Why Polycystic Ovary Syndrome?

- Arguably the most prevalent medical condition in women
- Likely to have a life-long impact on patient.
- Patients with PCOS have multiple symptomatology: endocrine, gynaecological, obstetrical, diabetic, dermatological, eating disorder psychiatry etc.
- Annual economic cost of diagnosis and treatment recently calculated in USA to be $4.36 billion
Why PCOS?

- Approximately 20% of population have PCO (male also)
- 50% in Indian sub-continent Asians
- PCOS 5-10% of women of reproductive age
- Major cause of anovulatory infertility
- Major cause of hirsutism and acne
- Link with type II diabetes
- Likely to become one of the major health issues in the future due to long-term sequelae
- Wide range of presentation creates problems with definition and diagnosis
Towards a consensus definition?

The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group

- PCOS is a syndrome of ovarian dysfunction with hyperandrogenism and PCO morphology.
- Diagnosis: 2 out of
  - Polycystic ovaries
  - Irregular cycle
  - Androgen excess

- Insulin resistance, obesity and elevated serum LH levels are common features
- PCOS is associated with an increased risk of type 2 diabetes and cardiovascular events

Hum Reprod. 2004; 19: 41-7
Anovulatory PCO
Prevalence

- **PCOS present in**
  - 32% of patients with amenorrhoea
  - 87% with oligomenorrhoea.
  - 87% with hirsutism/acne and regular cycles
  - 73% of women with anovulatory infertility

- **PCO present in**
  - 22% of ‘normal’ population
What causes the morphological changes?

Counting of follicles in sections of ovary has revealed:
- numbers of resting follicles appears unchanged
- there are many more growing follicles even at the earliest stages
- reduced follicle death?
Aetiology

- Familial aggregation
- Monozygotic twins twice as likely to both have PCOS than dizygotic
- Common finding of raised androgen led to belief that PCOS is caused by an inherited disorder - most likely in the steroid biosynthetic pathway
- Many candidate genes were investigated: all ‘obvious’ ones ruled out.
The PCO ‘gene’

- Genetic linkage analysis (short-tandem repeat polymorphisms) in 367 families
- Found susceptibility linkage to area on chromosome 19p13.2 (D19S884)
- Gene close to this is encodes for fibrillin-3
- Fibrillins are extracellular matrix proteins present in connective tissue
- Mutations in fibrillin-1 cause Marfan syndrome
But what does it do in the ovary?

- Fibrillins interact with transforming growth factor beta (TGFβ) family members
- TGFβs are essential for ovarian follicle growth
- Expression of fibrillin-3 in adult ovary very low and no difference in PCO
- Levels higher in fetal ovary
- Staining of adult ovary sections shows fibrillin-3 present around very early growing follicles, ie those increased in number
- Less fibrillin-3 around follicles in PCOs
What causes anovulation?

- Possibly insulin and androgens
- New finding of raised anti-Mullerian hormone (AMH)
- Produced by small follicles and therefore now in use as a marker of ‘ovarian reserve’
- Serum levels higher in PCOS, but thought to be due to increase in small follicles
- Production per follicle 75 times higher
- Acts as an inhibitor of follicle growth
- Only those with fall in AMH respond to induction of ovulation
- Watch this space!
Endocrine Profile

- increased androgen
  - anov > ov > normal
  - increased androgen production by the ovary, even in ovPCO
- May lead to hirsutism and acne
- In quality of life surveys consistently described as the most distressing symptom
Effects of acne on self-esteem
Dermatological Presentations

- Hirsutism 66%
- Acne 35%
- Alopecia 6%
- Acanthosis Nigricans 3%

- Almost 80% of women in dermatology clinic with acne had PCOS...never had cycle history taken
## hirsutism/acne treatment

<table>
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<th>Medical Management</th>
<th>Other therapies</th>
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<td>Combined OCP*</td>
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*beware of androgenic progestogens…norethindrone, norgestrel*  
Yasmin contains drospirenone which is spironolactone analogue with no androgenic activity
Eflornithine (Vaniqua)

inhibits the enzyme orthinine decarboxylase (ODC) responsible for catalysing orthinine to polyamine critical to regulation of cell growth and differentiation

Testosterone Stimulates ODC synthesis

Eflornithine HCL Synthesis of polyamines leads to proliferation of matrix cells Growth of hair
SHBG levels in PCO

Vast majority of testosterone is bound to SHBG. Small change in SHBG causes large change in free testosterone.

