Chapter 21

Therapy-related issues: endocrine system

Diabetes mellitus

Diabetes mellitus (DM) affects approximately 4% of the UK population. In 2009, Diabetes UK reported that 2.6 million people in the UK have diabetes.

Type 2 diabetes accounts for 90% of all diabetes and is a result of insulin resistance and pancreatic β-cell dysfunction. Type 1 diabetes results from an absolute insulin deficiency secondary to autoimmune dysfunction.

Diabetes is the leading cause of kidney failure and the leading cause of blindness in 20–74-year-olds. Among diabetics, the risks for stroke, heart disease, and death from heart disease are 2–4 times higher than those of the non-diabetic population. Diabetes accounts for more than 60% of all non-traumatic lower limb amputations.

Diabetes is likely to reach epidemic proportions in the UK unless there are significant efforts to tackle lifestyle issues such as obesity and lack of exercise.

Oral therapy is used alone in the early stages and in combination with insulin to treat type 2 diabetes. Insulin is used as monotherapy in type 1 diabetes and in some type 2 patients.

Diagnosis

The main symptoms with which a patient with undiagnosed diabetes can present include:

- polydipsia
- polyuria
- nocturia
- extreme tiredness
- unexplained weight loss
- reduced wound-healing rates
- blurred vision
- genital itch/frequent episodes of thrush.

Together with these symptoms, a diagnosis of diabetes can be confirmed when any of the following results are noted in clinical tests.

- A random plasma glucose level ≥11mmol/L.
- A fasting plasma glucose ≥7mmol/L.
- A 2h plasma glucose concentration ≥11mmol/L after 75g glucose load in an oral glucose tolerance test.

NB: in practice, evidence of sugars in urine together with the symptoms stated is sufficient to instigate serious investigation.

Management

The management of diabetes involves lifestyle and pharmacological therapy. Pharmacological therapy includes insulin and oral hypoglycaemics. Adjustments to diet and increasing exercise remain the cornerstones for treatment of diabetes.

When glycosylated haemoglobin (HbA_{1c}) or blood glucose goals are not met by oral monotherapy, combination therapy is more effective than switching to another monotherapy. Switching or replacing drug therapy is not recommended.

Combination therapy allows for greater glucose lowering, addressing both major physiological defects of type 2 diabetes—insulin secretory failure and insulin resistance. It is important to keep in mind the percentage degree of HbA_{1c}-lowering achievable from monotherapy, combination, and triple therapy when making decisions to help patients reach HbA_{1c} goals. Remember that statistical significance in trials needs to translate to clinical significance for patients.

Approximate HbA_{1c}-lowering values (not including insulin) are:

- monotherapy ~0.6–2.5%
- combination therapy ~2%
- triple therapy ~2%–2.5%.

HbA_{1c}-lowering value from insulin has no ceiling, but is limited by hypoglycaemia.

Insulin

Insulin is necessary for type 1 diabetics and for type 2 diabetics who are inadequately controlled or during periods of stress. Insulin is also used in gestational diabetics inadequately controlled by diet and exercise.

There are various types of insulin based on onset and duration of action (see Table 21.1) as well as premixed combination products.

- Generally mixing of insulins should be discouraged.
- Insulin glargine and detemir may not be mixed with any other insulins.

Table 21.1 Insulin types: human and insulin analogues

Insulin	Onset	Peak	Duration
Rapid-acting analogues (lispro, aspart, glulisine)	10–15min	1–2h	3–5h
Short-acting human regular (soluble)	30–60min	2–4h	5–8h
Intermediate-acting human (e.g. isophane)	1–2h	4–12h	10–16h
Protamine zinc is longer-acting			
Long-acting analogues			
Detemir*	3–8h	None	~24h
Glargine*	2–4h	None	Up to 24h

*Two or more injections may be required in some patients

- Insulin is stable for 28 days once opened (with the exception of detemir which is stable for 42 days) and can be stored in or out of the refrigerator, although generally pens in use are not stored in a refrigerator. Unopened refrigerated insulin is stable until the manufacturer's expiration date.
- The goal of any insulin regimen or combination is to target control, avoid hypoglycaemia, and be acceptable to the patient.
- Consider insulin therapy when HbA_{1c} >8% and the patient is already on combination or triple therapy and exhibits hyperglycaemia. Oral agents are often continued if a once- or twice-daily insulin regime is chosen.
- Although premixed insulin offers the advantage of decreased injections, it is difficult to adjust either insulin component successfully.
- Insulin dosage can be adjusted every 3–7 days on the basis of patient's self-monitoring of blood glucose. However, patients who have developed an understanding of the process will adjust more frequently to manage changes in lifestyle such as intensive exercise or a larger than normal meal.
- Insulin regimes are often tailored to fit preferences and lifestyle. Initiation of insulin therapy can be a challenging concept, and patients need time to adjust. There may be benefits in starting on a once- or twice-daily regime and moving to four times a day if control is difficult.

Insulin pens

- Insulin pens offer flexibility in patient schedules as they are more discreet and may offer an alternative to those who fear injections or have dexterity or visual impairments.
- Pens are either disposable or have replaceable cartridges.
- Pens hold 300 units (3mL) of insulin and come in boxes of five.
- The stability of insulin pen contents in use is usually 28 days, but this should be checked with the SPC as there are variations.

