Thyroid and other endocrine disorders in pregnancy

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Abstract
Endocrine disorders are increasingly encountered in pregnancy. To optimize pregnancy outcome, it is essential to understand the physiology underlying these conditions, as well as which investigations and treatments are safe to use. Thyroid disease is the second most common endocrine condition encountered in women of childbearing age after diabetes. Other endocrine disorders, such as pituitary dysfunction and adrenal and parathyroid disease, are less frequently encountered in pregnancy due to lower population prevalence in combination in some cases with associated subfertility. Women whose pregnancies are complicated by endocrine disease are at risk of maternal and foetal complications, but these can be minimized with appropriate multidisciplinary management.

Keywords Addison’s disease; congenital adrenal hyperplasia; Conn’s syndrome; diabetes insipidus; hypopituitarism; parathyroid; phaeochromocytoma; pituitary adenoma; thyroid disease; vitamin D

Thyroid physiology and pregnancy
Thyroid dysfunction is frequently encountered in pregnancy, although has usually been diagnosed prior to conception. Symptoms of thyroid disease are similar to and may often be attributed to those of pregnancy, therefore delaying initiation or optimization of treatment. Appropriate antenatal management requires knowledge of thyroid embryology and physiology, and in addition which investigations and medications are safe to use.

During pregnancy a suppressed TSH may be evident in up to 13% of women in the first trimester, 4.5% in the second and 1.5% in the third. As a result of heterogeneity between the β subunit of Thyroid Stimulating hormone (TSH) and human Chorionic Gonadotrophin (hCG), rising titres of hCG may stimulate the thyroid gland and mimic biochemical changes of thyrotoxicosis. A corresponding increase in free thyroid hormones is often found in women with symptoms attributable to hyperemesis gravidarum; however these biochemical features are usually self-limiting and do not require treatment with thioamide (antithyroid) medication.

Hypothyroidism
Approximately 2% of pregnant women are either overtly hypothyroid or have evidence of subclinical disease. The majority of cases are due to Hashimoto’s thyroiditis (TPO antibodies positive) and may be associated with additional autoimmune disease such as Type I diabetes mellitus. Other causes include previous thyroidectomy for benign nodule(s), goitre, or malignancy and following surgery or radioactive iodine treatment for hyperthyroidism.

Traditionally the dose titration of exogenous T4 has been judged in accordance to the TSH. Preconception and during the first trimester some clinicians advocate titrating T4 replacement to a TSH of <2.5 mU/L and then 3 mU/L until delivery; however such a prescriptive approach appears short sighted unless it takes into account the levels of the free thyroid hormones. T4 requirements may increase during pregnancy (by up to 30%) due

Controversy surrounds the optimal target range for TSH during pregnancy to ensure foetal and maternal wellbeing (see below). Several studies have showed TSH levels to be lower and have greater variability in the first trimester than the second. This finding was confirmed in a recent cross sectional study of a UK general antenatal population demonstrating that the normal range of TSH may be broader and higher than outside pregnancy (Table 1).

While the literature is useful in identifying antenatal trends in thyroid parameters, the reference ranges cited above are to be used as a guide to clinical practice and not an absolute.

The thyroid hormones, thyroxine (T4) and triiodothyronine (T3) are 99% protein bound, however it is the free hormones which exert biological activity. From the second week of pregnancy, under the influence of rising levels of oestrogen, the concentration of thyroid binding globulin (TBG) increases and therefore total T4 and T3 rise too; however free hormone levels remain essentially unchanged. The transition to measuring free thyroid hormone levels has therefore helped reduce diagnostic ambiguity of thyroid status in pregnancy.

Development of the foetal hypothalamic-pituitary thyroid axis is evident from the seventh week of gestation in the production by the foetus of thyroid releasing hormone (TRH) and TSH; although T4 is only apparent from about the tenth to twelfth week. During the first trimester maternal T4 is able to cross the placenta in order to ensure normal foetal brain development, however by the second trimester foetal T4 requirements are autonomous. Placental enzymes (Type 3 Deiodinase) reduce the transfer of maternal T4 such that only 0.008% crosses by term.

