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Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Causes
• Intrasellar/parasellar masses
 Nonsecretory pituitary macroadenomas (≥ 10 mm in diameter) are the most common cause of hypopituitarism among adults (~ 40% of cases).
 Less common: internal carotid artery aneurysms, meningiomas, craniopharyngiomas,
• Pituitary apoplexy
 results in acute hypocortisolism and hypothyroidism, can present with sudden hypotension and hypovolemic shock • Sheehan syndrome: postpartum necrosis of the pituitary gland. Usually occurs following postpartum hemorrhage but can also occur even without clinical evidence of hemorrhage.
• Traumatic brain injury (especially around the skull base) • Infiltration of the pituitary and/or hypothalamus Hemochromatosis, Sarcoidosis
 Infections: meningitis, TB • Empty sella syndrome • Iatrogenic
 Hypophysectomy Pituitary irradiation • Congenital
 deficiency of hypothalamic hormones: GnRH deficiency (Kallman syndrome) Features (depends on which hormone is deficient). • Growth hormone deficiency: The first hormone to fall is the growth hormone
 in children →short stature in adults → tiredness, weight gain • ACTH deficiency → weight loss, weakness, Postural hypotension, chronic hyponatremia, hypoglycemia • TSH deficiency → weight gain, cold intolerance, lethargy, constipation, dry skin • FSH/LH deficiency
 Women → primary amenorrhea (delayed puberty), secondary amenorrhea, irregular menstrual cycles, infertility The presence of regular menstrual cycles in women rules out hypogonadism. Men → delayed puberty, loss of libido, infertility, testicular atrophy. • Intrasellar/parasellar masses (e.g., pituitary macroadenomas, craniopharyngiomas) can manifest with headache, visual field defects (bitemporal hemianopsia), and/or diplopia • Pituitary apoplexy → Severe headache, bilateral hemianopia, diplopia (due to damage to CN III), sudden hypotension. • PRL deficiency is rare, except in Sheehan's syndrome → failure of lactation • Houssay phenomenon: Amelioration of diabetes mellitus in patients with hypopituitarism due to reduction in counter-regulatory hormones.

In the majority of cases, the development of hypopituitarism follows a characteristic order, with secretion of GH, then gonadotrophins being affected first, followed by TSH and ACTH secretion at a later stage.

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Endocrinolog & Metabolism Investigations • Insulin stress test the gold standard dynamic test for the diagnosis of ACTH and GH deficiency in patients with suspected hypopituitarism. a weight-based dose of intravenous insulin to achieve a hypoglycaemia level below 2.2 mol/l. With normal pituitary function GH and cortisol should rise Contraindications: epilepsy, ischaemic heart disease and adrenal insufficiency • central/secondary adrenal insufficiency: low morning cortisol level + Low to normal ACTH • thyroid function tests → secondary hypothyroidism:↓ or normal TSH with ↓ serum free T4 and ↓ serum free T3 • MRI brain Management • Hydrocortisone: the most important replacement therapy to be started first to avoid the possibility of precipitating an adrenal crisis. Fludrocortisone is only necessary in patients with adrenal insufficiency who are unable to maintain normal blood pressure control. • Thyroxine replacement: should be begun after commencing hydrocortisone because levothyroxine increases the clearance of cortisol and may precipitate an adrenal crisis. • GH therapy: licensed for treatment of symptoms with reduced quality of life on adult growth hormone deficiency assessment (AGHDA) questionnaire score.
• Testosterone: the most appropriate treatment to prevent the progression of bone loss
• In addition to pituitary hormone replacement, the underlying cause of hypopituitarism should be treated.

Patients with TSH deficiency should not be treated with levothyroxine until ACTH deficiency has been ruled out and/or treated because levothyroxine increases the clearance of cortisol and may precipitate an adrenal crisis

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Growth hormone (GH)

Secretion • Hypothalamus → release Growth hormone releasing hormone (GHRH) → stimulates the somatotrophs in the anterior pituitary gland → release GH.
• Secreted in a pulsatile manner. The highest level of GH is seen around midnight during the sleep period. • GHRH uses two second messengers cAMP and IP3/Ca2+ to stimulate growth hormone release.

Which signaling pathways does growth hormone (GH) use? Tyrosine kinase receptor

Mechanism of action • Direct action via tyrosine kinase receptor on target tissues, such as skeletal muscle, liver, or adipose tissue ↓ Glucose uptake into cells (↑ insulin resistance) → ↑Blood insulin levels ↑ Lipolysis ↑ Protein synthesis in muscle ↑ Amino acid uptake • Indirect action via insulin-like growth factor 1 (IGF-1), primarily secreted by the liver Growth stimulation Anabolic effect on body

Growth hormone (GH) counteracts in general the effects of insulin on glucose and lipid metabolism but shares protein anabolic properties with insulin.

GH along with cortisol and adrenalin (called counter-regulatory hormones) tell the body to increase the availability of glucose – so it counters the effect of insulin.

GH regulation
↑ GH secretion ↓ GH secretion • Deep sleep • Fasting → Hypoglycaemia • Alpha adrenergic activity • Stress • Exercise • Ghrelin the "hunger hormone" • Amino acids (Arginine) • Pregnancy • Increased age
• Glucose • Chronic glucocorticoid therapy

• Sex steroids (estrogen or testosterone) • Puberty • CKD • Thyroid hormone, thyroxine • Estrogen, testosterone • Short-term glucocorticoid exposure
• An increase in GH levels is seen in patients with Type 1 DM, while in patients with Type 2 DM the levels may be increased, normal or decreased. • GH levels increase in malnutrition in contrast to a decrease in IGF-1 levels. • In poorly controlled diabetics GH levels are invariably raised whilst normal or low levels of IGF-I are found, indicating a dissociation between the two factors.

