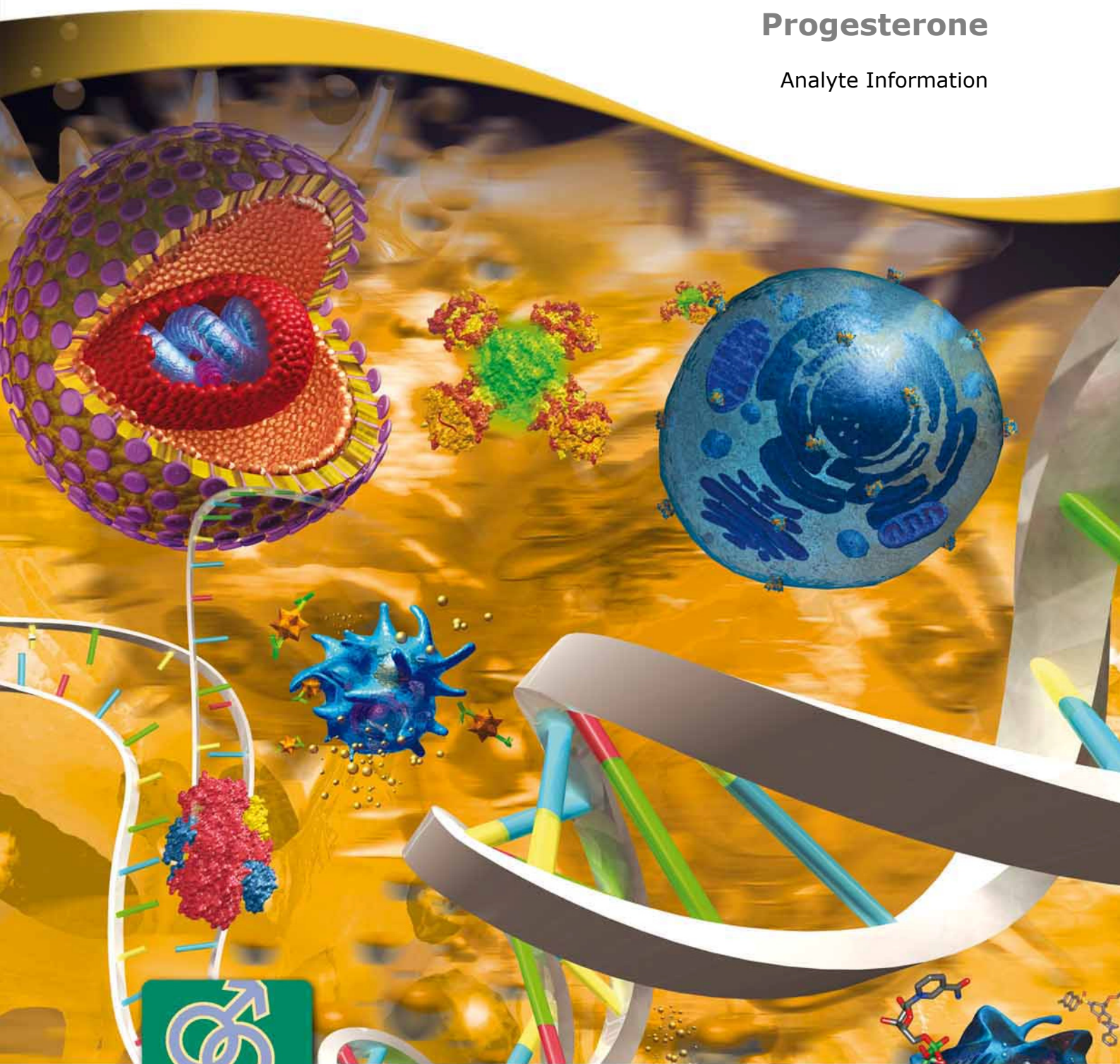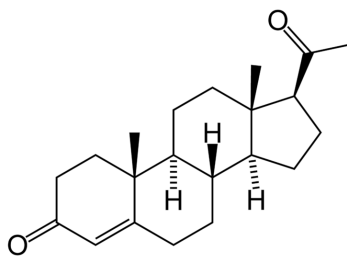# Reproductive

Progesterone

Analyte Information

Progesterone

Introduction

Progesterone is a natural gestagen belonging to the C_{21} steroid group. It is also known as P4 (or pregn-4-ene-3,20-dione, or 4-pregnene-3,20-dione). It belongs to a class of hormones called progestogens and is the major naturally occurring human progestogen belonging to this group of steroid hormones. The summary formula of progesterone is $C_{21}H_{30}O_2$; its structural formula is shown in Fig.1. Its molecular weight is 314.47 Da.

