

GP Refresher Course

10 minute consultation – “my periods have become irregular”

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Menopause Physiology

- Definitions & Background
- History
- Examination
- Investigations
- Referral
- Interventions
- Take Home Points

Definitions

- **Primary amenorrhoea**
 - **No periods**
- **Secondary amenorrhoea**
 - **Cessation of periods for at least six months**
- **Premature Ovarian Failure**
 - **<40yrs**

Aetiology

- **CNS Dysfunction**
 - e.g. hypothalamic amenorrhoea
- **Gonadal Dysfunction**
 - e.g. POF, PCOS
- **Genital Tract Disorders**
 - Imperforate Hymen
- **Endocrine Disorders**
 - Thyroid disorders, Hyperprolactinaemia
- **Drug therapy**
 - Anti-psychotics

Aetiology

- **Commonest causes of irregular periods**
 - **Pregnancy**
 - **Age related Anovulatory cycles**
 - **Menopause**

Ovarian Failure

- Follicle cohort shrinks throughout life
 - Newborn 2 million
 - Puberty 3 - 400 000
 - 40y + Few thousand
 - Postmenopause Few or no ova
- Number of ovarian follicles available to mature each cycle is depleted (3-400 cycles on average)
- As one oocyte ovulates 1000 become atretic through apoptosis

Ovarian failure

- **Genotype/phenotype correlations in prem ovarian failure**
 - Turner's commonest identified cause
 - Driscoll et al 2000
 - Fragile X / X chromosome deletions
 - POF 1 & POF 2 genes
 - Anasti 1998
 - Forkhead Genes (FOXO3A defect) – early follicle activation
 - De Baere et al Am J Hum Gen 2003
 - FSH receptor polymorphism in Finnish Population
 - Follicles present but unable to respond to FSH due to loss of FSH receptor
 - Aittomaki 1995

Ovarian Failure

Landmarks in Ovarian Failure Process

- Two critical levels
 1. Marked decline in fertility (no cycle dysfunction)
 2. Cycle changes become noticeable
 1. Shortened follicular phase
 2. Luteal dysfunction

Effects of ovarian failure

Compensated Failure

- Reduced follicle pool for stimulation by Gonadotrophins
- Oestrogen levels start to fall → FSH levels ↑ by negative feedback – even from 29-30y!
 - Ebbiary, Cooke Clin Endoc 1994, Cocchi Aging 1992
- Evidence for reduced number of gonadotrophin receptors in perimenopausal ovaries
 - Vinko K et al Eur J Endocrinol. 1996

Effects of ovarian failure

Compensated Failure

- Inhibin production from granulosa cells falls leading to reduced Inhibin : FSH ratio
- Early follicular Inhibin B & FSH predictive of ovarian reserve / response to gonadotrophin stimulation

- **26th Jan 2006 Yorkshire Post**
- **179 mail order home fertility kit is launched!**
- Ground-breaking development by Yorkshire doctors will help women decide when to have babies

The Plan Ahead kit, which costs £179, assesses the number of eggs in a woman's ovaries compared with the levels expected for others of the same age.

- It can predict the ovarian reserve for the following two years
- The test developed by one of the country's leading fertility experts, Professor Bill Ledger, of Sheffield University, measures three hormones in the blood – two ovarian hormones, Inhibin B and AMH, and the pituitary hormone called FSH.
- The kit is being launched by Sheffield-based Lifestyle Choices, a spin-out company from Sheffield University.

