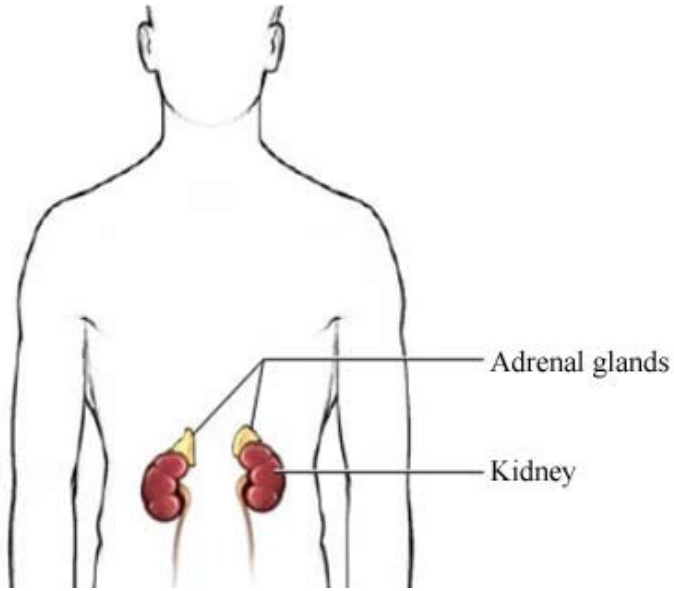
The adrenal in health and disease: essentials for specialists in reproductive medicine



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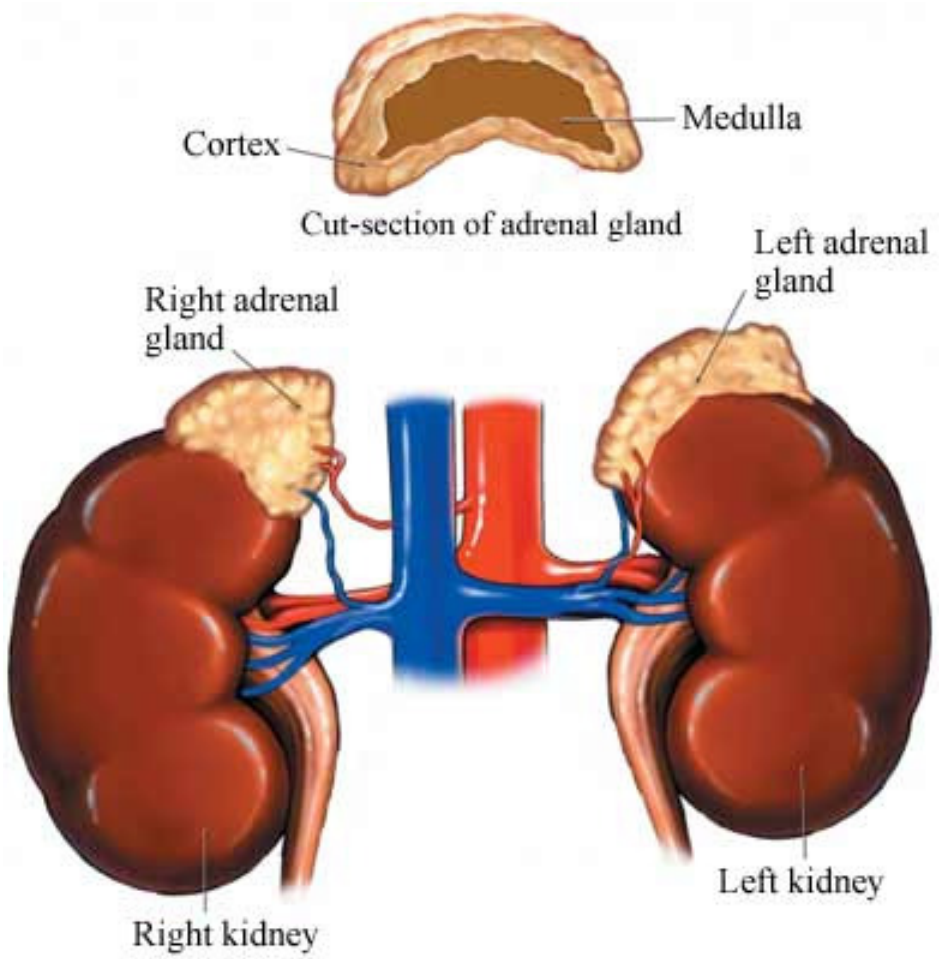
The adrenal glands



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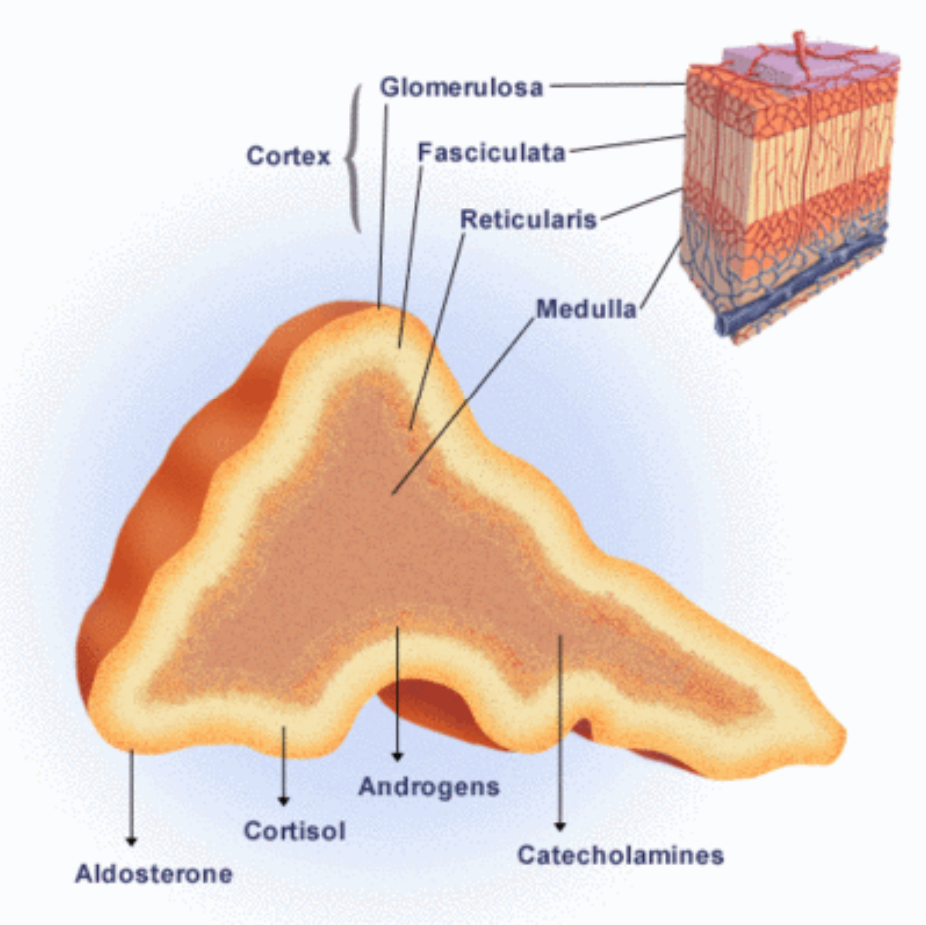


