnancy rate, which is the aim of this study, would bring more security and hope for these couples, who experience high levels of anxiety and uncertainty. Although no correlation between follicle size and pregnancy rate has been found, this result is valid because it leads patients to change their behavior. For example, to reduce the frequency of ultrasound examinations, to offer them greater comfort, to reduce costs for both the Brazilian National Health System as to the private one because there would be no reason for triggering ovulation with hCG, since the pregnancy rates are similar with any follicle size at the time of rupture, corroborating the study by Agarwal and Bualyos [18].

Farhi et al. have reported that even though CC is in use for at least 50 years and that few changes have occurred in the treatment protocol, some questions remain unanswered about its best use [19]. According to Opsahl et al., the average size of the preovulatory follicle in the successful induction of ovulatory cycles by CC ranges from 19 to 30 mm; however, the best time to administer hCG is not well defined [10]. Farhi et al. observed as ideal hCG administration in CC-induced cycles for women with PCOS, follicular diameter between 18 and 22 mm [19], which is below what is commonly accepted by the literature [8,9]. The authors also reported in their study that the follicle size at the time of CC-induced ovulation was significantly higher than that of spontaneous ovulatory cycles [7,10,20]. According to other authors, there was no advantage in monitoring CC-induced cycles by ultrasound [21,22] or the use of hCG to trigger ovulation [18,23].

The results found in these studies were similar to those found in our study, in which no correlation between follicle size and pregnancy rate was observed. As accepted in literature, the pregnancy outcome after CC-induced ovulation should be influenced not only by the follicle size, but also by the oocyte competence [13]. Therefore, the ideal situation is if these two parameters were correlated so that patients with PCOS could be more successfully treated with the use of CC. However, our study points to the lack of correlation between them, since the most reliable way to evaluate the oocyte competence is the occurrence of pregnancy. In conclusion, pregnancy rates of women with PCOS stimulated with CC seem not to correlate with follicle size at the time of spontaneous rupture, both analyzing random follicle size or considering 25 mm as the cut-off.

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Declaration of interest

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References