Conditions associated with GH disorders • GH deficiency: resulting in short stature • excess GH: acromegaly

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• Somatostatin • Beta adrenergic activity • Hyperglycaemia (initially) • Obesity • Free fatty acids • Hypothyroidism • IGF-1

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Growth hormone deficiency (GHD)

Causes • Pituitary tumours or their treatment, (e.g. surgery, cranial irradiation) is the most common cause. • Any other cause of hypopituitarism (see hypopituitarism topic)

Features
• In infancy are hypoglycemia and micropenis is the primary manifestations • In early childhood: growth failure is the primary manifestation. causes premature fusion of the epiphyseal portion of the bone. • In adults
 ↑↑ fat mass
 ↓↓ lean body mass
 ↓↓ bone mineral density (BMD) → osteopenia/osteoporosis ↓↓ energy, ↓↓quality of life (QoL)
 ↓↓ sweating → Dry skin
 ↑↑ greater mortality , ↑↑cardiovascular risk ↑↑ insulin resistance Dyslipidaemia (↑LDL).
Diagnosis
• Decreased serum insulin-like growth factor-1 (IGF-1) levels: may be normal in up to 50%. • Dynamic tests of GH secretion Insulin tolerance test (ITT): the gold standard for the diagnosis insulin-induced hypoglycaemia → GH response of less than 9 mU/L (3 ng/ml) → GHD Causes of false positive test: Obesity →↓ GH response to insulin → false positive test
 Contra-indications to ITT:

 seizures (eg: in epilepsy) IHD, Abnormal ECG basal cortisol levels <100 nmol/L Glycogen storage disease Elderly (due to high risk of hypoglycaemia) Alternative test if ITT is contraindicated: arginine-GHRH stimulation test glucagon-GH-releasing hormone stimulation test • Two tests of GH stimulation test are required before making the diagnosis.

Treatment → Subcutaneous injections of recombinant human growth hormone. • Criteria for GH treatment: only if all the following three criteria are met 1- Severe GH deficiency, defined as a peak GH response of less than 9 mU/litre (3 ng/ml) during an insulin tolerance test. 2- Impairment of Quality of Life (QoL): 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) score ≥ 11. 3- Treatment for other pituitary hormone deficiencies

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Adverse effects of GH replacement
• Sodium and water retention Weight gain Carpal tunnel syndrome • Hyperinsulinaemia • Arthralgia (possibly due to intra-articular cartilage swelling) • Myalgia • Benign intracranial hypertension (resolves on stopping treatment)

Contraindications to GH replacement • Active malignancy • Benign intracranial hypertension • Pre-proliferative/proliferative retinopathy in diabetes mellitus

Which treatment is most appropriate for patients with preserved pituitary function and deficiencies in growth hormone (GH) and adrenocorticotrophic hormone (ACTH)? • Cortisol replacement therapy only.
 GH deficiency can be caused by hypoadrenalism. Concomitant cortisol and GH replacement therapies are not appropriate because cortisol alone may be sufficient to restore GH secretion.

MRCP-UK. SCE .Sample question patients with childhood-onset GHD who are candidates for GH therapy after adult height achievement. What is the most appropriate next step in management? → should be retested for GHD

Acromegaly

Approximately 30% of growth hormone (GH) secreting pituitary tumours is associated with mutation of the Gs protein alpha subunit

Definition • Acromegaly is the clinical condition resulting from prolonged excessive GH and hence IGF1.

Epidemiology • Most cases are diagnosed at 40–60 years. Causes • Pituitary adenoma (95%)
• ectopic GHRH or GH production by tumours e.g. pancreatic mechanism: GH secreting tumours → mutation in the alpha sub-unit of the stimulatory guanosine triphosphate (GTP) binding protein → persistent elevation of cyclic adenosine monophosphate (cAMP) → production of excess growth hormone.

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Features • Headaches
• Visual field loss (attributable to optic chiasmal compression) , diplopia (due to cranial nerve palsy) • Increase in shoe size • Increased sweating : due to sweat gland hypertrophy
• Hands: spade-like hands • Face: general coarse facial appearance, prognathism, , eyes, bitemporal hemianopia
• Mouth: large tongue → Sleep apnea , interdental spaces

Macroglossia: Causes • Hypothyroidism • Acromegaly • Amyloidosis • Duchenne muscular dystrophy • Mucopolysaccharidosis (e.g. Hurler syndrome) • Down's syndrome

Complications • Hypertension (40%). • Insulin resistance and impaired glucose tolerance (40%)/diabetes mellitus (20%). • Obstructive sleep apnoea: due to soft tissue swelling in nasopharyngeal region. • ↑ risk of colonic polyps and colonic carcinoma • ↑ Ischaemic heart disease and cerebrovascular disease. • ↑ Congestive cardiac failure and possible ↑ prevalence of regurgitant valvular heart disease. • Cardiomyopathy → heart failure
• Osteoarthritis, Arthralgia, Pseudogout • Carpal tunnel syndrome: Positive Tinel's sign • 6% of patients have MEN-1, hypercalcemia → primary hyperparathyroidism → MEN 1.

Investigations

• Serum insulin-like growth factor 1 (IGF-1) IGF-1 measurement is the most appropriate initial investigation May also be used as a screening test , sometimes used to monitor disease Normal IGF-1 levels rule out acromegaly If ↑ IGF-1 → conduct OGTT with baseline GH → measure GH after 2 hours:
 if GH suppressed → acromegaly ruled out if GH not suppressed: confirmed acromegaly → conduct pituitary MRI Growth hormone (GH) levels vary during the day and are therefore not diagnostic. • Oral glucose tolerance test (OGTT) with serial GH measurements. The definitive test
 Lack of suppression of GH to < 1 µg/L following documented hyperglycemia during an oral glucose load.
 False +ves: Chronic renal and liver failure, malnutrition, diabetes mellitus, heroin addiction, adolescence (due to high pubertal GH surges).

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• Assess for other pituitary functions • Pituitary MRI: usually demonstrates the tumour (98%) • If no pituitary tumor detected → serum GHRH + radiology of the chest and abdomen to detect ectopic GHRH-secreting tumor (usually a GHRH-secreting carcinoid of lung or pancreas.)

• Associated laboratory features Serum calcium: GH stimulates renal 1α-hydroxylase→↑ 1,25Dihydroxycholecalciferol (DHCC) → hypercalcaemia → hypercalciuria (which occurs in 80%)

→↑likelihood of renal stones. elevated Phosphate levels Raised prolactin in 1/3 of cases → galactorrhoea

In active acromegaly with associated diabetes mellitus → There is insulin resistance

Acromegaly → ↑risk of colon cancer → regular colonoscopy screening, starting at the age of 40 years.

