ABNORMAL PITUITARY FUNCTION

Specialist Portfolio Seminar

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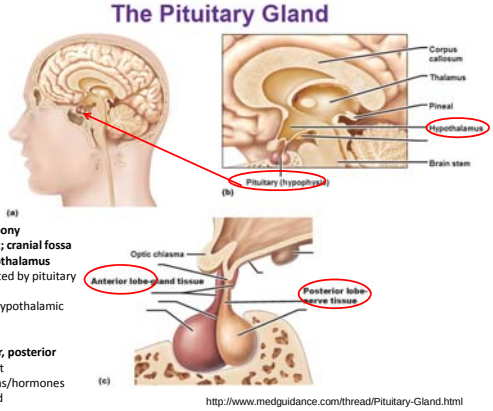
Overview

- Where/what is the pituitary gland?
- Anterior pituitary overview
- Posterior pituitary overview
- Pituitary dysfunction (example cases)
- Analytical considerations

The Pituitary Gland



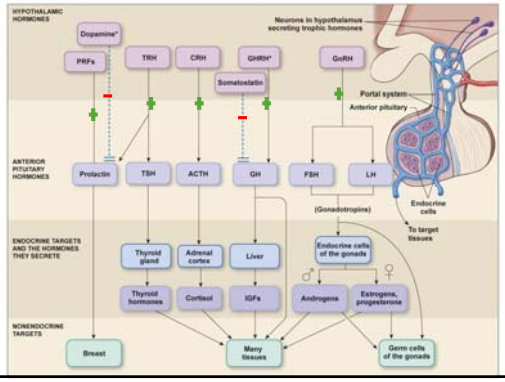
- **Located in a bony compartment; cranial fossa beneath hypothalamus**
  - Connected by pituitary stalk
  - Under hypothalamic control
- **2 lobes:**
  - **Anterior, posterior**
  - Different functions/hormones secreted

http://www.medguidance.com/thread/Pituitary-Gland.html

Anterior pituitary

- Secretes majority of **peptide and glycopeptide (glycoprotein) hormones** that control function of peripheral endocrine organs:
  - **Corticotrophs** – Adrenocorticotrophic hormone (ACTH)
  - **Lactotrophs** – Prolactin (PRL)
  - **Gonadotrophs** – Luteinizing hormone (LH), Follicle Stimulating Hormone (FSH)
  - **Thyrotrophs** – Thyroid Stimulating Hormone (TSH)
  - **Somatotrophs** – Somatotrophin or Growth Hormone (GH)
- Secretion controlled by releasing and inhibiting factors (predominantly peptides) released into portal circulation from hypothalamus….
- Any disease process that interferes with this blood supply (e.g. non-functioning tumours of pituitary/hypothalamus) will result in severe pituitary function.

Anterior pituitary systems

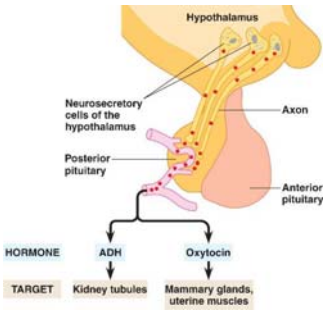


Anterior pituitary Hormone Functions

Cell type	Hormone secreted	Target organ	Effect on target organ	Release stimulated by	Release inhibited by
Corticotroph	ACTH	Adrenal cortex	Production of cortisol	CRH	Cortisol
Lactotroph	Prolactin	Mammary glands	Milk production/ lactation (in conjunction other hormones)	Suckling TRH	dopamine
Gonadotroph	LH & FSH	Gonads (ovaries / testis)	Production of sex steroids (androgens, Estrogens, progesterone)	GnRH	Sex steroids
Thyrotroph	TSH	Thyroid gland	Production of thyroid hormones T4 & T3	TRH	T4 & T3
Somatotroph	GH	Liver	Production of IGF-1	GHRH	somatostatin
		Other tissues	Directly stimulates growth		

Posterior pituitary

- **Embryo-logically derived from the brain**
  - Direct arterial blood supply, not controlled via a portal circulation.
- **Hormonal secretions directly from nerve terminals of vasopressin (antidiuretic hormone, ADH) and Oxytocin neurons**



http://first-youmedshops.com/posterior-pituitary-hormones.html

Posterior pituitary Hormone Functions

Hormone secreted	Target organ	Effect on target organ	Release regulated by
Oxytocin	Mammary gland	Milk ejection	Suckling
	Uterus	Contraction	Stretch receptors
AVP (arginine vasopressin)	Renal collecting duct	Resorption of water (insertion of aquaporin water channels)	Osmoreceptors & baroreceptors
	Smooth muscle	Arteriole & capillary vasocontraction, also promotes intestinal contraction	

