POLYCYSTIC OVARY SYNDROME

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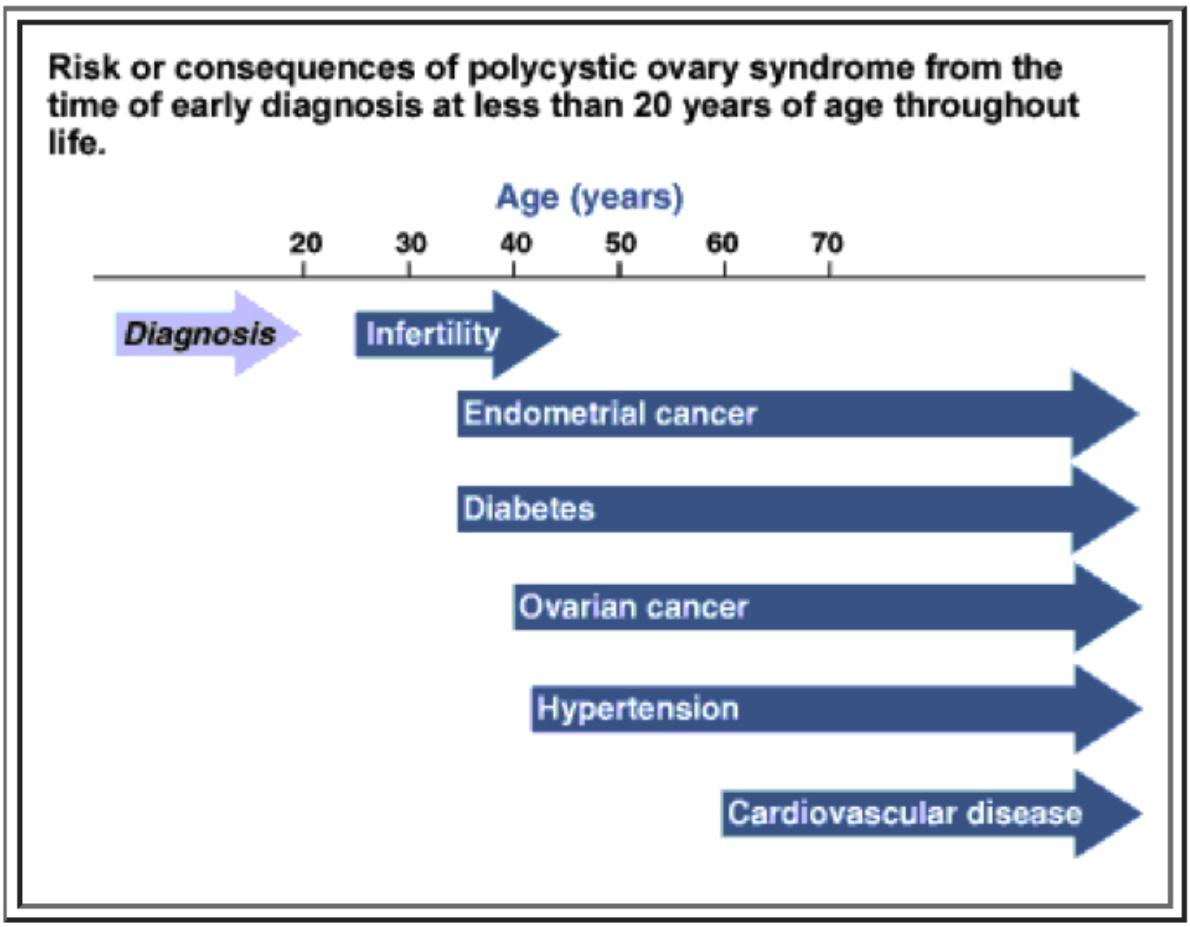
Heterogeneous group of disorders characterized by:

- Disturbed ovulation
- hyperandrogenism

affecting multiple systems at various stages of a woman's life with lifelong issues:

- reproductive organs
- metabolic effects
- cardiovascular
- psychological effects



first observed by Stein and Leventhal 1935

prevalence: 5-10% have PCOS
12%-21% Australian women reproductive age PCOS (higher in aboriginals)
20% have PCO

70% PCOS undiagnosed due to lack of consumer and health care provider awareness
complex multigenetic disorder

Diagnosis:

NIH criteria 1990

- menstrual irregularity due to disturbed ovulation
- hyperandogenism (clinical or biochemical)
- exclusion other causes hyperandrogenism eg CAH, adrenal tumours

Rotterdam consensus 2003 (broader inclusion of patients)
2 out of 3

- oligoovulation (menses >42 days apart) or anovulation (no menses 3 months)
- clinical or biochemical hyperadrogenism
- PCO on US (≥12 follicles 2-9mm or ovarian volume >10ml in at least 1 ovary)

4 phenotypes PCOS

	severe	**Hyperandrogenism+ chronic anovulation**	**Ovulatory PCOS**	**Mild PCOS**
menses	irregular	irregular	regular	irregular
US features	PCO	no	PCO	PCO
androgens	increased	increased	increased	Mild raised
insulins	raised	raised	raised	normal
risks	Potential long term	Potential long term	unknown	unknown
prevalence	61%	7%	16%	16%

Androgen Excess Society (AES)

- Hyperandogenism
- Ovarian dysfunction either menstrual irregularity or PCO
- Exclude other hyperadrogenic disorders

Other features (not essential for diagnosis)

- Obesity
- Hyperinsulinaemia and metabolic syndrome (syndrome XX)
- Dyslipidaemia
- Hypertension
- Macrovascular disease
- Obstructive sleep apnoea (independent of BMI)
- Cancer : endometrial; ovarian, breast (theoretical)

Clinical features PCOS

Menstrual disturbances

90% PCOS have some menstrual disturbance related to anovulation

- amenorrhoea 60%
- DUB 30%

Small amounts weight loss can improve menstrual function
Exclude hyperprolactinaemia and hypothalamic pituitary dysfunction:

- Prolactin
- FSH/LH/E2

In adolescents regular ovulatory cycles (21-35 days) occurs in 40-95% after 2 years menarche
Test for PCOS if irregular cycles 2 years post menarche.
If on OCP stop 3 month before testing

Infertility and miscarriage

- anovulation
- poorer quality oocytes
- impaired implantation endometrial defects

Hyperandrogenaemia

Free testosterone Elevated in 60-80% in PCOS
60% PCOS have hirsutism and 90% hirsutism due to PCOS
FAI most sensitive as insulin + androgens reduce SHBG production
Source mainly ovary with some adrenal contribution
Androstenedione and DHEAS (elevated 25% cases) often elevated less reliable

Clinical features of increased androgens (dependent on androgen receptors sensitivity eg Asians rarely have hirsutism)

- Acne
- Hirsutism
- Male pattern baldness

Rarely virilsation (think tumour)

- Increased muscle
- Deepening voice
- clitoromegaly

natural history of hyperandrogenaemia unknown, but some evidence reduction with age

PCOS is very common

- amenorrhoea patients 30%
- infertility patients 30%
- anovulatory infertility 75%
- idiopathic hirsutism 90% have PCOS

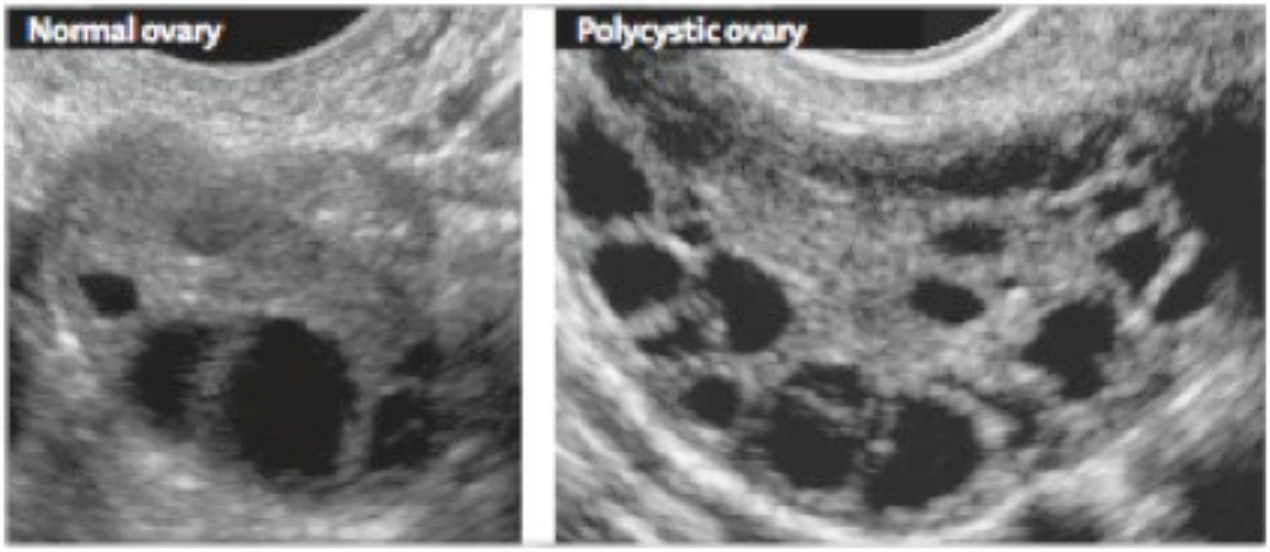
Classical picture PCOS
(1) oligo/amenorrhoea
(2) infertility
(3) hirsutism 60%
(4) obesity 50%

Polycytic Ovary characteristics
Polycystic ovaries (PCO) are a sign NOT a disease ∴ it is NOT essential to demonstrate it in making a diagnosis PCOS (although 90% of PCO will have at least 1 abnormal hormone parameter and 80-100% PCOS will have PCO)

PCO is thought to be results high androgens effects on the ovary

Characteristics of PC ovaries:

- Increased volume>10ml or ≥12 peripheral follicles (2-9mm) around increase stroma
- ↑ atretic and growing primary follicles with reduced number primordial follicles (total pool of preantral follicle increased) based on TV US
- ↑ tunica 50% → thick ovarian capsule
- x 4 ovarian hilus cell nests (hyperplasia)



AMH
may be surrogate marker PCO
Higher levels found more severe PCOS with hyperinsulinaemia + amenorrhoea
AMH reduces sensitivity to FSH preventing folliculogenesis
1 study chinese adolsecents 61% sensitivity 70% specificity

compared to **multicystic ovaries**:

- little stromal tissue
- cysts both central and peripheral

usually secondary to :

- weight loss
- hypothalamic amenorrhoea

Metabolic disturbances

Insulin Resistance leading to Hyperinsulinaemia

PCOS woman thought to have a post-insulin receptor defect → ↑ insulin resistance.
hyperinsulinaemia →

- increased androgens via
  - (i) direct stimulation IGF1 receptor in ovary → androgen secretion
  - (ii) ↓ SHBG (direct effect on liver)
  - (iii) ↓ IGF BP1 (inhibits IGF1 receptor)
- ↑ sensitivity pituitary to GnRH

obesity → exaggerated response of hyperinsulinaemia → ↑ androgens but is NOT necessary for PCOS

obesity occurs in 50% PCOS

unselected population obese women 30% have PCOS vs 5% lean women
30% lean PCOS have hyperinsulinaemia compared to 70% obese PCOS have hyperinsulinaemia
PCOS women 10% will have diabetes by 4th decade and 35% glucose impairment vs 2% of the normal population