Changes in thyroid function tests in pregnancy

- FT4 pmol/l
- FT3 pmol/l
- TSH μU/ml

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Table 1
to the rise in TBG, reduced absorption from vomiting or the concomitant use of omeprazole, iron, or calcium supplements; in order to minimize the latter, these medications should be taken 2–3 h after T4. Unfounded concerns about teratogenicity may also result in some patients reducing their medication. Untreated hypothyroidism or suboptimal T4 replacement is possibly associated with an increased risk of miscarriage, preterm delivery, pre-eclampsia and low birth weight, although most studies are observational and flawed by multiple confounders. There are also some data showing that T4 prevents these adverse endpoints, but again these are weak. The effect of untreated or undertreated maternal hypothyroidism on foetal brain development is not so clear, although there is an association between suboptimal T4 replacement during the first trimester and reduced intelligent quotient (I.Q.). Cretinism (severe permanent brain damage in childhood) is related to maternal iodine deficiency rather than a direct effect of neonatal hypothyroidism.

In order to ensure foetal wellbeing, all hypothyroid women should ideally have their thyroid function checked prior to conception and in early pregnancy. This will allow optimal T4 replacement prior to and during the first trimester. Additional assessments of T4 requirement after this time are for maternal reasons only.

In patients who have had a total thyroidectomy following a diagnosis of thyroid cancer, T4 replacement is to fully suppress TSH, as this reduces the risk of tumour recurrence. Only very small amounts of T4 cross the placenta and the foetus is therefore not at risk of thyrotoxicosis from maternal T4 replacement.

Controversy surrounds the management of women who, despite being euthyroid, have thyroid peroxidase (TPO) antibodies. These antibodies are common and are present in up to 10% of women of childbearing age. Several studies have found a higher incidence of miscarriage and/or preterm delivery, pre-eclampsia and low birth weight, although most studies are observational and flawed by multiple confounders. There are also some data showing that T4 prevents these adverse endpoints, but again these are weak. The effect of untreated or undertreated maternal hypothyroidism on foetal brain development is not so clear, although there is an association between suboptimal T4 replacement during the first trimester and reduced intelligent quotient (I.Q.). Cretinism (severe permanent brain damage in childhood) is related to maternal iodine deficiency rather than a direct effect of neonatal hypothyroidism.

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Babies born to women with autoimmune hypothyroidism are not at increased risk of neonatal thyroid dysfunction. They are however at significant risk of developing abnormal thyroid function in adult life.

**Hyperthyroidism**

Hyperthyroidism affects about 0.2% of pregnancies. The majority of cases are due to Graves’ disease, an autoimmune disorder in which the clinical manifestations are determined by the titre of TSH receptor stimulating antibodies (TRAbs). Other causes of hyperthyroidism include an autonomous ‘hot’ thyroid nodule or de Quervain’s thyroiditis, an acute viral inflammatory condition giving rise to pain over the thyroid gland and fever. Most women with thyrotoxicosis in pregnancy have pre-existing disease and are therefore already on treatment. Occasional de novo cases may occur possibly related to hCG driven stimulation of the thyroid gland in trophoblastic disease or due to those reasons listed above. A careful history and examination in conjunction with biochemical and radiological investigation will help determine the aetiology. Imaging with ultrasound may help in differentiation between an inflammatory/autoimmune process (thyroditis) and a toxic autonomous nodule. TRAbs are specific to Grave’s disease with their absence making the diagnosis unlikely. Although contraindicated during pregnancy a diagnostic radio iodine (I131) scan is permissible postpartum however breastfeeding should be discontinued for 24 h after the procedure.

Pregnancy does not affect the long-term course of hyperthyroidism, although Graves’ disease may temporarily improve, especially in the second and third trimesters. Falling titres of TRAbs commonly result in reduced treatment requirements, with up to one third of women temporarily discontinuing thioamide medication over this period. Exacerbation of symptoms may occur in the puerperium as the relative state of immunosuppression attributed to pregnancy declines. This may be avoided by increasing the dose of the thioamide medication (back to prepregnancy levels) following delivery. Pregnancy appears to have no effect on Graves’ ophthalmopathy.