Produce numerous hormones

Cortex

Glucocorticoids

Cortisol

Mineralocorticoids

Aldosterone

Androgens

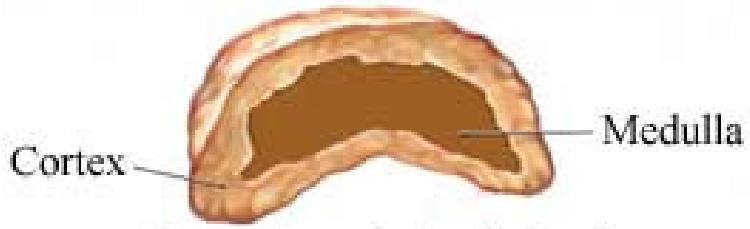
Synthesised from cholesterol

Medulla

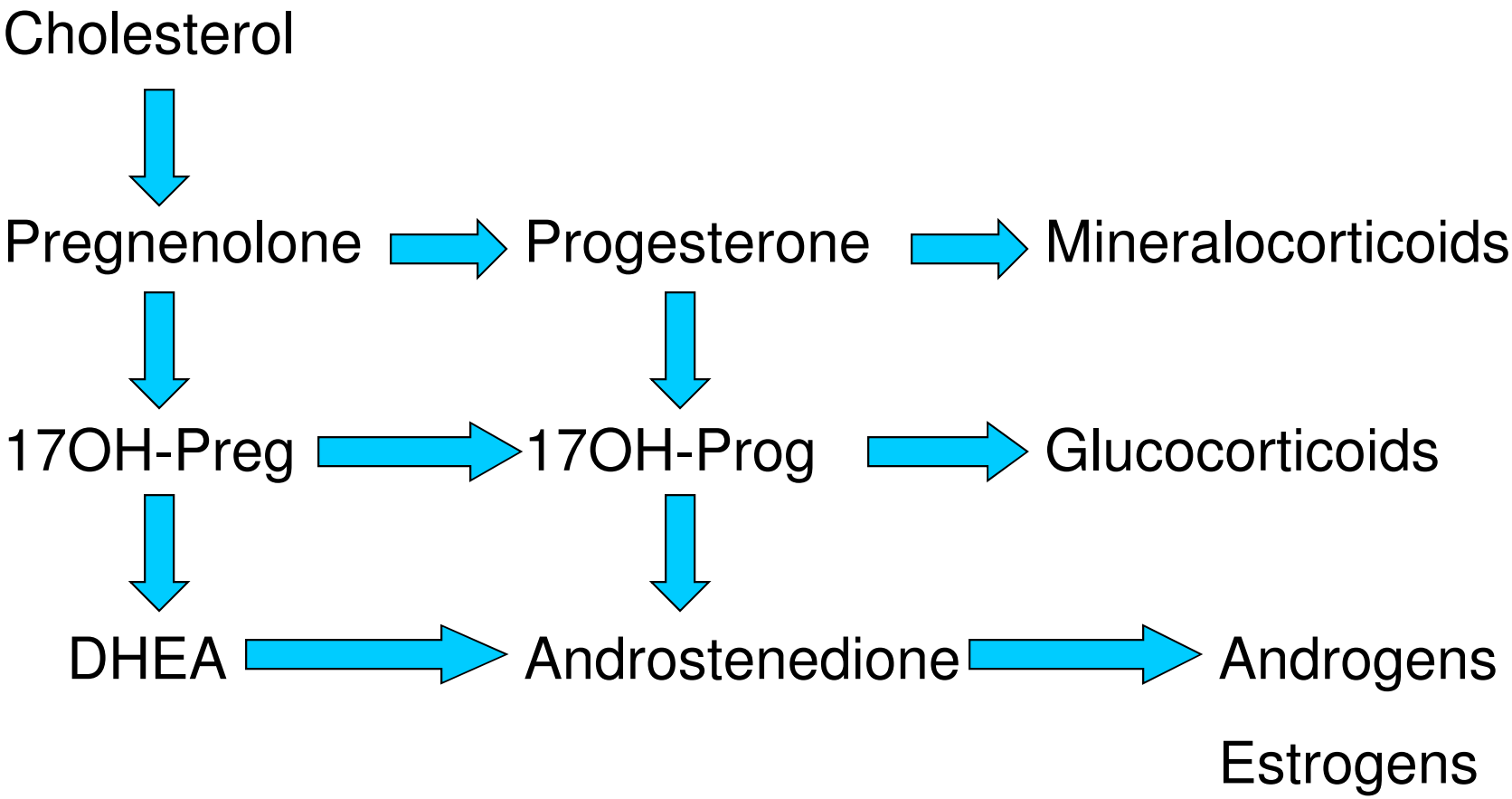
Catecholamines

Adrenaline and noradrenaline

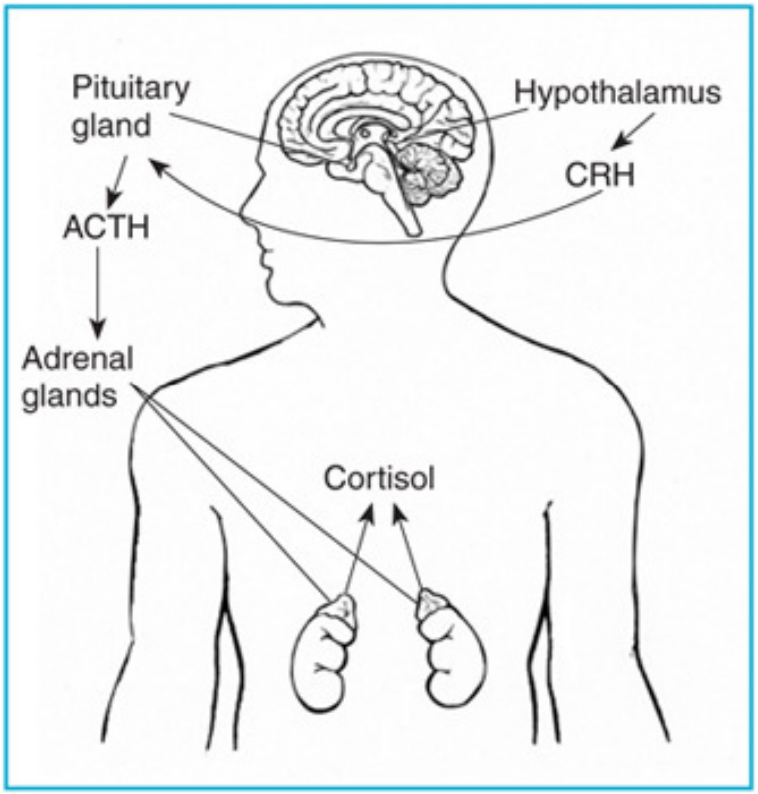
Hormones of the adrenal cortex



Synthesis of adrenocortical hormones



Glucocorticoids - Cortisol (hydrocortisone)



ACTH released from the pituitary stimulates the production of cortisol from the adrenal.

It is released into the bloodstream in a diurnal fashion with a peak of cortisol in the morning.

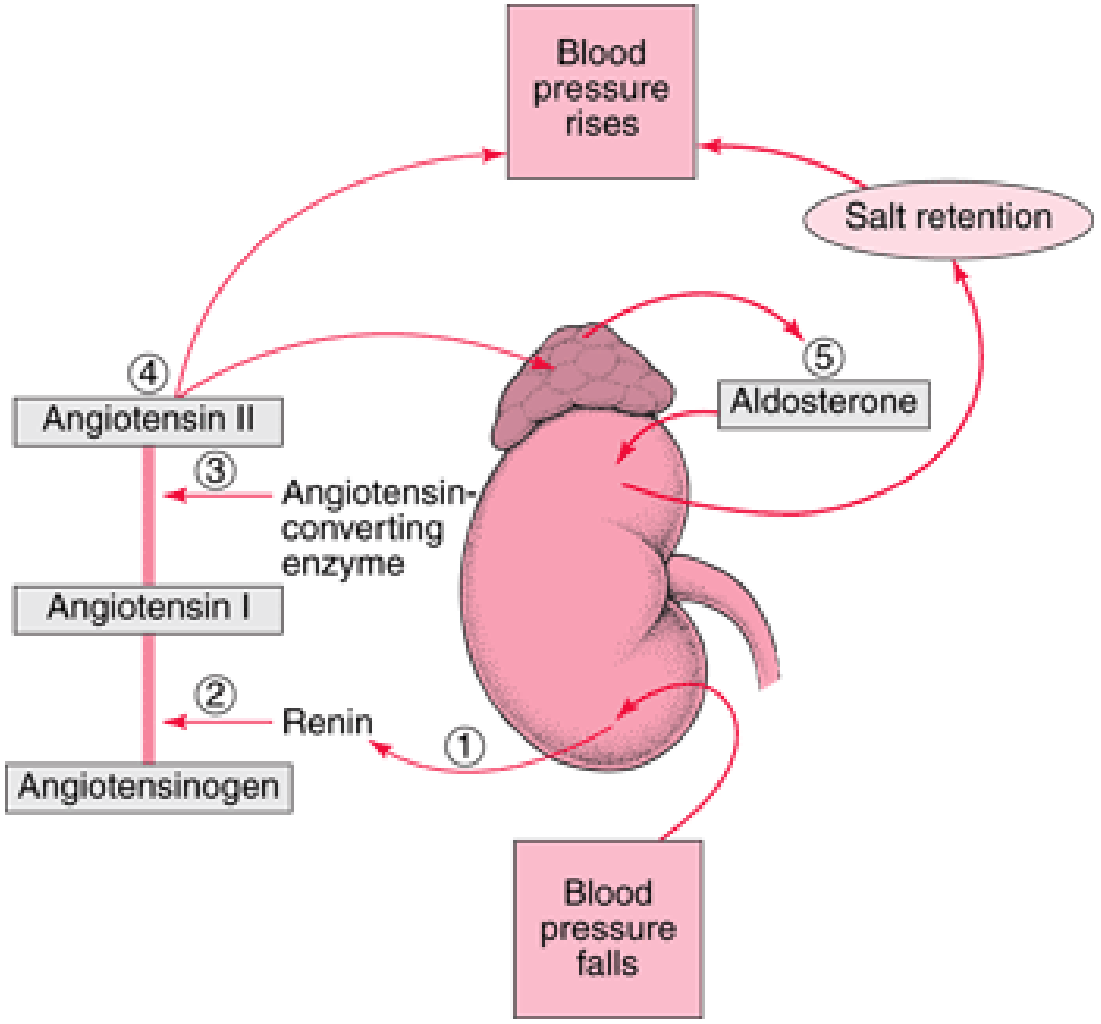
Stress causes a temporary increase in cortisol

Cortisol is essential for life

It acts on the liver to produce glucose.

It acts as a potent anti inflammatory.

Mineralocorticoids - Aldosterone



Aldosterone is released from the adrenal in response to ACTH from the pituitary and also angiotension

Aldosterone causes kidney to retain sodium

This leads to water retention by the kidney and the sensation of thirst and increased drinking

Which leads to increased blood pressure

Androgens

The adrenal cortex produces precursors of androgens such as testosterone

In sexually mature males the testes are the major source of androgens so adrenal production probably has little physiological significance

Adrenal excess production can cause premature puberty in boys

In women the adrenal cortex is the major source of androgens

Hormones of the adrenal medulla

Adrenal medulla

The adrenal medulla consists of a mass of neurons from the sympathetic nervous system

It releases:

- adrenaline (epinephrine)
- noradrenaline (norepinephrine)

In response to neural stimulation triggered by stress

Leads to fight and flight response:

- increased heart rate, blood pressure, rise in blood glucose

The adrenal in disease

Producing too much hormone

Adrenal excess

Producing too little hormone

Adrenal insufficiency

Adrenal Insufficiency

Destruction of adrenal cortex leading to lack of cortisol, aldosterone (and in women – androgens)

Cause:

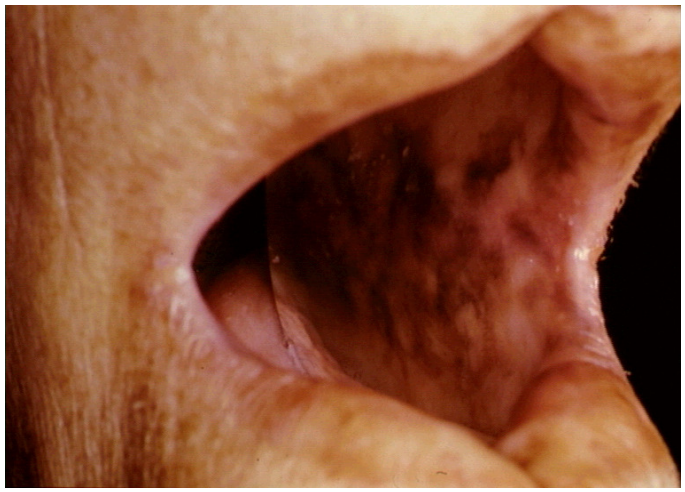
Autoimmune (Addisons disease) 70% (adrenal antibodies)

Infection (TB)

Infiltration – metastasis of tumour to adrenal

Infarction (shock/hypovolaemia)

Adrenalectomy



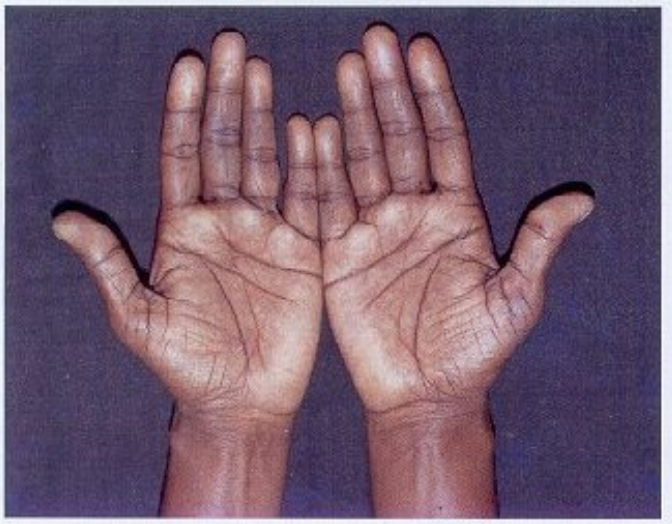


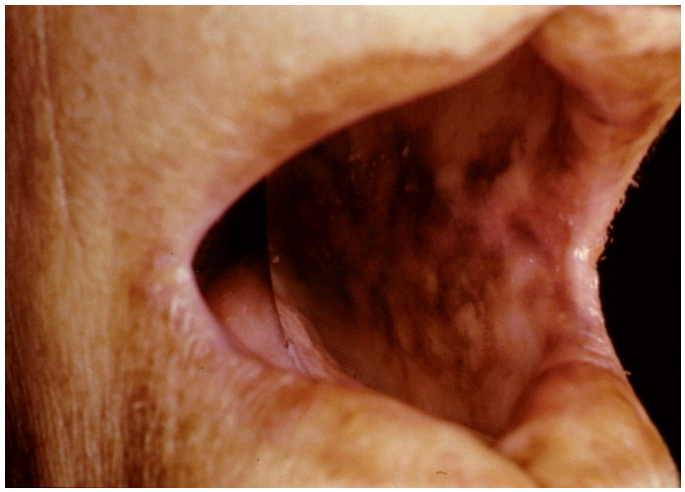
Fig. 2 Addison's disease – hyperpigmentation involving the palms of the hand.

Adrenal Insufficiency

Damage of the adrenal gland means that the pituitary responds by increasing ACTH simulation to try and drive cortisol and aldosterone production

The excess ACTH stimulates pigment cells in the skin – hyperpigmentation.