Oral agents

Second-generation sulfonylureas

- Mechanism: stimulate insulin release from binding to sulfonlyurea β-cell site.
- Target post-prandial glucose.
- Place in therapy: monotherapy, combination therapy, can be first line.
- Reduction in HbA_{1c}: 0.9–2.5%.
- Examples: gliclazide, glibenclamide.
- Risks: hypoglycaemia, weight gain.
- No additional benefit at doses >50% of maximum dose.

Biguanides

- Mechanism: decrease gluconeogenesis and increase peripheral utilization of glucose.
- Target fasting blood glucose.
- Place in therapy: considered first line, monotherapy, combination therapy.
- Reduction in HbA_{1c}: 1–1.3%.
- Available as metformin immediate release and metformin extended release (MR); no real advantage over standard formulation.

- Increase dose by 500mg/day weekly.
- Maximum effective dose is 2000mg/day.
- Lactic acidosis rare (<0.3%, but 50% fatal).
- Does not cause hypoglycaemia.
- Contraindicated with serum creatinine 133μmol/L in men and 124μmol/L in women.
- Use with caution in patients aged >80 years (should have normal renal clearance) and in those with hepatic dysfunction, alcoholism, unstable congestive heart failure (CHF), or dehydration.
- GI side effects (nausea, vomiting, diarrhoea) occur in up to 50% of patients; can give with food; start low and go slow.
- Improved lipid profile; weight neutral or weight loss.
- Decreased macrovascular events.

Meglitinides

- Mechanism: stimulate insulin release from binding to sulfonlyurea β-cell site.
- Target post-prandial glucose; short-acting.
- Place in therapy: monotherapy or combination therapy.
- Reduction in HbA_{1c}: 0.6–0.8%.
- Examples: repaglinide, nateglinide.
- Risks: hypoglycaemia; weight gain.
- The need for frequent dosing may adversely affect compliance.

Thiazolidinediones

- Mechanism: activate PPAR-G (peroxisome proliferator-activated receptor gamma), increasing peripheral insulin sensitivity in skeletal muscle cells.
- Target fasting blood glucose.
- Place in therapy: considered second line, but could be monotherapy in patients with lower HbA_{1c} range(6.5–8%), combination therapy.
- Reduction in HbA_{1c}: 1.5–1.6%.
- Example: pioglitazone.
- Oedema and weight gain occur more in combination with insulin.
- Contraindicated in NYHA Class III and IV heart failure; do not use in patients with underlying liver dysfunction.
- An increase in bone fracture rates has been reported in women.
- Delayed onset of action; may be 6–8wks (or as much as 12wks).
- Pioglitazone may have positive effects on lipids (↑HDL, ↓TG).
- In September 2010, following a Europe-wide review of available data on the risks and benefits of rosiglitazone, the UK Commission on Human Medicine (CHM) withdrew this product from clinical use in the UK because of increased risk of cardiovascular disorders including MI and cardiac failure.

α-glucosidase inhibitors

- Mechanism: slow carbohydrate absorption in gut.
- Target post-prandial glucose.
- Place in therapy: monotherapy or combination therapy.
- Reduction in HbA_{1c}: 0.6–1.3%.
- Example: acarbose.
- Must take with carbohydrate-containing meal.

- Decrease post-prandial glucose; must be taken with first bite of food.
- Start low and go slow to avoid GI intolerance.
- If hypoglycaemia occurs (risk if on insulin or sulfonylurea), must treat with glucose, not sucrose, as acarbose interferes with sucrose absorption.

Dipeptidyl peptidase inhibitors (DPP IV)

- Mechanism: slows inactivation of incretin hormone GLP-4, suppressing glucagon secretion and increasing glucose-dependent insulin release.
- Target post-prandial blood glucose.
- Place in therapy: monotherapy or combination therapy.
- Reduction in HbA_{1c}: 0.8%.
- Examples: sitagliptin, vildagliptin.
- Dosage adjustment necessary in renal dysfunction.
- Increase satiety.
- Delay gastric emptying.
- Weight neutral.

Newer antidiabetic treatments

Exenatide

- Glucagon-like peptide-1 (GLP-1) incretin mimetic; mimics incretin hormone given by injection.
- Mechanism: stimulates insulin secretion in response to glucose load; inhibits release of glucagon following a meal; increases satiety; slows absorption of nutrients through delayed gastric emptying.
- Place in therapy: adjunct therapy for use in combination with sulfonylureas, metformin, or a combination of these.
- Reduction in HbA_{1c}: 0.8–0.9%.
- Common side effects include nausea and vomiting (dose-related).
- Recent reports of possible exenatide pancreatitis have arisen.
- Currently its use is not recommended in patients with a history of pancreatitis.

Biphasic insulin

A wide range of biphasic (mixed) insulins are available. Readers are referred to the *BNF* or relevant SPC for up-to-date information.

Monitoring and control

Monitoring

The place of blood glucose monitoring is well recognized in patients with diabetes who require insulin treatment. There are now a wide range of meters available, in addition to finger-pricking devices. It is important to be familiar with a range of machines. The list of those available can be found on the Diabetes UK website.[1] Most companies provide meters at low cost directly to patients, and this route is considerably cheaper than purchasing over the counter.

