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Pages 226-250

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

High triglycerides and low high-density lipoprotein (HDL) cholesterol are the commonest lipid abnormality seen in type 2 diabetes.

Complications • Increased risk of CVD events
• Increased insulin resistance

Management
• With DM → the first priority in this patient is to improve the glucose control. • JBS2 guidelines suggest that all patients with type 2 diabetes should be prescribed a statin, even if their cholesterol is within the target range. • If triglyceride level > 20 mmol/l that is not a result of excess alcohol or poor glycaemic control, refer for urgent specialist review (i.e. at a regional lipid clinic). • If triglyceride level between 10 and 20 mmol/L: Repeat the triglyceride with a fasting test (following a meal, the chylomicron level rises in the serum which will lead to a rise in triglyceride levels) Look for secondary causes
 Address lifestyle factors: encourage weight loss, healthy diet and exercise Commence high-potency statins (atorvastatin, rosuvastatin) if unable to address the triglyceride level through lifestyle measures.

Fibrates (e.g. fenofibrate).
• The best initial medical treatment for hypertriglyceridemia. • Action: PPAR alpha receptor agonists → increasing the activity of lipoprotein lipase • Does not reduce cardiovascular events in the presence of diabetes, while statins have. Thus, an isolated hypertriglyceridaemia in the presence of significant cardiovascular risk factors, in a patient not currently on a statin, should be managed with the introduction of a statin. • Concomitant fibrate-statin use is associated with an increased risk of myopathy.

Omega-3 • Trials of omega 3 supplementation suggest that it is associated with triglyceride reduction of up to 38%. • OMACOR (omega-3-acid ethyl esters) : Mode of action → Increases peroxisomal beta-oxidation of fatty acids in the liver
• 2019 ESC/EAS Guidelines for the management of dyslipidaemias: (In high-risk patients with TG between 1.5 and 5.6 mmol/L (135 - 499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 2g/day) should be considered in combination with statins • Icosapent ethyl is an ethyl ester

of the omega-3 fatty acid eicosapentaenoic acid (EPA).

Nicotinic acid • it lower both cholesterol and triglyceride concentrations by inhibiting synthesis and increases HDL-cholesterol when used in doses of 1.5-3g daily. • It is recommended for use by specialists in combination with a statin, where a statin alone

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

• Add of nicotinic acid raise HDL cholesterol level by great amount • the value of nicotinic acid is limited by its side-effects (especially vasodilatation)
• may increase blood glucose in some patients. many mechanisms have been suggested for this:
 Since nicotinic acid inhibits triglyceride synthesis, it may be that the increased availability of free fatty acids stimulates hepatic glucose output by increasing gluconeogenesis or replacing glucose as the primary energy source.
 Higher levels of fatty acids may also block glucose uptake by skeletal muscle. Direct effects on beta-cell function have also been postulated.

• For people with a triglyceride concentration between 4.5 and 9.9 mmol/L, optimize the management of other CVD risk factors present.

Which lipid abnormalities are most likely to be detected in a patient with type 2 diabetes? • Small dense LDL molecules (LDL is not typically elevated in type 2 diabetes) • ↓↓ HDL
• ↑↑Triglycerides

Question Analysis of a patient lipoprotein profile shows a deficiency of apolipoprotein C-II. All other lipoproteins are normal. Which lipid profile is most likely to be shown? Answer Elevated levels of both chylomicrons and VLDLs Apolipoprotein C-II (Apo C-II) is an essential co-factor of lipoprotein lipase, which hydrolyzes triglyceride in chylomicrons and VLDLs.

Xanthomas • Tuboeruptive xanthomas occur in type III hyperlipoproteinaemia
• Eruptive xanthomas are associated with hyperchylomicronaemia (type I and type V hyperlipoproteinaemia)
• Xanthoma tendinosum, which are nodular swellings of tendons, usually occur in type II hyperlipoproteinaemia

Notes & Notes for MRCP
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____Hyperlipidaemia: management

Graphic showing choice of statin.

Statins reduce all-cause mortality (not just cardiovascular mortality) in primary prevention

Primary prevention - risk assessment
• NICE recommend use the QRISK2 CVD risk assessment tool for patients aged ≤ 84 years. • High risk of cardiovascular disease (CVD), defined as a 10-year risk of 10% or greater.
• QRISK2 should not be used in the following situations: Patients ≥ 85 years are already at high risk of CVD due to their age
 type 1 diabetics patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria. patients with a history of familial hyperlipidaemia. • NICE suggest QRISK2 may underestimate CVD risk in the following: people treated for HIV Serious mental health problems people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs Autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus. • Measuring lipid levels The samples does not need to be fasting. repeat sample (fasting or non-fasting) before deciding on further management

In the primary prevention of CVD using statin aim for a reduction in non-HDL cholesterol of > 40%

Chapter 1

Endocrinolog & Metabolism Primary prevention management (No established cardiovascular disease) • If the QRISK2 10-year risk is ≥ 10% → Atorvastatin 20mg should be offered first-line + Lifestyle changes
• People with Type 1 diabetes mellitus: atorvastatin 20 mg should be offered if type 1 diabetics who are: age ˃ 40 years, or diabetes for more than 10 years or nephropathy or CVD risk factors. • People with type 2 diabetes → If the QRISK2 10-year risk is ≥ 10% → atorvastatin 20 mg • People with Chronic kidney disease (CKD): atorvastatin 20mg should be offered to all patients with CKD

Secondary prevention management (established cardiovascular disease) • All patients with CVD should be taking a statin in the absence of any contraindication. • Atorvastatin 80mg should be offered first-line. • Follow-up patients at 3 months: if the non-HDL cholesterol has not fallen by at least 40% → ↑the dose of atorvastatin gradually up to 80mg.

