

REVIEW ARTICLE

Management of endocrine disorders in pregnancy. Part II—pituitary, ovarian and adrenal disease*

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Pituitary

The scope of the problem of the management of pregnancies occurring in women with pituitary disease is indicated by the fact that 20% of non-pregnant women with amenorrhoea have hyperprolactinaemia and 40% of women with hyperprolactinaemia have pituitary tumours (Franks *et al.*, 1975). We concentrate therefore on disturbance of prolactin secretion and discuss other pituitary diseases only briefly.

During normal pregnancy, prolactin concentrations in serum rise to levels of 4,000–5,000 mIU/l, because of an oestrogen-mediated increase in the number of pituitary lactotrophs and an increase in prolactin secretion. Pituitary prolactin release during pregnancy does, however, remain under dopaminergic control. The high concentration of prolactin in amniotic fluid is due to local production by the decidua, which is not influenced by the factors that determine pituitary prolactin secretion (Jacobs, 1980). After delivery, serum prolactin concentrations fall in parallel with the fall of oestrogen levels but they increase in response to suckling, through activation of the neuro-humeral suckling reflex. During breast feeding, prolactin promotes milk production, but 'let down' is mediated through suckling-induced release of oxytocin.

Prolactinoma

Fully 40% and possibly an even greater proportion of women with hyperprolactinaemia have prolactin-secreting pituitary tumours (prolactinomas) (Jacobs, 1981). Most prolactinomas are confined to the pituitary fossa but they may extend upwards to compromise the optic chiasma, laterally into the cavernous sinus or downwards into the sphenoidal sinus. For many years clinicians have worried that if

a patient with a prolactinoma conceived, the prolactinoma might enlarge in response to the increase of oestrogens produced during pregnancy. While such case reports do indeed exist (Magyar and Marshall, 1978; Gemzell and Wang, 1979) recent prospective studies of induction of ovulation in women with prolactinomas, treated with bromocriptine as sole therapy, have indicated that expansion of a prolactinoma during pregnancy is, in fact, unusual (Bergh *et al.*, 1982) (Table 1). This is because treatment with bromocriptine, in addition to suppressing prolactin secretion, results in remarkably rapid shrinkage of prolactinomas and so, by the time a patient enters pregnancy, the enlarged fossa usually contains only a small and shrunken pituitary tumour (Franks and Jacobs, 1983).

Patients with prolactinomas who become pregnant can usually therefore be managed conservatively. Treatment with bromocriptine should be stopped as soon as the pregnancy is diagnosed. Although there has been no suggestion of an increased hazard to the fetus of women whose ovulation was induced with bromocriptine (Griffith, Turkalj and Braun, 1979), or to the fetus of women given bromocriptine throughout pregnancy (Turkalj, Braun and Krupp, 1982; Krupp and Turkalj, 1984), there is nevertheless evidence that bromocriptine, or at least an active metabolite of it, does cross the term placenta (Bigazzi *et al.*, 1979). On general principles, therefore, it seems wise to avoid such drugs during pregnancy unless the need can be proven. In our opinion, patients most likely to experience expansion of a prolactinoma are the occasional few in whom some method of induction of ovulation has been used other than bromocriptine-induced suppression of prolactin secretion. Patients with very large prolactinomas, even after treatment with dopaminergic agonists, are also presumably vulnerable to tumour expansion during pregnancy, though the literature is in fact remarkably free of such case reports.

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TABLE 1. Prevalence of tumour complications during bromocriptine-induced pregnancies in women with untreated prolactinomas

Author	Patients <i>n</i>	Pregnancies <i>n</i>	Tumour complications
Nillius <i>et al.</i> , 1978	26	31	4
Hancock <i>et al.</i> , 1978	5	6	1
Mornex <i>et al.</i> , 1978	7	7	0
Weinstein <i>et al.</i> , 1978	17	17	0
Corenblum, 1979	21	21	0
Jewelewicz and Van de Wiele, 1980	25	25	0
Lamberts <i>et al.</i> , 1979	7	7	1
Rjosk <i>et al.</i> , 1979	9	10	0
Rolland, 1978	17	23	3
Zarate <i>et al.</i> , 1979	14	17	0
Total	148	164	9

From Jacobs, 1981 with permission.

