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Mifepristone may inhibit the midcycle gonadotropin surge at both ovarian and pituitary sites of action

The ability of mifepristone to delay ovulation is thought to be based on the antigonadotropic effects of the drug. In the current work, late-follicular phase administration of mifepristone resulted in decrease in both circulating FSH and inhibin B, suggesting both central and ovarian sites of action. (*Fertil Steril*® 2005;84:1545–6. ©2005 by American Society for Reproductive Medicine.)

Preovulatory administration of mifepristone postpones ovulation by inhibiting the midcycle surge of gonadotropin secretion (1, 2), a property that has been employed in emergency contraception (3). Recently, a novel protocol for controlled ovarian hyperstimulation (COH) using a combination of mifepristone and FSH has been shown to inhibit premature LH surges effectively (4). However, the mechanism by which mifepristone inhibits gonadotropin secretion and ovulation has remained enigmatic. We (2) and other investigators (5) have speculated that the ability of mifepristone to delay ovulation is based mainly on its antigonadotropic effects. In addition, direct ovarian effects have been proposed (6, 7). In the current work, we evaluated the possible direct ovarian effects of the late-follicular phase administration of mifepristone by using a granulosa cell marker, inhibin B.

We investigated seven healthy, regularly menstruating women who received a single dose of mifepristone (10 mg) on cycle day 10 or 11 (study day 0). Serum samples were collected daily for 7 days and then on day 10. Ovarian ultrasonography was performed on study days 0 and 6. Serum concentrations of LH, FSH, progesterone, E_2 , mifepristone, and leptin, as well as follicular size in these subjects, have been described elsewhere (2). In the present work, that study was expanded upon by the use of a specific inhibin-B ELISA, devoid of cross-reaction with free inhibin- α subunits (8).

Mifepristone suppressed the circulating concentrations of FSH and inhibin B (Fig. 1A), as measured on the day after its administration. Because inhibin B has been proposed to be the main inhibitor of FSH secretion in the late follicular phase (9), these data confirm the antigonadotropic effect of mifepristone. However, the ability of mifepristone to suppress inhibin B and FSH clearly was associated with follicular size—transient suppression of inhibin

B, but unchanged levels of FSH were encountered in women ($n = 3$) with small (<11 mm) leading follicles on the day of mifepristone administration (Fig. 1B), suggesting a direct effect of mifepristone on the ovary. In contrast, profound and long-lasting suppression of both inhibin B and FSH was evident in women ($n = 4$) with larger leading follicles (>11 mm) on the day of mifepristone administration (Fig. 1C). On the basis of these observations, we propose that during the follicular phase, mifepristone acts mainly on the ovary when the follicular size is <11 mm, whereas at larger follicle sizes, the antigonadotropic effect of the drug becomes more important.

Previous studies have shown that mifepristone attenuates E_2 secretion in response to exogenous FSH (10). Similarly, on the day of hCG administration after COH involving mifepristone and FSH, circulating levels of E_2 have been found to be lower in comparison with those associated with traditional COH (4). Thus, these previous data are suggestive of the fact that mifepristone acts on the ovary, whereas our results provide direct evidence. We speculate that mifepristone decreases the sensitivity of granulosa cells to FSH.

The effect of mifepristone on the health of the oocyte has been studied previously in women receiving clomiphene and hCG for COH; administration of mifepristone 1 hour before hCG had no effect on the number of oocytes, rate of fertilization, or subsequent in vitro development of the embryos obtained (11). After COH using mifepristone, FSH, and hCG, the mean number of oocytes retrieved was smaller, but their maturational stage more advanced when compared with oocytes harvested after a traditional COH protocol (4), suggesting a possible modulatory effect of mifepristone on oocyte maturation. However, no harmful effects on oocyte quality after mifepristone have been reported.

In conclusion, mifepristone appears to delay the midcycle gonadotropin surge at both central and ovarian levels. Before mifepristone is introduced into COH programs, its effects on follicle development should be carefully evaluated, and a regimen of mifepristone should be defined that is sufficient to inhibit preovulatory LH surges with minimal direct effects on the developing follicles.

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FIGURE 1

Circulating levels (mean $\pm$ SE) of FSH and inhibin B in seven healthy women after ingestion of 10 mg of mifepristone on cycle day 10 or 11 (A). Concentrations of both FSH and inhibin B declined significantly from pre-mifepristone values to day 1. The results also are displayed according to the size of the leading follicle (<11 mm; n = 3 [B] or >11 mm; n = 4 [C]) on the day of mifepristone administration. * $P < .05$ compared with the pretreatment values.

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