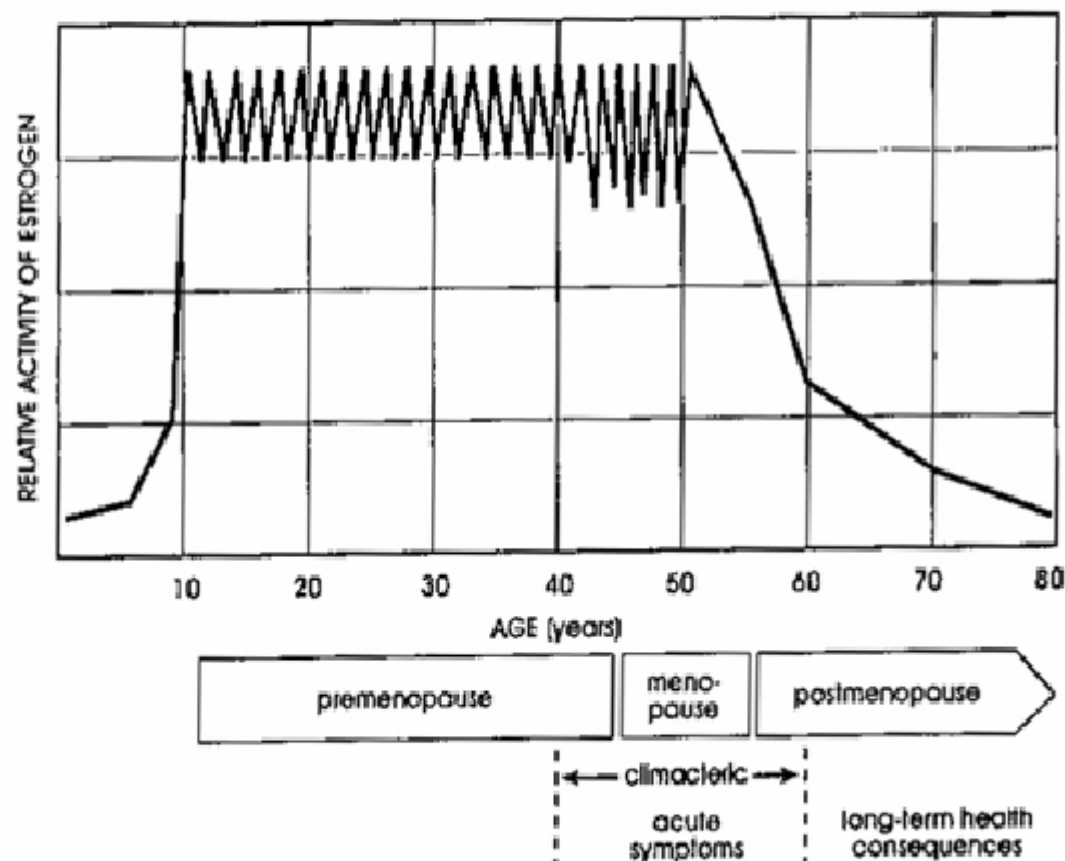
Effects of ovarian failure

Decompensated Failure

- Follicle pool very low
- FSH rises further (10 to 20 fold); LH rises threefold (shorter ½ life)
 - Metcalf 1981 & 82
- Oestrogen levels drop due to reduction in follicle number and qualitative effect on granulosa cell ageing
 - Gosden RG Faddy MJ 1994
- Permanent cessation of progesterone production
 - **Endometrial proliferation & hyperplasia**