Recent developments have both ↓ the volume of blood required and ↓ the speed of analysis to 75s. Some can link to computer programs and estimate average levels according to chosen parameters.

Monitoring of patients with type 2 diabetes tends to be frowned upon by pharmaceutical advisers. However, there are good reasons for regular, if less frequent, monitoring, and it should be encouraged. A sensible pattern might be to monitor twice weekly to ensure that there are no major changes in glucose levels. It is also useful to monitor for lifestyle changes such as ↑ exercise, change of diet, fasting, and other influencing factors (e.g. mild illness).

Finger-pricking devices are often supplied with meters, which are not prescribable (the lancets are) but can be purchased from community pharmacies. Unfortunately, they all seem to be somewhat painful to use. Laser devices claim to be painless but are very expensive.

Control

Target glucose levels are usually set at 4–7mmol/L for fasting and <9mmol/L for post-prandial levels. In the UK, glucose is measured in units of mmol/L. Other countries use mg/100mL. The conversion is 1mmol/L equivalent to 18mg/100mL.

Regular monitoring of HbA_{1c} gives a good pattern of levels in the previous 3 months. The target level for HbA_{1c} should be <7%. However, some authorities set lower levels.

1 http://www.diabetes.org.uk/home.htm

Thyroid disorders

The thyroid gland is the only endocrine gland to store large quantities of pre-formed hormones. Found anterior to the trachea in the lower neck, it is the largest endocrine organ of the human body and regulates the body's metabolism through the release of thyroid hormones in response to thyroid-stimulating hormone (TSH) formed by the anterior pituitary gland. Cells are arranged within the gland in spherical follicles that surround a thyroid hormone store and release two hormones:

- thyroxine (T_4)—a pro-hormone that acts as a plasma reservoir
- tri-iodothyronine (T_3)—the active hormone

These hormones are derived from two molecules of iodine and the amino acid tyrosine, with T_3 containing three iodine atoms and T_4 containing four. The iodine required is acquired mainly from iodized salt, meat, and vegetables in the diet. The recommended daily intake of iodine is 150mg, though only a fraction of this amount is absorbed as the thyroid gland cells are the only cells in the body that can actively absorb and utilize plasma iodine. Iodine is then returned to the plasma by the breakdown of these hormones and excreted from the body mainly via the kidneys.

The T_3 and T_4 hormones released by the thyroid gland regulate the rate of metabolism in almost every cell in the body, oxygen consumption, and heat production. They also have a role in growth and development, as well as sensitizing the cardiovascular and nervous system to catecholamines.

Regulation of thyroid hormones

Hypothalamic thyrotrophin-releasing hormone (TRH) stimulates the release of TSH from the anterior pituitary gland which, in turn, acts on extracellular receptors on the surface of the thyroid follicular cells to stimulate the synthesis and secretion of T_3 and T_4. TSH also has long-term actions on the thyroid gland, increasing its size and vascularity to improve hormone synthesis.

Thyroid hormone release is inhibited by the presence of excess thyroid hormones in the bloodstream and glucocorticoids (e.g. cortisol) which act on the anterior pituitary to suppress TSH.

The active hormone T_3 affects almost every cell in the body. Peripheral tissues can regulate the amount of T_3 in circulation by increasing or decreasing the amount of T_3 synthesis. Most of the deiodination is carried out by the liver and kidney. T_4, a relatively inactive molecule, is converted to T_3 by deiodination. It is important to note the following.

- The majority of plasma T_3 is formed by deiodination of T_4 and not directly from the thyroid gland.
- The concentration of T_4 in circulation is much higher than that of T_3 by a ratio of 50:1.
- T_4 has a longer half life than T_3 (7 days versus 1 day).

Transport of the thyroid hormones

T_3 and T_4 hormones are carried in circulation bound to plasma proteins produced in the liver, thus protecting them from enzymic attack. 70% is bound to thyroid-binding globulin (TBG) and 30% to albumin.

Only 0.1% of T_4 and 1% of T_3 are carried unbound. It is this free (unbound) fraction which is responsible for their hormonal activities.

Disorders of the thyroid gland

The thyroid gland is prone to a number of diseases that can alter its function and structure. As nearly all body tissues are affected by thyroid hormones, an alteration in their level of secretion affects the activity of virtually all body systems, giving rise to a wide range of presenting symptoms. The main categories of disease are:

- hyperthyroidism
- hypothyroidism
- goitre formation
- adenoma of the thyroid
- carcinoma of the thyroid.

Thyroid function tests

First-line diagnosis of primary hyper- and hypothyroidism is made from examination of serum TSH concentrations. However, this test alone is misleading in patients with secondary thyroid dysfunction.

Free hormone concentrations are unaffected by changes in binding protein concentration or affinity and usually correlate better with the metabolic state than do total hormone concentrations. Therefore serum T_3 and T_4 concentrations are measured using highly specific and sensitive radio-immunoassay.

As the presenting symptoms of thyroid disorders can be varied and non-specific, biochemical confirmation is necessary, but it is important to remember that these tests should never be used alone to diagnose and decide whether treatment is necessary as clinical features need to be taken into account. Indeed, abnormalities are noted in thyroid function tests during systemic illnesses. Therefore a diagnosis of hyper- or hypothyroidism should not be made in the presence of any recognized concurrent systemic illness, and the tests should be repeated once the illness has resolved to ensure an accurate representation of a patient's thyroid function. In instances where abnormal test results are detected in the absence of any signs or symptoms, close monitoring of the patient is required but no treatment.