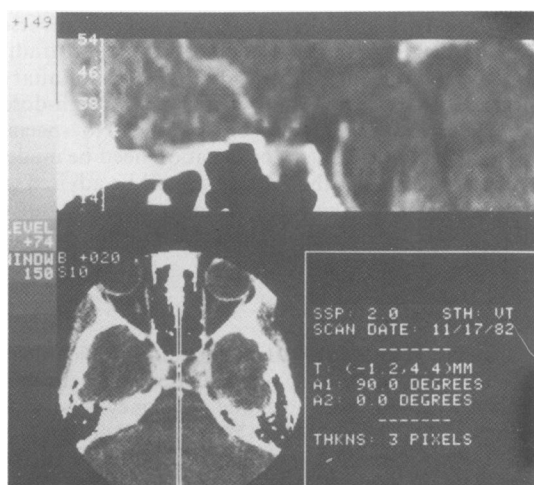


FIG. 1. Pretreatment CT scan of pituitary showing large prolactinoma. The adenoma is indicated by the radiotranslucent area in the lower part of the fossa, as seen in the sagittal reconstruction.

after treatment was started, at a time when it subsequently emerged that she was 3 or 4 days post-conception. Because of this very satisfactory shrinkage of the tumour, treatment with bromocriptine was stopped once the pregnancy was diagnosed. Six weeks later, however, she re-presented with a 2-week history of increasingly severe headaches, nausea and vomiting and evidence of regrowth of the pituitary tumour (Fig. 3). There were no visual field defects. Treatment with bromocriptine was restarted and on 10 mg/day in divided doses her symptoms remitted within 24 hr. The serum prolactin fell from 54,000 miu/l before restarting treatment to 2,800 miu/l 5

We have however recently seen a patient in whom this complication did occur. This 29-year-old woman gave a 6-month history of amenorrhoea and galactorrhoea and a pretreatment computed tomographic (CT) scan of her large prolactinoma is shown in Fig. 1. Her serum prolactin concentration was 22,000 miu/l but the remaining endocrine tests were normal. She was treated with 15 mg bromocriptine daily in divided doses. The serum prolactin concentration fell into the normal range and the menstrual cycle rapidly evolved. Fig. 2 shows the considerable shrinkage of the prolactinoma on CT scan 12 weeks

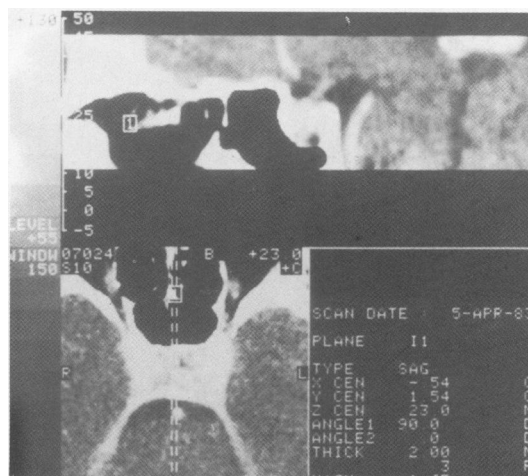


FIG. 2. CT scan after 12 weeks of bromocriptine therapy demonstrating shrinkage of the tumour. The overall size of the pituitary has probably not changed.

days later and to 500 mIU/l a week afterwards. It has remained between 450 and 600 mIU/l for 20 weeks despite our decreasing the dose of bromocriptine to 5 mg/day.

