14.11 Endocrine disease in pregnancy 2638

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ESSENTIALS Thyroid Many pregnant women will develop goitre. Gestational thyrotoxi- cosis needs to be differentiated from Graves' disease, which requires treatment with propylthiouracil in early pregnancy and carbimazole in later pregnancy. Overt hypothyroidism is associated with ad- verse maternal and fetal outcomes and should be treated to main- tain thyroid-stimulating hormone within the trimester-specific reference range. Adrenal The diagnosis of both Addison's disease and Cushing's syndrome can be challenging in pregnancy. Patients with adrenal insufficiency may require higher replacement steroid doses, particularly in the third trimester. Pituitary Prolactinomas are commonly encountered in pregnancy. Women with macroprolactinomas should have visual field monitoring throughout pregnancy. Lymphocytic hypophysitis is increasingly recognized as a cause of hypopituitarism arising in late pregnancy and in the post-partum period. Thyroid disease Thyroid physiology in pregnancy Pregnancy has a significant impact on thyroid physiology. The fetal thyroid does not secrete active thyroid hormone until 18–20 weeks of gestation, hence maternal thyroid hormone production must in- crease by up to 50% in order to provide enough thyroid hormone for the developing fetus. As a result, many pregnant women, particu- larly in iodine deficient areas, will develop goitre. Interpretation of thyroid tests is also affected by pregnancy. Thyroid-stimulating hormone (TSH) closely resembles β-HCG at a molecular level, and due to cross-reactivity in pregnancy normal TSH ranges are lower. Trimester-specific reference ranges for use in pregnancy have been developed in many laboratories: these should be used wherever possible, since TSH ranges will depend upon the population and ethnicity of the women studied. Gestational thyrotoxicosis In early pregnancy, particularly in those with excessive vomiting or with twin pregnancies, excessively high β-HCG levels can lead to apparent thyrotoxicosis. Most women with gestational thyrotoxi- cosis can be managed conservatively with fluids and antiemetics, although it is important to differentiate from Graves' disease pre- senting in pregnancy: several clinical features can help to discrim- inate (Table 14.11.1). Treatment of Graves' disease in pregnancy Graves' disease affects around 0.2% of pregnancies. Carbimazole (methimazole) is the most commonly used drug for thyrotoxicosis. Case reports (although not larger studies) have associated this drug with rare congenital malformations including aplasia cutis and oesophageal atresia, and so propylthiouracil has traditionally been recommended for use pre-

pregnancy. Propylthiouracil, how- ever, has been associated with hepatotoxicity in late pregnancy, so a balance between the small risks associated with these two medi- cations is required. Treatment, which can usually be down-titrated, should be continued throughout pregnancy and into the early post- partum period to reduce the risk of early recurrence post-partum (see Box 14.11.1). Block and replace regimes should be avoided in pregnancy. If antithyroid medications are ineffective or not tolerated, then surgical treatment should be considered; the use of radioactive iodine is contra-indicated in pregnancy and while breastfeeding. 14.11 Endocrine disease in pregnancy David Carty Table 14.11.1 Differentiation of Graves' disease from gestational thyrotoxicosis Graves' disease Gestational thyrotoxicosis Goitre √ X Thyroid receptor antibodies √ X Symptoms prior to pregnancy √ X Eye signs √ X