Management Trans-sphenoidal surgery is first-line treatment for acromegaly in the majority of patients

• Surgery: transsphenoidal adenomectomy first-line treatment for acromegaly in the majority of patients
 the percentage likelihood of cure from surgery: > 85% for microadenomas and 40–50% for macroadenomas • Medication: In patients with inoperable tumors or unsuccessful surgery, medication and radiotherapy are indicated to reduce tumor size and limit the effects of GH and IGF-1.
 Somatostatin analogs (e.g., octreotide, lanreotide, pasireotide)
 first line medical therapy.
 side effects: gallstone disease
 Dopamine agonists (e.g., bromocriptine, cabergoline):
 less effective than somatostatin analogues. may be helpful if there is coexistent secretion of PRL → significant tumour shrinkage. Cabergoline is more effective than bromocriptine GH receptor antagonists (e.g., pegvisomant)
 Indicated for somatostatin non-responders. Third-line treatment when surgery, radiotherapy and somatostatin analogues are not effective. Very effective - decreases IGF-1 levels in 90% of patients to normal Pre-operative: may improve metabolic risk factors for surgery, such as hypertension and hyperglycaemia Monitoring: liver function tests → discontinue pegvisomant if the transaminases are greater than 3-fold elevated. Octreotide can be used as an adjunct to surgery in patients with acromegaly

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• Radiotherapy Indications: residual tumor mass following surgery, and if medical therapy is unavailable, unsuccessful, or not tolerated.
 stereotactic radiotherapy (SRT) is preferred over conventional radiation therapy Side effects: Danger of hypopituitarism → do annual hormonal testing

Long acting somatostatin analogue • Mode of action → ↓↓meal-time related superior mesenteric artery blood flow
• One intra-muscular injection should be given every 14 days. • Common side effects : pain at injection site, GIT disturbances , Cholelithiasis, Sinus bradycardia , Hypoglycaemia, hyperglycaemia

Which test is the best way to monitor for recurrence after trans-sphenoidal surgery for resection of a growth hormone-secreting pituitary adenoma? • Insulin-like growth factor 1(IGF-1)

Prognosis • Left ventricular failure is the most common cause of death if treatment is unsuccessful

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Laron's syndrome

Definition • an autosomal recessive disorder characterized by an insensitivity to (GH), usually caused by a mutant growth hormone receptor.
Features • short stature
• Reduced risk of developing acne, cancer and diabetes mellitus type II. • Seizures are frequently seen secondary to hypoglycemia.
• low levels of insulin-like growth factor (IGF-1) and its principal carrier protein, insulin-like growth factor binding protein 3. Treatment • injections of recombinant IGF-1.
• Not respond to growth hormone treatment due to a lack of GH receptors.

Nelson syndrome (post adrenalectomy syndrome)

Aetiology • bilateral adrenalectomy in patients with a previously undiscovered pituitary adenoma

• occurs in 30% of patients adrenalectomised for Cushing's disease. Pathophysiology • Bilateral adrenalectomy → no endogenous cortisol production → no negative feedback from cortisol on hypothalamus → increased CRH production → uncontrolled enlargement of preexisting ACTH-secreting pituitary adenoma → increased secretion of ACTH and melanocyte-stimulating hormones (MSH) → symptoms of pituitary adenoma and ↑ MSH.

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Features
• Headaches, bitemporal hemianopia (mass effect) • Cutaneous hyperpigmentation: arises from the MSH products of the proteolysis of POMC, which also produces ACTH.
Diagnosis • High levels of beta-MSH and ACTH • Pituitary adenoma on MRI confirms the diagnosis.
Treatment • Surgery (e.g., transsphenoidal resection) and/or pituitary radiation therapy (e.g, in the case of tumor residues after surgery) Monitoring • ACTH levels • serial pituitary imaging.

Pituitary adenoma

Epidemiology • Small pituitary tumours (<4 mm) are common and have been reported in up to 10% of MRIs in the general population.
• Only a small fraction of such tumours are associated with clinical features suggestive of pituitary disorder.

Classifications • According to size: Microadenoma: ≤ 10 mm Macroadenoma: > 10 mm • According to hormone secretion Secretory pituitary adenomas (60%): hormone secretion → hyperpituitarism Lactotroph adenoma: Prolactinoma 35–40%.
 Somatroph adenoma: Growth hormone (acromegaly) 10–15%.
 Corticotroph: ACTH adenoma (Cushing’s disease) 5–10%.
 Thyrotroph: TSH adenoma <5% Non-secretory pituitary adenomas 'chromophobe' : Non-functioning 30–35%. Which nonfunctioning pituitary adenoma subtype is characterized by a high recurrence rate, invasion, and increased risk of hemorrhagic infarction? Corticotroph adenoma

Prolactinomas are the most common pituitary adenomas

Features: depends on the tumor size and whether the tumor produces hormones • Secretory microadenomas → hyperpituitarism according to which hormone is secreted • Secretory macroadenomas → hyperpituitarism + mass effects (e.g., headache, bitemporal hemianopsia, diplopia) • Non-secretory microadenomas → Asymptomatic • Non-secretory macroadenomas → Hypopituitarism + mass effects (e.g., headache, bitemporal hemianopsia, diplopia)

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• Mass effects
 Superior extension → firstly compression of the optic apparatus and later the hypothalamus. Lateral extension → compression or invasion of the cavernous sinus can compromise third, fourth, or sixth cranial nerve functions, manifest as diplopia in 5 to 15% of pituitary tumour patients.

Diagnostics • Hormone assays Basal prolactin levels
 Insulin-like growth factor-1 (IGF-1)
 24-hour urine cortisol
 Thyroid function tests
• Cranial contrast MRI (initial test) : reveals an intrasellar mass
 CT scan may be considered
• Perimetry: to assess visual field defects

Treatment • Non-secretory pituitary microadenomas (incidentalomas) → no treatment (only follow-up with serial MRI)
• Prolactinomas (PRL is usually >6000mU/ml) First-line: dopamine agonists (e.g., cabergoline, bromocriptine) → shrink pituitary adenoma. Second-line: trans-sphenoidal hypophysectomy ± adjuvant radiotherapy • Other pituitary adenomas First-line: transsphenoidal hypophysectomy
 Second-line: Medications ± pituitary irradiation

Differentiate between non-functioning adenoma and macroadenoma: • Although stalk compression with a non-functioning tumour may cause hyperprolactinaemia the concentrations of prolactin are usually below 2000 mU/L and galactorrhoea would be rare.

