Anovulatory Infertility and PCOS

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Disclosures: Medical advisor to Ferring, Organon SP

Causes of Anovulatory Infertility

Learning Objectives

1. To understand the causes of anovulation
2. Knowledge of the correct diagnostic tests
3. Effective assessment and diagnosis to plan appropriate ovulation induction therapy

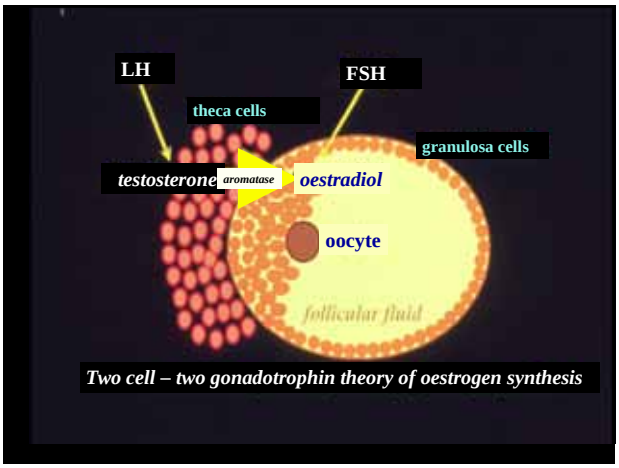
Hypothalamus

GnRH

Pituitary

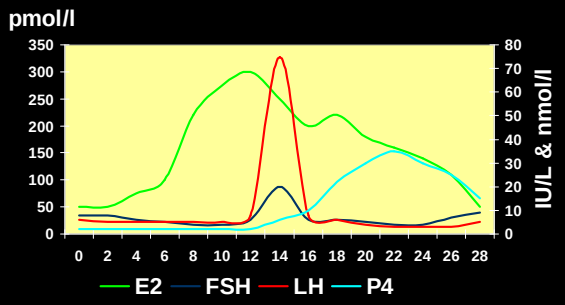
FSH LH

Oestradiol, inhibins
Progesterone…….



Two cell – two gonadotrophin theory of oestrogen synthesis

The Menstrual Cycle



Causes of Anovulatory Infertility

	weight loss, systemic illness
Hypothalamic/ pituitary failure	Kallmann's syndrome
	hypogonadotrophic hypogonadism
	Hyperprolactinaemia
	Hypopituitarism
	PCOS
h/p dysfunction	
	Premature ovarian failure (POF)
Ovarian failure	Resistant ovary syndrome (ROS)

Causes of Anovulatory Infertility

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	Hypopituitarism
Group II:	**PCOS**
h/p dysfunction	
Group III:	**Premature ovarian failure (POF)**
Ovarian failure	**Resistant ovary syndrome (ROS)**

Causes of Anovulatory Infertility

Group I:	**weight loss, systemic illness**	**5%**
Hypothalamic/ pituitary failure	**Kallmann's syndrome**	
	hypogonadotrophic hypogonadism	
	Hyperprolactinaemia	
	Hypopituitarism	
Group II:	**PCOS**	**90%**
h/p dysfunction		
Group III:	**Premature ovarian failure (POF)**	**5%**
Ovarian failure	**Resistant ovary syndrome (ROS)**	

Investigations

1. **FSH, LH, oestradiol**
2. **Prolactin / TFTs**
3. **Testosterone (SHBG)**
4. **AMH.....**
5. **GTT, lipid profile**
6. **Ultrasound scan**
7. **Semen analysis**
8. **Tubal patency assessment**