Targets of management Total cholesterol
LDL cholesterol Triglycerides < 4.0 mmol/l < 2.0 mmol/l ˂ 1.7 mmol/L Joint British Societies

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Lipid-lowering agents

Mechanism of action and adverse effects The following table compares the side-effects of drugs used in hyperlipidaemia:

Drugs Mechanism of action Adverse effects Statins HMG CoA reductase inhibitors Myositis, deranged LFTs Ezetimibe Decreases cholesterol absorption in the small intestine Nicotinic acid Decreases hepatic VLDL secretion Flushing, myositis Fibrates Agonist of PPAR-alpha therefore increases lipoprotein lipase expression Cholestyramine Decreases bile acid reabsorption in the small intestine, upregulating the amount of cholesterol that is converted to bile acid PPAR-α agonists (The fibrate) → ↓serum triglyceride levels and ↑ HDL-cholesterol PPAR-γ agonists (the glitazones) → ↓free fatty acid levels → ↓insulin resistance → ↓blood glucose levels Notes & Notes

for MRCP
By Dr. Yousif Abdallah Hamad

Headache Myositis, pruritus, cholestasis GI side-effects

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Statins

Action • Statins inhibit the action of HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis Metabolism • Simvastatin, atorvastatin and lovastatin are mainly metabolized by cytochrome P450 (CYP) 3A4. • Fluvastatin and rosuvastatin is metabolized by CYP2C9 • Pravastatin is excreted largely unchanged.

Pravastatin may be suitable for primary prevention, but in high-risk secondary prevention patient, a stronger agent is required such as rosuvastatin.

Adverse effects • Myopathy: includes myalgia, myositis, rhabdomyolysis and asymptomatic raised creatine kinase.
 Occurs in up to 5%. More common in lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (rosuvastatin, pravastatin, fluvastatin) If only myalgia (muscle pain): continue treatment as long as creatinine phosphokinase (CK) remain normal.
 Before offering a statin, if CK levels are 5 times the upper limit of normal (repeated 2 times), do not start statin treatment. If CK levels are raised but less than 5 times the upper limit of normal, start statin treatment at a lower dose. Starting at a low dose and gradually titrating up can also minimise the risk of side effects: for example, start at 5 mg of rosuvastatin. • Hepatotoxicity:
 Occurs in ~ 2% of patients ↑ LFTs due to the involvement of cytochrome P450 systems (CYP3A4 and CYP2C9) in the breakdown of statins
 Check LFTs at baseline, 3 months and 12 months, but not again unless clinically indicated. Statins should be discontinued if serum transaminase concentrations rise to and persist at 3 times the upper limit of the reference range. If LFT are raised but less than 3 times the upper limit of normal:
 1st step: NICE advises reducing the dose in the first instance.
 2nd step: Consider an alternative statin. • Statins may increase the risk of intracerebral haemorrhage in patients who've previously had a stroke. For this reason the Royal College of Physicians recommend avoiding statins in patients with a history of intracerebral haemorrhage. This effect is not seen in primary prevention.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

Maintain a high index of suspicion for rhabdomyolysis if muscle pain occurs after administering statins Drug interactions with statins P450 inhibitors ↑ CK and myopathy

• P450 inhibitors (e.g. HIV protease inhibitors, Macrolides (especially erythromycin and clarithromycin), Azole antifungals, Cyclosporine, grapefruit juice) → ↑ serum statins → precipitate Myopathy or rhabdomyolysis • Other lipid-lowering agents (e.g. Fibrates and Nicotinic acid) • Agents which can precipitate Myopathy or rhabdomyolysis calcium channel blockers Which statin is associated with the lowest risk of rhabdomyolysis? Fluvastatin

Lipid lowering drugs and pregnancy
• Normally in pregnancy, cholesterol can increase by up to 50%
• Omega-3 fatty acids can be used safely in pregnancy as monotherapy, and function to decrease maternal TG levels.
• With the exception of the bile acid sequestrants (BAS) such as cholestyramine , cholesterol-lowering medications should be stopped prior to pregnancy • NICE guidelines recommend stopping cholesterol-lowering medications 3 months before attempting to conceive.

Contraindications

1. Active liver disease
2. Muscle disorder
3. Pregnancy, breastfeeding: stop taking statins 3 months before attempt to conceive and do not restart until breastfeeding is finished.

Fibrates
Agents • bezafibrate, fenofibrate, and gemfibrozil Mechanism of action • Activation of the peroxisome proliferator-activated receptor alpha (PPAR–α) → ↓ LDL, ↑ HDL, ↓↓↓ triglyceride
• Enhance lipoprotein lipase activity Indication • second-line drug of choice in hyperlipidemia, most effective for lowering triglycerides Contraindications • Renal insufficiency
• Liver failure • Gall bladder diseases Side effects • Dyspepsia • Myopathy
• Cholelithiasis (Cholesterol gallstones) • ↑ LFTs (hepatotoxicity) Interactions
• enhance the effect of other drugs by inhibiting hepatic CYP450 (e.g., sulfonylureas, warfarin)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Ezetimibe

Ezetimibe → reduces the absorption of cholesterol through the gut.