In summary, in our opinion if a patient known to have a prolactinoma develops severe headache or restriction of the visual fields during pregnancy, she should be admitted to hospital and have a CT scan of the pituitary. Using a 4th generation scanner, the usual radiation dose to the pelvis is less than 10 μ Gy (Hall, 1984), and it can be even further reduced by screening the abdomen and pelvis. If the tumour has enlarged and obstetric conditions permit, she should be delivered forthwith. Prolactin secretion and the volume of the prolactinoma will then recede as oestrogen levels fall. If, for obstetric reasons, delivery is better deferred, treatment with bromocriptine in rapidly escalating doses should be given, starting with 5 mg/day and doubled every day until symptoms have resolved, the patient is taking 20 mg/day in divided doses, or she has developed side effects. If the visual fields (as assessed daily) continue to deteriorate, or headache persists, treatment with dexamethasone (8 mg/day in divided dosage) should be added, both to reduce intracranial swelling and to reduce foeto-placental production of oestrogen. The patient should then be delivered, if possible, in the next 48 hr. Symptoms and signs that persist thereafter despite continued treatment with bromocriptine can be treated by neurosurgical decompression, although in the event surgery is rarely required (Bergh and Nillius, 1984).



Fig. 3. CT scan demonstrating regrowth of prolactinoma: suprasellar extension has occurred during pregnancy 6 weeks after stopping treatment with bromocriptine.

Patients with prolactinomas may breast feed, there being no evidence that suckling has any adverse effects on the prolactinoma. If bromocriptine is used in the puerperium, the contraceptive risk must be clearly appreciated, since reduction of prolactin secretion leads to an early resumption of ovulatory menstrual cycles. Contraception should not involve the use of oestrogens unless treatment with bromocriptine is given concurrently (Moult *et al.*, 1982).

Acromegaly

Pregnancy in patients with active acromegaly is unusual, probably because 25% also have co-existing hyperprolactinaemia (Franks, Jacobs and Nabarro, 1976). When acromegalic patients with hyperprolactinaemia are treated with bromocriptine, prolactin levels fall and fertility then returns (Bigazzi *et al.*, 1979; Luboshitzky, Dickstein and Barzilai, 1980). There is no evidence that pregnancy has any adverse effect on patients with acromegaly—indeed traditionally, before the advent of modern pituitary surgery, acromegaly was treated with high-dose oestrogen and/or progestogen therapy. No special arrangements for delivery or lactation need be made, but after pregnancy the patient should be advised to have definitive treatment (Williams *et al.*, 1975), since the disease carries a twofold increase in mortality at every age (Wright *et al.*, 1970).

Hypopituitarism

Sheehan found the destruction of 80–90% of the anterior pituitary was often necessary before a clinically recognisable hormone deficiency syndrome occurred (Sheehan, 1961). The syndrome originally described by Sheehan—post partum pituitary necrosis following profound shock—usually results from acute blood loss, in the form of a post-partum haemorrhage in 80% of cases and an ante-partum haemorrhage in 20% (Daughaday, 1978).

Patients with Sheehan's syndrome characteristically fail to lactate and are amenorrhoeic. The onset of ACTH failure is indicated by loss of pubic and axillary hair together with pallor of the skin. Hypothyroidism usually develops late. The clinical picture varies from severe panhypopituitarism to partial pituitary deficiency and the evolution of the syndrome is surprisingly gradual despite the abrupt causal factor (Sheehan and Davis, 1982). Patients with Sheehan's syndrome are managed along conventional lines with hormone replacement therapy. If the patient wishes to conceive, induction of ovulation with gonadotrophins is usually necessary. During pregnancy, conventional hormone replacement therapy is continued and no specific alteration is necessary simply because of the pregnancy (Grimes and Brooks, 1980).

Posterior pituitary disease

Since vasopressin is synthesised in the hypothalamus and only stored in the posterior pituitary, the clinical syndrome of diabetes insipidus is always caused by a hypothalamic disturbance. Such disturbances may be structural or functional, congenital or acquired.

The course of diabetes insipidus in pregnancy in 67 cases has recently been reviewed by Hime and Richardson (1978). In most cases these authors found some deterioration in the diabetes insipidus and the dose of desamino-D-arginine vasopressin (DDAVP) had to be increased. However, in a small proportion of patients the diabetes insipidus actually improved during pregnancy.

