Polycystic Ovarian Syndrome
Pathogenesis & Treatment

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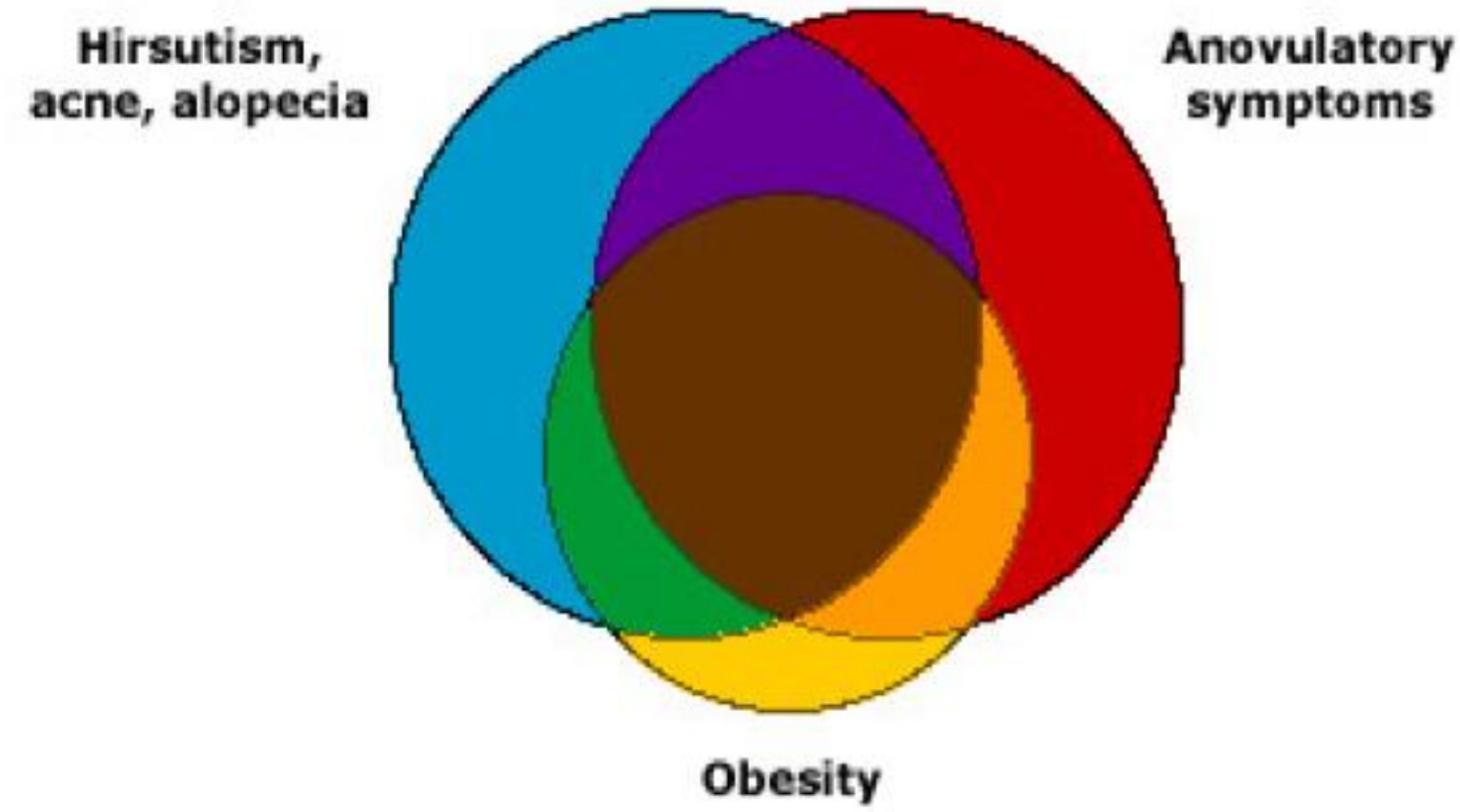
Common names and confused with…

- Stein-Leventhal Syndrome
- Polycystic ovary disease
- Functional ovarian hyperandrogenism
- Hyperandrogenic chronic anovulation
- Ovarian dysmetabolic syndrome
- Polycystic ovarian syndrome

