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Review

Adrenal disease and pregnancy: an overview

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Key content

- Although uncommon, adrenal disorders in pregnancy are associated with severe complications, especially if undiagnosed or poorly managed.
- Some women are on long-term steroids (especially those known to suffer from adrenal insufficiency) that suppress endogenous adrenal function. Under stress, these can become insufficient – particularly around labour and the puerperium.
- Adrenal insufficiency, for example, has been associated with maternal and fetal morbidity and mortality if untreated, while phaeochromocytoma is associated with considerable maternal mortality.
- Clinical features, diagnosis and management of the disorders of the adrenals in pregnancy are discussed, including Cushing's syndrome, adrenal insufficiency, phaeochromocytoma and paragangliomas, primary aldosteronism and congenital adrenal hyperplasia.

Learning objectives

- To understand the physiological changes in the adrenal system during pregnancy.
- To understand the clinical features of common adrenal problems in pregnancy and how they can be diagnosed and managed to minimise complications, especially acute adrenal insufficiency.
- To understand how the management of adrenal disorders is altered in pregnancy and the effect of adrenal diseases on pregnancy.

Ethical issues

- Is there a role for in utero therapy if a prenatal diagnosis is made?
- Does treatment of the mother affect the fetus?
- Is optimal treatment of the mother limited by concerns for the fetus?

Keywords: adrenal insufficiency / corticosteroids / Cushing's syndrome / hyperaldosteronism / phaeochromocytoma

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Introduction

Adrenal disease complicating pregnancy is rare[1] and, as such, presents considerable challenges for timely diagnosis and treatment.[2] Delay in recognition and diagnosis during pregnancy has been responsible for the increased fetal and maternal morbidity and mortality associated with these disorders.[3,4] The average practising obstetrician has limited experience in the management of pregnancies complicated by adrenal disease, underscoring the need for increased awareness of the differentiating features of the major adrenal disorders encountered. These disorders include primary adrenocortical insufficiency (Addison disease), Cushing's syndrome, primary aldosteronism (PA), congenital adrenal hyperplasia (CAH) and phaeochromocytoma and paraganglioma (PPGL). In addition, developments in assisted reproduction and advances in medical diagnostics and treatment of disorders previously associated with reduced fertility (e.g. Cushing's syndrome) have led to more women achieving pregnancy with coexisting adrenal disorders. Therefore, timely recognition, diagnosis and involvement of clinicians with appropriate expertise are essential for optimising fetal and maternal outcomes in these high-risk pregnancies.[5] This article presents an overview of adrenal diseases complicating pregnancy, highlighting differentiating features, diagnosis and risk reduction management approaches during pregnancy.

Primary adrenal insufficiency (Addison disease)

Adrenal insufficiency (AI) can be classified into primary, secondary and tertiary.[6] Primary AI in pregnancy is uncommon, with an estimated prevalence of about 1 in 3000 to 5.5 in 100 000 pregnancies.[1,4,6,7] It results from

adrenocortical disease, while secondary and tertiary AI are associated with adrenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH) secretion disorders, respectively. Primary AI results from both glucocorticoid (GC) and mineralocorticoid (MC) deficiencies, whereas secondary and tertiary AI result mainly from cortisol deficiency; this is because the hypothalamic–pituitary–adrenal axis does not regulate MC production. Autoimmune atrophy of the adrenal gland accounts for 70–90% of primary AI.[8] Other causes include haemorrhage secondary to sepsis, or major burns, lymphoma, metastasis and infections such as tuberculosis.[8,9]

Figure 1 shows the changes in cortisol secretion during pregnancy. Cortisol levels increase to a peak, on average at the 26th week of pregnancy.[10] Estrogen increases the production of corticosteroid-binding globulin (CBG), while the placenta increases the production of both CRH and ACTH, thus increasing their circulating levels, as well as free and total cortisol levels.[11,12] Importantly, the diurnal rhythmic variation in cortisol levels is maintained, with the nadir around bedtime.[13]

Diagnosis

Women with primary AI tend to have lower fertility rates; hence, most are diagnosed before pregnancy and are therefore likely to be on established doses of both GC and MC replacements.[14] Diagnosing primary AI for the first time in pregnancy is challenging, especially as the symptoms – such as nausea, vomiting, lethargy and increased pigmentation – overlap with those of pregnancy.[15,16] However, features highly suggestive of primary AI include significant weight loss, prolonged vomiting, hyperpigmentation in skin folds, hypoglycaemia, hyponatraemia and hyperkalaemia.[1] The hyperpigmentation in AI is commonly on mucous membranes, extensor surfaces and nonexposed regions of the body. This differentiates it from pregnancy-associated changes.[17] Symptoms of adrenal crisis could also be triggered by stress, induced, for example, by hyperemesis, infections, vaginal delivery or caesarean sections.[14]

The physiological changes associated with pregnancy make the interpretation of biochemical tests for diagnoses of AI problematic. These physiological changes include increased circulating cortisol levels (2 to 3-fold higher at term than in nonpregnant women), estrogen-induced increased corticosteroid binding globulin (CBG), increased cortisol half-life secondary to decrease in hepatic clearance and placental production of cortisol-releasing hormone (CRH), which induces adrenal hypertrophy and enhances its responsiveness to synthetic ACTH administration.[18] In nonpregnant cases, the diagnosis is highly likely if morning cortisol level is <140 nmol/L in combination with an elevated plasma ACTH concentration (>2-fold above the upper limit of the reference interval).[19] A short Synacthen stimulation test (SST) should be performed in suspected cases unless basal results are unequivocal. The test involves the intravenous or intramuscular administration of 250 micrograms (ug) of a synthetic ACTH, preferably in the morning. A normal response to the SST is a rise in serum cortisol concentration after either 30 or 60 minutes to ≥500–550 nmol/L. This cut-off value is, however, unreliable in pregnancy: following stimulation with 250 ug synthetic cortisol, Suri et al.[18] showed that all second and third trimester women had values exceeding 20 ug/dl (555 nmol/L), implying that using this will result in underdiagnosis of AI in pregnancy.[18] Furthermore, such a response (of serum cortisol >20 ug/dl (555 nmol/L) from the SST) also excludes primary and secondary AI.[17] It has been suggested that salivary free cortisol may be consistent, generalisable and a physiologically rational measure of adrenal function in pregnancy, rather than total cortisol. Its use offers