Fig.1: Structural formula of progesterone

Progesterone is a female hormone essential to the regulation of ovulation and menstruation. It is also used to encourage conception in assisted reproductive technology (ART) cycles such as in vitro fertilization (IVF). Furthermore, progesterone is being investigated as potentially beneficial in treating multiple sclerosis. Vaginally-dosed progesterone is being investigated as potentially beneficial in preventing preterm birth.

Biosynthesis

Progesterone plays a major role in the female menstrual cycle, conception and embryogenesis. In non-pregnant women, the major sites of progesterone biosynthesis are the ovaries (after ovulation, in the corpus luteum specifically) and the adrenal cortex.

Progesterone synthesis in the corpus luteum is stimulated by luteinizing hormone (LH) and by human chorionic gonadotropin (hCG). In young corpus luteum (i.e., shortly after follicular rupture), LH-specific receptors are most prevalent; hCG-specific receptors predominate by the middle of the luteal phase.

The corpus luteum graviditatis is responsible for progesterone secretion until the 8th-10th week of gestation. Thereafter, progesterone is generated in placenta from maternal cholesterol and its major role is to maintain pregnancy by reducing womb contractility. The fetus utilizes placental progesterone for the production of corticosteroids.

As with other steroids, progesterone is synthesized from cholesterol via a series of enzyme-mediated steps[1,2]. The first step is mediated by the enzyme P450scc and involves conversion of cholesterol to 20,22-dihydroxycholesterol and then pregnenolone. The subsequent conversion of pregnenolone to progesterone is catalyzed by 3beta-hydroxysteroid dehydrogenase / delta(5)-delta(4)isomerase (Fig.2).

Progesterone is also important for aldosterone (mineralocorticoid) synthesis. Progesterone is the precursor of the mineralocorticoid aldosterone and, after conversion to 17-hydroxyprogesterone (another natural progestogen), the precursor of cortisol and androstenedione (Fig.2).