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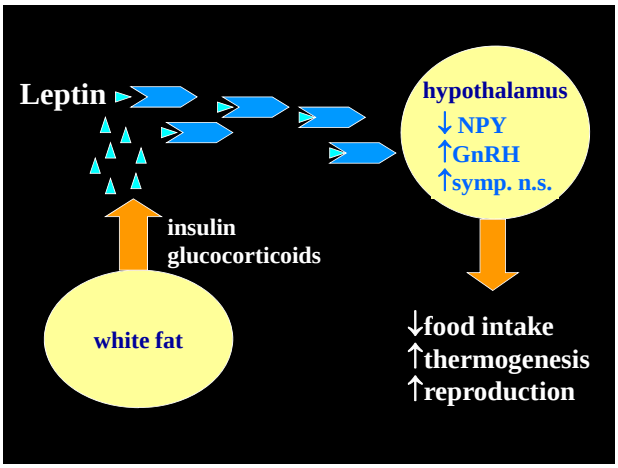
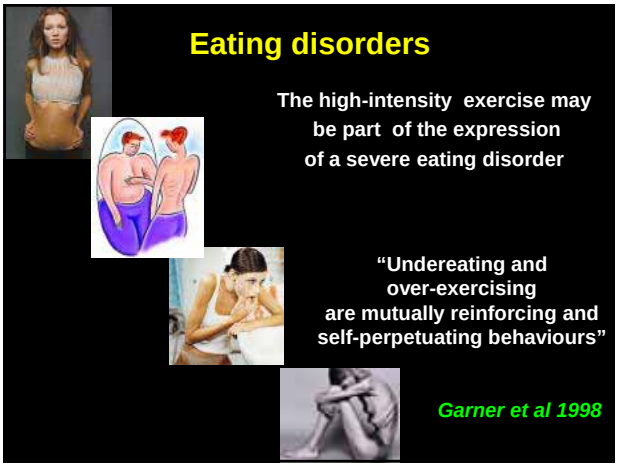
Hypothalamic causes *(hypogonadotropic hypogonadism)*	**Kallmann's syndrome** **Exercise** **Psychological distress** **Idiopathic**
Causes of hypothalamic/ pituitary damage	**Tumours (e.g. craniopharyngiomas)** **Cranial irradiation** **Head injuries** **Sarcoidosis** **Tuberculosis**
Systemic causes	**Chronic debilitating illness** **Weight loss**
Endocrine disorders	**Thyroid, Cushing's syndrome …**


Leptin
hypothalamus
↓NPY
↑GnRH
↑symp. n.s.
insulin
glucocorticoids
white fat
↓food intake
↑thermogenesis
↑reproduction


Exercise


Eating disorders
The high-intensity exercise may be part of the expression of a severe eating disorder
"Undereating and over-exercising are mutually reinforcing and self-perpetuating behaviours"
Garner et al 1998

Causes of Anovulatory Infertility

Group I:	weight loss, systemic illness
Hypothalamic/ pituitary failure	Kallmann's syndrome hypogonadotrophic hypogonadism Pulsatile GnRH or FSH/LH (hMG)

Causes of Anovulatory Infertility

Hypothalamic:	↓FSH, ↓LH, ↓Oestradiol (E2)
underweight	n FSH, ↓LH, ↓E2
Hyperprolactinaemia	↓FSH, ↓LH, ↓E2
Ovarian failure / menopause:	↑↑FSH, ↑LH, ↓E2
Mid-cycle	↑FSH, ↑↑LH, ↑E2
PCOS:	↓/n FSH, ↑/n LH, ↑/n E2

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Hyperprolactinaemia	↓ FSH, ↓ LH, ↓ E2
	Prolactin >1000 miu/l
Ovarian failure / menopause:	↑↑ FSH, ↑ LH, ↓E2
Mid-cycle	↑ FSH, ↑↑ LH, ↑ E2
PCOS:	↓/n FSH, ↑/n LH, ↑/n E2

Treatment of hyperprolactinaemia

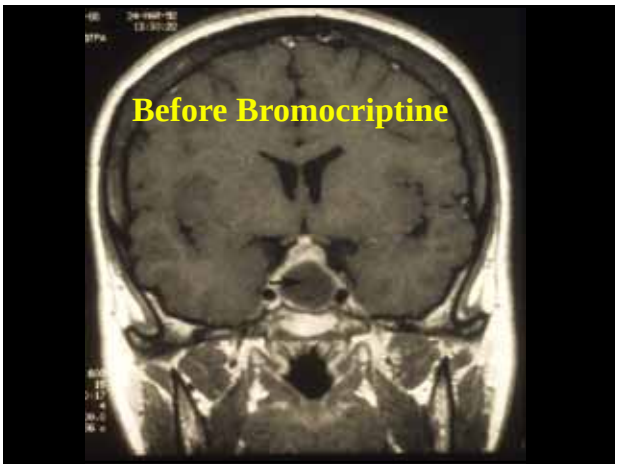
Dopamine agonists:

