Understanding the young PCOS

A multifaceted task

M.D., DGO, FCPS, DFP, FICOG. (Mum)

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Adolescent PCOS

- ☑ Incidence of PCOS and see if PCOS start before puberty?
- ☑ Are the adult criteria for PCOS applicable in adolescent patients and what are the problems in diagnosis?
- ☑ What are the clinical and metabolic features of normal puberty and is an adolescent PCOS different?
- ☑ Is hyperandrogenemia and insulin resistance an early feature in girls with PCOS?
- ☑ Managing PCOS in adolescence – is it different?

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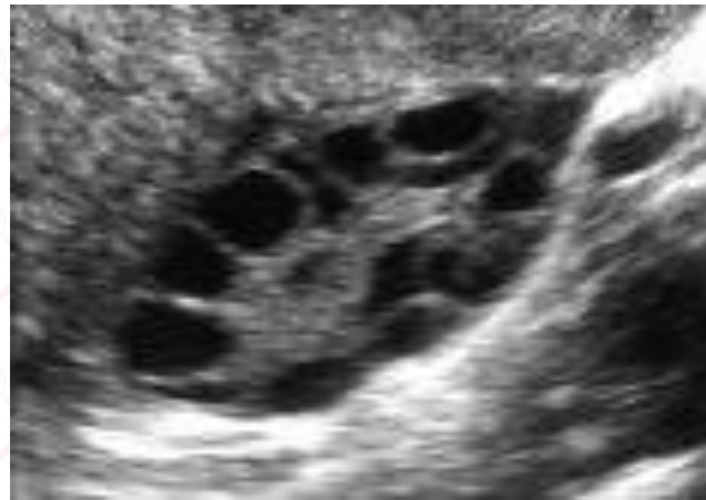
PCOS, starts in adolescence or teenage years

But

Unfortunately, not always diagnosed at that age

As Clinical Expression varied



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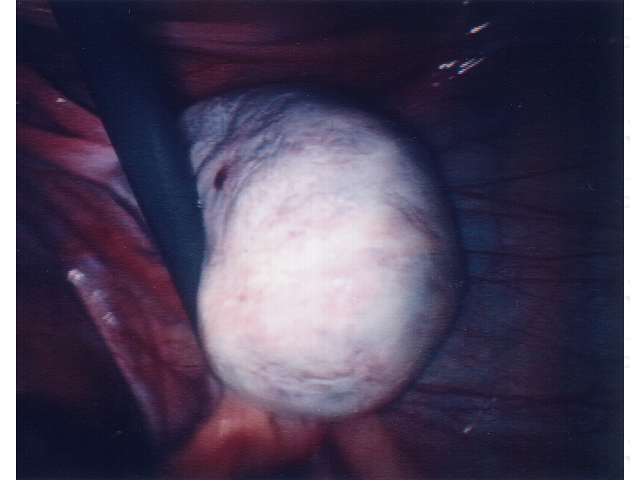
Incidence

Rate of detection of PCOS



6 years - 6%

10 years - 18%

15 years - 26%

Bridges et al
F & S 1993

Easy to detect in older girls as ovarian size increases

30 % detection rate by TAS

100% detection rate by TVS

Fox et al

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Polycystic ovaries in pre-pubertal girls

7.6 + 0.6 years

93% (14/15) had PCO if their mothers had PCOS

Vs

0% in control daughters

Battaglia et al Human Reprod 2002; 17: 771-776

Low birth weight and rapid postnatal weight gain

- ✓ precocious Adrenarche / Pubarche
- ✓ increases the risk for progression to functional ovarian hyperandrogenism and PCOS

J Clin Endocrinol Metab, 1998

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Etiology

Multifactorial disease with full clinical expression

being the result of

synergistic pathological interaction of

genetic, epigenetic and environmental factors

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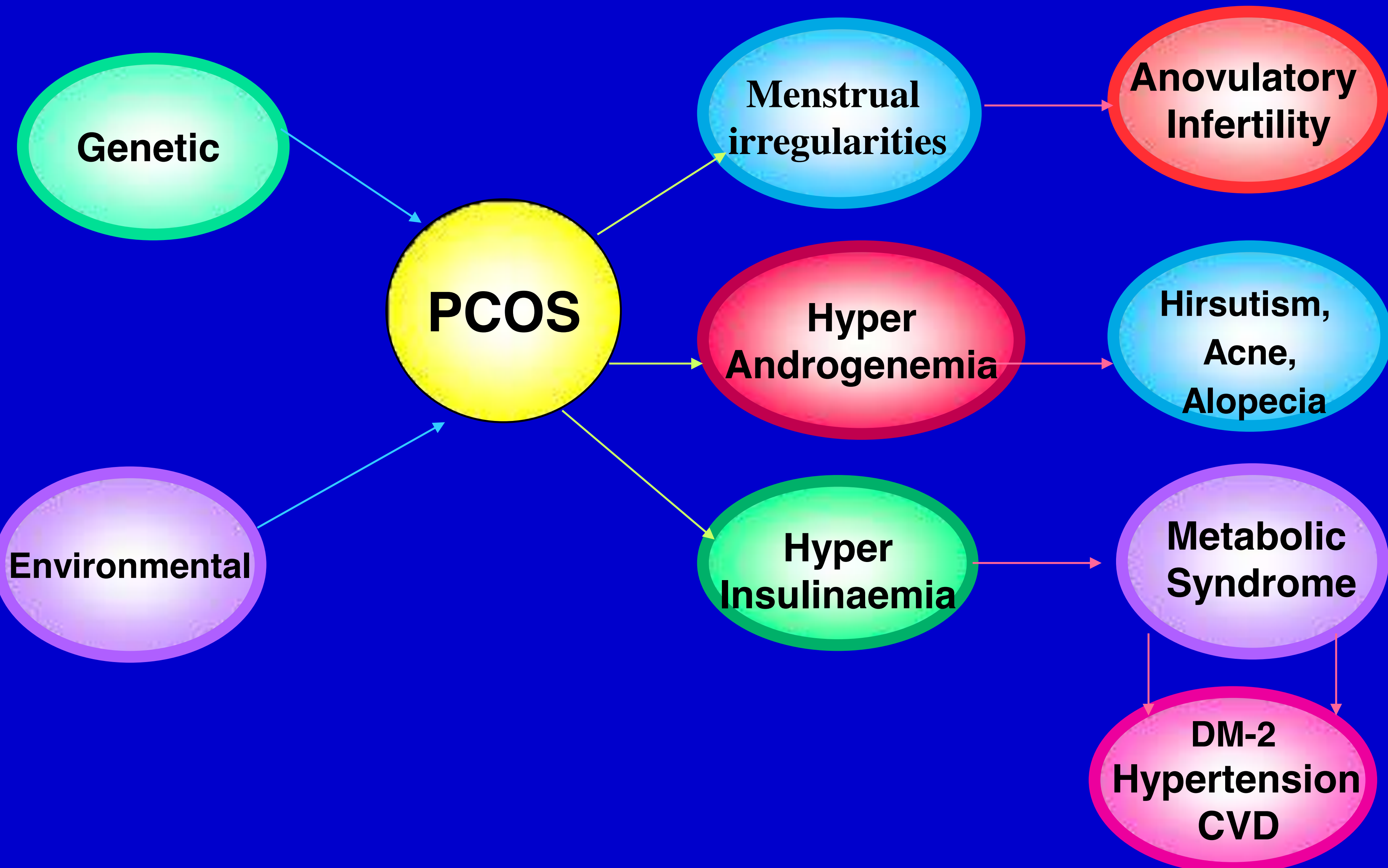
Polycystic ovarian syndrome



