Prescribing in Pregnancy

Treatment of endocrine diseases

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This article reviews the use of drugs in pregnancy in all the main endocrine disorders with the exception of diabetes mellitus, which is dealt with separately in this series and in an excellent review by Vaughan and Oakley.¹

Drugs are used in both diagnosis and management of endocrine diseases. Diagnosis entails assessing basal function of an endocrine gland followed by tests to suppress or stimulate the gland. Further diagnostic measures may well include procedures to localise a lesion. Medical management usually takes the form of hormone replacement treatment in the case of endocrine failure or suppressive treatment in the case of hyperfunction.

Diagnosis

Pregnancy usually requires a state of endocrine balance—that is, the chances of conceiving are reduced unless the endocrine milieu is normal. Endocrine disease does, however, arise de novo in both pregnancy and the puerperium. This section deals with the appropriate tests which require the use of drugs.

Thyrotoxicosis—After diabetes, thyrotoxicosis is the most common endocrine disorder developing in pregnancy, many of the signs mimicking those of normal pregnancy. Until recently diagnosis of borderline cases would have used the thyrotrophin releasing hormone test to assess pituitary thyrotrophin (thyroid stimulating hormone) response. Doubts have been expressed about the use of thyrotrophin releasing hormone in early pregnancy because it produces smooth muscle contraction.² The sensitive radioimmunoassay for thyroid stimulating hormone has virtually replaced the thyrotrophin releasing hormone test, at least in pregnancy. Other diagnostic measures in thyrotoxicosis include measurement of iodine-131 uptake, a test which is totally contraindicated in pregnancy because of the risk of fetal uptake of the isotope and subsequent damage to the thyroid, although complete destruction of the thyroid has not been documented with the diagnostic dose.³

Other less common conditions that may present in pregnancy are the adrenal disorders which cause hypertension.

Phaeochromocytoma may be suspected with increased excretion of catecholamines or their metabolites. Pentolinium, a quaternary ammonium ganglion blocking compound, has been used as a diagnostic agent. Failure to reduce plasma catecholamine concentrations after intravenous injection of 5 mg pentolinium provides additional evidence for establishing the diagnosis,⁴ but no experience of this test in pregnancy has been described. Localisation procedures for phaeochromocytoma include the use of ¹³¹I-met-

iodobenzylguanidine, but this should be avoided in pregnancy because of the radiation risk to the fetal thyroid.

Conn's syndrome—Mineralocorticoid excess, which occurs in Conn's syndrome, is rare but may be suspected in patients with hypertension and hypokalaemia. The hypertension is rarely severe and full investigation may be postponed until after pregnancy, when localisation procedures such as the use of radio labelled selenium cholesterol may be used without fear of affecting the fetus.

Cushing's syndrome—Though rare, glucocorticoid excess presenting in pregnancy is much more serious, and needs urgent investigation because of the high risk (16%) of malignancy of the adrenal cortex.⁵ Dexamethasone crosses the placenta, causing suppression of the fetal pituitary-adrenal axis,⁶ but in the doses used for diagnosis this suppression is short lived. The use of metyrapone is discussed in the section on management.

Pituitary disorders—Investigation of pituitary disorders usually includes assessing the response to insulin induced hypoglycaemia. The transient nature of the hypoglycaemia is without serious risk to the fetus. The usual precautions of having an intravenous line open, with hydrocortisone and dextrose drawn up ready, as well as using a smaller dose of insulin for patients with suspected hypopituitarism, apply in pregnancy as much as for non-pregnant patients.

Management

HORMONE REPLACEMENT TREATMENT

Hypothyroidism

Hypothyroidism is usually diagnosed and treated before pregnancy as the hypothyroid state is associated with infertility. Patients with untreated hypothyroidism have a high risk of spontaneous abortions, a stillbirth rate twice that in normal pregnancies, and an increased incidence of premature labour and subnormal neonatal neurological development in their children.³ An increased risk of congenital abnormality in the children of these patients has been refuted.⁷ Thyroid replacement is achieved with thyroxine 100-200 µg/day as a single dose; the response is monitored by the fall in the serum concentration of thyroid stimulating hormone. Thyroxine requirements do not change in pregnancy; the dose can usually be maintained despite the oestrogen mediated rise in thyroxine binding globulin that occurs in normal pregnancy.⁸ The important point is to monitor and treat patients according to biochemical findings rather than by clinical judgment. If the dose of thyroxine has been increased during pregnancy it will need to be reduced in the puerperium. There is no contraindication to breast feeding.