If there is failure of pituitary production of ACTH (e.g tumour) it leads to loss of adrenal hormones but ***no*** excess pigmentation



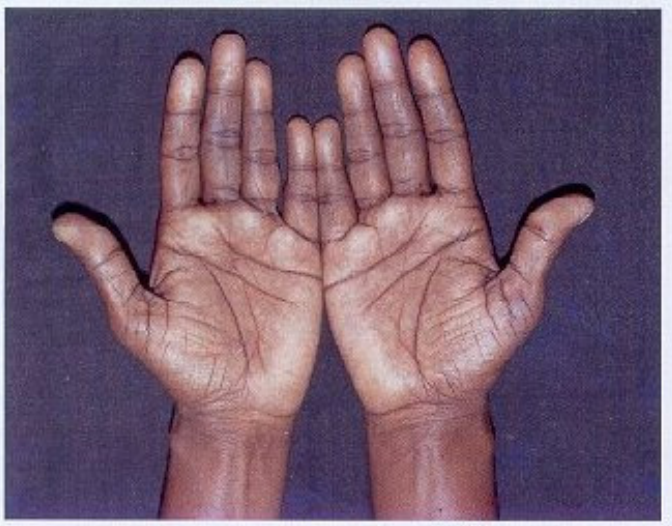
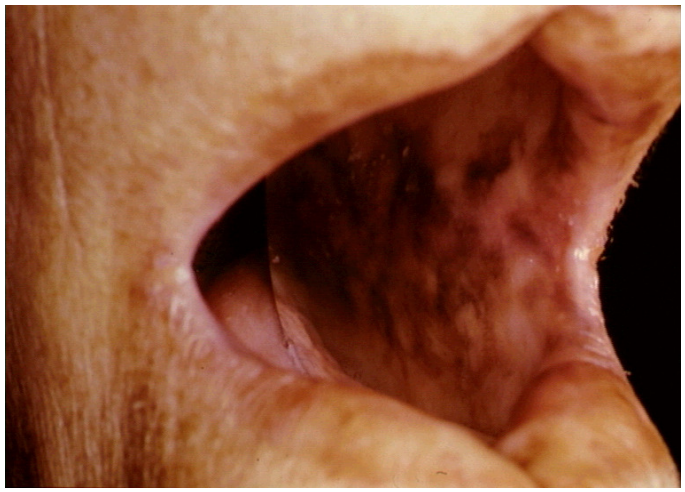


Fig. 2 Addison's disease – hyperpigmentation involving the palms of the hand.

Adrenal Insufficiency

Symptoms

- Anorexia and weight loss
- Weakness and tiredness
- Nausea, vomiting, abdominal pain
- Decreased axillary and pubic hair and libido (in women)



Signs

- Pigmentation
- Postural hypotension

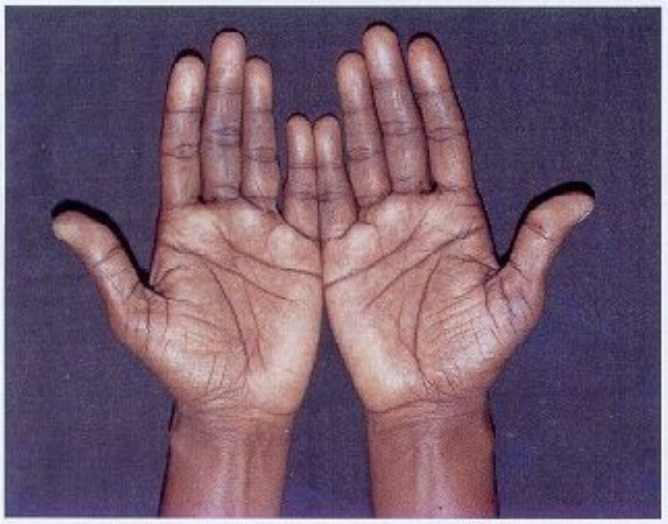


Fig. 2 Addison's disease – hyperpigmentation involving the palms of the hand.

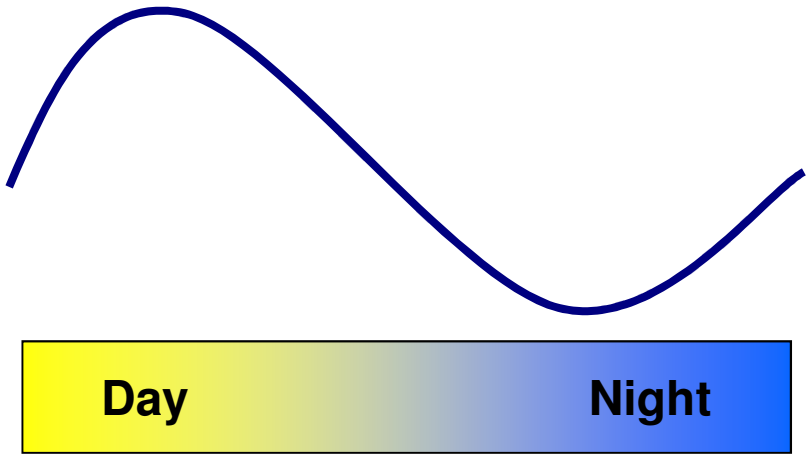
Adrenal Insufficiency

Making the diagnosis

Hyponatraemia, hyperkalaemia

Short synacthen test – inadequate production of cortisol in response to synthetic ACTH injection

Measure 9am ACTH level (to determine if pituitary/ adrenal cause



Treatment

Replace with hydrocortisone

10mg, 5mg, 5mg

20mg, 10mg

May well need fludrocortisone also

Key points for reproductive medicine

A woman with adrenal insufficiency may present with loss of libido and loss of secondary sexual hair

In situations of stress/illness/vomiting they will not have enough oral hydrocortisone to survive

Needs to be doubled up orally for 3 days, or given parenterally.

Never stop their hydrocortisone

MedicAlert®
A Registered Charity

Key points for reproductive medicine

Pregnancy

Continue usual glucocorticoid and mineralocorticoid replacement

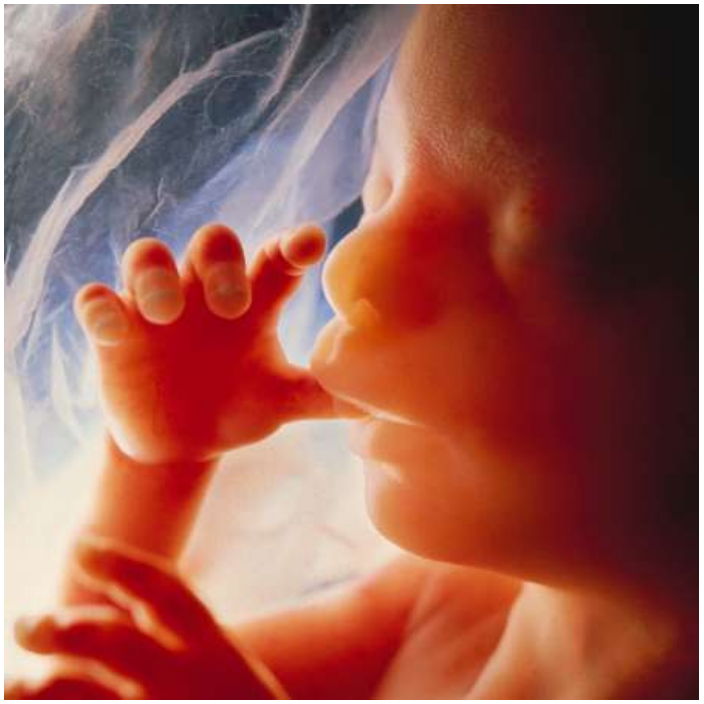
Severe hyperemesis gravidarum may necessitate temporary parenteral therapy (warn patient)

During labour parenteral glucocorticoid administered

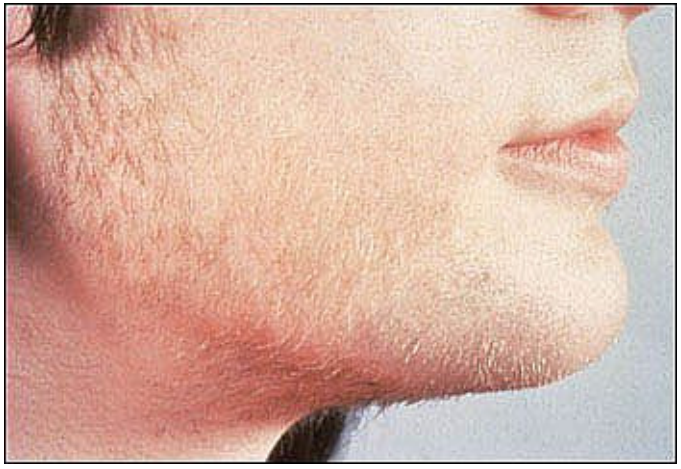
Key points for reproductive medicine

Pregnancy

No associated fetal morbidity as fetus produces and regulates its own adrenal steroids



Adrenal excess



Excess cortisol

Cushings syndrome

Excess aldosterone

Conn's,

Bilateral adrenal hyperplasia

Excess androgens

Androgen secreting tumours

Congenital Adrenal Hyperplasia

Excess glucocorticoids

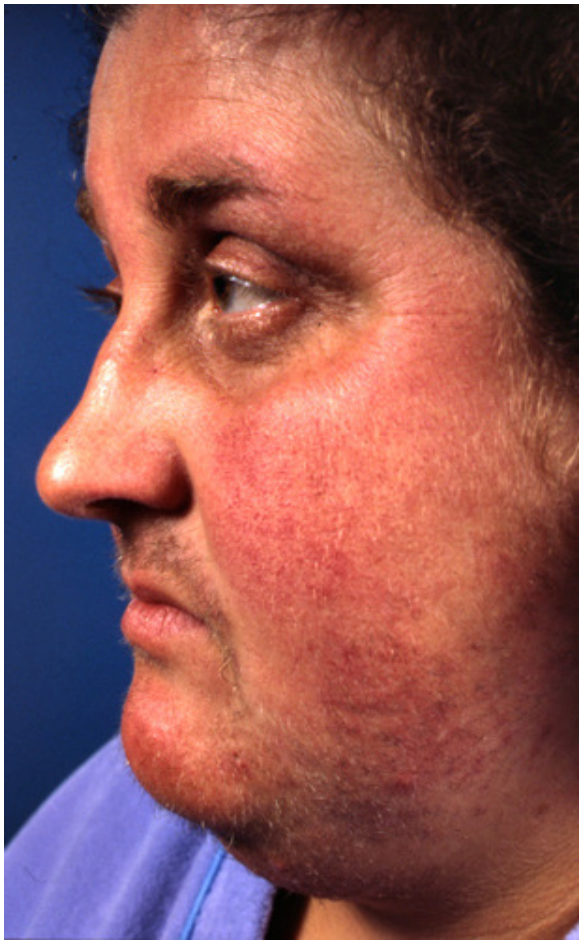
Elevated levels of cortisol

Due to:

excess production of ACTH by pituitary

or excess cortisol by adrenocortical tumour

or exogenous steroids



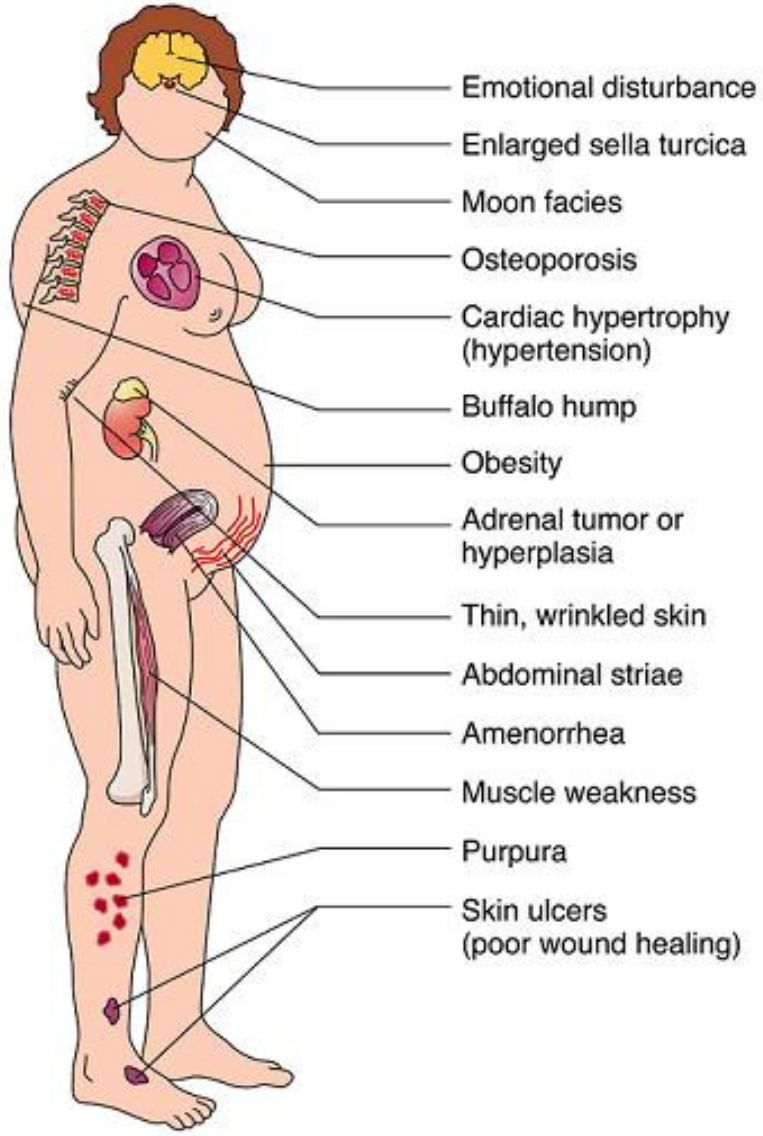
Excess glucocorticoids

Symptoms

Change in appearance
Muscle weakness
Type 2 Diabetes
Osteoporotic fracture
Psychiatric
Amenorrhoea