Since the glomerular filtration rate increases during pregnancy, in cases of partial deficiency an increased demand for vasopressin may be unmasked, perhaps analogous to the unmasking of diabetes insipidus in patients with complete hypothalamic hypopituitarism that occurs when the deficiency of cortisol and thyroxine has been repaired. Pregnancy itself is unaffected by diabetes insipidus and labour progresses normally with no increased incidence of uterine inertia or Caesarean section (Hime and Richardson, 1978; Chau, Fitzpatrick and Jamieson, 1969). Data concerning lactation are sparse, although most of the patients reported did lactate satisfactorily. In pregnancies complicated by pre-eclamptic toxæmia, some cases of diabetes insipidus improved when toxæmia developed (Bloemers, 1961; Campbell, 1980).

The ovary

During pregnancy, the corpus luteum secretes the polypeptide, relaxin, and a number of steroids, notably progesterone and 17-hydroxy-progesterone (Yoshimi *et al.*, 1969; Weissetal, 1977). Relaxin causes relaxation of the pelvic joints and alteration in the collagen of the cervix, producing changes which are important for cervical dilatation and vaginal delivery. It may also play a role in uterine relaxation during pregnancy (Weiss, O'Byrne and Steinetz, 1976; Klopfer, 1980).

Virilizing tumours in pregnancy

After ovarian malignancy has been excluded there are two main conditions that require consideration—'hyperreactio luteinalis' and pregnancy luteoma. In 'hyperreactio luteinalis' there are multiple luteinised cystic tumours, usually enlarging both ovaries. The condition occurs when there is an abnormally high rate of secretion of chorionic gonadotrophin, so it is usually seen in pregnancies associated with large placentas, e.g. trophoblastic disease, multiple pregnancies and erythroblastosis

(Scully, 1979). Although in up to 25% of non-molar pregnancies complicated by 'hyperreactio luteinalis' the mother is virilized, foetal masculinization does not apparently occur (Hensleigh and Woodruff, 1978). It is thought that conversion of androgens to oestrogens in the (enlarged) placenta is responsible for protection of the fetus against the abnormally high maternal plasma androgen concentrations.

Pregnancy luteoma is a solid tumour that is bilateral in a third of cases (Scully, 1979). The condition is characterised by one or more nodules of lutein cell hyperplasia, which may grow into tumours of 20 cm or more in diameter. About 80% of the reported cases have been in black women. And there are no obstetric associations. The condition may be found incidentally at Caesarean section. Although there is no association with abnormally high chorionic gonadotrophin concentration, since the condition may regress in the puerperium, its existence probably does depend on stimulation by chorionic gonadotrophin. Ten to fifteen per cent of patients with pregnancy luteoma have been virilized and in 50% of these cases, the female infants were also masculinized (Hensleigh and Woodruff, 1978).

Management of both these conditions is basically conservative. 'Hyperreactio luteinalis' regresses when the pregnancy ends, so management is directed at the underlying condition and not at the ovarian enlargement. The luteoma is sometimes diagnosed during pregnancy and is then treated surgically, mainly because the finding of a solid tumour of the ovary is regarded as an indication for surgical intervention (Hensleigh and Woodruff, 1978; Wolff *et al.*, 1973; Malinak and Miller, 1965). However since this condition too usually regresses in the puerperium, attempts should be made to conserve the ovary (Scully, 1979).

Adrenal cortex

The small but progressive rise in plasma ACTH concentration that occurs during pregnancy is associated with a two- to threefold increase of the plasma concentrations of total and unbound cortisol. Excretion of free cortisol in urine is also elevated, values of up to the astonishing figure of 500 $\mu\text{g}/24$ hr (1380 nmol/24 hr) being recorded in normal pregnant women (Gibson and Tulchinsky, 1980). These values are more than twice the upper limit of normal for non-pregnant women. During pregnancy, cortisol secretion suppresses poorly on treatment with exogenous glucocorticoids. The failure of the raised cortisol levels to suppress ACTH secretion and their resistance to suppression by exogenous glucocorticoids suggests that the normal feedback relation between cortisol and ACTH is lost. One source of the increased plasma ACTH is the placenta, from which

material with biological and immunological properties of ACTH has been extracted (Rees and Lowry, 1978).

