Review of presentation, diagnosis and management of pituitary tumours in pregnancy

Kimberley Lambert MRCP MBChB and **Catherine Williamson** MD FRCP

Maternal and Fetal Disease Group, Institute of Reproductive and Developmental Biology, Imperial College London, Du Cane Road, London W12 0NN, UK

Summary: Although pituitary tumours are relatively uncommon, their association with menstrual irregularity and infertility brings them into the domain of obstetrics and gynaecology. This review addresses the range of pituitary tumours with particular regard to diagnosis, growth and behaviour and management during pregnancy.

INTRODUCTION

Pituitary tumours comprise 15% of intracranial tumours. The actual incidence is low as many remain undiagnosed. Current published data indicate that prolactinomas are the commonest hormone-secreting tumour in pregnant women, followed by growth hormone (GH)-secreting and adrenocorticotrophic hormone (ACTH)-producing tumours. However, postmortem findings have shown that 10% of the general population have undiagnosed microprolactinomas.¹ The annual incidence of all pituitary tumours (non-pregnant and pregnant) is shown in Table 1. The commonest presenting feature of pituitary tumours in women of reproductive age is menstrual disturbance.

PHYSIOLOGY

The pituitary gland enlarges up to 45% in normal pregnancy.¹ The principal cause is believed to be hyperplasia and hypertrophy of lactotroph cells stimulated by raised oestrogen levels in pregnancy.² The pituitary is located below the optic chiasm. As the pituitary increases in size throughout pregnancy, compression of the optic nerve may occur if there is a pituitary tumour present, and this may result in a visual field defect, potentially leading to visual loss.

PROLACTINOMA

Physiology

Prolactin is produced by lactotroph cells. It stimulates the proliferation of breast tissue and inhibits pulsatile gonadotrophin secretion, thereby affecting ovulation. Prolactinomas are classified according to size and are described as microadenomas if they measure <1 cm and macroadenomas if ≥ 1 cm on

magnetic resonance imaging (MRI). Prolactin release is under inhibitory control by dopamine and its secretion is stimulated by oestrogen. Dopamine binds to lactotroph D2 receptors. In prolactinomas this negative feedback is generally maintained and hence prolactinomas respond well to the dopamine agonists bromocriptine, cabergoline or quinagolide. Transphenoidal surgery can be performed if there is no response to medication or if the optic nerve is compressed. This is less likely to achieve a cure in macroadenomas than microadenomas and it can affect future fertility, as there is a greater risk of hypopituitarism.

Effect of pregnancy

Prolactinomas most commonly present with menstrual disturbance, infertility or galactorrhoea and are therefore normally diagnosed before pregnancy. Outside pregnancy prolactinomas are diagnosed following detection of a raised prolactin level and classified by subsequent MRI imaging. It is important to be aware that some pharmacological agents and other physiological disorders may cause increased prolactin levels (see Box 1). In all pregnancies prolactin levels increase; therefore, values cannot be interpreted for diagnosis or response to treatment.

In pregnancy there is a risk that compression of the optic nerve may occur either due to increased size of a prolactinoma or as a consequence of normal lactotroph hyperplasia. Macroadenomas have a 26% risk of tumour enlargement in pregnancy, while the risk is lower if a woman has been treated with surgery or radiation prior to pregnancy (Table 2).³

Management in pregnancy

The Pituitary Society guidelines on management of prolactinoma in pregnancy (2006) advise close surveillance during pregnancy.⁴ A pragmatic interpretation of this could be visual field assessment each trimester in cases of microprolactinoma and monthly checks in those with a macroprolactinoma. Symptomatic enlargement can present with progressive headache, nausea or visual field defect. If this occurs an MRI scan should be performed. Dopamine agonists can be restarted if

Correspondence to: Prof Catherine Williamson, Maternal and Fetal Disease Group, Institute of Reproductive and Developmental Biology, Division of Surgery and Cancer, Faculty of Medicine, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK
Email: catherine.williamson@imperial.ac.uk

Table 1 Annual incidence of pituitary tumours

Tumour type	Annual incidence (cases per million)
Prolactinoma	10
Acromegaly	4
Cushing's syndrome	2
Non-functioning pituitary adenoma	6

Box 1 Physiological, pharmacological and pathological causes of hyperprolactinaemia**Physiological causes of hyperprolactinaemia**