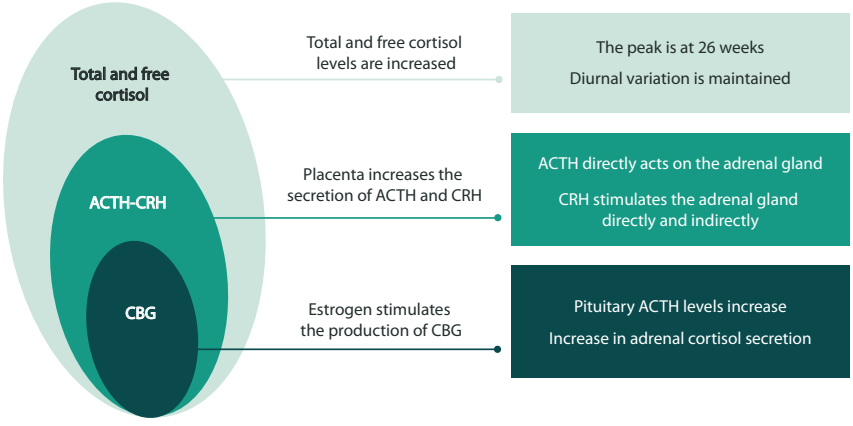

Figure 1. Changes in the pituitary–adrenal physiology with pregnancy.Abbreviations: ACTH = adrenocorticotropic hormone; CBG = corticosteroid-binding globulin; CRH = cortisol-releasing hormone

advantages such as it is noninvasive and can be performed in an outpatient setting. However, owing to the increase in CBG, pregnant women with highly suggestive clinical features but an indeterminate SST should be offered treatment during pregnancy and retested after delivery. The presence of adrenal antibodies is suggestive of an autoimmune aetiology.[8] Radiological imaging is not routinely used in investigating pregnant women with suspected primary AI and should be deferred till after delivery.

Management

Management of primary AI is best provided by a joint team of obstetricians and endocrinologists.[7] The replacement regimen for primary AI in pregnancy is like that for nonpregnant patients. Hydrocortisone (HC) is the preferred GC because it is short acting and does not cross the placenta. Besides, a typical dose between 15–25 mg in two to three divided doses mimics the physiological diurnal variation in cortisol secretion.[19] Fludrocortisone at a dose of between 0.05 mg and 0.1 mg/day is sufficient for MC replacement in most patients. Prednisolone at a dose of 3–5 mg once daily could be used for GC replacement in patients with poor compliance. There are no data and no widely accepted recommendations for managing GC doses in pregnancy. There is an overlap between symptoms of AI and pregnancy, including postural hypotension and fatigue. However, the occurrence of these symptoms during pregnancy from the 24th week of gestation onwards might prompt an increase in the doses of GC and/or fludrocortisone.[19] HC has an MC effect: 40 mg of HC equals 0.1 mg of fludrocortisone. Hence, an increase in fludrocortisone is not essential. However, prednisolone does not have an MC effect and the fludrocortisone dose might be increased by 20–30%.

Acute adrenal insufficiency

Acute AI (Addisonian crisis) in pregnancy is a rare, life-threatening emergency. It could be confused with a surgical acute abdomen, owing to the presenting symptoms of abdominal pain, vomiting and shock.[2] Therefore, a high index of clinical suspicion is required. Adrenal crisis may occur in patients with primary or secondary AI, especially in the setting of severe hyperemesis with decreased absorption of medications. In patients not previously known to have adrenal disease, it may result from sudden bilateral adrenal necrosis caused by haemorrhage, sepsis or adrenal vein thrombosis.[9] It may also occur in women who are being treated with pharmacological doses of steroids[20,21] during pregnancy; for example, if their GC or MC requirements are acutely unmet during stressful events such as illness, labour or surgery. Sudden withdrawal of therapeutic doses of systemic GCs (both oral and inhaled) during pregnancy may precipitate adrenal crisis, hence systemic steroids should always be tapered off gradually. Therefore, patients who have used 5–20 mg or more of prednisolone (or equivalent) per day for 3 weeks or more during pregnancy should have intravenous HC intrapartum at a dose of 50–100 mg 8-hourly for up to 24 hours to reduce the risk of acute AI.

Prompt evaluation and concurrent treatment is needed to reduce morbidity and mortality following diagnosis. Intravenous access should be secured, and blood samples taken for ACTH, cortisol, glucose and serum electrolytes, while treatment is initiated promptly with intravenous saline as well as intravenous HC. Two to three litres of 0.9% saline or 5% dextrose in 0.9% saline should be administered as quickly as possible for patients in shock. Fluid rate should be subsequently adjusted based on urine output and volume status. HC is administered at a dose of 100 mg every 6–8 hours, or as a continuous infusion of 200–300 mg in 24 hours, with monitoring of vital signs and serum electrolytes. Recovery is typically quick, usually within 24 hours of commencing treatment. Parenteral HC should be tapered over 1–3 days; after this, most patients can be switched to oral treatment with HC and fludrocortisone.[1,4] The precipitating cause of acute adrenal crisis should be carefully investigated and treated to prevent a recurrence. Box 1 summarises the management of this medical emergency. The 'sick day rules' have been developed to reduce the risk of acute AI.

Sick day rules and stress doses

The 'sick day rules' are a set of measures aimed to prevent the occurrence of adrenal crisis. Women with primary AI should be educated on these rules. During pregnancy, hyperemesis, infections, delivery and surgery could trigger adrenal crisis. Figure 2 summarises the sick day rules that should be reviewed in every single visit.[22] When there is a birth partner, we recommend they are also trained on the use of intramuscular HC injections. Women with primary AI who

Box 1. Treatment of acute adrenal insufficiency (adrenal crisis) in pregnancy1

1. Prompt intravenous access with wide bore cannula
2. Take blood samples for serum electrolytes, glucose, adrenocortocotropic hormone (ACTH) and cortisol
3. Administer 2–3 litres of 0.9% saline or 5% dextrose saline and titrate rate based on urine output and improvement of shock
4. Give intravenous hydrocortisone 100 mg administered 6–8 hourly, or a continuous infusion of 200–300 mg/24 hours
5. Monitor vital signs using the modified obstetric early warning scores parameters
6. Search for the cause of the adrenal crisis and treat appropriately
7. Fetal assessment and monitoring (gestation dependent)
8. Taper intravenous hydrocortisone over 1–3 days as the patient recovers and start oral replacement therapy