Signs

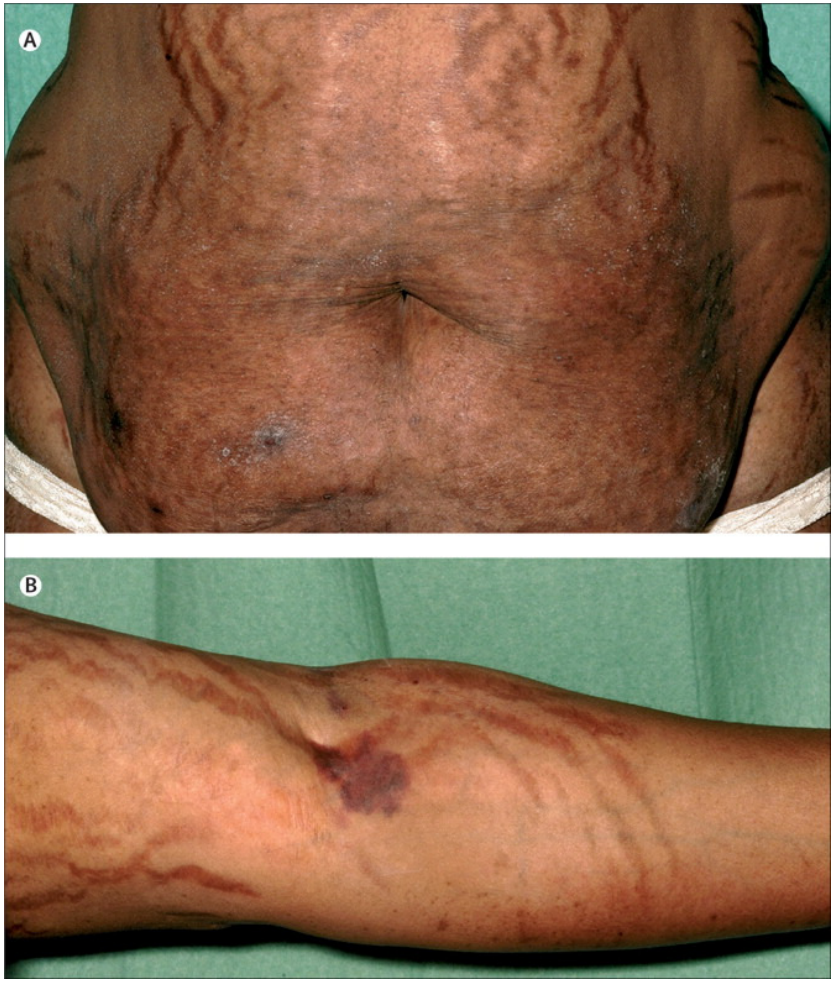
'Lemon on matchsticks'
Bruising, deep purple striae, thin skin
Hirsuitism
Proximal muscle weakness
Hypertension



Excess glucocorticoids

Making the diagnosis

- 24hour urinary free cortisol
- Measure midnight cortisol
- Try to supress cortisol by dexamethasone supression test
- Measure ACTH to determine if pituitary or adrenal



Treatment

- Surgical
- Medical – metyrapone, ketoconazole

Excess aldosterone

Aldosterone causes sodium retention and potassium loss, which increases fluid retention, increases blood pressure and impairs renin production by kidney

Presents

Hypertension (resistant to treatment)

Hypokalaemia

Due to an isolated adrenal adenoma (Conn's)

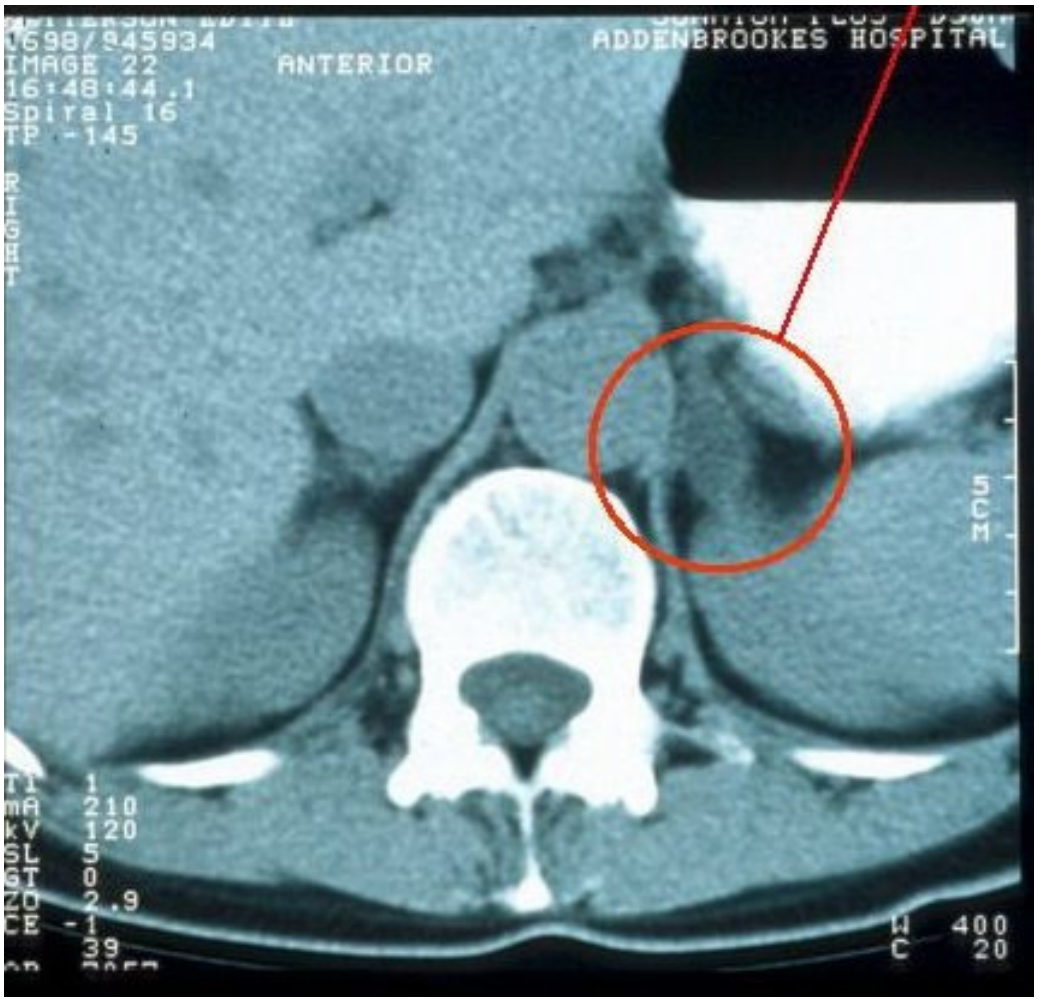
Or bilateral adrenal hyperplasia

Diagnosis

Made by measuring aldosterone:renin ratio

(aldosterone ↑ renin ↓)

Conn's tumour



Treatment

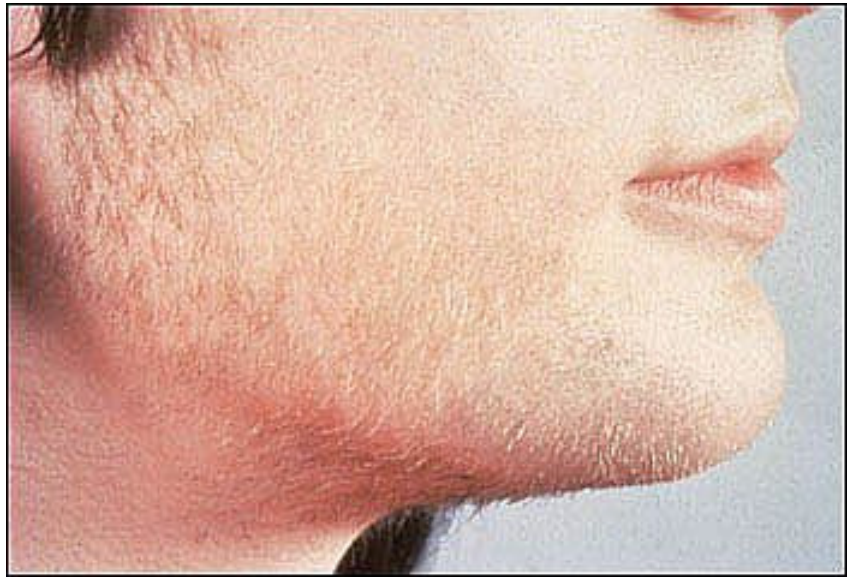
Surgical

Medical

Spironolactone

(aldosterone antagonist)

Excess Androgens

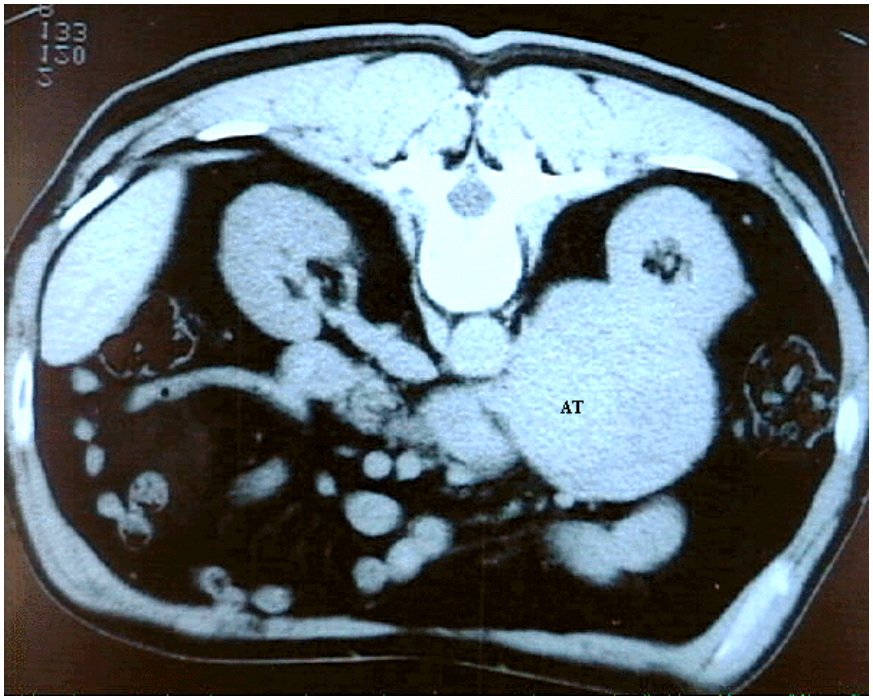


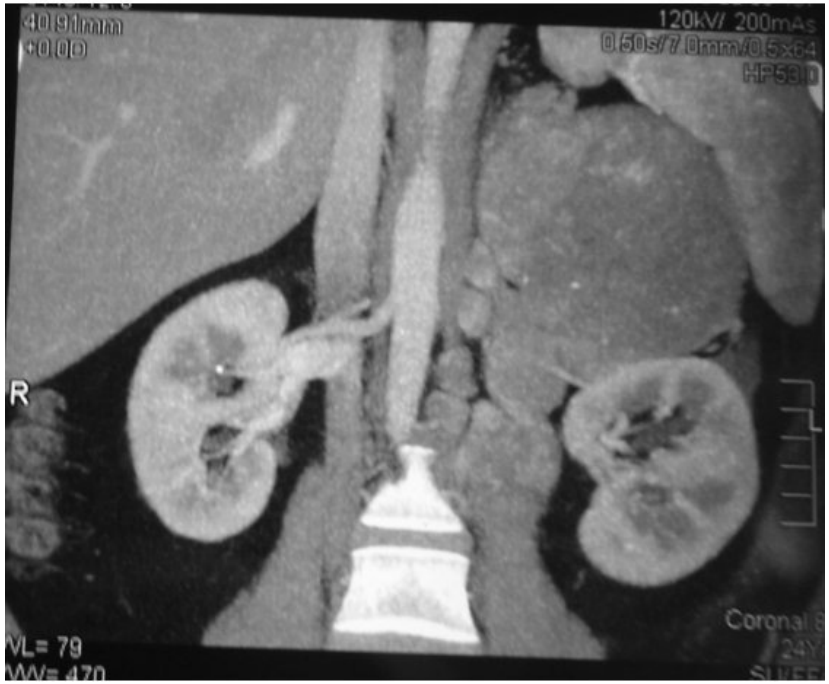
In women the adrenal cortex is the major source of androgens