Except Prolactinomas, all other functioning adenomas are treated primarily by surgery (i.e.; for secondary hyperthyroidism, acromegaly etc).

If the CT scan shows a pituitary tumour with suprasellar extension, which structures is likely to be compressed?
• Optic chiasm
 The optic chiasm lies 5-10 mm above the diaphragm sellae and anterior to the stalk. Adenomas > 1.5 cm frequently have suprasellar extension, and the MRI will show compression and upward displacement of the optic chiasm.

The presence of an elevated prolactin level along with secondary hypothyroidism and hypogonadism is indicative of stalk compression due to pituitary adenoma

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Pituitary apoplexy

Definition
• Sudden hemorrhage into the pituitary gland. Most commonly occurs in patients with a preexisting pituitary adenoma which may be asymptomatic before presentation.

Predisposing factors • pituitary adenomas (most common)

Features • Features of raised intracranial pressure (↑↑ICP) Sudden-onset retro-orbital headache, similar to that seen in subarachnoid haemorrhage vomiting visual disturbance: diplopia due to pressure on the oculomotor nerves
• Features of pituitary insufficiency
 The main initial problem is ↓↓ ACTH, → ↓↓ cortisol → features of an 'Addisonian crisis', i.e. hypotension, hyponatraemia, hyperkalaemia and hypoglycaemia.
 Subacutely, there can be ↓ TSH and gonadotropins (LH and FSH). Diagnosis
• Magnetic resonance imaging

Treatment • Urgent steroid replacement
• Indications for neurosurgical decompression: severe neuro-ophthalmic signs (e.g. severely reduced visual acuity, severe and persistent or deteriorating visual field defects or deteriorating level of consciousness) Ocular paresis because of involvement of III, IV or VI cranial nerves in the cavernous sinus in the absence of visual field defects or reduced visual acuity is not an indication for immediate surgery. Resolution will typically occur within days or weeks with conservative management • Over the long-term → corticosteroid, testosterone and thyroid hormone replacement.

Prognosis • Nearly 80% of the patients will need some form of hormone replacement after apoplexy. Growth hormone deficiency is the most commonly observed deficit after apoplexy and is present in almost all patients but rarely replaced.

Sudden-onset retro-orbital headache, vomiting, visual disturbance and hormonal dysfunction should lead you to consider a diagnosis of pituitary apoplexy Pituitary Incidentaloma • Asymptomatic, pituitary tumors that are detected on MRI or CT scans done for other reasons without hormonal hyper- or hyposecretion and has a benign natural history. • The most appropriate strategy →observation and repeat scanning.

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Endocrinolog & Metabolism Hyperprolactinaemia

The first test to do when seeing anyone with hyperprolactinaemia is to exclude pregnancy, as it is the most common cause.

Prolactin hormone overview
• Secreted by lactotrophic cells of the anterior pituitary gland • Effects on females: ↑ breast tissue growth and lactation, ↓ ovulation, ↓GnRH secretion, amenorrhea, galactorrhea, ↓libido • Effects on males: ↓ spermatogenesis and ↓ libido. • Stimulated by thyrotropin-releasing hormone (TRH) • Inhibited by hypothalamic dopamine and γ-aminobutyric acid (GABA). Epidemiology • Hyperprolactinemia is the most common form of hyperpituitarism. • Post-mortem studies show microadenomas in 10% of the population. • Microprolactinomas are commoner than macroprolactinomas • More common in females Pathophysiology

Which hormones are expected to be low in hyperprolactinaemia? • Hyperprolactinaemia suppresses the release of gonadotropin-releasing hormone (GRH), which leads to reduced production of luteinising hormone (LH) and follicle-stimulating hormone (FSH).
Causes

• Physiological: Pregnancy, Sexual intercourse, Nipple stimulation/suckling, Stress.
• Pituitary tumour:
 Prolactinomas. the most common cause (~ 50%) of pathological hyperprolactinemia Microprolactinoma → prolactin level usually of 1,000-3,000 mU/L. Macroprolactinoma: prolactin level usually greater than 3000 mU/L. Prolactin → ↓GNRH → hypogonatrophic hypogonadism (↓LH and FSH → ↓ estrogen, ↓ testosterone) Causes of raised prolactin – the Ps

- pregnancy
- prolactinoma
- physiological
- polycystic ovarian syndrome
- primary hypothyroidism
- Phenothiazines, metoclopramide, domperidone

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 Mixed GH/PRL-secreting tumour. Acromegaly (1/3 of patients) Macroadenoma compressing stalk.

 Empty sella. Multiple endocrine neoplasia (MEN): Occur in 20% of patients with MEN-1 (prolactinomas are the commonest pituitary tumour in MEN-1). MEN type 1should be considered in presentation with microprolactinoma and recurrent dyspepsia (gastrinomas, insulinomas, carcinoid). • Hypothalamic disease: mass compressing stalk (craniopharyngioma, meningioma, neurofibromatosis). • Infiltration : sarcoidosis, Langerhans cell histiocytosis. • Stalk section: head injury, surgery. • Cranial irradiation. • Drug induced: → ↓dopamine release → ↓dopamine inhibition effect on prolactin → ↑ prolactin release. (Levels less than 1000 are most likely to be drug related)
 Dopamine receptor antagonists (metoclopramide most common, domperidone). Neuroleptics (perphenazine, flupentixol, fluphenazine, haloperidol, thioridazine, chlorpromazine, trifluoperazine, risperidone, sulpiride). Antidepressants (tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, sulpiride, amisulpride, imipramine, clomipramine, amitriptyline, pargyline, clorgiline). Cardiovascular drugs — verapamil, methyldopa, reserpine. Opiates Cocaine Protease inhibitors — e.g. ritonavir, indinavir, zidovudine. • Oestrogens. • Others— bezafibrate, omeprazole, H2 antagonists. • Metabolic: Hypothyroidism: TRH increases PRL.
 Chronic renal failure: reduced PRL clearance.
 Severe liver disease — disordered hypothalamic regulation. • Other:
 Polycystic ovarian syndrome (PCOS): can make differential diagnosis of menstrual problems difficult. Chest wall lesions—zoster, burns, trauma (stimulation of suckling reflex).
 Temporal lobe seizures, due to close proximity to the hypothalamus. • No cause found: ‘Idiopathic’ hyperprolactinaemia. • Macroprolactinemia (‘big’ PRL) aggregates of prolactin and antibodies (in particular, antiprolactin autoantibodies) that range in size from approximately 150 to 170 kilo Dalton (kD). The most common form of native prolactin in serum is 23 kD in size
 These complexes are immunologically detectable but not biologically active, so they appear to cause no clinical abnormality. Typically, there is hyperprolactinaemia with regular ovulatory menstrual cycles.

