SIX KEY HORMONES IN PREGNANCY

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Introduction

"Who is in charge of the pregnancy? Mother or the fetus?"[1] Pregnancy is a complex endocrinological and immunological process of interaction for the coexistence of two lives. Hormones along with the messengers across the feto-maternal unit influence the exchange of nutrients, metabolites; fetal growth and differentiation as well as the fetal existence in utero

PREGNANCY - A PROGRAMMED PHENOMENON

Endocrinology of pregnancy is distinctly different from the de novo synthesis of hormones in other endocrine organs. Maternal, fetal or placental compartments are inter-dependent in production of final hormonal end products and individually do not possess the necessary enzymatic capabilities.

Endocrine milieu of pregnancy is constituted by various hormones like Human chorionic gonadotropin, Progesterone, Estrogen, Prolactin, Relaxin, Oxytocin, Human placental lactogen, Placental gonadotropin-releasing hormone (GnRH), Corticotropin-releasing hormone (CRH), Thyrotropin-releasing hormone (TRH), Somatostatin, Human growth hormone variant (IGF-I, IGF-II, Platelet-derived growth factor, Fibroblast growth factor, Activin,Inhibin) Thyroid hormones, cytokines and so on. The six key hormones

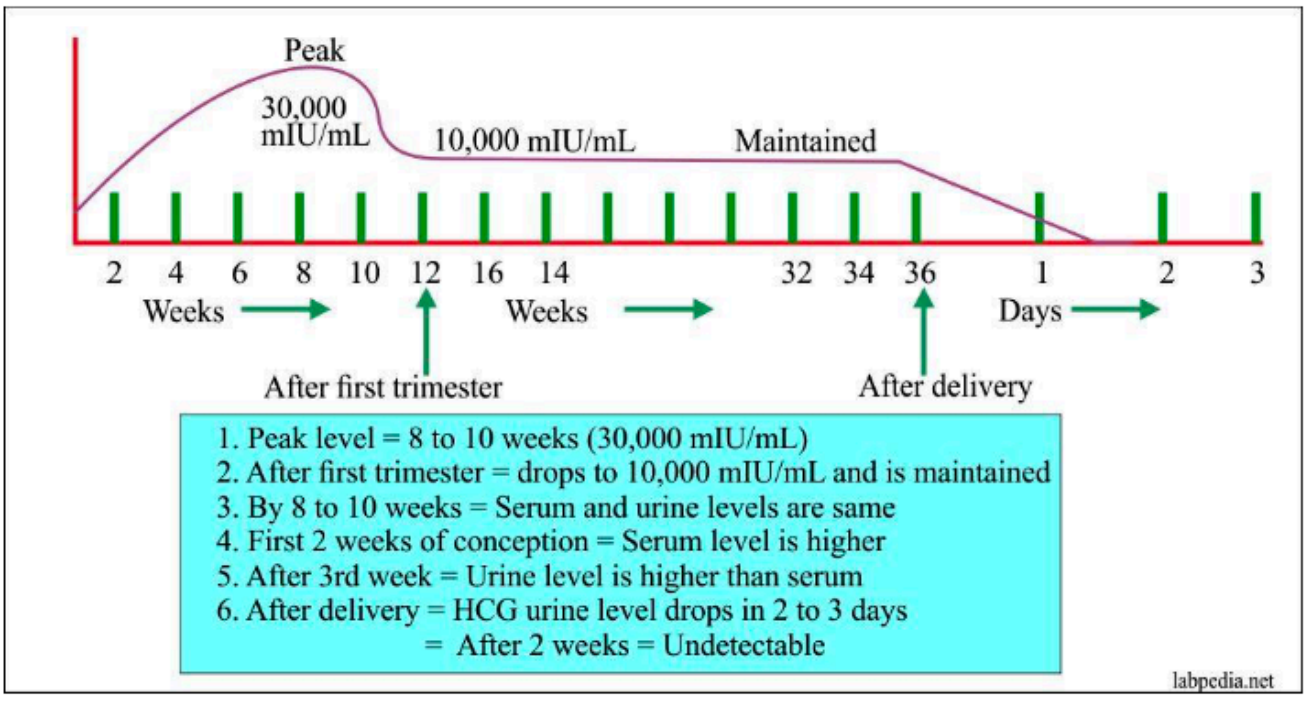
responsible for Pregnancy are Human chorionic gonadotropin (hCG), Progesterone, Estrogen, Prolactin, Relaxin and oxytocin.