Table 21.2 shows thyroid hormone concentrations seen with various thyroid abnormalities, and Table 21.3 shows the reference ranges against which variances are determined.

When interpreting the results of thyroid function tests, the effects of any drugs that the patient is taking should be borne in mind. Table 21.4 shows how the processes of the thyroid gland can be affected by certain medications.

Table 21.2 Thyroid hormone concentrations associated with various thyroid abnormalities

Condition	TSH	Free T_4	Free T_3
Primary hyperthyroidism	Undetectable	↑↑	↑
T_3 toxicosis	Undetectable	Normal	↑↑
Thyrotoxicosis	↓	↑	↑
Subclinical hyperthyroidism	↓	Normal	Normal
Secondary hyperthyroidism (TSHoma)	↑ or normal	↑	↑
Thyroid hormone resistance or consider adherence to treatment	↑ or normal	↑	↑
Primary hypothyroidism	↑	↓	↓ or normal
Secondary hypothyroidism	↓ or normal	↓	↓ or normal
Subclinical hypothyroidism	↑	Normal	Normal
Pituitary disease/sick euthyroidism	↓	↓	↓

Table 21.3 Typical reference ranges used in thyroid function tests

Test	Range
TS	0.4–4.5mU/L
Free T_3	3.5–7.8pmol/
Free T_4	9.0–25.0pmol/

Table 21.4 Influence of drugs on thyroid function tests

Metabolic process	Increased	Decreased
TSH secretion	Amiodarone (transiently: becomes normal after 2–3mo)	Glucocorticoids, dopamine agonists, phenytoin, dopamine
T_4 synthesis/ release	Iodide	Iodide, lithium
Binding proteins	Oestrogen, clofibrate, diamorphine	Glucocorticoids, androgens, phenytoin, carbamazepine
T_4 metabolism	Anticonvulsants; rifampicin	
T_4/T_3 binding in serum		Salicylates, furosemide, glucocorticoids, mefenamic acid, amiodarone, β-blockers

Hyperthyroidism

Hyperthyroidism affects approximately 1% of the UK population and is six times more common in women. It is defined as overactivity of the thyroid gland leading to the release of excess T_3 and T_4 hormones which, when symptomatic, is called thyrotoxicosis. The two main causes in the UK, which account for more than 90% of cases, are as follows.

- Graves' disease—an autoimmune disease which is the most common cause of hyperthyroidism in the 20–50 age group. It is characterized by the presence of thyroid-stimulating antibodies in the blood which bind to TSH receptors in the thyroid and stimulate them to produce excess thyroid hormones in the same way as TSH stimulates the receptors.
- Solitary toxic nodule/toxic multinodular goitre (depending on the number of nodules).

Other causes are as follows.

- Solitary toxic adenoma.
- Thyroiditis due to viral infection, pregnancy, or some drugs such as amiodarone or interferon—usually transient.
- Exogenous iodine and iodine-containing drugs.
- Excessive T_3 and T_4 ingestion.

Clinical features

The presenting features in mild cases are often noted to mimic an anxiety state. The most common clinical features of hyperthyroidism are:

- weight loss (but normal appetite)
- sweating; heat intolerance
- increased rate and depth of respiration
- diarrhoea/increased frequency of defecation
- fatigue
- generalized muscle weakness and muscle tremor
- cardiac symptoms (palpitations, sinus tachycardia or atrial fibrillation, angina, heart failure).

Other symptoms include:

- agitation
- hyperkinesis
- insomnia
- oligomenorrhoea, infertility
- goitre
- eyelid retraction, lid lag.

Features specific to Graves' disease include periorbital oedema, proptosis, diplopia, opthalmoplegia, corneal ulceration, and loss of visual acuity, with pre-tibial myxoedema occurring in one-third of these patients. Untreated Graves' disease has a natural history of remission and relapse; 30–40% of patients only ever have a single episode of hyperthyroidism.

On rare occasions, patients with thyrotoxicosis present with a thyroid storm or crisis, which is considered a medical emergency as features include hyperpyrexia, dehydration, and cardiac failure.

Treatment of Graves' disease and nodular thyrotoxicosis

Anti-thyroid drugs

Carbimazole (the first choice of anti-thyroid drug in the UK) and propylthiouracil are both thionamides which inhibit thyroid peroxidase-catalysed iodination of T_4 residues and the coupling of iodotryosyl residues to reduce the synthesis of T_4 from iodine. These drugs are the first choice of therapy in younger patients with Graves' disease and are usually given for a period of 1–2 years, monitoring thyroid status during this time and after. A delay in effect of up to 4wks from initial administration is often seen because the pre-formed hormones are still being released from the thyroid gland when using this prescription.

Once thyroid function tests have revealed that the patient has reached a state of normal gland function (i.e. a euthyroid state), the prescribed dose can usually be reduced to a lower maintenance dose. The actual dose is determined by regular monitoring of thyroid function tests. 30–40% of patients treated with these drugs stay euthyroid for 10 years after discontinuation of therapy, with a further course of the same or alternative treatment given if the patient relapses.