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 Can be misdiagnosed and treated as prolactin hypersecretion Detection Misdiagnosis can be avoided by asking the laboratory to pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin. Gel filtration chromatography (gold standard).

Quetiapine, clozapine, aripiprazole, and olanzapine are antipsychotics, with little or no effect on prolactin (lower binding affinity to D2 receptors).

Cranial irradiation may initially cause hyperprolactinaemia but a low PRL is typical after a year.

A patient presented with elevated oestradiol and prolactin with suppressed (LH/FSH) and recent amenorrhoea. what is the most likely diagnosis? • Pregnancy

Features of excess prolactin • Hyperprolactinaemia (microadenomas and macroadenomas) Men: impotence, loss of libido, erectile dysfunction, rarely galactorrhoea Women: amenorrhoea,

galactorrhoea, reduced libido • Mass effects (macroadenomas only):
 Headaches and visual field defects (uni- or bitemporal field defects). Hypopituitarism. Invasion of the cavernous sinus may lead to cranial nerve palsies. • Long-term risk of d ↓BMD.
Investigations • Serum prolactin (PRL) stress of venepuncture may cause mild hyperprolactinaemia, so 2–3 levels should be checked, preferably through an indwelling cannula after 30min Serum PRL <2,000mU/L is suggestive of a microprolactinoma or a non-functioning macroadenoma compressing the pituitary stalk. Serum PRL >4,000mU/L is diagnostic of a macroprolactinoma. Hook effect: Very high prolactin concentrations can interfere with immunoassay systems resulting in falsely low prolactin determination. this is due to "hook effect" which describes the inhibition of immune complex formation by excess antigen concentrations.
 this is an important consideration in patients with large pituitary adenomas when the clinical suspicion of prolactinoma is strong, as in patients with amenorrhoeagalactorrhoea or longstanding hypogonadism.
 appropriate dilution of the serum in such cases helps in accurate estimation of serum prolactin concentration. • Thyroid function and renal function: Hypothyroidism and chronic renal failure are causes of hyperprolactinaemia. • MRI of the brain: the most accurate diagnostic test. Be aware MRIs do not rule out small microadenomas.

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Levels of prolactin
• < 1000 → drug-induced prolactinaemia
• 1000 -- 3000 mU/l → microprolactinoma. • > 3000 → macroprolactinoma.

Treatment of prolactinomas

• Dopamine agonist (DA) (Cabergoline and Bromocriptine)
 Dopamine agonists are first-line treatment for prolactinomas, even if there are significant neurological complications they are able to normalize the prolactin levels, restore gonadal function and reduce tumor size A meta-analysis suggested that cabergoline is more efficacious than bromocriptine in normalising prolactin and has a better side effect profile and is therefore the treatment of choice. If patient is asymptomatic, there is no absolute requirement for treatment.
 Side effects:
 Both pergolide and cabergoline may be associated with pericarditis, cardiac valve regurgitation, pericardial effusion and pulmonary hypertension.
 Ropinirole may be an appropriate alternative in this case, otherwise surgery would be the next most appropriate step. Although cabergoline in higher doses used for Parkinson’s disease can cause right-sided cardiac fibrosis, there is no evidence for this using the lower doses necessary for the control of PRL levels. Contraindications cardiac valve fibrosis
 pulmonary fibrosis.

• Pituitary surgery
 rarely required in prolactinomas and is generally reserved for patients intolerant of or resistant to dopamine agonist therapy.
• Radiotherapy can be used to reduce the chance of tumour recurrence, but is rarely required.

Prolactinomas in pregnancy
• Risk of pregnancy The main concern for the mother is adenoma growth with potential mass effect and visual loss The risk of tumor enlargement during pregnancy is found to depend on tumor size:
 3% for microprolactinomas 32% for macroprolactinomas that were not previously operated on
• Before pregnancy: For women with macroadenomas 1st line: dopamine agonist 2nd line (if size does not decrease) : transsphenoidal surgery pregnancy is not recommended in women with drug resistant large macroprolactinomas and they should not conceive even if the tumor is intrasellar, until the size is reduced by transsphenoidal surgery.

Dopamine agonists (e.g. cabergoline, bromocriptine) are first-line treatment for prolactinomas, even if there are significant neurological complications

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• During pregnancy If possible, stop dopamine agonists as soon as the pregnancy is confirmed except in: invasive macroprolactinomas or pressure symptoms. There is no evidence that DA is teratogenic, but Once pregnancy is established, DA is not necessarily required, and so most physicians recommend stopping it for the duration. It is clearly not needed to treat hypogonadism and it is not needed to control size of adenoma as microprolactinomas almost never spontaneously increase in size.

