

TOPICS:

- (1) Gynaecomastia
- (2) Galactorrhoea
- (3) Hirsutism

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(1) GYNAECOMASTIA



Case presentation

- Mr. IT, a 40 year old man from Eersterust

Social history:

- Married, security worker
- Ex-alcohol binger (no alcohol for 5 years)
- Smoker: 20 pack years
- No recreational drugs or cannabis

- Referral to SBAH for:

→ **Gynaecomastia**

Medical history:

- Gynaecomastia started 2 - 3 years ago
- Non-tender breasts
- Asymmetrical (left larger than right)
- No galactorrhoea
- Erectile dysfunction x 2 years with decreased morning erections as well
- Decreased libido
- Decreased shaving
- One child, 11 years of age; wife off contraceptives x 6 years, has not fallen pregnant yet

Medical history (cont):

- No marital problems
- Stress at work
- Past peptic ulcer disease: uses Ranitidine chronically and Metoclopramide on and off
- Did have mumps as a teenager
- No other chronic medical problems / medications

Examination:

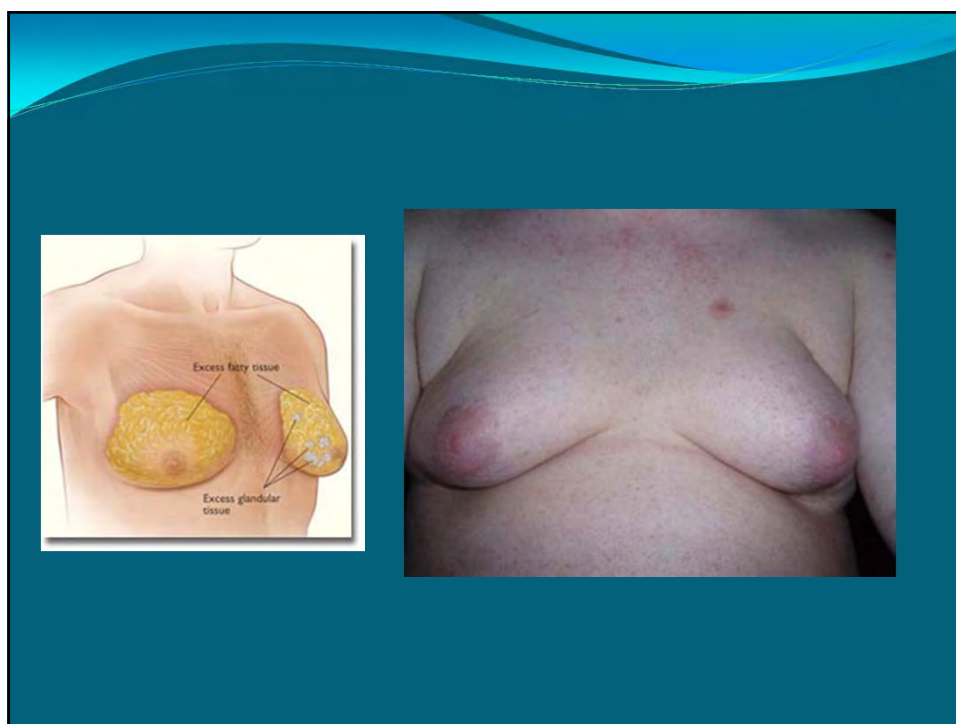
- Clear gynaecomastia (C-cup); left larger than right; not tender; no breast nodules/masses
- L testis = 10ml, R testis = 12ml (slightly small); no masses palpable
- Signs of hypogonadism (decreased body hair)
- No signs of chronic liver disease or of thyrotoxicosis
- No features of Klinefelters' syndrome
- No anosmia (Kallman's syndrome)

What is gynaecomastia?

- = Benign proliferation of the glandular tissue of the male breast
- Clinically: presence of a rubbery or firm mass extending concentrically from the nipple(s)
- Can be unilateral or bilateral
- Caused by an increase in the ratio of oestrogen to androgen activity

Who develops it?

- Common in:
 - infancy (60-90%)
 - adolescence (up to 65%)
 - middle-aged to older adult males
- Pseudogynaecomastia
 - is often seen in obese men ("moobs")
 - fat deposition without glandular proliferation
 - doesn't require evaluation



Causes?

