Ovarian Cysts
A Review of Human Polycystic Ovarian Syndrome and Other Species as Models

Beth Spizziri
Christianne Magee

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Ovarian Cysts: Species

- Human: Polycystic Ovary Syndrome
- Canine
- Bovine
- Induced Ovulators: Camelid, Felid
- Inducible Models PCOS
  - *Rattus norvegicus*
  - Rhesus Monkey
  - Ewe
Polycystic Ovarian Syndrome

- Heterogenous condition characterized by
  - LH hypersecretion
  - Ovarian hyperandrogenism
  - Hyperinsulinemia
  - Reduced fertility

- Prevalence ~ 6.8%

- Metabolic and reproductive endocrine disorder

Diamanti-Kandarakis 2006
Common names and confused with…

- Stein-Leventhal Syndrome
- Polycystic ovary disease
- Functional ovarian hyperandrogenism
- Hyperandrogenic chronic chronic anovulation
- Ovarian dysmetabolic syndrome
- Polycystic ovarian syndrome
PCOS: History

- **1721**
  - Antonio Vallisneri
  - “...Young peasant woman, married, moderately plump, infertile, with ovaries larger than normal, like doves’ eggs, lumpy, shiny and whitish”

- **1935**
  - Dr. Irving Stein and Dr. Michael Leventhal
  - Coined Stein-Leventhal disorder

- **1980**
  - Linked to hyperinsulinemia and impaired glucose tolerance

- **2006**
  - What causes PCOS?
PCOS: Diagnostic Criteria

- Two of three clinical features as of 2003
  - Oligo- or anovulation
  - Clinical or biochemical signs of hyperandrogenism
  - Polycystic ovaries on u/s w/o other etiologies

- Other concurrent manifestations
  - Insulin resistance
  - Features of metabolic syndrome
  - Increased risk for diabetes mellitus II, cardiovascular disease, endometrial bleeding or cancer

Milnar et al. 2006
Carmina 2006
Clinical Signs: Anything

- Oligomenorrhea or Amenorrhea
- Anovulation
- Elevated Androgens
- Enlarged ovaries
- Hyperinsulinemic Insulin Resistance
- Dermatologic abnormalities
- Obesity
- Chronic pelvic pain
- Sleep apnea
Secondary Clinical Complications

Metabolic Syndrome – Essah 2006

- 43% increase MS regardless of body weight

Insulin resistance

- Type II diabetes
  - 5x increase risk

Cardiovascular disease

- 2x increase risk
- High cholesterol
- High blood pressure

Wikipedia 2006, Natl Womens Health 2004
Physical Examination

- Vaginal ultrasound

- Cysts
  - 2-8 millimeter diameter
  - Often a “string of pearls”
  - Enlarged ovary

- Thickened endometrium
  - Lack of menses
Blood Test Diagnosis

- ↑ Testosterone
- ↑ DHEA
- ↑ Androstenedione
- ↑ Prolactin
- ↓ Progesterone

- LH:FSH
  - 3:1 instead of 1:1

- Thyroid-Stimulating hormone (TSH)
- Fasting glucose
- Triglycerides
- Cholesterol
Is this PCOS?

- Hypothalamic Pituitary Gonadal or Adrenal Dysfunction
  - Excessive Cortisol
    - Cushing’s disease
    - Congenital adrenal hyperplasia
  - Hyperprolactinemia

- Thyroid dysfunction
  - Increased TSH
Insulin Receptor: Mechanism

In the context of the diagram, the insulin receptor is shown with various modifications and interactions. Key components include:

- **IRS-1** and **IRS-2** proteins connected to the receptor.
- **ATP** interaction with the receptor.
- Phosphorylation sites indicated by **P** for **Tyr** and **Ser**.

This mechanism illustrates how insulin binding to the receptor can lead to phosphorylation and subsequent signaling events.
Genetic Factors

- Difficult to study
  - Heterogeneous phenotypes
  - Lack of universal definition
  - Family tree mapping extremely difficult

- Chromosome 19
  - Near insulin receptor (VNTR)
  - TII D insulin resistance

- Postulated genes
  - CYP17A - encodes for P450c17α enzyme
  - CYP11A - insulin gene
  - Tandem repeats of insulin gene (INS VNTR)

Dunaif 2006, Franks 2006
Treatment Plans

➢ What are your goals?