Hypersecretion produces male pattern body hair and cessation of menstrual periods

Hiruitism – of rapid onset and/or with virilisation suggests androgen secreting tumour

Androgen secreting tumour

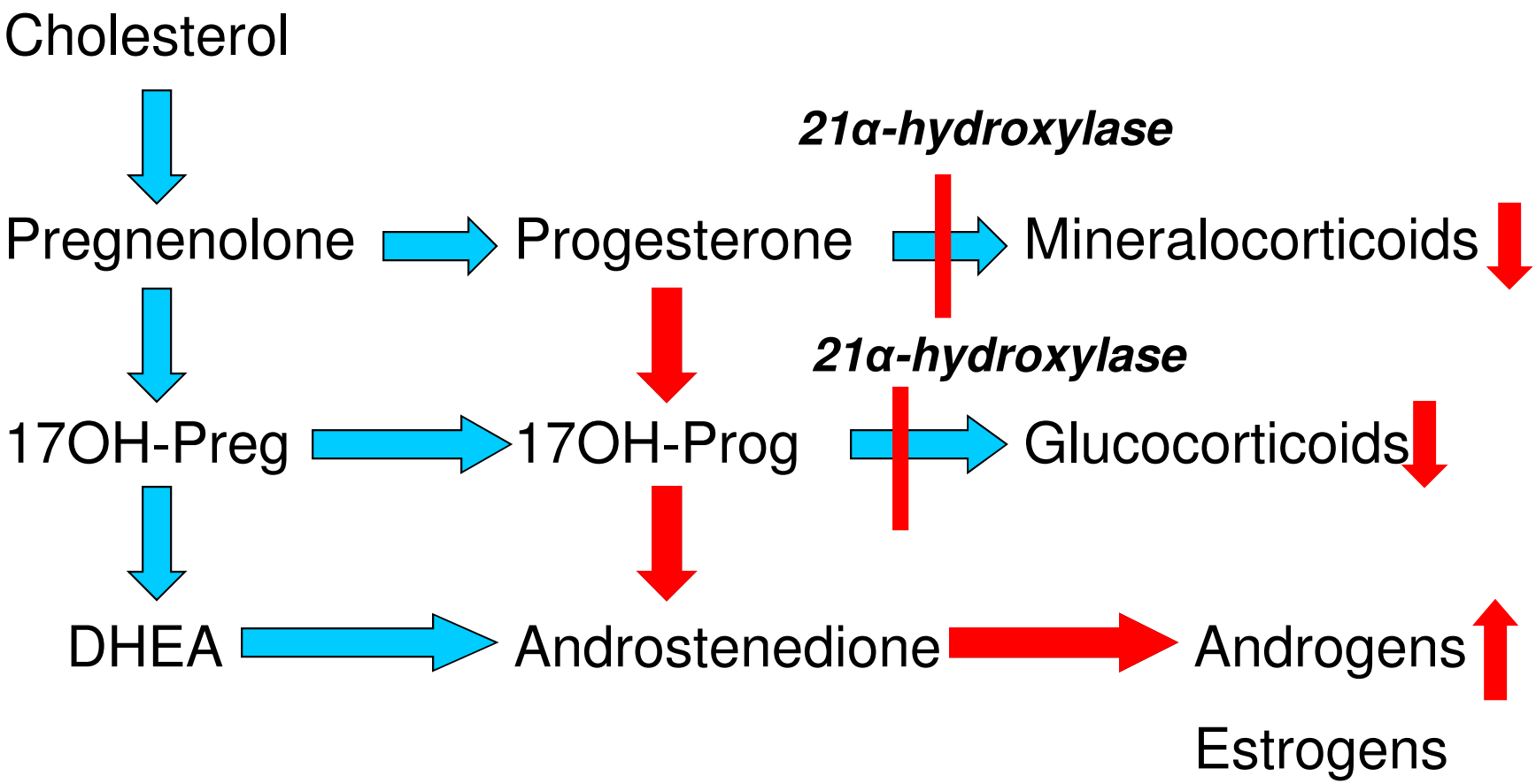




Would expect serum testosterone >5 nmol/l

Congenital Adrenal Hyperplasia

An inherited group of disorders characterised by deficiency of one of the enzymes necessary for cortisol synthesis



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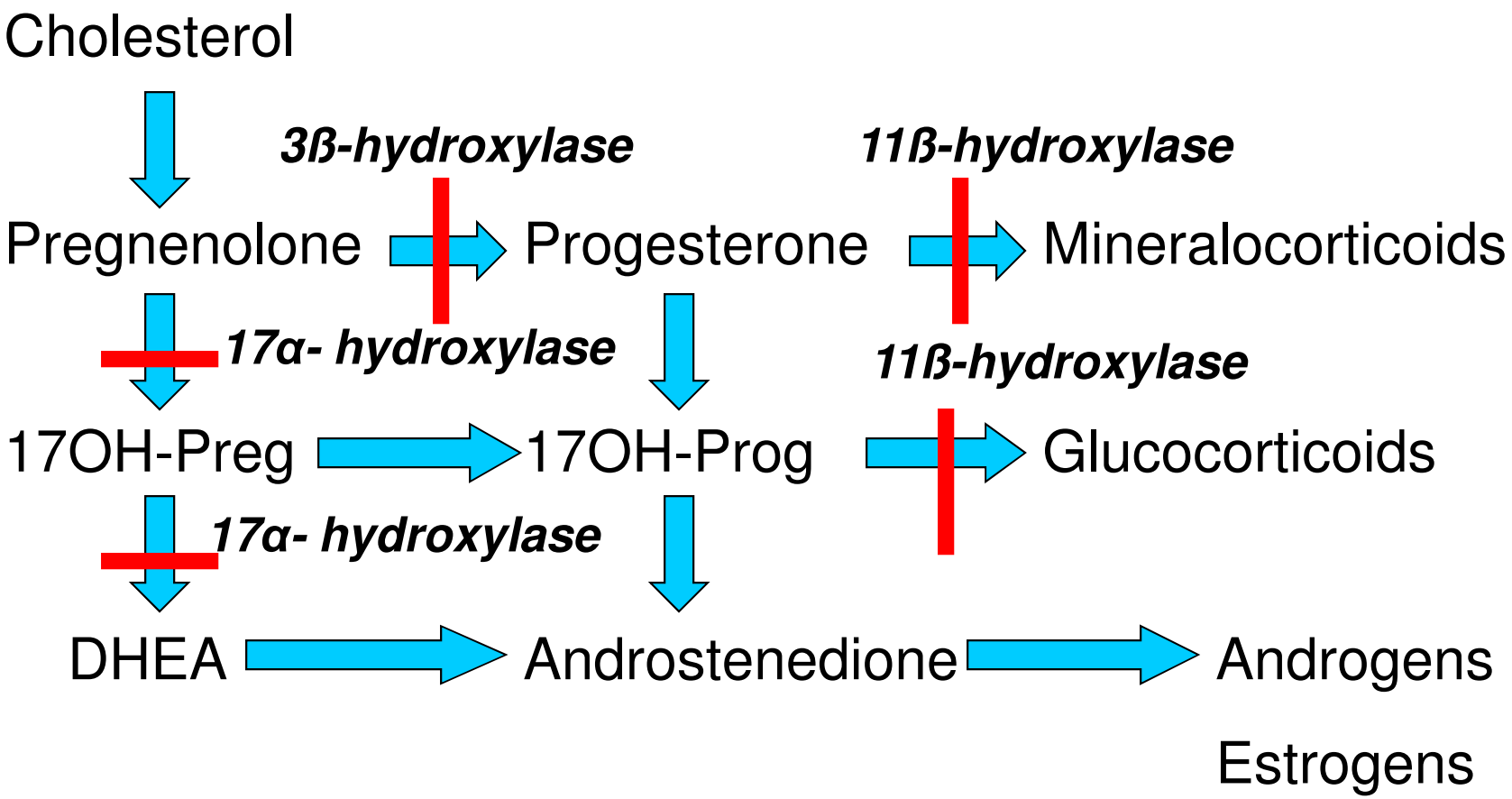
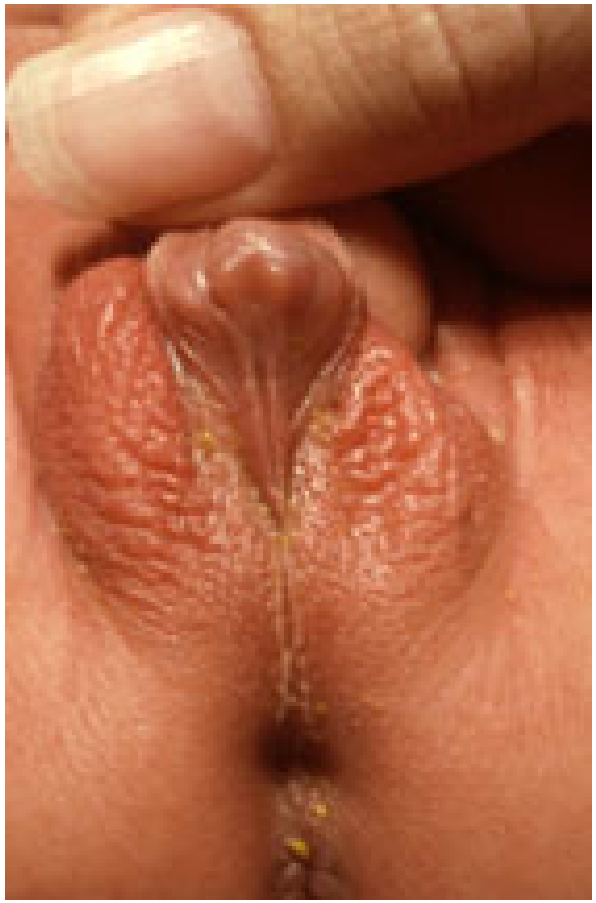


Congenital Adrenal Hyperplasia



>90% of cases are due to 21α-hydroxylase deficiency

Wide clinical spectrum, from salt wasting and virilisation in neonatal period, to non-classic CAH in adulthood

