Open

Citation: J Med Discov (2020); 5(3):jmd20034; DOI:10.24262/jmd.5.3.20034

Case Report

Idiopathic baseline elevated progesterone and estradiol levels did not alter the normal menstrual cycle of a woman: a case report and review of the literature

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Background: Progesterone and estradiol are arguably the most important secretory products of ovarian steroid production. Estradiol is essential to initiation of the luteinizing hormone surge needed for ovulation and for proliferation of the endometrium. Progesterone is essential for conversion of the endometrium to the secretory phase. Serum progesterone level in the late follicular phase of the stimulated cycle has been accepted to be important to the chance of achieving pregnancy. Recently, the importance of early baseline follicular serum progesterone has become more evident.

Case: A woman presented with a history of secondary infertility with a known male factor component. She was found to have significantly elevated baseline levels of serum progesterone and estradiol. The patient continued to have normal ovulatory menstrual cycles. After thorough investigation, a reason for the baseline elevated levels could not be identified.

Conclusions: Although we identified no cause for this patient’s elevated baseline ovarian hormone levels, we found that this phenomenon did not result in alterations of the bimodal gonadotropin and ovarian hormones and endometrial changes characterising a normal menstrual cycle.

Keywords: Infertility; Serum Progesterone; Serum Estradiol; Endometrial dating; Menstrual cycle; Adrenal

How to cite: Olga Haakman et al.,Idiopathic baseline elevated progesterone and estradiol levels did not alter the normal menstrual cycle of a woman: a case report and review of the literature. J Med Discov (2020); 5(3):jmd20034; DOI:10.24262/jmd.5.3.20034; Received April 16th, 2020, Revised June 22nd, 2020, Accepted July 04th, 2020, Published July 11st, 2020.

Introduction

The human menstrual cycle is characterized by the menstrual, follicular and luteal phases corresponding with bleeding, proliferative and secretory endometrial histological features (1). This allows characterization into distinct proliferative and secretory phases and provides evidence of quantitative progesterone effects and potentially the time of ovulation (2).

In the follicular phase, the dominant follicle accelerates estrogen production causing a rise in the serum level which stimulates endometrial proliferation. Following ovulation in mid cycle, the luteal phase, characterized by production of estrogen and progesterone by the corpus luteum, further prepares the endometrium for potential implantation and nurturing of the embryo (1). The end of the menstrual cycle occurs with functional luteolysis when the corpus luteum regresses in the absence of pregnancy. This results in a decline in serum progesterone and break down and shedding of the endometrium (3).

Although higher than normal baseline progesterone levels have been observed in the early follicular phase, this has been thought to be related to an ongoing production from a previous corpus luteum and tends to occur in women at a higher reproductive age (3, 4). This variation has been associated with a lower pregnancy chance potentially related to detrimental effects of progesterone on endometrial receptivity or a poor endocrine environment for the growth of a new follicle (3).

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The control and source of progesterone secretion in the follicular phase of the natural cycle are not well characterized (3) with other potential sources including the developing follicle and the adrenals (5). The enzyme 3-β-hydroxysteroid dehydrogenase, responsible for progesterone synthesis, is expressed in the adrenal cortex, theca interna and granulosa cells of the Graafian follicle of some species (6, 7). Early follicular basal serum progesterone has been shown to be mainly produced in the adrenal cortex with the ovaries becoming the main source in the late follicular phase (3, 4, 6).

In one study, baseline serum progesterone levels and a history of progesterone elevation predicted progesterone elevation at the time of ovulation trigger in In Vitro Fertilization (IVF) cycles (8). Also, basal progesterone level is an important predictor of pregnancy achievement in fresh IVF cycles, as shown in a meta-analysis of over 60 000 IVF cycles (9). The importance of serum progesterone levels throughout the cycle to the chances of successful implantation in infertile women are becoming increasingly apparent. Herein, we describe a unique case of significant idiopathic baseline progesterone and estradiol elevation in a patient who presented with a history of secondary infertility due to male factors.

