Endocrine disorders in pregnancy

Advances in the treatment of endocrine diseases have enabled many women to become pregnant who previously would have been unable to do so. This article discusses a range of nondiabetic and nonthyroid problems that GPs may encounter in pregnant patients.

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Medical disorders seen in pregnancy can predate or develop during pregnancy. It is important to consider the impact of the pregnancy on the disease, as well as the effect that the disease has on the mother and fetus.

This article describes endocrine problems involving calcium metabolism, and disorders of the pituitary and adrenal glands. Thyroid disease, which is common in women of childbearing age, can also occur in pregnancy and was discussed in an earlier article in *Medicine Today*.[1] Diabetes in pregnancy will not be discussed in this article.

Prior to beginning any drug therapy to treat maternal disease, the potential fetal effect of the treatment must be discussed with the mother. For drugs mentioned in this article, the Australian categories for risk of drug of use in pregnancy are stated. Readers are referred to the categorisation prepared by the Medicines in Pregnancy Working Party of the Australian Drug Evaluation Committee for further information.[2]

Disorders of calcium metabolism

A full-term pregnancy involves the active transport of 30 to 35 g of calcium across the placenta to the developing fetus, and lactation requires the active transport of calcium into milk. Changes in maternal hormone levels regulate calcium metabolism to meet these needs as described in the box on page 42.

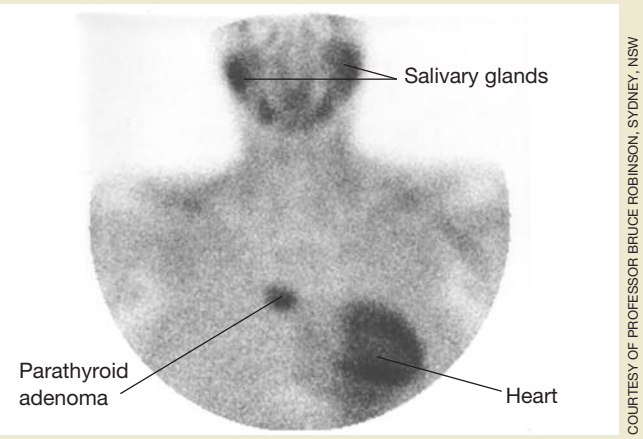
Hypercalcaemia

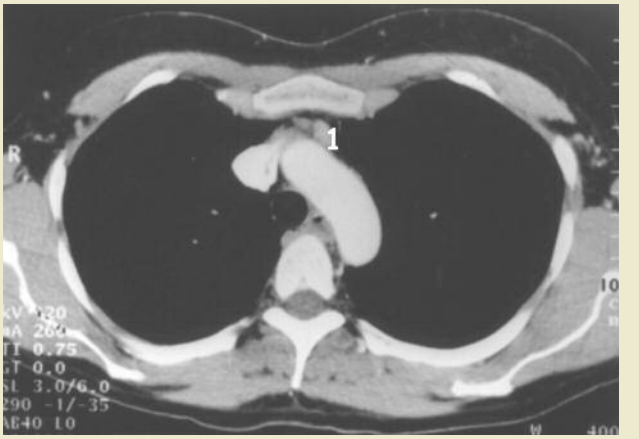
The incidence of primary hyperparathyroidism in women of childbearing age is approximately eight per 100,000 per year. Its causes in pregnancy are similar to those seen in the nonpregnant state,

IN SUMMARY

- **Drug therapies for pre-existing endocrine disorders should not be ceased when pregnancy is confirmed. Specialist review is recommended.**
- **During pregnancy, the recommended daily intake of calcium is raised from 800 to 1200 mg per day. Calcium supplementation is not routinely recommended during lactation, but could be considered for women who are nursing more than one infant or have had closely spaced pregnancies, and for lactating adolescents.**
- **Women with mild asymptomatic primary hyperparathyroidism may be monitored without treatment throughout pregnancy with a good outcome. However, surgical parathyroidectomy is recommended for more severe disease, preferably in the second trimester.**
- **Patients with prolactinomas and other pituitary tumours should be reviewed regularly throughout pregnancy and questioned about symptoms of tumour enlargement and pituitary dysfunction.**
- **Patients taking corticosteroids during pregnancy for Addison's disease or for other reasons will need to increase their dosage at times of stress.**
- **Breastfeeding is generally not contraindicated in women with endocrine disorders.**