- N.B. AVP = ADH (anti-diuretic hormone) = vasopressin

Examples of Pituitary Dysfunction

Disease	Hormone	Excess or deficiency
Anterior hormones:		
Prolactinoma	Prolactin	Excess
Cushing's syndrome (pituitary form)	ACTH	Excess
Acromegaly / gigantism	GH	Excess
Hypopituitarism	One or more pituitary hormones ('Pan-hypopituitarism')	Deficiency
Growth retardation (uncommon cause)	GH	Deficiency
Posterior hormones:		
SIADH	AVP	Excess
Diabetes Insipidus (cranial form)	AVP	Deficiency

Case 1

- 32 yr male presents to GP
- Clinical details: TATT, on thyroxine, 'ED'
- Testo very low: 2.0 nmol/L (9.9-27.8)

- LH & FSH added: <1, 2 respectively
- Prolactin added: 9706 miU/L (73-407)
- Cortisol added: 146 *[11am sample – difficult to interpret]*

- *Q: Why is the TSH / fT4 not useful in this case?*

- Macroprolactin added but prolactin result phoned out anyway *– Why?*

Hyperprolactinaemia

- Common
- Variable effects:
  - Infertility – in both sexes
  - Amenorrhoea, Galactorrhoea – early indication in women
    - No early signs in men (first signs may be visual disturbance, as below…)
  - Low libido / impotence

- Q: Why might men usually have larger tumours on presentation?

- If due to a tumour may have direct symptoms from this
  - Headache
  - Visual disturbance

- Q: Why do pituitary tumours cause these symptoms?

Hyperprolactinaemia

Causes:

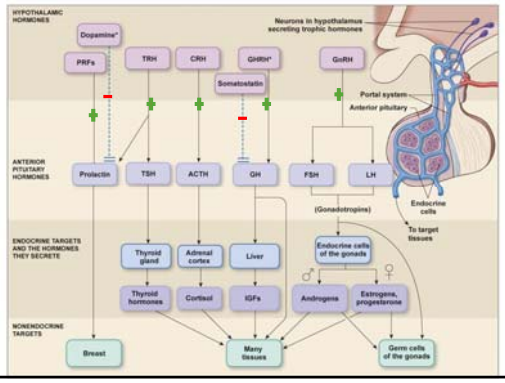
- Dopamine antagonists *Q: Why do these cause increased prolactin?*
- Other medications (oestrogens)
- Stress (venepuncture in itself!)
- Pregnancy
- Elevations in PCOS

Usually <1000 mIU/L

"Anti-psychotics" commonly used to treat schizophrenia, bipolar disorder (e.g. clozapine, olanzapine, risperidone).

- Renal failure
- Breast stimulation / chest wall trauma
- Primary hypothyroidism *Q: Why does this cause increased prolactin?*
- Pituitary adenoma (commonly microadenoma)
  - Prolactin secreting (see higher prolactin levels)
  - Compression of stalk and inhibition of dopamine action on pituitary

Anterior pituitary systems



Macroprolactin

- Immunoglobulin (usually IgG) complex with prolactin
- Low bioactivity, i.e. no pathological consequences
- Laboratory artefact
- Should be screened to avoid unnecessary investigations
  - All samples with a total prolactin result >700mIU/L should be tested for macroprolactin

Method:

- Precipitate any high MW complexes with PEG (polyethylene glycol)
- Measure prolactin pre- and post- PEG (accounting for dilution)
- Check recovery of prolactin in the sample
- If macroprolactin present – monomeric prolactin must be reported *Q: Why?*

Diagnosis of prolactinoma

- Exclude other causes:
  - Pregnancy
  - Medication
  - Stress etc…
- Imaging – MRI pituitary
  - Size defines as macroprolactinoma or microprolactinoma

    Q: any possibilty of confusion with "macroprolactin" here?!
- Pituitary screen

  (check for co-secretion or for loss of function)
  - Prolactin
  - TSH & fT4
  - Cortisol
  - LH & FSH
  - IGF-1

  } Baseline pituitary function tests

Treatment

- Medical - Dopamine agonists
  - E.g. Bromocriptine, Cabergoline
  - Especially for microprolactinomas
  - May be used to shrink large prolactinomas before surgery

Q: Why does this work?

