Hormonal regulation of perturition

Parturition means birth of the baby. Toward the end of pregnancy, the uterus becomes progressively more excitable, until finally it develops such strong rhythmical contractions that the baby is expelled. The two major categories of effects that lead up to the intense contractions responsible for parturition: (1) progressive hormonal changes that cause increased excitability of the uterine musculature and (2) progressive mechanical changes.

Parturition in most animals results from changes in circulating hormone levels in the maternal and fetal circulations at the end of pregnancy.

Effect of hormones on uterine contractibility:

1. Increased Ratio of Estrogens to Progesterone.
    a. Estrogen-to-progesterone ratio increases sufficiently toward the end of pregnancy to be at least partly responsible for the increased contractility of the uterus.
    b. Estrogens have a definite tendency to increase the degree of uterine contractility, partly because estrogens increase the number of gap junctions between the adjacent uterine smooth muscle cells. Gap junctions are essential for normal labor and delivery for synchronous contraction of the muscle of the uterus. As such Estrogens promote a series of myometrial changes that allow coordinated uterine contractions during labour.
    c. Progesterone is one of the main hormones of pregnancy. It is produced by corpus luteum and later in pregnancy by placental conversion of cholesterol coming from maternal circulation through the activity of two specific enzymes, cytochrome P450 side-chain cleavage (P450scc) and 3beta-hydroxysteroid dehydrogenase (3βHSD).

       Progesterone in-vitro decreases myometrial contractility and inhibits myometrial gap junction formation. Progesterone activity stimulates the uterine NO synthetase, which is

a major factor in uterine quiescence. Progesterone down-regulates prostaglandin production, as well as the development of calcium channels and oxytocin receptors both involved in myometrial contraction. Calcium is necessary for the activation of smooth muscle contraction.

d. Both progesterone and estrogen are secreted in progressively greater quantities throughout most of pregnancy, but from the seventh month onward, estrogen secretion continues to increase while progesterone secretion remains constant or perhaps even decreases slightly. The change to estrogen dominance prepares the uterus for a stronger and more rhythmic response to the process of fetal expulsion.

e. Increased estrogen levels are also important in a general relaxation of the birth canal and dilatation of the cervix and vagina. These latter effects may also be due to the action of relaxin produced by the placenta, uterus and/or the ovary.

   The placenta is the primary source of estrogens, and concentrations of estrogens increase in the maternal circulation with increasing gestational age. Placental estrone and 17β-estradiol are derived primarily from maternal C19 androgens (testosterone and androstenedione), whereas estriol is derived almost exclusively from the fetal C19 estrogen precursor. The human placenta lacks significant amounts of 17-hydroxylase/17–20 lyase, the enzyme needed for the synthetic pathway of estradiol from progesterone. Thus, human placenta relies on dehydroepiandrosterone sulfate (DHEAS) from the fetal and maternal adrenal glands for the supply of precursor for estrogen synthesis The fetal zone of the adrenal gland produces DHEAS, which may be hydroxylated to 16-OH-DHEAS in the fetal liver and then aromatized by the placenta to produce estriol, the major circulating estrogen of human pregnancy.

2. Role of Oxytocin

a. The uterine muscle increases its oxytocin receptors and, therefore, increases its responsiveness to a given dose of oxytocin during the latter few months of pregnancy.

b. The rate of oxytocin secretion by the neurohypophysis is considerably increased at the time of labor.

c. Estrogen increases oxytocin receptor expression and progesterone suppresses such estrogen-induced increase in cultured human myometrial cells. Placental oxytocin acts directly on the myometrium to cause contractions and indirectly by up-regulating prostaglandin production.

d. Additionally, Relaxin is a peptide hormone that is a member of the insulin family. Relaxin consists of A and B peptide chains linked together by two disulfide bonds. Relaxin receptors are present on the human cervix. Circulating relaxin is a product of the corpus luteum of pregnancy, which is present in the ovary for the duration of pregnancy. However, relaxin is also a product of the placenta and decidua and acts locally

   Relaxin is also capable of inhibiting contractions of non-pregnant human myometrial strips. However, relaxin does not inhibit contractions of pregnant human uterine tissue. This may be because of the competitive effects of progesteron.

