HYPERANDROGENISM

POLYCYSTIC OVARY SYNDROME

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Introduction

- Hyperandrogenism
  - Androgens
  - Definition
  - Hirsutizm
- Polycystic ovary syndrome
  - Pathophysiology
  - Clinical presentation
  - Examinations
  - Lab tests
  - Treatment
  - Complications
- Other causes of hyperandrogenism
- Summary
Androgens

- C19-steroids:
  - dehydroepiandrosterone (sulfate) DHEA(S)
  - androstendione
  - testosterone
  - 5α-dihydrotestosterone
20mg/day

androstenedione

3 mg/day

testosterone

Target tissue

ovary

adrenal

5α-dihydrotestosterone (5α-DHT)
Hirsutism: a clinical diagnosis

defined as excessive and increased hair growth in women in locations where the occurrence of terminal hair normally is minimal or absent. It refers to a male pattern of body hair
differential diagnosis: Hypertrichosis

Virilization (masculinization)

in a woman can manifest as clitoral enlargement, increased muscle strength, acne, hirsutism, frontal hair thinning, deepening of the voice, and menstrual disruption due to anovulation
Effects of androgens on body hair

5-α-reductase enzyme converts testosterone to dihydrotestosterone (DHT)

DHT binds to the androgen receptor (AR), and stimulate the terminal hair growth

The growth phase – so called anagen phase – lasts about 4 months
circa 1910: Josephine Boisdechene Versoix, later Josephine Clofullia, who appeared as the bearded lady of P T Barnum's circus as Madame Zorro, or The Bearded Lady of Geneva
Modified Ferriman-Gallwey score:
9 body regions
0-4 score
Maximum: 36
> 8: hirsutism

Less than 5% of the afroamerican and caucasian women have more than 7 points

Comments: - subjective
- focale hirsutism ?
- „patient-important hirsutism?”

mild hirsutism: 8-15
Intermediate or severe hirsutism: >15

The FG score does not correlate with the elevation of the plasma androgen level
Hirsutizm
Polycystic ovary syndrome (PCOS)

Previous: Stein-Leventhal syndrome (1935)

Diagnostic criteria: Many guidelines are available from different societies, no real consensus

The most frequent endocrinological disorder in women of fertile age.

Incidencia: 5-10% in women between 18-55 years

PCOS is not equal with PCO morphology

- 40-60 % obese
- 60-90 % hirsute
- 50-90 % amenorrheic
- 7-16 % regular menses
- 55-70 % infertility
PCOS diagnostic criteria

- **NIH (1990):** elevated serum androgen and chronic anovulation

- **Rotterdam Consensus Conference (2003):**
  - clinical or biochemical signs of hyperandrogenism
  - oligo/anovulation
  - polycystic ovarian morphology

  no other causes of hyperandrogenism

  any 2 out of 3 : PCOS

- **Androgen Excess and PCOS Society (2008):**
  hyperandrogenemina (clinical or biochenical) and ovary dysfunction (ovulatory disturbances or PCO morphology)
1. **Increased intrinsic production of androgens in the ovary theca cells**
2. Disturbances in the hypothalamic-pituitary-ovary axis
3. Inzulin resistance- hyperinsulinemia
4. Increased adrenal andogen production
5. Genetic and environmental factors
Steroid biosynthesis

P450scc: P450-sidechain cleavage

17β-HSD: 17β-hydroxysteroid-dehydrogenase

3β-HSD: 3β-hydroxysteroid-dehydrogenase

P450c17α: 17α-hydroxylase és 17/20-liase
Steroid biosynthesis in PCOS

- **P450scc**: P450-side chain cleavage
- **17β-HSD**: 17β-hydroxysteroid-dehydrogenase
- **3β-HSD**: 3β-hydroxysteroid-dehydrogenase
- **P450c17α**: 17α-hydroxylase and 17/20-liase

The diagram illustrates the pathway from cholesterol to testosterone, with key enzymes and metabolites labeled.
Citochrome P450-17α

- dual enzymatic function (17α-hydroxylase és 17/20-liaise)
- central mediator of androgen synthesis in the ovary
- serine-phosphorylation increases the enzymatic activity