Progesterone is natriuretic and antagonizes the action of aldosterone on the distal renal tubules. The increased progesterone concentrations of pregnancy result therefore in a compensatory increase in plasma renin activity which is augmented by the increased production of angiotensinogen stimulated by oestrogen. The rise in plasma renin activity in turn results in a six- to tenfold increase in plasma aldosterone concentrations and of urinary aldosterone excretion (Wilson *et al.*, 1980; Bay and Ferris, 1979). Increased prostaglandin activity may also contribute to these changes.

Adreno-cortical hypofunction—Addison's disease

The prevalence of Addison's disease is about 40 per million of the population. Autoimmune adrenalitis is the most common cause in the United Kingdom and 50% of such patients have other associated autoimmune disorders (Nabarro and Brook, 1975; Nerup, 1974). Addison's disease may also be caused by destruction of the adrenal glands by tuberculosis, metastatic carcinoma, fungal infection or amyloidosis.

Patients with Addison's disease have reduced rates of secretion of cortisol, aldosterone and sex steroids. The reduced secretion of aldosterone results in hyponatraemia, hyperkalaemia and a diminished extracellular fluid volume with resultant hypotension and a reduced glomerular filtration rate. The low plasma cortisol concentration accentuates the hypotension and reduction in glomerular filtration rate and, because of reduced gluconeogenesis, it also predisposes to hypoglycaemia. Plasma concentrations of ACTH are raised.

Patients with Addison's disease present with fatigue, anorexia and weight loss. There is loss of pubic and axillary hair, associated with a skin that is hyperpigmented. The blood pressure is low, with a further postural fall (to a systolic pressure of below 100 mmHg standing) and the heart is small. When the condition becomes severe, the patient is prone to vomiting, dehydration and syncope. The profile of low plasma cortisol and raised plasma ACTH levels is, of course, diagnostic, as is the impaired response of plasma cortisol to exogenous ACTH stimulation. Circulating adrenal antibodies are usually present in patients with autoimmune adrenalitis and plain X-ray examination of the abdomen may show calcification of the adrenal if the condition is tuberculous in origin.

These patients are usually maintained on between 25 and 37.5 mg of oral hydrocortisone and 0.1–0.2 mg of fluorocortisone per day. During most of pregnancy the usual maintenance dose of both steroids should be adequate. There are however two danger periods

—in early pregnancy the patient with undiagnosed Addison's disease may present with an adrenal crisis and her nausea and vomiting may be mistaken for the symptoms of early pregnancy. The second danger period is during labour and delivery when, as in all stress situations, glucocorticoid demands increase (Hendon and Melick, 1955).

During pregnancy, electrolyte disturbance secondary to nausea and vomiting should be anticipated. Blood pressure and weight, blood urea, electrolyte and glucose concentrations are monitored at the regular antenatal visits. Hormone replacement therapy is continued at pre-pregnancy doses until labour commences. The patient should then be given parenteral hydrocortisone (200 mg intramuscularly or 100 mg intravenously) 6-hourly throughout labour. Once the patient has been delivered, the dose is halved every 48 hr until the pre-pregnancy dosage is reached. There is no contra-indication to breast feeding or to the oral contraceptive pill.

Acute adrenal failure

Acute adrenal failure may be caused by under-treated or undiagnosed Addison's disease, the onset of a pregnancy-related stress such as massive ante- or post-partum haemorrhage or, rarely, adrenal haemorrhage secondary to anti-coagulant therapy (Nabarro and Brook, 1975). These patients may present with an 'acute abdomen'. Another group presenting problems of this kind are patients who have been on steroid therapy for some chronic condition such as asthma (Shearman, 1957; Graber *et al.*, 1965). Immediate treatment is by rehydration with saline and intravenous hydrocortisone (100 mg intravenously 6-hourly). Oral fludrocortisone (0.1 mg bd) and hydrocortisone are given once the patient can take fluids by mouth.