 Women are at risk of recurrence of Graves' disease in the post- partum period, and thyroid function tests should be monitored regularly after delivery. Loss of ability to breast-feed can be an early sign of recurrence. Both carbimazole and propylthiouracil are de- tectable in breast milk, although there is no evidence of harm to the baby: in general, if further pregnancy is desired then propylthiouracil is preferable. Hypothyroidism in pregnancy Overt hypothyroidism is associated with several adverse maternal and fetal outcomes, including pre-eclampsia, intrauterine growth restriction, preterm delivery, and reduced intelligence quotient (IQ) in the offspring. Treatment of overt hypothyroidism leads to an improvement in these outcomes and for this reason many clinicians advocate the universal screening of thyroid function in pregnant women. The aim in pregnancy is to maintain TSH within the trimester-specific reference range. Some women with hypothyroidism will require an increase in daily dose of thyroxine of 25–50 mcg to attain this: those with no thyroid gland because of previous radio iodine or surgical treatment are more likely to need a dose increase than those with autoimmune hypothyroidism. T3 does not cross the placenta, and its use should be avoided in pregnancy. Subclinical hypothyroidism describes TSH above the trimester- specific reference range, but with a normal fT4. Depending on the population studied, rates of this condition are reported to be up to 15%. Although associated with adverse fetal and maternal outcomes in some studies, evidence that thyroxine treatment leads to an improvement in these outcomes is limited and con- flicting. Recent guidelines from US and European Societies advo- cate treatment with thyroxine of women found to have subclinical hypothyroidism, although definitions differ between guidelines. Fetal and neonatal thyroid dysfunction In women with uncontrolled thyrotoxicosis or high thyroid re- ceptor antibody (TRAB) titres, additional fetal ultrasound moni- toring of fetal heart rate, growth, amniotic fluid volume, and assessment for fetal goitre should be undertaken. The diagnosis of fetal thyrotoxicosis can be confirmed if necessary by fetal blood sampling. Treatment is by maternal administration of high-dose propylthiouracil (300–450 mg/day) together with thyroxine during gestation to prevent maternal hypothyroidism. Involvement of fetal medicine specialists is required. Neonatal hypothyroidism may very rarely occur at birth due to maternal TSH receptor blocking anti- bodies, maternal antithyroid drug administration, iodine deficiency, and maternal goitrogen ingestion. All these conditions are transient, and the mother can be reassured. Post-partum thyroid dysfunction Up to 15% of women in the general population have positive thyroid peroxidase antibodies; of these 50% will develop a degree of post- partum thyroid dysfunction. The condition is thought to be caused by autoimmune-associated release of preformed hormone from the thyroid. In general, the disease is characterized by transient thyro- toxicosis, followed by hypothyroidism, and then a return to normal (Fig. 14.11.1) The thyrotoxic phase is usually asymptomatic; in contrast the hypothyroid phase will often be associated with symptoms

and re- quire thyroxine treatment. There is a high risk of recurrence in fu- ture pregnancies, and up to 65% of women will develop permanent hypothyroidism during long-term follow-up. TSH should be meas- ured annually in affected women. Thyroid nodules in pregnancy Thyroid nodules occur in up to 10% of pregnant women, and in general these should be dealt with in a similar manner to outwith Box 14.11.1 Management of Graves' disease in pregnancy • Confirm diagnosis • Treat with propylthiouracil if diagnosed prior to planned pregnancy or in first trimester • Consider switch to carbimazole in second trimester — Aim to continue treatment until delivery • Monitor thyroid function tests 4–6 weekly — Titrate dose where necessary • Check thyroid receptor antibodies (TRAB) in third trimester — Inform neonatologist if positive (risk of fetal thyrotoxicosis) • Review post-partum — Check for recurrence Reference range TSH levels fT4 and T3 levels Thyrotoxic phase 2–6 months Hypothyroid phase 3–12 months Recovery Fig. 14.11.1 Pattern of thyroid dysfunction in post-partum thyroid dysfunction.