Incidence DM in PCOS 3-7% depending on test used

For normoglyemicc PCOS annual incidence developing DM 2.6%
For IGT PCOS annual incidence developing DM 8.7% with 60% developing DM
Obese PCOS (>30) have x10 incidence developing IGT or DM vs non obese PCOS (<25)
Risk factors for diabetes in PCOS:

- obesity
- history of GDM
- first degree relative with DM
- race eg hispanic; african American etc

also consider:

- HT
- Smoking
- Physical inactivity

Hyperinsulinaemia → acanthosis nigricans (30%)
HAIR – AN syndrome → special sub group of PCOS
D/Dx of AN:

- visceral malignancy
- metabolic / endocrine disorders

Exact role of ↑ insulin is unknown:

(i) ↑ insulin → ↑ obesity may trigger PCOS
(ii) ↑ insulin → ↑ androgen → PCOS

increased RR metabolic syndrome 1.5-2 times

- abdominal obesity
- hyperglycemia
- HT
- dylipidaemia

Dyslipidemia
PCOS have:

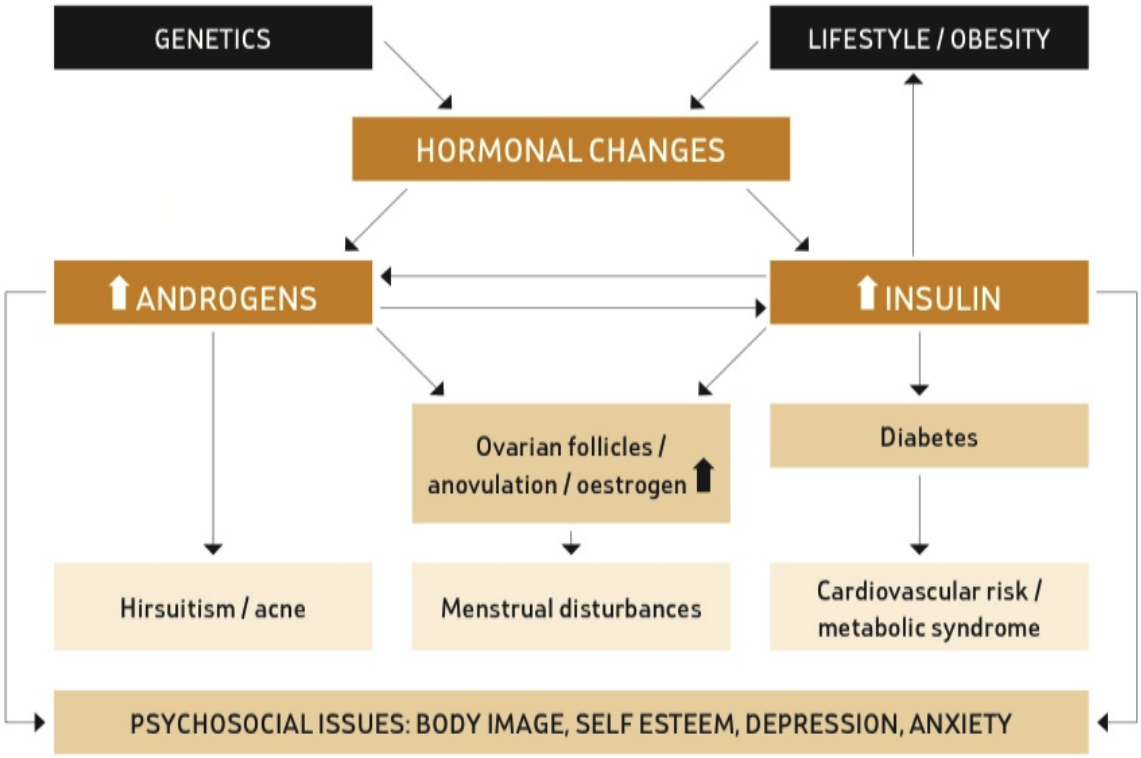
- reduced HDL
- elevated LDL + TG

even after matching for BMI and other cofounders (RR1.53 of dyslipidaemia)
15-30% PCOS have adverse lipid levels
Coronary artery disease
Theoretical excess risk CAD with PCOS and metabolic syndrome (obesity; insulin resistance; diabetes and dylipidaemia), however not well established.
Most studies non randomized and measure surrogate markers of CAD risk
No studies directly measuring CAD
Sleep apnoea
Increase incidence sleep apnoea PCOS patients controlled for BMI with RR x3-9
Incidence 30%-50%
Sleep apnoea appears to be marker insulin resistance (RR x2 PCOS +IR vs no IR)
Patients asked about daytime somnolence
Mood disorders and psychologic disturbances
Low self esteem and negative body image via acne, hirsutism, obesity, infertility etc
Increase incidence of depression , anxiety and eating disorders
Neglected aspect PCOS
Recommended screen for mood disorders
Optimal psychological assessment TBD
Non alcoholic Steatohepatitis (type of hepatitis associated with fatty liver)
PCOS have higher incidence compared to normal; diabetics & obese women
Hyperprolactinaemia
mild found in 25% of PCOS
Mechanism

- ↑ estrogen sensitizes lactotrophs
- ↓ dopamine which lead to: ↑ LH ;↑ PRL
- GnRH stimulation
- opioids

Factors affecting phenotype expression PCOS

- genetic eg risk diabetes
- racial /ethnic origin eg. Hispanics /Caucasians increase obesity
  Asians / Hispanics increase diabetes (adjusting BMI)
  Blacks more HT
  Asians less hirsutism
- diet + Lifestyle



Pregnancy complications PCOS

Miscarriages

Debatable PCOS have increased MC rates

Poor quality studies suggest metforrmin may reduce MC rate but no RCT

PIH OR 3.61
PET OR 3.47
GDM OR 2.94
PTbirthOR 1.75
PNM OR 3.07
(above independent of obesity ; multiple pregnancies)