- Pregnancy
- Nipple stimulation
- Stress

Pharmacological causes of hyperprolactinaemia

- Methyl dopa
- Reserpine
- Phenothiazines
- Butyrophenones
- Benzamides, e.g. metoclopramide
- Oestrogens

Diseases that cause hyperprolactinaemia

- Hypothalamic disease, e.g. sarcoidosis, tumour, arteriovenous malformation
- Disruption of the pituitary stalk, e.g. tumour, lymphocytic hypophysitis
- Hypothyroidism
- Polycystic ovary syndrome

Table 2 Likelihood of symptomatic enlargement of pituitary tumours in pregnancy

Tumour type	Prior therapy	Number of patients	Symptomatic tumour enlargement
Microadenoma	None	363	5 (1.4%)
Macroadenoma	None	84	22 (26.2%)
Macroadenoma	Yes	67	2 (3.0%)

Data are taken from 19 case series of 363 women with microprolactinoma and 151 with macroprolactinoma.³ Symptomatic tumour enlargement was defined as headache, visual disturbance or both

Box 2 Approach to management of prolactinoma in pregnancy**Microprolactinoma**

- Stop dopamine agonist treatment
- Check visual fields each trimester
- Consider additional investigations for tumour enlargement if abnormal visual fields or symptoms of headache, diabetes insipidus or new visual symptoms

Macroprolactinoma (≥ 10 mm diameter)

- Continue dopamine agonist treatment
- Six weekly visual field assessment using perimetry
- Increase dose of dopamine agonist if abnormal visual field assessment
- Consider additional investigations for tumour enlargement if abnormal visual fields or symptoms of headache, diabetes insipidus or new visual symptoms

enlargement is suspected or demonstrated on scan. Transphenoidal surgery has been performed in pregnancy⁵ and the optimal time for surgery is the second trimester.

Dopamine agonists are very effective at restoring fertility and women can become pregnant before they have had their first menstruation following commencement of treatment, unless adequate contraception is used. Management of women with a macroadenoma in pregnancy should be assessed on an individual basis. Medication may need to be continued throughout the pregnancy in macroadenoma to prevent optic chiasm compression. There are limited data about the risks associated with dopamine agonist use throughout pregnancy but data from the current published literature indicate that bromocriptine and cabergoline are safe. A pragmatic approach used by the authors is proposed in Box 2. The published studies relating to fetal exposure to dopamine agonists in the first trimester are summarized below.

Bromocriptine

Bromocriptine has been in use since 1971. It is a semi-synthetic derivative of ergoline and functions as a D2 receptor agonist. The typical starting dose is 1 mg nocte and the dose may be gradually increased to a maximum of 5 mg every six hours. Bromocriptine can cause a dramatic reduction in the level of prolactin but variable reduction in tumour size. The common side-effects associated with its use are nausea, constipation, headache and postural hypotension. Bromocriptine is a vasoconstrictor and its use is known to be associated with Raynauds syndrome.

Bromocriptine has been used in over 6000 pregnancies with no increase in the rates of congenital abnormalities,

spontaneous abortions or miscarriages.³ It is thought to cross the placenta.⁶ A study of children exposed to bromocriptine *in utero* demonstrated normal psychological development at nine years of age.⁷

In 1995 the USA withdrew the license for the use of bromocriptine for suppression of lactation due to adverse postpartum events because the Food and Drug Administration reported that 23% of postpartum women had at least one side-effect.⁸ In France between 1985 and 1993 there were over one million prescriptions for bromocriptine to suppress lactation and 115 incidents of adverse reactions were recorded in this period. These included 12 cases of hypertension, three myocardial infarctions, three arterial thromboses, five ischaemic strokes, four convulsions and 16 cases of hallucination including two suicide attempts and two deaths.⁹ Vasospasm may contribute to some of the above events and coronary vasospasm has been reported following re-challenge with bromocriptine.¹⁰ The British National Formulary advises caution when prescribing bromocriptine to pregnant women with hypertension, and particularly in those with pre-eclampsia.

Cabergoline

Cabergoline is an ergoline derivative with high affinity for D2 receptors. It has a very long half-life and can suppress prolactin levels for up to 120 days. The starting dose is 0.25 mg once or twice a week. Cabergoline is generally better tolerated than bromocriptine, with fewer side-effects.