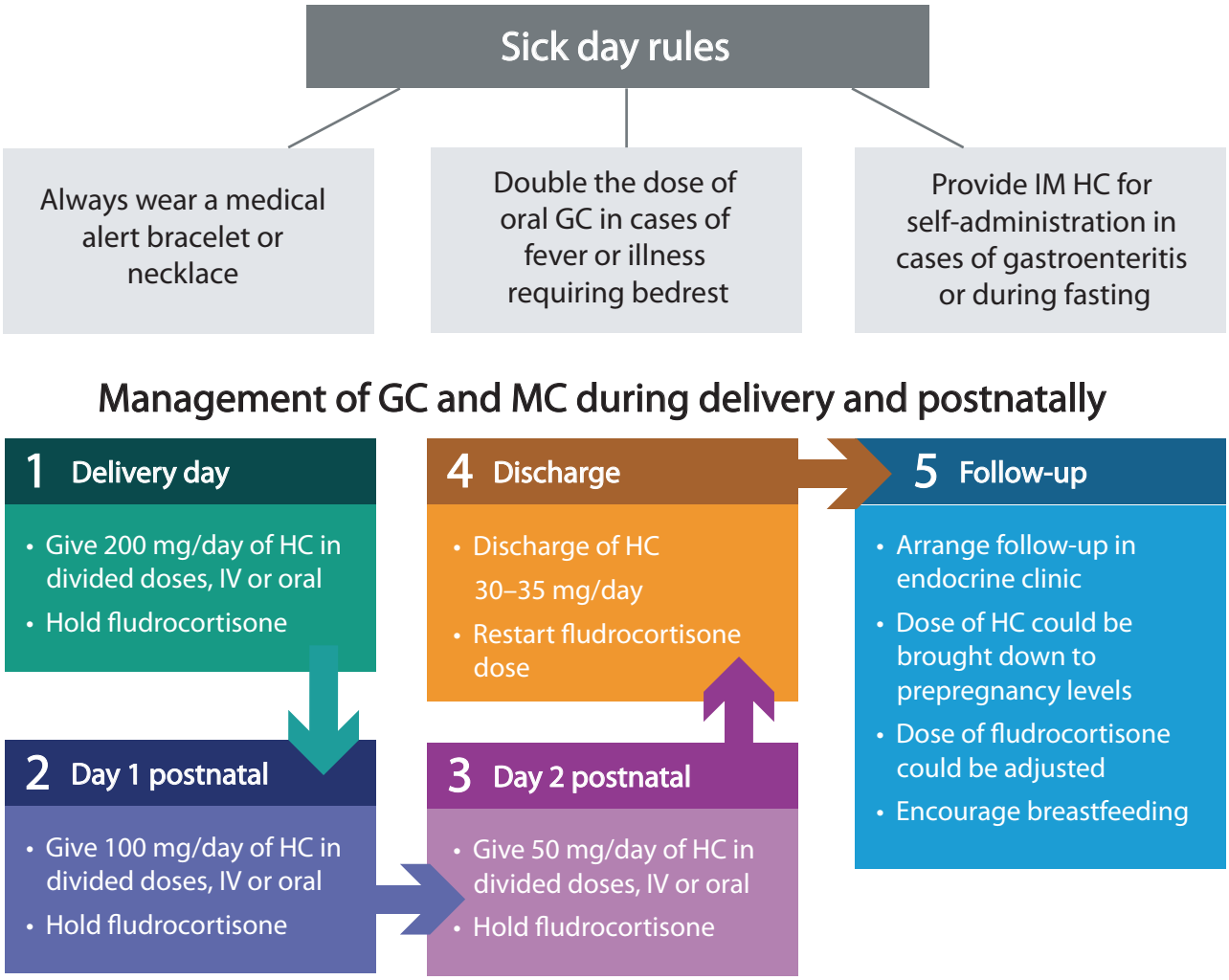

Figure 2. Management of glucocorticoids and mineralocorticoids during delivery and in the puerperium. Abbreviations: GC = glucocorticoids; HC = hydrocortisone; IM = intramuscular; IV = intravenous; MC = mineralocortocoids

present with hyperemesis should receive intravenous HC, typically at a dose of between 100 and 200 mg/day, together with appropriate fluid resuscitation.[18] During labour and delivery, stress doses of GCs should be administered, but there are no controlled studies on optimal dosing. Figure 2 summarises a proposed approach to labour and delivery.[23]

Pregnancy outcomes and breastfeeding

Vaginal delivery should be encouraged in women with primary AI, and caesarean delivery should be reserved for obstetric indications. Close attention should be paid to risk assessment for venous thromboembolism, especially in the peripartum period, and appropriate prophylaxis instituted.[7] The outcome for patients with adequately treated primary AI is good, but there is an increased risk of adverse fetal outcomes, such as fetal growth restriction (FGR). There is also an increased risk of maternal morbidity in untreated patients or those with delayed diagnosis during pregnancy.[1,7] Suboptimal replacement therapy, especially in stressful scenarios, as well as poor maternal education and compliance can also increase maternal risks. These risks include preterm delivery, caesarean section, poor wound healing, thromboembolism and acute adrenal crisis.[2,7,10] Although maternal adrenal antibodies cross the placenta, there is no significant effect on the fetal adrenal gland. Both HC and prednisolone are excreted in breast milk in very low amounts that are unlikely to harm the baby.[24,25]

Cushing's syndrome

Cushing's syndrome is characterised by increased cortisol levels and, in the ACTH-dependent types and some adrenal cancers, elevated androgens. It is rare for untreated women to be pregnant because most will be amenorrhoeic, anovulatory

and suffer from irregular periods.[15, 26,27] A timely diagnosis, early initiation of treatment and individualised care by a multidisciplinary team of specialists are therefore critical for optimising pregnancy outcomes because, when improperly treated, these are invariably poor.