PCOS 40% will have pregnancy complications

Preconception counseling

- BP
- OGTT
- Optimise weight

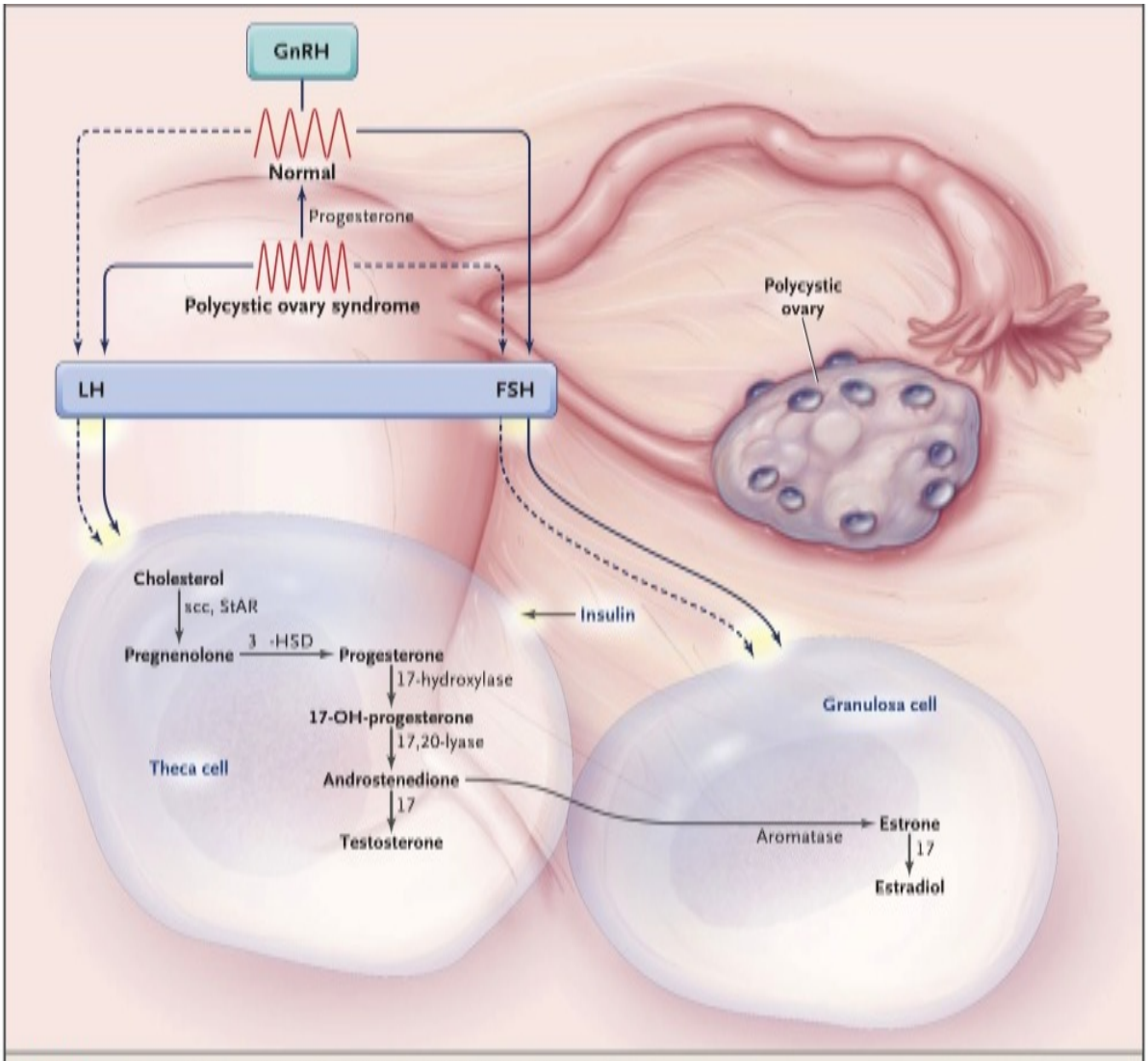


Figure 2. The Hypothalamic–Pituitary–Ovarian Axis and the Role of Insulin.

Increased ovarian androgen biosynthesis in the polycystic ovary syndrome results from abnormalities at all levels of the hypothalamic–pituitary–ovarian axis. The increased frequency of luteinizing hormone (LH) pulses in the polycystic ovary syndrome appears to result from an increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses. The latter can result from an intrinsic abnormality in the hypothalamic GnRH pulse generator, favoring the production of luteinizing hormone over follicle-stimulating hormone (FSH) in patients with the polycystic ovary syndrome, in whom the administration of progesterone can restrain the rapid pulse frequency. By whatever mechanism, the relative increase in pituitary secretion of luteinizing hormone leads to an increase in androgen production by ovarian theca cells. Increased efficiency in the conversion of androgenic precursors in theca cells leads to enhanced production of androstenedione, which is then converted by 17β-hydroxysteroid dehydrogenase (17β) to form testosterone or aromatized by the aromatase enzyme to form estrone. Within the granulosa cell, estrone is then converted into estradiol by 17β. Numerous autocrine, paracrine, and endocrine factors modulate the effects of both luteinizing hormone and insulin on the androgen production of theca cells; insulin acts synergistically with luteinizing hormone to enhance androgen production. Insulin also inhibits hepatic synthesis of sex hormone–binding globulin, the key circulating protein that binds to testosterone and thus increases the proportion of testosterone that circulates in the unbound, biologically available, or "free," state. Testosterone inhibits and estrogen stimulates hepatic synthesis of sex hormone–binding globulin. The abbreviation scc denotes side-chain cleavage enzyme, StAR steroidogenic acute regulatory protein, and 3β-HSD 3β-hydroxysteroid dehydrogenase. Solid arrows denote a higher degree of stimulation than dashed arrows.