Section 14 Medical disorders in pregnancy 2640 pregnancy. A suggested algorithm for investigation is shown in Fig. 14.11.2. Surgery, if required, should be undertaken in the second trimester. Investigation of nodules identified in late pregnancy can be deferred until the post-partum period. Parathyroid disease Diseases of the parathyroid glands are uncommon in women of childbearing age, but hyperparathyroidism during pregnancy can lead to acute pancreatitis or severe hypercalcaemia. There is an in- creased incidence of prematurity and neonatal hypocalcaemia and tetany if maternal calcium levels are high. The high maternal cal- cium levels suppress fetal parathyroid hormone causing the neonatal calcium to fall following cord clamping at delivery. Surgical man- agement can be undertaken safely in pregnancy and ideally in the second trimester. Hypoparathyroidism is treated with vitamin D analogues, with dosage often needing to be increased during pregnancy to maintain normocalcaemia, hence calcium levels should be monitored regu- larly throughout pregnancy, at least once in each trimester. Adrenal disease Addison's disease Addison's disease can rarely present in pregnancy. Diagnosis can be difficult, but should be considered in women with unexplained hypotension, hyponatraemia/hyperkalaemia, or pigmentation. In women already known to have the condition, many will require an increase in steroid dose particularly in the third trimester, if hyperemesis develops, or during any intercurrent infection. Higher doses of intravenous hydrocortisone are required for labour or op- erative delivery, and anaesthetists should be informed of the patient's condition. Cushing's syndrome Cushing's syndrome is associated with several adverse pregnancy outcomes, including diabetes, pre-eclampsia, and wound healing problems. The presentation of Cushing's syndrome in pregnancy is similar to outwith pregnancy, but diagnosis can be challen- ging: elevated cortisol levels are seen in the second and third tri- mesters in normal pregnancy, dexamethasone suppression testing is less reliable in pregnancy, and reference ranges for urinary free cortisol in pregnancy have not been established. Unlike the gen- eral population, where adrenocorticotropic hormone-dependent Cushing's is more common, the proportion of Cushing's syn- drome due to adrenal lesions is higher in pregnancy than in the nonpregnant population. Since ongoing cortisol excess is associ- ated with significant maternal and fetal morbidity, a surgical cure should be pursued. Adrenal tumours Adrenal tumours in pregnancy are rare, but as with other tumours there is a risk of enlargement in pregnancy. Phaeochromocytoma can be mistaken for pre-eclampsia, and should be considered in women with episodic hypertension, associated symptoms of head- ache or palpitations, or a family history. Diagnosis involves measure- ment of 24-hour urinary or plasma metanephrines. In general, the lesion should be removed laparoscopically if identified in the first or second trimester; if the lesion is identified in the third trimester then adrenalectomy is usually deferred until a few weeks

later. Women should be adequately α-blocked (and then, if necessary, β-blocked) prior to surgery and/or delivery. Congenital adrenal hyperplasia Congenital adrenal hyperplasia is a group of autosomal reces- sive conditions characterized by impaired cortisol synthesis. 21-Hydroxylase deficiency is the most common cause, present in over 95% of cases. Fertility in women with the more severe variant (classical) congenital adrenal hyperplasia is reduced, owing to an- drogen excess, oligoanovulation, and chronically elevated levels of adrenal-derived progesterone. Although androgen levels are often elevated in pregnancy, placental aromatase production prevents virilization of unaffected female fetuses. Fertility is less likely to be affected in women with the less severe (nonclassical) form of the dis- ease. Management of congenital adrenal hyperplasia in pregnancy involves adequate steroid replacement and adrenal androgen sup- pression. In women with classical congenital adrenal hyperplasia, hydrocortisone should be used in pregnancy; dexamethasone, which can cross the placenta, should be avoided. Genetic counsel- ling may be considered for an index case desiring pregnancy, or in families with a previously affected infant. Pituitary Prolactinomas Prolactinomas are the most common type of functioning pitu- itary lesion and since they have a peak incidence in women during childbearing years they are commonly encountered in pregnancy. Monitoring of prolactin levels in pregnancy is unhelpful: the normal pituitary expands by 30% in pregnancy, largely due to lactotroph ex- pansion, and so normal pregnancy is associated with a 10-fold in- crease in prolactin levels. Medical therapy with dopamine agonists is the treatment of choice for prolactinoma: these reduce tumour bulk and Thyroid nodule detected in pregnancy History and examination TFTs Ultrasound reveals nodule >1cm Benign ultrasound appearances Defer further investigation until after pregnancy Consider FNA Refer for surgery Compressive symptoms Ultrasound suspicious for malignancy Fig. 14.11.2 Investigation algorithm for thyroid nodules.