Mechanism of action
• Blocks cholesterol reabsorption at small intestine brush border via inhibiting NPC1L1 in the gut lumen → ↓ LDL
Indication • Monotherapy: in contraindications or statin intolerance • Combination therapy (statin and ezetimibe): in insufficient LDL cholesterol reduction by statins
Side effects (especially in combination therapy, otherwise rare):
• ↑ liver enzymes,
• angioedema,

• diarrhea,
• myalgia Contraindication • coadministration with a statin during active liver disease

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Nicotinic acid (niacin)

Mechanism of action • Inhibits lipolysis and fatty acid release in adipose tissue → ↓ triglyceride and LDL synthesis, ↑ HDL • Niacin lowers LDL-C and increases HDL-C by: ↓ hepatic VLDL synthesis and secretion into circulation,
 ↓ lipolysis in peripheral adipose tissue. Indication
• high LDL cholesterol and lipoprotein(a) levels (> 50 mg/dL) despite statin and ezetimibe therapy (or if statins are contraindicated) • Nicotinic acid is highly effective at raising high density lipoprotein (HDL) cholesterol

Adverse effects • Flushing: NSAIDs (e.g., aspirin, ibuprofen) taken 30–60 minutes before niacin can prevent flushing by inhibiting prostaglandin synthesis.
• Hyperglycemia (impaired glucose tolerance) →↑ HA1c in diabetics • Irritates the gastric mucosa, exacerbates gastroesophageal reflux. contraindicated in patients with active peptic ulcer disease • Myositis • Hyperuricemia → precipitates acute gout • ↑ LFTs Contraindications

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

• Liver failure • Gout • Hemorrhage • Gastric ulcer • Cardiovascular instability

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Cholestyramine Mechanism of action • bile acid sequestrant • bind bile acids in the intestine to prevent reabsorption and recycling forces liver to consume cholesterol in the process of making more bile salts binds bile acids in the intestine → interruption of enterohepatic circulation (↓ bile acid absorption and ↑ bile acid excretion) → lowers cholesterol • The main effect on lipid profile reduce LDL cholesterol (↓ unbound LDL), causes ↑ in LDL-receptor synthesis Indications • management of hyperlipidaemia. Combination treatment with statins in hypercholesterinemia • Digitoxin overdose • Pruritus associated with elevated bile acid levels (cholestasis) • Bile acid diarrhea • Bowel obstruction • occasionally used in Crohn's disease for treatment resistant diarrhoea. Adverse effects • abdominal cramps and constipation • decreases absorption of fat-soluble vitamins (e.g: vitamin D absorption will be reduced) consider fat-soluble vitamin (vitamins A, D and K) and folic acid supplementation • cholesterol gallstones • ↑ LFTs • Myalgia • may raise level of triglycerides

Contraindications • Hypertriglyceridemia > 300–500 mg/dL • Hypertriglyceridemia-induced pancreatitis

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Tangier disease
Overview • rare autosomal recessive metabolic disorder. • also known as familial alpha-lipoprotein

deficiency or hypoalphalipoproteinemia
Features • Decreased levels or even a complete absence of high-density lipoproteins (HDL)
• Low cholesterol levels
• cholesterol ester depositions especially in: Tonsils → enlarged, yellow-orange tonsils. Liver and spleen resulting in hepatosplenomegaly.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Abetalipoproteinemia

Pathophysiology • Rare autosomal recessive disorder
• Mutation in the microsomal triglyceride transfer protein → deficiency of apolipoprotein B48 and B-100 (both necessary for chylomicron formation and fat absorption) → deficiency of LDL, VLDL and chylomicrons.
Features Typically presents in early childhood with steatorrhea, abdominal distension, and failure to thrive. During childhood or adolescence, progressive ataxia, neuropathy, and vision impairment develop.

• Neurologic: caused by deficiency of vitamin E) cognitive decline
 Clumsiness may be the first neurologic manifestation • Low visual acuity, caused by:
 Retinitis pigmentosa → do fundoscopy Vitamin A deficiency Treatment • high-dose vitamin E
• other fat-soluble vitamins (A, K, and D) should also be supplemented
• restriction of long-chain fatty acids

Causes of hypocholesteraemia • Acquired: Malignancy Malabsorption (Short-bowel syndrome, blind loop syndrome, celiac disease, pancreatic exocrine insufficiency, giardiasis) Anaemia (Thalassemia, pernicious anaemia) Chronic infection and infestations Severe illness in hospitalised patients • Genetic:
 Hypobetalipoproteinemia (most common genetic cause),
 Abetalipoproteinemia

Treatment of abetalipoproteinemia involves dietary restriction of fats, and high-dose vitamin E therapy Disease associations with low LDL-C include malignancy and malabsorption

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

Gynaecomastia Definition
• Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen: androgen ratio.
Causes
• It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia • physiological: normal in puberty • syndromes with androgen deficiency: Kallman's, Klinefelter's (47, XXY karyotype) • testicular failure: e.g. mumps • liver disease • testicular cancer e.g. seminoma secreting hCG • ectopic tumour secretion • hyperthyroidism • haemodialysis • starvation/refeeding • drugs: see below

Drug causes of gynaecomastia (10-25% of cases) Relatively Common causes • spironolactone (most common drug cause) • cimetidine • digoxin • cannabis • diamorphine • cyproterone • finasteride • gonadorelin analogues e.g. Goserelin, buserelin • oestrogens, anabolic steroids Very rare drug causes of gynaecomastia • tricyclics • isoniazid • calcium channel blockers • heroin • busulfan • methyldopa

September 2010 exam: H/O developed excessive amounts of breast tissue bilaterally. Which one of the following drugs is most likely to be responsible? Goserelin (Zoladex)

Physiological changes during pregnancy – endocrine

pregnancy → ↑ oestradiol & prolactin + ↓ LH/FSH.