Primary hyperparathyroidism





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Figures 1a and b. Parathyroid adenoma as a cause of hyperparathyroidism seen in two pregnant women. a (left). A sestamibi scan of a hypercalcaemic patient showing an adenoma of ectopic mediastinal parathyroid tissue located in the chest. Surgical treatment resulted in resolution of symptoms. b (right). A chest CT scan showing a mediastinal parathyroid adenoma in pregnancy (the position is marked by '1'). This woman's symptoms resolved after successful surgical treatment.

including single adenoma (80 to 90% – see Figures 1a and b), hyperplasia (10%), multiple adenomas (3%) and parathyroid carcinoma (1 to 2%). Most cases are asymptomatic and diagnosed by routine biochemical analysis.

Primary hyperparathyroidism in pregnancy is associated with increased maternal and fetal morbidity. Effects on the mother are dependent on the serum level of calcium – she may be asymptomatic or have nonspecific symptoms such as fatigue, weakness, anorexia, depression, mild cognitive dysfunction and constipation. More severe disease may result in severe muscle weakness, nausea and vomiting (which may be misdiagnosed as hyperemesis gravidarum), dehydration, coma, pancreatitis, osteoporosis and peptic ulcer disease. The placental transfer of calcium to the fetus offers some protection to the mother, but she may be at increased risk of hypercalcaemic crisis postpartum when this protection has ceased.

The current treatment of primary hyperparathyroidism in pregnancy is surgical parathyroidectomy, preferably in the second trimester, but women with mild asymptomatic hyperparathyroidism may be followed throughout pregnancy without operation and with a good outcome. Prior to 1976, fetal mortality associated with primary hyperparathyroidism approached 25%; a review of cases from 1976 to 1990 documented a rate of 5% – this reduction is the result of routine maternal parathyroidectomy in the second trimester for severe disease. Other fetal complications include neonatal hypocalcaemia (due to transplacental passage of parathyroid hormone) and prematurity.

Other causes of hypercalcaemia in pregnancy include:

- familial hypocalcuric hypercalcaemia
- thyrotoxicosis
- parathyroid hormone-related peptide induced hypercalcaemia
- adrenal insufficiency
- malignancy
- vitamin A or D overdose
- granulomatous disease
- milk alkali syndrome (due to excess consumption of absorbable alkali, such as milk or calcium carbonate)
- renal failure.

Hypocalcaemia

Hypoparathyroidism as a complication of thyroid surgery is the most common cause of hypocalcaemia in young women. Other causes include rickets, osteomalacia (Figure 2), hypomagnesaemia,

and polyimmune hypocalcaemia (which may be associated with polyendocrine failure).

Prior to maternal therapy, fetal morbidity and mortality due to hypoparathyroidism were high. Fetal complications are prevented by treating the mother with calcium and calcitriol (Citrihexal, Kosteo, Sitriol, Rocaltrol), a Category B3 drug. The mother requires frequent testing of serum calcium and phosphate levels and adjustments to her therapy to maintain the calcium in the low to normal range. Calcium homeostasis is changed postpartum due to the effect of parathyroid hormone-related peptide, and the calcitriol dosage should be reduced. Both mother and infant should be monitored postpartum for hypercalcaemia.