Criteria for Diagnosis of PCOS

PCOS definition NIH *1990*	Rotterdam criteria 2003 (ESHRE/ASRM)	AES Criteria 2006
Patient demonstrates both:	Two of the following three manifestations:	Patient demonstrates both:
1. Clinical and/or biochemical signs of hyperandrogenism	1. Irregular or absent ovulation	1. Hirsutism and/or hyperandrogenemia
2. Oligo- or chronic anovulation	2. Hyperandrogenism (clinical or biochemical)	2. Oligo-anovulation and/or polycystic ovaries
	3 PCO on USG	*Azziz et al. JCEM 2006; 91: 4237-45*

Exclude other etiologies of androgen excess - Late onset congenital adrenal hyperplasia, Androgen secreting tumours, Cushing's syndrome

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Can we use these criteria to diagnose PCOS in Adolescence?

No

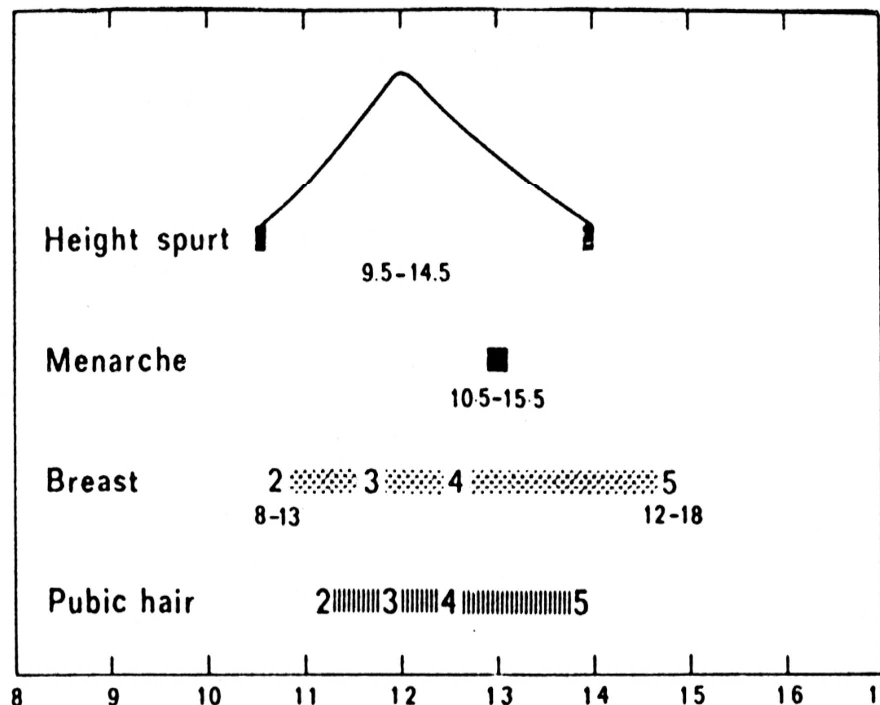
Normal Adolescents

Oligomenorrhoea

Amenorrhoea

Acne

"Multicystic" ovaries



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Problems in Diagnosis of PCOS in Adolescence

Using a broader definition may be problematic

- Several features may be in evolution, or only be transitory during the transition to adulthood
- All Rotterdam criteria may be transient during adolescence
- AES PCOS criteria more adapt but need to be modified to be specific

Prematurely assigning a diagnostic label of PCOS to an adolescent

- May be incorrect
- May result not needed treatments
- May worsen psychological distress as PCOS is associated with disorders and therapies involving body image

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Why Adult Criteria not applicable to Young PCOS?

Normal adolescent

Anovulation:

*85 percent of cycles anovulatory in first year of menstruation.

*59 percent of cycles anovulatory in the third year

*25 percent of the cycles still anovulatory in the sixth year

Metabolic features

Insulin resistance

↑ insulin due high GH

hyperpulsatile GnRH secretion

decreased levels ↑SHBG

ovarian & adrenal androgen

PCOM at USG

in 40%, 35% & 33.3% at 2, 3 & 4 years after menarche

Corresponds to a physiologic condition during early adolescence

Not associated with abnormalities in

ovulation

menstrual ↑cycle duration

androgens or IR

However all return to normal at the end of normal puberty but remain elevated in PCOS

RCOG Scientific Study Group, 2010

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Hallmark of adult PCOS that seems to be most reliable in young PCOS is

elevated androgen levels

Christine M. Schroeder, Ph.D.

www.inciid.org/pcos/PCOS-paedatrics

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Menstrual irregularities in Adolescence

Age at menarche and ovarian function

	Controls	PCOS	POF
	n = 957	265	98
Age at menarche			
< 11y	12%	16%	21%*
12-14y	74%	59%	58%
➢15y	14%	26%*	21%