PCOS

- 25% of females with amenorrhoea
- 90% of females with oligomenorrhoea
- 90% of females with idiopathic hirsutism
- 33% of females with infertility

Manifestations of polycystic ovary syndrome in approximate proportion to their relative incidence and coincidence



Prevalence of hyperinsulinemia and insulin resistance in PCOS

In ~ 65% of obese PCOS women

In ~ 20% of lean PCOS women

*Dale et al., Fertil Steril 1992; **58**:487-91*

Abbott
A Promise for Life

PCOS and risk of type II diabetes

- Evidence from small long-term cohort studies, case-control studies and case series, points to a risk of type II diabetes in middle age of 10-20% with higher rate of impaired glucose tolerance suggesting that further cases of diabetes will develop later

Type 1 Diabetes Mellitus and Polycystic Ovary Syndrome

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Endocr Pract 2009 Jan; 15(1):80-81.

Definition Clinical Features of PCOS

In the:

1. USA - Endocrine Profile

2. UK & Europe - Ultrasound Signs

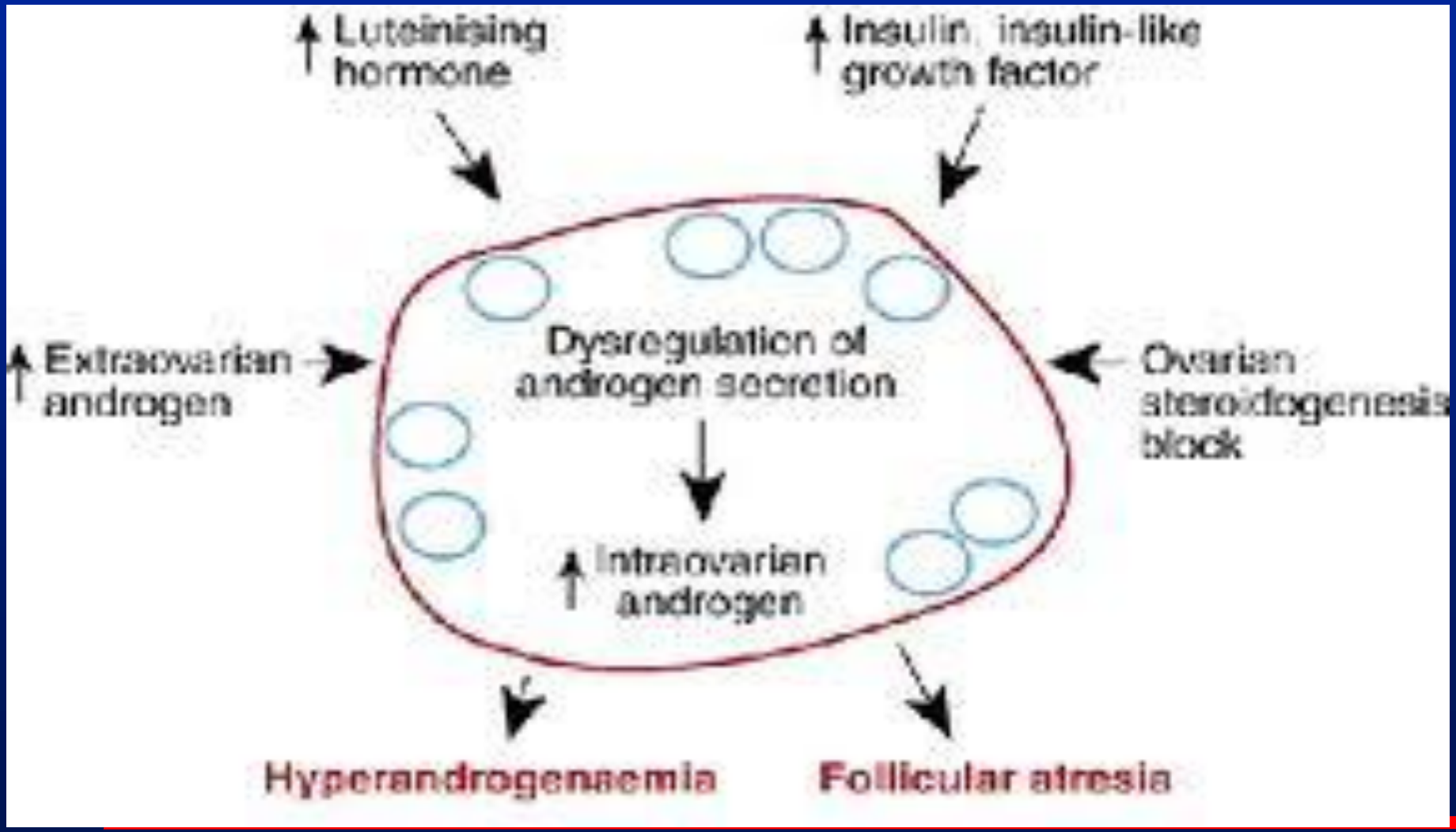
Revised Diagnostic Criteria

- 2003 Rotterdam Criteria
  - **Presence of at least two of the following**:
    - Oligo/anovulation
    - Hyperandrogenism
    - Polycystic ovaries on ultrasound
  - And the exclusion of other causes

Endocrine Features

- Acyclic increase in pulsatile LH levels
- Raised LH to FSH ratio
  (test in early follicular phase)
- Raised androgens
- Reduced sex hormone binding globulin