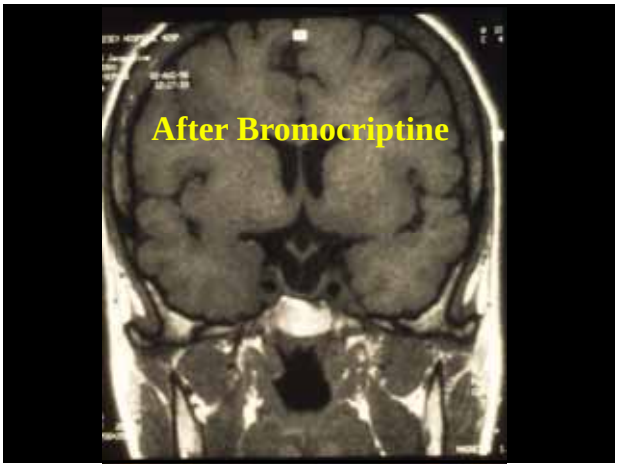
Restore ovarian function in 85%
85% conceive

Macroadenomas: 70% shrink
65% ovulate
50% conceive

Dopamine agonists

Bromocriptine	2.5 - 20mg daily
Cabergoline	0.25 - 1 mg twice weekly
Quinagolide	25 - 150 mcg daily





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The Rotterdam ESHRE/ASRM Consensus Group Revised 2003 Diagnostic Criteria for PCOS

2 out of 3 criteria required

- Oligo- and/or anovulation
- Hyperandrogenism (clinical and/or biochemical)
- Polycystic ovaries

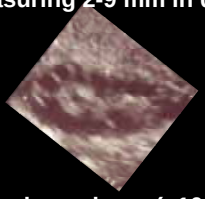
Exclusion of other causes of menstrual disturbance and hyperandrogenism

Human Reproduction 2004; 19: 41-47. Fertility & Sterility, 2004; 81: 19-25.

Ultrasound Assessment of the Polycystic Ovary: International Consensus Definitions

The polycystic ovary contains 12 or more follicles measuring 2-9 mm in diameter

and/or



increased ovarian volume (>10 cm^3)

Balen, Laven, Tan & Dewailly; Hum Reprod Update 2003; 9: 505
ESHRE/ASRM Consensus 2003

Chronic anovulation and unopposed oestrogen

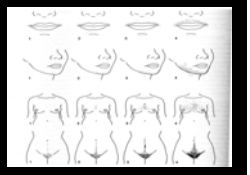
Normal endometrium

Endometrial cystic glandular hyperplasia

Endometrial carcinoma, invading myometrium

Hyperandrogenism:

Alopecia:
Androgen mediated, iron deficiency



Hirsutism: subjective
Ferriman Gallwey Score
ethnic variations

Acne:

54% of women over 25y have physiological acne
Correlates variably with hyperandrogenemia

Biochemistry of Hyperandrogenism

- Testosterone : free or total ?
  (0.5 – 3.5, usually < 5nmol/l)
- SHBG - surrogate for insulin resistance
  (16-119 nmol/l)
- Free Androgen Index (T/SHBG)x100
- Androstenedione, DHEAS, 17-OH P …. ?

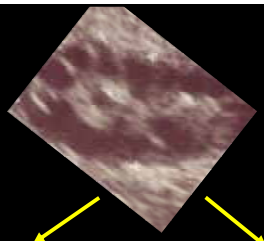
Kane et al, Ann Clin Biochem 2007; 44: 5-15
Barth & Balen, Clin Endocrinol 2007; 67: 811

Controversies

- How to assess HA biochemically?
  Mass spectrometry superior to immunoassays
- Variations:
  Diurnal (am > pm),
  Cyclical (luteal > follicular)
  Seasonal (summer > winter)
- Age-related changes
- Ethnic differences

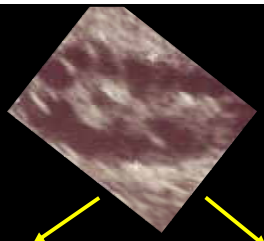
Other causes of androgen excess

- Late onset congenital adrenal hyperplasia
- Androgen secreting tumours
- Cushing's syndrome



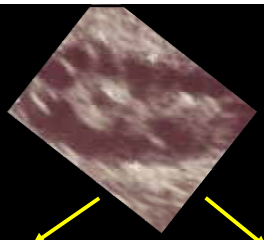
Hyperandrogenism
Menstrual disturbances

↑ testosterone



Hyperandrogenism
Menstrual disturbances

↑ testosterone
↑ luteinising hormone

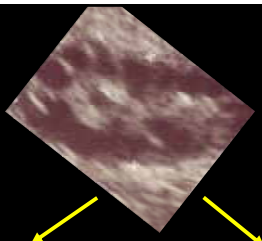


Hyperandrogenism
Menstrual disturbances

↑ testosterone
↑ luteinising hormone

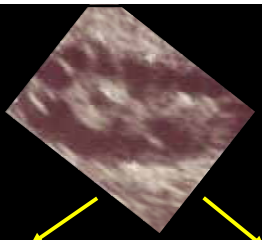
Elevated Luteinising Hormone:

- not mandatory for diagnosis
- 40% of PCOS
- most likely to be elevated in slim women
- may help predict outcome of fertility therapy:
  - Worse outcome after CC if elevated day 8
  - Better prognosis for response to ovarian drilling



Hyperandrogenism
Menstrual disturbances

↑ testosterone,
↑ luteinising hormone
↑ insulin



Hyperandrogenism
Menstrual disturbances

↑ testosterone, ↓ SHBG
↑ luteinising hormone
↑ insulin

Insulin Resistance and PCOS

	Ovulatory normal	Ovulatory PCO(S)	Anovulatory PCOS
Testosterone	N	↑	↑
LH	N	↑	↑
Insulin	N	N	↑

Steve Franks

Insulin Resistance and PCOS

- Failure of insulin action at receptor
- Selective insulin resistance:

  Glucose uptake by cells impaired

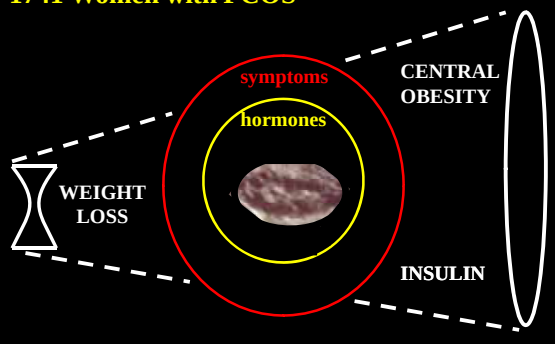
  Trophic actions of insulin continue

  Insulin augments LH → ↑ testosterone

75 g Glucose Tolerance Test

	Diabetes Mellitus	Impaired Glucose Tolerance (IGT)
Fasting glucose (mmol/l)	≥ 7.0	< 7.0
2 hour glucose (mmol/l)	≥ 11.1	≥ 7.8 < 11.1

1741 Women with PCOS

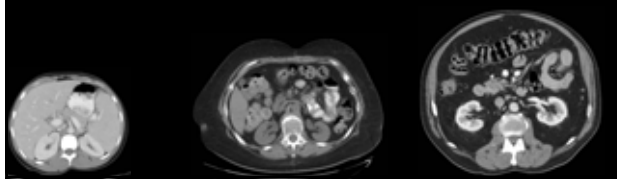


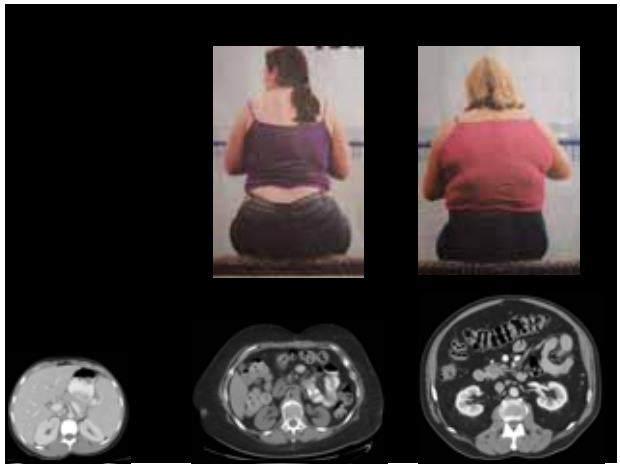
Balen et al Hum Reprod 1995; 10: 2107

Obesity:

BMI – WHO criteria (overweight 25-30, obese > 30 kg/m^2)

Waist Circumference > 80 cm





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Infertility in Practice, *Third Edition* , Balen AH
Informa Healthcare, London, 2008

Clinical Management of Polycystic Ovary Syndrome
Balen AH , G. Conway, R. Homburg, R. Legro
Taylor & Francis, London & New York, 2005, 234 pages. 1st reprint: 2005.

Obesity and Reproductive Health. Edited by P Baker, A Balen, L Poston and Naveed Sattar. Proceedings of 53rd RCOG Study Group, RCOG Press, London 2007.

Polycystic Ovary Syndrome. Edited by A Balen, S Franks and R Homburg. Proceedings of 56th RCOG Study Group, RCOG Press, London 2010.