Osteoporosis

Rarely, women develop frank osteoporosis with fracture during pregnancy (Figures 3 and 4). Patients at increased risk include those with repeated miscarriages in the second trimester which, if occurring in close succession, create an insufficient interval for restoring bone mass. Other women who are at risk are those taking corticosteroids, anticonvulsants or heparin in pregnancy – these drugs are associated with increased bone loss and, in combination with the physiological reduction in BMD that occurs in pregnancy, may increase risk (see Figure 3). The reduction in BMD that occurs in

Calcium metabolism: physiological adaptations to pregnancy and lactation

Pregnancy results in significant alterations in calcium homeostasis. In the nonpregnant state, about 50% of circulatory calcium is bound to plasma proteins (predominantly albumin), 10% is complexed with anions, and 40% circulates free as ionised calcium. During pregnancy, the total serum calcium decreases slightly as a result of physiological hypoalbuminaemia, an increase in extracellular fluid volume, increased glomerular filtration rate (causing urinary loss), and transfer of calcium to the fetus. However, the ionised calcium level remains constant. Intestinal calcium absorption is increased (especially in the last trimester), and the recommended daily intake is raised from 800 to 1200 mg. Increased maternal intestinal absorption of calcium may be insufficient for the fetal requirements, and calcium may be obtained from the maternal skeleton.

Hormone changes

Parathyroid hormone and vitamin D are the main regulators of calcium homeostasis in pregnancy. Thyroid and adrenal hormones – as well as glucagon, growth hormone and sex hormones – also have a role.

The primary function of parathyroid hormone is to maintain the normal serum calcium concentration. A fall in ionised calcium results in increased secretion of parathyroid hormone, leading to reduced renal calcium excretion, increased mobilisation of calcium from bone stores and, via increased production of calcitriol, increased gastrointestinal calcium absorption. Parathyroid hormone levels decrease with increasing gestation and tend to rise postpartum.

Calcitriol, the physiologically active form of vitamin D, increases throughout pregnancy and has more than doubled by term. Its role is to maintain serum levels of calcium and phosphate by acting on the intestine, bone and kidney. After delivery, calcitriol levels fall within three days to nonpregnant levels and urinary calcium excretion returns to normal.

Parathyroid hormone-related peptide, which is responsible for the humoral hypercalcaemia of malignancy, is believed to be involved in the transport of calcium from the maternal to the fetal circulation, and also from the mammary glands into milk. Levels of parathyroid hormone-related peptide increase throughout pregnancy, and postpartum levels correlate with the degree of breastfeeding.

Changes in bone turnover

Throughout pregnancy, there is an increase in urinary markers of bone resorption (free pyridinoline crosslinks and N-telopeptides). On the other hand, bone formation markers (serum bone specific alkaline phosphatase, carboxyl-terminal propeptides of type 1 collagen and osteocalcin) are static in early pregnancy and increase from about 28 weeks' gestation.

This uncoupling of bone turnover helps to supply the fetus with calcium and to maintain maternal calcium homeostasis, while leading to the decrease in maternal bone mineral density (BMD) seen in pregnancy. The reduction in BMD ranges from 1 to 4% and occurs predominantly in the axial skeleton (spine and hip). Lactation is associated with a decrease in maternal BMD (1 to 2% over the whole body), particularly the axial skeleton (3 to 5% at the lumbar spine). BMD changes in pregnancy and lactation are transient, returning to normal a few months after cessation of breastfeeding.

Calcium requirements in breastfeeding

Calcium supplementation during breastfeeding has been thought necessary to compensate for the secretion of 200 to 300 mg of calcium per day into the milk. However, four recent studies have shown supplementation to have no impact on the breastmilk calcium concentration or on bone mineral changes associated with lactation. Calcium supplementation is therefore not routinely recommended during lactation, but it could be considered for women who are nursing more than one infant or have had closely spaced pregnancies, and for lactating adolescents.

pregnancy may also unmask pre-existing occult disease.

Epidemiological studies to date have not suggested that parity and lactation are risk factors for postmenopausal osteoporosis.