PCOS : Hormonal changes

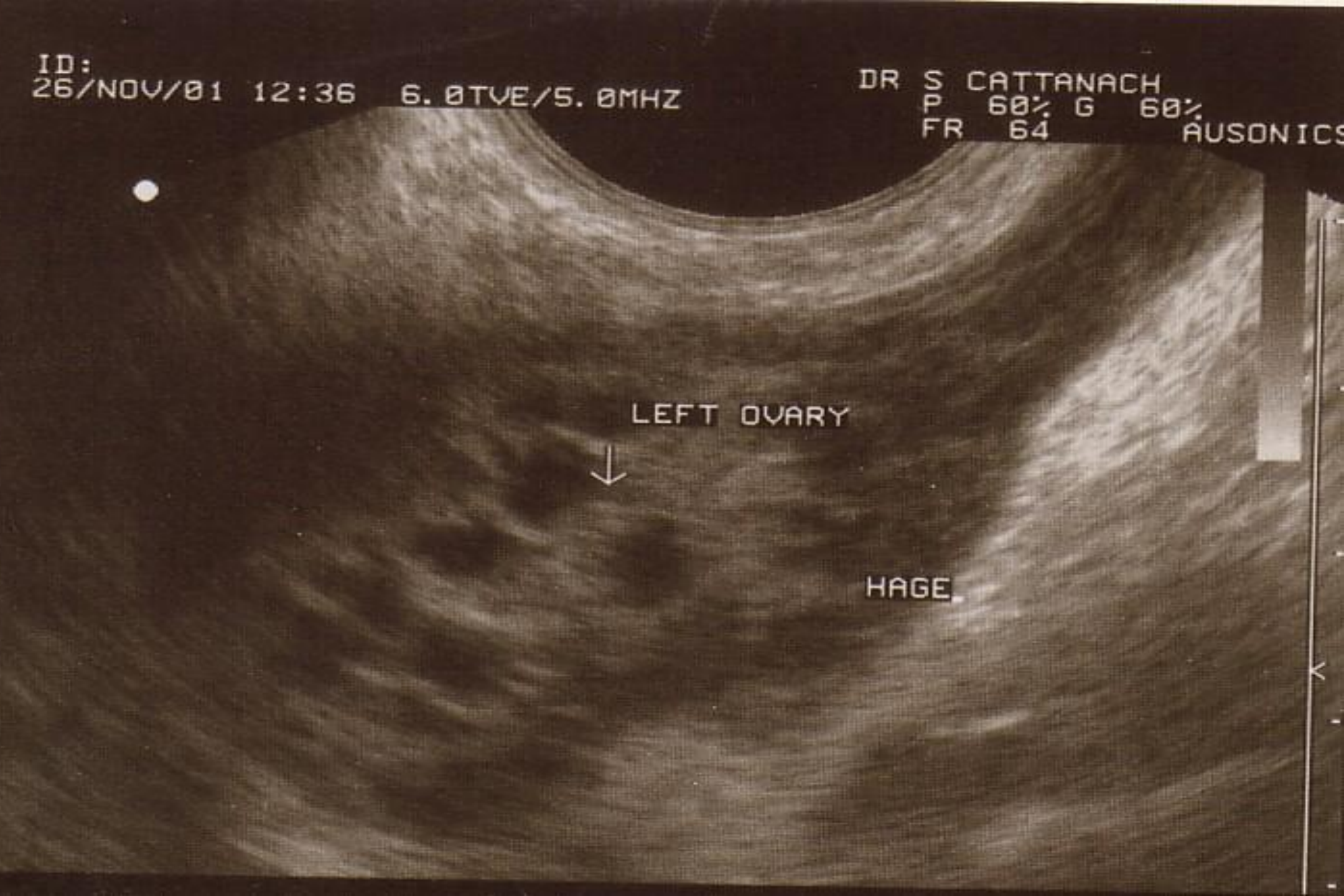


Pathophysiology of Polycystic Ovary Syndrome

- LH Hypothesis
- Insulin Hypothesis
- Ovarian Hypothesis

Ultrasound Features

- Increased stomal echo
- 10 or more follicles in one plain
- Follicles 2-10mm in diameter
- Increased ovarian volume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P 60% G 60%
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AUSONICS
LEFT OVARY
HAGE

Polycystic Ovarian Syndrome: Mechanism

- Androgens converted to estrone ► endometrial proliferation ► irregular periods
- ▲ Serum estrogen and testosterone
- Insulin resistance once believed to be due to ovarian androgen overproduction
- **Current theory is that Hyperinsulinism causes ovarian androgen overproduction**

PCO is not PCOS.

PCO on USS found in 20% of randomly selected women of reproductive age.

(While most of these women are cycling normally this group are significantly more likely to have infertility, irregular bleeding, hirsuitism and elevated testosterone)

1. Familial - Strong family history

? autosomal dominant but > 50% occurrence

?epigenetic factors

(related to male pattern premature baldness and NIDDM)

2. Ovarian & adrenal steroidogenesis disorder