Pathophysiology:

Basic pathophysiology of PCOS

(i) ↑ theca lutein cell activity → androgen production
(ii) ↓ granulosa cell activity → lack of follicular development

- elevated LH secretion leads to increase androgen production in the ovary
  tonic elevated LH → LH:FSH > 3 (however 30% PCOS have normal ratio)

  Mechanism:
  Central defect → ↑ GnRH pulse frequency inherently → ↑ LH over FSH secretion
  NB: LH → direct stimulation IGF 1 receptor ovary → ↑ androgen production
  Peripheral defect
  excess estrogens / low progesterone → sensitizes the hypothalamus to increase pulse frequency of GnRH → favours LH secretion over FSH

  Increased androgens mainly from ovaries (stimulated by ↑ LH)
  Some contribution adrenals (50% PCOS → ↑ DHEAS, which improves with ovarian suppression).
  Hyperandrogenaemia →
  (i) block action E2 on granulosa cells → ↓ FSH receptors and prevents normal follicular maturation → multiple small cysts that become atretic → further androgen secretion → vicious cycle (prevents ovulation)
  (ii) direct inhibitory effect hypo-pit axis
  (iii) ↓ SHBG → exaggerated androgen bioactivity
  NB: 70% of PCOS have hirsutism
- hyperinsulinaemia effects:
  1. acts synergistically with LH to enhance androgen production
  2. reduces SHBG production enhancing effects androgens
- Increased estrogens especially estrone and estradiol from peripheral conversion of androstenedione and testosterone.
  - Reversal E_1/E_2 ratio
  - Increased biological activity of the oestrogens due to ↓ SHBG secondary to:
    (1) ↑ androgen
    (2) obesity

  Hyperestrogenic state →
  - Endometrial cancer x3
  - Breast cancer (theoretical)
  - Modest raised prolactin

Aetiology

Aetiology of PCOS is unknown, but 2 theories

- Central
  inherent ↑ frequency GnRH pulses leads to ↑ LH secretion lead to increase androgen secretion
- Peripheral
  ↑ androgen / ↑ insulin → appropriate central response
  2 peripheral theories:
  (1) Genetic defect P450 enzyme which converts androgen → estradiol in ovary, ∴ there is increased androgen milieu in the ovary (linked to production of insulin receptor) → PCOS.
  (2) Virilized ovary theory ie androgen from outside the ovary eg adrenals/exogenous hyperandrogenaemia → PCOS

Differential diagnosis of PCOS

hirsutism

- CAH early or late onset
- Cushings syndrome
- androgen secreting tumours
- ovarian hyperthecosis

ovulation dysfunction

- hyperprolactinaemia
- hypothalamaic pituitary dysfunction

Investigations

hormones taken in the early follicular phase as:

- periovulatory rise in all hormones
- luteal phase progesterone suppresses hormones

- SHBG/FAI/testosterone
- LH/FSH/E2
- TV ultrasound PCO + endometrial thickness
- OGTT then every 2-3 years
- Fasting Lipid profile
- fasting BSL/insulin ratio (< 3 ⇒ hyperinsulinaemia) controversial

progesterone withdrawal if amenorrhoea
if hirsutism DHEAS + 17(OH) progesterone
if suspect CAH then do: - 17 OH progesterone
- ACTH stimulation for 17 OH progesterone
For Cushings: dexamethasone suppression

Management

Aims of treatment:

1) treat hirsutism
2) prevent effects chronic anovulation (endometrial hyperplasia)
3) induce ovulation for fertility
4) prevent and treat cardiovascular disease and metabolic syndrome:

Management of metabolic and cardiovascular effects

Lifestyle changes

- Caloric restriction
- Change dietery composition
- Physical activity / exercise
- Behavioural therapy

Most studies non randomized
Should be used throughout lifespan of the woman to optimize general health and fertility
Metabolic / cardiovascular assessment

- BP
- BMI
- Waist circumference
- Lipids
- OGTT every 2nd year
- Stop smoking & increase physical activity

weight reduction 5-10% (aim BMI <25)

- return to normal menstrual function in 80% + ovulation
- reduction miscarriages
- improves hirsutism in 80% + improves adverse androgen profile
- improves insulin sensitivity

insulin sensitizing agents eg metformin/troglitazone →

- improvement in adverse androgen profile
- reduction diastolic BP 10%
- can restore menstrual cycles and fertility

Hirsutism

Drug therapy needed for at least 6 months before improvement.
OCP

- inhibits LH → ↓ androgen production
- Non androgenic progestogen e.g Diane 35, Yasmin
- Theoretical concern oestrogen → impaired glucose tolerance + insulin resistance + procoagulant

Antiandrogens

- cyperterone acetate 50-100mg D5-15 cycle with oestrogen
- spironolactone 100-200mg daily in divided dose used with OCP or other contraception
- finasteride

metformin
reduction in androgens but no reduction in hirsutism (based 1 small study)
GnRH analogues
Theoretically may be used
can only be used 6 months unless with add back therapy
Dexamethasone
0.25-0.5mg nocte in combination OCP if ↑ DHEAS
cosmetic methods

- waxing
- electrolysis
- laser / creams etc

Chronic anovulation effects

endometrial protection from endometrial cancer

- progestins
  MPA / primolut 10mg / 5mg for 12 days of month or continuously
- OCP probably ideal unless C/I
  Advantages:
  - contraception
  - treats hirsutism
  - ↓ androgen and improved lipid profile
- Metformin
  - Improves menstrual cycle 60%
  - Potentially first line in obese
  - Combined with OCP

Infertility

Lifestyle changes

Aim BMI <30

Those with BMI >35 (morbidly obese) should loose weight prior to fertility treatment via