Pituitary disorders

Adenomas

Adenomas are the most common pituitary disorder in pregnancy. Symptoms of pituitary tumours in pregnancy are due to hormone oversecretion as well as mass effects (visual field defects and headache), and hypopituitarism from compression of the pituitary stalk and hypothalamus.

The risk of developing visual field loss during pregnancy is small for patients with microadenomas, and higher for those with adenomas larger than 1.2 cm in diameter. Symptoms of mass effect should be investigated by MRI during pregnancy.

Hyperprolactinaemia

Pregnancy is a physiological cause of hyperprolactinaemia – the normal pituitary enlarges by up to 50% in pregnancy, due predominantly to hyperplasia of prolactin-producing lactotroph cells. Prolactin levels begin to rise from 5 weeks' gestation; at term, the level is 10 times the nonpregnant level.

The major issues to be considered in a pregnant woman with a past history of prolactinomas are the effect of pregnancy on the tumour size and the effect of treatment on the fetus. Dopamine agonists commonly used in the treatment of hyperprolactinaemia include bromocriptine and cabergoline (Dostinex); these are Category A and B1 drugs, respectively.

Prolactinomas are divided into macroprolactinomas (which occur in less than one-third of cases and are greater than 10 mm in diameter) and microprolactinomas (less than 10 mm in diameter). Patients with microprolactinomas who have conceived on dopamine agonist therapy can generally discontinue treatment when the pregnancy is confirmed, whereas those with macroprolactinomas are maintained on dopamine agonists throughout pregnancy because of the risk of tumour expansion if therapy is ceased.[3]

Patients with prolactinomas should be reviewed regularly throughout pregnancy and questioned about symptoms of tumour enlargement and pituitary dysfunction; visual fields should be assessed. Routine testing of prolactin levels to ascertain tumour expansion is of no value; breastfeeding is not contraindicated and should be discussed with the specialist. Low dose oral contraceptives do not result in tumour expansion and are an effective method of oestrogen replacement following pregnancy in patients with hyperprolactinaemia.

Acromegaly

Acromegaly results from hypersecretion of growth hormone by the somatotroph cells of the anterior pituitary. It is a rare condition with an estimated incidence of 3 to 4 cases per million per year.

Pregnancy is uncommon in patients with acromegaly because their fertility is reduced as a result of hyperprolactinaemia (occurring in 40% of patients), hypopituitarism and decreased gonadotrophin reserve. The metabolic and cardiovascular complications of the disorder impact on pregnancy in several ways. Patients are at greater risk of glucose intolerance and require an oral glucose tolerance test at 12 weeks' gestation and, if the result is

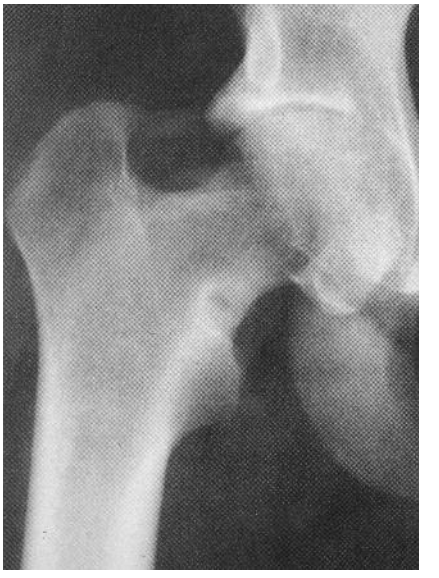


Figure 2. X-ray of a proximal femur showing a Looser zone (translucent transverse band) due to osteomalacia in a patient with x-linked hypophosphataemic rickets.

Osteoporosis in pregnancy

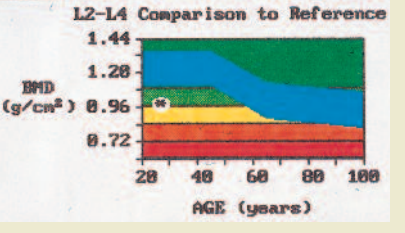


Figure 3. Osteoporosis of the lumbar spine in a woman who had been taking heparin during pregnancy. The BMD of her L2 to L4 vertebrae, measured about one month postpartum, was 0.982 g/cm^2, which is below the reference range for her age-matched population (shown in blue).

