Does corpus luteum locally affect follicular growth negatively?

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In this study bilateral ovarian follicular growth during the luteal phase was investigated in relation to the ovary where ovulation occurred. The diameter of the largest follicle in the contralateral ovary without corpus luteum and in the ipsilateral ovary with corpus luteum was measured using vaginosonography in a total of 66 natural cycles of 27 normally cycling women undergoing treatment with intrauterine insemination (IUI). None of the women received ovarian stimulation or luteal support. Follicles from 2 to 11 mm in diameter were measured in early luteal phase (day +1 to +4), mid-luteal phase (day +5 to +9) and late luteal phase (day +10 onwards). The mean diameters of the largest follicle in the contralateral ovary without corpus luteum during the early, mid- and late luteal phases were 6.81 ± 1.33 (mean ± SD), 6.14 ± 1.29 and 5.71 ± 1.17 mm respectively, while those of the ipsilateral ovary with corpus luteum were 6.48 ± 1.40, 5.65 ± 1.47 and 4.98 ± 1.19 mm respectively. While there was no significant difference during the early luteal phase, the mean diameter of the largest follicle in the ipsilateral ovary with corpus luteum was significantly smaller than that of the contralateral ovary without corpus luteum during the mid-luteal phase (P < 0.004) and the late luteal phase (P < 0.0005). These results indicate that the corpus luteum locally affects neighbouring follicular growth negatively during the luteal phase of the menstrual cycle, with the most pronounced effect expressed in the mid- and late luteal phases.

Key words: corpus luteum/follicle diameter/follicular growth/natural cycle/transvaginal ultrasound

Introduction

During the early follicular phase of the menstrual cycle, concentrations of follicle stimulating hormone (FSH) rise and follicles from both ovaries start to grow. Around cycle day 8 selection of the dominant follicle, which will undergo full maturation and ovulation, has occurred. It is generally believed that the follicular phase provides a hormonal milieu which secures an optimal selection and maturation of the follicle destined to ovulate. However, we have recently demonstrated that the health of the dominant follicle is superior when it develops in the contralateral ovary where no ovulation took place in the preceding cycle rather than in the ovary where the preceding ovulation took place (Fukuda et al., 1996). When the dominant follicle develops contralaterally to the previous ovulation, the follicular fluid contains a more favourable androgen to oestrogen ratio and the oocyte more often fertilizes and undergoes pre-embryo development in vitro (Fukuda et al., 1996). From these studies, it was suggested that the corpus luteum secreted local ovarian factors which negatively affected follicular health of the responsive cohort of follicles of the next menstrual cycle. The present study was undertaken to evaluate whether the corpus luteum exerted a local negative effect on follicular growth during the luteal phase. Using vaginosonography the diameter of the largest follicle in the ipsilateral ovary with corpus luteum was compared to that of the largest follicle in the contralateral ovary without corpus luteum.

Materials and methods

This study included a total of 27 women (aged 28.1 ± 4.7 years, mean ± SD, range 24–37) undergoing 66 natural cycles in which intrauterine insemination (IUI) was performed. A male factor was the indication for IUI in all cases. None of the women received exogenous gonadotrophin or clomiphene citrate for ovarian stimulation, or human chorionic gonadotrophin (HCG) or progesterone for luteal support. None of the women had experienced ovarian surgery. The mean number of cycles examined in each woman was 2.4 (range 1–3).

Inclusion criteria

Regular menstrual period within 24–39 days (29.3 ± 3.0 days). Normal values of FSH < 10 IU/l, luteinizing hormone (LH) < 12 IU/l and prolactin < 30 ng/ml on cycle days 2–5. Normal value of CA125 < 30 U/ml.

Exclusion criteria

Patients with one or more cysts (i.e. persistent follicular cyst, chocolate cyst) observed by transvaginal ultrasound. Measurement of follicles in one ovary only. Cycles in which the luteal phase had a length of < 11 days. Cycles in which women became pregnant were also excluded.