Thioamide medications such as carbimazole and methimazole inhibit thyroid peroxidase, reducing the synthesis of T3 & T4. Propylthiouracil also blocks the enzyme Type 1 Deiodinase preventing the conversion of T4 to the more biologically active hormone T3. These drugs are safe in pregnancy and should not be stopped due to concerns about teratogenicity. Previous reports suggesting an association between carbimazole and aplasia cutis (a rare condition resulting in deficits in skin and hair growth) have been discredited following larger more recent studies confirming this link to be spurious or at worst exceptionally rare. Women who conceive despite poorly controlled thyrotoxicosis have increased rates of miscarriage, intrauterine growth restriction (IUGR), premature labour and perinatal mortality than those who conceive with optimal control, reaffirming the need for antenatal treatment. All antithyroid drugs cross the placenta in small amounts, but are unlikely to cause foetal hypothyroidism. This risk can be minimized by ensuring that the lowest dose of treatment is used to maintain maternal free thyroid hormones in the upper third of the normal range for pregnancy. TPT should be checked every 4–6 weeks and the dose of thioamide medication titrated against maternal wellbeing and her biochemical results.

Women with thyrotoxicosis may experience feelings of anxiety and palpitations. The β-blocker, propranolol may help alleviate these symptoms and is not associated with intrauterine growth restriction or other adverse outcomes if used after the first trimester. In women with asthma, the calcium channel antagonist verapamil is a suitable alternative although safety data regarding its use in pregnancy are more limited; both would appear safe in breast-feeding.

Foetal or neonatal thyrotoxicosis complicates 2–5% of cases of mothers with active Grave’s disease, and is the result of high levels of maternal TRAbs (>40 U/L) crossing the placenta after 24 weeks’ gestation. The presence of maternal TRAbs should be sought early in the third trimester, not only in patients with active Graves’ disease on medication [in whom foetal thyrotoxicosis is less likely since the antithyroid medication also crosses the placenta] but also in those euthyroid women who have had previous radioactive iodine therapy or thyroid surgery for autoimmune thyrotoxicosis.
Suspected foetal thyrotoxicosis (excessive foetal movements and foetal tachycardia) should be investigated with serial growth scans to assess for IUGR and foetal goitre. If the woman is close to term, delivery may be considered; if not, the diagnosis can be confirmed by foetal blood sampling and the dose of maternal thioamide medication increased as necessary. If iatrogenic maternal hypothyroidism develops supplementary T4 (which does not cross the placenta) should be commenced. After delivery, neonatal thyrotoxicosis occasionally develops since the half life of the placentally derived antithyroid medication is less than that of the TRAb.

Thioamide medications are safe in breastfeeding. Propylthiouracil is preferred as it is more highly protein bound with lower amounts crossing into the breast milk compared to carbimazole or methimazole. For this reason it is often the drug of choice for women who need to start treatment during pregnancy, but there is no need to routinely switch women who are well controlled on carbimazole.

**Thyroid nodules**

Thyroid nodules are seen in approximately 1% of Caucasian women of childbearing age, with increasing numbers of asymptomatic lesions diagnosed following ultrasound. Rapidly growing nodules or those over 1 cm in diameter should be assessed by clinical examination, ultrasound and fine needle aspiration due to their higher incidence of malignancy. Features suggestive of benign disease are associated thyrotoxicosis or acute pain consistent with a haemorrhagic thyroid cyst.

**Calcium metabolism in pregnancy**

During pregnancy approximately 30 g of calcium is transferred from the mother to the foetal skeleton. This is reflected by a transient reduction in maternal bone mass density of up to 8% in breastfeeding mothers. In order to compensate for this increased demand, daily maternal vitamin D requirements rise facilitating a doubling of dietary calcium absorption. Endocrine factors influencing maternal calcium metabolism in pregnancy and lactation are summarized in Table 2.

**Primary hyperparathyroidism**

Primary hyperparathyroidism is rare. Excessive parathyroid hormone secretion increases serum calcium levels and although most women are asymptomatic, some may develop symptoms relating to ‘bones, moans, stones and groans’.

Mild antenatal hypercalcaemia may be managed conservatively (low calcium diet, increased fluid intake and phosphate supplements). Unresolved hypercalcaemia is associated with an increased risk of miscarriage, intrauterine death and preterm labour, so women with resistant hypercalcaemia should be considered for parathyroid surgery (in the second trimester).