- * Significant compared with controls

Sadrzadeh et al Hum Reprod 2003; 10: 2225

❑ Obesity associated with early menarche and PCOS

Stoll, Cancer Res Treat 1998; 49: 187-193 van Hoff et al, JCEM 2000; 85: 1394-1400

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PCOS in adolescence

Adolescents, mean age 16.7 + 0.9 years

Regular cycle (58)	Irregular (50)	Oligomenorrhea (29)
PCO 9%	PCO 28%	PCO 45%

van Hoff et al F&S 2000;74:49

The later the onset of menarche, the longer until start of regular menses

< 11 y : 14% took > 5 y

> 17 y : 33% took > 5 y

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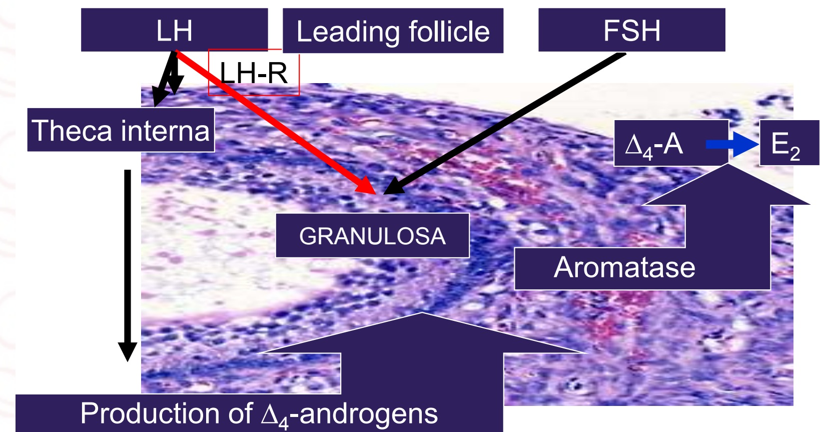
During adolescence, menstrual irregularities are

not a proof of adult chronic anovulation



Persistent Oligomenorrhoea

for 2 years post menarche with elevated LH and androgens

Diagnostic of PCOS

Homburg & Lambalk Human Reprod 2004; 19: 1039-1042

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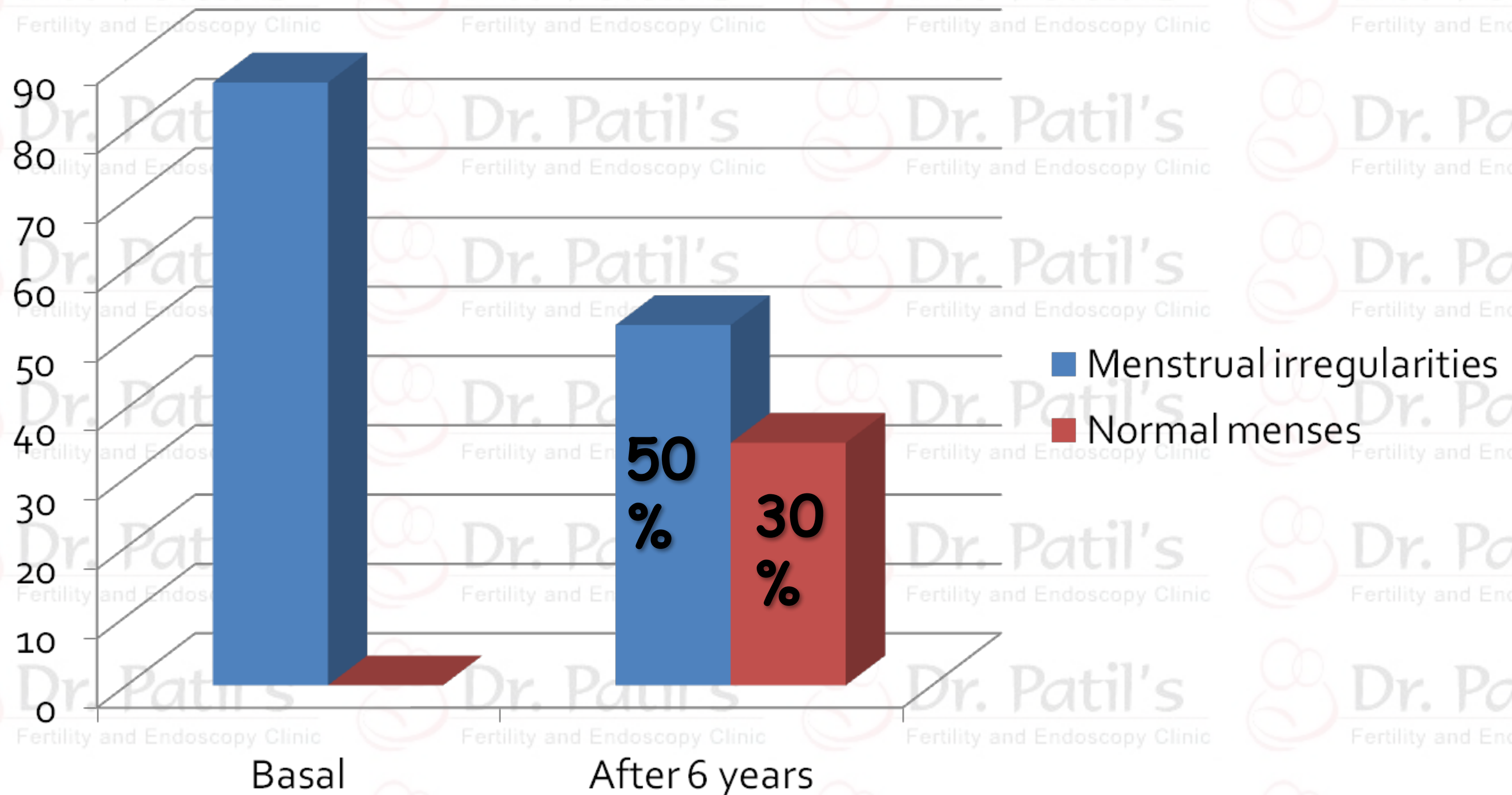
Follow-up of Adolescent Menstrual disorders in 87 Swedish Girls