SIX KEY HORMONES- ESSENTIAL ROLE

1. Human chorionic gonadotropin (hCG):

Human chorionic gonadotropin (hCG) is a large glycoprotein composed of α and β subunits, of which the α subunit is identical to luteinizing hormone (LH), Follicle stimulating hormone (FSH) and Thyroid stimulating hormone (TSH). Hence, hCG can interact with LH, FSH and TSH receptors. In women, hCG is secreted from the syncytiotrophoblast, the functional cell of the placenta, as early as 7 days of gestation and is thought to be the first placental hormone to act on the mother (Ogueh et al., 2011). Human chorionic gonadotropin (hCG) levels reach a peak between 8 to 10 weeks of gestation and is maintained in a plateau thereafter (Fig 1). In contrast to all other tissues which produces hCG, placenta is different in having the ability to glycosylate the protein, thus reducing its rate of metabolism and giving it biologic activity through a long half-life. The main function of hCG is to support the corpus luteum; it also stimulates steroidogenesis in the early fetal testes, to ensue androgen production and masculine differentiation.

Figure.1 Human chorionic gonadotropin (hCG) levels in pregnancy



2. Progesterone:

Progesterone is produced by the corpus luteum until about 10 weeks of gestation (17α-hydroxy progesterone), while feto-placental unit becomes competent from 10 to 12 weeks gestation. Thereafter, progesterone is produced by the placenta, under the stimulation of Human chorionic gonadotropin (hCG) from developing embryo. Placenta, a way station between the foetus and mother ,gets the precursors of steroid (acetate/ cholesterol/ pregnenolone) ,from either of the duo ,even though in majority from the endocytosis of LDL-Cholesterol in maternal blood ,to circumvent its own deficiencies of enzymes. The levels of progesterone progressively increase to a production rate of 250 mg/day. Amniotic fluid progesterone is maximal between 10 and 20 weeks and decreases thereafter, but in contrast ,myometrial levels of progesterone are 3 times higher than maternal plasma levels in early pregnancy and remains equivalent to plasma levels at term.

Metabolism of progesterone is also mystified in pregnancy. There is a 10-fold rise of 5 α reduced metabolite, 5 α-pregnane-3,20-dione ,which contributes to inherent resistance prevalent in pregnancy against the vasopressor action of angiotensin II.