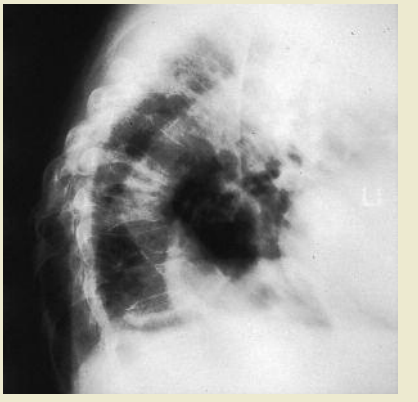


Figure 4. X-ray showing osteoporosis with crush fractures of the mid-thoracic spine.

normal, at 28 weeks. Pre-existing hypertension occurs in 25 to 35% of acromegalic patients, and regular review of blood pressure is required in pregnant women. Patients should be questioned regularly about symptoms of tumour expansion because the normal increase in pituitary size that accompanies pregnancy may result in tumour enlargement (a review of reported cases found exacerbation in four of 24 patients).[4]

Therapy for acromegaly includes transsphenoidal surgery and radiation, as well as medical therapy with bromocriptine or octreotide (Sandostatin). Octreotide is a Category C drug with limited case reports describing its use in pregnancy and, to date, no reported adverse effects on the fetus. The decision to cease medical therapy is dependent on the size and location of the adenoma and the woman's clinical state. Patients need to be assessed monthly, and GPs should liaise with the patient's endocrinologist early in the pregnancy. Breastfeeding is not contraindicated and should be discussed with the specialist.

Cushing's syndrome

Cushing's syndrome results from an excess of cortisol. Most cases are caused by Cushing's disease – that is, excess production of ACTH by the pituitary (see Figure 5). Other causes include:

- excess corticotrophin-releasing hormone
- non-ACTH dependent tumours of the adrenal cortex (benign or malignant)
- ectopic ACTH production (e.g. by small cell lung carcinoma).

Obesity, alcohol dependence and administration of excess corticosteroid may produce clinical features suggestive of Cushing's syndrome.

Pregnancy is associated with increases in the total serum cortisol, plasma free cortisol, 24-hour urinary free cortisol, and ACTH. These normal physiological changes need to be considered when investigating and diagnosing Cushing's syndrome in pregnancy.

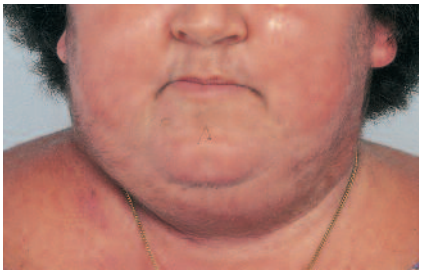


Figure 5. Cushing's disease in a woman of childbearing age showing facial plethora and hirsutism. Pregnancy is rare in the untreated disease because fertility is reduced.

Pregnancy in the face of untreated Cushing's syndrome is rare because the incidence of infertility is high due to elevated corticosteroid levels suppressing the hypothalamic–pituitary–gonadal axis. A review of Cushing's syndrome in pregnancy published in 1994 reported significant maternal morbidity due to hypertension, hyperglycaemia, poor wound healing and congestive cardiac failure.[5] In contrast, six pregnancies were reported two years later in patients with previously treated Cushing's disease and persistent hypercortisolism that were well tolerated without serious maternal morbidity.[6] Neonatal morbidity and mortality are increased due to prematurity, intrauterine growth restriction and abortion. Patients should be reviewed regularly for development of hyperglycaemia, hypertension and visual field defects.