The diameter of the follicles from 2 to 11 mm was measured by transvaginal ultrasound with fine calipers showing 0.1 mm at the minimum (Sonovista EX Mochida scanner with a 5.0, 6.0 or 7.5 MHz vaginal probe; Mochida, Tokyo, Japan) as shown in Figure 1. All ultrasound assessments were performed by the same observer (M.F.). Each whole ovary was carefully observed in at least two planes (vertical and horizontal planes; if necessary an oblique plane as well) at almost the highest magnification (depth 3 cm). Follicles
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A preliminary study was performed to evaluate the accuracy of the present sonographic measurements of follicle diameter. Salmon eggs (egg size, 5.77 ± 0.62; range, 3.1–7.1 mm) were used. Salmon eggs are round or oval and their shape and size are quite similar to those of follicles during the luteal phase. The longitudinal diameters of salmon eggs covered with physiological saline in a plastic cup were first measured by transvaginal ultrasound. Then the longitudinal diameters were measured by ophthalmic calipers. The mean diameter of eggs was 5.69 ± 0.53 (n = 50) by ultrasound and 5.77 ± 0.62 mm (n = 50) by calipers. The identical diameter was observed in 15 of 50 (30%) with two different methods of measurements. The difference in the diameter measured by ultrasound and by calipers was 0.3 mm in 49 out of 50 eggs (98%). One measurement showed a difference of 0.4 mm (2%).

Statistical evaluation was performed using Student’s t-test. Results are presented as mean ± SD.

Figure 1. Sonogram of follicles in both ovaries. Left sonogram shows follicles (5.2×6.1 mm) in the right ovary without corpus luteum and right sonogram shows a follicle (3.2×4.4 mm) near to the corpus luteum (arrow) in the left ovary.

Figure 2. The diameter of the largest follicle (mm) in contralateral ovary without corpus luteum (upper line) and ipsilateral ovary with corpus luteum (lower line) during the early (EL), the mid- (ML) and the late (LL) luteal phase. CL, corpus luteum. Mean ± SD.

The hormonal profiles confirmed normal ovulatory cycles for the 27 women: FSH, 5.8 ± 1.8 IU/l (range 1.6–8.8); LH, 6.0 ± 2.5 IU/l (range 3.0–11.6); prolactin, 11.5 ± 5.1 ng/ml (range 4.8–26.9). In addition, all women showed CA 125 values within the normal range: 16.8 ± 6.1 (range 6.0–29.3) IU/ml.

The mean diameters of the largest follicle in the contralateral ovary without corpus luteum during early, mid- and late luteal phases were 6.81 ± 1.33, 6.14 ± 1.29 and 5.71 ± 1.17 mm respectively, while those of the ipsilateral ovary with corpus luteum were 6.48 ± 1.40, 5.65 ± 1.47 and 4.98 ± 1.19 mm respectively. While there was no significant difference between
the mean diameters observed during the early luteal phase, the mean diameter of the largest follicle in the ipsilateral ovary with corpus luteum was significantly reduced compared to that of the contralateral ovary without corpus luteum during the mid-luteal phase ($P < 0.004$) and the late luteal phase ($P < 0.0005$) (Table I and Figure 2). Looking at the luteal phase as a whole and pooling measurements from ipsilateral and contralateral ovaries respectively, the mean diameter of the largest follicle in the ipsilateral ovary (5.64 ± 1.48 mm) was significantly ($P < 0.0001$) smaller than that of the contralateral ovary (6.17 ± 1.33 mm). The decrease in the mean diameter of the largest follicle in the ipsilateral ovary during the luteal phase (1.5 mm) was larger than that of the contralateral ovary (1.1 mm) as shown in Table I.

### Discussion

This study shows that the mean diameter of the largest follicle in the ovary containing the corpus luteum is significantly smaller than that of the contralateral ovary without corpus luteum. Furthermore, during the luteal phase the decrease in the diameter of the largest follicle is larger in the ovary containing the corpus luteum compared to the contralateral ovary. This latter finding confirms an earlier study (Pache et al., 1990).

It is now well established that healthy follicles show lower androgen concentrations and a higher oestrogen to androgen ratio than atretic follicles (McNatty et al., 1979; Westergaard et al., 1986; Yding Andersen, 1993, 1995; Fukuda et al., 1995). We have previously shown that follicular fluids from dominant follicles developing in the ovary contralateral to the ovary where the preceding ovulation took place show lower androstenedione and higher oestradiol/androstenedione ratio plus higher oestradiol/androstenedione + testosterone ratio than follicular fluids from dominant follicles developing in the same ovary as the preceding dominant follicle (Fukuda et al., 1996). It was suggested that dominant follicles developing contralateral to the previous dominant follicle were healthier than dominant follicles developing in the same ovary as the previous dominant follicle. Therefore, our former study supports the present study, suggesting that the corpus luteum affects local follicular growth negatively.