Viksten-Almstromer M et al Acta Obstet Gynecol Scand 2007; 87:1162-8

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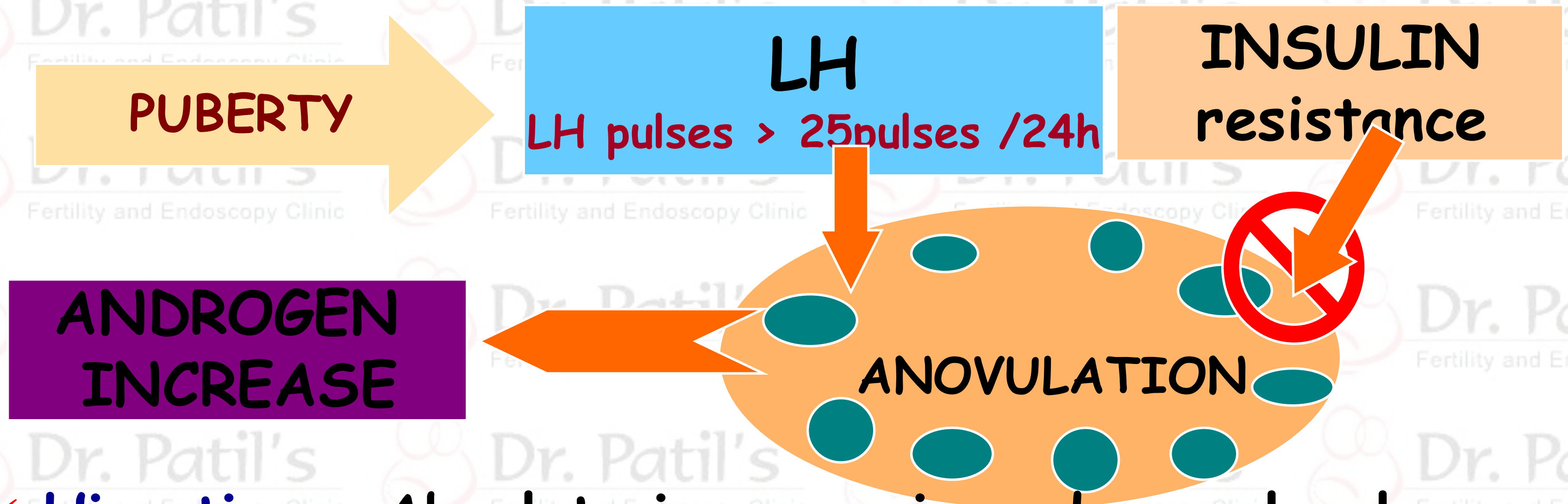
Hyperandrogenemia in Adolescent PCOS



- ✓ **Hirsutism** - Absolute increase in androgen levels, alteration in ratio of hormone levels, exaggerated response of the skin to relative normal androgen levels
- ✓ **Acne** - transitory phenomenon in normal adolescents
- ✓ **Alopecia** - Minimal data available
- ✓ **Acanthosis Nigricans**

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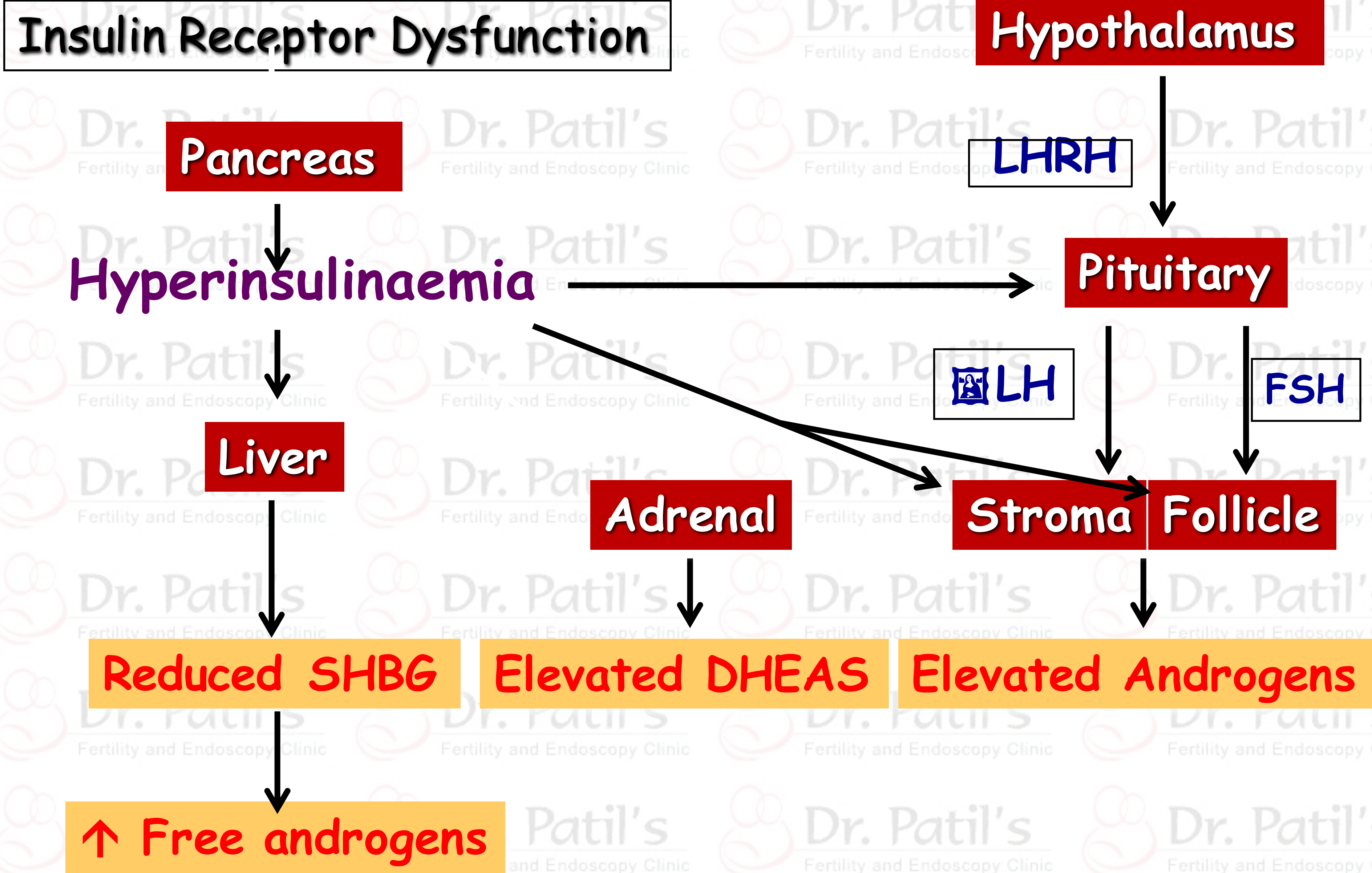
Hyperinsulinaemia & Hyperandrogenaemia