 normalize prolactin levels in most patients. Women with lesions that are resistant to dopamine agonists or who are intolerant should be counselled regarding the benefits of surgery prior to pregnancy. Women with microprolactinomas should, in general, stop dopamine agonists when they find out they are pregnant, since the risk of enlargement causing visual field impairment is less than 1%. In women with macroprolactinomas, however, the risk is much higher, and such women may require to stay on their dopamine agonist therapy. After careful counselling they may wish to discontinue treatment in the last month of pregnancy to facilitate breast-feeding. Women with macroprolactinomas should have visual field monitoring throughout pregnancy, par- ticularly if dopamine agonists are discontinued or if they develop symptoms. Symptoms indicative of expansion include headache, visual field deterioration, and cranial nerve palsies. If a lesion enlarges in pregnancy, then restarting or increasing dose of dopa- mine agonist therapy should be considered; there are now exten- sive safety data available for both cabergoline and bromocriptine in pregnancy. Acromegaly Fertility is reduced in women with acromegaly because of co- secretion of prolactin along with growth hormone, and because of decreased gonadotrophin reserves due to the tumour expansion. In affected women wishing to conceive, growth hormone and prolactin levels should be normalized prior to conception. In general, women with microadenomas should discontinue medical therapy in pregnancy and be assessed at each trimester. Women with macroadenomas should be monitored closely, with visual field monitoring in each trimester and MRI scan when necessary. There are limited safety data for the use of somatostatin analogues in pregnancy, and if necessary use of dopamine agonists can be con- sidered instead. Nonfunctioning pituitary adenomas Although nonfunctioning pituitary adenomas represent 30% of pi- tuitary adenomas overall, they tend to present in older age and are associated with reduced fertility, hence they are rarely encountered in pregnancy. Nonfunctioning

lesions do not usually increase in size in pregnancy,s but monitoring of visual fields is recommended for women with macroadenomas. If symptomatic enlargement occurs, medical treatment with dopamine agonists or trans-sphenoidal sur- gery can be considered. Diabetes insipidus Central diabetes insipidus may present during pregnancy. It is seen in women with lymphocytic hypophysitis (see next) and in women with infiltrative disorders such as Langerhans' cell histiocytosis. Synthetic desmopressin is normally used in the management of dia- betes insipidus and can be given orally or intranasally. Use during pregnancy seems to be safe for both mother and baby: synthetic desmopressin does not affect delivery and has no adverse effects on the neonate. Diabetes insipidus may be seen transiently at the end of otherwise normal pregnancy and in women with acute fatty liver of pregnancy. This is related to production of vasopressinase by the pla- centa, the breakdown of which is delayed in acute fatty liver. Lymphocytic hypophysitis Lymphocytic hypophysitis is increasingly recognized as a cause of hypopituitarism arising in late pregnancy and in the post-partum period. The underlying aetiology is thought to be autoimmune, and pathology is characterized by dense infiltration of lympho- cytes. Women may present with a pituitary mass lesion, headache, or visual field disturbance, and imaging resembles a pituitary ad- enoma in 80% of patients. Affected women will commonly have par- tial hypopituitarism, with adrenocorticotropic hormone and TSH the most common deficiencies, and relative sparing of luteinizing hormone (LH) and follicle-stimulating hormone. Treatment is usu- ally with corticosteroids. It has been speculated that many cases of Sheehans's syndrome, a now rare condition characterized by hypo- pituitarism associated with post-partum haemorrhage, may in fact have been caused by lymphocytic hyophysitis. FURTHER READING Casey BM, et al. (2017). Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. N Engl J Med, 376(9), 815–25. de Groot L, et al. (2012). Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab, 97, 2543–65. Frise CJ, Williamson C (2013). Endocrine disease in pregnancy. Clin Med, 13, 176–81. Lazarus J, et al. (2014). 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J, 3, 76–94. Lindsay JR, Nieman LK (2006). Adrenal disorders in pregnancy. Endocrinol Metab Clin North Am, 35, 1–20, v. Stagnaro-Green A, et al. (2011). Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid, 21, 1081–125.

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