Aetiology

Adrenal adenomas account for 60% of reported cases in pregnancy, whereas pituitary-dependent Cushing's syndrome accounts for 70% of those outside pregnancy.[28] Adrenal adenomas do not cause excess androgen secretion hence are less likely to cause menstrual irregularities. On the other hand, adrenal hyperplasia and some adrenal carcinomas produce large amounts of androgens and spontaneous pregnancy is very unlikely. Pregnancy-associated Cushing's syndrome is defined as onset occurring during gestation or within 12 months of delivery or miscarriage.[29] This may result from nodular hyperplasia of the adrenals stimulated by placentally produced ACTH, or as a result of stimulation of ACTH receptors in a pre-existing but undiagnosed adrenal adenoma by ACTH from the placenta.[28,30]

Diagnosis

The timely diagnosis of Cushing's syndrome in pregnancy presents a unique challenge. As shown in Figure 1, pregnancy is associated with elevated cortisol levels, which affect the results of some diagnostic tests, especially the low-dose dexamethasone suppression test.[30] In addition, pregnancy-associated features, such as weight gain, hypertension, striae, fatigue and glucose intolerance, overlap with features of Cushing's syndrome.[15,17] Differentiating clinical features of Cushing's syndrome include proximal myopathy, easy bruising, osteopenia/osteoporosis-induced fractures and hirsutism from increased androgens, early onset hypertension in pregnancy and the presence of red or purple striae (instead of pale striae of normal pregnancy).[15,26]

A composite of diagnostic tools should be considered in pregnant women who present with features suggestive of active Cushing's syndrome. A midnight plasma cortisol level could be used as the preliminary screening test because the diurnal variation of cortisol is maintained during pregnancy, although with a higher nadir than in the nonpregnant population.[26] The use of salivary cortisol at night, in combination with urinary free cortisol (UFC), are reliable confirmatory diagnostic tools in pregnancy. Late-night salivary cortisol and UFC values greater than three times the upper limit of normal are diagnostic of Cushing's syndrome in pregnancy.[26,30] Recommended thresholds for salivary cortisol for the first, second and third trimesters are <6.9 nmo/l, <7.2 nmol/l and <9.1 nmol/l, respectively; however, this may vary depending on the assay.[12,31] The low dose (1 mg) dexamethasone suppression test may lead to false positive results because of pregnancy-induced hypercortisolism, but failure to suppress cortisol following a high dose of dexamethasone (8 mg) is in keeping with a diagnosis of Cushing's syndrome in pregnancy.[15,26] However, the usual postdexamethasone ACTH suppression in Cushing's syndrome (which is confirmatory of diagnosis) is often not observed in pregnancy, probably because placental ACTH production is not suppressed by dexamethasone.[26] Patients without cortisol suppression after high doses of dexamethasone and with a normal to low ACTH (<4.4 pmol/l) level are likely to have adrenal Cushing's syndrome, while patients with cortisol suppression following dexamethasone, but with a high ACTH (>4.4 pmol/l) are likely to have pituitary dependent Cushing's syndrome. Magnetic resonance imaging (MRI) is a useful imaging modality for suspected pituitary lesions, as well as adrenal masses. Indeed, it is better than ultrasound scan for imaging the adrenals.[32] It is important to note that gadolinium-based MRI is contraindicated in pregnancy. There is no useful guide on the use of CRH as a diagnostic tool during pregnancy.[26]

Management

Previously well-treated Cushing's syndrome in complete remission does not significantly alter the course of pregnancy. However, untreated or poorly treated Cushing's syndrome and Cushing's syndrome diagnosed during pregnancy are associated with significantly more maternal and fetal adverse outcomes.[15] Maternal complications include gestational diabetes, gestational hypertension, pre-eclampsia, wound infection, heart failure, psychiatric disorders and – rarely – maternal death.[9,28] The fetus is relatively shielded from maternal hypercortisolism through the enzymatic conversion of cortisol to the biologically inactive cortisone by the placental enzyme 11-β hydroxysteroid dehydrogenase type 2. Despite this relative protection, active Cushing's syndrome is associated with significantly more fetal risks including miscarriage, FGR, preterm delivery, stillbirth and neonatal AI.[14,28,31]

Pregnancies in women with Cushing's syndrome should be managed by a team of specialists including obstetricians, endocrinologists, anaesthetists, neonatologists and surgeons. This provides a holistic approach with an individualised timely treatment decision. Ideally, prepregnancy treatment of known cases of Cushing's syndrome should be undertaken to achieve successful treatment before conception. Once diagnosis is made during pregnancy, early initiation of treatment for Cushing's syndrome is associated with improvement in the live birth rate.[30]

Surgical treatment, which is more successful than medical treatment for both adrenal and pituitary dependent Cushing's syndrome, is regarded as the treatment option of first choice.[15,26] Successful laparoscopic unilateral adrenalectomy and trans-sphenoidal surgery have been reported with good outcomes in the second trimester of

pregnancy and, for refractory cases, bilateral adrenalectomy may be considered.[26,28,30,31] Adequate preoperative assessment and close monitoring in a critical care setting in the immediate postoperative period are essential to reduce maternal and fetal morbidity. The role of empirical tocolysis in the perioperative period is uncertain and should be decided on an individualised basis. Surgically treated patients who are in remission should be managed as having AI and should receive HC supplementation to maintain urinary cortisol in the normal pregnancy range. This supplementation is particularly important in the intrapartum and immediate postpartum period.

Medical treatment is a reasonable second-line option in those patients who are not fit or suitable for surgery. Metyrapone, a steroidogenesis inhibitor, is the most widely used. It reduces cortisol level by inhibiting the conversion of 11-hydroxycortisol to cortisol.[26] Metyrapone use increases the risk of hypertension through the accumulation of MC precursors, so careful monitoring is required. Ketoconazole, which has a theoretic risk of teratogenicity,[33] and mitotane, should be avoided in pregnancy because of the risk of teratogenicity.[1,2] Cabergoline can be used as an alternative to metyrapone in pituitary-dependent Cushing's syndrome.

Optimal treatment of gestational hypertension, adequate glycaemic control and prompt assessment and management of preterm labour are all equally important in improving pregnancy outcomes in patients with Cushing's syndrome. In the absence of specific contraindications, vaginal delivery should be encouraged, particularly because of the increased risks associated with caesarean delivery, including poor wound healing. A plan for follow-up in the endocrinology service should be made postpartum to ensure a seamless transition of care.

Primary aldosteronism (Conn's disease)

In primary aldosteronism (PA) disorders, aldosterone production is inappropriately high for sodium status, relatively autonomous of the major regulators of secretion (angiotensin II and plasma potassium concentration), and non-suppressible by sodium loading.[34] The inappropriately elevated aldosterone leads to tissue damage, suppression of plasma renin and hypokalaemia, sodium retention, hypertension, cardiovascular and renovascular diseases.[34] The most common causes of PA are bilateral idiopathic hyperaldosteronism (60–70%) and unilateral adrenal adenoma (30–40%). Unilateral adrenal hyperplasia, familial hyperaldosteronism type I, and pure aldosterone-producing adrenocortical carcinoma are rare causes.