Lymphocytic hypophysitis

Lymphocytic hypophysitis, which is thought to be an autoimmune disease, can occur during pregnancy or postpartum. The presentation can be related to mass effects or symptoms of varying degrees of hypopituitarism. Definitive diagnosis requires a pituitary biopsy, which reveals infiltration with lymphocytes and plasma cells and destruction of normal pituitary tissue.

Treatment consists of appropriate hormone replacement therapy. Surgery should be reserved for worsening mass effects or radiological evidence of progressive enlargement. The natural history of the disease is not well known, and some women have shown complete regression of the mass and return of pituitary function.[3]

Hypopituitarism

A diagnosis of hypopituitarism usually predates pregnancy. It can be caused by:

- tumour
- prior neurosurgery or irradiation
- infarction
- granulomatous disease
- aneurysms
- encephalocoele
- Sheehan's syndrome
- lymphocytic hypophysitis.

Hormone deficiencies can affect both the anterior and posterior pituitary and may be partial or complete. Fertility is impaired so pregnancy is unlikely unless patients have received prior treatment; the risk of abortion is increased if they do fall pregnant. If hypopituitarism is suspected, the diagnosis is confirmed by demonstration of impaired pituitary target hormone production and a low level of pituitary hormones that does not rise on stimulation.

During the first trimester of pregnancy, the daily dose of thyroxine (Oroxine), a Category A drug, usually needs to be increased by 0.05 mg due to increased thyroxine turnover. Thyroid function tests should be monitored in each trimester. Glucocorticoid replacement can be maintained at the usual dosages throughout pregnancy unless the patient is undergoing stress, such as hyperemesis gravidarum, infection or delivery – intravenous hydrocortisone (Solu-Cortef), a Category A drug, will be required at these times.

Sheehan's syndrome

Sheehan's syndrome comprises postpartum necrosis of the anterior pituitary due to postpartum haemorrhage and shock. The posterior pituitary is involved in 5 to

15% of cases. Criteria for diagnosis include:

- a history of significant postpartum haemorrhage
- varying grades of loss of pituitary hormone reserve
- failure of one or more target glands
- exclusion of a pituitary mass lesion
- a good response to hormone replacement therapy.

Diagnosis is rarely made in the early postpartum period, the mean time to diagnosis being 6.6 to 10 years. Presentation depends on the severity and extent of the infarction, and may be either acute or chronic (Table).

If the diagnosis is considered, appropriate pituitary investigations should be undertaken (Figures 6a and b). Treatment with corticosteroids should be initiated promptly if ACTH deficiency is suspected. Additional hormone replacement therapy can be commenced when the patient is stabilised.

Diabetes insipidus

Water balance is maintained by antidiuretic hormone (vasopressin), secreted by the posterior pituitary, and by thirst. Diabetes insipidus is diagnosed by demonstration of a high urine volume and failure to concentrate the urine with a water deprivation test.

Fertility in patients with diabetes insipidus is not impaired. Treatment in pregnancy is the same as that in the non-pregnant state with desmopressin (Minirin Nasal Spray; Minirin, Octostim), a Category B2 drug that is an analogue of antidiuretic hormone. Desmopressin has not been associated with any adverse fetal effects, and breastfeeding is not contraindicated.

Transient diabetes insipidus may develop peripartum and is thought to be related to elevated placental production of vasopressinase, resulting in increased clearance of antidiuretic hormone.

Adrenal gland disorders

Addison's disease

Addison's disease results in atrophy of the adrenal cortex and deficient glucocorticoid and mineralocorticoid production. If presenting for the first time in pregnancy, it may be difficult to diagnose because many of the symptoms occur in normal pregnancies; hence, a diagnosis may be made postpartum when the patient suffers an addisonian crisis.

Prior to the availability of therapy for Addison's disease, maternal mortality in pregnancy approached 80%. With full replacement therapy, however, pregnancy should not be associated with increased mortality.