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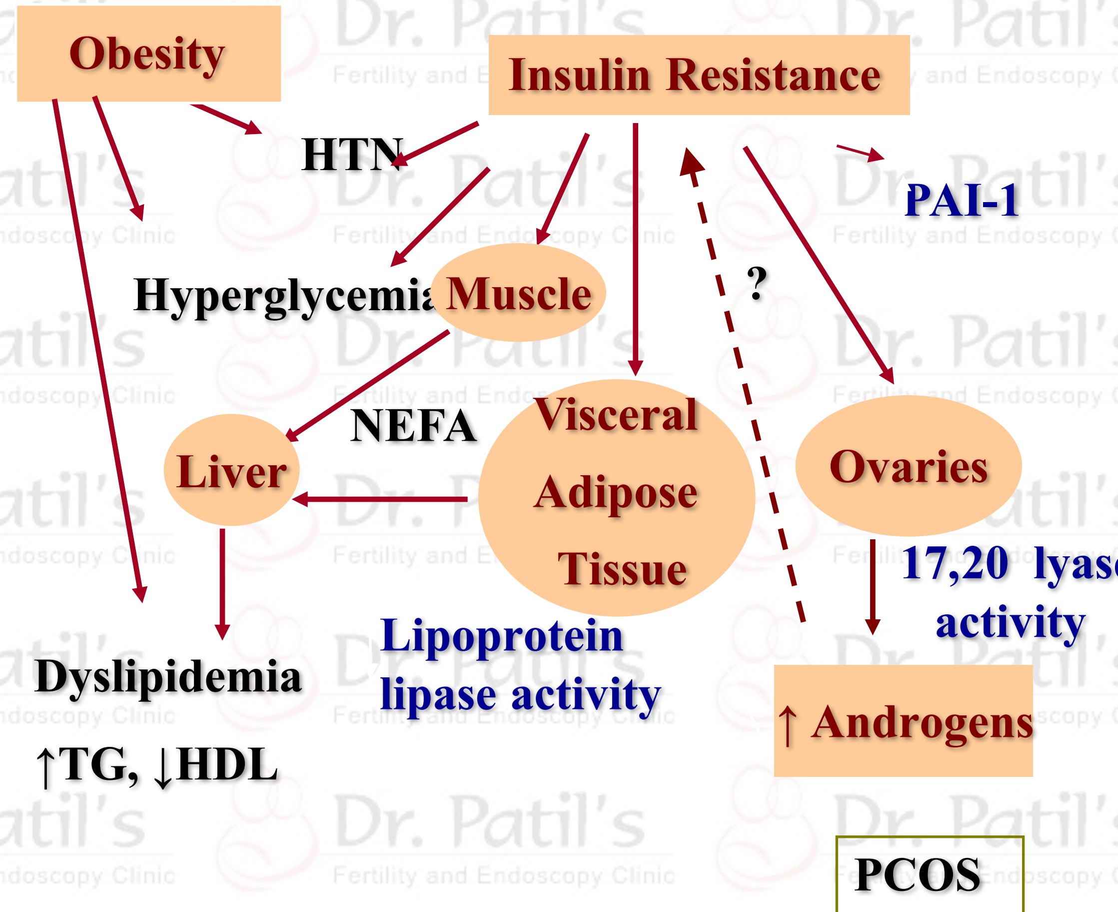
Hyperinsulinaemia and Insulin Resistance in Adolescent PCOS

- Impaired GTT
- Early development of type 2 diabetes
- Dyslipidemia
- Central obesity
- Acanthosis Nigricans

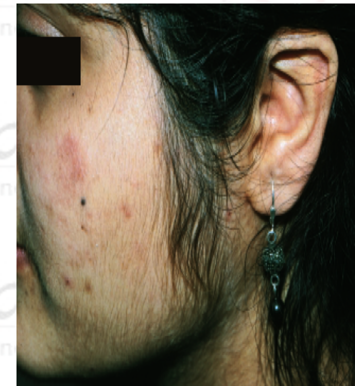


Clinical features of PCOS in Adolescence
Mainly due to Hyperinsulinaemia & Hyperandrogenaemia

1. **Hirsutism** – good marker of hyperandrogenism

Hirsutism represents

Diagnosis of PCOS only in presence of



- Progressive hirsutism
- Biochemical hyperandrogenemia and not biological

2. **Alopecia** – Frontal balding and anterior hairline recession seen only in more severe cases of androgen excess

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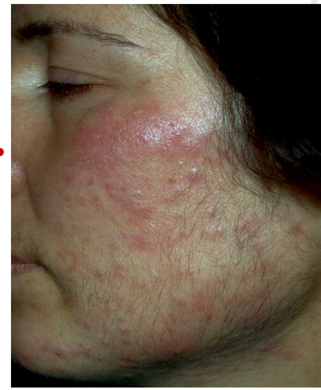
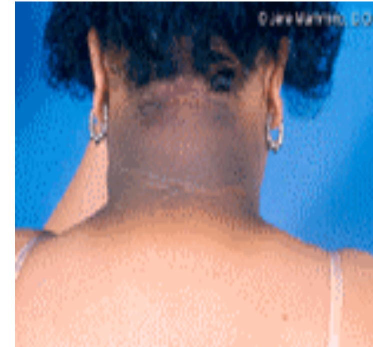
3. Acne and seborrhea