It has been used in over 380 pregnancies with no increase in congenital abnormalities, spontaneous abortions or miscarriages.^{11,12} There have been six cases reported in which abortions were performed due to major fetal abnormalities in pregnancies of women taking cabergoline.¹¹ These include three cases of Down's syndrome and three separate cases

complicated by either limb-body wall complex, hydrocephalus or prune belly syndrome.¹² Otherwise, of 250 live born infants exposed to cabergoline *in utero* there were 11 cases of major malformation.¹² Postnatal development was assessed in 107 children who were followed up for 1–72 months (61 followed up for 12 months or more) and all showed normal physical and mental development.¹¹

Quinagolide

Quinagolide is a non-ergot derived D2 agonist that can be used to treat prolactinoma. Its starting dose is 25 µg nocte increasing every three days to a daily maintenance dose of 75 µg. It has a lower incidence of side-effects when compared with bromocriptine. However, there is less known about quinagolide use in pregnancy. In one study of 176 pregnancies in women who took quinagolide for a median duration of 37 days, there was a higher incidence of congenital abnormalities than the background rate. Nine fetal malformations occurred; these included spina bifida, trisomy 13, two cases of Down's syndrome, talipes, cleft lip, arhinencephaly, multiple unspecified malformation and Zellweger syndrome.¹³ Further studies are required to clarify the extent to which quinagolide causes an increased rate of congenital malformations when used in the first trimester.

Breast feeding

If a woman wants to breast feed it will be necessary for dopamine agonists to be stopped prior to delivery as lactation requires prolactin release. The decision to stop medication needs to be made after a full assessment by the endocrinologist and discussion with the patient of the risks involved. The possibility of tumour expansion on stopping medication should be considered and in some cases the high risk of optic chiasm compression may mean a woman is advised against stopping medication.

Summary and new controversy

The European Medicine Agency has issued warnings about the association between the use of the ergot derived dopamine agonists, cabergoline and bromocriptine, and cardiac fibrosis. Studies in patients with Parkinson's disease taking high doses of cabergoline have shown an increased incidence of pulmonary, retroperitoneal and pericardial fibrotic reactions. Cabergoline and bromocriptine bind to serotonin receptor subtype 2B located on heart valves. It has been suggested that activation of this receptor by these agents induces proliferation of interstitial cells and that this can cause valvular heart disease.^{14,15} The dose used in pituitary patients is markedly lower than that used in those with Parkinson's disease. Several retrospective studies have not shown any increase in the rate of valvulopathy in patients with prolactinoma treated with cabergoline.

The British Medicine and Healthcare Products Regulatory Authority advice in 2008 was that pregnancy should be excluded before administration of cabergoline and women planning pregnancy should stop cabergoline one month before they try to conceive.¹⁶ This advice is not consistent with current and previous management of pregnant women with macroprolactinoma where treatment with cabergoline is usually continued as there are relatively good safety data as described above^{11,12} (Box 2). Research is needed into this area

Box 3 Complications of acromegaly in pregnancy

- Hypertension
- Diabetes
- Obstructive sleep apnoea
- Colonic polyps
- Ischaemic heart disease
- Congestive heart failure

to provide evidence-based advice for patients about the best dopamine agonist to use. In the meantime one option is to start women who want to become pregnant on bromocriptine as there is large body of data about the use of this drug in pregnancy and it is only a partial agonist of the 5HT_{2B} receptor.¹⁷ However, it has also been associated with valvular heart disease in Parkinson's patients.¹⁸ Quinagolide does not bind to the 5HT_{2B} receptor and therefore theoretically should not cause fibrotic valvopathy. Quinagolide may be considered a preferable drug to use to treat pregnant women with macroprolactinoma. However, there are fewer data on use in pregnancy.¹³

ACROMEGALY

Physiology

Acromegaly is caused by increased secretion of GH from the somatotroph cells of the pituitary gland. GH stimulates synthesis of IGF1 (insulin-like growth factor 1), a growth factor that stimulates bone growth, lipolysis, increases protein synthesis, stimulates water and sodium retention and antagonizes insulin action. A GH secreting adenoma can be slow growing and have an insidious onset. When caused by a macroadenoma, it can cause compression of the surrounding tissue and disruption of secretion of other pituitary hormones.