Hypoadrenalism

As with hypothyroidism, adrenal insufficiency is usually diagnosed and treated before pregnancy. Replacement treatment (hydrocortisone 20-30 mg/day, fludrocortisone 0.05-0.20 mg/day) is

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essential and does not need to be changed in pregnancy unless intercurrent stress or illness develops, when increased or parenteral doses should be given. The oestrogen mediated rise in cortisol binding globulin during pregnancy does not seem to affect steroid requirements. There is one report of an increased incidence of infants who were small for gestational age in patients with Addison's disease, but it is not clear whether this was due to the disease or the treatment.⁹ No other complications, either fetal or maternal, associated with steroid replacement treatment have been reported. There is no contraindication to breast feeding.

Hypopituitarism

Anterior pituitary deficiency states require thyroxine and corticosteroid replacement treatment as described above, with the exception that fludrocortisone is not required since mineralocorticoid secretion is independent of the pituitary. Untreated, hypopituitarism has a high mortality for both fetus and mother.¹⁰ Hypogonadotrophic states may require exogenous gonadotrophin or, more physiologically, pulsatile gonadotrophin releasing hormone treatment to achieve ovulation. Once pregnancy is achieved, however, maintenance treatment is not necessary because gonadotrophin and sex steroids are produced by the fetoplacental unit. Lactation may be impaired because of prolactin deficiency.

Posterior pituitary failure is associated with diabetes insipidus and requires replacement treatment with the vasopressin analogue desmopressin (5-10 µg twice daily). A review of 67 cases showed that 58% of patients deteriorated during pregnancy.¹¹ The mechanism for this is unclear but may reflect the increase in glomerular filtration rate in pregnancy. No ill effects of desmopressin in pregnancy have been reported apart from the small risk of increased uterine contractility owing to its oxytocin like structure and activity.¹² This effect, however, is seen when desmopressin is used intravenously as a diagnostic agent rather than with the normal replacement regimen using nasal insufflation. The oxytocic action of desmopressin is only a fraction (1/5) of that of arginine vasopressin.

Hypoparathyroidism

Hypoparathyroidism usually occurs as a complication in patients who have undergone thyroidectomy, but occasionally it is seen as part of an autoimmune condition or as a hormone resistant syndrome. Hypoparathyroidism in the mother poses severe risks of fetal hyperparathyroidism with neonatal hypocalcaemic rickets, which may be fatal. Treatment with calcium (1600-2000 µg/day) and either vitamin D (1.25-2.5 mg/day) or dihydrotachysterol (250-1000 µg/day) is essential, and maternal serum calcium and phosphate values should be monitored regularly to maintain normocalcaemia.¹³ Vitamin D requirement increases twofold to threefold during pregnancy.¹⁴ The use of calcitriol has been associated with fetal hypermineralisation in one of twin fetuses.¹⁴ In the puerperium the requirement for calcium and vitamin D should be reassessed; they may not be required at all.¹⁵ In healthy women an insignificant amount of vitamin D is secreted in the breast milk,¹⁶ but the high doses of vitamin D required in lactating hypoparathyroid women may cause neonatal hypervitaminosis.

Ovarian failure

Until recently the prospect of pregnancy in a patient with ovarian failure seemed remote. The development of techniques of embryo transfer, however, has made pregnancy a real possibility for these patients. Preparation of the patient includes the use of oestrogen and progesterone to prepare the recipient uterus and endometrium before embryo transfer and subsequently to maintain the hormonal environment until the fetoplacental unit can take over. The use of sex steroids in pregnancy is discussed below.