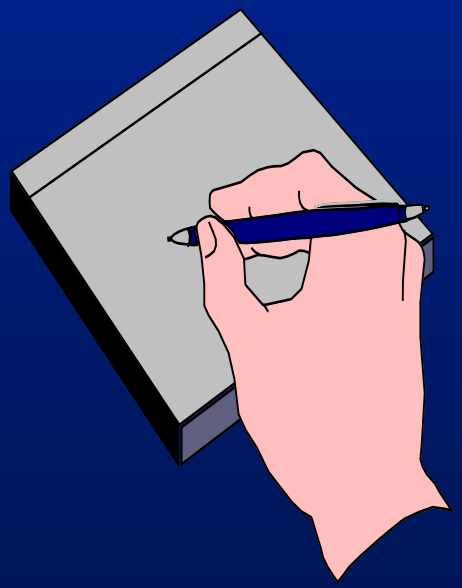
An abnormality of the gene controlling the cytochrome P450 mixed function oxidase system complex. Increased activity of 17 x hydroxylase, 17, 20 lyase enzyme results in increased androgen production

Other factors

- High androgens & LH causes granulosa cells to fail perpetuating anovulation
- Intra-ovarian endocrine & paracrine disorder
- Exogenous or excess endogenous androgens will produce PCOS (inutero,at puberty or in adult life)

Investigations

- Ultrasound / transvaginal ultrasound
- LH/FSH.
- Free testosterone
- SHBG



OTHER INVESTIGATIONS

- 17 hydroxy progesterone
- ACTH
- 24 hour urinary cortisol
- Dexamethasone suppression test
- TFT's
- Biopsy
- CT,MRI

Differential Diagnosis

- **Late onset congenital adrenal hyperplasia**

  DHEAS > 18mmol/l

  17 OH Prog > 6 mmol/l

- **Ovarian + adrenal androgen secreting tumours**

  V. high teslosterone > 6mmol/l

- **Cushings Syndrome**

  - Dexamethsone suppression test
  - 24 hours urinary cortisol
  - DHEAS > 13 mmol/l

Differential Diagnosis Continued

- Iatrogenic and illegal androgen ingestion
- **Hypothyroidism**

Original Articles

Hypothyroidism and obesity

Cause or Effect?