- Surgical
  - Trans-sphenoidal hypophysectomy = standard procedure
  - NB: Patients given hydrocortisone in case they can't mount adequate cortisol response to stress of surgery
  - Post-op assessment of pituitary reserve deferred for several days
- Radiotherapy
- Combinations
- Follow up/monitoring
  - E.g. annual DFT of anterior pituitary reserve required after radiotherapy

Case 1 Outcome

- Diagnosed with microprolactinoma
- Treated with cabergoline
- Symptomatically improved
- Prolactin now 149 mIU/L

Case 2

- A previously healthy male patient is diagnosed with persistent hypertension at their GP. They have some baseline bloods done:

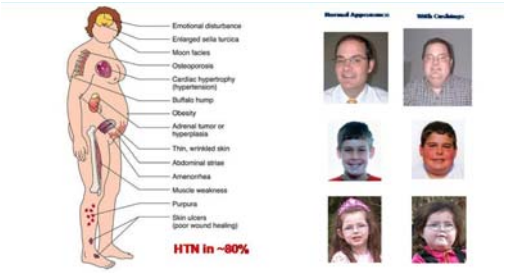
Na:	143 mmol/L	(133-146)
K:	3.0 mmol/L	(3.5-5.3)
Creatinine:	60 µmol/L	(44-133)

- On examination the patient shows central obesity with purple stretch marks on their abdomen
- The patient reports weight gain over the past year or so
- The patient mentions that they bruise easily

- In view of the history and results the GP organises some further tests…

Q: Any guesses of diagnosis, further tests?

Cushing's Syndrome



http://www.veomed.com/files/powerpoints_images/node314354/Slide4.JPG

Cushing's Syndrome

- Prolonged exposure of body tissues to excess cortisol
- 'A Syndrome' – different causes:
  - Pituitary – ACTH secreting tumour = Cushing's disease
  - Adrenal – cortisol secreting tumour
  - Ectopic ACTH production
  - Iatrogenic - Exogenous corticosteroids (most common)
- Does the patient actually have Cushing's Syndrome?
  - Exclude high BP due to obesity or other causes
  - Check if patient is on steroid medications
  - Then establish cause of cortisol excess…
    - Diagnosis important due to increased CHD risk (CV risk factors) therefore prompt treatment required

Differential Diagnosis of Cushing's

1. Confirm excess cortisol:

- 24 hour urinary free cortisol excretion
  - Excess cortisol rapidly exceeds available capacity of cortisol binding globulin (CBG) – unbound cortisol filtered readily into urine. Multiple collections if possible
- Midnight salivary cortisol (lose circadian rhythm)
- Low dose dexamethasone suppression test (DST) – 1mg at 11pm
  - Bloods post dex (~8am) for cortisol measurement – Normal response = Cortisol <50 nmol/L (excludes). Failure to suppress = Diagnostic.

Differential Diagnosis of Cushing's

2. Measure ACTH:
- Low/suppressed = appropriate: suggestive of adrenal tumour
- Normal/Raised = inappropriate: suggestive of excess ACTH (Pituitary Cushing's Disease, ectopic – higher ACTH levels)

3. Further dynamic function testing:
- High dose DST: suppression of cortisol seen in ~50% pituitary adenoma. No response if ectopic ACTH or adrenal tumour

4. Imaging: Pituitary MRI
- Pituitary lesion present? (I.e. Cushing's Disease?)

Selective venous sampling with ACTH measurement – to locate ACTH source (sometimes)

Treatment

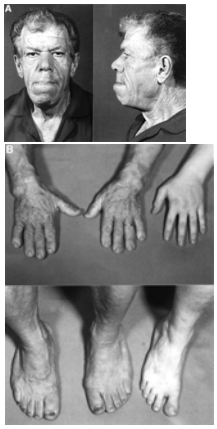
- Pituitary tumour:
  - First line = surgery
  - Radiotherapy if not successful
- Medical therapy:
  - Possible for Cushing's disease of all types but usually for pre-op preparation where surgery has failed.
    - Metyropone, ketonazole – to maintain circulating [cortisol] between 150-300 nmol/L.
  - If co-secretes prolactin may respond to medical therapy to shrink tumour first
- Patient's cured of Cushing's disease require steroid replacement therapy and regular monitoring

Case 3

- 45 yr old female patient presents to their GP with headaches.
- She also mentions that her foot size is increasing and her rings no longer fit.
- The GP notices that her teeth are slightly spaced on their lower jaw.