ENDOCRINE GLAND HYPERFUNCTION

Thyrotoxicosis

The mainstay of medical treatment of thyrotoxicosis is the thionamide agents: carbimazole, propylthiouracil, and, less commonly in the United Kingdom, methimazole. Propylthiouracil is less lipid soluble and more highly protein bound than carbimazole or methimazole, and is less readily transferred into breast milk¹⁷ or, theoretically, across the placenta. No teratogenic effects have been reported for propylthiouracil or carbimazole, but there have been five cases of a scalp defect, aplasia cutis, occurring in neonates whose mothers had been treated with methimazole.¹⁸ One study suggested that maternal thyrotoxicosis may itself be associated with fetal malformation and that the risk may be reduced by antithyroid drug treatment.¹⁹ Perinatal mortality is also high in untreated thyrotoxicosis, with an increased incidence of premature delivery; this can be reduced to normal with treatment.²⁰ Fetal hypothyroidism is a definite risk with all thionamide treatment, and the lowest possible dose to maintain biochemical euthyroidism in the mother must be used, with (at least) monthly measurements of the serum concentrations of free thyroxine (or free thyroxine index) and thyroid stimulating hormone. Fetal goitre formation may occur but is not dose related, being also affected by the antibody status and iodine intake of the mother.⁸ The intellectual development of children exposed to antithyroid drugs in utero is reported to be unaffected.²¹ Autoimmune thyrotoxicosis often improves during pregnancy so that the dosage may be reduced. After delivery, however, sudden overactivity is common, requiring an increase in treatment.²²

Other agents used to control thyrotoxicosis include β blocking drugs, potassium iodide, and radioactive iodine. β Blocking drugs are discussed in full in the article on cardiovascular disease. Potassium iodide, which is often used in preparation for thyroid surgery, is well recognised as a cause of fetal goitre.⁴ Cases of fetal goitre have been reported when the mother took as little as 12 mg iodide a day. Radioactive iodine (¹³¹I) in therapeutic doses is liable to ablate the fetal thyroid and also has the potential to induce maternal thyroid storm. Oddly, the risk to the fetus is least in the first trimester before the fetal iodine trap is operational.²³

In the light of the above, propylthiouracil is probably the drug of choice in both pregnancy and puerperium. Initially, 100-150 mg should be taken every 8 hours, and this should be reduced to 50 mg every 6-8 hours once the hyperthyroid state is controlled clinically and, more importantly, biochemically. The lowest possible maintenance dose should be used to maintain the serum free thyroxine concentration in the high normal range. If thyrotoxicosis recurs or is not controlled up to 600 mg/day in divided doses may be used.²⁰ Failure to control symptoms may indicate the need for partial thyroidectomy, in which case propranolol 40 mg may be given every 6 hours to control residual symptoms and reduce vascularity before the operation.⁸

Fetal and neonatal thyrotoxicosis may occur as a result of transplacental passage of thyroid stimulating antibodies in the absence of maternal signs after thyroid ablation or, rarely, in maternal autoimmune hypothyroidism. Fetal thyrotoxicosis has been successfully treated with thionamide using the fetal heart rate as a guide to dosage.²⁴ Intra-amniotic administration of thyroxine has been used in a case of suspected fetal hypothyroidism,²⁵ but experience with this is limited and careful screening and follow up of such infants is needed.

Cushing's syndrome

Drugs used in the management of Cushing's syndrome include metyrapone and trilostane. Both of these drugs block various points in the biosynthetic pathway of cortisol. Experience of their use in pregnancy is limited because of the rarity of the syndrome. Both agents cross the placenta and affect fetal and placental steroid metabolism. Metyrapone has not been shown to have any adverse effects on the fetus or mother in normal pregnancy,²⁶ but its effect on urinary oestrogen excretion is uncertain.⁵ Studies in baboons

have shown an inhibition of surfactant release, although the infants did not develop respiratory distress.²⁷ Trilostane, which antagonises 3β OH-steroid dehydrogenase, inhibits placental progesterone production with the risk of abortion or premature labour²⁸; it is therefore contraindicated in pregnancy. Metyrapone has been used successfully in a pregnant woman with Cushing's syndrome with survival of both mother and infant.⁵ In another case, however, the use of metyrapone coincided with the onset of severe pre-eclampsia at just over 26 weeks' gestation, and the baby died as a result of a complication of premature delivery.²⁹ The link between the use of metyrapone, which increases 11-deoxycorticosterone production, and the exacerbation of maternal hypertension in this case is not clear.

In view of the high incidence (16%) of adrenal malignancy among pregnant patients with Cushing's syndrome, active surgical or obstetric management, or both, has been recommended in the first and last trimesters; metyrapone should be reserved for difficult cases in the second trimester.³⁰ Metyrapone is lipid soluble and is therefore likely to be excreted into the breast milk; there are no data on its use by lactating women.