- Treat short-term problems?
- Prevent long-term risks?
- Pregnancy?
- Have other options failed?
Treatment

➤ Short-term management
  • Infertility
  • Hirsutism
  • Acne
  • Obesity
  • Miscarriage
Treatment

- Long-term management
  - Cardiovascular risks
    - Obesity
    - Cholesterol
    - Diabetes
    - High blood pressure
  - Endometrial Cancer
Treatment

- Counseling
  - Healthy diet
  - Regular exercise
  - Weight loss
Treatment

- Weight loss
- Oral Contraceptives
- Diabetes Medication
- Hirsutism Medication
- IVF
- Surgery
  - Laparoscopic Ovarian Drilling
Oral Contraceptives

- **Combined-Oral Contraceptive (COC)**
  - Decrease Androgen production
  - Break continuous estrogen
  - Decrease risk of endometrial cancer
  - Corrects abnormal bleeding

- **Progesterone**
  - 10-14 days a month
  - Regulates menstrual cycle
  - Prevents endometrial cancer
  - Does not improve androgen levels
Diabetes Medication

**Metformin (Glucophage, Glucophage XR)**

- Type II Diabetes Medication
- Treats insulin resistance
- Improves ovulation
- May reduce androgen production
  - even in non-obese women

Does it prevent endometrial cancer?
Is it safe for pregnant women?

Mayo Clinic 2006
Nestler and Jakubowicz 1997
Hirsutism Medication

- **Spironolactone (Aldactone)**
  - Blocks androgen effects
  - Reduces androgen production
  - **Problems**
    - Diuretic
    - Heartburn
    - Headache
    - Fatigue

- Prescription topical cream
Fertility Treatment

- Achieving Pregnancy
  - Clomiphene Citrate
  - Laparoscopic ovarian drilling (LOD)
  - IVF
Clomiphene Citrate

- Clomid or Serophene
  - Anti-estrogen medication
  - First five days of menstrual cycle
  - 70% ovulation rate
  - 30% conceive within 3 months

If ovulation doesn’t occur, it must be taken with Metformin

Mayo Clinic 2006
Laparoscopic Ovarian Drilling

- Lasers burn holes in enlarged follicles
- Stimulates ovulation by reducing LH and androgen hormones
Surgery Complications

- Scar tissue
- Lasts a few months
- 80% ovulation rate
- 50% pregnancy rate
- Only used if failed previous treatments
Contemporary Medical Therapy

- Statin Medication + COCs
  - Lowered testosterone levels
  - Normalized gonadotropin levels

Lanham 2006
Pregnancy Complications

- Gestational diabetes
  - Obesity
  - Insulin resistance
  - Birth defects

- Pregnancy-induced hypertension
  - Women over 40
  - Obese
  - Insulin resistance

- Premature delivery
Miscarriage

- Controversial

- Increase in PAI-I
  - Fibrinolysis inactivator
  - Placental insufficiencies

- Elevated serum LH levels

- Hyperinsulinemia

IVF 2006, Hart 2006
PCOS at Menopause

- **Theory**
  - Ovarian function changes
  - Menstrual cycle normalizes
  - Hirsutism continues
  - Male pattern baldness

- **Limited Data**
  - Persistent metabolic abnormalities
  - Cardiovascular Disease

Margolin 2005, Natl Womens Health 2004
Ovarian Cysts: Other Species and Models for PCOS

- Canine
- Bovine
- Induced Ovulators: Camelid, Felid
- Inducible Models PCOS
  - *Rattus norvegicus*
  - Rhesus Monkey
  - Ewe
Canine Ovarian Cysts

- Follicular (including atretic follicles)
- Luteal
- Germinal
- Corpora lutea
- Rete ovarii
- Granulosa cell tumors
- Paraovarian cysts

Johnston 2001
Bitch: Follicular Cysts

- Unknown pathogenesis
- Lined with granulosa cells, degenerate cumulus, rarely luteal cells, never oocyte
- Elevated estrogen
- Treatment - induction of OV or OHE

Johnston 2001
Bitch: Other Ovarian Cysts

- **Luteal Cysts - 9%**
  - Luteinized anovulatory follicles
  - Insufficient LH for ovulation
  - Unknown clinical significance

- **Germinal Cysts - 20-38%**
  - Microscopic cystic structures within ovarian cortex and do not impair ovarian function

Johnston 2001
Bitch: Other Ovarian Cysts

- **Rete Cysts - 9-35%**
  - Irregular anastomosing tubules with cystic changes in the hilar region of the ovary
  - No clinical disease, but replace normal tissue

- **Parovarian cysts**
  - Remnants of the para-/mesonephric tubules
  - Do not impair ovarian function

- **Cystic Corpora Lutea - rare**

Johnston 2001
Ovarian Cysts: Bovine

- Anovulatory fluid filled structures >25mm diameter for > 10 days

Economic importance

- Primarily dairy cows
- Affect >1 million dairy cows USA/year
  - 10-28% in some herds
- Extended calving intervals = economic loss and reproductive dysfunction