Inherited autosomal recessive

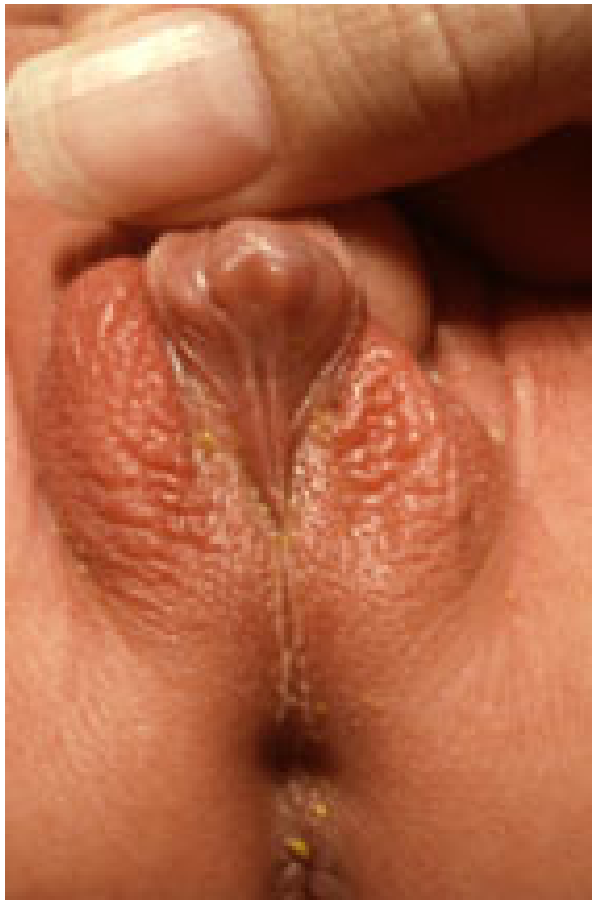
1:15 000 live births (classic form)

1:1000 (non classic form)

Wide racial variations in carrier frequency

Very common in those of Jewish origin

Congenital Adrenal Hyperplasia



Classic CAH

Most diagnosed in infancy

Girls - ambiguous genitalia

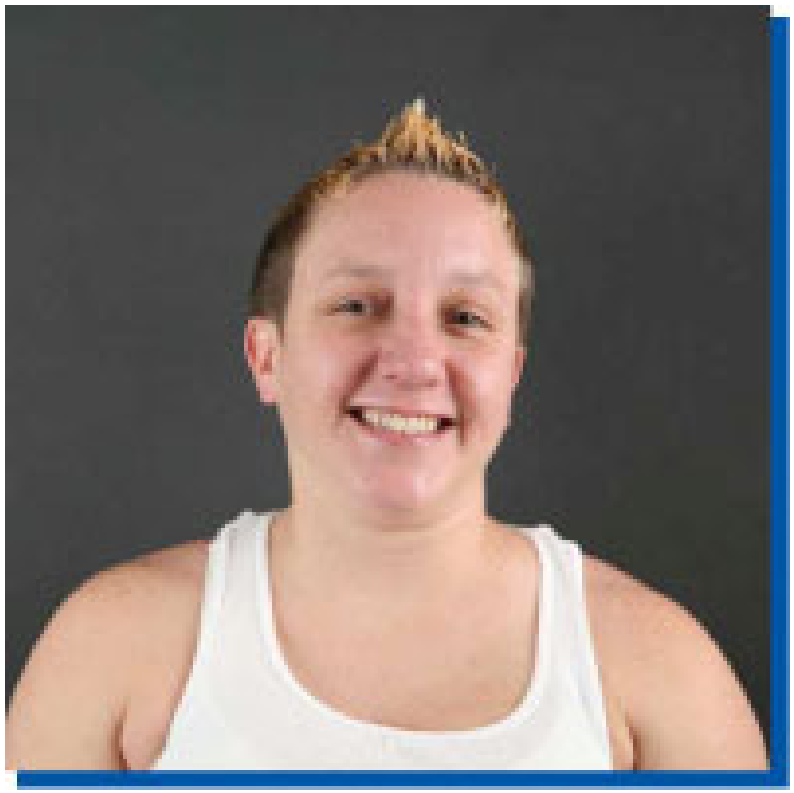
(due to exposure to high concentrations of androgens in utero)

Boys- no signs apart from subtle hyperpigmentation and possible penile enlargement

Cortisol and aldosterone deficiency leading to salt losing adrenal crisis in neonatal period

Vomiting, weight loss, dehydration, hyponatraemia, hyperkalaemia.

Congenital Adrenal Hyperplasia



Classic CAH

Problems that persist into adulthood:

Women

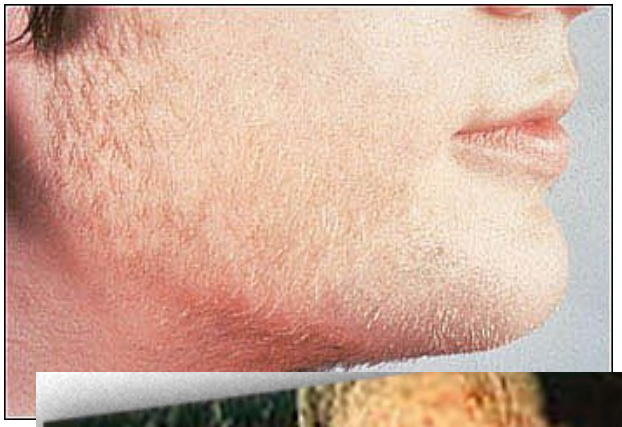
Sexual dysfunction and subfertility (if salt wasters)

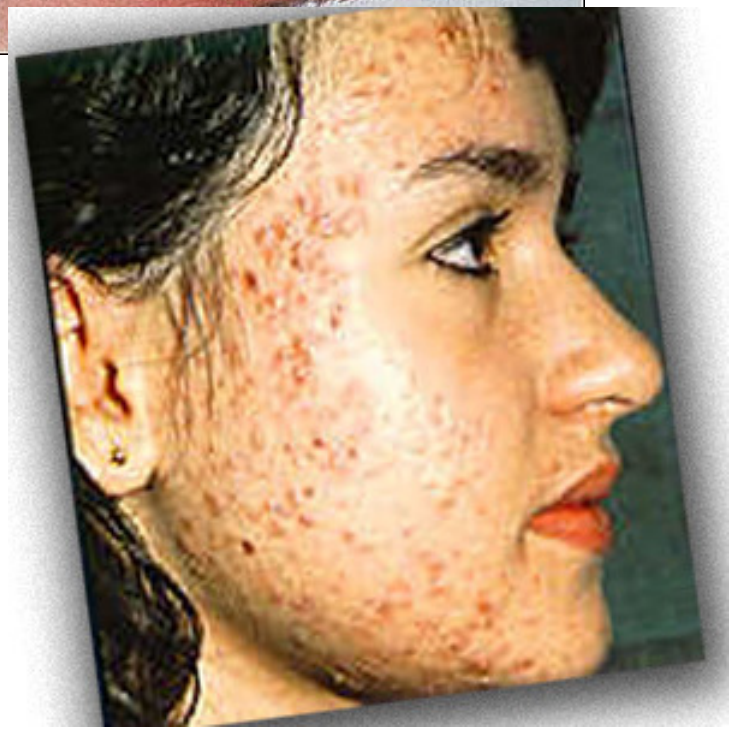
Men

High levels of adrenal androgens suppress gonadotrophins and therefore testicular function

Spermatogenesis may be affected if CAH poorly controlled

Congenital Adrenal Hyperplasia





Non- Classic CAH

Due to partial deficiency of 21α- – hydroxylase

Don’t have cortisol deficiency, but do have hyperandrogenism.

Present with premature puberty, or hirsuitism, acne, oligomennorrhoea often at puberty

Subfertility due to chronic anovulation in 50%

Common to see polycystic ovaries on USS (30%)

Assymptomatic in males

Diagnosis

Classic CAH

17-hydroxyprogesterone – very high level, diagnostic

>242nmol/l

(normal <3nmol/l at 3 days in full term infant)

Non-classic CAH

Random 17OHP can be normal

(test at 9am, follicular phase. If<5nmol/l = normal; 5-15 – ACTH test; >15 = CAH)

Synacthen test with measurement of 17OHP at 60 minutes

(any time of day and any time of menstrual cycle)

17OHP>45nmol/l is diagnostic

Many carriers will have slightly raised 17OHP ~30nmol/l

Treatment of CAH

Classic CAH

Glucocorticoids given in sufficient doses to suppress adrenal androgen secretion (but without totally suppressing the HPA axis). Aim to get 17OHP 12-36nmol/l

Mineralocorticoids to return electrolytes and plasma renin activity to normal

Hydrocortisone used initially (15-20mg/day split) (concerns over child growth)

Adults may need prednisolone (5-7.5mg/day split) or dexamethasone (0.25-0.5mg nocte)

Do need extra doses of hydrocortisone in physical stress/illness

Treatment of CAH

Non Classic CAH

Many don’t need treatment

Some may need treatment for hyperandrogenism with glucocorticoids and adjuvant anti androgen therapy, together with OCP.

When fertility desired may well need ovulation induction. Stop anti androgens and take care to use glucocorticoids that don’t cross the placenta

Classic CAH and pregnancy

Reduced fertility (particularly if they have salt wasting forms). Related to inadequate introitus (despite reconstructive surgery); Annovulation as a result of persistent hyperandrogenaemia

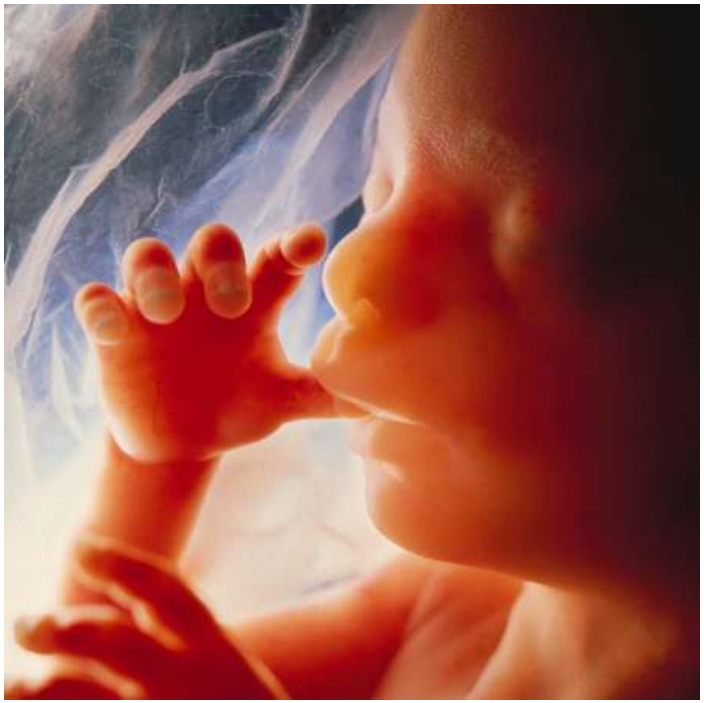
30-60% are fertile

Fertility maximised by optimal suppression of androgens by glucocorticoid therapy

No major complications in pregnancy

Mum will need increased hydrocortisone in labour

Classic CAH and pregnancy



Risks to fetus

No risk of virilisation from maternal androgens as placenta aromatizes androgens to estrogens

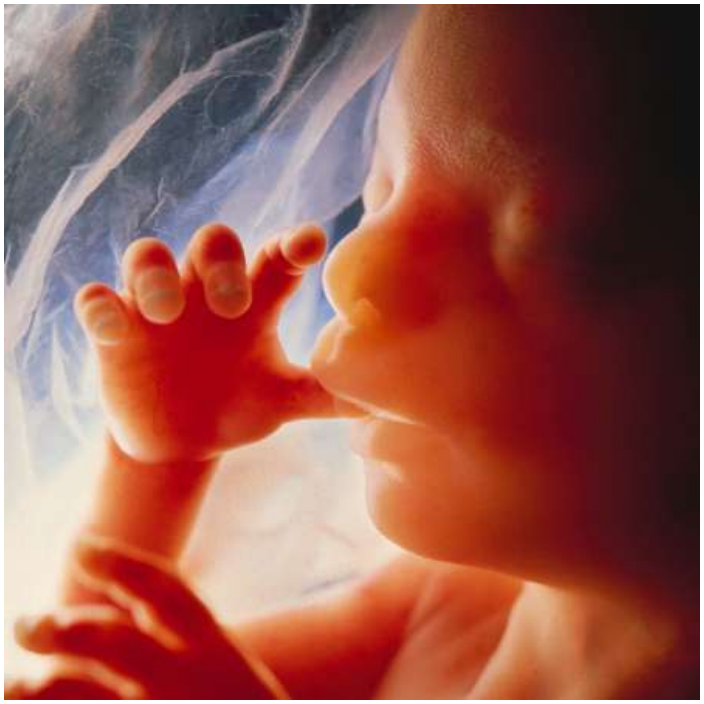
Glucocorticoids do not increase risk of congenital abnormalities