Fig.2: Scheme of progesterone biosynthesis
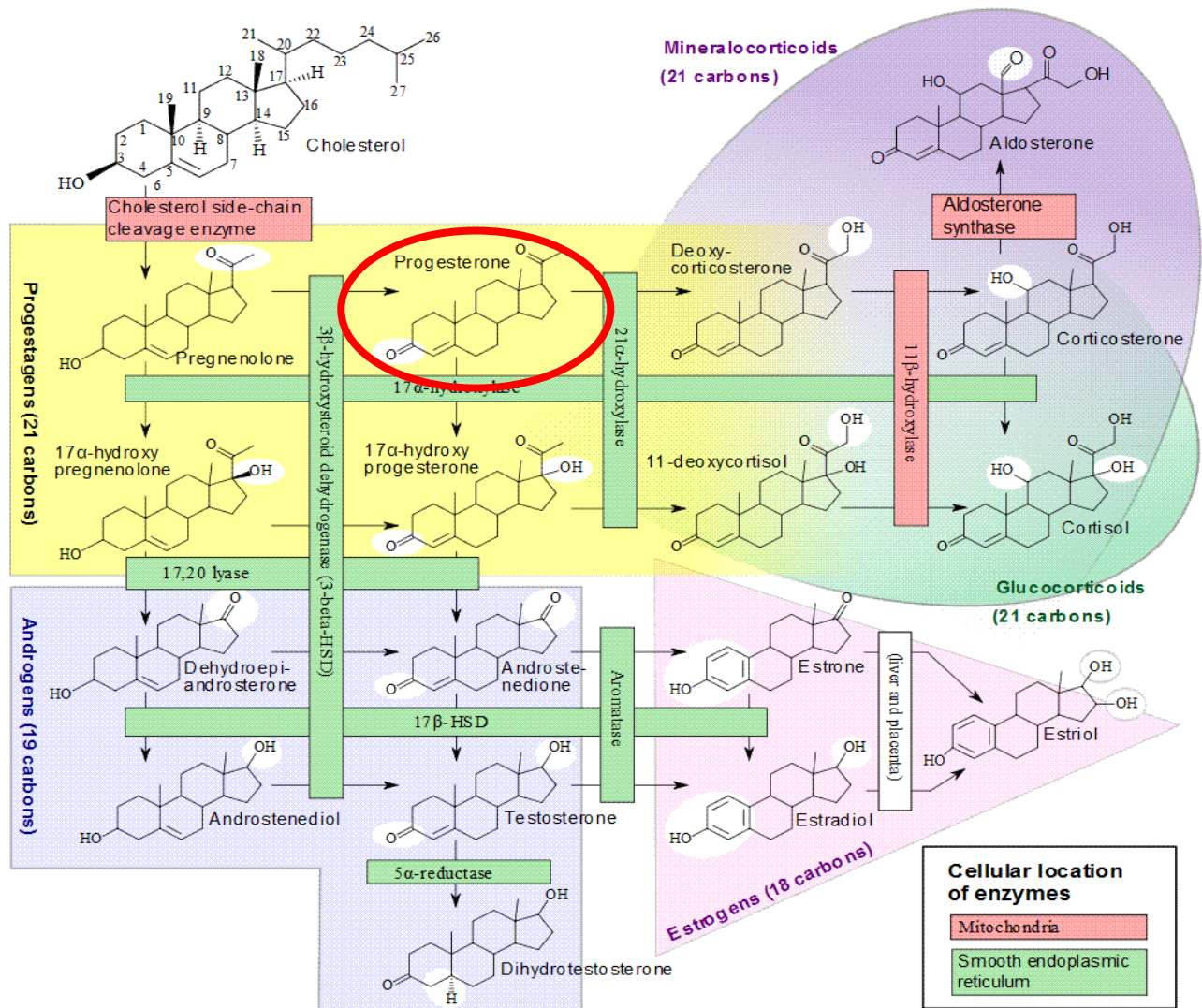
Metabolism

The most important metabolic steps leading to the inactivation of progesterone are reduction and conjugation[3]. Progesterone is metabolized to pregnanediols and pregnanolones, primarily in the liver (over 60%). Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and/or sulfate metabolites.

The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are then excreted in bile and urine. Progesterone metabolites which are excreted in bile may undergo enterohepatic recycling or may be excreted in feces.

The biological half-life of progesterone is very short (several minutes). Seventy percent of progesterone is metabolised within eight hours, and 90% within 24 hours[4].

Physiological Function

Progesterone is a very important hormone in pregnancy. Its many roles include preparing the uterus for pregnancy, protecting the fetus and maintaining pregnancy.

Progesterone induces the endometrium to enter the secretory stage in order to prepare the uterus for implantation. At the same time progesterone affects the vaginal epithelium and cervical mucus, making it thick and impermeable to sperm. If fertilization does not occur, progesterone levels will decrease. Thus normal menstrual bleeding is, in fact, progesterone-withdrawal bleeding. Progesterone participates in the feedback regulation of pituitary gonadotropins and ovarian estrogens. Some $5\text{-}\beta\text{-}$reduced progesterone metabolites are considered to be responsible for the increase of basal body temperature during the luteal phase.
During implantation and gestation, progesterone appears to mitigate the maternal immune response to the fetus.

Progesterone reduces the contractility of uterine smooth muscle. A drop in progesterone levels may be one of steps facilitating the onset of delivery.
Progesterone inhibits lactation during pregnancy. The fall in progesterone levels following delivery is one of the triggers for milk production.
The fetus metabolizes placental progesterone to produce adrenal steroids (corticosteroids).