Abhyuday Verma, MD, Muthukrishnan Jayaraman, MD, Hari K. V. S. Kumar, MD, Kirtikumar D. Modi, MD, DM.

Saudi Med J 2008 Aug; 29(8): 1135-8.

Original Articles

Association between thyroid hormones, insulin resistance, and metabolic syndrome

Hari K. Kumar, MBBS, MD, Raj K. Yadav, MBBS, MD, Jayaram Prajapati, MBBS, Challa VK. Reddy, MSc, PhD, Manchala Raghunath, MSc, PhD, Kirtikumar D. Modi, MD, DM.

Saudi Med J 2009 Jul; 30(7): 907-11.

Original Article

Obesity and Thyrotropinemia

K.V.S. Hari Kumar, A. Verma, J. Muthukrishnan and K.D. Modi

Department of Endocrinology, MEDWIN Hospitals, Hyderabad, AP, India

Indian J Pediatr 2009 Sep; 76(9): 933-5.

Treatment

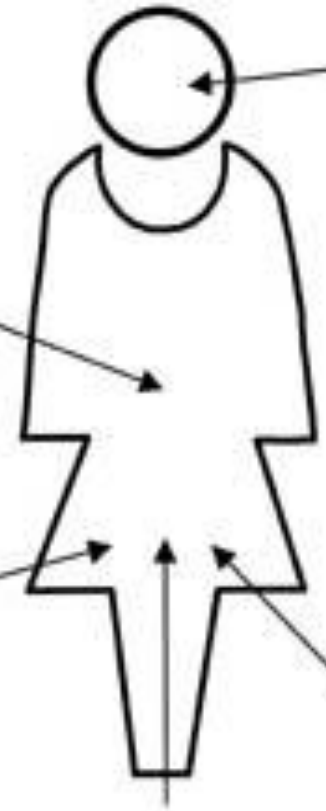
Weight Loss

PCO with obesity:

- poor responder to ovulation therapy than non obese PCO,
- higher maternal complications,
- poor obestretric outcome

5-10 % wt loss restores ovulation

despite relatively small amounts of weight loss



Obesity

1) Diet
2) Exercise
3) Anti-obesity drugs
4) Cosmetic surgery

Hirsutism/Acne

1) Oral contraceptives
2) Progestins
3) Cyproterone acetate
4) Spironolactone
5) Finasteride
6) Flutamide
7) Cimetidine
8) Electrolysis
9) Laser vaporization
10) GnRHa suppression

Infertility: Ovulation Induction

1) Clomiphene citrate
2) hMG
3) Pulsatile GnRHa
4) Neurotransmitter modulators
5) Surgical-wedge resection/ ovarian drilling

Dysfunctional Uterine Bleeding

1) Oral contraceptives
2) Progestins
3) Neurotransmitter modulators
4) Surgical: D & C, oophorectomy
5) Acupuncture
6) Ultraviolet irradiation of the blood

Recurrent Abortion (?)

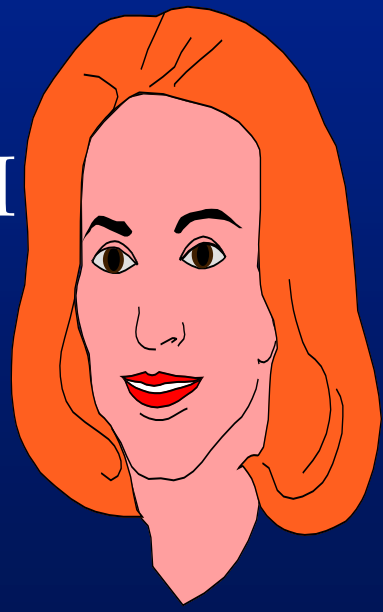
1) hCG
2) Progesterone supplementation
3) GnRHa suppression

