HORMONAL CONTROL OF MAMMARY GLAND GROWTH

Suporn Katawatin
Technical Terms

- **Mammogenesis**: Growth and morphological development of the mammary gland.
- **Lactogenesis**: Last stages of biochemical and structural differentiation of the alveolar epithelial cells during the periparturient period, required for onset of copious milk secretion.
- **Galactopoiesis**: Maintenance of lactation.
- Development of the mammary gland is a by-product of reproduction
- Hormones responsible for mammary growth are the same hormones responsible for reproduction

Further reading: RegulatorsMammaryFunction
Figure 3. Location of the major endocrine glands of the cow.
Evidences on ovarian support of mammary development

Ovariectomy:

- regress mammary gland during pregnancy but not during lactation
- stops allomettric growth; gland returns to isometric growth pattern
- implicates pituitary-ovary-mammary gland relationship
Ovariectomy + hormone (in ruminant):

- $E_2$ primarily responsible for mammary duct development
- $P_4$ primarily responsible for lobulo-alveolar development; cattle must have a functional CL
- $E_2 + P_4$ synergistic on mammary growth (not comparable to growth resulting from pregnancy)
Exogenous hormones

- $E_2$ elicits
  - extensive duct growth and considerable lobulo-alveolar growth
  - but abnormality do occur: cystic alveoli, folded epithelium, immature lobules, deficiency of alveolar surface

- $P_4$ eliminates abnormalities,
  - increases alveolar surface
  - increases amount of parenchyma
  - increases ensuing milk yields
Steroid hormones on mammogenesis & lactogenesis

- sources
- action
Estrogens: follicle, placenta, adrenal cortex

- stimulate PRL release & duct growth
- synergizes with PRL + P₄ to stimulate protein synthesis & duct growth (greater than separately)
**Progesterone: corpus luteum, placenta, adrenal cortex**

- synergizes with $E_2 + \text{PRL}$ stimulates lobulo-alveolar growth
- retards milk synthesis
  - prevents synthesis and accumulation of enzymes ($\alpha$-lactalbumin) necessary for lactogenesis in prepartum gland
  - but does not interfere to same extent during lactation
- $P_4 + \text{PRL}$ stimulates aa incorporation into protein
Mammogenesis

- Placental $E_2$ + Luteal $P_4$
  - Duct development
  - Lobulo-alveolar development
  - Suppression of milk synthesis
**Glucocorticoids:** cortisol; adrenal cortex

- Stimulated by maternal, fetal ACTH
- Receptors on mammary cells
- Essential to lactogenesis (as seen adrenalectomized females no lactation)
- Cortisol potentiates prolactin on mammary epithelial cell (lactogenic)
**action of cortisol:**

- cortisol synergizes with prolactin
  - cause differentiation of epithelial cells
  - stimulate protein synthesis:
    - increase prolactin receptor synthesis
    - increase casein synthesis
- permissive to action of prolactin
- $P_4$ binds to corticoid receptors: thus antagonistic

- BUT, milk fat globule sequesters $P_4$ during lactation!
  (thus allowing action cortisol/PRL)
Lactogenesis = initiation of milk synthesis

- initiated in $E_2$ primed mammary gland when $P_4$ is removed
  - corpus luteum regresses & $P_4$ declines
  - cortisol increases
  - PRL, GH increase
- cortisol synergizes with PRL stimulate PRL receptors
  - synthesis
- these circumstances occur at parturition
Lactogenesis: when $P_4$ present

- $P_4$ inhibits full synthesis of $\alpha$-lactalbumin, casein mRNA, casein
- $P_4$ prevents induction of prolactin receptors
- $P_4$ blocks cortisol receptors
- Thus, $P_4$ retards milk synthesis in non-lactating

$P_4$ drops rapidly just prior to parturition
Lactogenesis: changes when \( P_4 \) declining