Untreated maternal hypercalcaemia may also lead to suppression of the foetal parathyroid glands increasing the risk of neonatal hypocalcaemia and seizures 1–2 weeks postpartum.

**Secondary hyperparathyroidism**

Secondary hyperparathyroidism is commonly encountered in pregnancy due to the rising prevalence in society of vitamin D deficiency and the increased pregnancy-related requirement for vitamin D. In order to maintain normocalcaemia in the absence of adequate vitamin D reserves and/or calcium, parathyroid hormone levels increase: PTH measurements are rarely required in pregnancy, measurement of calcium and vitamin D levels will usually suffice. Those with poor diets, malabsorption syndromes or women who skin is pigmented or covered are at increased risk. These women should be offered 25 hydroxylated vitamin D (calcidiol) supplements 400–1200 IU daily (e.g. Adcal D3 TM containing calcium 600 mg and vitamin D3 400 IU per tablet).

**Hypoparathyroidism**

 Normally the result of thyroid surgery or autoimmune disease, hypoparathyroidism is treated with 1,25 hydroxylated vitamin D (alphacalcidol), as PTH is required to stimulate1-alpha hydroxylation. The dose will usually need to be increased in pregnancy, since the pregnancy-related vitamin D requirements increase. Suboptimal replacement may result in maternal hypocalcaemia manifesting as muscle cramps, paraesthesia, or seizures; the risk of second trimester miscarriage and foetal hypocalcaemia leading to bone demineralization and foetal rickets are also increased. Corrected calcium (not vitamin D) should be measured monthly to ensure that the dose of alphacalcidol is sufficient and the dose reduced to pre-pregnancy requirements after delivery.

**Pituitary**

During pregnancy the anterior pituitary increases in size by up to 35%, with levels of serum prolactin rising 10-fold. Luteinizing (LH) and follicle stimulating (FSH) hormone release are suppressed; basal growth hormone (GH) levels, pituitary ACTH and antidiuretic hormone levels remain unchanged.

During investigation for an often unrelated complaint non-functioning pituitary incidentalomas are increasingly diagnosed on magnetic resonance imaging. Their incidence is approximately 10–20% and although often asymptomatic, over time they may cause symptoms of local mass effects or hypopituitarism.

Prolactinomas are the most common functioning pituitary tumour encountered in pregnancy, the majority having been diagnosed prior to conception as a result of menstrual

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**Maternal adaptive changes to calcium metabolism in pregnancy & lactation**

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Table 2
irregularities or galactorrhoea. Women with macroprolactinomas (>1 cm) may present with visual disturbance and frontal headaches.

There is a small risk that prolactinomas will enlarge during pregnancy causing visual field defects (classically a bitemporal hemianopia), headaches or diabetes insipidus. Symptomatic expansion may occur in up to 1.5% of microprolactinomas (<1 cm) and 15–35% of macroprolactinomas and is most evident during the third trimester. Pre-pregnancy treatment of a macroprolactinoma with dopamine agonists, surgery or radiotherapy may reduce this risk (4–7%). However overall cure rates following surgical intervention are poor and the beneficial effects of radiotherapy are slow. Both procedures are also not devoid of significant complications.

The management of prolactinomas during pregnancy is dependent upon the tumour size and the patient’s wishes. Women with a microprolactinoma taking a dopamine agonist (bromocriptine or cabergoline) usually discontinue treatment once pregnancy is confirmed. Women with a macroprolactinoma are usually advised to continue their dopamine agonists through pregnancy, in order to minimize the risks of expansion. Women who have a microprolactinoma, or macroprolactinoma in conjunction with ongoing medical treatment, should be assessed at least every trimester (symptoms and visual field assessment); or sooner if they develop symptoms suggestive of tumour enlargement. However women with a macroprolactinoma who discontinue treatment during pregnancy require monthly reviews including formal visual field perimetry. There should be a low threshold for restarting dopamine agonists and performing a pituitary MRI in the event of suspected tumour enlargement.