Adreno-cortical hyperfunction—Cushing's syndrome

Cushing's syndrome occurs in about two per million of the population and the mortality without treatment is about 50% in 5 years, usually from infections or cardiovascular problems. The condition is either caused by hypersecretion of ACTH by the pituitary (usually associated with a pituitary micro-tumour) or by an ectopic (non-pituitary) source, or it may be caused by overproduction of corticosteroids by a primary lesion of the adrenal. The physical appearance of these patients is very striking—they have a moon-shaped face, with a buffalo hump and marked and pigmented abdominal striae. They are overweight, with central obesity and they are usually hypertensive. There is often a proximal myopathy. Women may present with hirsutism and acne and are usually amenorrhoeic or oligomenorrhoeic, and therefore subfertile.

TABLE 2. Outcome of pregnancy in Cushing's syndrome related to aetiology where known

Aetiology	Number of pregnancies	Successful pregnancies
Pituitary-dependent	14	11 Pre-term*
		5 Term*
Adrenocortical adenoma	12	8 Pre-term
		4 Term
Adrenocortical carcinoma	5	4 Pre-term
		2 Term
Total	31	23 Pre-term
		12 Term

Term indicates gestation >37 weeks. From Gormley *et al.*, 1982 with permission.

In pregnancy Cushing's syndrome is a very serious condition indeed. There is a very high rate of fetal loss and the mother's health, and indeed her life, may be seriously jeopardised. Monitoring these pregnancies biochemically is complicated too, because the high circulating levels of cortisol in the mother may suppress fetoplacental production of oestrogens and, if oestriol is being used to monitor fetal well-being, deceptively low values may be obtained (Khakoo *et al.*, 1982; Reschini *et al.*, 1978). Placental conversion of maternal cortisol to cortisone (Campbell, Pearson and Murphy, 1977), may however provide the fetus with some protection.

A recent review described 35 pregnancies in 30 patients with Cushing's syndrome (Gormley *et al.*, 1982). The outcome in 31 pregnancies, related to the primary diagnosis, is shown in Table 2. It was a striking finding that adrenal carcinoma occurred in 15% of the patients and that the remainder were almost equally divided between adenomas of the pituitary and of the adrenal.

At present the most certain way of establishing the cause of Cushing's syndrome is by a combination of the usual endocrine tests (Nabarro and Brook, 1975) with computed tomographic imaging of the adrenals and pituitary. The usual endocrine assessment of Cushing's syndrome is difficult during pregnancy because of the pregnancy associated changes in circulating cortisol, in ACTH and in the urinary excretion of cortisol (see earlier) (Grimes, Gayez and Miller, 1973; Kreines, Perrin and Salzer, 1964). Although, as mentioned, earlier, high grade CT scanning of the pituitary is relatively safe, scanning of the adrenals obviously causes considerable irradiation of the fetus; the routine CT scan of the adrenals delivers 2,000 mrad (20 mGy) to the abdomen which is in fact the upper limit of radiation regarded as 'acceptable' in pregnancy. Nonetheless, reference to Table 2 shows that once pituitary dependent Cushing's disease has been excluded, there is a one in three risk of the patient suffering from an adrenal carcinoma. We therefore recommend that if a high resolution CT scan of the pituitary is normal,

pregnant women with Cushing's syndrome should have an adrenal CT scan. These patients must, of course, be warned of the risk to the fetus; however the dose of irradiation can be reduced if only a few selective views are taken, and ultrasound scanning sometimes allows the diagnosis to be made.

