Progesterone: Physiology and Clinical Utility

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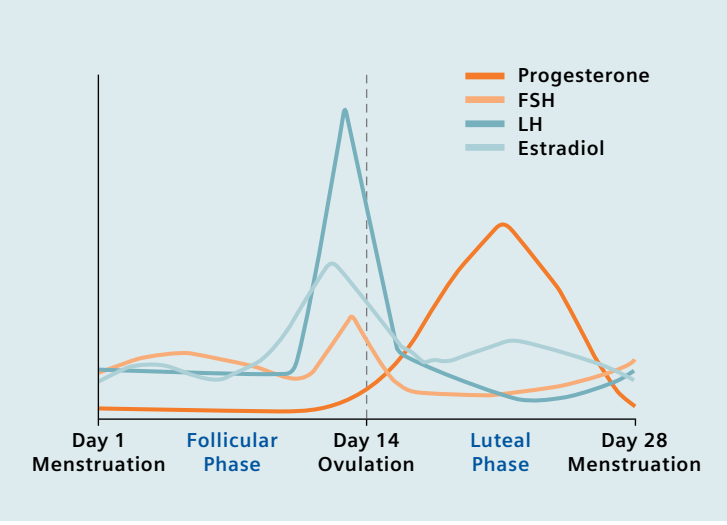
Progesterone, along with estradiol, is one of two major female sex hormones produced by the ovaries. Although not involved in the development of secondary sexual characteristics, progesterone is essential for normal reproductive function. The major target organ is the uterus which, under the influence of progesterone, undergoes changes in preparation for implantation by a fertilized ovum. During pregnancy, progesterone maintains the placenta, inhibits contractility of the uterus and prepares the breasts for lactation. Progesterone measurements are important for the evaluation of female reproductive function.

Progesterone in the Menstrual Cycle

The inner mucosal lining (endometrium) of the uterus undergoes cyclic changes in response to changes in the concentrations of ovarian female sex hormones, primarily estradiol and progesterone. Cycle duration is measured from the onset of menstrual bleeding (day 1) until the next onset, and normally ranges between 25 and 30 days. (See Figure 1.) Levels of estradiol and progesterone are regulated by two pituitary gonadotropins: follicle-stimulating hormone (follitropin, FSH) and luteinizing hormone (lutropin, LH). During the first phase of the cycle (follicular), progesterone levels in the circulation are low (<1.5 ng/mL; median 0.4). The rise in FSH levels, which begins during the last few days of the previous cycle, continues, and begins to stimulate development of ovarian follicles and production of estradiol. Levels of estradiol increase—gradually at first, and then much more rapidly as the midcycle (ovulatory) phase approaches. The negative feedback effect of estradiol now becomes positive and causes a surge in LH and FSH levels, terminating the follicular phase. The rising LH levels stimulate progesterone production by the follicle. Approximately 12 hours after LH peaks, the dominant preovulatory follicle ruptures and expels the egg cell (oocyte). This initiates the luteal phase of the cycle, during which the structure and function of the residual follicle (corpus luteum) changes dramatically. LH stimulates the corpus luteum to secrete increasing amounts of progesterone, and concentrations rise to peak levels (3.5 – 25 ng/mL; median 15) during the midluteal phase, approximately 8 days after the midcycle LH surge. The thermogenic properties of progesterone cause a characteristic rise in basal body temperature of approximately 0.5˚C. Also under the influence of progesterone, the endometrium of the uterus transforms from a proliferative to a secretory state in preparation for implantation by a fertilized ovum. In the absence of pregnancy, the corpus luteum atrophies 9 to 11 days after ovulation. Progesterone levels then decrease, returning to concentrations characteristic of the follicular phase. These events signal the end of the luteal phase. The onset of menstruation begins the follicular phase of the next cycle.

Figure 1. Hormonal Profiles Throughout the Menstrual Cycle



The monthly menstrual cycle prepares an egg for maturation, ovulation and fertilization. The human menstrual cycle comprises three phases:

Follicular Phase – initiates the growth and maturation of an ovarian follicle, which actually begins during the last few days of the previous Luteal Phase.

Ovulatory Phase – the interval in which the LH surge induces ovulation.

Luteal Phase – the last portion of the cycle that prepares the endometrium for implantation of a fertilized ovum.