Oestrogen levels relative to age

Estrogen levels relative to age



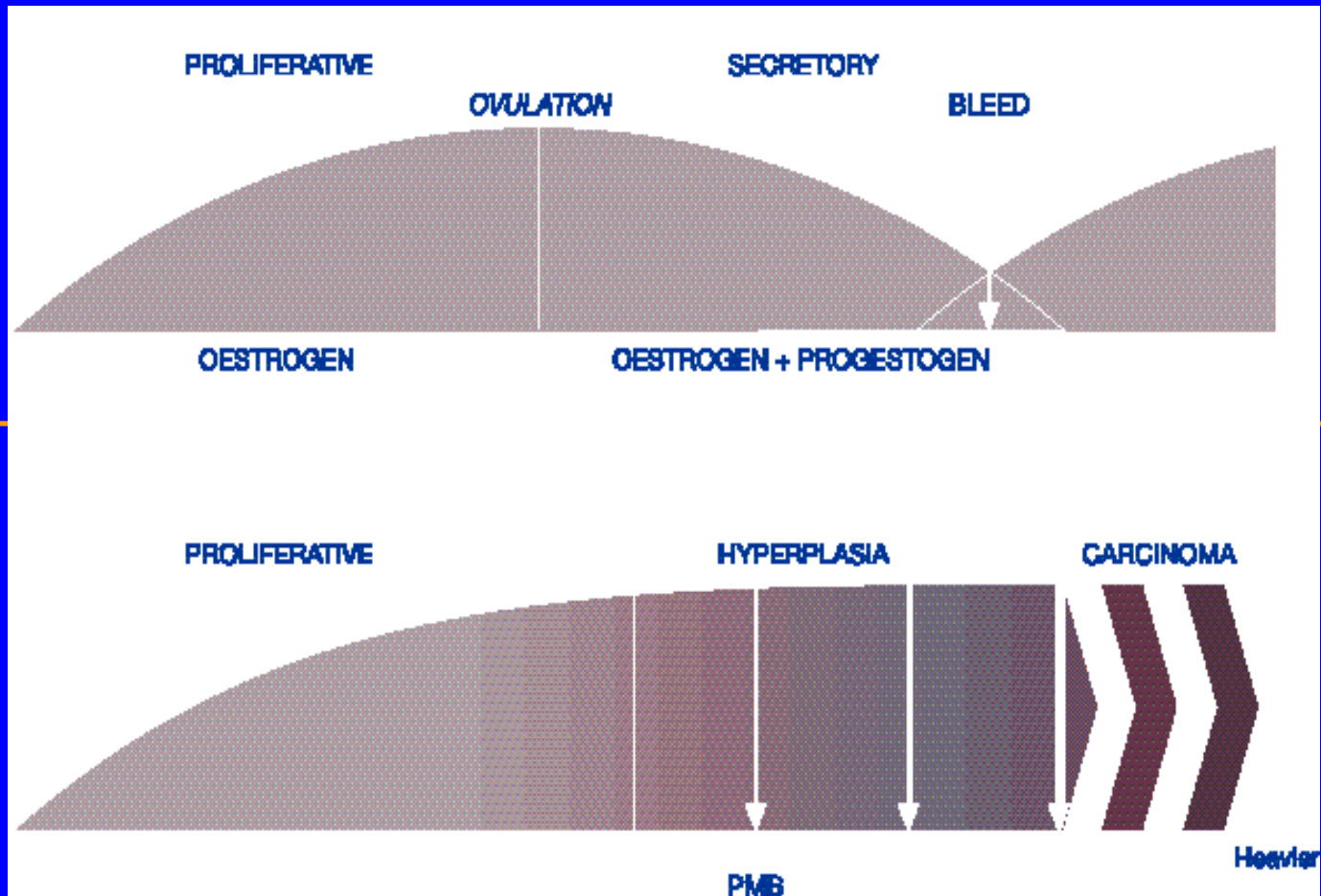
Effects of ovarian failure

- **Late Menstrual Transition**
 - When episodes of >3 months amenorrhoea
- Final Menstrual Period occurs in most women
within 4 years
 - Taffe et al 1997