Pathophysiology

1. Increased intrinsic production of androgens in the ovary theca cells
2. **Disturbances in the hypothalamic-pituitary-ovary axis**
3. Insulin resistance- hyperinsulinemia
4. Increased adrenal androgen production
5. Genetic and environmental factors
Disturbances in the hypothalamic-pituitary-ovary axis

- **endogen opioids** (↓)
- **dopamine** (↓)
- **adrenerg system** (↑)

**GnRH pulsation** (↑)

**LH secretion** (↑) / **FSH secretion** (↓)

**Follistatine** (↑)

**Steroid synthesis** (↑)

- **estrogens**
- **Androgens synthesis** (↑)
- **progesterone** (↓)
- **inhibin** (↑)

**Hypothalamic**

**Pituitary**

**Ovary**
Pathophysiology

1. Increased intrinsic production of androgens in the ovary theca cells
2. Disturbances in the hypothalamic-pituitary-ovary axis
3. **Inzulin resistance- hyperinsulinemia**
4. Increased adrenal androgen production
5. Genetic and environmental factors
Insulin resistance - hyperinsulinemia

- LH-synergic effect on theca cells
- P450c17α
- ACTH-sensitivity
- LH

Insulin

Hyperandrogenism

- SHBG
- IGFBP-1
- IGF –1/2

Hyperinsulinemia
Insulin resistance - hyperinsulinemia

Adipocyte from PCOS patients

Fibroblast from PCOS patient

- Insulin-stimulated phosphorylation
- Tyrosine
- Serine
- Insulin-dependent glucose uptake
- GLUT-4 translocation
- Insulin-dependent glycogen synthesis
- GSK-3 phosphorylation
- PKB
- Insulin-dependent tyrosine autophosphorylation
- IRS-1/2
- PI3K
- GLUT-4 phosphorylation
- Insulin-serine basal autophosphorylation
- TRENDS in Molecular Medicine
Insulin resistance - hyperinsulinemia

Ovarian theca cells from PCOS patient
Insulin resistance - hyperinsulinemia

- P450c17α
- ACTH-sensitivity
- LH secretion
- SHBG
- IGFBP-1
- IGF – 1/2

Hyperandrogenism
Pathophysiology

1. Increased intrinsic production of androgens in the ovary theca cells
2. Disturbances in the hypothalamic-pituitary-ovary axis
3. Inzulin resistance- hyperinsulinemia
4. Increased adrenal androgen production
5. Genetic and environmental factors
Increased adrenal androgen production

- 5α/β-reductase activity
- 11β-HSD1 activity
- Cortisol metabolism
- Adrenal androgen
- ACTH
- Normal serum cortisol
- PCOS
Pathophysiology

1. Increased intrinsic production of androgens in the ovary theca cells
2. Disturbances in the hypothalamic-pituitary-ovary axis
3. Insulin resistance - hyperinsulinemia
4. Increased adrenal androgen production
5. Genetic and environmental factors
<table>
<thead>
<tr>
<th>Patofiziológiai mechanizmus</th>
<th>gén</th>
<th>eredmények</th>
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</thead>
<tbody>
<tr>
<td><strong>Androgén bioszintézis és metabolizmus</strong></td>
<td>LH és receptora</td>
<td>nincs asszociáció vagy kapcsoltság</td>
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<tr>
<td></td>
<td>CYP11-P450scc</td>
<td>5’-pentanucleotiddal asszociáció</td>
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<td></td>
<td>P450c17α</td>
<td>nincs asszociáció vagy kapcsoltság</td>
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<td>P450c21-hidrox.</td>
<td>Szign. gyakoribb PCO-ban</td>
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<td>Androgén receptor</td>
<td>CAG ismélődésekkel inverz asszoc.</td>
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<tr>
<td></td>
<td>SHBG</td>
<td>(TAAAA)n-val asszociált</td>
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<tr>
<td><strong>Inzulin szekréció és hatás</strong></td>
<td>Inzulin gén VNTR</td>
<td>Lehetséges asszociáció class III alléllel</td>
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<td>Inzulin receptor gén</td>
<td>Tirozin-kináz polimorfizmussal asszociációt mutattak ki</td>
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<td>Inzulin receptor gén régió</td>
<td>19p13.3 kromoszómán D19S884 marker asszociált PCO-val</td>
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### PCOS genetikai mechanizmusai