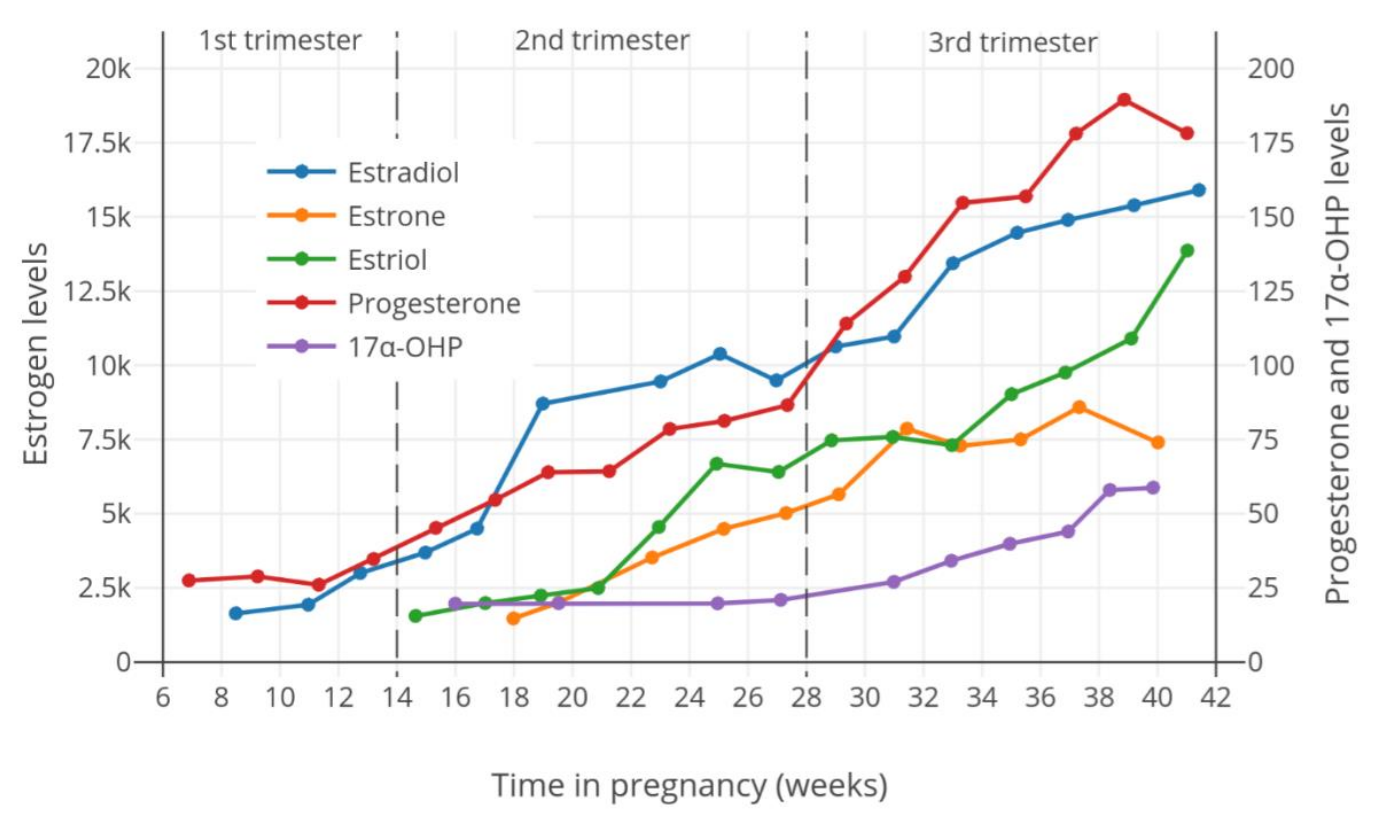
Progesterone not only prepares the endometrium for implantation, but also exerts a multipronged action, in imparting the needed uterine quiescence and fetal survival.It suppresses the maternal immunological response to fetal antigens, preventing maternal rejection of trophoblast.It also serves as a substrate for fetal adrenal gland production of gluco-corticoids and mineralo-corticoids. Progesterone levels continue to be high until birth ,as shown in Figure 2. Commencement of labor is therefore, proposed to be related to a functional withdrawal of progesterone activity in the myometrium of women (Brown A. G. et al., 2004; Norwitz and Caughey, 2011)

3. Estrogen

Estrogen is a mirror of fetal wellbeing. It is under the direct fetal signaling process. Estrogen influences uteroplacental blood flow, mammary gland development, and fetal adrenal gland function. Estrogen to some extent ,controls progesterone production by inducing LDL cholesterol synthesis ,in fetal liver and increasing the

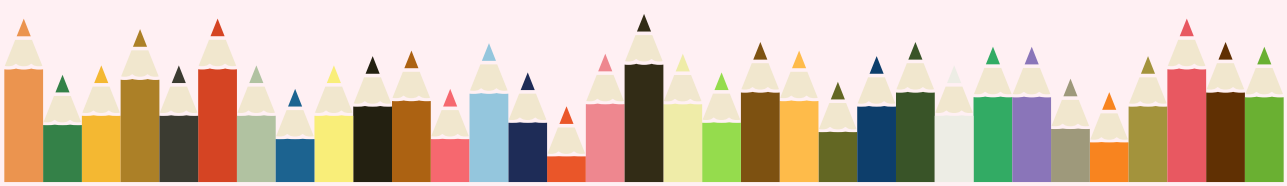
placental P450scc enzyme activity of converting cholesterol to pregnenolone. Like progesterone, estrogen produced by the placental aromatase (P450arom) enzyme system , must depend on maternal circulating androgens and fetal adrenal gland precursors. This is further evidenced by detection of Estriol at 9 weeks , when the fetal adrenal gland secretion of precursor begins. Estriol rises thousand-fold during pregnancy concentrations plateau at 31 to 35 weeks and then increase again at 35 to 36 weeks (Figure 2). Measurement of estrogen in a 24-hour urine collection, a standard hormonal method of assessing fetal well-being , has been replaced by immunoassay of unconjugated estriol in the plasma. Because of its short half-life (5 to 10 minutes) in the maternal circulation, unconjugated estriol has less variation than urinary or total blood estriol.

Figure 2 Oestrogen and progesterone-its subtypes levels in pregnancy



Conditions like fetal anencephaly and fetal demise are found to have estrogen deficiency but lack impact on progesterone production.