Progesterone • Responsible for pregnancy maintenance • Produced by the corpus luteum until the 10–12 weeks of gestation, after which it is produced by the fetoplacental unit

Human placental lactogen: a hormone synthesized by syncytiotrophoblasts of the placenta, which promotes the production of insulin-like growth factors. • Increases insulin levels • Causes insulin resistance

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• Increases serum glucose levels and lipolysis to ensure sufficient glucose supply for the fetus • Maternal insulin resistance begins in the second trimester and peaks in the third trimester.

Pituitary gland
• Hyperplasia of lactotroph cells in the anterior pituitary → physiological enlargement of the pituitary gland (up to 40% increase from pregestational volume)

Thyroid gland • Thyroid gland hypertrophy The thyroid gland needs to produce 50% more thyroid hormone during pregnancy to maintain an euthyroid state. A 10–20% increase in thyroid mass occurs. • Increase in thyroid-binding globulin and albumin due to increased hepatic synthesis. Pregnancy → ↑↑ thyroxine-binding globulin (TBG) → ↑↑ total thyroxine but does not affect the free thyroxine level • Increase in total T3 and T4 in normal pregnancy (T3) and T4 levels show a slight increase with suppressed (TSH) in the first trimester due to the partial thyroid-stimulating action of human chorionic gonadotrophin (beta-HCG). Free T3 and T4 remains within normal ranges • β-hCG-mediated hyperthyroidism (↓TSH) β-hCG molecule has a similar structure to that of the TSH molecule. β-hCG binds to TSH receptors of the thyroid gland → thyroid stimulation → hyperthyroidism

• Factors influence thyroid function tests in the pregnant patient.
 thyroid stimulatory effects of hCG.
 HCG → activation of the TSH receptor → transient gestational hyperthyroidism.
 HCG levels will fall in second and third trimester
Lipids • ↑ Triglycerides and cholesterol (due to increased lipolysis and fat utilization)

↑ SHBG (Sex hormone-binding globulin) and corticosteroid-binding globulin

Beta-HCG has a degree of thyroid stimulating activity →↓↓ TSH. No intervention is needed

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Physiological effects of LH, FSH, and sex hormones • ♀: Ovaries FSH: follicular maturation → ↑ estrogen LH: ↑ estrogen, ovulation, and ↑ progesterone
• ♂: Testicles FSH: production of sperm, ↑ inhibin LH: stimulation of Leydig cells → ↑ production of testosterone

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

Dihydrotestosterone (DHT) Composition • Testosterone is a steroid hormone and can be converted to oestradiol. Production • LH stimulates testosterone production and FSH spermatogenesis Binding • It binds to intracellular receptors and is mostly bound to sex-hormone binding globulin (SHBG) Conversion • Testosterone converted to dihydrotestosterone (DHT) in the body by the enzyme 5αreductase. DHT is a more active compound than testosterone. • The absence of 5α-reductase or the absence of DHT receptors leads to testicular feminisation. Function • During fetal development and early life: differentiation of the penis, scrotum, and prostate.
• expression of male secondary sex characteristics • During late adulthood: prostate growth, male pattern baldness, and sebaceous gland activity.
Deficiency • →↓ testosterone is due to either:
 ↓ free level due to ↓ production (Leydig and pituitary dysfunction) (Lead to ↑ synthesis of SHBG) increasing age: total testosterone concentrations fall slightly, and free testosterone fall more. ↓ activity at receptor often due to androgen receptor deficiency (5α-reductase deficiency).

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

 Patients with 5α-reductase deficiency will have ambiguous genitalia at birth until they reach puberty, when the testosterone surge causes growth of external male genitalia, however, these patients are otherwise healthy. Individuals with this deficiency sometimes change their gender role in adolescence. obesity (hyperinsulinaemia of obesity → ↓SHBG levels → ↓testosterone (low SHBG and normal free testosterone)
Evaluation • Initial evaluation: serum testosterone in the early morning, fasting. • Testosterone levels vary according to the degree of binding to albumin and SHBG; (↑SHBG ↑total testosterone

- when testosterone production is low-). • The equilibrium dialysis method is most useful for measurement of free testosterone (not bound to protein) • If the testosterone is low: measurement of LH and FSH to determine if the hypogonadism is primary or secondary. If secondary assessment of other pituitary hormones.
 If the patient has multiple pituitary hormonal deficiencies and/or if the testosterone is less than 200 ng/dL, we suggest MRI of the sella. Testosterone therapy • Indications hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency.
 Older men (>65 years) with age-related decline in testosterone concentration: routinely prescribing testosterone therapy is not recommended
 In symptomatic (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone, testosterone therapy may be offered on an individualized basis after discussion of the potential risks and benefits. HIV-infected men with weight loss and low testosterone (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain. • Target
 For patients receiving testosterone enanthate, the testosterone level should be between 400 and 700 ng/dL at about half-way between administrations (one week after injection) which are generally given every two weeks. • Which type of testosterone therapy is most likely to result in an increase in dihydrotestosterone level? Dihydrotestosteone levels increase with the use of a testosterone scrotal patch due to the high concentration of 5α-reductase in genital skin. Levels may return to normal after discontinuation; however, they often remain elevated.