- **Physiologic** gynaecomastia
 - infants
 - adolescents
- **Pathologic**
- **Idiopathic**

Puberty

- Transient increase in oestradiol concentration at the onset of puberty
- The serum oestradiol concentrations rise to adult levels before the testosterone concentration
- Thus: **transient imbalance of oestrogen and androgen**
- Usually resolves spontaneously within 6m – 2 years of onset, but may persist

Adults

- **Persistent pubertal** gynaecomastia (25%)
- **Drugs** (10-25%)
- **Idiopathic** / no detectable abnormality (25%)
- **Cirrhosis** or malnutrition (8%)
- **Hypogonadism** – primary (8%); secondary (2%)
- **Testicular** tumours (3%)
- **Hyperthyroidism** (1.5%)
- **Chronic renal insufficiency** (1%)

Drugs

Antiandrogens/inhibitors of androgen synthesis:

- Cyproterone acetate
- Finasteride
- Spironolactone
- Ketoconazole
- Tea tree oil

Antibiotics:

- Ethionamide
- Isoniazid
- Ketoconazole
- Metronidazole

Antiulcer drugs:

- Cimetidine
- Ranitidine
- Omeprazole

Cancer chemotherapeutic drugs:

- Methotrexate
- Vinca alkaloids
- Combination chemotherapy

Cardiovascular drugs:

- ACE-inhibitors: captopril, enalapril
- Amiodarone
- Calcium channel blockers: diltiazem, nifedipine
- Digoxin
- Methyldopa

Drugs of abuse:

- Alcohol
- Amphetamines
- Heroin
- Marijuana



Psychoactive drugs:

- Diazepam
- Haloperidol
- Phenothiazines
- Tricyclic antidepressants

Hormones:

- Androgens
- Anabolic steroids
- Estrogens
- Growth hormone

Other:

- HAART
- Metoclopramide
- Phenytoin
- Theophylline

HIV

HAART:

- = usually due to **fat tissue** (pseudogynaecomastia) as part of a fat redistribution syndrome (lipodystrophy)
- True gynaecomastia can be caused by **hypogonadism**
- Oestrogen-like effects of some **drugs**, especially Efavirenz
- **Malnutrition**

Cirrhosis or malnutrition

- Prevalence of gynaecomastia in **cirrhotic** patients as high as 67%
- **Starvation / refeeding** gynaecomastia



Male hypogonadism

- **Primary hypogonadism**
 - testicular problem
 - Klinefelter's syndrome
- **Secondary hypogonadism**
 - pituitary or hypothalamic problem
 - Kallman's syndrome