Placental sulfatase deficiency in syncytiotrophoblast , is a X-linked metabolic disease characterized by the pre and postnatal ichthyosis, occurring in about 1 in 2,000 to 3,000 newborn males. Patients with the placental sulfatase disorder are unable to hydrolyze DHAS or 16α-hydroxy-DHAS; therefore, the placenta cannot form normal amounts of estrogen. A deficiency in placental sulfatase is usually discovered when patients go beyond term and are found to have extremely low estriol levels and no evidence of fetal distress. The patients usually fail to go into labor and require delivery by cesarean section.



4. Prolactin :

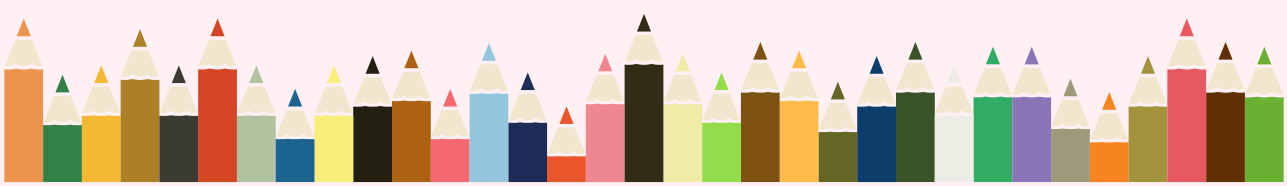
Prolactin is synthesized during a normal menstrual cycle, from decidualized endometrium by day 23. During pregnancy, prolactin secretion is limited to the fetal pituitary, the maternal pituitary and the uterus , under the influence of combined effects of progestin and estrogen hormones plus the presence of other placental and decidual factors, including relaxin, IGF-I, and specific stimulatory and inhibitory proteins. Neither trophoblast nor fetal membranes synthesize prolactin, but both the myometrium and endometrium can produce prolactin. It contributes to the regulation of fetal water and electrolyte balance by acting as an antidiuretic hormone. Amniotic fluid concentrations of prolactin parallel maternal serum concentrations until the tenth week of pregnancy, rise markedly until the 20th week, and then undergo a decrease until delivery. No clinical significance can be attached to maternal and fetal blood levels of prolactin, however, there is an idiopathic uncertain pathognomonic low level in hypertensive pregnancies and polyhydramnios (Luciano AA, Varner MW 1984). Post pregnancy rise in titers of prolactin represents maternal pituitary secretion in response to estrogen, as the fetus prepares the mother for breastfeeding.

5.Relaxin:

Relaxin is a peptide hormone produced by the corpus luteum of pregnancy; It is not detected in men or nonpregnant women. The maternal serum concentration rises during the first trimester , when the corpus luteum is dominant and declines in the second trimester. Exact function of Relaxin is not known , but a decrease in collagen formation, an increase in vasodilation, an increase in vascular endothelial growth factor, and the release of histamine has been shown to be linked to it.

6.Oxytocin :

Oxytocin literally means “quick birth” in Greek. Essentially an absence of significant levels of oxytocin and its receptors is responsible for uterine quiescence. Increase in maternal levels of oxytocin , along with withdrawal of Progesterone, is detected prior to parturition, occurring at first only at night (explaining the more chances of getting into labor at night). Release of oxytocin from the fetal pituitary also proposed to be involved in onset of labor. Oxytocin is implicated in the formation of low-resistance pathways / gap junctions in the myometrium, formed by six special protein pores called connexin. It contributes to parturition , by the stimulation of prostaglandin synthesis in decidua and myometrium and also by imparting Cervical dilation.



SUMMARY

- "Endocrinology of pregnancy" is a unique physiological process of mother co-operated by fetus and placenta.
- HCG is the first and foremost hormone sustaining the corpus luteum, stimulating the steroidogenesis viz progesterone & estrogen in syncytiotrophoblast and androgens in fetal adrenals.
- Prolactin and Oxytocin - "The lactation hormones" from maternal as well as fetal pituitary.
- Prolactin has a role in water and electrolyte balance in fetus by acting as an antidiuretic hormone.
- Relaxin along with Oxytocin, imparts the cervical changes and initiates uterine contractions and is responsible for labor and child birth.

CONCLUSION

There is no doubt that these "Six key hormones make the journey of pregnancy a wonder".

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