NB: 5mg of carbimazole is roughly equivalent to 50mg of propylthiouracil, with propylthiouracil being the drug of choice during pregnancy and lactation because of its lower concentration in breastmilk and the possible association of carbimazole with aplasia cutis.

Two alternative treatment regimes are used.

Dose titration regime

As mentioned, the primary aim is to achieve a euthyroid state with high doses and then maintain euthyroidism with a low stable dose for approximately 18 months. The dose of thionamides is titrated according to the thyroid function tests performed every 4–8wks, aiming for a serum free T_4 in the normal range and a detectable TSH. A high serum TSH indicates a need for a dose reduction. TSH may remain suppressed for weeks or months.

The typical starting dose of carbimazole is 20–30mg daily and the treatment is continued for 18 months.

Block and replace regime

After achieving a euthyroid state on carbimazole alone, carbimazole at a dose of 40mg daily together with levothyroxine at a dose of 100micrograms daily can be prescribed. The main advantage of this regime is that fewer hospital visits are required and the duration of treatment is often reduced to 6 months. During treatment, free T_4 levels are measured 4wks after starting levothyroxine and the dose of levothyroxine is altered, if necessary, in increments of 25micrograms to maintain free T_4 in the normal range. Most patients do not require dose adjustments.

NB: relapses are common after either regime within the first year and are most likely in patients with large goitres and high T_4 levels at the time of diagnosis.

Side effects

Potential side effects of carbimazole and propylthiouracil are as follows.

- Pruritus and maculopapular rash—these can be treated with antihistamines without discontinuing treatment
- Sensitivity reaction (e.g. arthralgia, jaundice, lymphadenopathy, vomiting, pyrexia.)—withdrawal from treatment is required in this instance. There is rarely cross-sensitivity between the two drugs. Therefore, once the patient has recovered, the other drug can be tried.
- Agranulocytosis—characterized by fever, systemic upset, mouth ulceration, and sore throat. This rare but serious side effect of both drugs is seen in 0.1–0.5% of patients and occurs very suddenly (usually within the first 3 months of therapy) in equal frequency with both anti-thyroid drugs. All patients prescribed with these drugs should be told to report these symptoms to their GP or hospital consultant and stop the drug immediately.

NB: one drug should not be substituted for the other after this reaction has been diagnosed.

Compliance with these drugs can be a problem as the patient may initially feel worse in terms of their presenting symptoms, with women often concerned about weight gain. Patients should be counselled that they will have adjusted to the change in metabolic rate after a few months, and a general improvement in symptoms will be seen.

β-blockers

β-blockers (e.g. propranolol at a dose of 20–80mg, three times a day), may provide effective temporary relief of cardiac symptoms, particularly palpitations and tremor as well as anxiety, while the anti-thyroid drugs (thionamides) take effect, but should be avoided in patients with asthma. However, it is important to consider that many of the symptoms of hyperthyroidism have a β_2 component, therefore contraindicating the use of cardioselective β-blockers.

Surgery

Thyroid surgery, a total or sub-total thyroidectomy, is rarely performed as a primary course of action as the thyroid overactivity needs to be controlled, usually with anti-thyroid drugs, prior to such a procedure to make the use of anaesthetic safe and reduce the risk of precipitating a dangerous hyperthyroid crisis or 'thyrotoxic storm'. To this end, β-blockers, usually propranolol at a dose of 20mg three times a day, can be prescribed to provide temporary symptomatic relief prior to surgery.

A recognized side effect of surgery is hypothyroidism, for which lifelong levothyroxine replacement will be needed.

Radioactive iodine

This is the primary choice of treatment for toxic nodular hyperthyroidism, if the goitre is not large, and for Graves' disease, especially if there is a relapse after medical treatment or subtotal thyroidectomy, with further doses given at 2–4 months to patients who have not responded.

Radioactive iodine-131 causes necrosis of the overactive gland with minimal local or systemic side effects to the patient and minimal radiation hazard. It is administered as a tasteless oral liquid after ensuring that anti-thyroid drugs have been stopped 1wk prior to commencement of this treatment. β-blockers can be maintained throughout. The thyroid gland may be tender for a few days after treatment.

The following precautions should be taken.

- Careful evaluation of the risks and benefits of this treatment option is needed as patients with thyroid eye disease are more likely to worsen with this therapy. However, worsening of eye symptoms may be prevented with a short course of corticosteroids.
- Although fertility is not affected by this treatment, it is advised that women should avoid becoming pregnant for 6 months following treatment and men should avoid fathering a child within 4 months of treatment. This treatment is contraindicated during pregnancy and it is advised not to breastfeed after therapy.

Treatment of thyroiditis

Many forms of thyroid inflammation (thyroiditis) are described as 'self limiting'. In instances where thyroiditis is painful or prolonged, anti-inflammatory agents or corticosteroids may be helpful, with patients suffering from severe symptoms of thyrotoxicosis finding potential benefit from β-blockers.

Subclinical hyperthyroidism

In cases of subclinical hyperthyroidism, the TSH level is suppressed but the free T_3 and T_4 levels are seen as being normal. This condition, regarded as a precursor of clinical hyperthyroidism, is currently the subject of debate as to whether or not it should be treated. Although treatment may be worthwhile in the elderly, particularly if the heart rhythm becomes abnormal or there is thinning of the bones, the decision of prescribed treatment is a matter for individual clinical assessment and evaluation.