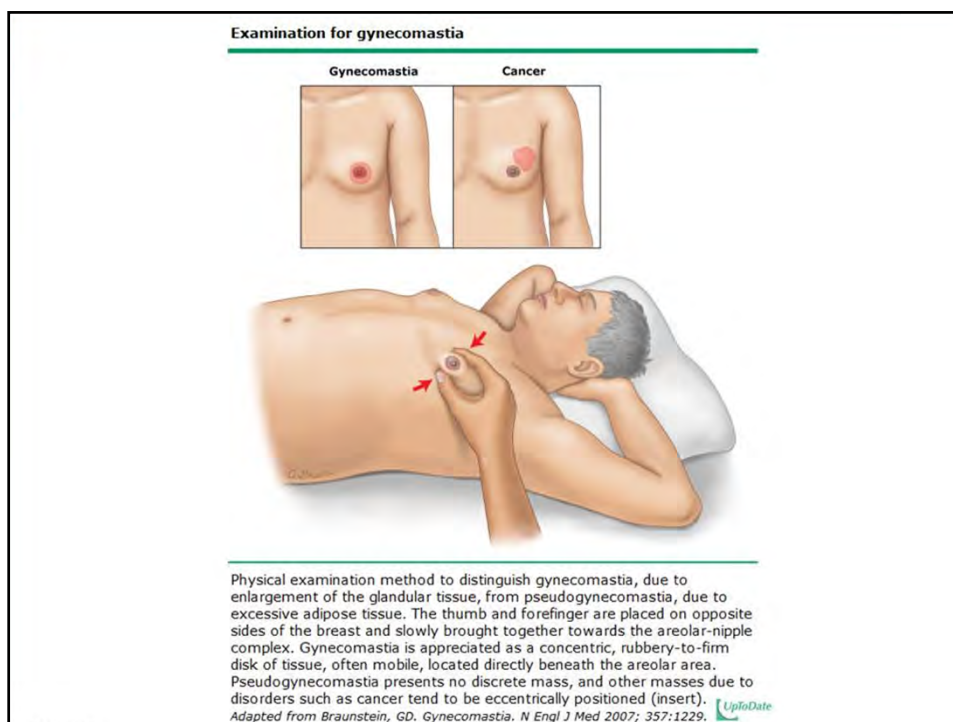


When to investigate?

- Recent onset
- Painful
- Signs or symptoms of hypogonadism
- Adolescents: just observe 6-monthly

How to diagnose?

- A palpable mass of tissue at least 0.5cm in diameter (usually underlying the nipple)
- NB: men can also get breast cancer!



How to investigate?

- **History:** NB – drugs!
 - how sudden was onset / pain / tenderness / associated complaints
- **Physical examination:**
 - pseudogynaecomastia / gynaecomastia / cancer
 - look for symptoms and signs of renal or liver disease / hyperthyroidism / intersex / anosmia / Klinefelter's syndrome / hypogonadism
 - abdominal mass / testicular mass

- **Special investigations:**

- Sonar / mammogram if not sure about gynaecomastia
- Karyotype if signs of Klinefelter's
- Testosterone (T), LH, oestradiol
- hCG

Possibilities in our patient:

- Drugs: - ranitidine
 - metoclopramide
- Past alcohol abuse (? liver disease)
- Past mumps (? testicular problems)

Our patient's results:

- Normal U&E, LFT, TFT, HCG, oestradiol
- Testosterone: 5.11 nmol/l (N = 6.07 – 27.10)
- LH: 2.6 IU/l (N = 1.2 – 8.6)
- FSH: < 1.7 IU/l (N = 1.3 – 19.3)
- Prolactin: 190.9 / 184.8 µg/l (N = 2.5 – 17)
- MRI of pituitary: pituitary not enlarged
but: ? hypodense lesion ? microadenoma
- Diagnosis:
= Hyperprolactinaemia due to a possible pituitary
microprolactinoma

How to treat?

Depends on:

- Aetiology
- Duration
- Severity
- Presence or absence
of tenderness

Spontaneous regression

- Recent onset (<6m) often regress spontaneously (adults and adolescents)
- Pubertal: regression in 85-90% within 6m – 2yr
- Persistence beyond age 17 is uncommon
- > 12 months: unlikely that medical therapy will cause significant regression in the late fibrotic stage

Treatment

- Observation only
 - initial step for most adolescents, and for most men after treating underlying cause
- Drug therapy
 - early therapy if severe breast enlargement, pain, tenderness, and embarrassment that interferes with daily activities
- Radiotherapy
 - prophylactic before therapy for prostate cancer
- Surgery
 - reduction mammoplasty
 - not before completion of puberty

Drugs

- **Androgens**
 - testosterone (only for hypogonadism)
 - dihydrotestosterone
- **Selective oestrogen receptor modulators**
 - tamoxifen, raloxifene
 - anti-oestrogen effects
 - particularly useful in reducing pain and swelling if gynaecomastia is of recent onset
- **Aromatase inhibitors**
 - anastrozole
 - block oestrogen biosynthesis
 - in trials: not effective

Spontaneous regression:



Post-surgery:

- only small scar



Therapy in our patient:

- Dopamine agonist:
 - Parlodel (Bromocriptine): 2.5mg bd (titrating up)
- Added now Sustanon (Depot Testosterone) 250mg IMI monthly for severe hypogonadal complaints
- Should be able to stop Testosterone once prolactin normalized
- Will most likely need mastectomies in near future

(2) HYPERPROLACTINAEMIA/ GALACTORRHOEA



Case presentation

- Miss PM, a 38 year old female from Mamelodi

Social history:

- Single, clerical work (now unemployed), 1 child
 - Alcohol: nil
 - Never smoked
 - No recreational drugs or cannabis
-
- Referral to SBAH for:
 - Galactorrhoea