CASE

This case report is from The Fertility Clinic in London, Ontario Canada. The report was exempt from evaluation by the Institutional Review Board. Signed consent was obtained from the patient. A 37-year-old woman, Gravida 1 Para 1, Body Mass Index (BMI) 25 kg/m^2, presented with secondary infertility related to male factors. Following vasectomy reversal in her partner, and one spontaneous uncomplicated pregnancy, the partner was found to have azoospermia. The patient was having regular, 28-day cycles. Other than taking thyroid replacement therapy, she was generally healthy and had no surgical history. She had been taking Levothyroxine for several years for a history of hypothyroidism with previous elevations noted in both thyroglobulin antibodies and thyroid microsomal antibodies. Her hypothyroidism was well controlled with a recent thyroid stimulating hormone (TSH) level measured at 1.58 mIU/L.

Investigations included a day-3 hormone profile, which was normal, and an Anti-Mullerian Hormone of 7 ng/mL, consistent with normal ovarian reserve. A transvaginal sonogram and a sonohysterogram showed normal pelvis and uterine cavity. There were no masses and antral follicle counts were 16 on the right and 12 on the left ovary.

The couple elected to start IVF treatment including sperm retrieval. In the treatment cycle, it was noted that both estradiol (674 pmol/L) and progesterone (28 nmol/L) levels were significantly elevated on day-3 of the patient's cycle. In the luteal phase, a gonadotropin releasing hormone (GnRH) antagonist was started for suppression in preparation for the following cycle. Estradiol remained elevated at 533 pmol/L and progesterone was 22 nmol/L. An intra-nasal spray of a GnRH agonist was started at 200 mcg twice daily. The serum progesterone, measured several times over the following cycle, remained consistently elevated between 20 and 30 nmol/L while the estradiol fluctuated between 350 and 1400 pmol/L. The injectable GnRH agonist arrested the patient's menstrual cycles but the progesterone remained elevated throughout the cycle despite evidence of pituitary suppression with a Luteinizing Hormone (LH) level of <0.31 IU/L and Follicle Stimulating Hormone (FSH) of 2.2 IU/L.

Imaging was arranged to rule out an ovarian or adrenal tumor that could be contributing to the baseline elevated progesterone. Pelvic and renal ultrasound assessment showed normal anatomy bilaterally. A simple right para-ovarian cyst measured 2.2 x 1.3 x 1.3 cm. This had previously been seen on multiple ultrasounds over the past two years and was stable in size. The kidneys appeared

normal with no hydronephrosis and no adrenal masses seen. A non-contrast CT scan showed no evidence of adrenal mass and no abdominal adenopathy. Magnetic resonance imaging showed a right, 2.3 cm, simple para-ovarian cyst. Both ovaries appeared normal.

Testosterone, dehydroepiandrosterone (DHEA), and androstenedione were normal. A non-steroidal aromatase inhibitor (Letrozole 2.5mg PO daily for ten days), was started to prevent a confounding effect of peripheral action of aromatase. Examination by an endocrinologist showed normal vital signs and no evidence of hirsutism or voice changes. There were no signs of cortisol excess including weight gain, purple striae or bruising. LH, FSH and Adrenocorticotropic Hormone (ACTH) were found to be appropriately suppressed and an ACTH stimulation test elicited normal cortisol response. 17-hydroxyprogesterone was normal. Serum testosterone was 1.0 nmol/L, Free Androgen Index was 2.1 and the Sex Hormone Binding Globulin (SHBG) was 47.1 nmol/L, while serum progesterone and estrogen levels remained elevated at 17.3 nmol/L and 383 pmol/L, respectively. Liver enzymes had previously been drawn and found to be normal, with an alanine aminotransferase of 20 U/L, an aspartate aminotransferase of 18 U/L and alkaline phosphatase of 80 U/L. The prolactin was measured on several occasions and was consistently normal between 5 µg/L and 11 µg/L.

The patient was monitored throughout a natural cycle and serum estradiol, progesterone, LH and FSH were assessed on cycle days 9, 16, 23, and 30 concomitantly with endometrial biopsies on the same days. Although both baseline progesterone and estradiol remained elevated throughout the cycle, a cyclical pattern of both gonadotropins (FSH, LH) **(Figure 1)** as well as progesterone and estradiol were observed **(Figure 2)**. The endometrial histology also showed distinct proliferative and secretory features consistent with an ovulatory cycle indicating that the patient's baseline elevation in hormone levels was not affecting her ability to have natural cycles, in keeping with her prior history of regular menstrual cycles.