3. Role of Corticotropin

a. Corticotropin releasing hormone (CRH) is a peptide hormone released by the hypothalamus but is also expressed by placental and chorionic trophoblasts and amnionic and decidual cells. Corticotrophin releasing hormone (CRH) is one of the most prominent neuropeptides involved in parturition, acting on stress induced hormonal, vascular and

inflammatory responses. In fact from second trimester (16thweek onwards), the placenta is the major source of CRH secretion. CRH induces the production of chemokines and cytokines in myometrium at term and subsequently results in the cascade of inflammation. The inflammation induced by CRH can lead to activation of uterine contractility. In fact, CRH stimulates the output of chemokines and pro-inflammatory cytokines in human pregnant myometrium, which could induce chemotaxis of monocytes to myometrium and promote inflammation, confirming that human parturition is an inflammatory event.

b. CRH also enhances prostaglandin production by amnionic, chorionic, and decidual cells.

c. Prostaglandins, in turn, stimulate CRH release from the decidual and fetal membranes. The rise in prostaglandins ultimately results in parturition. They stimulate myometrial contractility and ripen the cervix. There is good evidence that prostaglandins are involved in the final pathway of uterine contractility and parturition.

d. Prostacyclins, inhibitory prostaglandins present throughout early pregnancy, are also responsible for uterine quiescence during pregnancy.

4. Effect of fetal hormones on uterus.

a. The fetus's pituitary gland secretes increasing quantities of oxytocin, which might play a role in exciting the uterus.

b. The fetus's adrenal glands secrete large quantities of cortisol, another possible uterine stimulant. The increased fetal adrenal activity provides additional precursors for an increased estrogen synthesis by the placenta.

c. Also, the fetal membranes release prostaglandins in high concentration at the time of labor. These, too, can increase the intensity of uterine contractions. Increased prostaglandin production by the uterus follows the rise in fetal glucocorticoid production

and can be produced by administration of exogenous glucocorticoids, Prostaglandins may exert an effect on myometrial activity, cause a decrease in progesterone production, effect an oxytocin release and stimulate estrogen production by the placenta.

Finally the fetus is expelled from the uterus. In this process, myometrial contractions resulting from the stimulatory effects of prostaglandins and oxytocin and the abdominal press exerted by the musculature of the abdominal wall combine to bring about the delivery of the fetus or fetuses.

Phases of human perturition

Pregnancy may be considered as consisting of four parturitional phases.

- ✓ The first parturitional phase (phase 0 – quiescent phase) the uterus is kept in a quiescent state through the action of progesterone and other minor factors such as prostacyclin (PGI2), relaxin, parathyroid hormone-related peptide (PTHrP), calcitonin gene-related peptide, vasoactive intestinal peptide and nitric oxide (NO). All these agents act mediate an increased intracellular concentrations of cyclic adenosine monophospate (cAMP) or cyclic guanosine monophospate (cGMP) which inhibit the release of intracellular calcium for myometrial contractility.

- ✓ The second phase (phase 1 – activation phase) of parturition is associated with activation of uterine function. A rise in estrogen and CRH together, possibly, with mechanical stretch may lead to up-regulation of a panel of genes required for contractions. These CAPs include connexin 43, prostaglandin and oxytocin receptors (OTRs). Estrogens do not themselves cause uterine contractions in parturition, but do promote a series of myometrial changes, including increasing the number of prostaglandin receptors, oxytocin receptors, and up-regulating the enzymes responsible for muscle contractions (myosin light chain kinase, calmodulin) that enhance the

capacity of the myometrium to generate contractions. Indeed, estrogens increase connexin 43 synthesis and gap junction formation in the myometrium, allowing for coordinated uterine contractions. Estrogens control also cervical ripening, by the rearrangement and realignment of collagen, elastin, and glycosaminoglycans, mediated by the induction of collagenase and elastase.

- ✓ In the third phase of parturition (phase 2 – stimulation phase), the uterus can be stimulated by uterotonics including prostaglandins, oxytocin and CRH. The biochemical events within the uterus resemble an inflammatory reaction, with increased synthesis of cytokines.

- ✓ The fourth phase of parturition (phase 3 – involution phase) includes the uterine involution that follows the delivery of the fetus and the placenta.

<u>The process in nutshell</u>

uterus must be converted from a quiescent structure with dyssynchronous to

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an active co-ordinately contracting organ with complex interlaced muscular components resulting in regular phasic uterine contractions.

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gap junctions between myometrial cells allow for transmission of the contractile signal.

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fetus may coordinate this switch in myometrial activity through its influence on placental steroid hormone production.

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cervical connective tissue and smooth muscle dilate to allow the passage of the fetus from the uterus. These changes are accompanied by shift from progesterone to estrogen dominance.

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increased myometrial gap junction formation, decreased nitric oxide (NO) activity and increased influx of calcium into myocytes.

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Transformation of uterine myometrium from a state of quiescence to coordinated muscle contraction.

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Trigger for onset of labor and delivery of the fetus.