PARTURITION
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Six to 8 percent of all newborns arrive before term
Half are delivered early because of spontaneous premature labor
Uterus is essentially a relaxed bag of disconnected smooth muscle cells
Cervix kept firm and inflexible by tough collagen fibers
Structural features are maintained by progesterone

As maternal estrogen levels soar, cells of the uterine muscle (the myometrium) synthesize a protein called connexin

Connexin molecules then move to the cell membrane
form junctions that electrically link one muscle cell to another
estrogen also promotes the manufacture of prostaglandins by placental membranes
prostaglandins induce production in the cervix of enzymes that digest its collagen fibers
convert the cervix into a malleable structure
dilate progressively
finally open- response to pressure of fetal
cortisol, ensures that the infant's lungs undergo the final changes required for breathing air

1960s by Graham C. ("Mont") Liggins - National Women's Hospital in Auckland, New Zealand-
Discerned the basic regulatory mechanism in sheep.
The same mechanism operates in most mammals.
Placenta of humans lacks the glucocorticoid-inducible enzyme 17a-hydroxylase-17,20-lyase,
Near the middle of gestation in sheep
Hypothalamus of the developing fetal brain begins to secrete corticotropin-releasing hormone (CRH)

• Pituitary gland secretes adrenocorticotropic (ACTH) into the fetal circulation
• Cortisol activates enzymes in the placenta that convert progesterone to estrogen
• Progesterone in mother's circulation falls
• Estrogen rises
Toward the end of gestation cortisol in the fetus lacks this neg feedback system with ACTH (for reasons that are still unexplained)

Fetal levels of ACTH and cortisol, and hence maternal estrogen levels, rise

Ultimately, the mother's estrogen concentrations become high enough, and the progesterone levels low enough, for parturition to commence.

Humans

Fetal cortisol apparently did help the lungs to mature

Cortisol had no effect on parturition

Did not induce pregnant women to go into labor.

CRH drives fetal cortisol production and placental estrogen manufacture, and thus parturition, in humans as well as in sheep

Most of this CRH in humans comes from the placenta.

In addition, CRH induces placental estrogen secretion through a markedly different pathway than is the case in sheep and in most other non-primate mammals.

1980s. Tamotsu Shibasaki of Tokyo Women's Medical College

Human placenta contained CRH

CRH from the placenta became detectable

Rose sharply in the mother's blood toward the end of pregnancy

then disappeared

Signs that it might serve some role in parturition

Women who went into premature labor - higher blood levels of CRH

CRH values at 16 to 20 weeks of pregnancy roughly predicted when the women would give birth.
Mothers with the highest levels were most likely to deliver prematurely.

Those with the lowest levels were most likely to deliver past their official due dates.

"clock" that was set early in pregnancy.

Controlled the speed with which a pregnancy advanced.

CRH levels vary considerably from woman to woman.

Parturition - different process in people than in sheep.

In the late 1980s Robin S. Goland of Columbia University:

- Levels in baboons go up rapidly early in pregnancy.
- Then drop back to moderately elevated levels.
- Remain constant for the rest of gestation.

Adrenal gland of the primate fetus is different from that of the sheep fetus:

- Primate fetal adrenal has no medulla.
- Two-part cortex, - internal area called the fetal adrenal zone.
- The smaller, outer part of the cortex still produces cortisol.
- Fetal adrenal zone - dehydroepiandrosterone sulfate, or DHEA-S.

Primate placenta lacks the cortisol-responsive enzymes needed to make estrogen from progesterone.

Size of the baboon's fetal adrenal zone:

- Humans and rhesus monkeys peaked near the end of gestation.
- Baboon was largest in midgestation.
- Later zone grew more slowly.
- Disappeared after delivery.
CRH from the placenta was directly or indirectly controlling the secretion of DHEA-S from the baboon’s fetal adrenal zone

Human fetal adrenal tissue contains receptors for CRH

Human fetal adrenal zone cells do indeed respond to CRH by making DHEA-S

CRH, in addition to prompting estrogen production by the placenta
Acts directly on the uterus and cervix
Augments the changes induced by estrogen
Maternally circulating CRH enhances the concentration of prostaglandins in the cervix and thus facilitates its softening.
Strips of human uterine muscle that incubate with CRH can potentiate contractions
Different forms of the CRH receptor can appear on uterine muscle cells
Mix of receptors changes during parturition
Early in pregnancy, receptors that are bound by CRH react by causing intracellular reactions that normally promote the relaxation of muscle cells. Later the receptors on the laboring uterus promote contraction.
Once the placenta begins to release CRH, cortisol can support its continued secretion.
Placental production of CRH, which is made from about the 12th week of gestation
Stimulates the growing fetal adrenal zone to secrete small amounts of DHEA-S

CRH from the placenta, and probably from the fetal brain, signals adrenal gland to secrete some cortisol into the fetal circulation

- Cortisol, further stimulates placental release of CRH, thus forming a "feed-forward" system
- CRH production never shuts down
Critical thresholds of CRH, estrogen, prostaglandins
Uterus and cervix undergo many changes
Labor begins.