In the nonpregnant state, PA was estimated to account for <1% of hypertension, owing to the detection method that required the presence of hypokalaemia.[35] Since hypokalaemia is no longer a prerequisite, PA is currently estimated to account for 3–15% of all patients with hypertension.[36] In pregnancy, establishing a diagnosis of PA is challenging, as detailed below. While general hypertensive disorders complicate 5–10% of pregnancies, the estimated reported prevalence of PA in pregnancy is between 0.6% and 0.8%.[37] However, as only about 50 pregnant cases have been reported in the literature, PA in pregnancy is likely to be underreported owing to the challenging detection methods.[38]

Clinical features and pregnancy outcomes

The classical presentation of nonpregnant patients is with hypertension and hypokalaemia (present in less than 40% of patients).[39] In a review of 40 pregnancies in women diagnosed with PA during pregnancy, 81% had hypertension for the first time in pregnancy, while 19% had been previously diagnosed with hypertension but not screened for PA.[40] Hypokalaemia was common, occurring in 68% of the cases.[40] Hypertension was controlled in 19% (two on diuretics), uncontrolled despite medical treatment in 32% of cases, and 16% of cases required adrenalectomy during the pregnancy.[40] Besides, 23% developed pre-eclampsia, 61% had labour induced, 44% had a caesarean section and 9.3% had a stillbirth. The median gestational age at delivery was 35 weeks for those treated with diuretics and 31 weeks for those not receiving diuretics. A review of 35 pregnancies in 16 women with GC-remediable aldosteronism (GRA; an autosomal recessive disorder) showed no increased risk of pre-eclampsia.[41] However, 39% of women experienced aggravated hypertension and the birthweights of the infants were lower than in those women without aggravated hypertension. The caesarean section rate was approximately double that seen in the general population.[41]

Diagnosis of primary aldosteronism during pregnancy

The diagnosis of PA during pregnancy can be challenging because of the physiological changes that lead to extrarenal stimulation of the renin angiotensin aldosterone system (RAAS). Figure 3 summarises the physiological changes in the RAAS system during pregnancy, which are crucial to maintaining circulating blood volume, blood pressure and uteroplacental blood flow.[42] Renin activity increases 4-fold in the first 8 weeks of gestation and by 7-fold in the third trimester, while aldosterone levels increase 3 to 8-fold in the first and second trimesters and plateau in the third trimester.[30] However, progesterone antagonises the vasopressor effects of the RAAS and reduces urinary potassium excretion.[40] Therefore, despite the marked increase in blood volume necessary to obtain an adequate placental perfusion, pregnant women are usually normotensive and normokalaemic.[43]

The diagnosis of PA during pregnancy should be considered as a differential in women presenting with (1)

hypertension associated with hypokalaemia and (2) resistant hypertension – especially before 20 weeks of gestation. The diagnosis of PA in pregnancy is based on suppressed renin and elevated aldosterone-to-renin ratio (ARR). Confirmatory testing is not only needed in the presence of hypokalaemia, but is also not recommended in normokalaemic subjects because saline infusion could lead to critical volume expansion.[44,45] MRI may be performed during the second or third trimesters to determine the subtype of PA, whereas adrenal vein sampling is not performed because of high radiation exposure. If surgery is not considered as a treatment for PA during pregnancy, both MRI of adrenals and adrenal veins sampling, which helps localise the site of tumour for surgery, should be postponed until after delivery.[46,47]

Treatment of primary aldosteronism during pregnancy

Control of the blood pressure during pregnancy is essential for favourable maternal and fetal outcomes. There are currently no formal recommendations for the management of these patients. Hence, a multidisciplinary team approach is essential for their care. Approved antihypertensive medications, such as alpha-methyldopa and labetolol, are the first options during pregnancy. The choice of further treatment in those with uncontrolled hypertension requires understanding of the current evidence and proper counselling of the patients.

Spironolactone crosses the placenta and its anti-androgen effects can lead to feminisation of male offspring. It has also been linked to increased risk of FGR.[48] There are only five case reports of male offspring who were exposed to high-dose spironolactone in-utero.[49] Contrary to animal data, which showed high prevalence of male feminisation, all five cases had normal genitalia. Yet, until further data are available, we do not recommend the use spironolactone in pregnancy.

Eplerenone is a selective MC receptor antagonist that does not have anti-androgen activity. So far, no teratogenic effects have been reported and eplerenone is considered as class B by the US Food and Drug Administration.[47] Few cases of successful use of eplerenone during pregnancy have been reported.[47,50,51] Based on this limited evidence, eplerenone is preferred to spironolactone, if needed. The use of potassium-sparing diuretics, such as amiloride and thiazides, have been suggested in the literature; however, their safety in pregnancy remains a concern. A reasonable approach is to use drugs known to be safe during pregnancy in the first trimester and, in cases of poor control of hypertension and/or hypokalaemia, use of thiazides, amiloride or eplerenone could be considered during the second and third trimesters.

Laparoscopic unilateral adrenalectomy is the treatment of choice for adrenal adenomas and can be performed safely after strict control of blood pressure. However, adverse pregnancy outcomes were reported in four out of nine cases who had adrenalectomy during pregnancy despite biochemical cure.[52] There was one case of FGR at 26 weeks of gestation, two deliveries at 26 weeks of gestation because of FGR associated with fetal distress and one delivery at 34 weeks of gestation.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterised by impaired