Bromocriptine is safe in pregnancy, with no evidence of congenital abnormalities or long term intellectual developmental problems in children born to mothers who have taken the drug over this period; data for cabergoline use are less extensive but similarly reassuring. Labour and delivery are not affected by the presence of a prolactinoma.

Mothers with a microprolactinoma or macroprolactinomas may breast feed. Dopamine agonists are safe in breastfeeding but as they suppress lactation breastfeeding may be difficult.

Recent evidence has indicated that the long term cumulative use of bromocriptine or cabergoline is associated with a small but increased risk of heart valve fibrosis. Echocardiography should be considered in those at increased risk and found to have a heart murmur.

Hypopituitarism

Pre-existing hypopituitarism does not preclude successful pregnancy although ovulation induction is usually required to conceive. Glucocorticoid and thyroxine replacement must continue throughout pregnancy, with increased steroids during periods of acute intercurrent illness or stress such as labour. Limited safety data exist regarding recombinant GH during pregnancy with current NICE guidelines contraindicating it use. It is usually withdrawn at the end of the first trimester following the rise in placental GH (at around 8 weeks); however single case reports have advocated its safe use later in pregnancy.

The aetiology of hypopituitarism includes pituitary tumours and/or subsequent surgery or radiotherapy, pituitary infarction or inflammatory infiltration. Clinically hormone deficiencies progress in a characteristic sequence namely growth hormone (GH), luteinizing hormone (LH) follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH) and finally adrenocorticotropic hormone (ACTH). This loss of pituitary hormone secretion is usually a slow process, occurring over a period of months or years. However occasionally it may be sudden following pituitary infarction due to haemorrhagic necrosis or ischaemia, referred to as apoplexy.

Pituitary apoplexy

Pregnancy increases the risk of acute pituitary apoplexy due to the rapid expansion of a pre-existing pituitary tumour (e.g. prolactinoma). Although rare the clinician should be altered to the diagnosis in women presenting with sudden onset of headache, visual symptoms, (bitemporal hemianopia and/or III, IV or VI nerve palsy) altered mental status, and hormonal dysfunction (hypotension and hypoglycaemia). Alternatively, apoplexy in a non-tumorous pituitary gland may follow a more indolent course, with failure of lactation succeeding postpartum haemorrhage (Sheehan’s syndrome). Women with associated haemodynamic compromise suggestive of adrenal insufficiency should be given intravenous hydrocortisone immediately (100 mg QDS) and a pituitary MRI and endocrine assessment requested urgently.

Lymphocytic hypophysitis

Lymphocytic hypophysitis is an inflammatory lesion of the pituitary gland, which although rare, typically affects women during late pregnancy or in the postpartum period. Clinically it presents with features suggestive of an expanding pituitary tumour (see above) with a predilection for the corticotrophs (ACTH) and thyrotrophs (TSH). Antipituitary antibodies have been described however they are not helpful in the diagnosis, which may be suggested by (gadolinium enhanced) MRI; histological assessment is rarely available, but is highly suggestive of the diagnosis. A quarter of affected individuals may also have an additional autoimmune condition predominantly adrenalinits, thyroiditis or pernicious anaemia.

Diabetes insipidus

Diabetes insipidus (DI) is a deficiency (in the amount or functional ability) of antidiuretic hormone (ADH). Produced in the hypothalamus and stored in the posterior pituitary, ADH acts directly on the distal renal tubules to allow water re-absorption in response to dehydration. DI may result from a lack of ADH release from the posterior pituitary (cranial DI) or a lack of response to its action in the kidney (nephrogenic DI). The result is an inability to maintain a normal plasma osmolarity (275–295 mmol/L) and concentrate the urine (>300 mOsmol/kg). Polyuria (>3 L/24 h) stimulates increased thirst with compensatory polydipsia. The aetiology of DI is varied being either congenital or acquired. For the purposes of this paper only those salient to obstetrics will be discussed.

The diagnosis of DI is conventionally made with an 8 h water deprivation test and desmopressin (DDAVP) challenge. In pregnancy such dehydration is potentially hazardous and the diagnosis should be first attempted by admission and observation in...
conjunction with careful documentation of fluid balance and urine and plasma osmolarities.