Nutrient deprivation can precipitate delivery
- may occur when a fetus grows large
- if the placenta ages

Human Evidence
- pregnant Jewish women -fast of Yom Kippur
- reducing the nutrient supply to their fetuses
- peak in delivery rates that is not observed in non-fasting
- stress of inadequate nutrition activates the fetal stress system
- production of CRH by the hypothalamus in the fetal brain
- CRH boosts ACTH and cortisol levels
- amplify the activity of the entire parturition-inducing circuit.

LABOR = physiologic process by which a fetus is expelled from the uterus

Increase in myometrial activity - switch in the pattern of myometrial contractility
Irregular contractures (long-lasting, low-frequency activity $\rightarrow$ regular contractions (high-intensity, high-frequency activity)
Effacement and dilatation of the uterine cervix
Time-dependent relation between the biochemical changes in the connective tissue in the and cervical dilatation

Labor is a clinical diagnosis

Release from the inhibitory effects of pregnancy on the myometrium
Quiescent myometrial tissue will contract vigorously and spontaneously without added stimuli.
Regulation of uterine contractility - four distinct physiologic phases

Functional quiescence – (phase 0)
- progesterone
- prostacyclin
- relaxin,
- nitric oxide
- parathyroid hormone-related peptide
- corticotropin-releasing hormone
- human placental lactogen
- calcitonin gene-related peptide
- adrenomedullin
- vasoactive intestinal peptide

Activation (phase 1)
- estrogen
- increased expression of contraction-associated proteins
  - including myometrial receptors for prostaglandins and oxytocin
- activation of certain ion channels
- increase in connexin 43 (key component in gap junctions)

Stimulation (phase 2)
- Oxytocin
  - Prostaglandins E\textsubscript{2} and F\textsubscript{2}

Involution (phase 3)
- Oxytocin mediated

The Endocrine Control of Labor at Term
- increase in the synthesis and release of prostaglandins
- increase in the formation of myometrial gap junctions
- activation of myometrial oxytocin receptors

Endocrine, paracrine, and autocrine factors from the fetoplacental unit →
switch in the pattern of myometrial activity
irregular contractures → regular contractions

Fetus coordinates switch
- production of placental steroid hormones
- mechanical distention of the uterus
- secretion of neurohypophysial hormones
stimulators of prostaglandin synthesis

Final common pathway for labor in all species
  • activation of the fetal hypothalamic-pituitary-adrenal axis

PRETERM LABOR

Labor before 37 weeks' gestation
7 to 10 percent of all births
85 percent of all perinatal complications and death

Breakdown in the mechanisms responsible for maintaining uterine quiescence
  • choriodecidual enriched with 15-hydroxyprostaglandin dehydrogenase
  • enzyme responsible for degrading the primary prostaglandins
  • deficiency in choriodecidual 15-hydroxyprostaglandin dehydrogenase activity may impair the ability of the fetal membranes to metabolize the primary prostaglandins, thereby allowing prostaglandin E<sub>2</sub> to reach the myometrium and initiate contractions.

Short-circuiting or overwhelming of the normal parturition cascade
  • intrauterine environment became hostile
  • threatened the well-being of the fetus
  • 30 percent of preterm labors result from intra-amniotic infection
  • lipoxygenase and cyclooxygenase pathways are elevated
    o increased levels of cytokines
    o interleukin-1/3
    o interleukin-6
    o tumor necrosis factor α

*Thrombin* has been shown to be a powerful uterotonic agent
  • preterm labor due to placental abruption

Predictive Factors

Risk factors
  • previous preterm delivery
  • multiple gestation
  • uterine anomalies
  • Hydramnios
  • infection
  • smoking
• demographic variables
  • very young
  • older maternal age
  • black race
  • low weight before pregnancy
  • low socioeconomic status

50% of women who deliver prematurely have NO RISK FACTORS

increase in uterine activity is a prerequisite for preterm labor
Home monitoring of uterine activity in women at high risk does not reduce preterm delivery.
Serial digital evaluation of the cervix is useful if the results are normal
Abnormal cervical finding is associated with preterm delivery
4 percent of women at low risk
12 to 20 percent of those at high risk

Cervical length below the 10th percentile for gestational age - six times as likely to give birth before 35 weeks

Vaginal infections
• bacterial vaginosis
• Neisseria gonorrhoeae
• Chlamydia trachomatis
• group B streptococcus
• Ureaplasma urealyticum
• Trichomonas vaginalis

Biochemical markers of premature delivery
• activin
• inhibin
• follistatin
• fibronectin
• collagenase
• tissue inhibitors of metalloproteinases
Fetal fibronectin in cervicovaginal secretions
May reflect separation of the fetal membranes from the maternal decidua

Endocrine assays
• decrease in maternal serum progesterone cannot be used to identify women at risk
• maternal serum estriol levels accurately reflect activation of the fetal hypothalamic-pituitary-adrenal axis
• Salivary estriol levels mirror the level of biologically active (unconjugated) estriol in the circulation

  elevated levels of estriol in maternal saliva is predictive of delivery before 37 weeks