Polycystic Ovary Disease: A Common Endocrine Disorder in Women

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Case Presentation – Jenn A.

23 Y. O. G0 P0 menarche age 13
BMI 29. Hx of “weight problems”.
Menses Q 60 -180 days. Start BCPS age 15.
Moderate acne & hirsutism age 14-15
Family Hx T2 diabetes and infertility
Polycystic Ovary Syndrome

A Common Female Endocrine Dysfunction
Affects 1 of every 12 women in U.S.

Key Features:
- Oligo/Amenorrhea
- Abnormal Androgen Production & Metabolism

Probable Genetic Etiology
- Conveys evolutionary “metabolic efficiency”
- ? autosomal dominant/variable penetration
- ? serine hyperphosphorylation defect
PCOS: A NEW PARADIGM

“PCOS is a metabolic disorder affecting multiple body systems that requires comprehensive and long-term evaluation and management.”

John Nestler, M.D.  Fertility & Sterility  November, 1998
How Do Women with PCOS Present?

Irregular Menstual Periods
Hirsutism
Facial Acne
Overweight
Infertility
Acanthosis Nigricans (café au lait spots)
Sleep Apnea
PCOS: Diagnosis

N.I.H. Definition (2 of 2)

Oligo/Anovulation
- Cycles > 35 days apart or < 7 per year
Abnormal Androgen Production & Metabolism
- Clinical (Hirsutism/Acne) or Lab (T, A, DHEA-S)

ESHRE/ASRM Rotterdam 2003 (2 of 3)

Oligo/Anovulation
Androgen Excess
Polycystic Ovaries (12 or > follicles/ovary on U/S)

**PCOS: CVD Classification**

**Classic** (75%)
- RD/NIH Criteria + Overweight (BMI > 25)
- 40% Risk of IGT or T2DM by age 40 (5X controls)
- Dyslipidemia in 70% of Classic PCOS (IR effect)

**Ovulatory** (Lean) (12.5%)
- Medium risk profile

**Nonhyperandroogenic** (12.5%)
- Lowest Risk

*Assessment of Cardiovascular Risk in PCOS. JSEM May2010;95:5.*
PCOS

- Young:
  - Reproductive and hyperandrogenic dysfunction

- Later years:
  - Cardiometabolic disorders
PCOS: Evolutionary Benefits

Metabolic “Thriftiness”
Maximal caloric conservation

↑ Longevity in animal studies

Stress-induced ovulation (↓ LH P/F)

↓ Rate of oocyte atresia (↑ Insulin levels)
PCOS: Clinical Consequences

- Endometrial Cancer (3x risk, up to 1/5)
- Spontaneous Abortion (?↑ LH Effect)
- Gestational and Type 2 Diabetes (5-10x)
- Cardiovascular Disease (↑ LDL ↓ HDL)
- Hypertension
- Breast Cancer (3-4x risk in limited data)
- Ovarian Cancer
Evaluation of PCOS

BMI, Waist Circumference, BP
Baseline FSH, LH, TSH, Prolactin
Testosterone, DHEA-S
17-OH Progesterone (Follicular a.m.)
Fasting Glucose + Insulin/GTT
Fasting Lipids & Chemistry Panel
Transvaginal Ultrasound of Ovaries
Transvaginal Ultrasound of the Ovaries

“String of Pearls” in PCOS
PCOS: Insulin Resistance

Demonstrated in **60 - 80%** of PCOS
95% in Obese PCOS (BMI > 30)

Metabolic Effects:

- Decreased Hepatic SHBG Production (↑ Free T)
- Increased Ovarian Thecal Androgen Production
- Increased Triglycerides and Adverse Lipid Profile
- Obesity/Metabolic Syndrome
- Hypertension
- High Risk of T2 DM (25%)
Metabolic Syndrome: Diagnosis

Three or more of the following:

- Hypertension (130/85 or higher or on meds)
- Elevated Triglycerides (>150 mg/dL or on meds)
- Reduced HDL (Less than 50 mg/dL for women)
- Waist circumference > 35 inches for women
- Fasting Glucose >100 mg/dL or on meds
Metabolic Syndrome: What We Know