SHBG largely dependent on BMI. Production by liver is inhibited by serum insulin which rises as body fat increases.
PCO..the metabolic defect

- There is a metabolic defect associated with PCO
- The central feature is insulin resistance
- As a group, women with PCOS have insulin resistance at the cellular level
- Circulating insulin levels have to increase to compensate
- Even lean women with PCOS may be insulin resistant
- Insulin sensitivity declines with increasing weight at a faster rate than in women with normal ovaries
Insulin sensitivity in relation to weight

- Insulin Sensitivity
- Weight
- Normal
- PCO
Insulin Resistance and PCO

- Insulin resistance results in:
  - increased incidence of GDM
  - 60 women with previous GDM
  - 43% with PCO
- Increased risk of type II diabetes
  - in postmenopausal women incidence was 13% compared with 2% without PCO
  - many studies in USA show greatly increased risk, particularly in obese women.
PCOS and Insulin

- Recent study from Adelaide:
  - 18% of women with PCOS with BMI > 30 had impaired glucose tolerance
  - When studied 5 years later it was 33% and many now had diabetes.
- Study in large numbers in USA: women with PCOS are at significantly increased risk for IGT and type 2 diabetes at all weights and at a young age
Hyperinsulinaemia has consequences for ovulation

- Insulin resistance is linked to anovulation
- 1741 patients with PCOS, of those with BMI > 30, 70% had menstrual disturbance
- Women with PCOS who were obese at 23 were twice as likely to fail to conceive as those who are not obese
Inverse correlation between fasting insulin and no. cycles/yr

Conway G. PCOS: Clinical aspects. Baillieres Clin Endocrinol Metab 10:
Effect of obesity on PCOS

- **OBESITY**
  - **INSULIN RESISTANCE**
    - **INSULIN**
      - **ANOVULATION**
        - **ANDROGEN**
          - **FREE ANDROGEN**
            - **SKIN**
              - acne
              - hirsutism
Why do women with PCOS gain weight?

- 30-50% of patients with PCOS are overweight or obese
- Some debate about whether patients have increased intra-abdominal fat
- Normal-weight women with PCOS consistently maintain a lower-calorie diet than their over-weight counterparts
- PCO is associated with reduced energy expenditure
- One of the main contributing factors is reduced post-prandial thermogenesis.
Post-prandial thermogenesis in PCO

PPT
kJ

LEAN
OBESE

PCO
NORMAL
PCOS and weight

73,500 kJ (17,200 calories) per annum, equivalent to 1.9 kg of fat
Effect of obesity on PCOS

Obesity

- Insulin resistance
- SHBG
- Free androgen
- Skin: acne, hirsutism
- Miscarriage
- Anovulation
- Insulin
- Androgen

Insulin

- Skin acne
- Hair growth (hirsutism)

Androgen

- Insulin resistance
- SHBG
- Free androgen
- Skin acne
- Hair growth (hirsutism)
- Miscaerriage
- Anovulation
Long term sequelae

- Women with PCOS have all risk factors for cardiovascular disease
  - Central adiposity
  - T2D
  - Hypertension
  - Adverse cholesterol profile
  - Increased triglycerides
Increased markers of Cardiovascular disease

- Novel cardiovascular risk factor markers
  - Oxidative stress, inflammation, impaired fibrinolysis
- Early markers of atherosclerosis
  - Endothelial dysfunction, impaired pulse wave velocity, increased carotid intima media wall thickness, carotid plaque and coronary artery calcification