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<tr>
<td>Inzulin szekréció és hatás</td>
<td>IRS 1/2</td>
<td>Gly972Arg SNP alacsony SHBG-vel és magas HOMA-val asszociált</td>
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<td>IGF2</td>
<td>Spanyol populációban Apal gén G-alléllal asszociációt találtak</td>
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<td>Gonadotropin hatás és reguláció</td>
<td>Dopamin receptor gén</td>
<td>Spanyol populációban D3 rec. 2-es alléllal asszociációt mutattak ki</td>
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<td>Follistatin gén</td>
<td>nincs asszociáció</td>
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<td>Obesitás és inzulinreizsztencia</td>
<td>PPARγ</td>
<td>Finn populációban emelkedett Pro12Ala SNP prevalenciát mutattak ki</td>
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<td>Krónikus gyulladás</td>
<td>PAI-1</td>
<td>Görög populációban asszociációt találtak 4G5G SNP-vel</td>
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<tr>
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<td>TNFα és receptora</td>
<td>Met196Arg SNP spanyol PCO-sokban gyakoribb</td>
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<tr>
<td></td>
<td>IL-6</td>
<td>G597A és G74C hiperandrogenémiával asszociált</td>
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</tbody>
</table>
Increased energy intake + sedentary life

Abdominal obesity

- Insulin resistance
- Hyperandrogenism
- Oligo/anovulation

1 year forced lifestyle change’s effect in PCOS women
A PCOS *in utero* origin

Hypothesis: Excess androgen exposition in utero at female foetus results PCO morphology

- animal studies (rodents, lamb, rhesus monkey)
- PCOS prevalence is increased at female children from obese mothers
- In case of CAH or virilisation by adrenal tumours in female newborns independently of the amelioration of androgen excess PCO morphology will develop
Pathology summary

Intrauterine factors
  - obesity
  - Genetic predisposition

Genetic predisposition
  - SHBG, IGFBP

Insulin resistance hyperinsulinemia

GnRH and LH/FSH

ovary

Adrenal gland
  - P450c17α

Glucose transport
  - Increased serine fosforilation

Androgens
  - Oligo/anovulation

P450c17α
Clinical presentation

- oligo- anovulation

  consequent oligo - amenorrhea after puberty and in young adults infertility

- clinical presentation of hyperandrogenism:
  hirsutism, acne, alopecia adrenogenic, obesity

- polycystic ovary morphology

- In family relatives more frequent disorder
Polycystic ovary morphology

- 10 or more 2-9 mm diameter cysts (follicles) in the ovary under the cortex, around the follicles there are hyperechogenic stroma

PCO morphology can appear in PCOS, in children before puberty, in congenital adrenal hyperplasia, hypothyreosis, hyperprolactinaemia and in insulin resistance cases
Carbohydrate metabolism

Type 2 diabetes mellitus or impaired glucose tolerance or impaired fasting glucose

Avarage population 10% vs. PCOS population 45%

T2DM in avarage population 5-7%,

In lean PCOS patients 20%, in obes PCOS 50-70%.

The pathophysiological background is the insulin resistance
Routine examinations

- Physical examination: signs of hyperandrogenism, BMI

- Lab tests:
  - hormone profile
  - carbohydrate and lipid profile

- Gynecological examination

- TVUS
Hormone profile

- **TSH**: 1,3 mU/l (0,4-4,9), **fT4**: 1,3 ng/dl (0,7-1,8)
- **Prolactin**: 11 ng/ml (1,4-24)
- **LH**: 7.5 mU/ml (2-9)*, **FSH**: 3,5 mU/ml (3,5-9)*, **LH/FSH**: 2,2
- **oestradiol**: 31,0 pg/ml (0-112), **progesterone**: 0,7 (0,2-1,5)
- **cortisol**: 18,4 mg/dl (8-25)
- **Testosterone**: 93 ng/dl (20-60), **DHEAS**: 310 mg/dl (130-330)
- **Androstendione**: 400 ng/dl (80-280)
- **17-OH-progesterone**: 88 ng/dl (40-250)
- **Fasting insulin**: 20 mU/ml (2,6-25) blood glucose: 5 mmol/l
- **HOMA-IR**: 4.4 (<2,5)
- **SHBG**: 11 nm/l (18-114)
New diagnostic marker?