- Occurs in 1/6 (16%) of the general population and 60% of obese men and women.
- 10% of people with NGT, 40% with IGT, 85% with T2 DM.
- Prevalence 24% higher in women (40% by age 60) and increases with age.
- Conveys a high risk of T2 DM and cardiovascular disease.
- Significant increased risk with PCOS
Metabolic Syndrome: Treatment

Lifestyle: Diet, Exercise, Weight Loss

Correction of Problems: HTN, DM, Lipids

Regular monitoring/follow-up

? Low-dose aspirin
PCOS: Cardiovascular Disease

- Dyslipidemia
- Hypertension
- Impaired Glucose Tolerance/Type2DM
- Metabolic Syndrome
- Frequent Positive FH CVD before age 55
- Carotid-IMT (10-15% over controls)
- Carotid Artery Calcification
- Multivessel CVD (32% vs. 25%)

Assessment of Cardiovascular Risk in PCOS. JSEM May 2010; 95:5.
PCOS: Treatment Options

Anovulation: Cyclic Progestins, BCPs  
Prevent D.U.B., Endometrial CA
Acne/Hirsutism: BCPs, Spironolactone
Contraception: Low-Androgenic BCPS
Fertility: Clomiphene, FSH/hMG
Weight Loss: Low Calorie ADA Diet
Role of Metformin & Thiazolidinediones
PCOS: Positive Effects of Insulin Sensitizing Agents

- ↑ SHBG (↑ Androgen Binding)
- ↓ Testosterone and Androstenedione
- ↓ Triglycerides and LDL

Regulation of Menstrual Cycles (30%)
Weight Loss (Slow)
Increased Sensitivity to Clomiphene
? Decreased Risk of Miscarriage
PCOS: Who to Treat with Metformin in 2015

- Obese (BMI > 30) PCOS patients
  - Adults
  - Adolescents (who can be compliant)
- Insulin resistant patients
  - Fasting Insulin > 12-20 or G/I ratio < 4.5
- Patients who need menses regulation and fail BCPs/Progestins
- Young patients (age < 30) desiring fertility
- Patients with impaired glucose tolerance (IGT) or Type 2 D.M.
PCOS: Management Summary

Tailor treatment to life stage
Induce regular menses
Identify & treat endocrinopathies
Identify & treat insulin resistance
Monitor BP, Lipids, DM, Liver Function, Cancer risk
With prescription drug prices rising exponentially, many drugstores now provide armed escorts to assure that customers reach their cars safely.
The Assisted Reproductive Technologies (ART)

• In Vitro Fertilization (IVF)
• Intracytoplasmic Sperm Injection (IVF/ICSI)
• Donor Oocyte IVF
• Frozen Embryo Thaw and Transfer
• Cryopreservation/In Vitro Maturation of Oocytes
An hMG–hCG Cycle

Adapted from Navot and Rosenwaks, 1987.
In Vitro Fertilization (IVF)

- Daily S/C or IM FSH/hMG injection
- Follicular monitoring with serum estradiol and transvaginal ultrasound
- HCG given to trigger ovulation (LH surge)
- Transvaginal oocyte retrieval and insemination
- Embryo culture and transcervical embryo transfer
- Embryo cryopreservation for future F.E.T.
- Pregnancy rate of 40-50 % per cycle
In IVF, eggs are harvested from the woman’s ovary and fertilized in the laboratory with sperm. The embryos are then transferred into the uterus.
Intracytoplastic Sperm Injection (ICSI)

- Standard IVF Stimulation and oocyte retrieval
- Injection of a single sperm into each oocyte
- Embryo culture and transcervical embryo transfer
- Currently used in almost 50% of IVF cycles for treatment of male factor and unexplained causes
- Pregnancy rate of 40-50% per cycle
Intracytoplasmic Sperm Injection (ICSI)
Future Directions in ART

• The “-omics” Revolution
• Preimplantation genetic diagnosis (PGD)
  - with transgenic therapy?
  • Nuclear and/or cytoplasmic oocyte transfer
  • Embryonic Stem Cell Line Development
  • Gamete Stem Cell Development
Future Directions in ART (Con’t)

- Embryo Cloning - Reproductive/Therapeutic
- Adult Cell Gamete Cloning - sperm/oocyte
- Adult Somatic Cell Cloning
The “-omics” Revolution in Infertility

- **Genomics**: The branch of molecular biology concerned with the structure, function, evolution, and mapping of genomes.