Transient DI can occur during pregnancy due to placental production of vasopressinase, an enzyme which degrades ADH. In susceptible individuals (such as those taking lithium) this may unmask subclinical (nephrogenic) DI. Women with pregnancy related liver disease (pre-eclampsia, HELLP syndrome or acute fatty liver of pregnancy) are also at risk of developing DI due to reduced hepatic clearance of vasopressinase. In either circumstance DI will invariably regress following delivery.

Established DI tends to deteriorate during pregnancy (60%) due to

- An increase in the glomerular filtration rate.
- Antagonism of ADH by a rise in renal prostaglandins.
- Placental production of vasopressinase.

Treatment of DI is dependent upon its aetiology. Women with cranial DI may be given DDAVP (synthetic ADH) nasally, sublingually or orally with regular biochemical and clinical assessment to ensure optimal hormone replacement. In nephrogenic DI any known precipitating/exacerbating factors such as electrolyte abnormalities should be corrected. High dose DDAVP may be effective. DDAVP is not metabolized by placental vasopressinase and does not have sufficient oxytocin-like action to cause uterine contractions. Alternatively carbamazepine, which increases endogenous ADH production, can be used although its small teratogenic risk in the first trimester does not make it an optimal choice. Thiazide diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) although used successfully outside pregnancy are associated with oligohydramnios, and should be avoided in pregnancy. Furthermore, NSAIDs are contraindicated after 24/40 weeks’ gestation due to the risk of premature closure of the ductus arteriosus.

Suboptimal treatment of DI results in hypernatraemia, dehydration and seizures. Regular antenatal assessment of these patients is necessary with increasing treatment requirements often being required.

**Acromegaly and Cushing's disease**

Both conditions are rarely encountered in pregnancy, partly due to associated infertility. Acromegaly is a disorder of excessive growth hormone (GH) secretion from a pituitary adenoma, presenting with features of prognathism and soft tissue hypertrophy. In pregnancy significant tumour enlargement may occur. GH does not cross the placenta and has no direct deleterious effect on foetal development. During pregnancy somatostatin analogues (Octreotide) have been used to decrease GH although data regarding their safety in pregnancy are limited.

Cushing’s disease (CD) is a state of hypercortisolaemia secondary to an ACTH producing pituitary tumour. This condition is notoriously difficult to diagnose during pregnancy due to the relative state of hypercortisolaemia associated with normal pregnancy. The management of CD in pregnancy will be discussed in more detail in relation to adrenal disease.

Excessive growth hormone and cortisol secretion may result in diabetes mellitus and hypertension both of which may adversely affect foetal development. Standard antenatal treatment of these complications with insulin and antihypertensives will help reduce the risk of associated maternal and foetal morbidity.

### Adrenal disease

The adrenal gland has a three layered outer cortex responsible for the production of steroid hormones (glucocorticoids, mineralocorticoids and androgens) and an inner medulla which releases catecholamines. Adrenal incidentalomas are common and found in up to 5% of individuals, with lesions over 4 cm in diameter having a greater risk of malignancy. In the second trimester radiographic classification of adrenal adenomas may be safely facilitated through (gadolinium enhanced) MRI.

**Cushing's syndrome**

Cushing’s syndrome (CS) is a state of hypercortisolaemia. Up to three quarters of affected women experience oligo/anovulation, therefore the likelihood of pregnancy is reduced. Additional characteristics include weight gain, central obesity, hypertension (70%) and hyperglycemia (27%), symptoms and signs which may be difficult to distinguish from normal pregnancy and common complications such as gestational diabetes or pregnancy induced hypertension. This means that the diagnosis may be overlooked. In women with CS, despite the protective effects of the placental enzyme 11-β hydroxysteroid dehydrogenase 2, pregnancy complications are high including premature delivery (60%), pregnancy loss (40%) and neonatal adrenal insufficiency as well as a tentative association between hypercortisolaemia and foetal oral clefts. Similarly maternal morbidity (70%) and mortality (2%) are increased. Severe pre-eclampsia is common (10%), with other complications including poor wound healing, osteoporosis, psychiatric complications and cardiac failure.