Based on the data of White *et al.* (1982) and Brown *et al.* (1983) CT scanning of the adrenals and pituitary in a patient with Cushing's syndrome may be expected to show one of the following:

- (1) A normal or abnormal pituitary scan with normal or moderately enlarged adrenals if the condition is pituitary dependent (Cushing's disease).
- (2) A normal pituitary scan with bilaterally very enlarged adrenals if the cause is an ectopic source of ACTH.
- (3) A normal pituitary scan with one big, non-invasive, adrenal and a small contralateral gland if the cause is an adrenal adenoma or a non-invasive carcinoma.
- (4) A unilateral invasive picture on the adrenal scan if the cause is an adrenal carcinoma.

Definitive treatment obviously depends upon the precise diagnosis. Adrenal carcinoma is managed primarily surgically, but attempts should be made to deliver a viable fetus prior to radical surgery and subsequent cytotoxic chemotherapy. In patients with Cushing's syndrome due to an adrenal or pituitary adenoma, the first concern is to try to obtain a live infant and definitive surgical therapy is deferred until after that has been achieved. If obstetric circumstances do not permit early delivery, the clinician is faced with the alternatives of instituting medical therapy and trying to prolong the pregnancy, or offering definitive treatment immediately. An account of one patient treated with metyrapone has been reported recently and this patient and her infant both survived (Gormley *et al.*, 1982). Metyrapone predominantly blocks 11-beta-hydroxylase activity in the adrenal and so reduces cortisol secretion. Although treatment with enzyme blockers prior to definitive surgery is usually recommended for patients with Cushing's syndrome who are not pregnant

(Jeffocate *et al.*, 1977), it remains unclear whether in pregnancy this form of treatment will always be safe for the baby. Trilostane, which is a steroid competitive antagonist of the 3-beta-hydroxy-steroid dehydrogenase enzyme system, should certainly not be used in pregnancy because it also inhibits placental steroidogenesis, lowers maternal plasma progesterone concentrations and may therefore precipitate premature labour (van der Spuy *et al.*, 1983).

In summary then, for patients with Cushing's syndrome in pregnancy we recommend the following approach:

- (1) In the first trimester of pregnancy, in all women with adrenal carcinoma we recommend termination of pregnancy followed by definitive therapy. In those women with non-pituitary dependant Cushing's syndrome where the diagnosis remains uncertain, surgical exploration of the adrenals should be undertaken since it is not advisable to leave a possible malignancy untreated for 28 or more weeks. The implications of a full diagnostic assessment at this stage of pregnancy must be discussed in detail with the patient. In patients with pituitary-dependant Cushing's, we recommend pituitary surgery as definitive treatment.
- (2) In the third trimester of pregnancy, we recommend prompt delivery of the baby, followed by definitive therapy. Vaginal delivery is not contraindicated. If it is thought preferable to defer delivery until the fetus is more mature, the patient may be treated with metyrapone (500 mg 6-hourly). Glucocorticoid replacement therapy, as for patients with Addison's disease (see earlier) is required at delivery, which is then followed by definitive therapy.
- (3) Presentation of Cushing's syndrome in the second trimester represents the most difficult problem. Most cases are likely to abort because of the severe adverse effects of hypercortisolism (e.g. diabetes and hypertension). In those pregnancies that continue the decision lies between medical treatment with metyrapone (Gormley *et al.*, 1982) or definitive therapy preceding delivery.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia embraces a variety of enzyme defects in the pathway of steroid biosynthesis. Ninety-five per cent of cases have 21-hydroxylase deficiency (Brook *et al.*, 1974) and the incidence of this deficiency in Europe is about 1 per 5,000 live births—giving a gene frequency for heterozygosity of 1 in 35.

Patients who reach adulthood undiagnosed present with infertility, hirsutism and menstrual disturbances. Jones and Verkauf (1971), in a review of 33 patients, report that even on treatment these patients tend to have a delayed menarche and so their reproductive potential has been difficult to assess.