Hirsuitism and Acne

- Weight loss and exercise
- OCP e.g. Diane 35
- Cyproterone acetate 50-100mg first 10 days with OCP
- Spironolactone 100-200mg daily
- Dexamethasone 0.25 - 0.5mg nocte
- Ovarian wedge resection or laparoscopic drilling

Infertility

- Weight loss/exercise
- Clomiphence citrate
- Laparoscopic drilling
- Gonadotrophins plus/minus GnRH analogues
- Wedge resection
- Dexamethasone 0.25 - 0.5mg daily

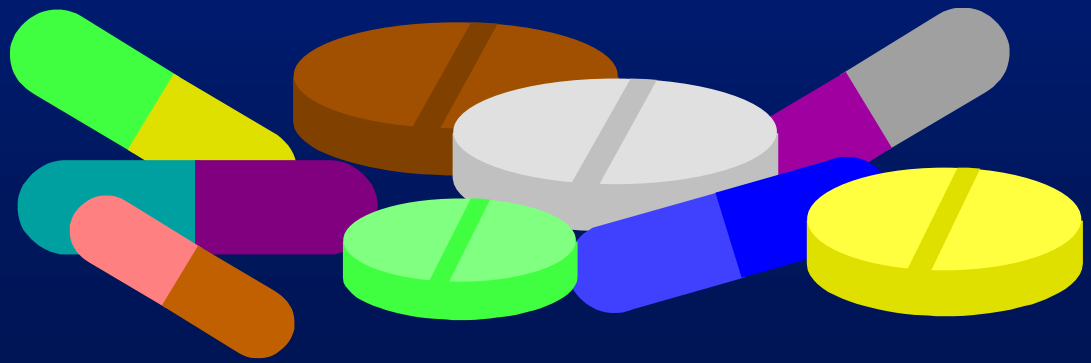


METFORMIN

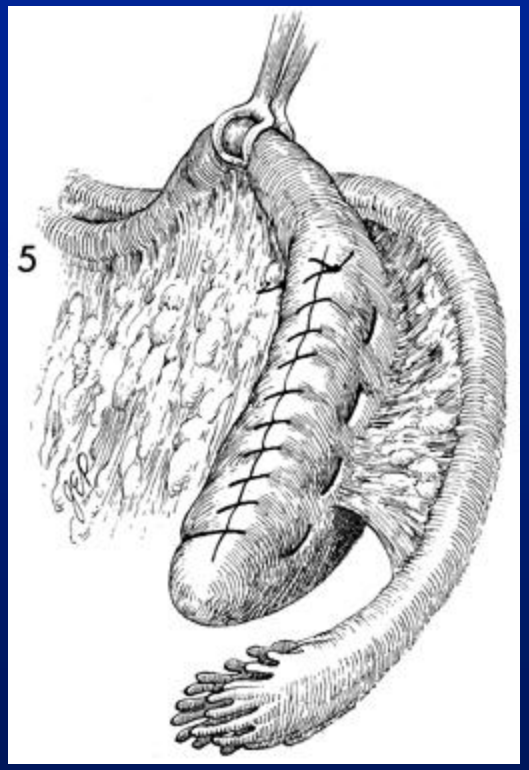
- INCREASES OVARIAN RESPONSE TO OVULATION INDUCTION
- MAY HAVE A FUTURE WITH WEIGHT CONTROL
- ?TREATMENT OF HIRSUITISM
- NO LONG TERM STUDIES YET
- **CC + Metformin versus CC alone:**
  ▲Ovulation rate but pregnancy rate same :
  Meta analysis 2003 Obest Gynecology

