PCOS and type 2 diabetes mellitus

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There is no conflict of interest to declare

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PCOS and type 2 diabetes mellitus: topics covered

- Insulin resistance and PCOS
- Prevalence of impaired glucose tolerance and diabetes
- Diabetes genes and PCOS
- Risk groups for IGT and T2D
- Prevention of T2D in PCOS
Polycystic ovary syndrome

- Characterised by anovulation with clinical (hirsutism/acne) and/or biochemical evidence of androgen excess
- Typically presents during adolescence
- Affects >5% women of reproductive age
- Commonest cause of menstrual dysfunction (>80% cases of anovulatory infertility) and hirsutism
- Typical endocrine features are raised testosterone and LH
- Also associated with metabolic abnormalities and increased risk of type 2 diabetes
PCOS and type 2 diabetes mellitus: topics covered

• **Insulin resistance and PCOS**
• Prevalence of impaired glucose tolerance and diabetes
• Diabetes genes and PCOS
• Risk groups for IGT and T2D
• Prevention of T2D in PCOS
Insulin sensitivity is reduced in lean and obese women with PCOS

Robinson et al, *Clin Endocrinol* 1992 36 537
Obesity amplifies insulin resistance in women with PCOS

(Adapted from Holte et al, *J Clin Endocrinol Metab* 1994, **78** 1052)
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Metabolic syndrome: definitions

- National Cholesterol Education Program - 3rd Adult Treatment Panel (NECP-ATPIII)
  - 3 from 5
    - Central obesity (waist circumference >88cm)
    - Triglycerides ≥150mg/dL (1.69mmol/l)
    - BP ≥130/85
    - Fasting glucose ≥110mg/dL (6.11mmol/l)
    - HDL<50mg/dL (1.29mmol/l)

- International Diabetes Federation (IDF)
  - Central obesity (waist circumference >80cm)
  - + 2 from 4
    - Triglycerides ≥150mg/dL
    - BP ≥130/85
    - Fasting glucose ≥110mg/dL
    - HDL<50mg/dL

Skilton et al, Atherosclerosis 2007 109 416-22
Prevalence of metabolic syndrome in young women with PCOS

![Bar chart showing prevalence of metabolic syndrome](chart.png)

Prevalence (%):
- Ehrmann et al, 2006 (n = 368)
- Dokras et al, 2005 (129)
- Apridonidze et al, 2005 (106)
- Glueck et al, 2003 (138)

References:
- Glueck et al, *Metabolism* 2003 52 908-915
- Dokras et al *Obstet Gynecol* 2005 106 131-137
Prevalence of metabolic syndrome in young women with PCOS

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Glueck et al, *Metabolism* 2003 52 908-915
Dokras et al *Obstet Gynecol* 2005 106 131-137

PCOS = Female Metabolic Syndrome (or Syndrome XX) (*Dunaif*)
Prevalence of IGT and diabetes in young women with PCOS

Legro et al, 1999 (n = 254) BMI: 30/36, age 27/28
Ehrmann et al, 1999 (122) BMI: 38, age 26
Robinson et al, 1996 (55) BMI: 32, age 28

Robinson et al, Clin Endocrinol 1996 44 277-84
Ehrmann et al, Diabetes Care 1999 22 141-146
Legro et al, J Clin Endocrinol Metab 1999 84 165-9
Longitudinal study of prevalence of IGT and diabetes in PCOS

Legro et al, J Clin Endocrinol Metab 2005 90 3236-42
Gestational diabetes in women with PCOS

- High prevalence (52%) of polycystic ovaries in women with history of GDM
  - Kousta et al, Clin Endocrinol 2000 53 501-7

- Women with PCOS at increased risk of GDM (OR 2.94 (1.7 - 5.1))
  - Boomsma et al, Hum Reprod Update 2006 12 673-683 (meta-analysis)

- High prevalence of GDM in women with PCOS (42% of 50 women)
  - Veltman-Verhulst et al, Hum Reprod 2010 (Epub, October)
Increased risk of T2D in older women with proven PCOS

- 319 cases of PCOS age 56.7 (38 - 98) with reference group of 1060 subjects
- Increased risk of diabetes after adjustment for BMI: OR 2.2 (0.9 - 5.2)
- Higher risk if obese subjects included: OR 2.8 (1.5 - 5.5)

Wild et al, Clin Endocrinol 2000 52 595-600
Increased risk of T2D in women with symptoms of “PCOS”