Due to androgen stimulation of pilosebaceous unit

- Skin problems that wax and wane with the menstrual cycle

4. Acanthosis nigricans - 5 - 10 %



Result of insulin resistance

- Diffuse velvety-thickening and hyperpigmentation of the skin

- Most often seen on the back of the neck, axillae and beneath the breasts and exposed areas (elbows, knuckles)

Obesity – 50%

✓ Typical obesity of PCOS is described as "centripetal," or "apple" type of fat distribution - center of the body, as opposed to the thighs and hips

Waist Circumference > 88 cm

marker of Central / Visceral Obesity

Body weight primary factor affecting quality of life

Trent et al, Ambul Pediatr 2005; 5: 107-11

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In Adolescence abnormalities in insulin metabolism evolve following weight gain

Obesity

↑ Insulin

↓ SHBG

↑ IGF-1

alfa reductase activity is stimulated

↑ Free testosterone

IGF*** insulin like growth factor

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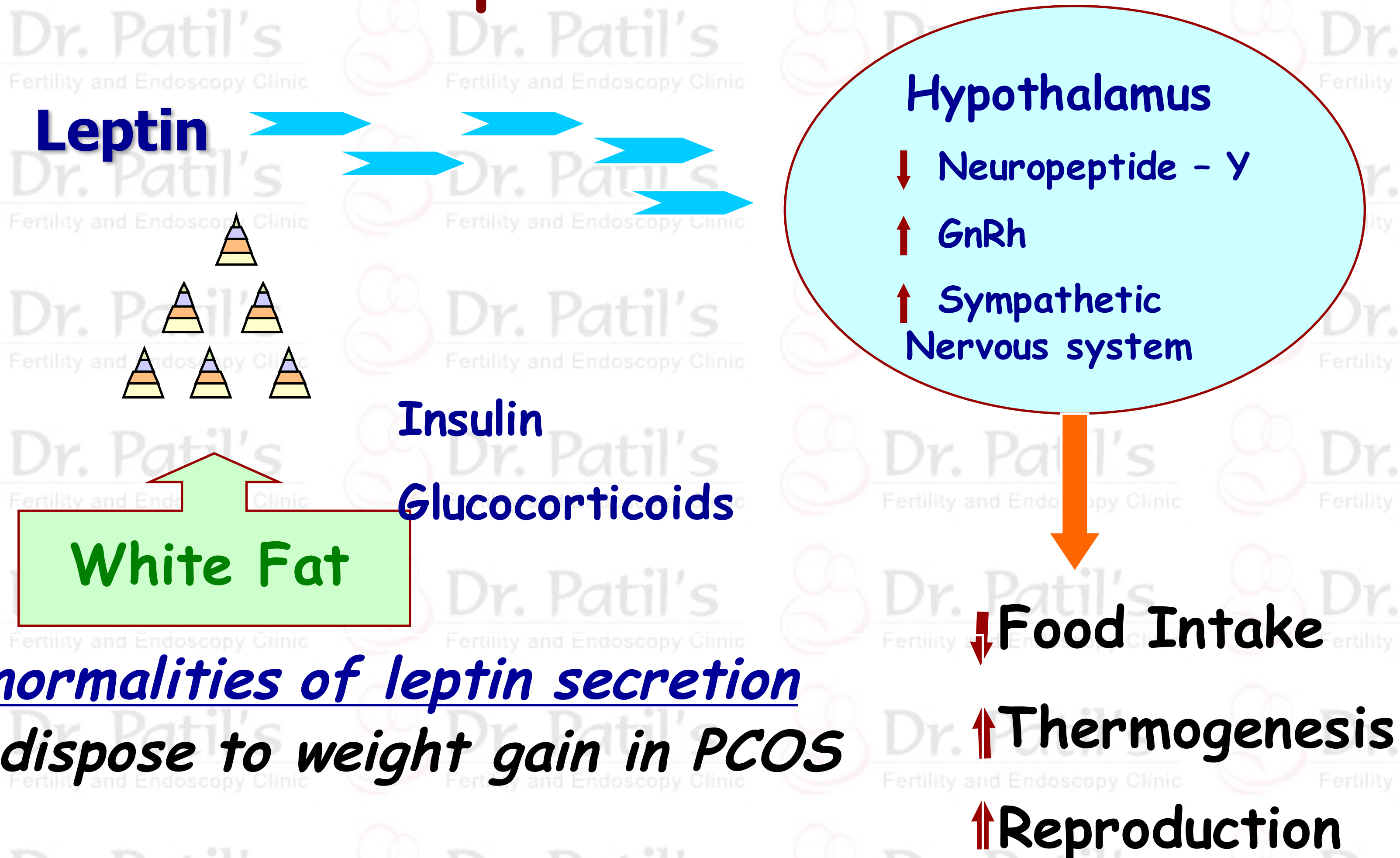
Body weight and Puberty
Leptin Resistance



Abnormalities of leptin secretion *predispose to weight gain in PCOS*

Leptin resistance seen in insulin resistant states & overweight women

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Characters of main PCOS Phenotype

	Androgen levels	LH/FSH	Insulin resistance	CV risk
Type I Classic PCOS	Increased	Increased	Increased	Increased
Type II Classic PCOS	Increased	Mild increase	Increased	Increased
Ovulatory PCOS	Increased	Normal	Mild increase	Mild increase
Normoandrogenic PCOS	Normal	Increased	Normal	Normal?

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PCOS Phenotype during Adolescence

- During adolescence, only most severe phenotype Type 1 Classic PCOS is diagnosed
- Other PCOS phenotypes cannot be diagnosed
- Patients who present incomplete symptoms have to be included in a strict follow up and the final diagnosis should be determined only after 18 years

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Proposed diagnostic criteria for PCOS during Adolescence

Sultan and coll. (Fertil Steril 2006; 86(Suppl 1) 56)

have suggested diagnosis on following criteria:

- ☑ Clinical Hyperandrogenism
- ☑ Biological Hyperandrogenism
- ☑ Hyperinsulinism
- ☑ Oligo/amenorrhea
- ☑ Polycystic ovaries

Diagnosis of PCOS requires the presence of 4 out of 5 criteria

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Proposed diagnostic criteria for PCOS during Adolescence