Ovarian failure

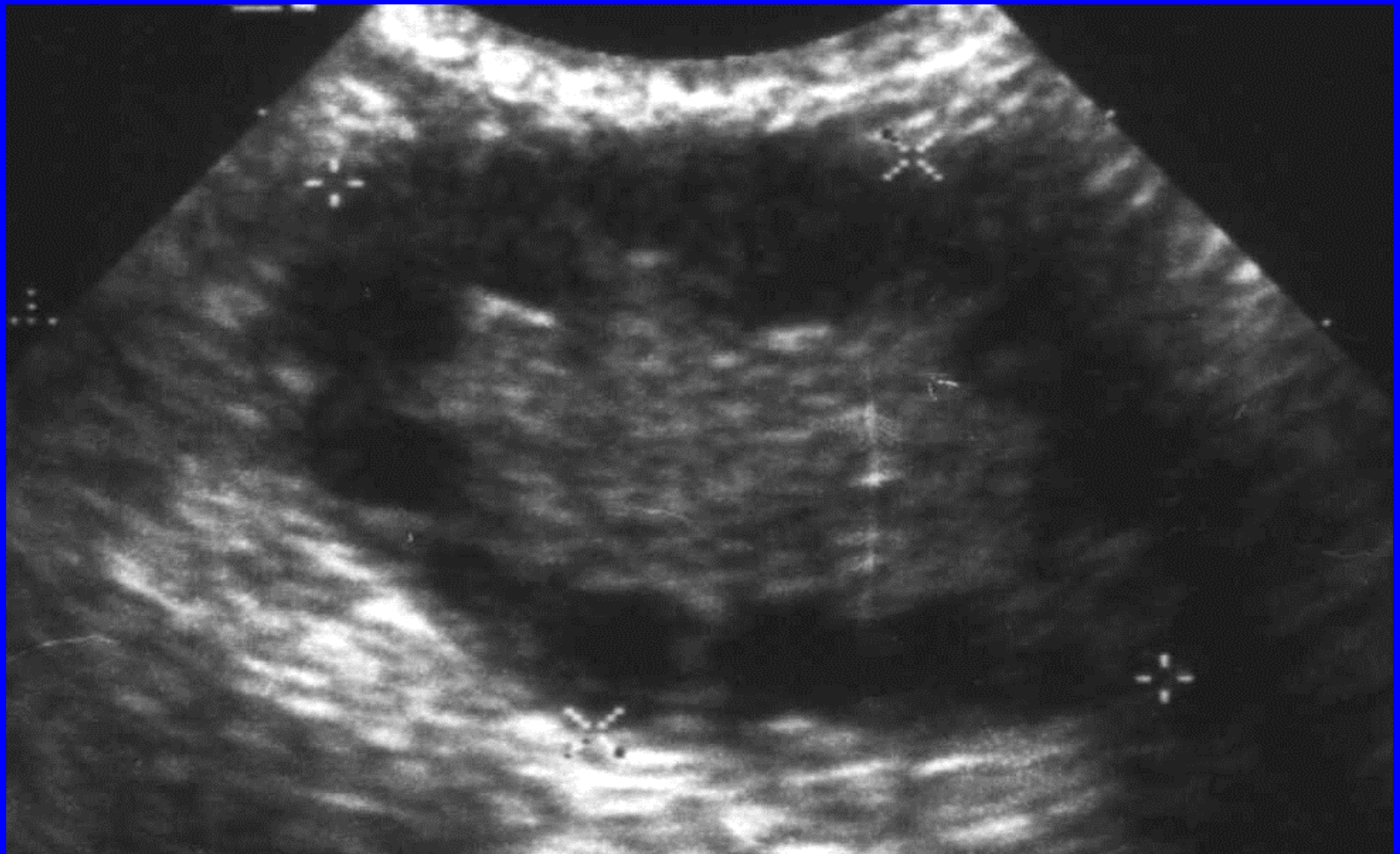
- Menstrual Cycle
 - $>3 < 12$ menses missed - MT completed in 4 years
 - Taffe et al 1997
 - Running range > 42 days – MT completed < 12 months
 - May be extremes of bleeding
 - Johannes et al 1996
 - Anovulatory cycles progressively common through MT
 - Massive E2 production in absence of progesterone
 - Santoro 1996 & 2002
 - Common finding not always associated with DUB
 - Park et al 2000