The aetiology of CS may be divided into three main groups:

| ACTH dependant CS | - Cushing’s disease (pituitary adenoma) |
| ACTH independent CS | - adrenal adenoma |
| Iatrogenic CS | - adrenal hyperplasia |
| | - adrenal carcinoma |
| | - exogenous steroids |

The diagnosis of ACTH-dependent CS in pregnancy is fraught with difficulty. Conventional dexamethasone suppression testing is associated with high false positive rates; furthermore ACTH levels may be increased, secreted both by the placenta and the pituitary. Case reports of CD diagnosed and treated with transphenoidal surgery during pregnancy have been published, however with such diagnostic uncertainty; the risk of inappropriate surgical treatment and potential complications is high. Foetal and maternal morbidity may be reduced with focused multidisciplinary management and delivery at 37/40; succeeded by investigation after the puerperium.

Adrenal disease accounts for over half the cases of CS diagnosed during pregnancy of which nearly a quarter are malignant. This is in contrast to outside of pregnancy when pituitary causes predominate. A diagnosis of adrenal (ACTH independent) CS in pregnancy is credible if there are clinical symptoms of hypercortisolaemia, an adrenal adenoma on ultrasound, a high plasma cortisol and suppressed ACTH. Under these circumstances a laparoscopic adrenalectomy (in the second trimester) should be considered.
Primary adrenal insufficiency (Addison's disease)

In the developed world primary adrenal insufficiency (PAI) is predominately due to autoimmune destruction of the gland (70%); although with increasing immigration, tuberculosis should also be considered. PAI is a condition of cortical hormone deficiency (androgens, glucocorticoids and mineralocorticoids) resulting in lethargy, weight loss, hypotension, hyperkalaemia, hyponatraemia and hypoglycaemia. Skin hyper pigmentation due to excessive ACTH stimulation of melanocytes is suggestive of suboptimal endogenous glucocorticoid levels or replacement. Although most women with PAI have been diagnosed prior to pregnancy and are on treatment, some may present antenatally. Interpretation of cortisol results in pregnancy (9 am cortisol level or following a Synacthen test) must be executed with caution as levels falling within the normal non-pregnant range may be abnormally low during pregnancy. Treatment with hydrocortisone and fludrocortisone has dramatically reduced maternal morbidity and mortality. During times of intercurrent illness or stress the dose of hydrocortisone should always be doubled and then reduced back during convalescence. At the onset of labour affected women must be given supplementary intramuscular/intravenous hydrocortisone (100 mg QDS) with tapering of the dose over the 3 days following delivery. An additional infusion of normal saline may also be given postpartum to compensate for the physiological naturesis. Provided PAI is diagnosed and treated before pregnancy maternal and foetal outcomes should be normal. In women with autoimmune adrenalitis despite the transplacental passage of antiadrenal antibodies, neonatal adrenal insufficiency is rarely encountered.

Conn’s syndrome

Conn’s syndrome, or primary hyperaldosteronism, is the result of an adrenal adenoma, hyperplasia or malignancy. It may present with hypertension, hypokalaemia and a mild metabolic alkalosis. Biochemical screening for Conn’s syndrome is performed by assessing the plasma aldosterone:renin ratio (ARR) where a ratio of >750 is suggestive. However during normal pregnancy aldosterone levels increase 10-fold; making interpretation of the results open to error. If the diagnosis is suspected an adrenal ultrasound or MRI should be requested. Case reports during pregnancy demonstrate equal success of tumour resection in the second trimester or medical management. It therefore seems appropriate to defer surgery until after delivery, unless the adrenal lesion is suggestive of malignancy. Conventional biochemical screening (ARR) should then be conducted after the puerperium and definitive treatment offered if indicated. Medical management includes potassium supplements, amiloride and standard antenatal antihypertensive treatment. Spironolactone (an aldosterone antagonist) should be avoided in pregnancy due to its additional antiandrogenic effects potentially causing feminization of a male foetus. Little is known regarding the safety of the aldosterone antagonist Eplerenone in pregnancy.