Acromegaly can present with increased sweating, headaches, joint pain, altered facial features and increase in shoe size. Acromegaly is associated with significant morbidity in the general population. Box 3 summarizes the common complications of the condition.

The diagnosis of acromegaly is confirmed by a failure to suppress GH to <0.6 mU/L during a 75 g glucose tolerance test and elevated IGF1 levels. MRI scans usually reveal a pituitary adenoma.

Acromegaly can potentially be cured by transphenoidal resection of the adenoma. The feasibility of surgery is dependent upon tumour size and whether it has invaded the cavernous sinus. If surgery is not possible or does not achieve cure, 60% of GH secreting tumours respond to somatostatin analogues, leading to normalization of GH levels.

Forty percent of GH secreting tumours co-secrete prolactin and are therefore responsive to dopamine agonists.¹⁹ This may occasionally result in affected women being given an incorrect diagnosis of prolactinoma, and clinicians managing pregnant women with 'prolactinoma' should be aware of this, particularly if they also have symptoms or signs suggestive of acromegaly.

Effect in pregnancy

Acromegaly in pregnancy is rare with 106 cases reported: 16 microadenomas and 74 macroadenomas. The size was not

Table 3 Complications of acromegaly in pregnancy

Complication	Number	Proportion of women affected (%)
Type 2 diabetes	1	2
Tumour enlargement (mainly headache)	12	21
Gestational diabetes	3	5
Pregnancy induced hypertension	5	9
Pre-eclampsia	3	5

Data are taken from two retrospective case series comprising 72 pregnancies in 58 women^{20,23}

recorded in the remainder.²⁰ Patients may conceive while on treatment due to the restoration of normal ovulation. Women who have surgery prior to conception could potentially be cured and they will have a lower risk of complications associated with active disease or tumour enlargement. The diagnosis of acromegaly in pregnancy can be challenging as the placenta also secretes GH. Placental GH is structurally slightly different but most assays are not capable of distinguishing between the two hormones. GH produced by the maternal pituitary is released in pulses while placental hormone release is non-pulsatile.²¹ IGF1 levels are elevated in normal pregnancy²² and therefore cannot be used for diagnosis or monitoring of acromegaly in pregnancy.

The excess maternal GH can cross the placenta but it is not thought to be associated with any increase in fetal size. GH is not believed to be involved in fetal growth, as babies with GH deficiency are of normal size at birth. It has been surmised that the fetus relies on other signals, such as human placental lactogen, to stimulate its own IGF1 production. When macrosomia occurs in the context of acromegaly it is believed to be a consequence of poorly controlled diabetes. GH antagonizes insulin action, which results in carbohydrate intolerance in 60% of cases and diabetes mellitus in 10%. Thus pregnant women with active acromegaly are at increased risk of gestational diabetes.

Acromegaly is also associated with hypertension. Blood pressure should be closely monitored during pregnancy, as there is an increased risk of developing pre-eclampsia. Acromegaly is associated with heart failure and cardiomyopathy but there have been no documented cases of this developing in pregnancy. The principal maternal complications of acromegaly are summarized in Table 3.

Management of acromegaly in pregnancy

Somatostatin analogues

Somatostatin inhibits the release of growth hormone and thyroid stimulating hormone (TSH) by binding to somatostatin receptor subtypes 2 and 5. The half-life of somatostatin is very short and therefore longer acting analogues have been designed, namely octreotide and lanreotide. The half-life of octreotide is approximately 110 minutes and its potency is 45 times greater than native somatostatin. The starting dose is normally 100 µg three times a day. There is a long-acting preparation that contains octreotide or lanreotide that only needs to be given once every four weeks by intramuscular or subcutaneous injection. Somatostatin analogues are associated with some reduction in tumour size. Side-effects are related to suppression of the release of gastric and pancreatic hormones. This can result in gallstone formation, nausea and abdominal

cramps. Placental growth hormone secretion is not inhibited by octreotide as the placental receptors are mainly subtype 4. No fetal toxicity was seen in rats or rabbits receiving 16 times the maximum human dose.²⁴

Women are advised to discontinue somatostatin analogues when conception is confirmed. Treatment may need to be restarted in pregnancy in cases of active disease or if tumour enlargement causes optic nerve compression. Bromocriptine and cabergoline have been used in pregnancy in patients who are known to co-secrete prolactin. There are limited data on the use of the somatostatin analogues octreotide and lanreotide in pregnancy. Of the 106 pregnancies recorded, 48 required medical treatment during the pregnancy.²⁰ There is limited information about other factors which would influence fetal/neonatal size such as the development of pre-eclampsia or gestational diabetes and gestational week at birth.