If partner is carrier for CAH then fetus has 50% risk of CAH

Screen partner using basal and ACTH stimulated 17OHP levels. If elevated go on and genotype

If heterozygote, prentatal treatment with dexamethasone necessary to avoid virilisation of a female fetus

CAH and pregnancy



Prenatal treatment protocol

Start dexamethasone 20mcg/kg per day (based on prepregnancy weight)

Crosses placenta to reduce fetal hyperandrogenism

Best results if started at 4-6 weeks gestation (certainly before week 9)

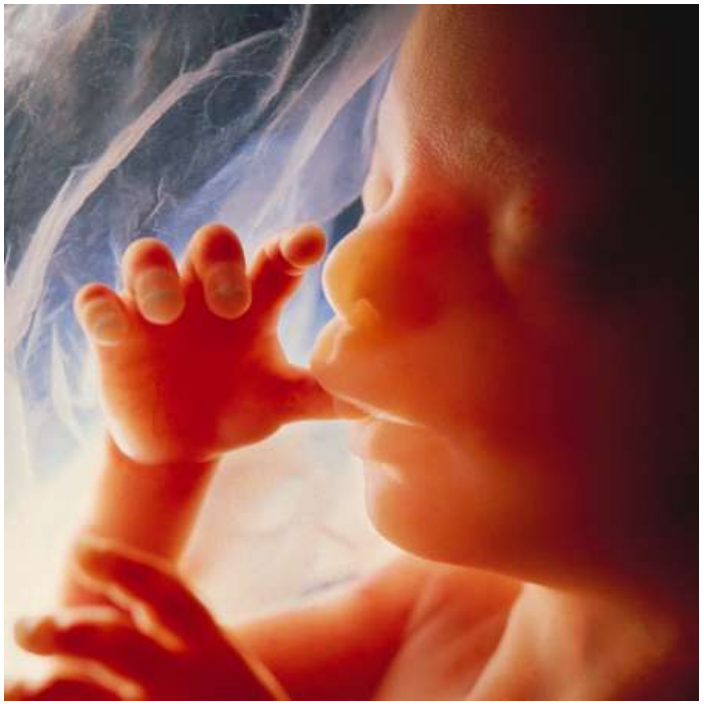
CVS at 10-12 weeks for fetal karyotype

46XX unaffected – discontinue treatment

46XY – discontinue treatment

46XX, affected (1:8) continue treatment to term

CAH and pregnancy



Outcome of prenatal treatment with dexamethasone

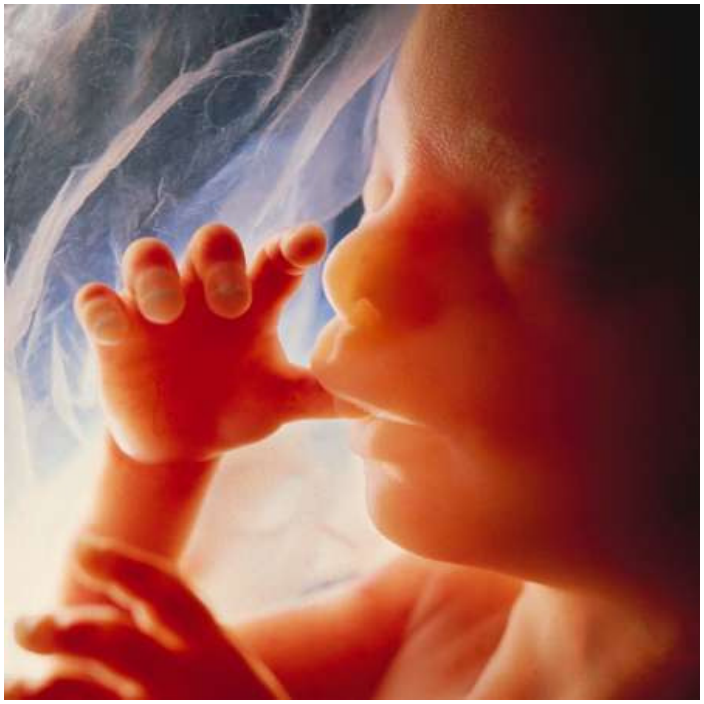
50% of affected females do not require reconstructive surgery

No fetal congenital malformations

Subtle effects on neuropsychological function unknown

Maternal complications of glucocorticoid excess in 1%

CAH and pregnancy



Non Classic CAH

Debate about prenatal treatment

No cases of women with non-classic CAH giving birth to virilised female

Risk of conceiving child with classic CAH is 1:1000

Treatment with dexamethasone therefore unwaranted

A Case

27 year old nurse

Married to Anaesthetist

12/40 Pregnant (Para 0)

Previously fit and well, apart from back ache

C/O palpitations and anxiety

O/E

- pulse 70 reg. ECG - Normal
- BP126/87
- 3+ glycosuria

A case

OGTT

0 hour glucose 6.5mmol/l

2 hour glucose 12.7mmol/l

Gestational Diabetes

Commenced on diet

Subsequent review

- Failing to reach targets commenced on insulin

A case

Glycaemic control achieved

However still complaining of episodes of severe anxiety, sweating and palpitations

24 hour tape NAD

Put down to pregnancy, reassured.

A case

28/40

Still complaining bitterly of periodic symptoms

BP 200/110

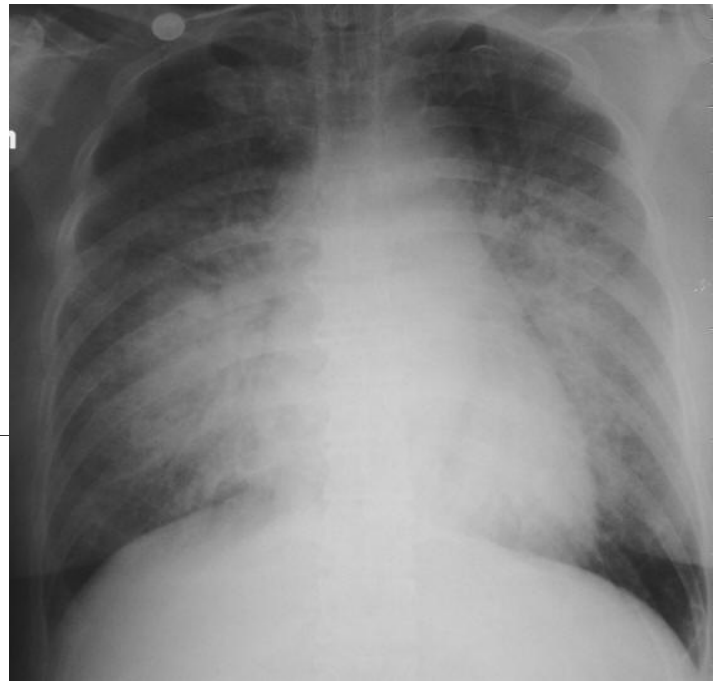
Admitted for monitoring

BP 170/90

BP 136/84

BP 127/80

A case



32/40

Complained of breathlessness

O/E breathless

ECG - sinus tachycardia

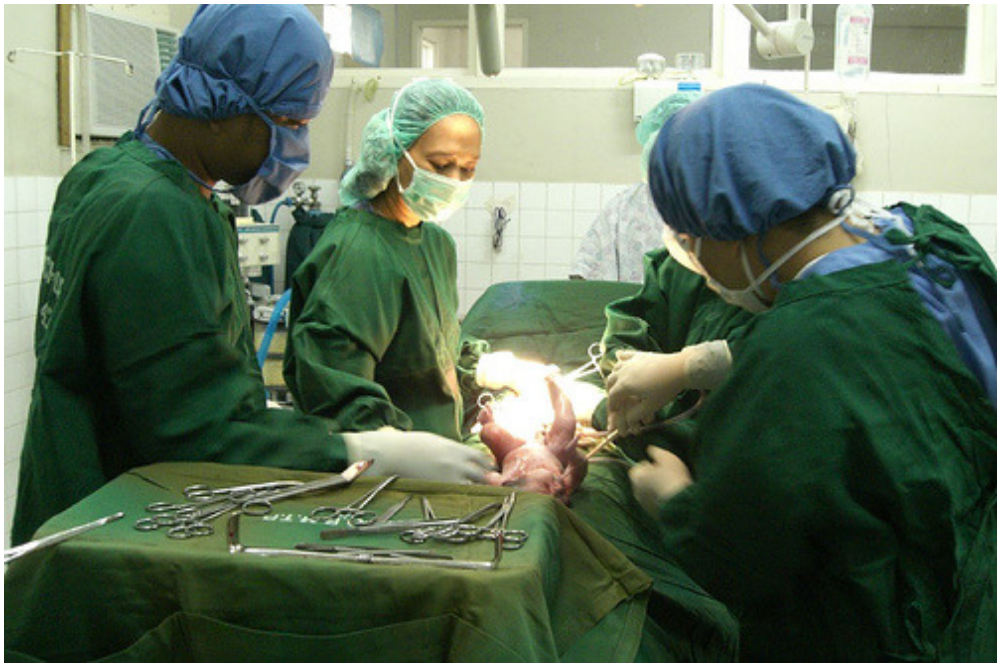
BP 206/118

CXR – large heart, pulmonary oedema

D-Dimer – normal

Echocardiogram – cardiomyopathy, poor function

A case



Admitted

Given Methyldopa

Frusemide

Betamethasone

Cardiology review

Condition deteriorated

Emergency caesarean section

Delivered live male infant

A case

Mothers condition deteriorated rapidly in theatre

Admitted to ICU

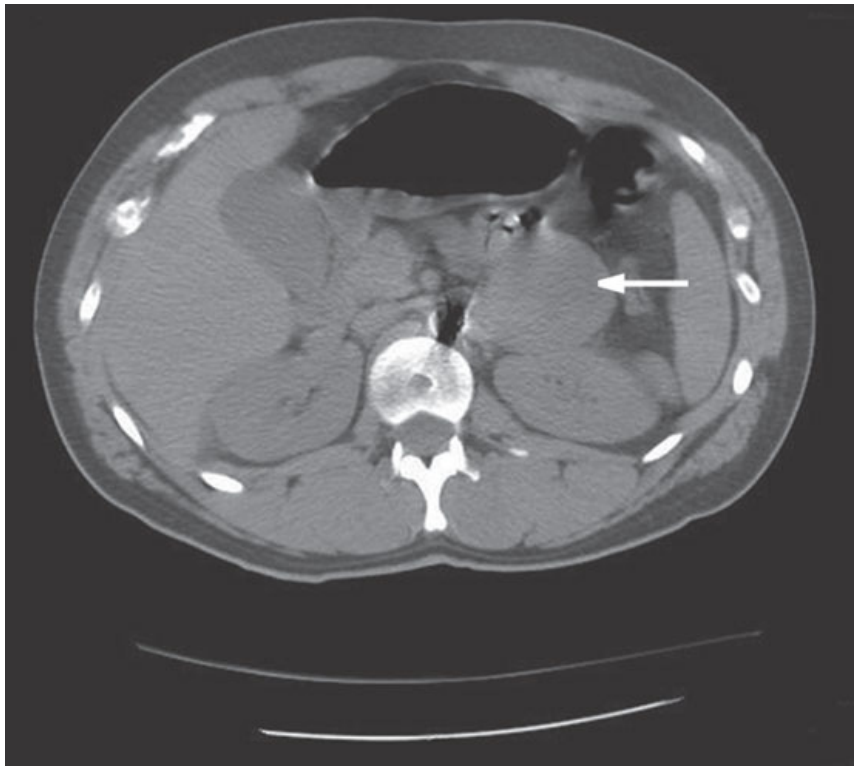
Tachycardic, hypertensive, breathless, hyperglycaemic

Renal function deteriorating

Medical review

Paroxysmal nature of symptoms noted ?? Phaeochromoctoma?