Congenital adrenal hyperplasia

Adrenal suppression in patients with congenital adrenal hyperplasia is achieved with replacement glucocorticoid and mineralocorticoid treatment, which should be maintained in pregnancy as for patients with hypoadrenalism (see above). In a recent study treatment of a fetus with adrenal hyperplasia was achieved by giving dexamethasone to the mother in the first and second trimesters to suppress fetal production of adrenocorticotrophic hormone, thus reducing fetal adrenal androgen output with its associated masculinisation of female genitalia.³¹

Phaeochromocytoma

Surgical treatment is required for phaeochromocytoma in pregnancy once the effects of circulating catecholamines have been controlled by α and β adrenoceptor blocking agents.

Hyperprolactinaemia and acromegaly

The dopaminergic agent bromocriptine is the drug of choice in the management of hyperprolactinaemia caused by pituitary microadenoma or macroadenoma, allowing ovulation to occur and reducing tumour size. Bromocriptine may be used in the management of acromegaly as it reduces growth hormone secretion, but treatment is not always successful. It is also used to suppress lactation. No adverse effects on the fetus have been reported, either in women in whom ovulation was induced with bromocriptine or in women given bromocriptine throughout pregnancy,³² although there is evidence that bromocriptine, or an active metabolite, crosses the placenta.³³

Treatment with bromocriptine in pregnancy should be reserved for the small number of women who present with symptoms and signs of tumour expansion in whom a high resolution computed tomography scan confirms the diagnosis and in whom immediate delivery is not practicable or desirable. Treatment starts at 5 mg/day in divided doses, doubling daily over three days until symptoms resolve or the patient is taking 20 mg/day or has developed side effects. An operation is rarely necessary. Lactation in such patients is both suppressed and contraindicated, and early contraception must be considered after delivery.

Hyperparathyroidism

Surgical treatment is required for symptomatic hyperparathyroidism in pregnancy. Fluid replacement may be necessary before the operation if the hypercalcaemia is severe.³⁴ The neonate

needs careful observation for signs of hypocalcaemia (secondary to parathormone suppression), which may present late in the postnatal period.

Sex hormones and pregnancy

Compounds which contain oestrogen are commonly used to inhibit ovulation and thus avoid pregnancy. In practice, pregnancy has often occurred during oestrogen treatment because of impaired absorption, a missed pill, or too low a dose. In the past oestrogens were also used to inhibit lactation. Non-steroidal oestrogens, such as stilboestrol, hexoestrol, and dienoestrol, are teratogenic and have a well documented association with adenocarcinoma of the vagina and cervix in the daughters of mothers who took these drugs before the 18th week of gestation.³⁵ Other changes of the female genital tract have been shown, and testicular, seminal, and other genital abnormalities have been found in the sons of such mothers.³⁶

Steroidal oestrogens do not have the same effects as the stilboestrol like compounds,³⁵ but there is disagreement about their teratogenicity. Anomalies of the cardiovascular system, limb deformities, neural tube defects, and renal and tracheo-oesophageal abnormalities have all been attributed to steroidal oestrogens.³⁷ Two large prospective studies, however, have not found any increased risk to babies born to mothers who conceived either after or while taking oral contraceptives.^{38, 39}

Many of the progestogens used as contraceptive agents, such as norethisterone and levonorgestrel, are 19-nortestosterone derivatives with mildly androgenic properties and could therefore cause virilisation of a female fetus. The small amounts present in oral contraceptives, however, are unlikely to do so. On the other hand, 17-hydroxyprogesterone derivatives, such as medroxyprogesterone acetate (Provera) and 17-hydroxyprogesterone caproate (Proluton), are pure progestational compounds and may have a role in the management of habitual abortion and premature labour, although their use remains controversial.³

The weak androgen danazol has been used in the treatment of endometriosis to suppress ovarian activity and menstruation. Ovulation does occasionally occur at low doses, and danazol treatment has been associated with masculinisation of a female fetus.⁴⁰ Concurrent non-hormonal contraception should be used.

The antiandrogen cyproterone acetate has been shown to inhibit masculinisation of the male fetus in studies in animals⁴¹ and should be given with oestrogen to provide contraception as well as to enhance the antiandrogenic effects. No such effects have been reported in the fetuses of women taking small amounts of cyproterone acetate such as those found in Diane.