• Benefits of testosterone treatment ↑sexual interest and activity, slight improvement in walking, slight improvement in mood, ↑ hemoglobin, and ↑ bone mineral density (BMD). No change in energy or cognition is expected. • Side effects Erythrocytosis leading to elevated haematocrit Haematocrit should be measured 3-6 months after initiating therapy and yearly thereafter.
 Guidelines suggest that if haematocrit is increased and no other underlying cause is found, the dose should be down-titrated. PSA
 Androgen replacement therapy is contraindicated in patients with prostate cancer and breast cancer.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

 Urological consultation is recommended if: ↑PSA > 1.4 ng/mL within a 12-month period,
 a PSA velocity > 0.4 ng/mL/year using the level after 6 months of testosterone therapy as the reference abnormality on digital rectal examination, or
 an I-PSS score of greater than 19.

Polycystic ovarian syndrome (PCOS)

Incidence • affect between 5-20% of women of reproductive age. Aetiology • not fully understood • Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS

Features • Oligo/amenorrhoea 70% • hirsutism, acne (due to hyperandrogenism) 60% • obesity 35%
• subfertility and infertility 30%.
 Chronic anovulation is the mechanism for infertility • acanthosis nigricans (due to insulin resistance) • psychological symptoms • Clitoromegaly is seen occasionally in PCOS but is normally associated with very high androgen levels. If clitoromegaly is found, then further investigations to exclude an ovarian or adrenal androgen secreting tumour are required.

Investigations • pelvic ultrasound: multiple cysts on the ovaries transvaginal ultrasound is said to have 91% diagnostic sensitivity
 The presence of more than eight follicular cysts of less than 10 mm and increased ovarian stroma is sufficient to make the diagnosis. • FSH, LH, prolactin, TSH, and testosterone are useful investigations: FSH will be normal or low, while LH will be elevated. Increased LH causes hyperplasia of ovarian theca cells. Increased LH causes increased testosterone and androstenedione Raised LH: FSH ratio is a 'classical' feature but is no longer thought to be useful in diagnosis. LH/FSH ratio is normally about 1:1 in premenopausal women, but with PCOS a ratio of greater than 2:1 or 3:1 may be considered diagnostic.
 Prolactin may be normal or mildly elevated. 10% of patients with PCOS have hyperprolactinaemia,
 elevation in prolactin due to the low oestrogen stimulating GnRH, which in turn stimulates the anterior pituitary hormones including prolactin.

 However, the elevation in prolactin in PCOS rarely exceeds 1000 mU/l. Testosterone may be normal or mildly elevated however, if markedly raised consider other causes The appropriate initial biochemical investigation Normal or elevated testosterone, but with a low sexhormone-binding globulin (SHBG) level, resulting in a high free androgen index. Sex hormone-binding globulin (SHBG) is frequently low (SHBG) is a transporter protein that binds to both testosterone and oestradiol;
 it is reduced in insulin resistance, which is common in (PCOS).
 (SHBG) is low in 50%, due primarily to hyperinsulinaemia. The reasons include that androgens reduce the globulin production, whereas oestrogen promotes production.
 Many women with PCOS have a high-normal or even a normal total testosterone, but a low SHBG because they have insulin resistance. hyperestrogenism
 Increased androstenedione/testosterone in PCOS can be peripherally converted in adipose tissue to estrone by aromatase. increased circulating levels of estrone endometrial hyperplasia which is a precursor to endometrial carcinoma

• Impaired glucose tolerance hyperinsulinaemia (insulin resistance → high circulating insulin levels due to peripheral insulin resistance).
 Up to 40% of women with PCOS have impaired glucose tolerance,
 up to 10% develop frank Type 2 diabetes mellitus

long term complication of PCOS: • risks of diabetes (due to peripheral insulin resistance),
• sleep apnoea,
• endometrial cancer, • mental health disorders.

Diagnostic criteria • According to the Rotterdam Consensus, two of the following three criteria are required for the diagnosis of the PCOS:

1. oligo-/anovulation
2. hyperandrogenism clinical (hirsutism or less commonly male pattern alopecia) or biochemical (raised free androgen index or free testosterone)
3. polycystic ovaries on ultrasound.

Management • General Weight reduction: the gold-standard treatment for PCOS. A loss in weight of only 5% reduces hirsutism by up to 40%.

• For associated hirsutism
o Dianette® (cyproterone acetate) combined oral contraceptive pill (COC) is the most effective o if doesn't respond to COC then topical eflornithine may be tried o Spironolactone, flutamide and finasteride may be used for its antiandrogenic properties

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

• For infertility Initial step →weight loss
 First- line drug: Anti-oestrogen therapies such as clomifene → the most effective treatment work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion Second-line drug: Metformin is also used, either combined with clomifene or alone, particularly in patients who are obese but is not a first line treatment
 Gonadotrophins: usually reserved for patients who are resistant to clomifene

MRCPUK-part-1-May 2009 exam: H/O infertility with PCOS. Apart from advising her to lose weight, which intervention is most effective in increasing her chances of conceiving? Clomifene (if clomifene – the first line - is not an option, metformin – the second line - is the right answer)

September 2009 exam: Which finding is most consistently seen in polycystic ovarian syndrome? Ovarian cysts on ultrasound

MRCPUK-part-1-January 2012 exam: What is the mechanism of action of metformin in PCOS? Increases peripheral insulin sensitivity

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Hirsutism Hirsutism is often used to describe androgen-dependent hair growth in women Hypertrichosis used for androgen-independent hair growth

