Ovarian and Uterine changes in relation to estrous cycle

Corbon G David
Estrous Cycle

- **Length of the estrous cycle**
  - Average 21 days (range 18 to 24 days)

- **Estrus (standing heat)**
  - 12 to 18 hours (range 8 to 30 hours)

- **Ovulation**
  - Approximately 30 hours after the beginning of standing heat (or 12 to 18 hours after the end of standing heat)
Phases of estrous cycle

- Proestrus
- Estrus  Follicular phase
          (3-4 days)  Progesterone
- Metestrus
- Diestrous  Luteal phase
           (1-17 days)  Estradiol
Estrous Cycle

- Major structures on the ovary are ...
  - Follicle ... a blister-like structure containing the egg (referred to as oocyte); produces hormone "estrogen"
    - High amount of estrogen causes "standing heat" and "ovulation"
  - Corpus luteum (referred to as "CL") ... looks like a hard yellow structure and produces hormone "progesterone" that is responsible for maintenance of pregnancy
Follicular Progression

- Primordial
- Primary
- Secondary
- Tertiary
Fate of follicles and oocytes.

<table>
<thead>
<tr>
<th>Age</th>
<th>Total # of follicles</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>100,000</td>
</tr>
<tr>
<td>12 months</td>
<td>75,000</td>
</tr>
<tr>
<td>4-6 years</td>
<td>21,000</td>
</tr>
<tr>
<td>Aged cow</td>
<td>2,500</td>
</tr>
</tbody>
</table>

Follicles grow to tertiary characteristic and degenerate.

Maximum number of oocytes ovulated for a cow

17 cycles/year x 8 year = 136 oocytes ovulated/lifespan

Can increase with superovulation with FSH to stimulate the rescue of follicles which would have undergone atresia.
Initial Follicular Growth

- Small Antral Follicle
- FSH
- Recruitment

Gonadotropin Independent

50 - 60 days
Gonadotropin Action Within the Follicle
Antral Follicle

- Granulosa
- Theca Internal
Theca Interna

Selection

Dominant Follicle Express LH Receptor

Granulosa

Testosterone

Cyclooxygenase

Cholesterol

LH

Receptor

cAMP

PKA

FSH

Receptor

Estradiol

Testosterone

PKA

cAMP
Oogenesis

Initiation of Meiosis
- Interphase
- DNA synthesis
- Meiotic prophase begins

Migration to germinal ridge
Mitotic divisions

Gonadotropin Independent

Gonadotropin Dependent

Primordial Germ Cells

Follicle Cells

Prophase of Meiosis
- leptotene
- zygotene
- pachytene
- diplotene
- dictyotene
- Meiotic Arrest

Meiotic prophase begins

Interphase

DNA synthesis

Mitotic divisions

Primary Oocyte

Growth

Migration to germinal ridge

Gonadotropin Independent

Gonadotropin Dependent

zona pellucida formation
mRNA production
protein synthesis
cortical granule formation

nuclear maturation
cytoplasmic maturation
Formation of the Zona Pellucida

Corona Radiata

Zona Pellucida

Oocyte
Corona Radiata  Zona Pellucida  Oocyte

Gap Junctions
During Oocyte Growth and Before the LH Surge

- OMI - Oocyte Maturation Inhibitor
- MPF - Maturation promoting factor
- GV - germinal vesicle (nucleus)

Gap Junctions Allow Cell to Cell Communication!
The LH Surge

Resumption of Meiosis

Gap Junctions are Destroyed!
LH Surge → Resumption of Meiosis → First polar body emitted, arrest at metaphase II of meiosis

Primary Oocyte
- Ovulation
  - Dog
  - Fox

Spermatogenesis

Secondary Oocyte
- Ovulation
  (most species)

Zygote (pronucleate egg)
Follicle Development
Hormonal Production by Follicles

- Recruitment: Estradiol
- Selection: Estradiol, Inhibin
- Dominant: Estradiol, Inhibin
- Atretic: Androgen or No steroid
Hypothalamo-hypophyseal ovarian axis

Hypothalamus

GnRH

Anterior Pituitary

LH, FSH

CL

Progesterone (-)

Estradiol

LH, FSH

Inhibin (-)

Estradiol

Ovary

Follicle

Hypothalamo- hypophyseal ovarian axis
Hypothalamo-hypophyseal ovarian axis

- Hypothalamus
  - GnRH
  - LH, FSH
  - Inhibin
- Anterior Pituitary
  - LH, FSH
  - CL
- Ovary
  - Estradiol (+)
  - Progesterone (-)
- Follicle
  - Estradiol

**Hypothalamo-hypophyseal ovarian axis**
Species Variation in Follicular Waves

- Cattle - 2 or 3 / cycle
- Sheep - 4 or 5 / cycle
- Pigs - 1 / cycle
- Horses - 1 / cycle
- Human - 1 / cycle

Cl-progesterone, inhibin
Follicle development occurs as a wave-like pattern consisting of “Recruitment”, “Selection”, “Growth”, “Dominance”, and “Regression” phases.

Usually 2 to 4 follicular waves occur during the estrous cycle in cattle.
Follicle Development
Follicle Stimulating Hormone (FSH)

- FSH precedes recruitment of follicles (causes follicles to start growing)
- FSH is the same hormone used for superovulation and embryo transfer in cattle
Follicle Development
Luteinizing Hormone (LH)

- Growth
- Selection
- Dominance
- Regression

- LH promotes further follicle growth and maturation of egg

LH pulses
LH stimulates follicle growth and a growing follicle produces high levels of estrogen.