Growth hormone receptor antagonist

Pegvisomont is a growth hormone receptor antagonist that is used in cases that are not somatostatin sensitive. It is given by subcutaneous injection 10 mg daily. Its main side-effects include gastrointestinal disturbance and abnormalities in glucose metabolism, including hyperglycaemia and hypoglycaemia. Its use has been reported in two pregnancies. In one case the drug was stopped after conception was confirmed.²⁵ The other case continued to take the drug throughout pregnancy.²⁶ Both had uneventful pregnancies and delivered normal healthy infants. Animal studies have not shown any teratogenicity associated with the use of pegvisomont. However, due to the paucity of safety data women are advised to stop it before conception.

Summary

The fetus expresses somatostatin receptors and the somatostatin analogues do cross the placenta. However there is a low incidence of fetal growth restriction reported in infants exposed to somatostatin analogues *in utero*. This is consistent with the published studies demonstrating that the fetus relies on other hormones to stimulate growth.²⁶ More data are required to allow a full assessment of the safety of these drugs.

CUSHING'S SYNDROME

Physiology

Cushing's syndrome is caused by the excessive production of cortisol either from the adrenal, pituitary or from an ectopic source. Cortisol increases hepatic gluconeogenesis, enhances appetite and inhibits the immune response by preventing the proliferation of T-cells and inhibiting the B cell mediated immune response. It also has a suppressive effect on neutrophils and monocytes. It rarely occurs in pregnancy due to menstrual disturbance and reduced fertility in affected women. At present there are 140 pregnancies in 126 subjects reported in the current literature.²⁷ The symptoms of Cushing's syndrome overlap with symptoms of normal pregnancy. These include central obesity, tiredness, depression and abdominal striae. However, the striae that occur in uncomplicated pregnancy are usually paler than the purple striae typically seen in Cushing's syndrome. As a consequence the condition can be difficult to diagnose. This is compounded by the fact that

cortisol levels increase in normal pregnancy. This is partly due to raised oestrogen levels stimulating hepatic production of cortisol binding globulin and is also a consequence of placental production of cortisol releasing hormone (CRH). This CRH is structurally identical to CRH produced by the maternal hypothalamus and is biologically active. The diurnal changes of cortisol secretion are retained in normal pregnancy but lost in Cushing's syndrome.

Diagnosis of Cushing's syndrome in pregnancy

Diagnosing Cushing's syndrome in pregnancy can be challenging, as diagnostic cortisol values are not validated for pregnancy.

There are three tests to confirm the diagnosis of Cushing's syndrome: urinary free cortisol (UFC), low-dose dexamethasone suppression test and midnight cortisol.

- (1) UFC measurements remain normal in the first trimester but increase up to threefold by term.²⁸ To interpret UFC in pregnancy values greater than four times the upper limit of normal are suggestive of increased cortisol production.
- (2) The low-dose dexamethasone suppression test may help confirm the diagnosis of Cushing's syndrome but has limited use in pregnancy as there is an increased risk of false-positive results.
- (3) Midnight salivary cortisol can be used to look for the absence of diurnal variation but cut-off values have not been validated in pregnancy.

Once excess cortisol production is confirmed the source needs to be found. ACTH is secreted by the corticotrophic cells of the pituitary and occasionally by ectopic neuroendocrine tumours. Inappropriately normal or raised ACTH levels suggest a pituitary or ectopic source. If ACTH is suppressed then the source is adrenal.

The high-dose dexamethasone suppression test can be used to distinguish between a pituitary or ectopic source. It relies on the fact that a pituitary adenoma retains some of the negative feedback effect from cortisol and a suppression of ACTH greater than 50% is expected. ACTH-secreting ectopic tumours do not show suppression after this test. This test can be used in pregnancy.