Medical history:

- Galactorrhoea started 1 year ago
- Both breasts involved, more than one duct
- Mainly occurs on pressing breasts, but occasionally spotting on bra
- White and yellow fluid present
- Regular menses, but menorrhagia, dysmenorrhoea and short cycles present

Medical history (cont):

- One child, age 21
- Never tried to fall pregnant after that, never used contraceptives (abstained)
- Iron deficiency anaemia, uses iron supplements
- Surgeons already performed a sonar of breasts and a mammogram: all normal
- No other chronic medical problems / medications / the Pill / hormones

Examination:

- Clear galactorrhoea: milky discharge from 3 ducts of the right breast, milky discharge from 1 duct of the left breast, yellow watery discharge from another duct of the left breast
- No masses palpable in the breasts
- No evidence of pregnancy
- No signs of hypothyroidism
- No visual field outfall

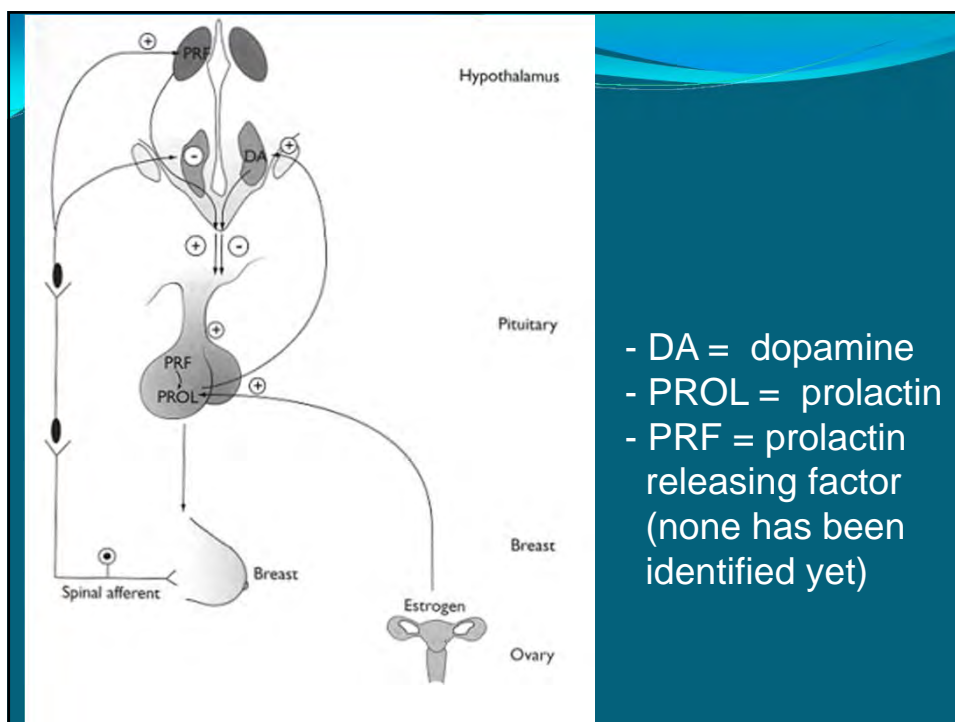
What is it?

- **Hyperprolactinaemia** = high serum prolactin
 - common abnormality which usually presents with hypogonadism and / or galactorrhoea
- **Galactorrhoea** = lactation in the absence of breastfeeding
- Most women who have hyperprolactinaemia do not have galactorrhoea
- Many women who have galactorrhoea have normal serum prolactin values

Galactorrhoea

- Milk secretion can continue for at least **6 months** after delivery or after cessation of breastfeeding
- Usually **bilateral** and white or clear
- May be unilateral and a **variety of colours** including yellow, green, brown, or gray
- Occasionally bloody during pregnancy or lactation
- **Prolactin** stimulates **milk secretion** but not breast development (needs oestrogen +/- progesterone)
- Galactorrhoea thus **rare in men** unless also gynaecomastia due to hypogonadism