Phaeochromocytoma

Phaeochromocytomas are rare adrenomedullary catecholamine secreting tumours. The majority of cases are sporadic and unilateral, with 10% being malignant, bilateral or familial (multiple endocrine neoplasia II, Von Hippel–Lindau syndrome and neurofibromatosis). Although their incidence is low in pregnancy (0.007%) a phaeochromocytoma should be considered in any women presenting with labile or sustained hypertension, headache, excessive sweating and palpitations (± impaired glucose tolerance). Symptomatic episodes may occur with increasing frequency as pregnancy progresses or when supine due to an increase in intra abdominal pressure. Potentially fatal hypertensive crises may be precipitated by opiates, metoclopramide or anaesthetic agents, with labour and vaginal or abdominal delivery posing the greatest risk. In undiagnosed cases maternal and foetal mortality may be as high as 15% and 25% respectively. With increasing awareness, more reliable antenatal testing modalities and early therapeutic intervention mortality rates have been reduced to 0% and 15%. The diagnosis is made by demonstrating elevated levels of urinary catecholamines (adrenaline, noradrenaline and dopamine) at least two times the upper limit of the normal range. Adrenal imaging with US or MRI should then be requested to localize the tumour with approximately 98% detected within the abdomen. MIBG (I 131meta-iodobenzylguanidine) are contraindicated in pregnancy due to the possible effects on the foetal thyroid.

Following confirmation of the diagnosis medical optimization is necessary prior to surgical removal of the tumour. Patients should receive intravenous fluid therapy prior to α blockade with phenoxybenzamine to minimize the risk of acute hypotension. Propranolol (β-blocker) should then be introduced 48 h later.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder characterized by a deficiency of one of the enzymes involved in cortisol synthesis. The majority of cases (>90%) are due to 21α hydroxylase deficiency, the clinical spectrum dependent upon the severity of the genetic defect involved. Classical CAH is typically diagnosed in infancy. Increased levels of serum androgens and the absence of cortisol and aldosterone lead to virilization of an affected female foetus in conjunction with profound salt wasting (hyponatraemia) and hypotension in a child of either sex in early neonatal life. Affected women often require reconstructive genital surgery to allow successful intercourse; and with glucocorticoid replacement restoring ovulation, pregnancy rates have improved.

During pregnancy adequate hormone replacement should be assessed regularly in relation to maternal levels of free testosterone and serum electrolytes.

Non-classical CAH is a milder form of the condition (due to a point mutation) and affected females often present later in childhood or adult hood with hirsutism and menstrual irregularities.

In northern Europeans the carrier frequency of 21α hydroxylase deficiency is approximately 1:60. Therefore partners of affected individuals should be assessed for subclinical disease (elevated 17 hydroxy progesterone level) and if positive, genetic screening offered prior to pregnancy. If the status of the partner is unknown the risk of the child being affected will be approximately 1%, however if he is heterozygous this risk will increase to 50%. With the advent of in vitro fertilization and pre-implantation genetic diagnostic testing (PGD) this risk can be minimized, although PGD is only available in specialist centres. Alternatively pregnant...
women at risk of having a baby with CAH should start high dose preconception dexamethasone, which crosses the placenta and therefore will suppress foetal adrenal androgen production until the result of chorionic villus sampling is known. Only if the foetus is male or an unaffected female should maternal dexamethasone be stopped and standard treatment with prednisolone and flu- drocortisone recommenced as appropriate. This practice has helped reduce the need for female reconstructive surgery in up to three quarters in those affected however is associated with an increased risk of maternal morbidity.

**FURTHER READING**

**Practice points**
- Thyroid disease is the second most common endocrine disorder of pregnancy.
- Women with hypothyroidism should ideally have their thyroxine dose optimized prior to pregnancy, and then reviewed each trimester.
- Patients with Graves’ disease should have TSH receptors antibodies checked by the beginning of the third trimester.
- Vitamin D levels requirements increase during pregnancy. It is important to assess women with regards the need for supplementation to help prevent osteopenia/osteomalacia in certain ‘at risk’ populations.
- Women with macroprolactinomas who require bromocriptine or cabergoline should continue treatment during their pregnancy to minimize the likelihood of expansion. Treatment can be continued during breastfeeding.
- Cushing syndrome is difficult to diagnose in pregnancy and requires multidisciplinary investigation and management.
- Women at risk of having a baby with congenital adrenal hyperplasia should be offered dexamethasone prophylaxis and then chorionic villus sampling; dexamethasone can then be discontinued unless it is an affected girl.