Endometrial Effects

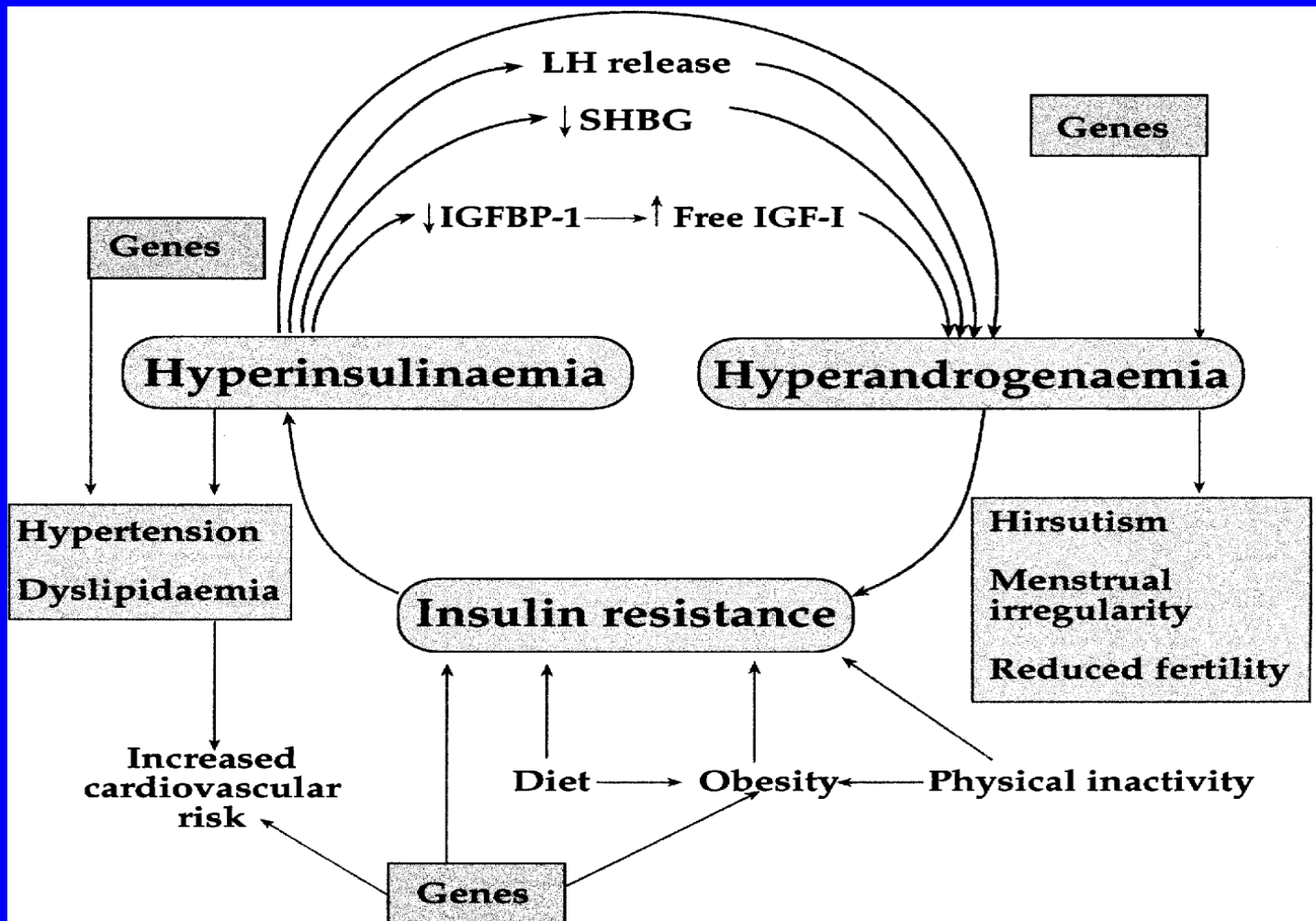


Reference: Blaustein's pathology of the female genital tract. 1994

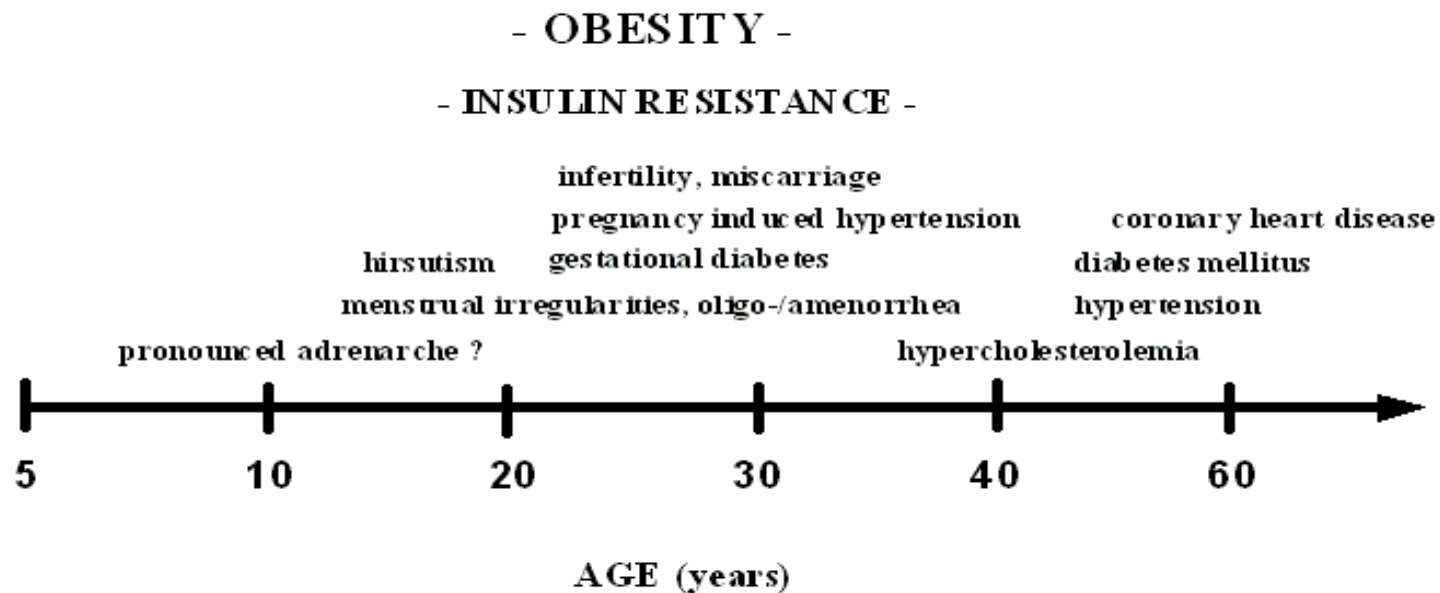
Polycystic Ovary



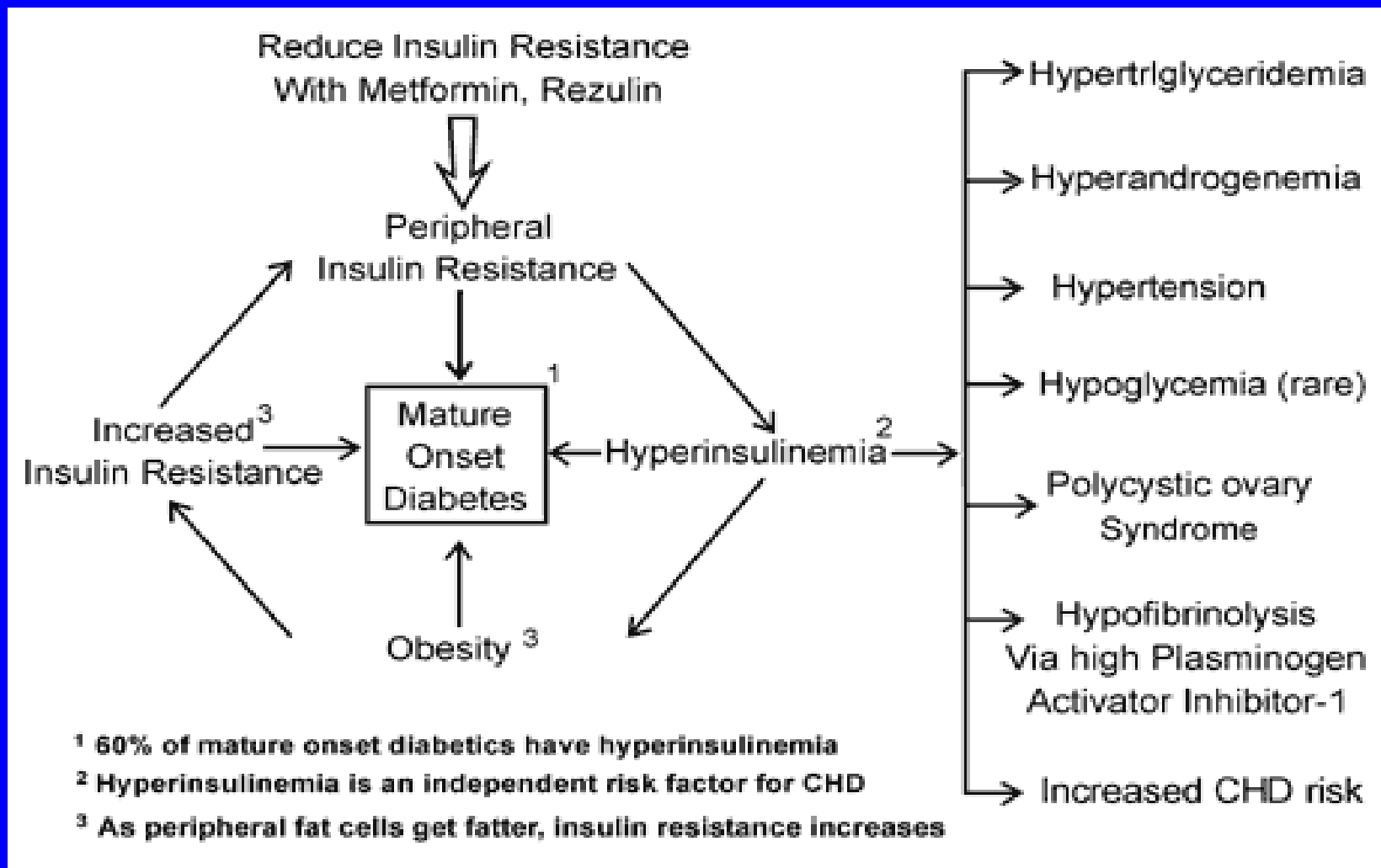
PCOS Mechanism



PCOS Mechanism



PCOS Insulin Resistance/Metformin



History

- **Key Points to Elicit**
 - **How irregular are periods - ?menstrual diary**
 - **Heavy/Clots/Sanitary wear**
 - **IMB/PCB**
 - **Pain / radiation / nature**
 - **Contraception ? IUCD/Mirena/Hormonal**
 - **Weight change**