High levels of estrogen, in turn, cause estrus and surge release of LH that triggers ovulation.
Length of the estrous cycle in cattle with 3 follicular waves is typically 20 to 24 days.
Length of the estrous cycle in cattle with 2 follicular waves is typically 18 to 20 days, slightly shorter than the estrous cycle with 3 follicular waves.
Endocrinology During the Estrous Cycle
Follicle Stimulating Hormone (FSH)

Example shown for cattle having 3 follicular waves during a 21-day estrous cycle.
Example shown for cattle having 3 follicular waves during a 21-day estrous cycle
Example shown for cattle having 3 follicular waves during a 21-day estrous cycle.
The estrus cycle of the cow (Senger, 2003)
Ovulation
Preovulatory LH Surge

- Cumulus Expansion
- Increased Blood Flow to Ovary and Follicle
- Protein Synthesis in and around Follicle
- Progesterone
- Plasminogen Activator
- Prostaglandin Synthesis
- PGE and PGF
- Plasmin
- Plasminogen
- Contraction of Smooth Muscle
- Oocyte Separates From Follicular Wall

- Collagenase (inactive)
- Collagenase (active)
- Follicular Wall Weakens

- Ovulation
Luteal Tissue

Large cells from granulosa cells

Small cells from theca interna
Corpus Luteum Formation: Luteinization

- Luteinization in the process that transforms the granulosa and theca cells into luteal cells.
- This process is triggered by the surge of LH at mid-cycle.
- The LH surge causes profound changes in the follicles that become corpora lutea.
Preovulatory Follicle

- steroid synthesis
  - progesterone
- collagenase
- theca interna
- present 1-3 days following ovulation
- blood vessels in follicle wall rupture
- walls collapse
- cells intermix
- old basement membrane becomes connective tissue of CL
- increases in size
  - papilla forms
- composed of cells from the granulosa and theca interna
- progesterone production increases
- a small cavity may be present where the follicular antrum was present
Steroidogenesis Before LH Surge

A: Antrum; GL: Granulosas; BM: Basement Memb
TI: Theca Int. TE: T Ext.; C: Capillaries

Ch: Cholesterol; P: Progesterone; A<sub>2</sub>: Endrogen; E<sub>2</sub>: Estradiol
Luteal Steroidogenesis

Ch: Cholesterol; P: Progesterone; A₂: Androgen; E₂: Estradiol
Corpus luteum develops from the ovulated follicle and takes approximately 10 days to reach mature size.
Corpus Luteum (CL) Progesterone

- Corpus luteum produces progesterone
- Progesterone is responsible for maintenance of pregnancy after conception occurs
Late in the estrous cycle, uterus produces PG which causes regression of corpus luteum.

PG is the same or similar hormone in “Lutalyse®”, “Estrumate®”, “ProstaMate®”, and “In Synch®”
Corpus Luteum (CL) Maintenance

When cow becomes pregnant ...

- Presence of embryo blocks uterus to produce PG late in the estrous cycle which causes maintenance of corpus luteum and production of progesterone for pregnancy.
Progesterone regulates LH Pulses
Luteinizing Hormone (LH)

- Progesterone regulates secretion pattern of LH pulses and hence, follicular development
Endocrinology of the Estrous Cycle

Relationships among estrogen, progesterone, and PG during the 21-day estrous cycle
Luteolysis
Luteolysis

- Luteolysis is the process by which the corpus luteum loses its capacity to synthesize and secrete progesterone.

- A luteolytic agent is any factor that can reduce luteal progesterone synthesis or secretion and/or prevent the action of a luteotrophic hormone.
Uterus-Ovary Connection

Prostaglandin synthesis by uterine endometrium is released into the uterine vein.

PGF is picked up by the ovarian artery and delivered back to the ovary where it causes lysis of the corpus luteum.
PGF2α action on CL

Ischemia (decreased blood flow to CL) - not complete Capillary degeneration

Vascular disruption - plays a role

Cellular mechanisms of PGF2α action

Activates protein kinase C to inhibit progesterone synthesis

Stimulates apoptosis

Causes an increase in intracellular calcium
Mechanism of Luteolytic Action of PGF$_{2\alpha}$

Pate & Keyes 2001
The immune system and luteolysis

Macrophages and lymphocytes are present in the CL and increase in number during luteolysis

Function:
These cells undergo phagocytosis of dying luteal cells

Cytokines are released by these cells and may cause cell death

May have a negative effect on progesterone production

May stimulate apoptosis of luteal cells
Uterine changes

• Endometrium
  – Ovarian hormones
  – Luminal fluid
    • Secretory cells
    • Volume, viscosity, concentration varies
    • Reproductive success
    • Environment for spermatozoa, ova and zygote survival

• Uterine fluid composition
  • DM-12%
  • Ash-0.5%
  • Protein – 10%
  • No glucose
  – Luteal stage – low Na
  – Oestrus – high Ca
  – Stage specific proteins
    • Maintain uterine environment
    • Deficiency – prenatal mortality
• Uterine luminal proteins
  – Molecular weight:
    • mostly small 15 to 70KDa
    • Few large proteins 600KDa to 1000KDa
  – concentration
    • Varies with stage of oestrus and pregnancy
    • High—d14,16 and 19 and just before rapid elongation of embryo
    • Lower - d4,8 and 12
  – Uterine specific proteins <2% of total uterine protein
Thank You