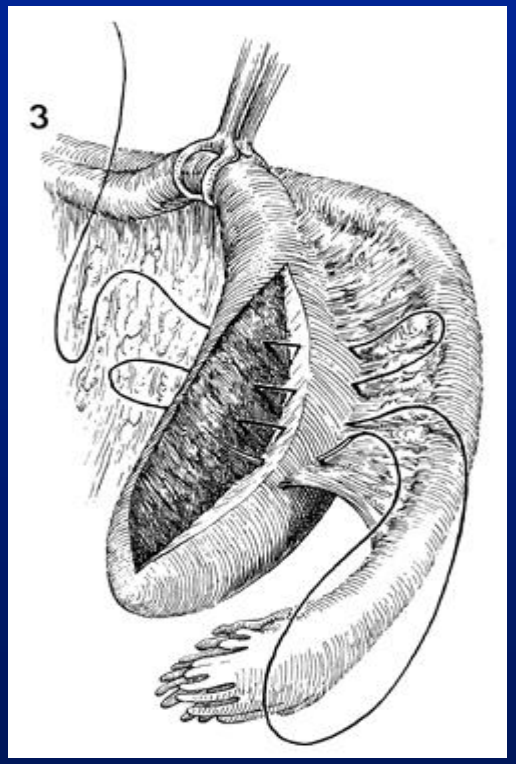
Oligo/Amenorrhoea

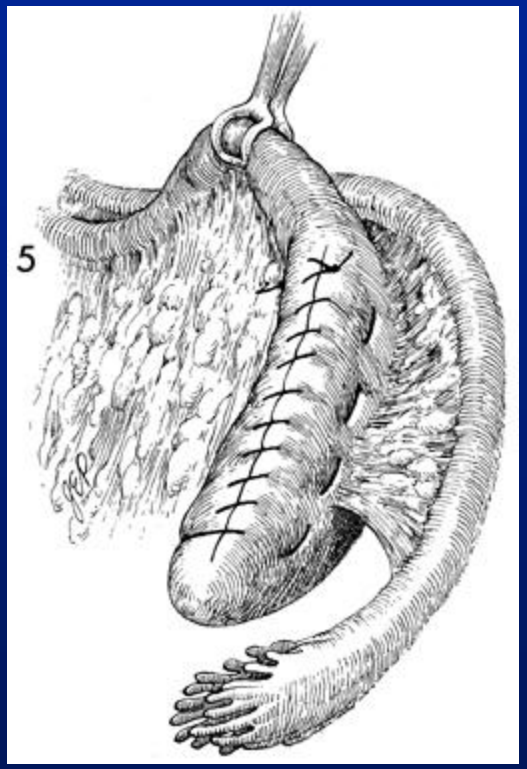
- OCP
- Cyclic provera or norethisterone



Ovarian wedge resection: creating focal areas of damage in the ovarian cortex and stroma







Ovarian drilling:

create thermal damage and necrosis of the "excess" ovarian stroma

Laproscopic electrocauterization, success rate

- Randomized controlled trials suggest that ovarian diathermy (electrocautery), when compared to gonadotropin therapy, results in similar success rates, but lower multiple gestation rates

Laprpscopic surgery: Mechanism

- Sudden drop in intraovarian androgens and perhaps estrogens that results in increased FSH secretion

- intrafollicular environment more conducive to normal follicular maturation and ovulation

Hormonal changes after laproscopic surgery

- S. androstenedione concentrations fall transiently
- LH, testosterone, and inhibin concentrations fall more permanently
- FSH concentrations rise.

Comparison between laparoscopic ovulation induction and gonadotropin ovulation induction

	Laparoscopy	Gonadotropin administration
Advantages	Pregnancy rates comparable to gonadotropins No additional procedures required Minimal monitoring required One treatment produces multiple ovulatory cycles Usually produces monovulatory cycles No increased risk of ovarian hyperstimulation No expensive medications required	High probability of successful ovulation induction Conception rates comparable to laparoscopy No known risk of adhesive damage
Disadvantages	Initial surgery not entirely risk-free Adhesions Ovarian atrophy	High cost Intensive monitoring required One ovulatory event per cycle Increased risk of multiple gestations Increased risk of ovarian hyperstimulation

Multistep approach to treatment of anovulatory infertility associated with polycystic ovary syndrome

Step	Intervention	Cost	Risk of multiple gestation pregnancy
1	Weight loss (if baseline weight is elevated)	Low	Not increased
2	Clomiphene*	Low	Modest increase in risk
3	If DHEAS >2 mcg/mL Clomiphene plus glucocorticoid	Low	Modest increase in risk
4	FSH injections	Resource intensive	Markedly increased
5	Ovarian surgery	Resource intensive	Not increased
6	In vitro fertilization	Resource intensive	Potentially increased but controllable (eg, single embryo transfer)•

The initial steps emphasize interventions that are low cost and associated with a low risk of multiple gestation. * Some clinicians add metformin to clomiphene if clomiphene alone is unsuccessful.