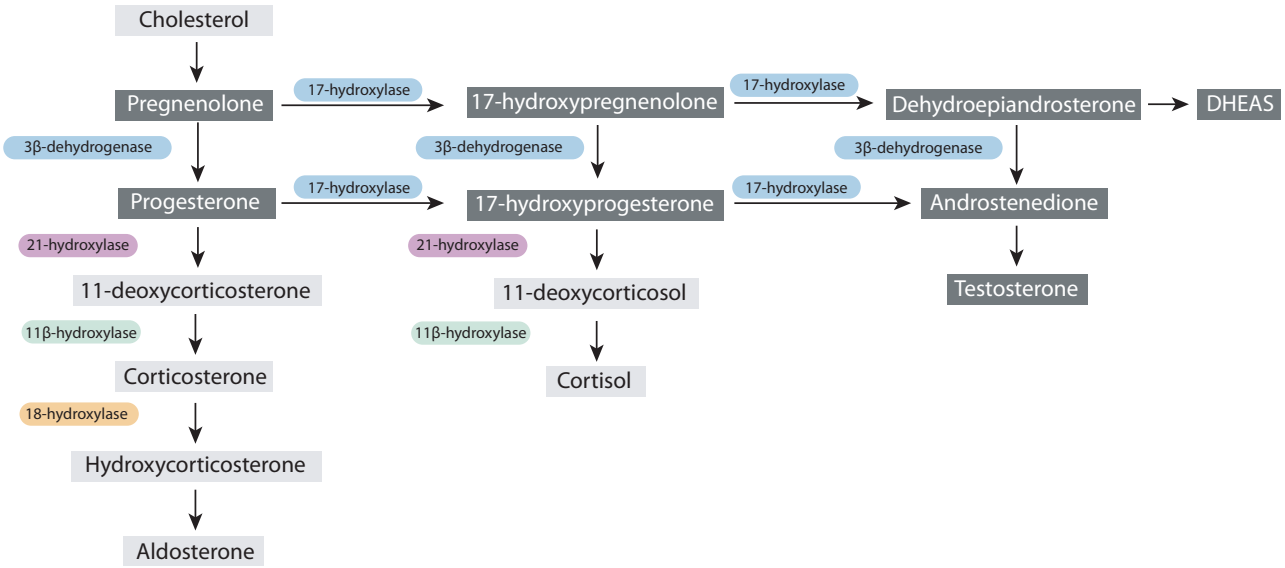

Figure 3. Pathway for biosynthesis of glucocorticoids and mineralocorticoids and the enzymes involved with consequences of their deficiency. Abbreviation: DHEAS = dehydroepiandrosterone sulphate

cortisol synthesis secondary to enzyme deficiency.[22] Based on national neonatal screening data, the worldwide incidence ranges between 1 in 14 000 and 1 in 18 000 births.[22] The most common enzyme deficiency is 21-hydroxylase deficiency (21-HD), with an incidence of about 1 in 500 to 1 in 1000 live births. In 95% of cases, CAH is caused by mutations in *CYP21A2*, the gene encoding the enzyme 21-HD.[53] As shown in Figure 3, deficiency in 21-HD leads to blockage of cortisol and aldosterone synthesis, resulting in the accumulation of cortisol precursors that are diverted to sex hormone biosynthesis. Other rare defects include 11β-hydroxylase deficiency and 17α-hydroxylase deficiency.[54,55]

Clinical manifestations: fecundity and fertility

Classical CAH secondary to 21-HD deficiency can present at birth. In girls, the enhanced ACTH levels drive excess adrenal androgen production, leading to clitoral enlargement and labial fusion, presenting as sexual ambiguity at birth and even inappropriate sex assignment. Seventy-five percent of patients of both genders present at birth with severe hyponatraemia caused by salt wasting as a result of severe aldosterone deficiency.[54] Non-classical CAH (NCCAH) secondary to 21-HD deficiency have features similar to polycystic ovary syndrome, including hirsutism, primary or secondary amenorrhea or anovulatory infertility.[56]

There are no long-term cohort studies on fertility rates in women with CAH. Mulaikal et al.[57] reported on 80 women with CAH; 40 of whom were sexually active, with a pregnancy rate of 40%. Most of these women had features suggestive of poor disease control, including hirsutism and irregular periods. In the 40 nonsexually active women, vaginal introital anatomical problems appeared to be the main barrier for engaging in sexual intercourse. On the other hand, Conway et al.[58] reported a fertility rate of 91%, similar to the rate in the background population, in women with well-controlled CAH.

As outlined above, fertility rates depend on disease control and genital structural changes from reconstruction surgery. The effects of excessive androgen production are thought to include anovulation from suppression of follicular development; induction of endometrial changes, which could have a negative impact on implantation; and increased luteinising hormone (LH)-to-follicle stimulating hormone (FSH) ratio through an increase in the gonadotrophin-releasing hormone (GnRH) pulse frequency.[23] Besides, the reported high progesterone levels in women with poorly controlled CAH could lead to anovulation, unfavourable cervical mucus, inhibited sperm migration, disruption of endometrial thickening and can negatively affect implantation.[59] In the past, clitoroplasty was regularly performed in early childhood, often together with vaginoplasty. Women who underwent clitoroplasty have reported lower rates of sexual satisfaction, likely because of a loss of sensitivity.[60] Almost 50% of those who underwent vaginoplasty had inadequate vaginal opening.[59]

Management of CAH and optimisation for pregnancy

Before planning pregnancy, the woman with CAH and the biological father (where present) should receive genetic counselling.[22] Women with classical CAH have a 1:120 probability of having a child with classical CAH, while women with nonclassical CAH have a 1:250 probability of having a child with classical CAH.[22] These risks will increase if the biological father is a carrier of the gene defect.

As outlined above, in sexually active women, optimising treatment can result in normal fertility rates. For those who do not conceive spontaneously on their routine steroid dose within 6 months of trying, follicular phase (days 2–8 of the cycle) progesterone should be measured and could be suppressed to <2 nmol/l using three divided doses of prednisolone.[58] Additionally, plasma renin activity could be suppressed to within the normal range, with an increase in a single daily dose of fludrocortisone.[58] In cases that are resistant to the above measures, bilateral adrenalectomy could be considered. Bilateral adrenalectomy was effective in treating primary infertility in three women, with successful post treatment pregnancies; an additional successful pregnancy was also achieved following bilateral adrenalectomy for difficult-to-treat hyperandrogenism.[61] However, adrenalectomy should be the treatment of last resort, after trying standard ovulation induction measures.

Choice of glucocorticoids during pregnancy

Two critical issues should be discussed during the first antenatal visit: (1) the choice of GC replacement and (2) GC stress dosing during pregnancy in intercurrent illness, in case of hyperemesis and during labour and delivery. As outlined above, women with CAH could require large doses of GC therapy to be able to conceive. HC and prednisolone are both inactivated by placental 11-β hydroxysteroid dehydrogenase type 2 (11βHSD2), therefore the fetus is protected from potentially supraphysiological GC doses taken by the mother.[59] On the other hand, dexamethasone is not inactivated by 11β-HSD2 and can cross the placenta freely, so can affect the fetal adrenal gland. The placenta aromatises androgens into estradiol and estrone, so the fetus is protected from excess androgens in women with CAH.[5]

The pituitary–adrenal axis is fully functional by 6 weeks of life. The production of adrenal androgens starts between weeks 6 and 7 of fetal life and the critical time for sexual differentiation of external genitalia occurs between weeks 7 and 12.[62] During this time, excess production of fetal androgens can lead to varying degrees of virilisation. Dexamethasone crosses the placenta and can suppress the high androgen production in affected females; however, it

does this by suppressing the pituitary–adrenal axis. One proposed approach is to treat all women with CAH with dexamethasone until the gender of the fetus is confirmed to be male or an unaffected female by amniocentesis performed from 15 weeks of gestation.[62] With the advent of noninvasive prenatal testing (NIPT)/noninvasive prenatal diagnosis (NIPD), such gender confirmatory testing can now be done by 8-10 weeks from maternal blood using free fetal DNA. A meta-analysis including 365 pregnancies of women with CAH treated with dexamethasone showed a reduction in virilisation in female offspring, with no adverse maternal or neonatal outcomes.[63] However, the unnecessary exposure of fetuses to dexamethasone at 7–8 weeks is an ethical dilemma. Despite this, termination is not usually considered an option for fetuses affected by CAH.