Even present in non-obese, but worse with obesity
PCO..long term sequelae

Pierpoint et al 1998

- Large UK based study
- Diabetes underlying cause of death in 6 with PCO (1.7 in controls)
- No other increase in mortality - in fact some reduction in rates of circulatory disease
- Increased chance of stroke in another study (Wild 1999)
- Main problem with these studies is age of patients..mean 55
More recent data

- Worse event-free survival in NIH study if had irregular cycle and elevated androgen
- Nothing else.................
Increased risks for family members

- Family studies have revealed:
  - 1st degree relatives of women with PCOS also have increased risk of CVD and have increased fasting insulin
  - Brothers of Indian subcontinent Asian women with PCOS had insulin resistance and endothelial dysfunction by USS of brachial artery (all <40yrs).
Weight loss and exercise as 1st line treatment

- Weight loss in all overweight women with PCOS improves all aspects of the syndrome
- Improvement of insulin resistance
  - diet and exercise
- Studies from Australia show diet is as successful as medical intervention (Clarke) for IoO but requires support system and frequent attendance and exercise programme
- No agreement regarding ‘best’ diets. All diets restricting energy intake have proven efficacy
- Patients adopting long term, low-fat, high carbohydrate diets appear to maintain weight loss longer.
- In light of the consequences of obesity in this group may be a role for pharmacological weight-loss agents.
Drugs which improve insulin sensitivity

- **Metformin....may**
  - reduce circulating insulin and androgens
  - return ovulatory cycles
  - side effects
  - *However metanalysis not convincing*
  - UK Long term double-blind randomised controlled trial with dietary advice
    - Improved menstrual frequency in both groups
    - Only weight loss showed correlation..no difference between groups
  - need to know target population..may be young
Infertility treatment

- Weight reduction is primary goal in the overweight
  - Increased chance of spontaneous ovulation
  - Lower drug requirement for induction of ovulation
  - Better rates of ovulation
  - Reduced chance of miscarriage
  - Reduction in GDM
- 5% of body weight or 10% improvement in BMI has been shown to be effective
Induction of ovulation

- Weight loss and exercise first
- Clomiphene citrate first line treatment
- Use of aromatase inhibitors appearing
- Seem equally effective and may have less endometrial effects
- Gonadotrophins next or
- Laparoscopic ovarian surgery
- IVF
Word of caution

- Strong link between PCOS and eating disorders.
- Irregular cycles are common in bulimia
- Pelvic ultrasonography showed 75% of patients with BN at St. George’s had PCO
- Study investigating IR found increased PCO in women with BN
Another word of caution

- Even when amenorrheic women with PCOS are well-oestrogenised
- Effects of unopposed oestrogen on endometrium risk factor for hyperplasia
- Recent study showed 4 fold increased risk of endometrial CA...even under 50
- Recommendation to have bleed at least every 3 months, more often if very heavy
PCO- summary

- PCOs are genetically acquired
- There is a basic defect in steroid metabolism
- Endocrine disturbances result in miscarriage, anovulation, infertility and hyperandrogenism
- There is a metabolic defect, central feature is IR, coupled to lipid abnormalities = increased risk of cardiac disease
- Obesity makes increases symptomatology
- Treatment is currently largely symptomatic
PCOS

- As the most common condition in the reproductive-age population PCOS is rightly the focus of intense research.
- Functional and genetic studies of the families may reveal some of the causative genes.
- Investigation of the physiological role of these factors may move us towards more evidence-based treatment.
useful information for patients from:

Verity
The polycystic ovaries self-help group
Unit AS20.01
The Aberdeen Centre
22-24 Highbury Grove
London N5 2EA
www.verity-pcos.org.uk
New organisation for healthcare professionals

- Established to stimulate interest in and raise awareness of PCOS in primary and secondary care
- Working in partnership with Verity
- Provision of educational support
- PCOS UK conference 26th Nov: (www.pcos-uk.org.uk)
Excellent reviews and papers


- **Teede H**

  PCOS: a complex condition with increased psychological, reproductive and metabolic manifestations. BMC medicine 8:41 2010