- Relative risk of T2D in women with history of oligomenorrhea/irregular cycle: 2.08 (1.62 - 2.66)
- Independent of obesity but RR increased further in obese subjects: 3.86 (2.33 - 6.38)
(studied at age 34)

Nurses Health II: Solomon et al, JAMA 2001 286 2421-6
Meta-analysis of studies reporting risk of T2D in women with PCOS

- IGT: OR 2.54 [1.44 - 4.47]
- T2D: OR 4.00 [1.97 - 8.10]

in BMI-matched groups

35 studies analysed

Moran et al. Hum Reprod Update 2010 16 347-63
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- Prevalence of impaired glucose tolerance and diabetes
- **Diabetes genes and PCOS**
- Risk groups for IGT and T2D
- Prevention of T2D in PCOS
Evidence for genetic basis of polycystic ovary syndrome

- Familial clustering of cases
- Concordance greater in identical than in non-identical twin pairs (tetrachoric correlation 0.71 vs 0.38; estimated genetic influence 79%, environment 21%; Vink et al, 2006)

Mode of inheritance uncertain. Complex endocrine disorder (like type 2 diabetes) likely to be oligogenic or polygenic (Franks et al, 1997; Urbanek et al, 2007)
Candidate genes in PCOS

• Steroid hormone production and metabolism
  • $CYP11a$ (P450scc)
  • $CYP17$ (P450c17)
  • $CYP19$ (P450$_{arom}$)

• Metabolic: insulin secretion and action; obesity
  • Beta cell function: $INS$ VNTR, $TCF7L2$, $KCNJ11$
  • Insulin resistance: $IR$, $PPAR_\gamma$
  • Obesity: $FTO$

• Androgen action
  – Androgen receptor

• Ovarian follicle development
  – Follistatin; $FBN3$
Familial Polycystic Ovary Syndrome

- **PCO**
- **uncertain ovarian morphology**
Problems with genetic studies in PCOS

- Presents only in women of reproductive age
- No obvious male phenotype
- Large affected families uncommon
- Heterogeneity of phenotype and disagreement about diagnostic criteria
Affected sister pairs with PCO
(affected = PCO on ultrasound)

Franks et al, J Clin Endocrinol Metab 2008 93 3396-3402
Serum testosterone in affected sister pairs with PCO

Franks et al, J Clin Endocrinol Metab 2008 93 3396-3402
Fasting insulin levels are similar in affected sister-pairs with PCO
Diabetes genes and PCOS

• Insulin gene VNTR
  – No clear evidence

• TCF7L2
  – No association with PCOS at TCF7L2 T2D locus but association of other polymorphisms with PCOS (rs11196236, rs11196229, rs7903146) (Barber et al, 2007; Christopoulous et al, 2008; Biyasheva et al, 2009)

• KCNJ11(E23K)
  – No association with PCOS (Barber et al, 2007; Christopoulous, 2008)

• Calpain 10 (CAPN10)
  – No clear evidence

• PPARγ (Pro12Ala)
  – No clear evidence

• FTO
  – Association with obesity in PCOS (Barber et al, 2008; Tan et al, 2010)
The *FTO* gene

- Fat mass and obesity associated gene (Chr16)
- SNP rs9939609 associated with obesity in the general population *(Frayling et al, 2007 Science 316:889-894)*
- Does FTO variant contribute to genetic basis of PCOS?
Case-control association analyses for variants at *FTO* rs9939609 and PCOS in UK samples


<table>
<thead>
<tr>
<th>Alleles</th>
<th>TT</th>
<th>AT</th>
<th>AA</th>
<th>P-value (Cases vs combined controls)</th>
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<tbody>
<tr>
<td>UK cases (n=463)</td>
<td>133 (28.7%)</td>
<td>231 (49.9%)</td>
<td>99 (21.4%)</td>
<td>5.3 x 10^{-4}</td>
</tr>
<tr>
<td>Combined female controls (n=1778)</td>
<td>642 (36.1%)</td>
<td>849 (47.8%)</td>
<td>287 (16.1%)</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>-7.4%</td>
<td>+2.1%</td>
<td>+5.3%</td>
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Data shown are genotype counts (and percentages); P values represent Cochran-Armitage test results

Following adjustment for BMI in the comparison between UK cases and combined control group, the association with PCOS was attenuated but not eradicated (P-value=2.9 x 10^{-3}).
**FTO in PCOS - case control study**