Definition • Excessive male pattern hair growth in women (e.g., on the chin, above the upper lip, and around the umbilicus) Causes • Idiopathic (the most common): normal menstrual cycle, normal serum androgen, , and no identifiable cause hirsutism. • Polycystic ovarian syndrome is the most common identifiable causes of hirsutism • Excess androgen (10% of cases): hirsutism, acne, menstrual dysfunction, alopecia. Cushing's syndrome congenital adrenal hyperplasia androgen therapy obesity: due to peripheral conversion oestrogens to androgens androgen secreting ovarian tumour • Drugs

Assessment of hirsutism • Mild hirsutism and normal menses → do not require laboratory workup and can be treated empirically. • Moderate or severe symptoms → early morning total testosterone level
 if moderately elevated, it should be followed by a plasma free testosterone level.
 A total testosterone level greater than 200 ng per dL (6.94 nmol per L) should prompt evaluation for an androgen-secreting tumor.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• Testing for endocrinopathies and neoplasms, such as polycystic ovary syndrome, adrenal hyperplasia, thyroid dysfunction, Cushing syndrome, and androgen-secreting tumors.

Management
• Advise weight loss if overweight • Hair removal (Shaving) • Pharmacologic measures
 Combined oral contraceptive pills: first-line pharmacologic treatment Facial hirsutism: topical eflornithine - contraindicated in pregnancy and breastfeeding Treatment response should be monitored for at least six months before making adjustment.

Hypertrichosis
Definition • excessive hair growth above the normal for the age, sex and race of an individual, in contrast to hirsutism, which is excess hair growth in women following a male distribution pattern.

Causes
• Drugs:
 phenytoin
 minoxidil (antihypertensive vasodilator. also used to treat androgenic alopecia slows hair loss and promotes hair regrowth) ciclosporin diazoxide • Congenital hypertrichosis lanuginosa, congenital hypertrichosis terminalis • Metabolic disorders thyroid dysfunction porphyria cutanea tarda
 anorexia nervosa Treatment • Hair removal

Amenorrhoea

Primary amenorrhoea
• Definition: failure to start menses by the age of 16 years
• Causes Turner's syndrome testicular feminisation congenital adrenal hyperplasia

congenital malformations of the genital tract Secondary amenorrhoea
• Definition absence of menses for more than 3 months (in women with previously regular cycles) or 6 months (in women with previously irregular cycles) • Causes
 Pregnancy → most common cause of secondary amenorrhea hypothalamic amenorrhoea (e.g. Stress, excessive exercise) ↓ FSH

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

 Weight-related amenorrhoea amenorrhoea can even be seen at the lower end of the normal range. often seen in ballet dancers, who maintain a low weight and undergo periods of extreme physical exercise. Gaining body weight to above the 50th centile for height normally results in the restoration of menstruation, but if this cannot be achieved oestrogen replacement might be considered. polycystic ovarian syndrome (PCOS) hyperprolactinaemia premature ovarian failure ↑ FSH thyrotoxicosis (hypothyroidism may also cause amenorrhoea) Hypothyroidism (↓ T3/T4 → ↑ TRH → ↑ prolactin → ↓ GnRH → ↓ estrogens) Sheehan's syndrome Asherman's syndrome (intrauterine adhesions) Initial investigations • exclude pregnancy with urinary or serum bHCG • gonadotrophins: low levels indicate a hypothalamic cause whereas raised levels suggest an ovarian problem (e.g. Premature ovarian failure) • prolactin • androgen levels: raised levels may be seen in PCOS • oestradiol • thyroid function tests

Primary ovarian failure means that the patient never has a normal menstrual cycle, and has the triad of

1. amenorrhea,
2. hypergonadotropinism,
3. hypoestrogenism.

Premature ovarian failure

The history of prolonged cessation of menses with a normal weight, normal thyroid function tests and a history of coeliac disease is pointed to a diagnosis of premature ovarian failure

Criteria for diagnosis

1. age under 40 years
2. menopausal symptoms (including no or infrequent periods)
3. and elevated FSH levels on 2 blood samples taken 4–6 weeks apart.

Epidemiology • occurs in around 1 in 100 women.

Causes • idiopathic - the most common cause • chemotherapy • autoimmune • radiation

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Features
• secondary prolonged amenorrhoea
• infertility • climacteric symptoms: hot flushes, night sweats

Investigations • raised FSH, LH levels • ↓↓oestradiol
• sex hormone releasing hormones would be elevated in an attempt to drive LH and FSH release.

Treatment

• Hormone replacement therapy (HRT) or a combined hormonal contraceptive to protect against osteoporotic fracture. HRT may have a beneficial effect on blood pressure when compared with a combined oral contraceptive both HRT and combined oral contraceptives offer bone protection HRT is not a contraceptive. • Spontaneous recovery of fertility is unlikely (occurs in only 5%).

Menopause

Definitions • Peri-menopause → aged over 45,vasomotor symptoms and irregular periods • menopause → aged over 45, no period for at least 12 months, not associated with a pathology and not using hormonal contraception.

Symptoms • Usually preceded by 4–5 years of abnormal menstrual cycles. • vasomotor symptoms (e.g. hot flushes and sweats): most common • musculoskeletal symptoms (for example, joint and muscle pain) • effects on mood (e.g. low mood) • urogenital symptoms (e.g. vaginal dryness) • Sexual difficulties (e.g. low sexual desire). • Women with obesity tend to suffer from fewer symptoms in menopause due to peripheral conversion of androgens to estrogen in adipose tissue. • Most symptoms will disappear spontaneously within 5 years after onset.