Progesterone operates primarily via intracellular progesterone receptors, although distinct, membrane-bound progesterone receptors have also been

posited[5,6]. Additionally, progesterone is a highly potent antagonist of the mineralocorticoid receptor (MR), the receptor for aldosterone and other mineralocorticosteroids.

Progesterone has a number of physiological effects that are amplified in the presence of estrogens. Estrogens upregulate the expression of progesterone receptors[7]. Elevated levels of progesterone also greatly reduce the sodium-retaining activity of aldosterone, resulting in natriuresis and a reduction of extracellular fluid volume. Conversely, progesterone withdrawal is associated with a temporary increase in sodium retention (reduced natriuresis, increase in extracellular fluid volume) and an increase in aldosterone production, which combats blockage of mineralocorticoid receptors due to previously-elevated progesterone levels[8].

Levels

Serum levels of progesterone are relatively high at birth due to placental production, fall rapidly in the first week after birth, and rise again during puberty[9]. In adult men, children and postmenopausal women, serum levels are relatively low and similar to levels seen in women during the follicular phase of the menstrual cycle. These levels reflect adrenal progesterone production. Serum progesterone levels are relatively high in women during the luteal phase of the menstrual cycle (Fig.3) and during pregnancy (Fig.4).
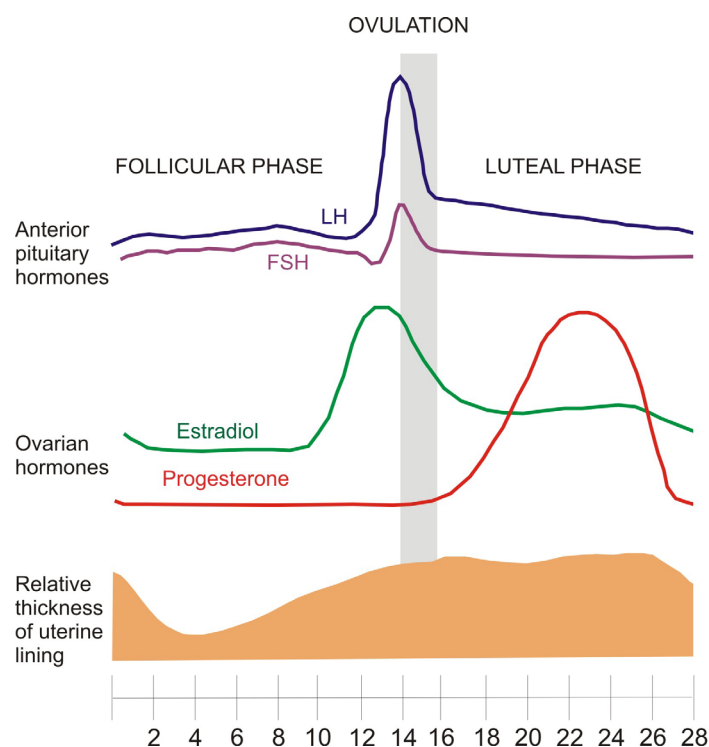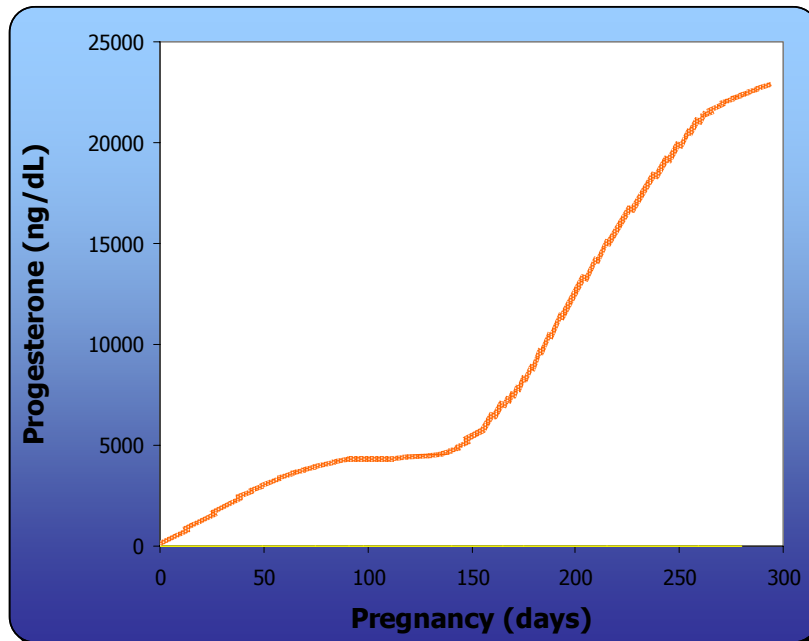
Fig.3: Menstrual cycle

