

Endocrine disorders and reproductive function

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Endocrine disorders and reproductive function: learning objectives

- To be aware of the many endocrine diseases that may compromise reproductive function
- To be aware of clinical features that may point to a specific underlying endocrine problem
- To understand the principles of investigation and management

Endocrine disease and ovulatory function

- Certain endocrine disorders are well known and common causes of menstrual dysfunction (eg hyperprolactinaemia, PCOS)
- Many other endocrine disorders are rare causes of menstrual dysfunction but commonly present with menstrual abnormalities

Causes of anovulation

- Primary ovarian failure
- Deficiency or disordered regulation of gonadotrophins
- Polycystic ovary syndrome

Investigation of anovulation

- High FSH, low E2 = **primary ovarian failure**
- Normal/low FSH, low E2 = **hypothalamic/pituitary disorder**
 - Measure prolactin
- Normal FSH, normal E2 (± high LH) = **PCOS**

Further investigation of hypothalamic amenorrhoea

(normal or low FSH, oestrogen deficiency)

- GnRH stimulation test
- Other anterior pituitary function tests
- Imaging of hypothalamic-pituitary area

Rarely needed!

Endocrine disorders associated with ovulatory dysfunction

- Hypothalamic-pituitary disease
 - prolactinoma
 - acromegaly
 - Cushing's
 - non-functioning tumours
 - Sheehan's syndrome
- Adrenal disease
 - CAH
 - virilizing tumours
 - Addison's disease
- Thyroid disease
 - hypothyroidism
 - hyperthyroidism
- Ovarian disease
 - virilizing tumours

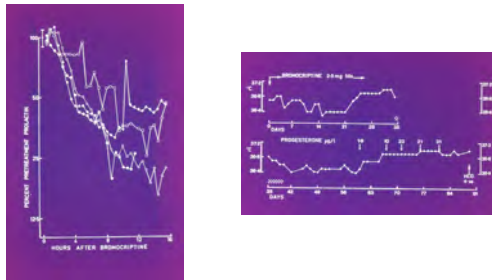
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Hyperprolactinaemia

- Common cause of amenorrhoea
- About 50% have pituitary adenomas
- Causes abnormalities of GnRH secretion
- Medical treatment is effective even in patients with pituitary tumours

Dopamine agonists normalize prolactin and restore ovulation

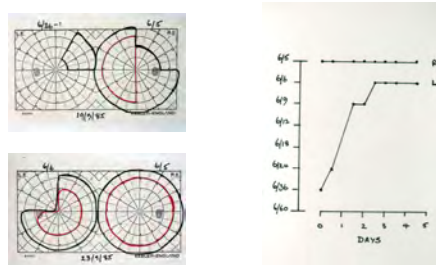


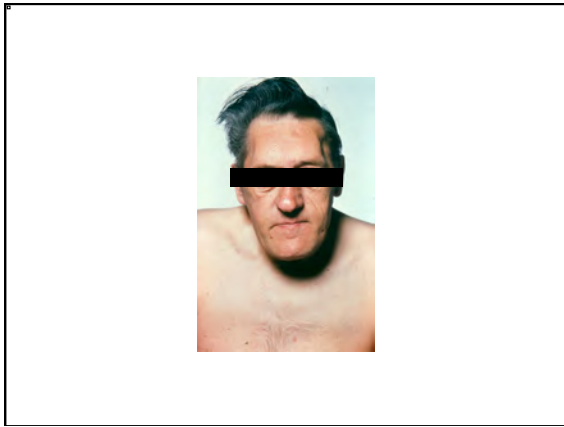
The incredible shrinking prolactinoma: effect of a dopamine agonist (cabergoline)



Hurley and Ho, *Med J Aust* 2004 180 491-25

Rapid improvement in vision after bromocriptine treatment of a large prolactinoma





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Acromegaly

- Changes in skin, digits and joints
- Weight gain
- Voice changes
- Excessive sweating
- Diabetes