- lifestyle
- drugs
- bariatric surgery

Genea fertility fit program

Clomid

successful in 80% of cases of inducing ovulation but pregnancy rate 40% (after 6 ovulatory cycles with upto 40% miscarriage rate

20% will not ovulate on Clomid (clomiphene resistant CCR vs clomiphene failure)

50mg for 5 days upto maximum 150mg daily + Monitor ovulation first cycle bloods + US

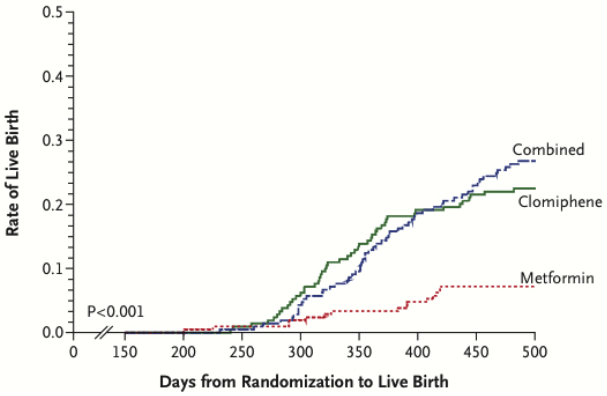
5-8% twins + 0.3% triplets or greater

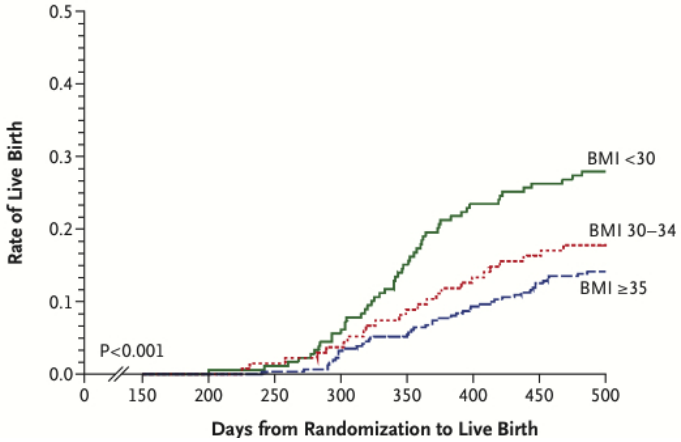
once ovulatory, treat for 6 cycles and aim progesterone >30nmol/L

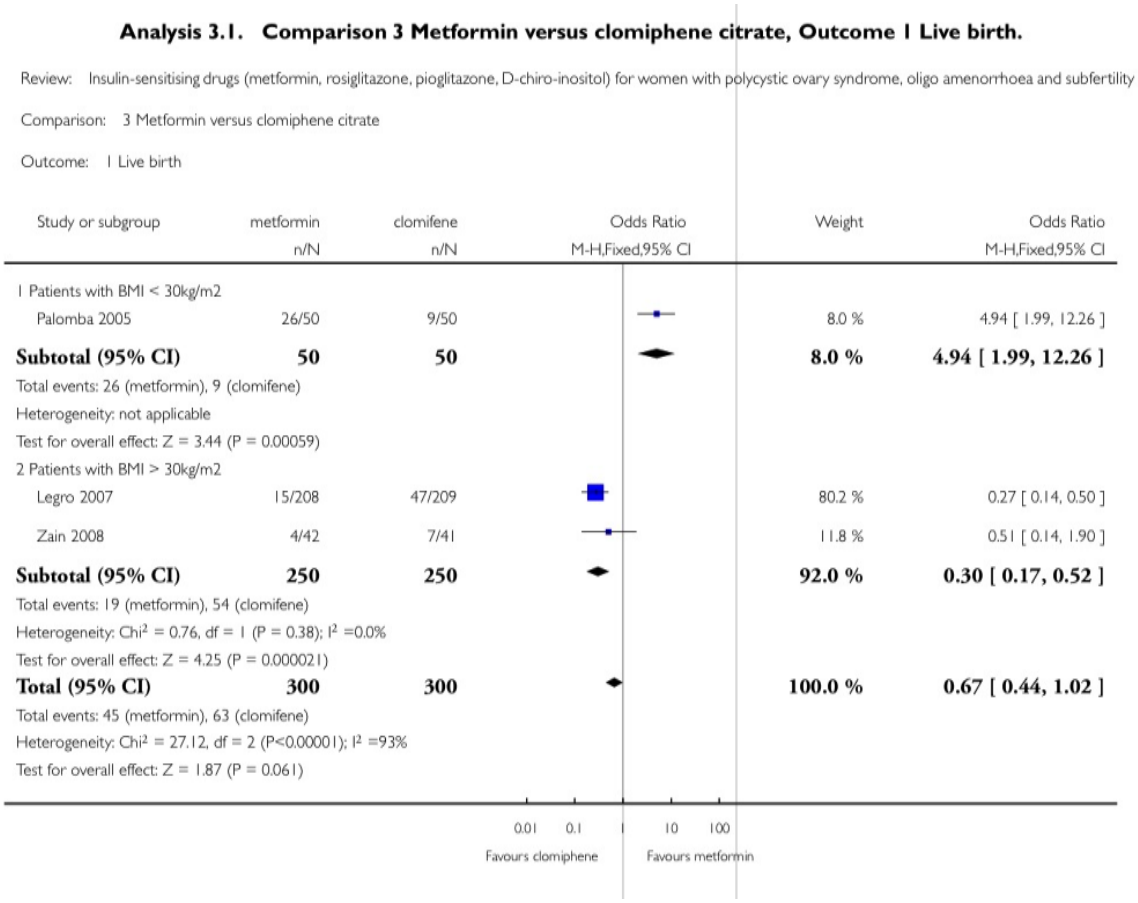
Negro RCT NEJM 2007 n= 626

Clomiphene vs Metformin vs combination concluded (in clomiphene naïve patients)