Q: Any guesses of diagnosis?

- The GP suspects Acromegaly (GH excess)…..
  - Overgrowth of skeleton & soft tissue coarse facial features; protuding jaw, forehead, hands ('spade-like'), feet, tongue
  - Arthritis, hypertension, sweating, impaired glucose tolerance or DM, CV disease

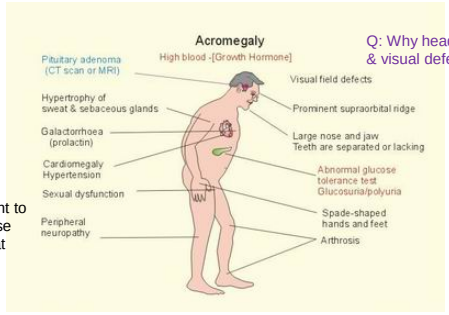


Gigantism

- If GH excess before long bone growth complete (i.e. childhood)
- Increase in linear growth also observed

http://www.physio-pedia.com/Acromegaly

Q: Why headaches & visual defects?



Important to recognise and treat

Causes of Excessive Growth

- Uncommon
- Most often due to GH secreting pituitary tumour (Acromegaly)
- Other causes of tall stature in children (rare):
  - Hyperthyroidism – or hypothyroid children over-treated with thyroxine
  - Inherited Disorders – e.g. Klinefelter's (47 XXY karyotype)
  - Congenital Adrenal Hyperplasia (CAH)

Diagnosis

- Confirming excess GH
- But… GH secretion episodic & pulsatile
- Therefore single measurement of GH not helpful

→Use IGF-1 as an indicator of GH status

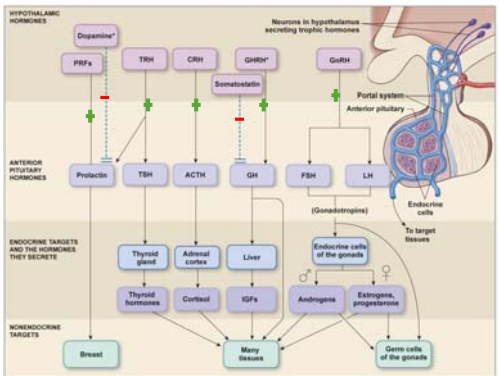
→Also used in monitoring of treated acromegaly

- Dynamic function testing: OGTT with GH measurement ('Gold standard')
  - Glucose load should suppress GH
  - Acromegaly: GH does not suppress in response to hyperglycaemia and may see paradoxical rise in GH

Treatment

- Surgery: First line
  - Trans-sphenoidal hypophysectomy
  - Success depends on size of tumour
- Radiation:
  - Usually reserved for active disease following surgery
- Medical treatment:
  - Dopamine agonists e.g. bromocriptine (if co-secretes prolactin)
  - Somatostatin analogues e.g. octreotide Why do these work?
  - GH-receptor antagonist: pegvisomant

Anterior pituitary systems



Case 4

- A 50 yr old male patient was diagnosed with a prolactinoma
- Following treatment with cabergoline to shrink the tumour he underwent pituitary surgery

- What is he now at risk of?

Hypopituitarism

- Deficiencies in one or more of the pituitary hormones

Causes:

- Pituitary or non-pituitary tumours
- Infiltrative processes e.g. sarcoidosis, haemochromatosis
- Infections e.g. cerebral abscess, meningitis, syphilis.
- Ischaemia and infarction e.g. Sheehan's syndrome (postpartum haemorrhage), pituitary apoplexy (caused by an acute infarction of a pituitary adenoma)
- Iatrogenic e.g. irradiation, neurosurgery
- Head injury (may have occurred up to several years before)
- Autoimmune

Case: post pituitary surgery

- Check remaining pituitary function
- May be transient or permanent loss of function in one or more axis

- Q: What is the most important pituitary hormone system to check?