The antioestrogen clomiphene citrate has been implicated in several case reports of neural tube defects. Large studies, however, have not shown any significant increase in the malformation rate.⁴²

The use of sex steroids by lactating women deserves comment. Administration of high doses of oestrogen to suppress lactation, for a long time considered a risk because of thromboembolism,⁴³ is now absolutely contraindicated, and bromocriptine should be used instead. On the other hand, the use of low dose (≤ 50 μ g) oestrogen compounds for contraception is unlikely to inhibit lactation.¹⁶ Because the risk of venous thromboembolism is greatest post partum, however, it is wise to avoid compounds containing oestrogen in the immediate and early puerperium. Progestogen only contraception may be preferable as it has no effect on lactation or coagulation.⁴⁴ If milk supply is diminishing or needs supplementation, or when menses return, transfer to a combined preparation is recommended if maximum contraceptive effectiveness is required. Cyproterone acetate is contraindicated until weaning is complete as it may be transferred into the breast milk,⁴⁵ although its effects on the neonate are unknown.

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For how long is it safe to take chloroquine in the dosage necessary for malaria prophylaxis?

The main danger of prolonged chloroquine administration is retinopathy, which in some cases is not reversible on discontinuing the drug. This complication has been seen most often in patients with rheumatoid arthritis and similar conditions receiving doses of chloroquine far higher than those used for malaria prophylaxis. Retinopathy does not occur provided that the total dose of chloroquine base ingested is below 100 g. This represents a conservative safe upper limit of chloroquine administration, and many people have exceeded this dose by a factor of several times without developing retinopathy, provided that the drug was given at the rate of only 300 mg base a week. With the normal dose of chloroquine used for malaria suppression (300 mg chloroquine base a week contained in 400 mg chloroquine sulphate or 500 mg chloroquine phosphate) the drug may be taken continuously for six and a half years before the 100 g dose of base is reached. Then the safest advice is to replace chloroquine with another antimalaria prophylactic for at least a year before resuming regular chemoprophylaxis with chloroquine again.—DION R BELL, reader in tropical medicine and honorary consultant physician, Liverpool.

Can sudden withdrawal of a cardioselective β blocking agent such as atenolol precipitate an acute myocardial infarction in a patient with angina pectoris? If so what might be the interval between the withdrawal of the drug and onset of the infarction?

The cardiovascular effects of sudden withdrawal of β blocking agents have been studied frequently, especially in clinical trials when active drug is substituted for placebo. There remains, however, some disagreement as to the importance and severity of the withdrawal syndrome. Most commonly reported is an exacerbation of exertional angina pectoris, but unstable angina and myocardial infarction may also occur. These may develop from one to 21 days after withdrawal and are much less common in patients in hospital, probably because physical exertion is a prerequisite for the full expression of the clinical consequences. The withdrawal syndrome is probably due to excess β adrenergic stimulation from the increased population of β adrenoceptors that develop during treatment with β blockers. Although there is no clear evidence, it may be that β blockers with a prolonged elimination half

life (atenolol and metoprolol) allow stabilisation of the β adrenoceptors. Thus it seems prudent to withdraw all β blocking agents gradually and to minimise exertion while the dose is being reduced and for the subsequent two to three weeks.—L M SHAPIRO, senior registrar in cardiology, London.

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What is known of the aetiology of benign hypertrophy of the prostate? Is there any differential incidence in relation to social class, occupation, or sexual activity?

Despite the enormous amount of scientific research that has been and still is being devoted to the aetiology of benign prostatic hypertrophy the basic cause remains obscure. It is known that it develops in a hormonal environment enriched in oestrogen relative to androgen¹ and that benign prostatic hypertrophy may reflect the summation of androgen effects on the prostatic epithelium and oestrogen effects on the prostatic fibromuscular stroma. Although there is no direct evidence for this in man, most studies support this concept. Fibromuscular hypertrophy of the prostate is inevitable with aging, and protection is only afforded by prepubertal castration. There have been no specific epidemiological studies designed to consider the influence of variables such as social class, occupation, diet, sexuality, and environmental exposures. Benign prostatic hypertrophy does appear, however, to occur most frequently in blacks, almost as frequently in whites, and infrequently in orientals. The incidence of benign prostatic hypertrophy in celibates is as high as in the general population, although "slightly less" among unmarried men.² In Scotland mortality and morbidity from benign prostatic hypertrophy seems to be higher in the upper social classes than in the middle classes³ and higher in Welsh speaking Welshmen than in English immigrants.⁴ Continued sexual activity in aging men neither predisposes to nor prevents benign prostatic hypertrophy.⁵—J C GINGELL, consultant urologist and lecturer in urology, Bristol.

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