Symptoms and signs of ↑ prolactin

- **Postmenopausal women:**
 - asymptomatic (already hypogonadal)
 - occasionally visual field outfall or headaches if large pituitary tumour
 - **Premenopausal women:**
 - galactorrhoea
 - hypogonadism: oligomenorrhoea
secondary amenorrhoea
anovulation with infertility
hot flashes
vaginal dryness
- = central hypogonadism (inhibition of LH +/- FSH)

Symptoms and signs (cont)

- Correlation between level of prolactin elevation, and:
 - symptoms
 - size of tumour if prolactinoma is present
- **Mild** elevation (20 – 50 ng/mL): can cause infertility even when menstruating normal; insufficient progesterone secretion with anovulation; present in 20% of women evaluated for infertility
- **Moderate** elevation (50 – 100 ng/mL): amenorrhoea or oligomenorrhoea
- **Significant** elevation (> 100 ng/mL): overt hypogonadism

Symptoms and signs (cont)

- **Men:**
 - galactorrhoea very rare
 - **hypogonadism**: decreased libido
impotence
reduced shaving frequency
infertility (4% of infertile men)
gynaecomastia
lethargy, decreased energy
 - **erectile dysfunction** not only due to hypogonadism, but is directly related to high prolactin
 - in long term hypogonadism causes: decreased body hair, osteoporosis, decreased muscle mass

Causes of hyperprolactinaemia?

- Physiological
- Drug-induced
- Pathological

Physiological:

- Stress (e.g. post-seizure)
- Pregnancy
- Lactation
- Nipple stimulation
- Sleep
- Coitus
- Exercise
- Baby crying

Partial list of drugs known to cause hyperprolactinemia and/or galactorrhea

Typical antipsychotics
Phenothiazine drugs (eg, chlorpromazine [Thorazine], clomipramine [Anafranil], fluphenazine [Prolixin], prochlorperazine [Compazine], thioridazine [Mellaril])
Haloperidol (Haldol)
Pimozide (Orap)
Atypical antipsychotics
Risperidone (Risperdal)
Molindone (Moban)
Olanzapine (Zyprexa)
Antidepressant agents
Clomipramine (Anafranil)
Desipramine (Norpramin)
Gastrointestinal drugs
Cimetidine (Tagamet)
Metoclopramide (Reglan)
Antihypertensive agents
Methyldopa (Aldomet)
Reserpine (Hydromox, Serpasil, others)
Verapamil (Calan, Isoptin)
Opiates
Codeine
Morphine

UpToDate

Pathological

- **Common:**

- disconnection hyperprolactinaemia / “stalk effect”
- prolactinoma (usually microadenoma)
- primary hypothyroidism
- polycystic ovarian syndrome
- macroprolactinaemia

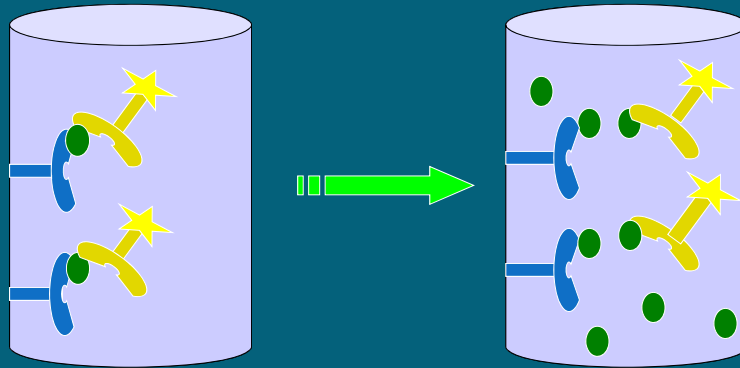
- **Uncommon:**
 - hypothalamic disease
 - renal failure
 - pituitary tumour secreting prolactin and growth hormone
- **Rare:**
 - chest wall reflex (e.g. post-herpes zoster)
 - ectopic source

Don't forget

- **Macroprolactin**
 - in some people: prolactin becomes bound to an IgG antibody or become glycosylated (=“macroprolactin”)
 - of no pathological significance
- **Stalk effect / disconnection hyperprolactinaemia**
 - anything that disrupts the inhibitory effect of hypothalamic dopamine on prolactin secretion
- **High dose “hook effect”:** caution in interpreting prolactin concentration between 20 and 200 µg/l in the presence of a macroadenoma

Analytical interference (The Hook Effect)

The huge excess of prolactin (if e.g. $>5000 \mu\text{g/l}$) saturates both specific and less specific binding sites on both antibodies (capture and signal) preventing "sandwich" formation in the assay



The Hook Effect

- Result is a prolactin level that is only modestly elevated (falsely lower than it is)
- Avoid this artifact by repeating the assay using a 1:100 dilution of serum

How to investigate?