- improved live birth rates CC / combination over metformin (22% vs 27% vs 7%)
- improved ovulation combination>CC>metformin (60% vs 49% vs 29%)
- increase MPR CC or combined vs metformin (6% vs 3.1% vs 0%)
- NSD MC rates
- BMI<30 had higher LBR







from Cochrane 2010

metformin

- In clomiphene naïve patients Metformin improves PR in women BMI<30 (RR 1.46), but NSD LBR vs placebo
- clomiphene resistant (CCR) PCOS metformin + clomiphene improved LBR (RR 6.4)
- With BMI >30 metformin + weight reduction may improve clomiphene sensitivity

Unknown optimal duration metformin prior to clomid (4 weeks or >weeks): Cochrane no studies

in CCR clomid + metformin vs clomid (favours C+M)
from Moll etal HRU 2007

Aromatase inhibitors
Letrazole (2.5-5mg for 5-10 days) / anastrazole
2nd line Used in clomiphene resistant (CCR)
Less adverse effect endometrium
Similar ovulation and pregnancy rates compared to clomiphene
Concern letrazole teratogenic (1 study) effects (cardiac and bone)
CCR patients ovulation rates 55% with PR 25%

dexamethasone
0.25-0.5mg nocte + clomid
indications

- increased DHEAS
- CC reisitance

OCP pretreatment
For CC resistance OCP pretreatment for 2 months can suppress LH / E2 and androgens and improve ovarian microenvironment
Followed by 100mgCC led to improved ovulation and PRs

Gonadotropins:
90% ovulate
35% pregnancy rate
30% miscarriage rate
25% multiple pregnancy rate
Issues with FSH stimulation

- require intensive monitoring
- expensive / time consuming
- PCOS unpredictable response esp risk of hyperstimulation (OHSS)

As a result with modern IVF success rates if FSH required IVF preferred:

- Controlled hyperstimulation
- SET less risk multiple pregnancy
- More cost effective

complications ovarian stimulation

- Multiple pregnancy
- OHSS
- Cancelled cycles

pulsatile GnRH
50% ovulation rate
15% pregnancy rate per cycle and high miscarriage rate
not as successful in PCOS in ovulation induction compared to other areas of GnRH (pulsed) use

Surgical Methods (induce ovulation)

Ovarian Wedge Resection (out moded today)

- restoration menses 90%
- ovulation rate 90%
- conception rate 50%
- relapse rate 30%

main problem → major surgery & risk of adhesions

Laparoscopic drilling procedures (LOD)

mechanism → (i) destruction of androgen secreting cells
(ii) destruction of inhibin → ↑ FSH
(iii) tissue damage → ↑ blood flow → ↑ FSH to ovary

endocrine changes:

- reduced testosterone / inhibin / LH
- increased FSH
- improved insulin sensitivity (mixed results)