Thyroid crisis

Thyroid crisis, or 'thyrotoxic storm', is a rare but life-threatening exacerbation of the manifestations of thyrotoxicosis and is associated with significant mortality. It is characterized by:

- severe hyperthyroidism associated with fever
- disproportionate tachycardia
- CNS dysfunction—especially confusion or severe irritability
- GI dysfunction—diarrhoea, vomiting, and jaundice

Treatment is needed immediately under intensive care, which is beyond the scope of this chapter.

Hypothyroidism

Hypothyroidism, defined as underactivity of the thyroid gland leading to deficient levels of serum T_3 and T_4, affects approximately 2% of the population in the UK and is 10 times more common in women than in men. When this becomes symptomatic, it is called myxoedema. The two

main causes in the UK, which account for more than 90% of cases, are as follows.

- Autoimmune hypothyroidism (Hashimoto's thyroiditis), which typically affects middle-aged and elderly women, where the thyroid cells are destroyed by lymphocytes. It is usually accompanied by the presence of thyroid peroxidase (TPO) antibodies, which can be detected in the blood and therefore are a useful tool for diagnosis.
- Post surgery, radioactive iodine, and anti-thyroid drugs.

Other causes include:

- viral agents (De Quervain's thyroiditis)
- idiopathic atrophic hypothyroidism
- congenital factors
- dyshormonogenic hypothyroidism
- secondary to pituitary or hypothalamic disease
- iodine deficiency
- drugs—reversible cause mainly by amiodarone, lithium, and iodine.

Clinical features

The presentation of hypothyroidism is more gradual than that of hyperthyroidism, with many symptoms often being ignored. The onset may be insidious, with occasional symptoms noted. The clinical signs and symptoms reflect the diverse action that thyroid hormones have on the body, the most common being:

- lethargy
- cold intolerance
- dryness and coarsening of skin and hair and subcutaneous swelling (myxoedema)
- hoarseness
- weight gain
- hyperlipidaemia

Other clinical signs and symptoms include:

- anaemia—usually macrocytic
- depression, dementia, psychosis
- constipation
- bradycardia, angina, heart failure, pericardial effusion
- muscle stiffness
- carpal tunnel syndrome
- infertility, menorrhagia, galactorrhoea
- vitiligo.

Children with hypothyroidism may present with growth failure, delayed pubertal development, or deterioration in academic performance.

Goitre can occur in patients who are hypothyroid, particularly in the presence of Hashimoto's thyroiditis due to the accumulation of lymphocytes in the thyroid gland. However, in many recorded cases there is no goitre present and the thyroid is destroyed by the time diagnosis is confirmed.

Treatment

Thyroid hormone replacement, usually with T_4 (levothyroxine), is the treatment of choice for hypothyroidism, whereby the metabolic rate and demand for oxygen is increased. However, angina or MI may be precipitated if the latter occurs too quickly. Treatment with levothyroxine is preferable to replacement with T_3 for most patients because of its slower onset of action. T_3 is used occasionally where a more rapid response is indicated.

The required dose of levothyroxine ranges from 25 to 200micrograms daily. The initial dose is usually 50micrograms, increasing in increments of 50micrograms every 3–4wks. However, elderly patients and those with ischaemic heart disease are prescribed an initial dose of 25micrograms daily or on alternate days as indicated. The dose should be taken at least 30min before breakfast as food can reduce its absorption.

Although symptomatic improvement is often seen within 2–3wks, it may take up to 6wks before TSH levels respond fully. As a result, TSH levels should be checked after 6wks of commencement of levothyroxine therapy and adjusted accordingly by increments of 25–50micrograms.

Once TSH and T_4 levels return to normal and the patient is symptom free, the adequacy of continuing treatment should be assessed by conducting annual thyroid function tests.

Most patients prescribed with levothyroxine therapy require lifelong treatment. Dose requirements rarely change once the TSH and T_4 levels are stable, with the exceptions of a dose increase which may be necessary during pregnancy and a dose reduction which is sometimes indicated in the elderly. Advice is given to patients not to stop taking the treatment without consulting their doctor as the symptoms would recur. Patients in the UK issued with this prescription can obtain a medical exemption certificate from having to pay for this medication from the NHS Business Services Authority, having filled out a FP92A form available from GP surgeries.

NB: If undertreated, hypothyroidism can progress to a life-threatening myxoedema coma—a medical emergency with high mortality rate where T_3 (oral or injection) is the main treatment advised. However, this may be precipitated by infection, therapy with sedative drugs, or hypothermia, particularly in the elderly population.

Further reading

Turner HE, Wass JAH (2009). Thyroid. In: *Oxford Handbook of Endocrinology and Diabetes* (2nd edn), pp. 2–81. Oxford: Oxford University Press.

Association of Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation (2006). *UK Guidelines for the Use of Thyroid Function Tests* (2006). Available at: http://www.btf-thyroid.org/images/stories/pdf/tft_guideline_final_version_july_2006.pdf (accessed 10 August 2010).

Toft AD (2002). Hyperthyroidism. In: Robinson S, Meeran K (eds), *Endocrine Specialist Handbook*, pp. 211–32. London: Martin Dunitz.