There are a few concerns with the use of dexamethasone during pregnancy. Possible maternal side effects of dexamethasone therapy include excessive weight gain, cushingoid features, hypertension, gestational diabetes, excessive striae and mood lability. While several studies have reported these side effects, they appear to be modest.[62] Possible fetal side effects are cleft palate and adrenal suppression. With the ensuing resetting of the fetal pituitary–adrenal axis, there is an increased risk of cardiometabolic disorders in adulthood. There has however, been no reported increased risk of cleft palate in CAH pregnancies treated with dexamethasone (there are no robust published data) and no long-term data on adrenal suppression risks.[63] The current recommendation is that dexamethasone should not be used during pregnancy.[22] HC is the commonest medication for CAH management; the pre-pregnancy dose should be continued during pregnancy.[22] As outlined, some women require treatment with prednisolone to conceive and it can also be continued during pregnancy. However, neither treatment reduces the risk of virilisation in affected females. Hence, we think the advantages and disadvantages of each GC agent should be discussed with the pregnant woman (and her partner, where present).

The need for GC therapy is uncertain in women with nonclassical CAH in the absence of strong evidence; however, those with a history of infertility or miscarriage may benefit from treatment. The resulting pregnancies should be closely monitored.

Monitoring of hormone therapy during pregnancy

Monitoring of hormone therapy during pregnancy is mostly clinical. Both androgen and cortisol levels increase gradually during pregnancy owing to increases in sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG). Maternal 17-hydroxyprogesterone (17-OHP) is elevated in normal pregnancy, hence cannot be used to monitor GC treatment.[22] Renal function should be monitored for hyponatraemia and/or hyperkalaemia. The treatment should otherwise follow the same principles described above for the management of primary AI. Women should be educated on the sick day rules, as outlined in Figure 2.

Pregnancy outcomes

Pregnancy outcome in women with CAH is reasonably good, with a slightly increased rate of small for gestational age.[59] Women with CAH are at increased risk of gestational diabetes and should be screened during pregnancy with an oral glucose tolerance test (OGTT).[64] However, the timing of the OGTT should be clinically judged. We recommend an early screening at 15 weeks of gestation and, if normal, to be repeated between 24 and 28 weeks of gestation. Most women with classical CAH deliver by caesarean section because of the high prevalence of previous vaginal surgery and cephalopelvic disproportion.[64,65] That said, vaginal delivery has been reported in 16–42% of cases, most of whom had a non-salt-wasting phenotype. GC management during labour is similar to that of primary AI (Figure 2).

Breastfeeding should be encouraged in women on cortisol replacement therapy. Both HC and prednisolone are excreted in breast milk in low amounts that are unlikely to harm the baby.[24,25]

Phaeochromocytoma and paragangliomas

PPGLs are rare neuroendocrine tumours arising from neural crest-derived cells of the sympathetic and parasympathetic nervous systems.[66] A phaeochromocytoma is a tumour causing excessive production of catecholamines (adrenaline [epinephrine], noradrenaline [norepinephrine] and dopamine) by the chromaffin cells of the adrenal medulla. A paraganglioma results from excessive production of catecholamines by the chromaffin cells located in the extra-adrenal sympathetic paraganglia, typically in the abdomen and pelvis. The prevalence of PPGL is variable, from 0.2–0.6% in patients with hypertension, to as high as 3–5% in patients with adrenal mass.[67] In pregnancy, however, the prevalence of PPGL is estimated to be 1 in 15 000 to 1 in 54 000 pregnancies.[68] Although PPGL can be sporadic, it can also form part of hereditary syndromes, such as Von Hippel–Lindau syndrome, multiple endocrine neoplasia-type 2 (MEN-2) and neurofibromatosis type 1 (NF1) – all of which have autosomal dominant patterns of inheritance.[69]

Catecholamines: basic physiological features and effects on pregnancy

There are three catecholamines: adrenaline (epinephrine), noradrenaline (norepinephrine) and dopamine. Adrenaline is

produced and stored in the medulla of the adrenal gland, from where it is released into the circulation, whereas noradrenaline is produced and stored both in the adrenal medulla and peripheral sympathetic nerves. Dopamine is a precursor of noradrenaline and is an important neurotransmitter.[56] Catecholamines affect many metabolic processes in the body, through the seven receptors listed in Table 1. They induce an increase in heart rate and blood pressure, as well as myocardial contractility. They are metabolised by catechol-*O*-methyltransferase (COMT) into metanephrines and normetanephrines.

Table 1. Catecholamine receptors

Receptors	Location	Function
α_1	Postsynaptic sympathetic nerve endings	Stimulation leads to vascular smooth muscle contraction, vasoconstriction and elevated blood pressure
α_2	Presynaptic sympathetic nerve ending	Stimulation inhibits norepinephrine release, suppresses the sympathetic nervous system and reduces the blood pressure
β_1	Mostly in the heart	Stimulation causes positive inotropic and chronotropic effects on the heart, increased renin secretion in the kidney and lipolysis in adipocytes
β_2	Bronchial, vascular and uterine smooth muscles	Stimulation causes positive inotropic and chronotropic effects on the heart, increased renin secretion in the kidney and lipolysis in adipocytes
β_3	Adipose tissue	Regulates energy expenditure and lipolysis
D_1	Cerebral, renal, mesenteric and coronary vasculatures	Stimulation causes vasodilation in these vascular beds
D_2	Presynaptic sympathetic nerve endings, sympathetic ganglia and the brain	Stimulation of D2 receptors in these locations inhibits the release of noradrenaline, inhibits ganglionic transmission, and inhibits prolactin release, respectively

Both adrenaline and noradrenaline are important in adaptation and response to stress stimuli during pregnancy and childbirth.[66] During healthy pregnancy, the levels of catecholamines are not increased. In women with eclampsia and pre-eclampsia, slight increases in the levels of catecholamines have been reported.[68] The placenta produces COMT, hence the fetus is protected from maternal catecholamines.