 In case the patient becomes symptomatic with visual disturbance or progressive headaches, an MRI without gadolinium (not a CT) should be performed to assess changes in tumor size. evidence of macroadenoma growth on MRI; performed for severe headaches or visual field abnormalities) → cabergoline or bromocriptine If treatment is required bromocriptine has the most safety data (the first drug of choice in symptomatic pregnant). Cabergoline may be considered if the adenoma does not respond to bromocriptine • Breastfeeding Asymptomatic: Breastfeeding is not contraindicated, but dopamine agonists should not be used, because they impair lactation. woman who has visual field impairment: should not breastfeed and should be treated with a dopamine agonist

Cabergoline VS Bromocriptine

Comparison
Cabergoline Bromocriptine Dopamine receptors D2 selectively
D2 and other dopamine receptors

long acting (once or twice weekly → better tolerability and patient compliance) Short acting (requires multiple doses per day) Effectiveness in lowering the prolactin More effective in lowering the prolactin Less effective
Safety during pregnancy
Less data about safety
Less teratogenicity than cabergoline

Physiological effects of thyroid hormones

Thyroid hormones production • The thyroid utilises tyrosine and iodine to manufacture thyroxine and T3. • Iodide is taken into the thyroid follicular cells by active transporters and then oxidised to iodine by thyroid peroxidase.
• Organification occurs when iodine is attached to tyrosine molecules which themselves are attached to thyroglobulin, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). The coupling of 2 molecules of DIT forms thyroxine. • Maternal TRH readily crosses the placenta; maternal TSH and T4 do not. • An enzyme called 5’-deiodinase in the blood removes an iodine molecule to convert T4 to the biologically active T3. So T4 can be considered a prohormone: it must be

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converted to T3 to exert any of its effects on the body. This conversion occurs throughout the body. In contrast, T4 can only be produced in the thyroid. • Peripheral metabolism of thyroxine is the most common source of T3. • Peripheral conversion is inhibited by glucocorticoids, β-blockers, and propylthiouracil(PTU) • T4 is much more abundant than T3 in the bloodstream. T3 is more biologically active than T4. • T3 has a much shorter half-life. T3 is more readily broken down by 5’-deiodinase. • The half-life of T3 is about one day (~ 20 hours), whereas the half-life of T4 is about one week (~ 190 hours). This longer half-life makes T4 suitable for use as a depot form that can be used replacement therapy. • Thyroid peroxidase first oxidizes iodide to iodine. Then, it attaches iodine to thyroglobulin. Then, it combines monoiodotyrosine (MIT) and diiodotyrosine (DIT) or two molecules of DIT to make T3 and T4, respectively. • Excess iodide inhibits thyroid peroxidase. This is called the Wolff-Chaikoff effect. Thyroid binding globulin (TBG) • In the blood, more than 99% of T3 and T4 are bound to thyroid binding globulin (TBG) and thus not biologically active. The small unbound is called free T3 and T4. This is the biologically active form. • TBG levels are increased during pregnancy and with oral contraceptive use because estrogen promotes liver TBG synthesis. In these patients, bound and total thyroid hormones are elevated while free T3 and T4 remain normal. Causes of altered concentration of TBG • ↑TBG • ↓TBG • Pregnancy • OCP and other sources of oestrogens • Tamoxifen • Hepatitis A; chronic active hepatitis • Biliary cirrhosis • Acute intermittent porphyria • Newborn state • Genetically determined • Androgens • Large doses of glucocorticoids • Cushing’s syndrome • Chronic liver disease • Severe systemic illness • Active acromegaly • Nephrotic syndrome • Genetically determined • Drugs, e.g. phenytoin • Factitious thyrotoxicosis Thyroid hormone receptors • The thyroid hormone receptor is a nuclear receptor. • The action of T3 requires entry into the nucleus, where the thyroid hormone receptors are found in cells throughout the body. • The TRH receptor uses the Gq pathway, while the TSH receptor uses the Gs pathway. Regulations • TRH binds to a Gq receptor on anterior pituitary tissue → activate membrane-bound phospholipase C →↑ inositol triphosphate (IP3) →↑intracellular calcium → activates protein kinase C →↑release of TSH. • TSH binds to a Gs receptor on thyroid gland tissue → activate adenylate cyclase → promotes conversion of ATP to cAMP, which acts as a second messenger →↑synthesis and secretion of T3/T4.

Endocrinolog & Metabolism

Functions of thyroid hormones: 7 B s • Brain maturation • Bone growth (synergism with GH) • β-adrenergic effects. β1receptors in heart CO, HR, SV, contractility; β-blockers alleviate adrenergic symptoms in thyrotoxicosis • Basal metabolic rate (via Na+/ K+ ATPase O2 consumption, RR ,body temperature) • Blood sugar (glycogenolysis, gluconeogenesis) (Enhance insulin sensitivity) • Break down lipids (lipolysis) • Stimulates surfactant synthesis in Babies

What is the defect Which responsible for thyroid hormone dyshormonogenesis? Defect in iodine organification

Thyrotropin is a glycoprotein hormone (glycosylated)

Calcitonin

Overview
• Polypeptide hormone • Produced by the parafollicular cells (also known as C-cells) of the thyroid,

Calcitonin receptor • found on osteoclasts, and in the kidney and regions of the brain,
• is a G protein-coupled receptor, which is coupled by Gs to adenylate cyclase and thereby to the generation of cAMP in target cells.
• It may also affect the ovaries in women and the testes in men.

Action • ↓bone resorption. Reduce blood calcium (Ca2+), opposing the effects of parathyroid hormone (PTH). • Calcitonin-gene related peptide causes vasodilatation. • Calcitonin lowers blood Ca2+ levels in two ways:

1. Major effect: Inhibits osteoclast activity in bones
2. Minor effect: Inhibits renal tubular cell reabsorption of Ca2+ and phosphate, allowing them to be excreted in the urine Regulation
   • Secretion of calcitonin is stimulated by: ↑serum [Ca2+] gastrin and pentagastrin. Calcitonin escape phenomenon • Despite high serum calcitonin levels, which mechanism best explains the normal calcium levels in a patient with thyroid nodule ? High levels of calcitonin down regulates its receptor Calcitonin's primary function is to act on osteoclasts and decrease serum calcium levels. Huge amounts of calcitonin are secreted in medullary carcinoma of the thyroid, or when calcitonin is used therapeutically to treat certain medical conditions, such as Paget's disease, osteoporosis, and hypercalcemia. Its effects on

osteoclasts disappear after one week of therapy. This is called the 'calcitonin escape phenomenon'.
 The biochemical basis for the 'calcitonin escape phenomenon' is the down regulation of its receptor.
 Whenever the levels of calcitonin become high, they down regulate the receptor by rapid and prolonged down regulation of calcitonin receptor messenger RNA.

To remember that calcitonin keeps the calcium in the bones, think: Calci-bone-in!