electrosurgery: 4-6 drillings
30-40watts
3 sec to depth 3mm

laser 30-40 drillings as less tissue damage

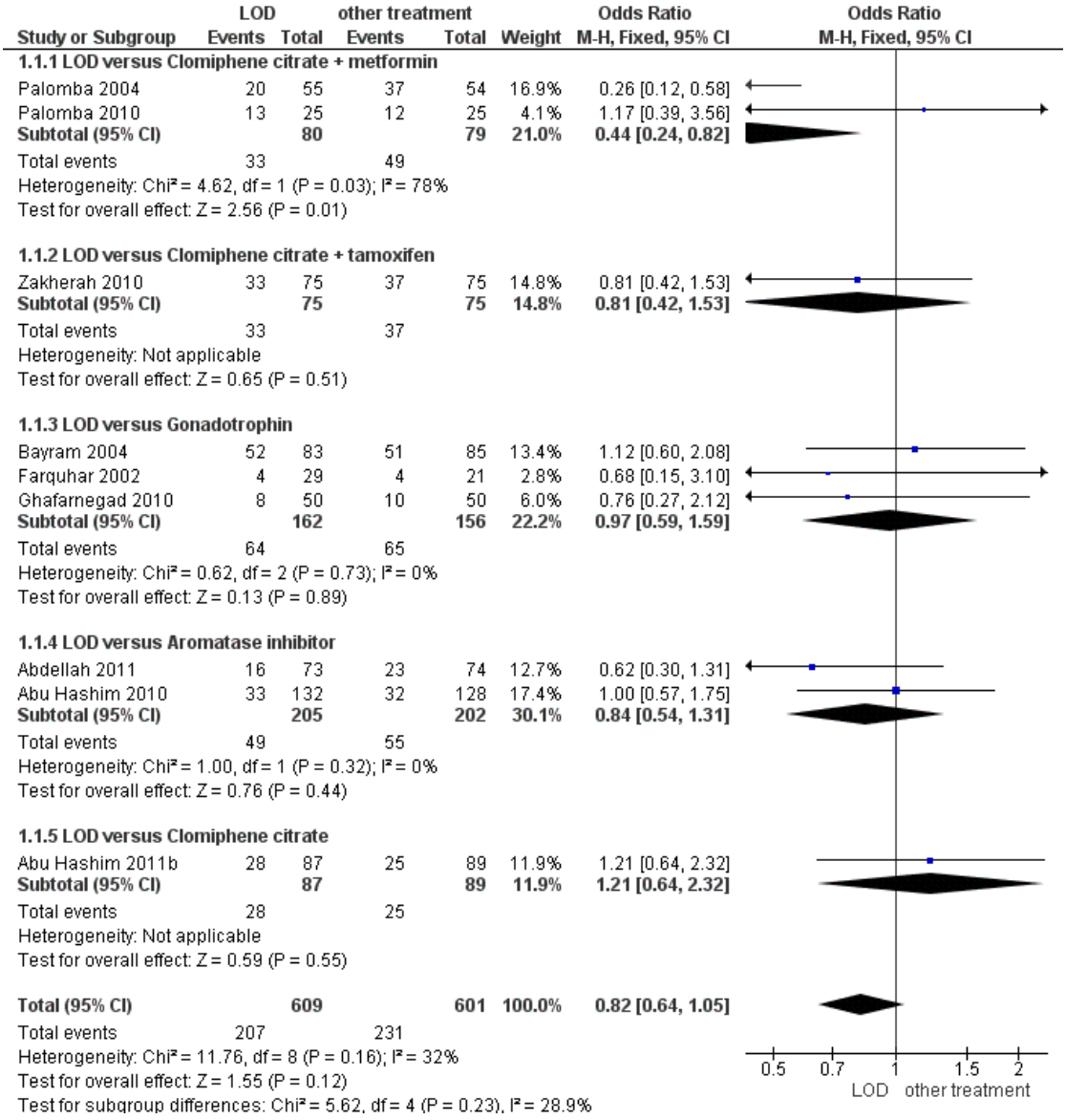
Results LOD

- LBR 25-45%
- ovulation rates 50-90% (more effective non obese PCOS)
- pregnancy rate (25%-50%) (most occur within 12 months)
- miscarriage rates 4-9%
- improves the responsiveness of medical induction agents (clomid /FSH & IVF)
- may also improve menstrual cycles and reverse endocrine profile (await further studies)

Cochrane 2012 LOD versus medical ovulation induction (n=1210)

- LBR NSD (OR 0.82) subgroup LOD vs CC+Met LBR OR 0.44 (high heterogeneity)
- PR NSD (OR 0.97)
- MC NSD (OR 1.1)
- MBP less with LOD vs GnTP (OR 0.13)
- LOD 1vs 2 ovaries NSD on ovulation and PR

Figure 4. Forest plot of comparison: 1 LOD ± medical ovulation versus other treatment, outcome: 1.1 Live birth rate.



from Cochrane 2012

indications:

- CCR anovulation PCOS
- all infertility PCOS patients undergoing laparoscopy for other reasons

Potential Risks

- adhesion formation. Upto 25%, but most are not clinically significant
  role of antiadhesives to be determined
  2nd look laparoscopy does not improve PR
- POF due to thermal damage to the ovaries }
- ovarian carcinoma 2^0 to tissue repair } theoretical

Metformin in PCOS

ISD theoretical beneficial in treating hyperinslinaemia of PCOS, but critical evidence often has been lacking.
Optimal dose 1500-2000mg per day
Metformin mechanisms:

- reduced hepatic production glucose + increased glycolysis
- increase peripheral uptake glucose
- reduced GIT absorption
- reduced peripheral lipolysis

main SE GIT disturbance in up to 25%

Lipids

Recent RCT show little change lipid profile
Non RCT reduced LDL in overweight PCOS (with OCP)

Atherosclerosis / inflammatory markers

Theoretical improvement in CRP / PAI-1 / endothelin (markers CAD risk), and some studies do show improvement, but no evidence in reducing CAD directly .

Metabolic effects

No effect on BMI; waist circumference; waist hip ratio
Small reduction hyperinsulinaemia in non-obese PCOS
Reduction in developing DM (from IGT PCOS reduction around 30%) but lifestyle changes had more sig reduction DM development

Hormone profile

Metformin reduces FAI and LH (more so in normal than obese PCOS)
With also improvement in hirsutism, but OCP is more effective in lowering testosterone and possibly hirsutism

Menstrual pattern

Improved menstrual pattern with metformin (60%), but OCP is better

Fertility

Metformin increase ovulation and PR but there is no increase in LBR compared to placebo
Metformin + CC improved LBR vs CC in CCR
CC significant increase LBR vs metformin
Maybe improved oocyte quality in IVF cycles, but no increase LBR in IVF cycles
Metformin reduce OHSS in IVF cycles (OR 0.27)
No evidence reduced MC

Conclusion:

- Metformin increase ovulation and PR but not LBR in non CCR PCOS
- In CCR PCOS metformin + CC improved LBR vs CC
- Improves menstrual function and maybe useful in obese PCOS where OCP is contraindicated or combined
- May reduce risk developing DM (but lifestyle changes more effective)
- No evidence that long term metformin reduces cardiovascular risks but theoretically attractive

Adolescent PCOS

More difficult to diagnose as :

- 85% cycles at menarche anovulatory and up to 60% may be anovulatory at 2 years (50% of adolescents with oligo/amenorrhoea will have long term ovulatory dysfunction)
- acne +/- mild hirsutism common, but hyperandrogenaemia and progressive hirsutism uncommon.
- Ovarian volumes amy be more difficult to measure on TA US and adolescent ovaries have increased volume compared to adult ovaries.

Diagnosis PCOS in adolescents stricter all 3 criteria

- Irregular cycles 2 years post menarche
- Hyperandrogenaemia (not acne)
- PCO

Clinical problems:

- Irregular cycles
- Hirsutism
- Metabolic syndrome (central obesity, dyslipidaemia, HT, impaired glucose tolerance) although no standard definition in adolescents occurs in up to 1/3 PCOS.

Treatments

- Lifestyle modification via diet, education, exercise, behavior changes which result in weight loss improves menstrual cycles and metabolic parameters.
- OCP or progestins
- Antiandrogens
- Metformin may be useful in obese, glucose impaired + those with strong family hx cardiovascular disease.

PCOS with ageing

Carmina et al 2012 n= 193 PCOS retrospective cohort followed over 20 year period from age 20-25 until 40-45 found:

- Decreased androgens
- Reduced ovarian volume
- Increased ovulation rates (prolonged fertility? Due to increase cohort follicles?)
- 10% no longer diagnosed PCOS
- increased waist circumference implying metabolic issues may persist

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