There are other reports supporting a local antifolliculogenic effect of corpus luteum. Following ablation of the active corpus luteum, folliculoproliferation resumed and a new subsequent ovulation was advanced in monkeys (Goodman et al., 1977; diZerega and Hodgkin, 1981). Likewise, in rats, an inverse correlation has been observed between the number of corpora lutea after the first pregnant mare’s serum gonadotrophin (PMSG)-HCG injections and the number of ova after the second PMSG-HCG injections, and follicular growth just before the second PMSG-HCG injections was strongly suppressed in the presence of a high number of corpora lutea (Fukuda et al., 1983). Moreover, the oestradiol concentrations of the antral follicles with healthy oocytes in an ovary with corpus luteum were significantly lower than those of the contralateral ovary during the luteal phase in women (Tsuiji et al., 1983).

A specific substance responsible for negatively affecting follicular growth during the luteal phase has not yet been identified. However, progesterone seems to be a strong candidate. Progesterone is secreted in high concentrations by the corpus luteum during the luteal phase, and several studies suggest a local inhibitory effect on follicular growth and/or on follicular oestradiol synthesis in humans (Hoffmann, 1962; Backstrom et al., 1982). Progesterone suppressed the binding of $^{125}$I-FSH to porcine granulosa cells in vitro (Akahori, 1978), and inhibited FSH-stimulated oestrogen production in cultured rat granulosa cells (Schreiber et al., 1980, 1981). Receptors for progesterone have been demonstrated in monkey or human ovaries (Jacobs et al., 1980; Iwai et al., 1990; Suzuki et al., 1994; Bukowski et al., 1996), and progesterone induced atresia in mouse ovarian fragments in vitro (Tyler et al., 1980). Ovulation is more likely to occur in the contralateral ovary with the lowest concentration of progesterone in the ovarian effluents (diZerega and Hodgkin, 1982). Also, progesterone administered before PMSG injection appears to inhibit early follicular growth and causes atresia by suppressing the proliferation of granulosa cells, and consequently suppresses PMSG-HCG induced superspontaneous in hypophysectomized rats (Fukuda et al., 1980). These reports strongly suggest an intra-ovarian antifolliculogenic effect of progesterone. However, it cannot be excluded that other substances from the corpus luteum participate in the process. One such substance may be inhibin, which is also secreted in high concentrations during the luteal phase. Inhibin has been shown to increase the follicular androgen production synergistically with LH, and may contribute to unfavourable conditions for follicular growth (Yding Andersen, 1995).

In conclusion, it is suggested that the corpus luteum.

### Table I. The diameter of the largest follicle (mm) in contralateral ovary (C) without corpus luteum (CL–) and ipsilateral ovary (I) with corpus luteum (CL+) during the luteal phase. Values are means ± SD

<table>
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<tr>
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<th>Early luteal (day +1 to +4)</th>
<th>Mid-luteal (day +5 to +9)</th>
<th>Late luteal (day +10 onwards)</th>
<th>Total</th>
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<td></td>
<td>C</td>
<td>CL–</td>
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<td>(n = 44)</td>
<td>(n = 44)</td>
<td>(n = 66)</td>
<td>(n = 57)</td>
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<tr>
<td>Mean diameter</td>
<td>6.81 ± 1.33</td>
<td>6.14 ± 1.29$^b$</td>
<td>5.71 ± 1.17$^c$</td>
<td>6.17 ± 1.33$^d$</td>
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<td>–</td>
<td>–0.7</td>
<td>–1.1</td>
<td>–1.5</td>
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<tr>
<td>1</td>
<td>6.48 ± 1.40</td>
<td>5.65 ± 1.47$^b$</td>
<td>4.98 ± 1.19$^c$</td>
<td>5.64 ± 1.48$^d$</td>
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<tr>
<td>Change$^a$</td>
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<td>–0.8</td>
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$^a$Change in diameter of largest follicle compared with that measured in early luteal phase.

$^b,c,d$Values with same superscripts were significantly different ($P < 0.004, 0.0005, 0.0001$ respectively).
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