Fig.4: Progesterone levels during pregnancy

In both cases, the progesterone increase is caused by gonadotropin stimulation.

Following follicular rupture and ovulation, luteinization of granulosa cells occurs as the burst follicle is converted to corpus luteum. This results in a remarkable increase in progesterone synthesis, which peaks about 7 days before the onset o the next cycle.

After delivery and during lactation, progesterone levels are very low.

Most circulating progesterone (about 97%) is bound to albumin and other protein carriers such as thyroxine binding protein (TGB) and especially corticosteroid binding globulin (CBG).

Typical progesterone serum levels[3] of adult females and males are shown in table 1.

For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

Table 1: Typical progesterone serum levels

Specimen (serum)	Reference interval (ng/dL)
Cord blood:	8,000 – 56,000
Premature:	84 – 1,360
Prepubertal child (1-10 years):	7 - 52
Puberty	
Tanner stage	
I, Male:	< 10 - 33
Female:	< 10 - 33
II, Male:	< 10 - 33
Female:	< 10 - 55
III, Male:	< 10 - 48
Female:	< 10 - 450
IV, Male:	< 10 - 108
Female:	< 10 – 1,300
V, Male:	21 - 82
Female:	10 - 950
Adult	
Male:	13 - 97
Female	
Follicular:	15 - 70
Luteal:	200 – 2,500
Pregnancy	
7-13 weeks:	1,025 – 4,400
14-37 weeks:	1,950 – 8,250
30-42 weeks:	6,500 – 22,900

Equation for the conversion of units: 1 ng/dL x 0.0318 = nmol/L

Diagnostic utility – prospects and possibilities

Measurement of serum progesterone is a useful tool in determining the cause of infertility, evaluating luteal function and ovulation, and diagnosing ectopic pregnancy or risk of miscarriage. Furthermore, progesterone levels are used to monitor pregnancy and to determine the cause of abnormal uterine bleeding.

Altered progesterone levels can be found in a broad spectrum of disorders, including:

Elevated progesterone levels

- defect in of 17α-hydroxylase and 17,20-desmolase activity (necessary for biosynthesis of steroid hormones from progesterone)

Decreased progesterone levels

- corpus luteum deficiency

- recurrent miscarriage

- infertility (anovulatory cycle, decreased progesterone level in luteal phase)

- defect in the activity of the cholesterol side-chain cleavage enzyme 20,22-desmolase (production of steroid hormones is limited and cholesterol is accumulated)

Diagnostic utility – Practical applications

Progesterone is often measured in conjunction with other hormones (LH, FSH, estradiol) in the evaluation of ovarian function, differential diagnosis of menstrual cycle disorders and amenorrhea, and management of breast carcinoma (in conjunction with progesterone receptor evaluation) [10,11].

Indications for progesterone determination:

In women

Ovulation abnormalities

Absence of ovulation with or without oligomenorrhea

Luteal insufficiency

Exact determination of time of ovulation

Induction of ovulation by hMG (Human Menopausal Gonadotropin) or by clomiphen (both with and without presence of hCG)

Confirmation of ovulation (in the second half of the cycle)

Control of in vitro fertilization process

Observation of ovulation in women with prior spontaneous abortions

Evaluation of ovarian function (together with FSH, AMH and inhibin B)

Extra-uterine pregnancy

Examination of placental and fetal health

In men and children

Defect in steroid biosynthesis

Defect in 20,22-desmolase activity

Defect in 17α-hydroxylase and 17,20-desmolase activity

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