Clinical examination:

History:

- drugs, pregnancy, breastfeeding, headaches, diplopia, renal / thyroid disease, underwear

Examination:

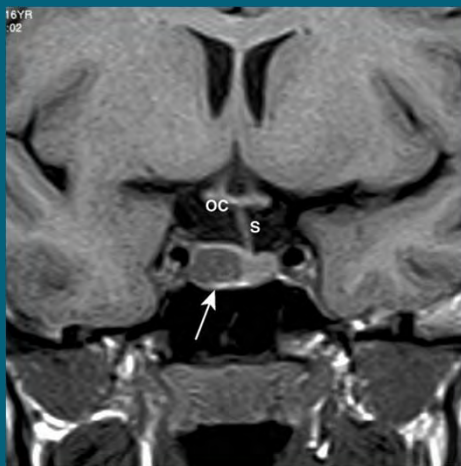
- Galactorrhoea:
 - type of nipple discharge (how many ducts, colour of fluid, unilateral / bilateral)
 - any masses palpable
- Features of hypogonadism
- Visual field defect
- Chest wall injury
- Signs of hypothyroidism

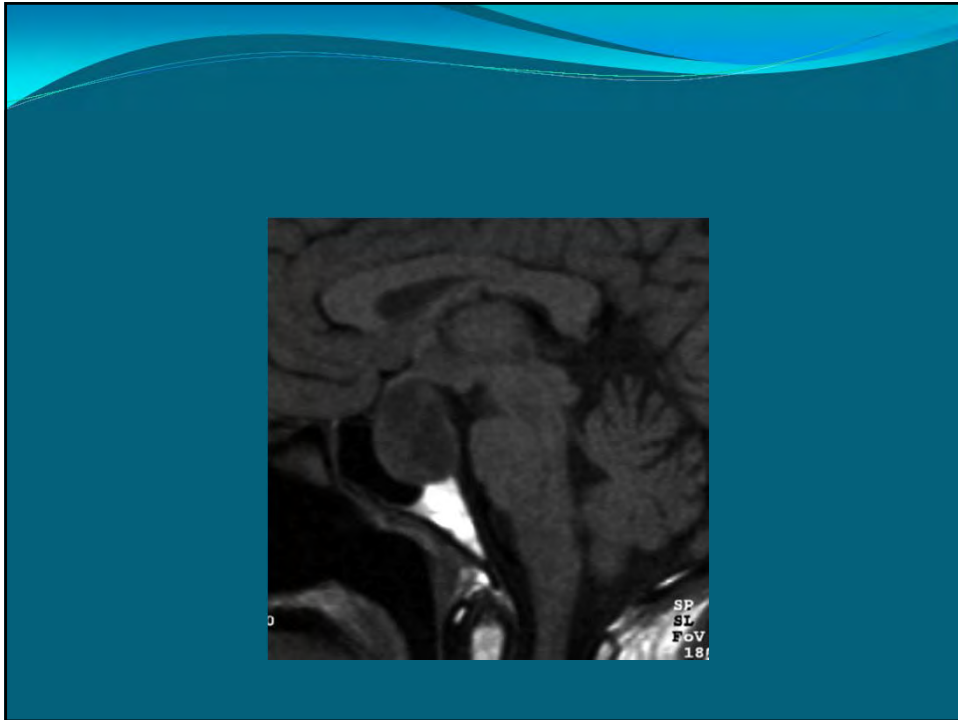
Red flags with a nipple discharge

- Risk of cancer higher if:
 - spontaneous discharge
 - bloody or positive for occult blood
 - unilateral or uniductal
 - associated with a breast mass
 - women over 40 years
- Benign discharge usually:
 - bilateral
 - multiductal
 - occurs with breast manipulation