Lazarus JH, Obuobie K (2002). Graves' disease. In: Robinson S, Meeran K (eds), *Endocrine Specialist Handbook*, pp. 233–42. London: Martin Dunitz.

Wahid ST, Robinson ACJ (2002). Hypothyroidism. In: Robinson S, Meeran K (eds), *Endocrine Specialist Handbook*, pp. 243–55. London: Martin Dunitz.

Daniels GH, Dayan CM (2006). *Fast Facts: Thyroid Disorders.* Abingdon: Health Press.

British Thyroid Association: http://www.btf-thyroid.org

Chapter 22

Therapy-related issues: obstetrics, gynaecology, and urinary tract disorders

Hormonal contraception

Contraception has been an important part of human lives since the time of the early Egyptians. While methods have changed dramatically over the years, the purpose remains the same—to control fertility.

Most methods used today are female-driven and involve hormones. These methods are very effective in preventing pregnancy when taken or used as directed. Barrier methods rely on their availability at the time of intercourse and are more efficacious when used with spermicides.

Factors that need to be considered when selecting a method of contraception include the woman's potential ability to adhere to treatment, the age of the patient, medical history, personal history, and reversibility of the agent.

Failure rates for methods include the *perfect rate*, when the method is used perfectly all of the time, and the *typical rate*, which is more consistent with normal use.

Oral contraceptive pills

- Combination (COC)—containing an oestrogen and a progestogen. These are the most reliable in general use.
- Progestogen-only (POP)—these are a suitable alternative where oestrogens are contraindicated or not tolerated but they have a higher failure rate than COCs as good adherence is essential.
- The perfect-use failure rates for COCs and POPs are 0.1% and 0.5%, respectively.
- The typical failure rate is 5% for both pill types.
- Pharmacists should ensure that women are counselled on what to do if a pill is missed—because of either forgetting to take it or a GI upset (Box 22.1).

Transdermal patch

- Evra® contains ethinylestradiol and norelgestromin, a metabolite of norgestimate.
- The patch is changed weekly for 3wks, with the fourth week remaining hormone free.
- The failure rate is 1% for both perfect and typical use.
- Approximately 60% more oestrogen is absorbed into the bloodstream than with traditional 35micrograms pills. This places women at higher risk for thrombosis and myocardial infarctions.
- The patch is less effective in women weighing >90kg, and other methods should be considered.

If a patch change is forgotten in the first week, change the patch-change day and use alternative contraception for the first week of the new cycle. Patch changes forgotten in the second and third week do not need alternative contraception as long as the duration was <48h. Apply a new patch and keep the same day for the next patch-change day. If it was >48h, restart the entire cycle and use alternative contraception for the first week.

Box 22.1 Advice to women who have missed an OCP

A pill counts as missed

- If you have completely forgotten to take it
- If you vomit within 2h of taking a pill or have severe diarrhoea

Combined oral contraceptives

If you miss ONE pill (for 20micrograms pills) or ONE or TWO pills (for 30–35micrograms pills) anywhere in the pack

- Take a pill as soon as possible and continue to take the pills in the pack (even if it means taking two pills in 1 day).
- Use condoms or abstain from sex until you have taken pills for 7 days in a row.
- Emergency contraception is not required. Any pills missed in the last week of the previous pack should be taken into consideration when deciding on emergency contraception.

If you miss TWO or more pills (for 20micrograms pills) or THREE or more pills (for 30–35micrograms pills)

- Take the most recent pill as soon as possible and then continue taking pills daily at the usual time.
- Also use condoms or abstain from sex until pills have been taken for 7 days in a row.
- If pills are missed in week 1 (pills 1–7) and unprotected sex occurs in week 1 or the preceding pill-free interval (PFI), consider the use of emergency contraception.
- If pills are missed in week 2 (pills 8–14), no emergency contraception is needed.
- If pills are missed in week 3 (pills 15–21), finish the pills in your current pack and start a new pack the next day. If you miss out the PFI, no emergency contraception is needed.
- Remember: it is extending the pill-free interval that is risky.
- Take into account any pills missed in the last week of your previous pack when deciding about emergency contraception.

For every-day pill regimens

- If you miss any inactive pills, discard the missed pills and then continue taking the pills daily, one each day.

Progesterone-only pill

- Take it as soon as you remember and take the next pill at the usual time.
- If the pill was 3h late (12h for Cerazette®), use alternative contraception for the next 2 days.
- If you have unprotected sex before two further tablets are taken correctly, consider the use of emergency contraception.

Transvaginal ring

Nuvaring® contains ethinylestradiol and etonogestrel, a metabolite of desogestrel.

- The ring remains in place for 3wks and is removed for the fourth. A new ring is used each month. It can be removed for up to 3h.
- Side effects include increased vaginal discharge, irritation, or infection.
- The perfect-use failure rate is <0.3%, and the typical-use failure rate is 2%.
- The ring can be dislodged with bowel movements.
- If the ring is removed for <3h it should rinsed and reinserted—no alternative contraception is required. If it is removed for >3h:
  - During weeks 1 or 2 rinse and reinsert, and use alternative contraception for 7 days.
  - During week 3 insert a new ring or allow a withdrawal bleed and insert a new ring no later than 7 days after the old ring was removed. No alternative contraception is required provided that a new ring is inserted within 7 days.

Intrauterine

Mirena® contains levonorgestrel and releases the equivalent of three POPs per week.