 - **Hair Growth / Greasy skin / Acne**
 - **Galactorrhoea**
 - **Drugs e.g.throxine / anti epileptics**
 - **Significant PMH / FH**

Examination

- **General**
 - **BMI / BP**
 - **Obesity / Anorexia / Hirsutism**
 - **Urine**
- **Visual fields**
- **Abdomen**
 - **Pelvic mass e.g. fibroids**
 - **Ovarian enlargement**
 - **Cervix – swabs / smear / pipelle**

Investigations

- **General**
 - **Fbc**
- **Hormonal**
 - **HCG**
 - **E2/FSH/LH**
 - **TFTs**
 - **Androgens:**
Testosterone/SHBG/Androstenedione/DHEAS (FAI)
 - **PRL**
- **Imaging**
 - **Pelvic USS**
 - **MRI pelvis / head**

Investigations

- **Micro**
 - **HVS, Endocervix, Chlamydia**
- **Path**
 - **Smear**
 - **Pipelle endometrium (if endometrial thickening)**

Referral Indications

- **Secondary Amenorrhoea (periods $> \text{/=}$ 6 months apart =/- subfertility)**
- **Abnormal Imaging**
 - **Endometrium thickened on USS/Fibroids/Polyps**
- **Elevated androgens / abnormal TFTs / hyperprolactinaemia / elevated FSH**
- **IMB/PCB/PMB/Persistent BTB on hormonal contraception / HRT**
- **Accompanying pain**