- **Proteomics**: The set of proteins expressed by the genetic material of an organism under a given set of environmental conditions.
The “-omics” Revolution in Infertility

- **Metabolomics**: The systematic study of the unique chemical fingerprints that specific cellular processes leave behind.

- **Embryomics**: The identification, characterization and study of the diverse cell types which arise during embryogenesis.
Preimplantation Genetic Diagnosis (PGD)

- Goal: Identify Genetically Abnormal Embryos

- IVF/ICSI + Embryo Culture

- Blastomere Biopsy of 8-cell Embryo

- FISH/PCR Genetic Studies (X,21,single gene, etc)

- Transfer of Normal Blastocysts/Frozen Embryos
PGD 8-cell Blastomere Biopsy
PGD FISH - Normal Embryo

White = Y
Yellow = X
Blue = 18
Red = 21
Green = 13
Oocyte Cryopreservation

- Preservation of Oocytes Prior to Fertilization
- TV Retrieval of Stimulated Oocytes
  - Future: Unstimulated Oocytes with IVM
- Desiccation and Cryopreservation
- Delayed Thaw and IVF/ICSI Embryo Culture
- Transfer of Healthy Embryos
Oocyte Desiccation for Cryopreservation
Fertility Preservation

A. Damage to follicular cells from radiation and chemotherapy.
   - Possible reduction of ovarian reserve.
   - Premature ovarian failure.
   - Natural pregnancy.
   - Donor egg or adoption.

B. In vivo:
   - Stimulation of follicle growth with exogenous hormones.

   Ex vivo:
   - Aspiration of oocytes.
   - Emerging techniques:
     - Cryopreservation of ovarian cortical strips.
     - In vitro follicle maturation.
     - Transplantation of ovarian cortical strips in patient.

   Live birth.

Mature oocyte → Embryo → Live birth.
**Fertility Preservation**

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<th>Method</th>
<th>Cryopreservation</th>
<th>Treatment</th>
<th>Recipient</th>
<th>Concerns</th>
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<td>Hormone stimulation</td>
<td>Zygote or embryo</td>
<td>Embryo transfer</td>
<td>Patient or gestational surrogate</td>
<td>Delay in cancer treatment</td>
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<td>Hormone cycle 2–3 weeks</td>
<td>Mature oocyte</td>
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<td>Hormone stimulation</td>
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<tr>
<td>Postpubertal girls</td>
<td>Laparoscopic oophorectomy</td>
<td>Ovarian cortical strips</td>
<td>In vitro follicle maturation and in vitro fertilization or ICSI with embryo transfer</td>
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<td>Potential reintroduction of cancer cells</td>
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<td>Women</td>
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IVF Treatment of Genetic Mitochondrial Disease

- “Mitochondrial DNA Replacement Therapy”
- Performed by Donor Egg Nuclear Transfer
- 1:200 incidence of pathogenic mtDNA mutation
- Recently approved by British Parliament
- Currently in active IRB-approved study at OHSU
Stem Cell Gamete Production

A. Goal is cost-effective, ethically-acceptable source of sperm and oocytes
   - Reduction of risks with donor gametes
   - Alternative to somatic cell cloning

B. Potential treatment for cancer patients, age-related infertility, and severe male factor

C. Reduction of multiple gestation by SET
In Vitro Fertilization (IVF) - 2014

- SART Data: 61,740 IVF babies born in 2012 in U.S.
- IVF babies now constitute almost 2% of U.S. births
- Estimated 400,000 IVF babies born in 2012 in world
- IVF births now almost 4% of births in Europe
- Estimated 5,000,000 IVF births by Oct. 2013

- Who Knew ?????