Special investigations

- Exclude pregnancy
- Stop offending drugs
- **Prolactin:**
 - mild elevation (20-40 $\mu\text{g/l}$): stress, drugs (repeat)
 - moderate elevation (20-200): drugs, microprolactinoma, disconnection hyperprolactinaemia
 - severe elevation (>200): macroprolactinoma
- Dilution of prolactin; macroprolactin
- TSH, T4, U&E
- CT-scan or **MRI** of hypothalamus/pituitary
- Complications:
 - LH, FSH, oestradiol or testosterone (hypogonadism)
 - DEXA-scan (osteoporosis)
 - Eye fields





Our patient's results:

- Normal U&E, LFT
- Normal TFT, negative β -HCG
- Oestradiol: 381 pmol/l (N = 99 - 1590)
- LH: 7.3 IU/l (N = 1.6 – 12.4)
- FSH: 5.3 IU/l (N = 1.2 – 9.6)
- Prolactin: 16.1 μ g/l (N = 3.3 – 26.7 μ g/l)
- Diagnosis:
= Galactorrhoea without hyperprolactinaemia
(idiopathic)

Galactorrhoea without hyperprolactinaemia

- Up to 46% of women with galactorrhoea have a normal serum prolactin (even higher if normal menses)
- Often represents persistent milk secretion following correction of elevated prolactin e.g. after nursing or drug-induced hyperprolactinaemia
- Not the result of ongoing disease, unless blood in fluid (test for occult blood and for fat)

Therapy

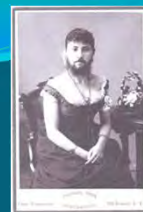
- Depends on cause
- Stop offending drugs
- Dopamine agonist therapy for hyperprolactinaemia
 - bromocriptine
 - cabergoline
- Troublesome physiological galactorrhoea: dopamine agonists

Therapy in our patient:

- Reassurance
- Dopamine agonist:
 - Parlodel (Bromocriptine):
 - 2.5mg nocte (x 3 months)
 - then: 2.5mg bd if still galactorrhoea
- Gynaecology referral for menstrual problems

(3) A HAIRY PROBLEM

Case presentation



- Mrs ECK, a 65 year old widow, with two children
- Referral from her GP for
 - hirsutism
- Longstanding hirsutism >20 years
- Progressively worse over the last year: now have to shave daily

Medical history

- Possible polycystic ovarian syndrome when young (PCOS)
- Longstanding hypertension; now on 5 drugs
- DM type 2 x 15 years
- Dyslipidaemia

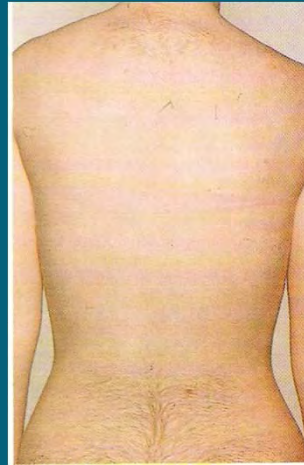
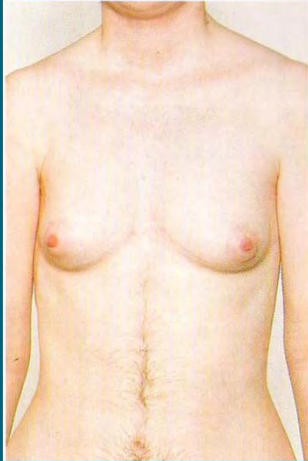
Examination

- BP=130/84
- Pulse=74/min
- BMI=35.6
- Metabolic phenotype; mainly central obesity
- Marked hirsutism and virilization