Carmina, Oberfield and Lobo. AJOG 2010

Hyperandrogenism
biochemically confirmed

+

Menstrual irregularities
Present for at least 2 years post menarche

+

Polycystic Ovaries
include both increased size and increased number of follicles

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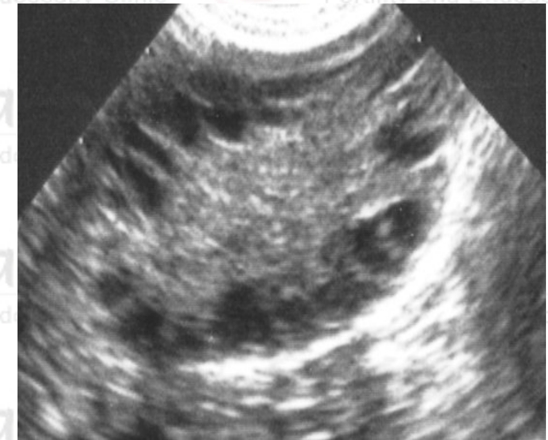
PCOS presentation during adolescence

- 30% Menstrual irregularities
- 60% Androgen excess
- 84% Overweight
- 9% IGT or T2D
- Infertility rarely an issue



Bekx. et al. Pediatric and Adolescent Gynecology 2009
Rosefeld. et al. Journal of Pediatric Endocrinology and Metabolism 2000

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Management of adolescent girls with PCOS

- Psychological support
- Lifestyle advice - Weight loss and exercise

  Healthy approach to eating
- Symptom oriented Rx
- Antiandrogens and Insulin-sensitizing agents
- Oral Contraceptive Pill - Low dose oestrogen, Drospirenone, Cyproterone acetate
- Endometrial protection

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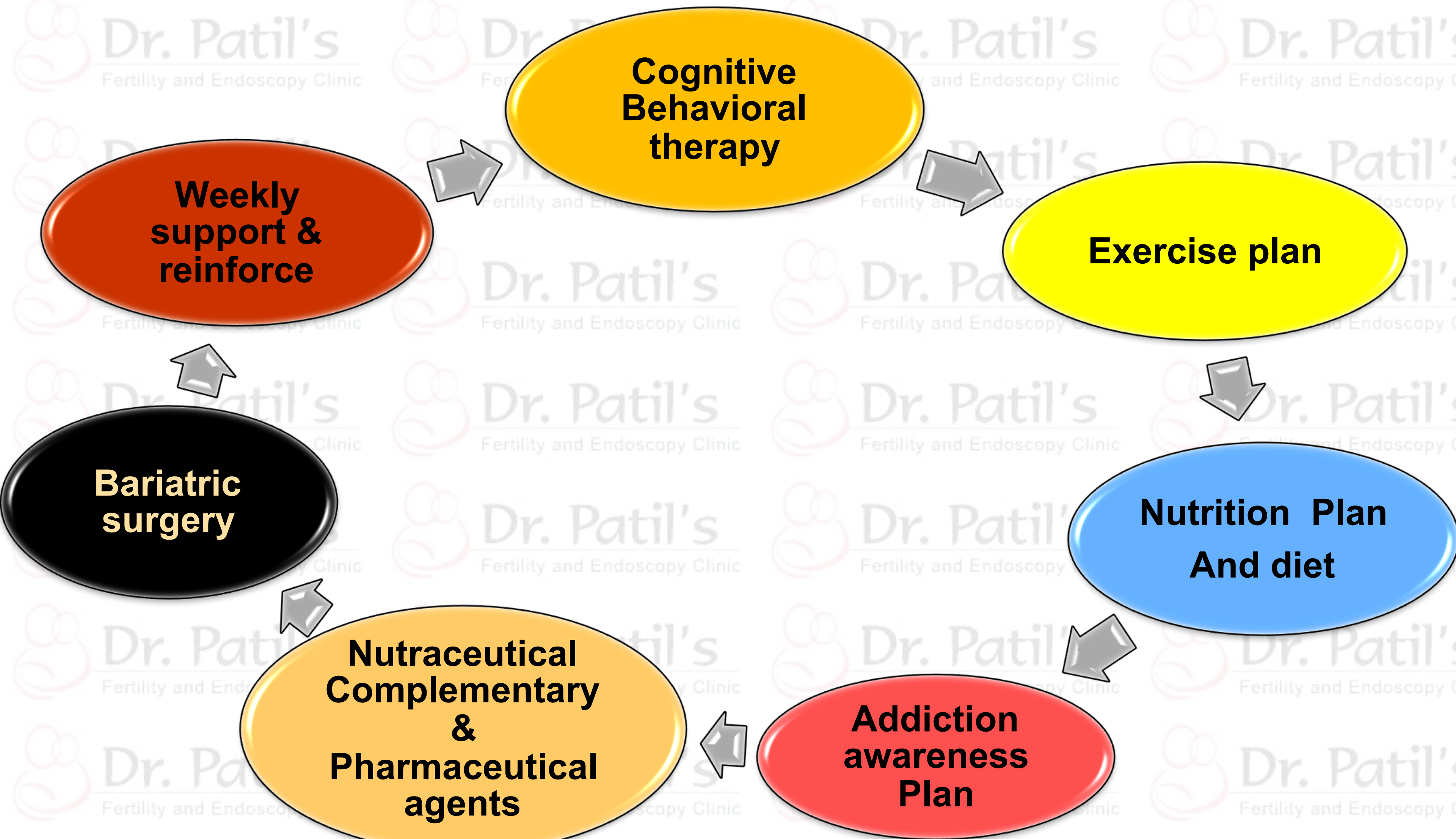
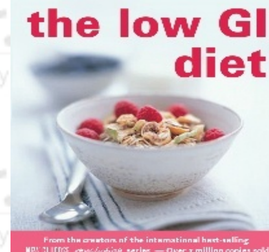
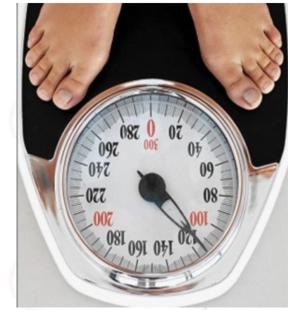
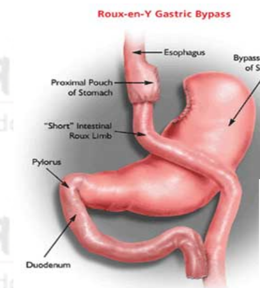
Integrated, Individualized, Comprehensive, Scientifically designed, Multi-faceted approach to address all aspects of Adolescent PCOS