Consequences • ↓↓ bone mineral density → osteoporotic fractures. • ischaemic heart disease, • ↓↓ insulin sensitivity
• ↑↑ thrombotic tendency.
• Increased possibility of developing Alzheimer's dementia Oestrogen deficiency might play a role in the development of dementia.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

Investigations
• ↓ estradiol, ↓ progesterone, ↓ inhibin B • ↑ GnRH, ↑↑ FSH and ↑LH (↑↑FSH is specific for menopause) • Vaginal pH > 4.5 • Lipid profile: ↑ total cholesterol, ↓ high-density lipoprotein (HDL)
• Testosterone and prolactin levels are within normal ranges (androstenedione is produced by ovarian stromal cells and the adrenal glands.)

Management • Vasomotor symptoms →hormone replacement therapy (HRT) women with a uterus → oestrogen and progestogen Women without a uterus →Oestrogen alone. • Psychological symptoms → low mood or anxiety → HRT & CBT
 women with low sexual desire → testosterone supplementation if HRT alone is not effective. • Urogenital atrophy → vaginal oestrogen (including those on systemic HRT), also in whom systemic HRT is contraindicated.

The ovaries' failure to produce estrogen begins in the late 30s and progresses to the degree that most women have near-complete loss of estrogen production by their mid-50s.

Whereas taking estrogen alone increases the risk of endometrial cancer, taking both estrogen and a progestogen in combination, as in most birth control pills, decreases the risk.

All postmenopausal women above the age of 65 should be screened for osteoporosis (i.e., using the DEXA scan to measure bone mineral density).

Hormone replacement therapy (HRT)

• Hormone replacement therapy (HRT) involves the use of a small dose of oestrogen, combined with a progestogen (in women with a uterus), to help alleviate menopausal symptoms.

Unopposed oestrogen therapy is most appropriate for patient who had a hysterectomy and combined hormone replacement therapy (HRT) is unnecessary.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Indications • vasomotor symptoms such as flushing, insomnia and headaches (The main indication) • Premature menopause: should be continued until the age of 50 years. Most important reason is preventing the development of osteoporosis

Types • Estrogen therapy: for women who have had a hysterectomy • Estrogen plus progestin therapy: for women with a uterus

Advantages of hormone replacement therapy (HRT)

1. improvement in menopausal symptoms
2. protection against fractures of the wrist, spine, and hip secondary to osteoporosis.
3. reduce incidence of colorectal cancer
4. reduce incidence of Alzheimer's

• Hormone replacement therapy and effects on bone mass Reduction in total-body bone mass begins in women in their late twenties This loss is accelerated at the menopause Both trabecular bone loss at the level of the vertebrae and cortical bone loss at the radius are prevented by oestrogen therapy The risk of osteoporotic fractures is reduced, but not eliminated, by oestrogen therapy If the uterus has been removed in a patient, there is no need for additional

progesterone therapy The effect of oestrogens on bone loss may be reduced after 10 years of oestrogen therapy

Adverse effects • Cancer Unopposed estrogen can result in endometrial hyperplasia → increased risk of endometrial cancer Estrogen plus progestin therapy → increased risk of breast cancer • Thromboembolism: Cardiovascular disease: coronary heart disease, deep vein thrombosis, pulmonary embolism, stroke

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Selective Estrogen Receptor Modulators (SERMs)

Raloxifene
• Mechanism of action estrogen antagonist in breast and endometrium agonist in bone to increase mineralisation
• Clinical use osteoporosis in menopausal women breast cancer prevention in women high risk for breast cancer

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By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism • Toxicity ↑ risk of venous thromboembolism induces menopause →hot flashes

Tamoxifen • Mechanism of action mixed oestrogen-receptor antagonist and partial agonist depending on the target tissue estrogen antagonist in breast estrogen agonist in endometrium and bone • Clinical use estrogen and progesterone receptor positive breast cancer breast cancer prevention in women high risk for breast cancer • Toxicity ↑ risk of venous thromboembolism
 ↑ risk of endometrial cancer secondary to agonist activity induces menopause →hot flashes

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Androgen insensitivity syndrome

The testosterone which is in the male range, the history of hernias as a baby and absence of acne or secondary sexual hair are all pointers towards androgen insensitivity syndrome.

The presence of breast development in the absence of secondary sexual hair, with a history of hernias as a child is suggestive of a diagnosis of androgen insensitivity syndrome. It is likely that the hernias were related to undescended testes. The vagina is blind ended, and there are no ovaries.

Pathophysiology
• X-linked recessive mutation of the gene encoding the androgen receptor (AR gene) → Defects in the androgen receptor → end organ insensitivity to androgens. end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype.
• Complete androgen insensitivity syndrome is the new term for testicular feminisation syndrome Features • Primary amenorrhoea • Undescended testes causing groin swellings, Cryptorchidism

(absence of one or both testes from the scrotum) • External genitalia ranges from normal female to female with clitoromegaly, to underdeveloped male (hypospadias) → Associated with abdominal hernias. • Breast development may occur as a result of conversion of testosterone to oestradiol • Blind-ended vaginal pouch, uterine and fallopian tube agenesis (due to testicular antiMullerian hormone secretion) • Scant or no pubic hair

Diagnosis • High level of LH
• ↑ Oestrogen • Normal/↑ testosterone levels (no virilization)
• Buccal smear or chromosomal analysis to reveal 46XY genotype