- Anti-Müllerian Hormone: AMH (Member of the TGF-beta family)
  - In male foetus inhibits the development of Müllerian-duct (produced by Sertoli cells)
  - What is the role in female?
  - Produced by the granulosa cells in the pre antral follicles (< 7 mm) Inhibits the maturation of too many follicles.
AMH in PCOS

- AMH is increased in PCOS vs control.

AMH seems to be a more sensitive diagnostic marker as LH or LH/FSH ratio!
PCOS treatment

The treatment of PCOS based on the patient’s purpose

- Child - family

- Skin manifestation of the hyperandrogenism

- Menstrual irregularity

- Metabolic disorder

Non-pharmacological treatment:

Body weight reduction!!!
Ovulation induction - pharmacological

- clomifene citrate: selective antioestrogen modulator from the 3. or 5. days of the cycle 100 mg/day. Ovulation 80–90% success rate
  Pregnancy 30–50% success rate.
  Results can be further ameliorate with hCG

- In cases of clomifene resistance recombinant gonadotrop hormones can be given, recombinant FSH, 50-75 IU/day
  FSH for 2 weeks followed with consequent increase by 25-37,5 IU/day till ovulation
Ovulation induction - surgical

Classical: laparotomic wedge resection

Present: laparoscopic drilling - electrocoagulation
- laser

Aim: reduce the perforation openings

The physiologic effect of the laparoscopic methods:
1. Mechanical destruction of the thick capsule.
2. Break the intraovarian dysregulation
3. Improve the feedback mechanism, consequent better LH/FSH ratio.
Laparoscopic „drilling”
Cycle reorganisation and amelioration of skin manifestation

Oral contraceptives: low-dose oestradiol and antiandrogenic gestagen

Ethynil estradiol + progestin
- decrease the GnRH, LH and FSH secretion through the feedback mechanism
- decrease the ovarian testosterone production
- increase the SHBG production of the liver
- decrease the free testosterone serum level
- may decrease the adrenal androgen production
  and the androgen – receptor binding

Progestin: desogestrel or norgestimate or cyproterone acetát
**Insulin sensitizers**

**Insulin resistance and consequent hyperinsulinaemia is frequent in PCOS**

Insulin sensitizers have been developed to the treatment of type 2 diabetes

Biguanid derivate: metformin

Peroxisoma proliferator-activated receptor gamma: rosiglitazone és pioglitazone

Although there is no official licence for PCOS, insulin sensitizers are frequent used
Metformin and clomifene in PCOS

Table 2 Summary of recent randomized, placebo-controlled trials of clomiphene citrate compared with metformin.

<table>
<thead>
<tr>
<th>Study, drug (dose, mg/day) and schedule</th>
<th>Number of patients</th>
<th>Mean age (years ± SD)</th>
<th>Mean (±SD) BMI (kg/m²); BMI &gt;25 kg/m² (%)</th>
<th>Ovulation rate (%)</th>
<th>Cumulative pregnancy rate (%)</th>
<th>Live birth rate (%)</th>
<th>Twins, triplets (%)</th>
<th>First-trimester abortion rate (%)</th>
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<tbody>
<tr>
<td>Paolbna et al. (2005)²⁴</td>
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<td>Clomiphene citrate (150); 6 cycles</td>
<td>45</td>
<td>25.9 ± 2.7</td>
<td>26.7 ± 2.9; 76; 0</td>
<td>62.9</td>
<td>34.0</td>
<td>NR</td>
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<td>37.5</td>
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<tr>
<td>IR metformin (1,700); 6 cycles</td>
<td>47</td>
<td>26.4 ± 2.9</td>
<td>27.0 ± 2.9; 78; 0</td>
<td>67.0</td>
<td>63.9³</td>
<td>NR</td>
<td></td>
<td>9.7³</td>
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<tr>
<td>Molt et al. (2006)⁵⁶</td>
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<tr>
<td>Clomiphene citrate (50–150); 6 cycles</td>
<td>114</td>
<td>26.4 ± 4.7</td>
<td>27.6 ± 0.7; 55; NR</td>
<td>72.0</td>
<td>46.0</td>
<td>NR</td>
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<td>22.6²</td>
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<tr>
<td>Clomiphene citrate (50–150) + IR metformin (2,000); 6 cycles</td>
<td>111</td>
<td>27.9 ± 3.7</td>
<td>28.5 ± 7.1; 57; NR</td>
<td>64.0</td>
<td>40.0</td>
<td>NR</td>
<td></td>
<td>29.5²</td>
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<tr>
<td>Legro et al. (2007)⁶⁸</td>
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<tr>
<td>Clomiphene citrate (50–150); 6 months</td>
<td>209</td>
<td>27.9 ± 4.0</td>
<td>36.0 ± 8.9; NR; 72.7</td>
<td>49.0d</td>
<td>29.7d</td>
<td>22.5c; 4.0; 2.0</td>
<td></td>
<td>22.6</td>
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<tr>
<td>ER metformin (2,000); 6 months</td>
<td>208</td>
<td>26.1 ± 4.0</td>
<td>35.0 ± 8.5; NR; 72.1</td>
<td>29.0</td>
<td>12.0</td>
<td>7.2; 0; 0</td>
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<td>40.0</td>
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<tr>
<td>Clomiphene citrate (50–150) + ER metformin (2,000); 6 months</td>
<td>209</td>
<td>26.3 ± 4.0</td>
<td>34.2 ± 8.4; NR; 68.9</td>
<td>60.4e</td>
<td>38.3e</td>
<td>26.8c; 3.1; 0</td>
<td>25.0</td>
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</table>