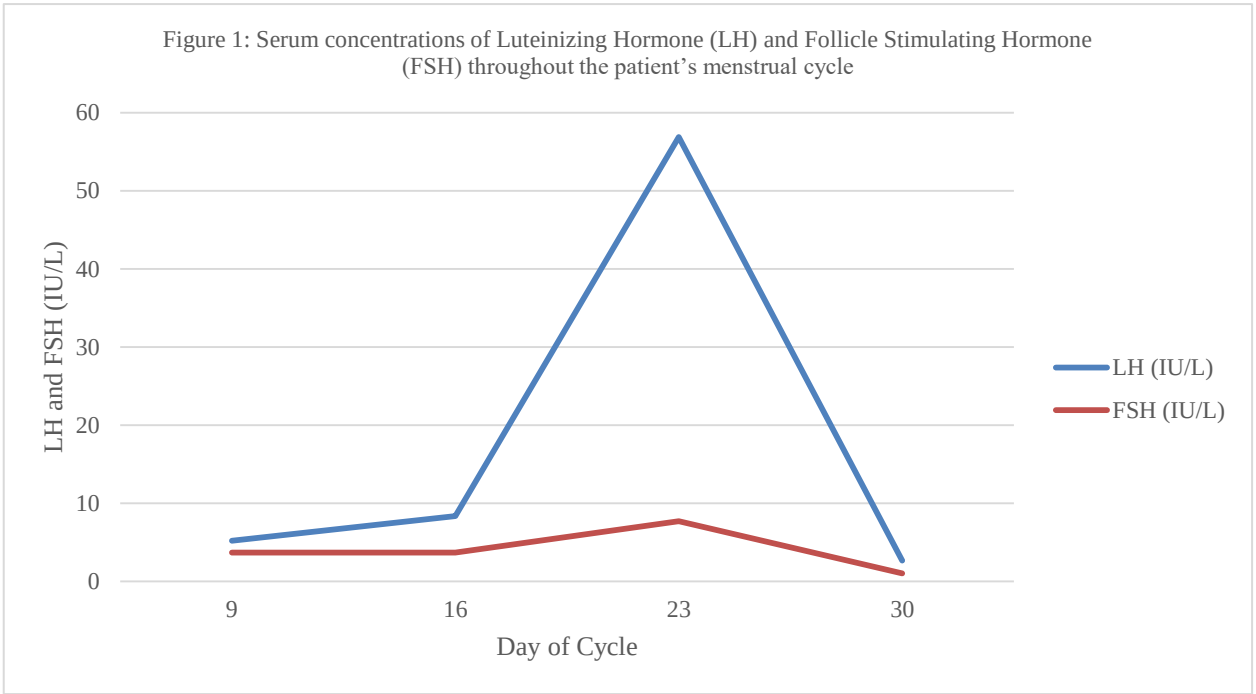

Figure 1: Serum concentrations of Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) throughout the patient's menstrual cycle