Progesterone During Pregnancy

Fertilization of the ovum, generally in the lateral portion of the fallopian tube, results in a diploid cell (zygote) which then undergoes a series of mitotic divisions. The resulting small ball of cells (blastocyst) grows and begins to differentiate as the number of cells increases. The cells on the periphery become arranged in a layer surrounding a central cavity into which an inner cell mass protrudes. The outer cells (trophoblast) later develop into the placenta, and the inner cells become the embryo. The blastocyst implants into the progesterone-primed endometrium approximately 6 days following fertilization, and develops into an embryo by approximately the second week after fertilization. Progesterone concentrations in the maternal circulation progressively increase during normal pregnancy from approximately 15 ng/mL during the midluteal phase to approximately 25, 55 and 110 ng/mL during the first, second and third trimesters of pregnancy, respectively. Once the blastocyst becomes implanted in the uterus, specialized cells of the placenta secrete increasing amounts of human chorionic gonadotropin (HCG) during the first trimester. Stimulation of the corpus luteum to produce increasing amounts of progesterone is now a function of the rising HCG levels, which replace LH in this role. After the first trimester, the placenta becomes the major source of progesterone; levels normally continue to increase throughout the course of pregnancy.

Clinical Utility of Progesterone Determinations

Progesterone determinations are commonly used to confirm ovulation, which is indicated by luteal phase progesterone levels of >3 ng/mL.[1] Other applications, both in routine use and under investigation, are described below.

Diagnosis of Luteal Phase Deficiency

Luteal phase deficiency (LPD) is a clinical diagnosis of inadequate endometrial maturation, usually associated with decreased corpus luteum function. It is evaluated as a possible cause of infertility and/or habitual miscarriages. The primary problem appears to be a deficiency in progesterone production, i.e. inadequate quantity and/or insufficient duration of adequate progesterone production. In research settings, an abnormally low, integrated progesterone value, calculated from daily luteal phase determinations, is the generally accepted reference procedure for the diagnosis of LPD. Several tests of luteal function—including basal body temperature, luteal phase length, preovulatory follicle diameter, timed endometrial biopsy, a single serum progesterone determination, and the sum of three serum progesterone determinations during the midluteal phase—were recently evaluated relative to corresponding integrated luteal phase progesterone results.[2] The results suggest that the most sensitive and specific prediction of low integrated progesterone (and therefore of LPD) was a value of <30 ng/mL for the sum of three (midluteal) serum progesterone measurements (100% sensitivity, 80% specificity).

Even a single (midluteal) progesterone result of <10 ng/mL was highly predictive of LPD (84% sensitivity, 82% specificity). However, a diagnosis based on a single progesterone determination continues to be controversial. Progesterone is secreted in a pulsatile manner, and serial samples obtained over a 24-hour period can range from 2.3 to 40 ng/mL.[3] Such fluctuations raise questions about the reliability of a single progesterone determination for the differential diagnosis of LPD. The pulsatile secretion of progesterone argues for either assaying multiple specimens separately or pooling multiple specimens for processing in a single assay.

Diagnosis of Ectopic Pregnancy

STAT progesterone determinations have been used to assist in the early detection of ectopic and abnormal intrauterine pregnancies. Abdominal and vaginal ultrasound examinations may not be able to detect normal or abnormal pregnancy when HCG levels are still low (<6,000 mIU/mL for abdominal and <1,400 mIU/mL for vaginal ultrasound examinations).[4] However, at these low HCG levels, a progesterone result of 5 ng/mL or less has been characterized as a reliable indicator of nonviable pregnancy (100% specificity).[5] Early detection of ectopic pregnancies based on progesterone determinations in at-risk patients has been reported to significantly reduce emergencies involving

unexpected rupture, hemorrhage and destruction of the fallopian tube. Values of 25 ng/mL or more exclude ectopic pregnancy (97.5% negative predictive value). Values falling between 5 and 25 ng/mL require follow-up with other diagnostic procedures.[6,7]

Prediction of Pregnancy Outcome in Assisted Reproductive Technologies

Progesterone determinations are routinely used to assess adequacy of luteal phase (diagnosis of LPD) after embryo transfer. Many IVF clinics also rely on progesterone determinations during stimulated cycles to identify time for oocyte retrieval.[8] However, recent editorial commentary states that current knowledge does not allow the use of periovulatory serum progesterone levels for deciding whether to proceed with embryo transfer or to cryopreserve embryos for transfer at a later time. To date, studies have yielded conflicting data: the use of progesterone determinations as a predictor of conception by assisted reproductive technologies (ART) is therefore considered investigational.[9]

Conclusion

Progesterone determinations are useful for evaluating the menstrual cycle, the corpus luteum and the placenta; for determining whether ovulation has occurred; and for the differential diagnosis of luteal phase deficiency. Progesterone measurements can also identify patients at risk for ectopic pregnancy earlier than can ultrasonography. ART provides additional applications, some already proven, while others remain to be established.

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