³P < 0.001 for metformin versus clomiphene citrate; ⁴P < 0.05 for metformin versus clomiphene citrate; ⁵recalculated from the actual pregnancy rate rather than by intent-to-treat analysis; ⁶P < 0.001 for clomiphene citrate versus metformin; ⁷P < 0.001 for clomiphene citrate plus metformin versus metformin alone; ⁸P < 0.01 for clomiphene citrate plus metformin versus clomiphene citrate alone. Abbreviations: ER, extended release; IR, immediate release; NR, not reported.


Nat Clin Pract Endocrinol Metab doi:10.1038/ncpendmet0787
Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome (Review)

Costello MF, Shrestha B, Eden J, Sjoholm P, Johnson N, Moran LJ

Analysis 1.3. Comparison 1 Metformin versus OCP (Clinical parameters), Outcome 3 Hirsutism - total (score and subjective).

Short and long term complications of PCOS

Short term complications:
- anovulation, infertility, missed pregnancy, abortion
  The main cause is the hyperandrogenism

Long term complications:
- metabolic disorder: metabolic syndrome, central type obesity
  hypertension, carbohydrate metabolism disorder – diabetes mellitus
  hyperlipidaemia – dyslipidaemia
  elevated cardiovascular risks
  steatohepatitis
  The main cause is the insulin resistance

- tumours:
  endometrium and ovary cancer are more frequent
Differential diagnostic

Other causes of hyperandrogenism

- Hypothyreoidism
- Hyperprolactinemia
- Androgen-producing ovarian or adrenal tumour
- Cushing-syndrome, glucocorticoid-resistance
- drugs (anabolic steroids)
- „late-onset” adrenal hyperplasia
- HAIRAN szindróma
HAIRAN syndrome

HyperAndrogenic
Insulin Resistance
Acanthosis Nigricans

- 1-5% of hyperandrogenic women
- often accompanying with HT and lipid abnormalities
- high circulating insulin level
  - fasting > 80 mU/ml
  - oGTT > 300 mU/ml at relatively normal glucose
- insulin’s multiple effect at hyperandrogenism
- comparing to PCOS where insulin resistance is much more milder, high HOMA-IR
Causes of Androgen Excess

- **Ovarian**
  - PCOS
    - hyperthecosis
      - ovarian tumor

- **Adrenal**
  - adrenal tumor
    - Cushing’s syndrome
      - non-classical adrenal hyperplasia
        - glucocorticoid resistance, altered glucocorticoid metabolism

- **Specific condition of pregnancy**
  - luteoma
    - hyperreactio luteinalis
      - aromatase deficiency in fetus

- **Other**
  - hyperprolactinemia, hypothyroidism
    - medication (anabolic steroids)
      - idiopathic hirsutism
Thank You!