A case



Commenced on α-blockade

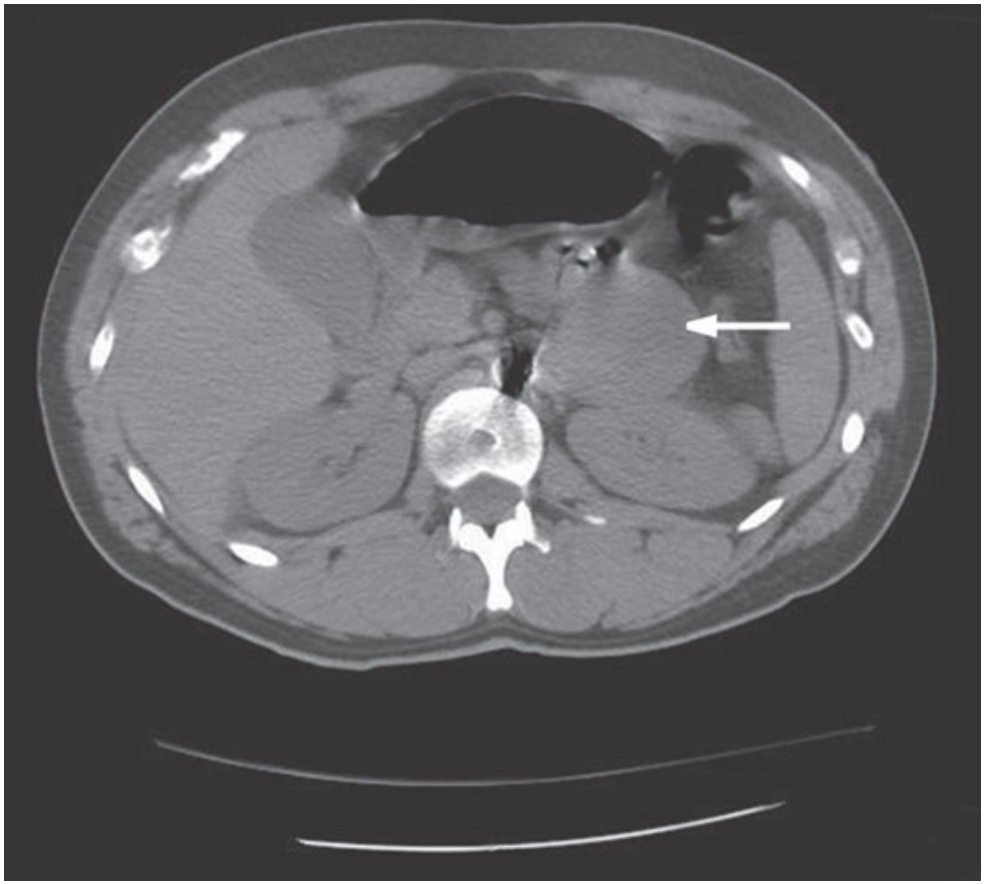
Then β-blockade

Condition improved

MRI – confirmed adrenal tumour

Urinary catecholamines – extremely elevated

Excess medullary adrenal hormones - phaeochromocytoma



Adrenomedullary catecholamine secreting tumours

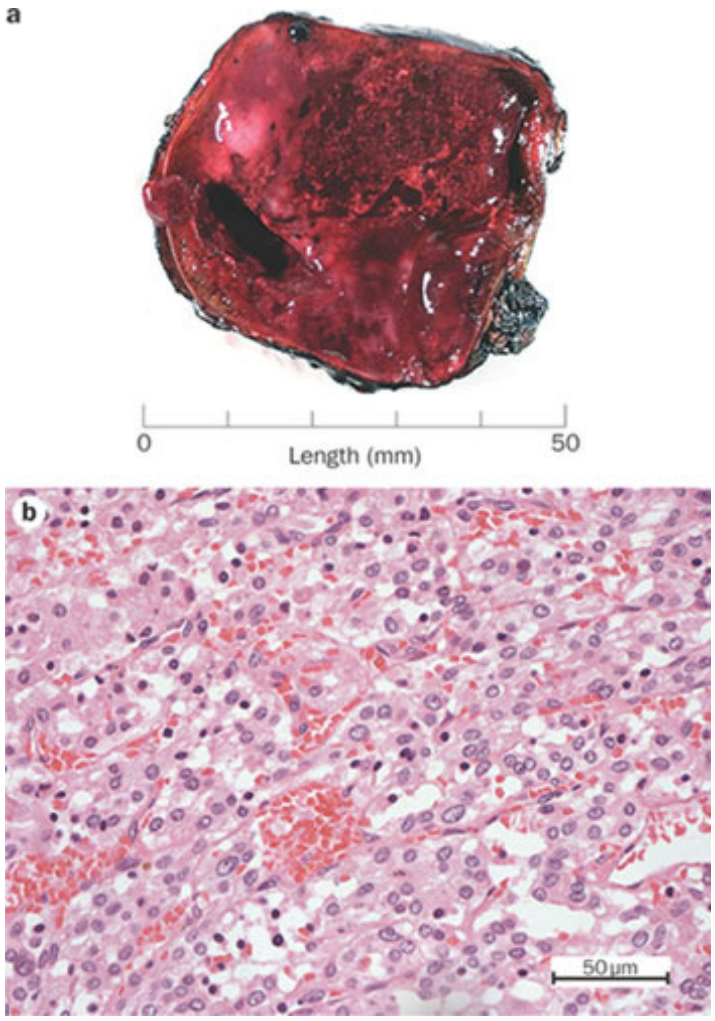
Majority sporadic >90%

10% inherited

Usually unilateral and <10cm diameter

15-20% malignant

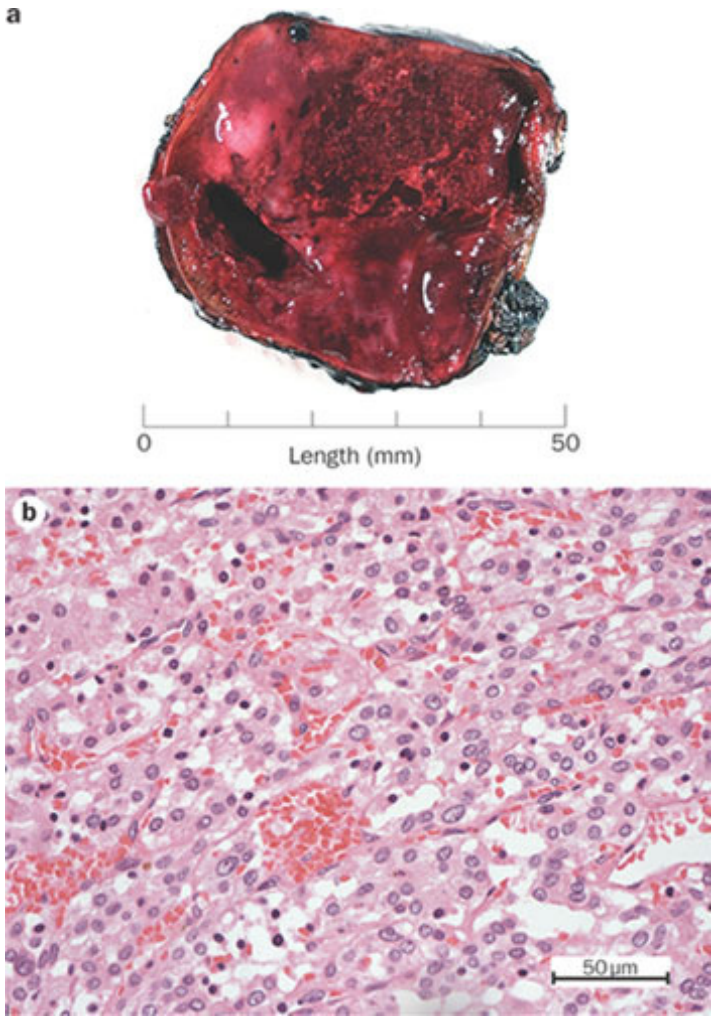
Phaemochromocytoma



Clinical features

- Sustained or episodic hypertension
- Sweating and heat intolerance
- Pallor/flushing
- Apprehension
- Headache
- Cardiovascular (palpitations)
- Abdominal pain

Phaemochromocytoma



Beware

Phaeochromocytoma crisis

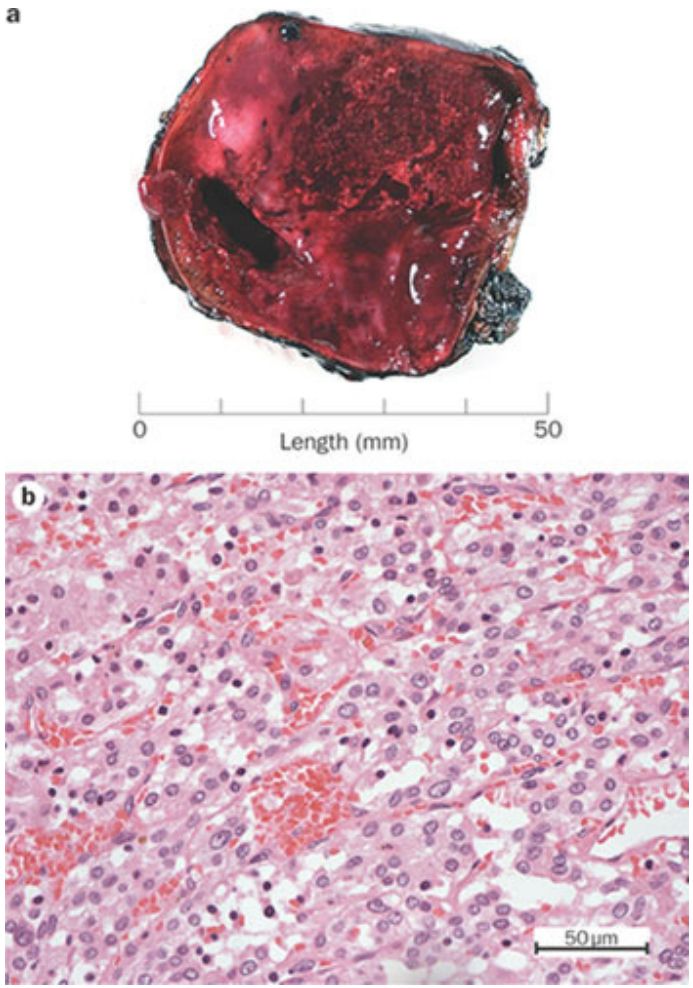
Arrhythmias, pulmonary oedema, heart failure, dysglycaemia, encephalopathy

Precipitated by:

straining, exercise, abdominal pressure, surgery, anaesthetics, drugs

labour

Phaemochromocytoma



Making the diagnosis

24hour urine catecholamine secretion

Localize tumour

Treatment

α blockade (phenoxybenzmine)

then β blockade (propanolol)

Then surgery

Phaemochromocytoma in pregnancy

Rare but potentially lethal in pregancy

Maternal mortality may be>15%

Fetal mortality –30% unless prompt recognition and treatment

Highest risk of hypertensive crisis and death is during labour

Phaemochromocytoma in pregnancy

Suspect in women with hypertension especially in the absence of proteinuria / oedema

Suspect if paroxysmal symptoms are present: palpitations, headache

Diagnose by urine catecholamines

MRI

Treatment

α blockade (phenoxybenzmine)

then β blockade (propanolol)

Then surgery before 24 weeks, or if past 24 weeks delay until fetal maturity then combine with caesarean section

Thank you for your time