An increase in replacement doses of glucocorticoid or mineralocorticoid is not required in uncomplicated pregnancies. Intravenous hydrocortisone is required if the patient is suffering nausea and vomiting; increased corticosteroid replacement will also be necessary at delivery and when any other stresses occur during pregnancy (for example infection).

Patients taking long term glucocorticoids for other chronic medical conditions should be managed with intravenous hydrocortisone peripartum and with increased corticosteroid dosage during other stressful situations.

Table. Features of Sheehan's syndrome

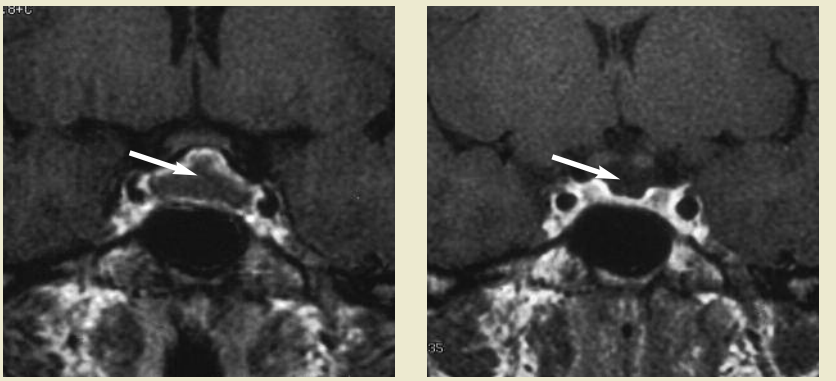
Acute form

- Hypotension
- Hypoglycaemia
- Hyponatraemia
- Headache
- Failure to lactate
- Fatigue
- Nausea and vomiting

Chronic form

- Amenorrhoea
- Loss of libido
- Failure to lactate
- Lightheadedness
- Fatigue
- Nausea and vomiting
- Changes in body hair and skin
- Cold intolerance

Sheehan's syndrome



Figures 6a and b. Sheehan's syndrome: coronal MRI scans after contrast enhancement with gadolinium. a (left). Peripheral enhancement of the pituitary and extension towards the optic chiasm (arrow) can be seen in this patient five days after delivery. b (right). No residual pituitary enhancement is visible four months postpartum.

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Congenital adrenal hyperplasia

Congenital adrenal hyperplasia is an autosomal recessive condition due to an inborn error of steroid hormone synthesis that results in reduced glucocorticoid and mineralocorticoid production. This results in excess ACTH, which stimulates the adrenal gland to produce alternative steroid hormones with virilising actions.

The severe 'salt losing' form of the condition is usually diagnosed in infancy, presenting as ambiguous genitalia in a female, hyponatraemia and hypoglycaemia. Milder forms can be diagnosed in adulthood. Glucocorticoids are used in therapy to reduce pituitary ACTH and thereby reduce production of alternate steroid hormones. Mineralocorticoids may also be necessary.

Fertility is reduced to about 15% in women with congenital adrenal hyperplasia. If a patient becomes pregnant, the gender of the fetus should be determined – excess maternal androgen may cause degrees of masculinisation of a female infant that can be reduced by continuing maternal adrenal steroid replacement. The placenta also metabolises maternal testosterone to oestradiol, which gives some protection to the developing female fetus.[7]

During pregnancy, a woman with congenital adrenal hyperplasia should be continued on adrenal steroid replacement with the aim of producing adrenal androgen suppression; her clinical and biochemical status should be determined throughout. Hydrocortisone (50 mg, four times daily) should be given intravenously during labour and quickly tapered after delivery. The infant should be examined for ambiguous genitalia.

Final comments

Pregnancy in the setting of endocrine conditions involving calcium metabolism and disorders of the pituitary or adrenal glands should not be associated with a significant increase in problems for the mother and fetus. Optimal treatment of the maternal medical condition prior to and during pregnancy will ensure this. A team approach involving obstetricians, physicians, GPs, midwives and neonatologists will provide co-ordinated care. MT

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