Johnson & McGregor 1990, Bailliere's Clin Endo & Metab 4 313

Acromegaly

- Menstrual disturbances are common and usually associated with hyperprolactinaemia
- Gonadotrophin deficiency can also occur, particularly after surgery or radiotherapy
- >70% of premenopausal women with acromegaly have oligo- or amenorrhoea
- Treatment may include pituitary surgery, dopamine agonists and gonadotrophin therapy

Johnson & McGregor 1990. *Bailliere's Clin Endo & Metab* 4 313; Kaltsas et al *J Clin Endocrinol Metab* 1999 84 2371-5

Acromegaly

- Investigations
 - Basal serum growth hormone
 - Post OGTT GH
 - IGF-1
 - Prolactin
 - Imaging

Johnson & McGregor 1990. *Bailliere's Clin Endo & Metab* 4 313; Kaltsas et al *J Clin Endocrinol Metab* 1999 84 2371-5



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Cushing's syndrome

- Typical onset between 20 and 60 y
- More common in women than men
- Weight gain with central adiposity
- Hirsutism
- Moon face
- Easy bruising
- Striae
- Muscle wasting

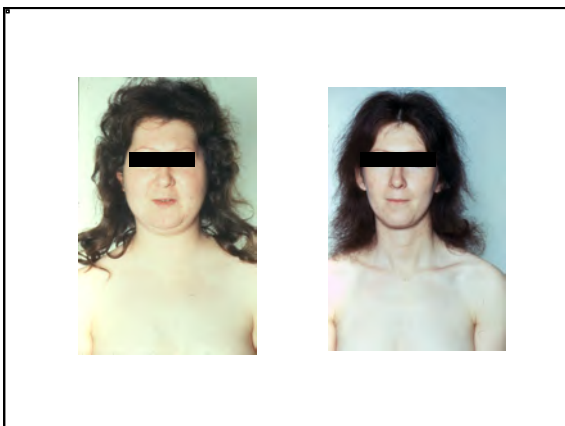
Cushing's syndrome

- Oligo- and amenorrhoea are common (60% of 45 pre-menopausal women)
- Often presents with symptoms similar to PCOS - but usually with shorter history
- Early significant findings are *hypertension* and *change in fat distribution*

Lado-Abeal et al 1998, *J Clin Endocrinol Metab* 83:3083







Mrs C K-H 34 yrs
Secondary amenorrhoea for 2 years
Weight gain
Hirsutism on face and breasts for 2+ years

Menarche 15, regular periods 4/28-30

LH, FSH, PRL, oestrogen - normal
testosterone 3.4nmol/l

Diagnosis PCOS

Received clomiphene - 6 courses; regular
Cycles but "low progesterone"

Examination

BMI 23.7
BP 130/90
Roundish, reddish face but not
obviously Cushingoid
No bruising or striae
Coarse hair under chin, on breasts,
abdomen and thighs

Investigations?

LH 8.4, FSH 6.9 u/l
Prolactin 162 mU/l
Progesterone withdrawal positive
Testosterone 3.4 nmol/l

Ultrasound PCO

Diagnosis?
Other tests?

24 hour urine free cortisol
950nmol/24h (normal <300)
820nmol/l

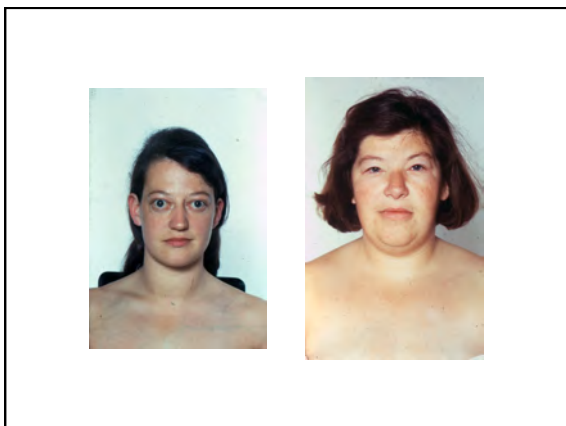
Overnight dex suppression
9am cortisol 616nmol/l

Diagnosis: **Cushing's syndrome**

Other tests?