Hypothyroidism

Epidemiology • Affects around 1-2% of women in the UK
• Around 5-10 times more common in females than males.

Causes • Hashimoto's thyroiditis
 Autoimmune disease, Associated with HLA-DR3 Most common cause 10 times more common in women May cause transient thyrotoxicosis in the acute phase Early in the course of disease, T4 and TSH levels are normal and there are high levels of thyroid peroxidase antibodies and, less commonly, antithyroglobulin antibodies.
 Thyroid radioiodine uptake may be increased because of defective iodide organification, together with a gland that continues to trap iodine. Associated with Other autoimmune diseases: IDDM, Addison's, pernicious anaemia, coeliac disease. Turner's syndrome, Down's syndrome Thyroid lymphoma Features Features of hypothyroidism (eg hair loss, hoarse voice and periorbital oedema) Goitre: firm, non-tender Antibodies
 anti-thyroid peroxidase (anti TPO) also known as (Anti-microsomal antibodies) anti-thyroglobulin antibodies (anti-Tg) • Dietary iodine deficiency Common in parts of central Africa, where the diet is poor in iodine and access to sea fish is relatively difficult. Uncommon in the developed world. Iodine daily requirement: according to WHO recommendations Age >12 and adults → 150 microgram Pregnant and lactating women → 200 microgram It may present as goitre without hypothyroidism, or in severe cases can progress to frank hypothyroidism. Urinary iodide excretion is the next investigation to establish the diagnosis As more than 95% of dietary iodide is excreted in urine, a 24 hour urinary excretion of iodide is an excellent index of dietary iodine intake and can unmask an iodide deficiency state.

• Postpartum thyroiditis (subacute lymphocytic thyroiditis) • De Quervain’s thyroiditis (subacute granulomatous thyroiditis) • Riedel thyroiditis: a dense fibrosis that replaces normal thyroid parenchyma • Iatrogenic: after treatment of hyperthyroidism with anti-thyroid drugs, thyroidectomy or radioiodine. • Drug- induced
 Amiodarone Lithium → goitre in up to 40% and hypothyroidism in about 20%.
• Secondary (central) hypothyroidism (rare):
 TSH is not appropriately elevated inspite of low T4.
 pituitary disorders → ↓ TSH levels → ↓ T3/T4 levels • Tertiary hypothyroidism: hypothalamic

disorders → ↓ TRH → ↓ TSH → ↓ T3/T4 levels

Features • Symptoms related to decreased metabolic rate Fatigue, decreased physical activity Cold intolerance Hair loss, brittle nails, and cold, dry skin Weight gain (despite poor appetite) Hypothyroid myopathy Woltman sign: a delayed relaxation of the deep tendon reflexes Entrapment syndromes (e.g., carpal tunnel syndrome) • Symptoms related to decreased sympathetic activity Decreased sweating Cold skin (due to decreased blood flow) Constipation (due to decreased gastrointestinal motility) Bradycardia • Symptoms related to generalized myxedema puffy appearance Myxedematous heart disease (dilated cardiomyopathy, bradycardia, dyspnea) Hoarse voice, difficulty articulating words Pretibial and periorbital edema: due to accumulation of glycosaminoglycans and hyaluronic acid within the reticular layer of the dermis. complex protein mucopolysaccharides bind water → nonpitting edema • Symptoms of hyperprolactinemia Abnormal menstrual cycle; secondary amenorrhea; menorrhagia Galactorrhea Decreased libido, erectile dysfunction, delayed ejaculation, and infertility in men • Further symptoms Impaired cognition; somnolence, depression Investigations • Thyroid function tests TSH: Best initial screening test. Normal TSH levels generally rule out primary hypothyroidism and hyperthyroidism FT4 • Anti-TPO antibodies present in 10% females without thyroid pathology Hashimoto's thyroiditis = Hypothyroidism + Goitre + Anti-TPO Hashimoto's thyroiditis is associated with thyroid lymphoma

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Associated laboratory manifestations
• Euvolaemic hyponatraemia often resulting from inappropriate production of antidiuretic hormone.
• Creatine kinase: increased in hypothyroid myopathy • Macrocytic anemia • Glucose intolerance • Dyslipidaemia ↓thyroid hormones → ↓ use of glucose and FFAs as fuel → hyperlipidemia and glucose intolerance. The predominant lipid picture in hypothyroidism is mixed dyslipidaemia (↑LDL , ↑ triglycerides) may well resolve following the appropriate replacement with thyroxine. Hypothyroidism is a risk factor for statin induced myopathy, therefore before increase statin dose it is important to correct thyroid profile
• Slightly raised bilirubin: In hypothyroidism, the activity of bilirubin UDP-glucuronyl transferase is decreased, resulting in a reduction in bilirubin excretion.
• Hyperprolactinemia → Hyperprolactin (hyperPRL) hypogonadism Hypothyroidism→ ↑↑TRH (thyrotropin-releasing factor) → act as prolactin-releasing factor→ release of prolactin and hyperprolactinaemia.
• Hypercarotenaemia (high blood levels of beta-carotene) → yellowing of the skin (xanthoderma). • Clinically silent pericardial effusion is common in untreated hypothyroidism (Pericardial or pleural effusions)

Anti-TPO antibodies are present in 10% females without thyroid pathology

Thyrotropin is a glycoprotein hormone (glycosylated)

If the thyroid peroxidase (TPO) antibodies during early gestation are strongly positive. What is the chance of developing hypothyroidism in the post-partum period? → 50%

Management • Levothyroxine: BNF recommends the initial starting dose as following:
 For patients with cardiac disease, or patients over 50 years: 25mcg od with dose slowly titrated.
 For other patients: 50-100mcg od • Follow-up: following a change in thyroxine dose TFT should be checked after 8-12 weeks • Target: TSH value 0.5-2.5 mU/l .

If you made a diagnosis of Hashimoto's, what is the next best step in the management?
• Rule out Addison's, short synacthen test even if the sodium is normal. Addison's may coexist with Hashimoto's, masked by the hypothyroid. Treating hypothyroid will unmask the Addison's and precipitate adrenal crisis.