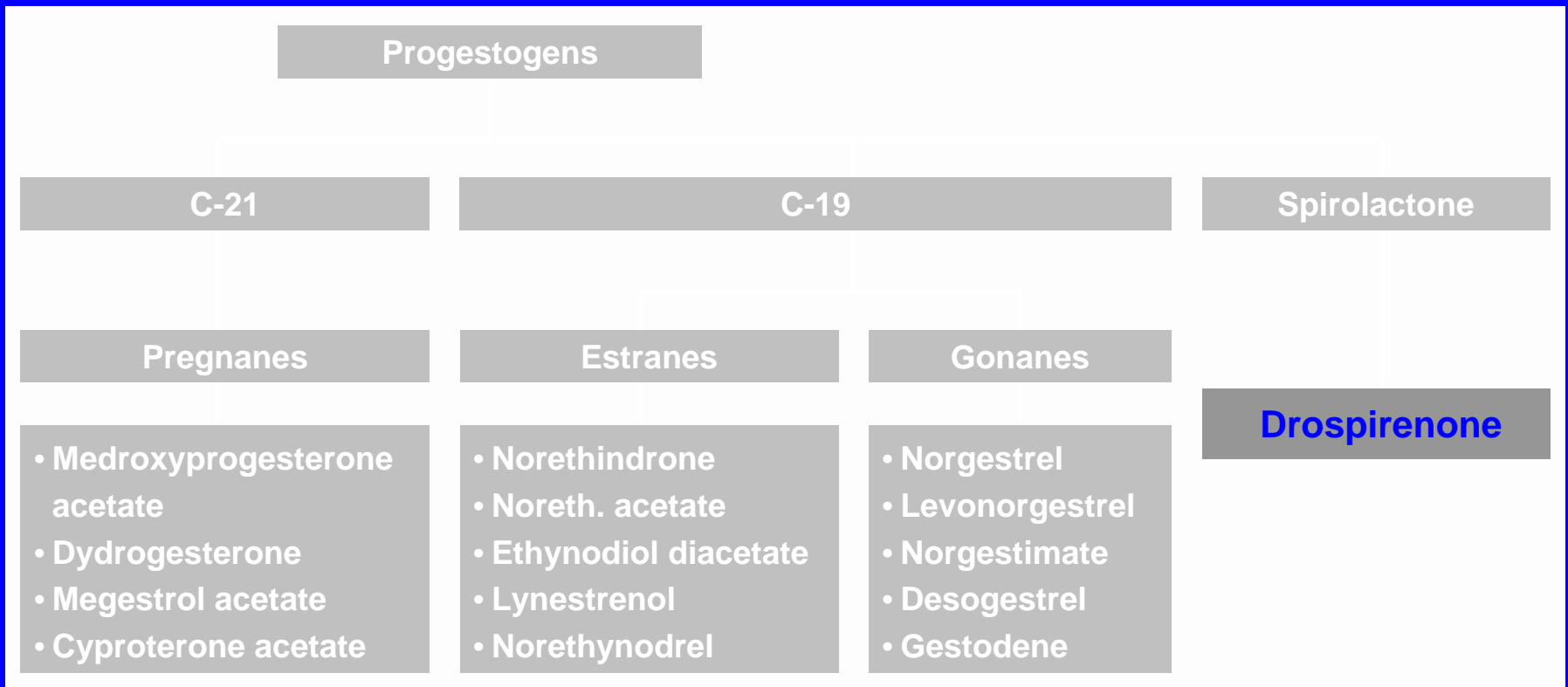
Interventions

- **Non Hormonal**
 - **Mefanamic / Tranexamic Acid**
 - **If periods heavy or painful**
- **Hormonal**
 - **Progestogens e.g. NETA 5mg /day (Day 8-28)**
 - **Particularly useful for anovulatory cycles**
 - **COC**
 - **Especially if contraception desired**

Interventions

- **Hormonal**
 - **COCP (PCOS)**
 - **Use for minimum of 12 months**
 - **Anti androgenic Progestogen e.g. cyproterone (Dianette), drospirenone (Yasmin)**
 - **HP/Insulin/BG baseline 6 & 12 months**
 - **USS repeat at 1 year**

Progestogen Classes



Comparison of progestogenic effects

	Estrogenic	Androgenic	Anti-androgenic	Glucocorticoid	Anti-mineralocorticoid
Progesterone	-	-	(+)	(+)	+
Drospirenone	-	-	+	-	+
Norethisterone	(+)	+	-	-	-
Dydrogesterone	-	-	-	-	(+)
Medroxyprogesterone	-	(+)	-	+	-

Key: + relevant activity; (+) activity not clinically relevant; – no activity

Interventions

- **Metformin**
 - **850mg bd or 500mg tds**
 - **Up to 3g per day**
 - **Combine with weight loss**
 - **Minimum of six months**
 - **Nausea, appetite suppression, congenital anomalies??**

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IUS

- **Useful if periods heavy and contraception to be ensured.**

References

- **NICE Menorrhagia Guideline Jan 2007**
- **BMJ Learning / Masterclasses for GPs**
- **Pitkin J DUB 2007; 334:1110-1111.**