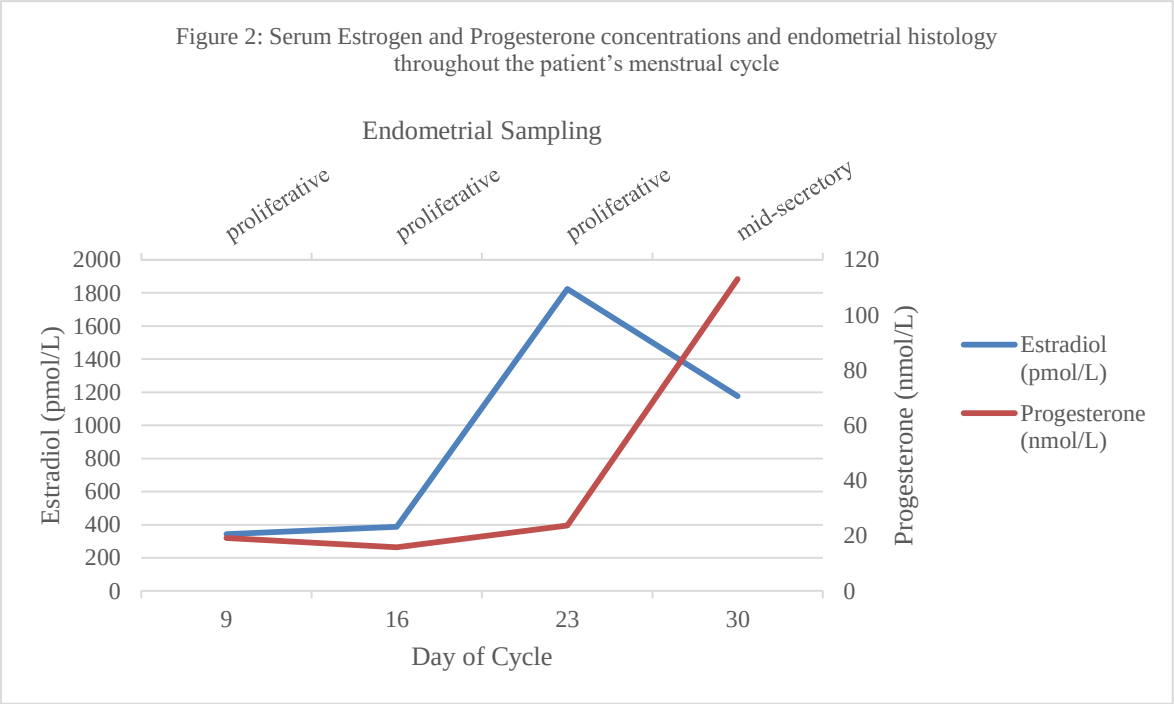

Figure 2: Serum Estrogen and Progesterone concentrations and endometrial histology throughout the patient's menstrual cycle

The patient underwent an antagonist IVF cycle. Stimulation occurred with 225 IU Follitropin alfa and 75 IU of menotropin. Oocytes were treated with ICSI after Percutaneous Epididymal Sperm Aspiration. The cycle resulted in cryopreservation of four day-3 embryos and two day-6 blastocysts. Unfortunately, although the patient underwent three frozen embryo transfer cycles, with a total of two blastocysts and two day-3 embryos transferred, a pregnancy was not achieved to date.

DISCUSSION

Elevated early follicular progesterone was reported in 36 (11.4%) of 316 patients treated for infertility in a study describing the incidence and significance of elevated progesterone levels early in the cycle. The baseline progesterone ranged between 1.5 and 3.1 ng/ml which is significantly lower than the levels in our patient (5). Early follicular basal serum progesterone levels are thought to be largely a production from the adrenals, whereas the levels in the late follicular phase reflect mainly ovarian production (3, 4, 6). In our patient, the adrenals were appropriately imaged with no masses seen. The serum androgen levels were normal with no clinical signs of hyperandrogenism and, the ACTH stimulation test elicited normal cortisol response. Estradiol is produced by the granulosa cells of the ovary in response to FSH from the precursor androstenedione (1). Levels can be elevated in patients with elevated BMI secondary to conversion from estrone in the adipose tissue. This patient, however, had normal androgen levels and a BMI of 25 kg/m^2.

A possible explanation for significantly elevated basal progesterone in some patients is an atypical presentation of cytochrome P450 oxidoreductase deficiency. This rare autosomal recessive type of congenital adrenal hyperplasia is usually diagnosed in the neonatal or pediatric population with presentation of ambiguous genitalia or abnormalities in skeletal development. A case series of five females between 19 and 28 years described their presentation with menstrual disorders and/or infertility and all five women had cytochrome P450 oxidoreductase deficiency. Although

all women had baseline elevated progesterone, they had low to normal estradiol and elevated 17-hydroxyprogesterone levels in contrast to our patient who had a normal 17-hydroxyprogesterone and elevated estradiol. 21-hydroxylase deficiency was excluded in these patients by genetic testing (10). Elevated progesterone in the early follicular phase can also be a symptom of congenital adrenal hyperplasia with 21-hydroxylase deficiency (5). Finally, thyroid dysfunction can contribute to elevated progesterone levels in certain cases. In this case, the thyroid function was well replaced and the patient was assessed by the Endocrinology service.

CONCLUSION

Although we found no identifiable cause for this patient's elevated baseline serum progesterone and estrogen, this phenomenon did not alter the bimodal hormonal and endometrial changes characterising a normal menstrual cycle. Despite the significantly elevated basal levels of progesterone (above 20 nmol/L throughout the cycle), there was a normal cyclical pattern observed in the patient's LH, FSH and estradiol. The progesterone also showed a rise in the luteal phase of the cycle and the endometrial histology was consistent with a distinct proliferative and secretory phase of the cycle.

Conflicts of Interest Disclosures

This manuscript has not been presented at a conference, nor is it part of any conference proceedings. All authors have no conflicting interests or financial disclosures to report.

Acknowledgments

The patient provided signed consent to publish her case. No funding was required.

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PubMed PMID: 32242900.