- ACTH: check by measuring 9am cortisol and SST if necessary
- If cortisol is low: steroid cover to avoid adrenal crisis
- Recheck for recovery later

- Remaining axis should be tested ~1 month post surgery

- N.B. Post-irradiation pituitary function should be assessed regularly (~6 monthly)

Diagnosis of Hypopituitarism

- Dependent upon patient history for degree of investigation

Example first line screen:

- 9 am cortisol
- TSH & fT4
- Pituitary-gonadal axis:
  - Females – regular menstrual cycle indicates intact axis
  - Otherwise check LH/FSH & oestradiol in females
  - Check LH/FSH & testosterone in males
- Prolactin
- Serum Na – although patients with 2ndry adrenal insufficiency don't usually develop severe electrolyte disturbances.

Why both? Hint: Pituitary hormone deficiencies occur in step-wise manner…

Depending on baseline results:

- DFTs e.g. SST, GnRH test, TRH test

Case 5

- Patient in hospital with pneumonia
- Persistent hyponatraemia

- Results:

Serum Na	126 mmol/L	(133-146)
Serum osmolality	258 mOsm/kg	(275-295)
Urine osmolality	300 mOsm/kg	(50-1500)
Urine Na	60 mmol/L	

- Are the urine results appropriate? Why not?

SIADH criteria

- Most common cause of hyponatraemia in hospitalised patients BUT other causes must be ruled out

Criteria for diagnosis: (Diagnosis of exclusion)

- Clinically euvolaemic patient
- Patient not on diuretics
- Hyponatraemia with low serum osmolality
- Normal renal, adrenal, cardiac, hepatic and pituitary function
- Urine osmolality less than maximally dilute
- Inappropriately high urine sodium (e.g. >20-40 mmol/L)
- Respond to water restriction (inc. plasma osmo and [Na])

SIADH

- Inappropriate AVP/ADH i.e. retention of water despite low serum osmolality & normal/increased plasma volume

Common causes

- Many drugs including tricyclic antidepressants, carbamazepine, omeprazole, vincristine, ACE inhibitors, narcotics, nicotine
- Post-operative stress
- CNS disturbances e.g. infections, stroke, trauma
- Pulmonary disorders e.g. smoking, pneumonia, tuberculosis, emphysema

Treatment of SIADH

- Fluid restriction (to increase plasma osmo/[Na])
- Underlying cause
- V2 receptor antagonist

Case 6

- A patient presents to their GP complaining of excessive urination (polyuria) and thirst (polydipsia)
- On questioning, the onset followed a car accident where they suffered a head injury.
- The GP organises some tests:
  - Serum ??
  - Urine ??
- Serum U&E's are normal
- 24 hour urine collection comprises 6 L

Diabetes Insipidus

- **Definition:** Excretion of excess, dilute urine in excess of 3L/24 hours or >40ml/L/Kg/24h (>100ml/Kg/24h in infants)
- Two types:
  - Central or Cranial DI (deficient AVP production)
  - Nephrogenic DI (resistance to AVP)
- Can be inherited or acquired
- Differential diagnosis:
  - Psychogenic polydipsia
  - Osmotic diuresis

Causes of DI

- **Central/Cranial (Hypothalamic**) – **Impairment of osmoregulated AVP production**
  - **Primary Causes –** Genetic: Wolfram's syndrome. Developmental: Septo-optic displasia, Lawrence-moon biedel, Idiopathic.
  - **Secondary causes** – Trauma (head injury, surgery), Tumours (germ cell, metastatic, pituitary adenoma), inflammation (meningitis, encephalitis, sarcoid, Guillan-Barre), vascular (aneurysm, infarction), pregnancy
- **Nephrogenic** – **Resistance to anti-diuretic effects of AVP**
  - **Primary Causes** – Genetic: X-linked recessive V2-R defect, aut dom/auto rec AQP2 defect. Idiopathic
  - **Secondary causes** – Chronic renal disease, drugs (e.g. lithium, demeclocycline), systemic (sarcoidosis, myelomatosis), pregnancy.
- **Dipsogenic (primary polydipsia) – primary excessive inappropriate drinking, normal AVP secretion/action**
  - Compulsive water drinking associated with affective disorders e.g. drugs, structural/organic hypothalamic disease (tumour sarcoidosis, tuberculose meningitis, head injury)

Diagnosis DI

- Confirm high urine output (distinguish frequency vs volume)
- Baseline tests:
  - Serum U&E
  - Serum osmolality – clue = initial low osmolality if dipsogenic
  - Early morning urine osmolality
    - N.B. early morning may help distinguish if excess water intake
- Exclude other causes:
  - HbA1c / fasting glucose – diabetes
  - 9am cortisol – adrenal insufficiency
  - TSH – thyroid dysfunction
- Water deprivation test to distinguish between types…