Hirsutism



Hirsutism



Male pattern baldness



Acanthosis nigricans

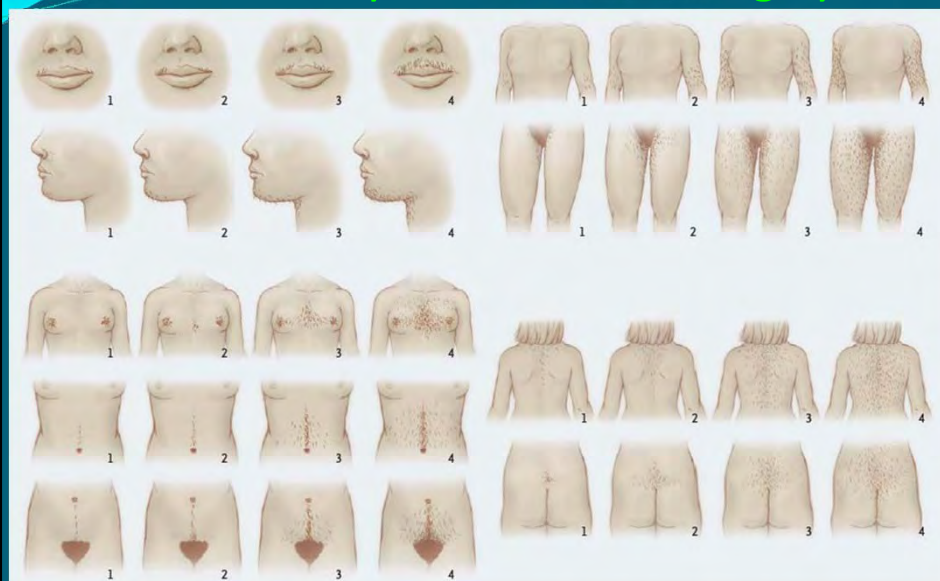


Examination

- No clear features of acromegaly
- No clear features of Cushing's syndrome
- Target organ damage of DM: microalbuminuria, early cataracts
- Rest of examination: normal

- Quantity
- Distribution
- Hair loss

Ferriman-Gallwey Hirsutism Scoring System



J Clin Endocrinol Metabol 1961;21:1440

Ferriman-Galwey score

- < 8: - not significant hirsutism
- 8 – 15: - mild hirsutism
 - only trial of oral contraceptives or cosmetic products
- > 15: - moderate hirsutism
 - do a 8h00 serum testosterone
 - check for risk factors for malignancy, polycystic ovarian syndrome, or endocrinopathies

Aetiology

- Drugs
- Familial
- “Hairy diabetic”
- Ovarian causes
- Adrenal causes
- Other endocrine causes

Special investigations

- Total testosterone = 7.3 / 10.3 nmol/l
(within male reference range)
- LH = 24.6; FSH = 44.9 (post-menopausal values)
- Oestradiol = 225; SHBG = 33.6 (normal)

Endocrine causes

- Hyperprolactinaemia
 - prolactin = 9.1 (normal)
- Thyroid abnormalities
 - T4 = 13.9; TSH = 0.81 (normal)
- Acromegaly
 - random GH = 0.2 (normal)
 - normal suppression on GTT

Adrenal causes

- Adrenal tumours (functional)
 - Cushing's syndrome
 - 8h00 cortisol = 515; 23h00 = 84
 - after Dex-suppression test = 33 (normal)
 - 24h urine cortisol = 389 / 466 (normal)
 - Adrenocortical carcinoma
 - DHEAS=1.8 / 1.6 (normal)
 - no adrenal masses seen on sonar
 - no evidence of hypercortisolaemia
 - but: high testosterone

Adrenal causes (cont)

- Non-classical congenital adrenal hyperplasia / 21 hydroxylase deficiency
 - 17OH progesterone = 3.2 (normal)

Ovarian causes

- PCOS
 - what happens to PCOS in post-menopausal women?
- Ovarian tumours
 - sonar: cystic lesion noted in the right ovary; fibroid uterus
 - normal Ca-125

Red flags

- The patient's age
- The rapid progression of hirsutism
- The virilization / degree of hirsutism
- The degree of androgen elevation
- The possible mass seen on sonography
- (Sudden onset)

Final diagnosis

- Total abdominal hysterectomy done, with bilateral salpingo-oophorectomy
- Bilateral hydrosalpinx found
- Benign leiomyomas
- **Bilateral stromal hyperplasia of the ovaries** on histology
- Post-op testosterone level = 0.4 nmol/l

Treatment of hirsutism

- Treat the **cause**
- **Weight** reduction
- **Medical** treatment of hirsutism
 - oral contraceptives (Diane-35; Yasmin)
 - cyproterone acetate
 - spironolactone
- **Insulin-sensitizing** drugs
 - Metformin

Treatment