An MRI scan should confirm a pituitary lesion. Bilateral inferior petrosal sinus sampling can be used to confirm a pituitary source and lateralize the adenoma. This test is invasive and involves catheterizing the petrosal sinuses that drain the pituitary. Samples are taken to measure ACTH levels after an injection of CRH. The radiation exposure for this procedure can be reduced in pregnancy by using the direct jugular approach rather than using the femoral vein. There is a very small risk of thrombosis or haemorrhage associated with this procedure and it should only be used in pregnancy in an experienced centre after all non-invasive tests have been performed and with careful evaluation of the risks and benefits of the procedure.

Effect of Cushing's syndrome on pregnancy

Cushing's syndrome is associated with significantly increased maternal and fetal mortality (Table 4). Pregnancies should be treated as a high risk and treatment instigated as soon as

Table 4 Maternal and fetal complications of Cushing's syndrome

Maternal complications	Fetal complications
Hypertension (68%)	Prematurity (43%)
Diabetes or impaired glucose tolerance (25%)	Stillbirth (6%)
Pre-eclampsia (14%)	Spontaneous abortion/intrauterine death (5%)
Osteoporosis and fracture (5%)	Infant death in two cases (acute hepatitis; sepsis and gastroenteritis)
Cardiac failure (3%)	Intrauterine growth retardation 21%
Psychiatric disorders (4%)	Hypoadrenalism (2%)
Wound infection (2%)	Single reports of cleft lip, patent ductus and coarctation
Maternal death (2%)	Intraventricular haemorrhage in two cases postpartum

Data are taken from a study that searched the Cochrane library and pubmed and reported 136 pregnancies in 122 women with Cushing's syndrome²⁷

the condition is diagnosed. The fetus is thought to be protected from high circulating cortisol levels by placental 11 β -hydroxysteroid dehydrogenase 2 which converts cortisol into its inactive metabolite cortisone. This has been proposed as an explanation for the low number of cases of hypoadrenalism in the neonate. The high fetal loss rates are a reflection of the high incidence of maternal morbidity.

Management in pregnancy

First-line treatment outside pregnancy is transphenoidal resection of the pituitary tumour. There have only been nine cases of transphenoidal resection for Cushing's disease during pregnancy reported in the literature.^{27,29}

In a review evaluating treatment outcomes of 136 women with Cushing's syndrome, there was a higher proportion of live births in the active treatment group compared with the no active treatment group (89% [$n = 50$] compared with 76% [$n = 59$]).³⁰ Medical therapy is limited in pregnancy to metyrapone or ketoconazole. Metyrapone inhibits 11 β -hydroxylase, blocking the final step in cortisol synthesis, and has been used in 11 pregnancies. It can increase androgen production and is associated with hirsutism. The starting dose is 250 mg daily. It is generally well tolerated although its use can be associated with the development of hypertension and there has been a report of a woman developing pre-eclampsia following metyrapone treatment.³¹ In another case the fetus was found to have hypoadrenalism.³²

Ketoconazole inhibits several enzymes in adrenal steroidogenesis. Its use can be associated with hepatitis and it inhibits testosterone production. The starting dose is 200 mg daily. It has been used in three pregnant patients^{30,33} with no adverse events reported, though in rats it was shown to be teratogenic. It is antiandrogenic and should be used with caution in pregnancies where there is a male fetus. However there has been a single re-assuring report of a normally developed male infant from a pregnancy where the mother was taking ketoconazole.³³

Other drugs that are used to treat Cushing's syndrome are contraindicated in pregnancy. Amino-glutethimide, a potent inhibitor of steroid biosynthesis, is contraindicated because its use is associated with fetal masculinization and it is structurally similar to thalidomide. There have been two reported cases of masculinization of female infants.³⁴ Amino-glutethimide use

in rats has shown masculinization of female pups but this was prevented by replacement doses of cortisone.³⁴ Mitotane crosses the placenta and is teratogenic. It has been used in two cases, one where the women had a therapeutic abortion and examination of the embryo revealed dysmorphic appearances in the cortical primordial.³⁵ In the other case it was used in pregnancy without complications.³⁶

TSHOMAS

Physiology

Thyroid stimulating hormone (TSH) secreting pituitary tumours are very rare, accounting for 2.8% of pituitary tumours. At the time of presentation they are usually macroadenomas. They typically present with signs of mass effect such as visual field defects, headache or menstrual disturbance. They can present with symptoms of hyperthyroidism, which include weight loss tremor, heat intolerance, palpitations and diarrhoea.