During pregnancy, the patient with congenital adrenal hyperplasia should continue on the glucocorticoid (and mineralocorticoid) therapy she will have already been taking. Blood urea and electrolytes and blood pressure should be monitored throughout the pregnancy. Because of the virilizing effect of androgens in early life, these women tend to have android pelvises and, in those patients going to term, delivery by Caesarean section has usually been necessary because of cephalo-pelvic disproportion (Jones, 1979). The glucocorticoid dosage during labour and delivery should be increased as for Addison's disease.

Antenatal diagnosis of 21-hydroxylase deficiency may be made using HLA typing of fetal cells and steroid hormone measurements in amniotic fluid, thus identifying affected infants of homo- and heterozygous mothers. This will alert the clinician to the need for prompt assessment of the newborn (Brook, 1981).

Adrenal medulla

Plasma levels of adrenaline and noradrenaline do not change in pregnancy but do increase during labour. The plasma adrenaline concentration returns to normal within 20 min of delivery, but noradrenaline concentrations may continue to rise (Lederman *et al.*, 1977).

Phaeochromocytoma

Phaeochromocytoma is a catecholamine-secreting tumour which may occur at any age, but most commonly in the fifties. It may be familial. Patients may present with paroxysmal or sustained hypertension and complain of palpitation, headache, vomiting and severe anxiety. During pregnancy there is an increased incidence of visual complaints and convulsions (which may be misdiagnosed as eclampsia or epilepsy). Diagnosis may be rapidly confirmed on the basis of increased plasma or urinary catecholamines (adrenaline and noradrenaline and their metabolites, e.g. vanillyl mandelic acid) (Brown, 1983).

Tumour localization in pregnancy is difficult because diagnostic methods such as aortography and vena cava sampling carry a considerable risk and radioisotope scanning is contraindicated. Computerised tomographic scanning of the adrenal gland is likely to be very helpful but it does expose the abdomen and therefore the fetus to considerable irradiation (see earlier). Ultrasound scanning by a skilled operator may localize an adrenal tumour and is the imaging technique of choice. Most tumours occur in the adrenal glands (50% in the right gland, 29% in the left and bilateral in 10%) and cause elevated adrenaline levels. In contrast, the 10% of all tumours that are extra-adrenal are usually pure noradrenaline sectors (Brown, 1983).

In pregnancy, the prognosis for patients with undiagnosed and therefore untreated, pheochromocytoma is very serious indeed. A maternal mortality of 48%, with a fetal loss of 54%, was reported in a series of 89 cases reviewed by Schenker and Chowers (1971). The maternal prognosis improved markedly if the diagnosis was made in the antenatal period and treatment instituted rapidly, but in the review quoted above, the fetal mortality remained high.

The differential diagnosis of pheochromocytoma in pregnancy is hypertension, pre-eclamptic toxæmia, thyrotoxicosis and epilepsy. Hypertension is of course the major clinical problem and may precipitate accidental haemorrhage. Management in pregnancy involves early hospitalization, adequate alpha adrenergic blockade and careful follow-up. With good control these patients now usually progress safely through pregnancy and deliver healthy infants (M. J. Brown and E. J. Ross, personal communication).

Labour and vaginal delivery may lead to a sudden discharge of catecholamines and so increase the maternal mortality. For this reason these patients should always be delivered by elective Caesarean section. Meticulous anaesthetic technique must be used and the patient should come to surgery under alpha adrenergic blockade—that is, having been stabilized on phenoxybenzamine in a dose of 10–80 mg per day in divided doses, adjusted according to the effects on the blood pressure.

Exploration of the adrenals and removal of the tumour may be considered in early pregnancy. It might also be considered at the time of Caesarean section provided the patient has been adequately investigated (Griffith *et al.*, 1974). Beta-adrenergic stimulators, as used in the management of pre-term labour, are extremely dangerous for these patients and maternal deaths have been described. Their use is absolutely contra-indicated.

Catecholamines do not cross the placenta and so if the fetus survives the pregnancy, its neonatal course should be normal*.

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*As illustrated by a clinical report in this issue (Parsons, Clunie and Letchworth, 1984) pheochromocytoma may also present as vascular collapse in the post-partum period.

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