Assessment – History	Cognitive Behavioural Assessment	Dietary counselling	Exercise	Pharmaco-therapy & Surgery	Regular Review
BMI & WHR to determine degree & distribution of fat Hormone – LH & Androgens, Glucose & Lipid profile USG If obese assess & Rx obesity & related co-morbidities	Screen for depression, mood & eating disorders Assess mental barriers & readiness to change Devise lifestyle modification strategies with patient & family Tackling addictions Smoking, Alcohol. Caffeine, Food	Low GI & Calorie restricted food Aim is to Achieve weight loss of 5-10% of body weight over 6 months	Daily moderate exercise for 30 mins & ↑ to high intensity for 60 mins	Antiandrogens Metformin Orlistat Bariatric surgery	Reinforce goals for weight loss Maintenance of discipline Prevent weight regain







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Reduce androgen excess

Androgen suppression

- Oral contraceptive pills
- GnRH agonists
- Ketoconazole
- Glucocorticoids/Dexa

Anti-androgens

- Cyproterone acetate 100mg/day
- Spironolactone 100-200 mg/day
- Flutamide - 250 mg TDS for 3 mts, gradually to 200 mg, then 150 mg

5 alpha Reductase inhibitors

- Finasteride

Insulin-lowering agents

Treatment- controversial

- Metformin 500 - 850 mg twice or thrice daily
- Thiazolidinediones
- D-Chiro-inositol

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Treatment of symptoms related to androgen Excess

Hirsutism -

Rule out idiopathic from functional

- ☑ Cosmetic measures
Waxing, shaving, laser
- ☑ Oral contraceptive
- ☑ Metformin
- ☑ Anti-androgens
- ☑ 5-alpha-reductase inhibitors

Acne - Antibiotic and topical therapies

- ☑ Tetracycline, erythromycin & minocycline
- ☑ Used in conjunction with antiandrogen Tx
- ☑ Topical non-steroidal antiandrogen, oncoterone acetate, benzoyl peroxide, 13-*cis*-retinoic acid (tretinoin)

Alopecia –2 % minoxidil BD with antiandrogen Tx

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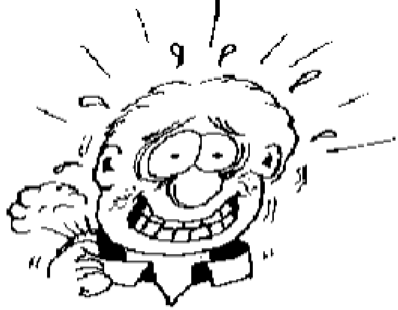

Prevent side effects of unopposed estrogen action

Progesterone in 2nd half of cycle - Synthetic progesterone or Dydrogesterone

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Weight loss of only 5 % of total body weight is associated with:

- ✓ Decreased insulin and LH levels
- ✓ Increased SHBG and Decreased Free E2
- ✓ Improved menstrual function
- ✓ Reduced hirsutism and acne
- ✓ Lower testosterone levels

Kiddy DS, Hamilton FD , Bush A.- Clin endocrinol 1992

Lifestyle Intervention - Diet and Exercise Important

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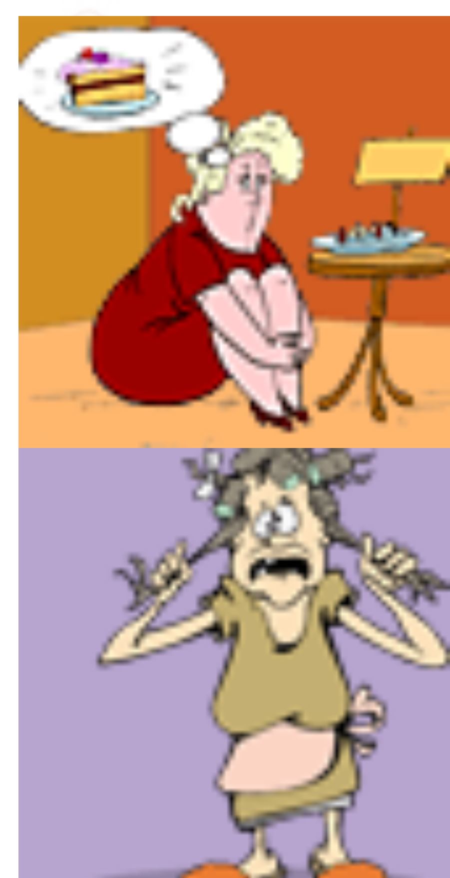
Psychological intervention

Psychological counseling

both individually and in group



- ☑ behavioral problem
- ☑ abnormal eating patterns (21% vs 2.5%)
- ☑ damaged self confidence due to acne, hirsutism and obesity
- ☑ increased levels of anxiety & depression

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MX of Adolescent PCOS Summary

Hassan A and Gordon CM, 2007 Curr Opin Peds

Diagnosis of PCOS

- **Overweight or Obese** → **Goal 5-10% weight loss** → Check fasting glucose, insulin, lipids
- **Normal weight** → Check fasting glucose, insulin, lipids

Check fasting glucose, insulin, lipids;
If overweight or familial T2D: Perform OGTT

↓

Assess symptoms, goals and future risks of patient

- **Hyperinsulinaemia, acanthosis nigricans, impaired glucose tolerance or obesity ---- consider Metformin**
- **Irregular menses** → **Oligo/amennorhoea, Dysfunctional uterine bleeding or menorrhagia – start OCPs or progestins**
- **Hirsutism +/- acne, consider OCPs, anti-androgens topicals/other cosmetic measures**
- **Sexually active, start OCPs**

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Conclusion

- Adolescent PCOS may present with early menarche and oligomenorrhoea / irregular bleeding, or in some with late menarche / primary amenorrhoea

- Obesity in adolescent PCOS associated with increased
  - insulin resistance leading to functional hyperandrogenism
  - ovarian and uterine volume and PCO
  - clinical manifestation in those with a genetic or developmental predisposition

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She is a Woman…