Water deprivation test

Procedure

Baseline investigations before commencing fluid restriction:

- Weigh the subject and calculate 95% of initial body weight.
- Take baseline urine for electrolytes and osmolality
- Baseline blood for osmolality, UE and glucose
- Check and record blood pressure

Commence fluid restriction

- Check patient weight, urine volume, urine osmolality, urine electrolytes, blood UE and osmolality **Hourly**
- **Record the information in the chart provided.**

Fluid restriction should be stopped if:

- **There is a fall in weight >5%**
- **Plasma osmolality increases > 300 mosm/kg**
- **Urine osmolality increases > 650 mosm/kg**

Proceed to DDAVP test if urine osmolality rises by <30 mosm/kg over 3 successive urine samples or if the urine osmolality fails to increase >650 mosm/kg after 8 hours of fluid restriction

DDAVP test

Procedure

- Administer DDAVP 2ug i.m or 20ug intranasally
- Continue checking the patient weight, urine volume, urine osmolality, urine electrolytes, blood UE and osmolality **Hourly**
- Should the patient require fluids, do not allow the intake to exceed the total volume of urine produced over the fluid restriction period. Encourage the patient to drink small amounts (not the full amount in one drink)
- The patient is allowed food (a light snack such as toast is recommended)

SWBH protocol

Water deprivation test

Interpretation of Water deprivation test

Post dehydration Osmolality (mOsm/kg)		Post DDAVP Osmolality (mOsm/kg)	Diagnosis
Plasma	Urine	Urine	
283-293	>750	>750	Normal
>293	<300	<300	Nephrogenic diabetes insipidus
>293	<300	>750	Cranial diabetes insipidus
<293	300-750	<750	Chronic polydipsia
<293	300-750	>750	Partial nephrogenic DI or primary polydipsia

Further Investigations…

- **Cranial/Central:** MRI head, anterior pituitary function, ?AVP abs
- **Nephrogenic:** Renal U/S, exclude tubulopathies, urine microscopy, ?genetic studies
- **Dipsogenic:** MRI head

Treatment

- Cranial DI:
  - Avoid severe dehydration
  - Primary cause
  - Replace the hormone – DDAVP (desmospray/desmopressin)
  - Medialert bracelet/pendant
- N.B. Nephrogenic DI cannot do this
  - Primary cause
  - Manage water intake
  - Medialert bracelet/pendant
- Dipsogenic: Primary cause, restrict fluid intake

Pre-analytical considerations

- ACTH
  - Rapidly degraded →Use cortisol/SST to test axis
  - Sensitive to freeze-thaw cyles
- AVP
  - Rapidly degraded
  - Limited assays available, no standardisation
- Circadian rhythms
  - Cortisol as a measure of ACTH function
- Pulsatile secretion
  - GnRH & LH, GH

Analytical considerations:

All are peptide hormones:

- Prolactin
- GH
- ACTH
- AVP
- Oxytocin

Some are glycoproteins:

- FSH
- LH
- TSH

share alpha subunit, also hCG

Assays

- 2 site immunoassays

Interferences:
- Hook effect
- Macroprolactin

Standardisation Why does this matter?
- Standardisation challenging for peptide hormones
- Definition of standard material – different circulating forms
- Immunoassays: different manufacturers use different antibodies against different epitopes
- Different buffers etc

Standardisation

E.g. GH
- Different forms
  - ~75% circulates in original 22kDa form
  - Also post-translation modification: 20kDa form
  - Also dimers and complexes with binding protein
- Assays now standardised to 22kDa form but may still show different cross-reactivity
- Method-specific cut-offs should be used for interpretation
- Also differing glycosylation of circulating glycoproteins to recombinant standards e.g. LH, FSH

Rarely measured

AVP
- Stability
  - sample must be separated & stored frozen until analysis
- Limited assay availability, RIA
- Long TAT
  - Useful?
- Standardisation?!

Oxytocin
- No relevance to reproductive disorders

References/Further Reading

- Text books:
  - Clinical Biochemistry (Allan Gaw et al, third edition)
  - Clinical Biochemistry: Metabolic and Clinical Aspects (Marshall and Bangert)
  - Tietz (Methodology)
- Abbott Kit inserts (peptide hormones)