Cushing's syndrome

- In Cushing's Disease, pituitary surgery is best option for cure, particularly if the adenoma is small (<1cm)
- Pituitary function may be restored (including normal gonadotrophin and androgen secretion)
- Post-treatment hypopituitarism is not uncommon and may require gonadotrophin therapy for restoration of fertility



Endocrine disorders associated with ovulatory dysfunction

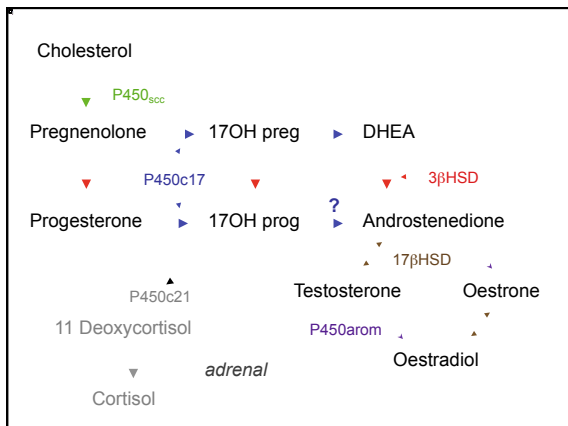
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Thyroid disease

- Menstrual disturbance in hyperthyroidism is uncommon except in overt thyrotoxicosis
- Menorrhagia is said to occur in hypothyroidism but is probably also uncommon
- Amenorrhoea occurs in hypothyroidism in association with hyperprolactinaemia and primary ovarian failure.
- The place of routine TFTs in investigation of menstrual disturbance is therefore questionable

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Congenital adrenal hyperplasia

- Most commonly due to 21-hydroxylase deficiency
- Classical (salt-losing) and non-classical (late onset) forms
- Presentation of non-classical form similar to PCOS
- **Diagnostic test?**
- Management with glucocorticoid replacement or (for hirsutism) anti-androgens

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Case report: Mrs Y 31y

- Presented with 10 month history of oligomenorrhoea and 2^o infertility
- Mild but increasing hirsutism and acne for 6 months
- Investigations: LH 11.0 u/l; FSH 4.5 u/l; PCO on ultrasound
- Ovulated with clomiphene

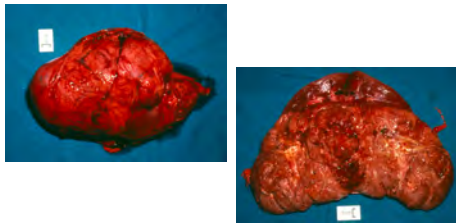
- Returned for assessment after 3 cycles of clomiphene
- Increasingly severe hirsutism; temporal hair recession; hoarse voice
- Testosterone 11 nmol/l (normal <3)

- Testosterone 15 nmol/l
- Androstenedione >70 nmol/l (<9)
- DHEAS 108 μmol/l (<10)
- 17-hydroxyprogesterone 23 nmol/l (<12)
- Urine free cortisol 1110 nmol/24h (<300)
- CT adrenals:

Mrs Y: CT of abdomen



10cm adrenal tumour



Post-operatively:

- Normalisation of testosterone
 - Resolution of hirsutism
 - Return of fertility
- BUT**
- Recurrence after 2 years with liver and lung metastases

Androgen-secreting adrenal tumours

- Rare
- Adenoma or carcinoma
- Often secrete cortisol
- Rarely secrete testosterone directly
- Carcinomas not radiosensitive

Endocrine disorders and reproductive function: summary

- Uncommon endocrine diseases commonly present with reproductive dysfunction and/or hirsutism
- Clinical clues are all important in determining further endocrine tests and imaging
- Correct diagnosis leads to appropriate treatment to restore reproductive potential