Clinical features

The clinical presentation of PPGL during pregnancy is similar to that in nonpregnant women. The classic triad of symptoms (headache, sweating and tachycardia) are not very common in pregnancy.[70] Less common symptoms and signs include orthostatic hypotension, arrhythmia, chest pain, convulsions, syncope, blurring of vision, weight loss, papilloedema, insulin resistance, hyperglycaemia, high erythrocyte sedimentation rates, psychiatry disorders and erythrocytosis.[71,72] Most patients become symptomatic with increasing gestation, most likely because of mechanical factors from the growing uterus and fetal movements.[73] Nevertheless, some patients can remain asymptomatic until they experience major stress, like birth or caesarean section.

Certain factors could help differentiate between pre-eclampsia and PPGL.[68,73] PPGL should be suspected in any patient with a previous or family history of PPGL, or any other associated condition such as MEN-2, Von Hippel–Lindau, neurofibromatosis, and familial paraganglioma syndromes. Pre-eclampsia is extremely rare before 20 weeks of gestation, while PPGL can present at any gestation. PPGL is not associated with proteinuria, ankle oedema or elevated uric acid levels, while pre-eclampsia often is. Most importantly, paroxysmal hypertension and orthostatic hypotension do not occur in women with pre-eclampsia. PPGL should be suspected in all pregnant women who present with life-threatening catastrophes, such as an acute coronary syndrome, cardiomyopathy, arrhythmias, stroke, syncope and shock. The risk of hypertensive crises during delivery appears to be lower in those with paraganglioma than those with phaechromocytoma.[74]

Effect of PPGL on pregnancy and fetal outcomes

While the fetus is protected from high maternal catecholamines, nonetheless these elevated levels cause uteroplacental vasoconstriction leading to FGR, fetal hypoxia and – possibly – fetal death. Moreover, paroxysmal increases in blood pressure may lead to placental abruption and rebound hypotensive episodes may lead to severe intrauterine hypoxia and adverse fetal outcomes.[73] Fetal mortality rates have been declining in recent years, from 50% in the 1960s to 25% in the late 1990s. In the last decade, fetal mortality has fallen to 9.5%. The fetal and neonatal mortality rate was 7% when PPGL was diagnosed antenatally; however,

it was 17% when an antenatal diagnosis was missed.[73] In a more recent case series and review of the literature, Wing et al.[74] concluded that there were differences in the maternal and perinatal mortality rates between those presenting with paraganglioma and phaechromocytoma: these rates were lower in those with paraganglioma.

Diagnosis

The diagnostic work-up outside and during pregnancy is largely similar. Once PPGL is suspected, the first step is to undertake biochemical testing for catecholamine excess; the recommended test is a 24-hour urine collection for plasma free metanephrines or urinary fractionated metanephrines.[67] This test has a sensitivity of 97%; hence, if normal, it rules out PPGL. Nevertheless, the specificity is quite low.[67] A combined measurement of fractionated metanephrines and catecholamines in a 24-hour urine collection has a sensitivity and specificity of 98%.[75] Plasma free metanephrines has a high sensitivity of almost 100%, but a specificity of 85%.[75] It is critical that all women are given written instructions on how to collect, store and deliver the 24-hour urine sample. Furthermore, the following medications can cause a false positive result and should be stopped: tricyclic antidepressants, resperine, phenoxybenzamines, clonidine, levodopa, amphetamines, ethanol, most antipsychotics, decongestants and prochlorperazine.

Once the biochemical presence of PPGL is confirmed, localising imaging is required. Both computed tomography (CT) of the abdomen and functional meta-iodobenzylguanidine (MIBG) scans deliver large doses of radiation; hence MRI is the imaging mode of choice for the adrenal gland.[68]

Management during pregnancy

Surgical resection is the treatment of choice. A multidisciplinary team including surgeons, obstetricians, endocrinologists and anaesthetics should deliver the care. However, the timing of resection should be planned carefully. Based on the available literature, the optimum timing of resection is before 24 weeks of gestation.[68] Beyond that, the anatomical changes of pregnancy are less favourable for surgical removal and the operation could be delayed until after delivery.

Medical therapy is required at all times, regardless of the timing of surgery. Treatment with α-adrenergic receptor blockers can counteract the effects of catecholamines on the uteroplacental blood flow; nonetheless, it can induce hypotension, which can itself compromise this blood flow. The aim of the treatment is therefore to alleviate the effects of catecholamines and avoid hypotension. Two α-blockers are used during pregnancy: phenoxybenzamine and doxazocin. Phenoxybenzamine blocks both α-1 and α-2 receptors, while doxazocin is a selective α-1 receptor blocker. Phenoxybenzamine use can lead to nasal congestion, orthostatic hypotension and reflex tachycardia, while doxazocin has fewer side effects. Both agents can cross the placenta; phenoxybenzamine has been associated with neonatal hypotension and respiratory depression, while doxazocin was not.[68,73] Beta-blockers can be added to reduce orthostatic hypotension and reflex tachycardia. Beta-blockers, including labetalol, can induce a hypertensive crisis if used without alpha-blockers. If more agents are needed to control the blood pressure, calcium channel blockers may be added. All women should be advised to increase salt and fluid intake. It is important to note that the long-term effects of these agents are not known; nonetheless, the maternal and fetal benefits outweigh these risks.

Mode of delivery

Delivery can be associated with acute haemodynamic instability, so requires careful planning and timing. In addition, neonates are at risk of hypotension and respiratory depression. Hence, a well-timed and planned delivery by caesarean section has been the preferred method of delivery because of the associated increased stress. Besides, agents like syntocinon[75] can cause adverse haemodynamic effects, such as hypotension and tachycardia. Nonetheless, vaginal delivery combined with epidural analgesia has been successful.[75]

The attending physician should be prepared to manage any hypertensive crises that can occur during labour. The three agents of choice are intravenous nitroprusside, phentolamine or nicardipine. Sodium nitroprusside is a rapid-acting vasodilator and is the treatment of choice; phentolamine is a non-selective α-blocker, while nicardipine is a calcium channel blocker.

Disclosure of interests

JCK is Lead CPD Editor for *The Obstetrician & Gynaecologist*; he was excluded from editorial discussions regarding the article and had no involvement in the decision to publish. The other authors have no other conflicts of interest.

Contribution to authorship

JCK conceived the idea. MME wrote the first draft. MB and GOO restructured the article and wrote the second draft. JCK contributed to the design of the article and revised the second draft. All authors revised and approved the final version.

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