NDSU Extension 2000
Sakaguchi et al. 2006
Coleman WVU Extension 2006
Ovarian Cysts: Bovine

- Follicular – thin walled, >25 mm
  - Follicular Cysts
    - Persists for >10 days in the absence of a CL
    - No hormone secretion, no response to GnRH, PGF2α
  - Cystic Follicle
    - Regressed or ovulated within 10 days
    - Secretes estradiol, luteinizes with GnRH, no response to PGF2α

NDSU Extension 2000
Sakaguchi et al. 2006
Ovarian Cysts: Bovine

- Luteal Cysts – thick walled, >25mm
  - Secretion of progesterone
  - Probably luteinization of follicular cysts
  - Can be confused with a normal CL containing a fluid filled cavity
  - Prevent return to estrus by suppressing LH
  - Responds to PGF2α
Ovarian Cysts: Bovine

Risk Factors

- Heredity, recurrence, repeatability vary\textsuperscript{1,3}
- Increased milk production\textsuperscript{1,2,3}
- Estrogen content in feeds
  - Zearalenone mycoestrogen from Fusarium spp in moldy feed effecting swine\textsuperscript{1}

\textsuperscript{1}NDSU Extension 2000
\textsuperscript{2}Sakaguchi \textit{et al.} 2006
\textsuperscript{3}Coleman WVU Extension 2006
Ovarian Cysts: Bovine

Nutrition

- Increased Body Condition at dry off 2.5X increase, but potentially not at calving
- Ketone concentrations in milk
- Vitamin Deficiencies

- IGF-1
  - Positive correlation between IGF-1 and steroidogenic capacity of first postpartum dominant follicle
  - IGF-1 increases the number of LH binding sites in bovine thecal cells and it changes LH induced production of progesterone and androstenedione

1NDSU Extension 2000
2Spicer and Stewart 1996
Ovarian Cysts: Bovine

➢ Treatment and Outcome
  • 30-71% may resolve without treatment\(^1,3\)
  
  • Anovulatory waves early post-partum may be beneficial for overall fertility\(^2\)
  
  • Treatment with GnRH at the first palpation, followed by PGF2α 7-10 days later should lead to a resumption of cyclicity within 23 days\(^3\)

\(^1\)NDSU Extension 2000  
\(^2\)Sakaguchi et al. 2006  
\(^3\)Coleman WVU Extension 2006
Ovarian Cysts: Induced Ovulators

- **Camelids**
  - Follicular, luteal, cystic CL, hemorrhagic cysts
  - 30-40% develop follicular cysts if not bred
  - Luteal cysts $2^0$ to follicular cysts

- **Queen**
  - Follicular cysts, incidence increases with age
  - Rete cysts

1Tibary 2000
2Johnston 2001
Modeling for Ovarian Cysts: 
*Rattus norvegicus*

- **Hormonal therapies**
  - Estrogens
  - Androgens
  - Neonatal androgenization

- **Environmental changes**
  - Continuous light induces POS within 13 weeks, but reversible

Salvetti 2004
Rattus norvegicus

Ovarian histology of a rat after being exposed during 15 weeks to permanent light. There are clear cystic follicles and luteal tissue is absent. (BAR=1mm)

Salvetti 2004
Modeling for Ovarian Cysts: Neonatal androgenization

- Rhesus monkey\textsuperscript{1,2} and ewes\textsuperscript{3,4}

- Mechanism
  - Testosterone injections coincide with developmental periods critical for reproductive and metabolic homeostasis
  - Link between Growth Hormone and IGF-1\textsuperscript{1,2}
    - Back to the “Thrifty” hypothesis?
  - LH hypersecretion, hyperinsulinemia, etc.

\textsuperscript{1}Abbot 2005
\textsuperscript{2}Dumesic 2005
\textsuperscript{3}Manikkam 2004
\textsuperscript{4}Savabieasfahani 2005
Figure 1. Gestational progression of aspects of differentiation and maturation of hypothalamic–pituitary–ovarian function, and pancreas and beta-cell function in rhesus monkeys, based upon the following publications: Baker (1966), Hoar and Monie (1981), Ellinwood et al. (1983), Romackiev and Resko (1990), Sperling (1994), Quebeck et al. (1997), Fischer (2003). The timing of exposures of females to androgen excess (early- and late-treated) is indicated in relation to fetal developmental progress.
Ovarian Cysts: Summary

- Etiology varies by species
- Primary lack of LH production or insufficient LH response by the follicle
- Metabolic component related to “Thrifty” hypothesis?
Questions?