Management • Counselling - raise child as female • Bilateral orchidectomy (increased risk of testicular cancer due to undescended testes) • Oestrogen therapy

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Disorders of sex hormones The table below summarises the findings in patients who have disorders of sex hormones: Disorder LH Testosterone Primary hypogonadism (Klinefelter's syndrome) High Low Hypogonadotrophic hypogonadism (Kallman's syndrome) Low Low Androgen insensitivity syndrome High Normal/high Testosterone-secreting tumour Low High

Menstrual cycle The menstrual cycle may be divided into the following phases: Follicular phase (proliferative phase) (from day 1 until day 14) Ovarian histology • A number of follicles develop. • One follicle will become dominant around the mid-follicular phase Endometrial histology • Proliferation of endometrium • Endometrium changes to Hormones • A rise in FSH results in the development of follicles which in turn secrete oestradiol • When the egg has matured, it secretes enough oestradiol to trigger the acute release of LH. This in turn leads to ovulation • Graafian follicle is a large mature tertiary follicle containing an oocyte that is ready to be ovulated.
• Ovulation occurs 14 days before menses, regardless of cycle length. • estradiol stimulates the growth of the endometrium. • Progesterone levels are low • FSH activates aromatase within Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Luteal phase (secretory phase) (From day 15 until day 28)
• Corpus luteum secretory lining under influence of progesterone • corpus luteum produces (3 hormones) estrogen, inhibin, and progesterone. • progesterone is significantly higher than in other phases of the menstrual cycle. • If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall

Chapter 1

Endocrinolog & Metabolism Follicular phase (proliferative phase) (from day 1 until day 14) granulosa cells, increasing estradiol production. • The main hormone controlling the follicular phase is estradiol, secreted by Granulosa cells.
Cervical mucus • Following menstruation the mucus is thick and forms a plug across the external os • Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed spinnbarkeit Basal body temperature • Falls prior to ovulation due to the influence of oestradiol

Which hormone levels would be most likely to indicate the occurrence of ovulation? Luteinising hormone

At which point in the menstrual cycle do progesterone levels peak? Luteal phase Progesterone is secreted by the corpus luteum following ovulation.

Which mechanism is most likely responsible for the missed period in early pregnancy? Syncytiotrophoblast produces human chorionic gonadotropin (hCG), which stimulates progesterone production by the corpus luteum.

Hypogonadism

Primary hypogonadism (Hypergonadotropic hypogonadism)

if LH and FSH are not elevated a primary hypogonadism is excluded. • Pathophysiology gonadal insufficiency (↓ testosterone, ↓ estrogen) → ↑ gonadotropin secretion (↑ FSH and ↑ LH) from the anterior pituitary (lack of negative feedback from the impaired gonads) • Causes Congenital abnormalities: (Primary gonadal insufficiency):
 Turner syndrome (females) Klinefelter syndrome (males) androgen insensitivity syndrome
 Acquired diseases: (Secondary gonadal insufficiency) →(damage to leydig cells or ovarian tissue): Notes & Notes for MRCP
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Luteal phase (secretory phase) (From day 15 until day 28)
• Under the influence of progesterone it becomes thick, scant, and tacky • Rises following ovulation in response to higher progesterone levels

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

 Medications (Radiation, chemotherapy, Ketoconazole, Glucocorticoids, toxins)
 Autoimmune disease Infections (mumps, tuberculosis) Tumour, infiltration (Testicular tumour) Chronic systemic illnesses (eg: Hepatic cirrhosis, Chronic renal failure) Ageing: Andropause (↓ testosterone with age ˃50). Primary testicular failure (idiopathic failure). • Investigations ↑LH & FSH + ↓ testosterone + ↓ sperm count
 Testicular ultrasound (the most important investigation after blood hormones)

Secondary hypogonadism (hypogonadotrophic hypogonadism)

• Pathophysiology ↓ pituitary gonadotropins (↓ FSH and ↓ LH) → ↓ testosterone and ↓ estrogen
• Causes Genetic defects: (e.g., Kallmann syndrome, Prader-Willi syndrome, Gaucher disease) Hypothalamic and/or pituitary lesions due to: Neoplasm (e.g. prolactinoma, craniopharyngioma, astrocytoma) Malnutrition (e.g., anorexia nervosa)
 Chronic diseases (e.g., inflammatory bowel disease, hypothyroidism, cystic fibrosis, diabetes and obesity.) • Investigations serum testosterone and sperm count are subnormal + normal or reduced LH and FSH

 Prolactin level (↑Prolactin reduces LH and FSH)
 measure of free testosterone (as total testosterone can be low due to SHBG being decreased in obesity and with ageing). Pituitary MRI : the best image to exclude other pituitary pathology.

Clinical features • Delayed puberty • Developmental abnormalities with genitalia (undescended testes, hypospadias) • Infertility (↓ sperm count), impotence, and/or ↓ libido • Secondary amenorrhea

Treatment
• Treat underlying cause: e.g., surgical excision of tumors, pharmacotherapy for prolactinomas • Hormone replacement therapy

Poor ability to concentrate is most consistent with post-pubertal loss of testicular function, whereas (High-pitched voice, Gynecomastia, Disproportionately long arms and legs, Scant pubic and axillary hair) are most consistent with hypogonadism that develops before puberty. In male patients with low libido have been found to have a low testosterone first line investigation should include prolactin and LH to assess for a central cause

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Revision #1
Created 2026-01-06 17:51:16 UTC by Omar Ayman
Updated 2026-01-06 17:51:16 UTC by Omar Ayman