The diagnosis of TSHoma is based upon the presenting symptoms. If the patient presents with a mass effect an MRI scan should detect the adenoma. If the symptoms are of hyperthyroidism, a raised free thyroxine level in the presence of a normal or raised TSH should increase the suspicion of TSH resistance or TSHoma. A thyrotropin-releasing hormone stimulation test can differentiate between the two conditions. If the diagnosis is TSHoma there is a blunted secretion of thyroxine, while there is a normal or exaggerated response if the diagnosis is TSH resistance.

TSHoma in pregnancy

There have been three cases reported in pregnancy, all of which required treatment.^{37–39} They all presented with thyrotoxicosis and galactorrhoea and were commenced on treatment prior to pregnancy. The first case was initially treated with bromocriptine and propylthiouracil. After five months she became pregnant and continued on treatment until 27 weeks of gestation when she developed a headache. MRI showed optic chiasm compression and transphenoidal decompression was undertaken. She made an uneventful recovery and had an elective caesarean section at 39 weeks delivering a healthy baby with no malformations.³⁷

The second case had transphenoidal resection of a macroadenoma. After surgery the levels of TSH remained elevated and the patient was commenced on octreotide, bromocriptine and a course of pituitary irradiation. Pregnancy was confirmed while receiving the triple therapy. The patient decided to continue the medication and complete the course of radiotherapy. She delivered healthy dizygotic twins at 36 weeks' gestation.³⁸

The last case was treated with octreotide and became pregnant while on treatment. Octreotide was subsequently discontinued and at six months of gestation MRI scan revealed enlargement of the tumour and raised thyroxine levels. Octreotide was re-started with good effect. She had an elective caesarean section at 35 weeks delivering a healthy infant.³⁹

Non-functioning pituitary adenomas

Clinically non-functioning pituitary adenomas (NFPA) have a prevalence of 70–90 cases per million. Affected individuals present with pressure symptoms as described above or detected incidentally on imaging. In the case of an incidental finding,

growth can be monitored by frequent visual field assessment. Macroadenomas are more likely to enlarge over time and if there are pressure effects; surgery or radiation is the treatment of choice. One study reviewed 40 people with NFPA in whom there was a 'watch and wait' management approach. In this study the risk of growth for a microadenoma was 19% but the risk for a macroadenoma was 44%,⁴⁰ usually with chiasm involvement.

Effect in pregnancy

There have only been two cases published in pregnancy. One patient presented at 18 weeks of gestation with a visual field defect and an MRI scan revealed a 2 cm macroadenoma. Endocrine investigations were normal and prolactin levels were uninterpretable. She was started on bromocriptine, her visual fields normalized and she had transphenoidal resection postpartum.⁴¹ Histology showed only 5% positive staining for prolactin. The second case was a woman with previously confirmed NFPA who developed mild visual loss in pregnancy.⁴² This was treated with frequent monitoring and, as there was no further deterioration, no intervention was needed.

SUMMARY AND CONCLUSIONS

Pituitary tumours are rare in pregnancy. There are relatively sparse published data on the effect of the hormones that are produced, the medication used to treat these tumours or the course and outcome of pregnancy.

The spectrum of pharmacological agents that can be used to manage pituitary tumours is enlarging, with newer treatments gaining license for use. The successful treatment of pituitary tumours restores ovulation and with it, the potential for fetal exposure to newer drugs about which there are limited safety data.

The current evidence relating to cabergoline and bromocriptine, the most commonly used drugs in pregnancy, is re-assuring overall, but recent guidance recommends caution with their use in pregnancy. This advice is not based on any new evidence demonstrating a detrimental effect observed in pregnancy and there is no real safe alternative. If there is increasing pituitary enlargement in pregnancy, with the subsequent potential risk of blindness, we recommend that treatment should be instigated with a dopamine agonist with counselling of the patient with regard to the potential risks and benefits of the drug. Surgical intervention should also be considered.

Advice about the use of somatostatin analogues and other newer medication should be given on a case by case basis. The initial publications regarding their use in pregnancy appear favourable but there are very few data to give fully informed advice on their safety in pregnancy. Therefore, until more information is available they should be prescribed with caution.

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