- increased cortisol binding to mammary cells
- increased induction of prolactin receptors
- Increased \( \alpha \)-lactalbumin, casein and enzyme synthesis
- Results in increased lactose and protein synthesis
- Thus, increase milk synthesis

- During lactation, \( P_4 \) elevated again but \( P_4 \) has high affinity for milk lipid, and much of it will be seized in milk fat globule
Hormones & lactogenesis

- Maintenance of elevated serum $P_4$ and receptors in epithelial cells during gestation serve to prevent premature onset of milk component biosynthesis.
- As parturition approaches, $P_4$ decrease with a consequent reduction in inhibition.
- During the same interval, enhanced secretion of $E_2$
  - increase PRL receptors in mammary gland
  - PRL and glucocorticoid concentrations increase
- Thus, lactogenesis relies on increasing positive stimulation and removal inhibition.
Lactogenesis: at parturition

- PGF$_{2\alpha}$ increase
- corpus luteum regresses
- $P_4$ declines
- fetal, maternal cortisol increase
- PRL, GH increase
- $\alpha$-lactalbumin, casein synthesis increase
- lactose synthesis increases > milk synthesis
Mammogenesis/ Lactogenesis

- Endocrine of mammogenesis/ lactogenesis:
  - $E_2$ (placenta, ovary) $\rightarrow$ mammary duct growth
  - $P_4$ (CL, placenta) $\rightarrow$ alveolar differentiation
  - cortisol (adrenal cortex) + PRL (ant. pit.) $\rightarrow$ protein synthesis + $\alpha$-lactalbumin (RER)
    - $\alpha$-lactalbumin $\rightarrow$ lactose synthesis (golgi apparatus)
Lactogenesis/Lactation

- During established lactation:
  - $P_4$ increase again during luteal phase
  - $P_4$ increase upon conception

BUT
- $P_4$ has high affinity for milk fat globule
  - thus $P_4$ will be seized by milk fat & exported from cell
  - cortisol will be free to bind to cell

- milk synthesis function
Lactogenesis/ Lactation

- Open heifers & Lactating cows:
  - P₄ & E₂ secretion are asynchronous

- กราฟประกอบ แสดงฮอร์โมน
Lactogenesis/ Lactation

- Pregnant heifers & Pregnant lactating cows:
  - $P_4$ & $E_2$ secretion is synchronous
  - $P_4$ is seized by milk fat globule until lactation ends (dry period)
Cyclic hormonal of estrous cycle on mammary function

- **Proestrus & Estrus:**
  - Estrogen increases:
    - mitotic activity increases
    - duct growth increases
- **Metestrus & Diestrus:**
  - Progesterone increases:
    - some alveolar differentiation occurs

During estrous cycle, E₂ and P₄ secretion is asynchronous; thus very little mammary development occurs.
Cyclic hormonal of estrous cycle on mammary function (cont.)

- Prior to pregnancy:
  - Majority of tissue is adipose; some ducts
  - No true functioning alveoli
    - Alveolar development requires simultaneous $E_2 + P_4$
Mammary gland changes during Pregnancy

- **1st & 2nd trimester:**
  - duct proliferation
  - development of gland cistern

- **2nd trimester:**
  - secretory tissue develops and replaces adipose tissue
  - end buds form
  - alveoli differentiate
  - lobules, lobes; connective tissue support develops
  - tissue DNA increases (25%)
  - vascular and lymph vessels proliferate

- **3rd trimester: (near 9th month)**
  - mammary cell secretory activity initiated
  - cellular membranes proliferate
  - cellular lipid and secretory granules become evident
  - mammary gland begins to become distended
Fig. 30-2. A simplified diagram showing the action of hormones on mammary growth and lactation. In the diagram of the gland: upper—rudimentary gland; right—prepuberal to puberal gland; lower—prolactational gland of pregnancy; left—lactating gland. From Lyons, Li, and Johnson: Rec. Prog. Horm. Res., 14, 1958.