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Endocrinolog & Metabolism

Monitoring Monitoring of thyroid status Thyroid-stimulating hormone (TSH) is the most sensitive indicator of thyroid status. • Normal TSH result suggests → adequate thyroxin replacement & euthyroidism • ↑↑ (TSH) with normal (T4) suggest → poor compliance
• ↓↓ (TSH) with normal - high (T4) suggests → over-replacement

Causes of persistently elevated TSH levels despite adequate thyroxine therapy: • Compliance (the commonest cause) • Drugs interaction such as: rifampicin calcium supplements (e.g. calcium carbonate) Amiodarone ferrous sulphate (give at least 2 hours apart)
 Omeprazole,
 Hormone replacement therapy (HRT) → ↑ thyroid binding proteins→ ↓ free thyroid hormone → requiring an increase in thyroxine dose. Treatment with estrogens may necessitate a dose increase. Glucocorticoids interfere with thyroid hormone metabolism and the dose of levothyroxine may need to be reduced. • Malabsorption syndromes like coeliac disease • Nephrotic syndrome

Complications • Myxedema coma
 Definition: potentially life-threatening decompensation. usually occurs in the elderly who are typically non-compliant.
 Features : impaired mental status; hypothermia; bradycardia, myxedema Treatment:
 Intravenous thyroid hormones : levothyroxine ; PLUS liothyronine Treatment with hydrocortisone is recommended until Addison’s disease can be excluded, as just giving thyroid hormone alone may precipitate an adrenal crisis. rewarming. • Primary thyroid lymphoma Hashimoto thyroiditis is the most common cause of hypothyroidism and the only known risk factor for primary thyroid lymphoma. Almost all primary thyroid lymphomas are non-Hodgkin large B-cell lymphomas. • Hashimoto's encephalopathy
 Extremely rare Considered to be part of an autoimmune encephalitis. Often, the condition presents prior to the development of hypothyroidism and patients can be entirely euthyroid yet with quite profound neurological dysfunction. Result in altered mental state, myoclonus and ataxia. Should be suspected in TSH derangement however there may be no clinical evidence of thyroid dysfunction. The next laboratory tests should be → Anti-thyroid peroxidase antibodies It is a steroid responsive encephalopathy Iron reduces the absorption of thyroxine

A history of an acutely painful, left-sided goitre in euthyroid and apyrexial patient with normal labs and no prior history of thyroid disease ? • Haemorrhage into a cyst

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Pendred's syndrome

signs of deafness and hypothyroidism Pendred's syndrome

Definition • Pendred syndrome is an autosomal recessive disorder that results in the reduced activity of pendrin. • Pendrin is importance for: Iodide transport in the thyroid gland: defect → hypothyroidism with goiter. Electrolyte homeostasis in the inner ear: defect → sensorineural hearing loss
 Maintain sodium chloride balance in the distal nephron: defect → if treated with a thiazide diuretic that inhibits NCC, severe hypovolemia and metabolic alkalosis develop.
Features • Hypothyroidism with goiter
• Sensorineural deafness • Hypovolemia and metabolic alkalosis in response to thiazide diuretics.

Diagnosis • genetic testing (Pendred's syndrome (PDS) gene, chromosome 7), (SLC26A4) • audiometry and MRI imaging to look for characteristic one and a half turns in the cochlea, compared to the normal two and a half turns.
Treatment • thyroid hormone replacement
• cochlear implants.

Riedel's thyroiditis

Definition • A chronic autoinflammatory disease, characterized by conversion of regular thyroid parenchyma to diffuse fibrous growth that may extend into the surrounding tissue.

Features • Typically presents as a painless, hard, solid thyroid enlargement (described as stony or woody.) • Extension beyond the thyroid differentiates this from the fibrosing variant of Hashimoto thyroiditis.
• Associated hypothyroidism (although most patients are euthyroid), absence of cervical adenopathy and slow course are differentiate this from anaplastic thyroid cancer. • Complications →Fibrotic invasion of adjacent anatomic structures (e.g. Hypoparathyroidism)

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Endocrinolog & Metabolism

Diagnosis • Open surgical biopsy is essential for the correct diagnosis.
• IgG4 levels are elevated in over 95% of cases.

Treatment • Steroids and tamoxifen to inhibit connective tissue proliferation. • wedge resection of the thyroid isthmus to alleviate tracheal obstruction is still the preferred surgical therapy

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Sick euthyroid syndrome

Definition
• A decrease in thyroid hormone levels that occurs in severe illness despite normal thyroid gland function. • Now referred to as non-thyroidal illness. Pathology
• Increase in 51 deiodinase Type 3 levels

Causes
• Any sever ill ness disease or organ failure
• Common in intensive care patients

Feature
• Low T4 and T3.
• TSH are typically low, but may be low-normal or normal.

Management • Changes are reversible upon recovery from the systemic illness. • the most appropriate next step in management → repeat thyroid function tests in 3 months

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Subclinical hypothyroidism

Subclinical hypothyroidism in a patient younger than 70: • TSH > 10mU/l Start levothyroxine replacement • TSH 4-10mU/l repeat the test in six months.

Diagnosis
• TSH levels above the range but with normal levels of thyroxine (T4) and triiodothyronine (T3).

Epidemiology
• found in 8–10% of the population,
• more common in young women and increases with age.

Significance • may be associated with an increased risk of cardiovascular disease

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• Adverse pregnancy outcome: ↑risk of severe preeclampsia, placental abruption, preterm birth subclinical hypothyroidism with positive anti-thyroid peroxidase (TPO) antibodies tend to have the highest risk of adverse pregnancy outcomes

Indications for treatment
• TSH > 10 • Hypothyroid symptoms (regardless TSH level) • Pregnancy or pregnancy planned in the near future

Management • TSH is between 4 - 10mU/L (on 2 separate occasions 3 months apart). If symptomatic < 65 years: give a 6-month trial of levothyroxine If there is no improvement in symptoms, stop levothyroxine In older people (especially ˃ 80 years) →follow a 'watch and wait' strategy, generally avoiding hormonal treatment' If asymptomatic → observe and repeat thyroid function in 6 months • TSH is > 10mU/L (on 2 separate occasions 3 months apart) →start treatment (even if asymptomatic)
Monitoring • Monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment

 With features suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid autoantibodies → once a year Without features suggesting underlying thyroid disease → once every 2 to 3 years.

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