- The rs9939609 variant associated with PCOS: OR 1.29 (1.14-1.49)
- Largely related to obesity (PCOS group have higher BMI) but still significant association after adjustment for BMI

Independent replication studies: association of FTO with PCOS (predominantly with obesity & metabolic parameters)

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Screening for metabolic disorders in PCOS

- No test of insulin resistance is needed to make diagnosis of PCOS or to select treatment
- Obese women with PCOS (and/or those with abdominal obesity) should have an OGTT (or fasting glucose) and lipid profile
- Utility of these tests in non-obese women with PCOS is not yet known
  - Rotterdam consensus meeting (Hum Reprod 2004 19 41-7)

- SHBG as a screening test for metabolic abnormalities?
Who is at risk of T2D?

<table>
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<tr>
<th>Risk Factor</th>
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<tr>
<td>PCOS (2-fold)</td>
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<tr>
<td>PCOS + obesity (3-fold)</td>
</tr>
<tr>
<td>PCOS + obesity + FH of diabetes</td>
</tr>
<tr>
<td>PCOS + obesity + GDM</td>
</tr>
<tr>
<td>PCOS + obesity + IGT</td>
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</tbody>
</table>
Diagnostic criteria for PCOS

NIH 1990
• Chronic anovulation
• Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other aetiologies, eg CAH)
  (both criteria needed)

Rotterdam 2003
• Oligo- and/or anovulation
• Clinical and/or biochemical signs of hyperandrogenism
• Polycystic ovaries
  (2 of 3 criteria needed)

Rotterdam ESHRE/ASRM sponsored PCOS Consensus Workshop Group (Hum Reprod 2004 19 41-7)
HOMA-IR according to PCOS phenotype

![Graph showing HOMA-IR distribution across PCOS phenotypes.](image)

(Geometric mean ± SD)

Barber et al, Clin Endocrinol 2007 66 513-7
HOMA-IR according to PCOS phenotype

<table>
<thead>
<tr>
<th>Metabolic syndrome (IDF):</th>
<th>29%</th>
<th>7%</th>
<th>7%</th>
<th>4%</th>
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<tbody>
<tr>
<td>BMI</td>
<td>29</td>
<td>24</td>
<td>24</td>
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Prevention of diabetes in women with PCOS

• Make an *early* diagnosis
• Lean women with PCOS should not get fat
• Obese women with PCOS should be advised re diet and lifestyle
• Those at high risk may need medication as well as lifestyle changes
Effect of diet/lifestyle on insulin and fertility in obese women with PCOS

- modest (5-10%) weight reduction associated with vast improvement in metabolic indices
- diet and lifestyle changes improve ovulation rate and fertility (Kiddy et al, 1992; Clark et al, 1995; Norman et al, 2002; Steele et al, 2005)
Metformin in treatment of PCOS

• Small number of properly-conducted clinical trials
  – Significant but very modest increase in ovulation rate
  – Questionable effect on unwanted body hair (no data on acne)
  – No effect independent of weight loss on ovulation rate (Tang et al, Hum Reprod 2006 21 80–89)

• Efficacy and indications for treatment unclear

• Recent large clinical trials (and review of evidence) suggest that the usefulness of metformin has been overestimated (Tang et al, Cochrane Database Syst Rev 2010 Issue 1. Art. No.: CD003053. DOI:10.1002/14651858)
Metformin in treatment of PCOS

- *Not* useful for treatment of infertility or menstrual disturbances
- *Not* very effective for treatment of hirsutism
- *Does* have a place in management of women at high risk of developing diabetes
Cumulative incidence of T2D at 3 years

3234 subjects with IGT

Knowler WC et al Diabetes Prevention Program Research Group

N Engl J Med 2002 346 393-403
Role of thiazolidinediones (glitazones) in PCOS

• Improvement in insulin sensitivity, androgens and cyclicity

• Lipids not significantly altered and weight increased

• Concern about safety, particularly in women of reproductive age
  – Similar concerns about glucagon-like peptides (GLP-1) agonists
Summary

- Insulin resistance and abnormal β-cell function are features of PCOS
- Women with PCOS are at increased risk of developing metabolic syndrome and T2D
- **PCOS is a prediabetic state that presents in young women - usually in adolescence**
- Diet and lifestyle changes are most important ways of improving fertility and in prevention of diabetes in women with PCOS