• This increased risk is dependent on the number of embryos transferred. *Courtesy of Robert L Barbieri, MD.*

Cycle fecundity with clomiphene treatment

Group	Fecundity, percent
Anovulatory women who respond to treatment	15
Anovulatory women who respond to treatment and have no other infertility factors	22
Women with unexplained infertility	3.4 to 8.1
Women with unexplained infertility treated with clomiphene and IUI	8.5 to 9.5

Commonly used medications for polycystic ovary syndrome

Drug type	Active ingredient	Examples	Major mechanism	Efficacy			Indications	Comments
				Hirsutism	Menstrual irregularity	Insulin-lowering		
Oral contraceptive pills	Ethinyl estradiol 30 mcg + drospirenone	Yasmin®	Suppress ovarian function	+	+		Menstrual irregularity, hirsutism	Contraindicated in patients with venous thrombosis, uncontrolled hypertension
	Ethinyl estradiol 35 mcg + norgestimate	Ortho Cyclen®						
	Ethinyl estradiol 50 mcg + ethynodiol diacetate	Demulen® 1/50; Zovia® 1/50						
Progestin	Micronized progesterone	Prometrium®	Normalizes endometrial cycle		+		Menstrual irregularity	Less efficacious than oral contraceptive pills
	Medroxyprogesterone acetate	Provera®						
Gonadotropin releasing agonists	Leuprolide acetate depot	Depot Lupron®	Suppress gonadotropins	+	+		Oral contraceptive alternative	Contraindicated in patients with osteoporosis without add-back estrogen

Antiandrogens	Spironolactone	Spironolactone	Competitive inhibitor of androgen-receptor binding	+	±		Severe hirsutism	Use only with appropriate contraception, because of adverse effects on fetus. Contraindicated in kidney or liver failure.
	Cyproterone acetate	Cyproterone acetate	Competitive inhibitor of androgen-receptor binding	+	±		Severe hirsutism	Use only with appropriate contraception, because of adverse effects on fetus
	Flutamide	Flutamide	Nonsteroidal competitive inhibitor of androgen-AR binding	+	±		Severe hirsutism	Use only with appropriate contraception, because of adverse effects on fetus. Monitor for liver failure. Contraindicated in liver disease.
	Finasteride	Finasteride	Competitve 5α-reductase inhibitor	+	±		Severe hirsutism	Use only with appropriate contraception, because of adverse effects on fetus
Cell cycle inhibitor	Eflornithine HCl 13.9 percent (topical)	Vaniqa®	Irreversible inhibitor of ornithine decarboxylase	+			Focal hirsutism	Contraindicated in pregnancy and lactation
Glucocorticoids	Glucocortioid	Prednisone	Suppresses adrenal function	+	+		Congenital adrenal hyperplasia	Efficacy poor except in patients with congenital adrenal hyperplasia. Contraindicated in patients with uncontrolled diabetes, obesity.
Biguanide	Metformin	Glucophage®, Glucophage XR®, Glumetza®	Reduces hepatic glucose production		±	±	Obesity and insulin resitance; type 2 diabetes	Efficacy poor without weight control
Thiazolidinedione	Pioglitazone	Actos®	Peroxisome proliferator-activated receptor agonist		±	+	Type 2 diabetes	Contraindicated in patients with hepatic or cardiac disease

Long term problems

- Endometrial cancer
- Diabetes
- Recurrent early pregnancy loss
  (poor IVF success rates)
- Clomiphere citrate > 12 cycles
  (may increase ovarian cancer risk)
- Ovarian hyperstimulation syndrome
- Adhesions
- Metrorragia


Thank You
Prakash
Arts
CHENNAI