

## Ovarian hyperstimulation after a short course of an oral contraceptive in a patient with premature ovarian failure

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*To the Editor:*

The paper by [Brahma and Kallen \(1\)](#) about ovarian stimulation after a short course of oral contraceptives in a woman with premature ovarian failure is one of many anecdotal observations that report pregnancies under similar conditions. In my practice I have observed several such cases.

Premature ovarian failure, no matter its etiology (genetic, immunologic, etc.), is always characterized by low levels of estradiol and high levels of FSH, suggesting that the ovaries do not respond to the high levels of gonadotropins. This can be due either to an absence of FSH receptors in the granulosa cells or to FSH isoforms with a low bio/immuno activity. If we consider the first possibility, it is known that in hypox rodents, estradiol can induce mitosis in granulosa cells. It is also well known that estradiol induces FSH receptors. Thus, exogenous estrogens can act at the ovarian level, where they may also increase the stromal blood supply, likely by an effect on the vascular endothelium. If this is the case, then the effect of a short course of an oral contraceptive might make the ovary responsive to the high circulating levels of FSH, resulting eventually in hyperstimulation, as was observed by Brahma and Kallen. Alternatively, if the ovary has enough FSH receptors in this case of premature ovarian failure, the possibility of low bioactivity of the circulating FSH isoforms, as suggested above, is not sufficient to bind and activate the receptors to induce follicular growth and estradiol biosynthesis. It is known that in the course of the menstrual cycle, under the influence of the pulsatility of GnRH and of the positive feedback of ovarian steroids at the pituitary level, there is a progressive change of the bio/immuno ratios of the secreted FSH isoforms. Therefore, it is possible that exogenous steroids may also influence them, eventually contributing to a higher bioactivity, if this was also the case in the reported patient.

Another lesson might be that in cases of resistant ovaries (IVF cycles), priming with estradiol might be justifiable. And, last but not least, impairment of ovarian stromal circulation should not be disregarded. Inadequate local gradients of FSH might prevent its bioactivity from being manifested at the level of the granulosa cells. Thus, vasodilating agents (e.g., pentoxifylline) might be useful, as well as drugs that act to oppose the vasoconstrictor effect of the autonomic nervous fibers present in the ovary.

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## **Reference**

1. Ovarian hyperstimulation after a short course of an oral contraceptive in a patient with premature ovarian failure. *Fertil Steril*. 2008 Jun 11. [Epub ahead of print]

## **The Authors Reply:**

The authors are grateful for the comments of Dr. Neves-e-Castro, offering additional mechanisms that might explain ovulatory responses to estrogenic therapies in patients with POF. Our case report was unique not only because it confirmed the potential for an ovulatory response to E+P, but because it was the first reported instance of ovarian hyperstimulation following a course of gonadotropin suppression. Our patient presented with abdominal pain, an estradiol level of 979 pg/mL, and multiple, bilateral, large ovarian follicles.

There exist diverse mechanisms by which estrogen treatments might promote spontaneous or induced ovulation in patients with POF (1). It remains unclear which clinical factors might be predictive of success. As we noted, some success was achieved in patients for whom serum FSH could be suppressed to  $\leq 15$  mIU/mL (2). A small minority (likely < 20%) of patients with the hormonal profile of POF will have significant numbers of primordial follicles if biopsied (3, 4), indicating a sub-population within POF: those with “gonadotropin resistant ovary syndrome” (a.k.a., Savage syndrome), some secondary to FSHR mutations. It is unclear whether the presence or absence of significant numbers of primordial follicles is in fact predictive of response to estrogen therapy or of future pregnancy (1, 5). In our patient, the low serum AMH value (<0.01 ng/mL) would suggest a dearth of follicles (although biopsy was not performed). A better understanding of the genetic factors leading to idiopathic POF in patients who are 46XX remains a research priority.

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## **References:**

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