- The device can remain in place for 5 years.
- Suitable for women taking drugs which are potent enzyme inducers (e.g. phenytoin).
- The failure rate is 0.1% for both perfect and typical use.

Injection

Depo-Provera®—medroxyprogesterone 150mg

- Given by IM injection every 3 months. First dose must be given within 5 days of the beginning of the cycle, or pregnancy must be ruled out if >5 days.
- Suitable for women taking drugs which are potent enzyme inducers (e.g. phenytoin).
- The failure rate is 0.3% for both perfect and typical use.
- Risk of reduction in bone mineral density and, rarely, osteoporosis. Avoid in adolescents or women with risk factors for osteoporosis unless other forms of contraception are unsuitable.

Noristerat®—norethisterone 200mg

- Given by deep IM within 5 days of the beginning of the cycle
- For short-term contraception only—may be repeated once only after 8wks.

Implantable

Nexplanon®—single-rod implant containing etonogestrel.

- Implanted within first 5 days of cycle
- Has a 3-year duration.
- Requires a specially trained professional for placement and removal.
- Failure rate is <0.1% for both perfect and typical use.

Risk of venous thromboembolism (VTE)

The risk of VTE is increased by oestrogen-containing hormonal contraception, though it is lower than the risk of VTE in pregnancy (Table 22.1). Progestogen-only methods appear not to be associated with increased risk of VTE (although evidence is limited). Factors which increase the risk are as follows.

- First year of use.
- Increasing age.
- Higher doses of oestrogen.
- Third-generation progestogen.
- Possible higher risk with transdermal patches than with COC.
- Presence of other risk factors (e.g. increased BMI).

Women should be counselled on the relative risks before starting hormonal contraception, and women on COC, transdermal patches, and the vaginal ring should be advised that they have an increased risk of VTE associated with long periods of immobility (e.g. long-haul travel). Women on oestrogen-containing contraception should be advised to stop their contraceptive 4wks before major elective surgery or any surgery involving immobilization of a lower limb. The contraceptive can be restarted at the beginning of the next cycle at least 2wks after mobility is restored. For non-elective surgery, where it has not been possible to stop the contraceptive in advance, VTE prophylaxis should be given.

Table 22.1 Risks of VTE associated with oestrogen containing contraception (cases per 100 000 women per year)

Healthy, non-pregnant, not using oestrogen-containing contraception	5–10
Using COC containing second-generation progestogen	15
Using COC containing third-generation progestogen	25
Pregnant women	60

Drug interactions

Enzyme-inducing drugs such as rifampicin (including 2 day course for meningitis prophylaxis), some anticonvulsants, St John's wort, and some antiretrovirals can significantly reduce the effectiveness of COCs, POPs, transdermal patches, and vaginal rings. Women should be counselled to use an alternative form of contraception while taking these drugs and until enzyme induction has completely resolved (4–8wks). Women on long-term therapy with enzyme-inducing drugs should use progestogen injection or an intrauterine device.

There is no evidence to support the theory that by reducing the bowel flora responsible for recycling enthinylestradiol from the large bowel, broad-spectrum antibacterials reduce the effectiveness of hormonal contraceptives. Women taking broad-spectrum antibacterials that are not enzyme inducers do not need to use alternative forms of contraception.

Counselling points

If a woman is using hormonal contraception for the first time or is switching from one form to another it is important that the pharmacist ensures that she is aware of the following points.

- Confirm that the risk of VTE has been explained when deciding on form of hormonal contraception—if not refer back to prescriber.
- When to take the first dose with respect to menstrual cycle and for how long alternative contraception should be continued after starting. This varies with the type of contraception—check SPC or *BNF*, Chapter 7
- What to do if a pill is missed, a patch is delayed or detached, or a vaginal ring is delayed, expelled, or broken.
- What to do if she vomits within 2h of taking pill.
- What to do if vomiting or diarrhoea last for >24h.
- Potential drug interactions, especially with respect to enzyme-inducing antibacterials and broad-spectrum antibacterials.
- Increased risk of VTE with long-haul travel if on oral contraception, patch, or vaginal ring.

Emergency hormonal contraception (EHC)

Two types of EHC are available in the UK.

- Levonorgestrel 1.5mg—single dose taken as soon as possible after unprotected intercourse and ideally within 72h. If a woman is on an enzyme-inducing drug, she should take two tablets (unlicensed dose).
- Ulipristal 30mg, a progesterone receptor modulator—single dose taken within 120h of unprotected intercourse. It is probable that enzyme inducers reduce the efficacy of ulipristal but there is no information at present on adjusting doses to compensate.

In the UK levonorgestrel 1.5mg tablets (Levonelle One Step®) can be sold as a P medicine to women aged >16. Pharmacists can supply EHC to women aged <16 on prescription or via a PGD.

Further reading

Biswas J *et al* (2008). Oral contraception. *Obstetrics, Gynaecology and Reproductive Medicine* **18**: 317–23 (http://cpd4gp.co.uk/PDF%20files/Contraception%20overview%20Dec%2008.pdf).

Guillebaud J (2007). *Contraception Today: A Pocketbook for Primary Care Practitioners* (6th edn). London: Informa Healthcare.

http://www.fsrh.org/pdfs/CEUguidanceEmergencyContraception11.pdf