Peripartum hypopituitarism and lymphocytic hypophysitis

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Received 6 February 1995; Accepted 18 April 1995

Summary

The classical cause of postpartum hypopituitarism is Sheehan’s syndrome, in which an obstetric catastrophe is associated with hypotension. However, with improvements in obstetric care, the most common cause now may be lymphocytic hypophysitis. Five women with postpartum hypopituitarism, whose symptoms occurred during or immediately after pregnancy, had detailed endocrine and pituitary imaging for the duration of follow-up. Two presented with visual symptoms, and three with non-specific illnesses related to varying deficiencies of anterior pituitary hormones. Four were unable to lactate, and four were initially amenorrhoeic. Initially, four of the five women had enlarged pituitary glands on magnetic resonance imaging. Four have to some extent recovered pituitary function. One patient had associated thyroiditis; in two cases antinuclear antibodies became positive during follow-up, and in one of these dsDNA antibody was also detected. In no case were pituitary antibodies detected. None had complicated pregnancies or deliveries, and the two who had caesarean sections had no episodes of hypotension. The presentation of secondary hypothyroidism combined with ACTH deficiency in four of the five women strongly suggests lymphocytic hypophysitis. This diagnosis should be considered in postpartum women with general malaise and persistent amenorrhoea, as well as in women who develop visual impairment in the last trimester of pregnancy without antecedent pituitary disease. A conservative policy of management of the pituitary enlargement should be pursued as this resolves.

Introduction

Hypopituitarism has many causes, including infarction, tumour, granulomatous disease, aneurysms, basal encephalocele, empty sella syndrome and lymphocytic hypophysitis. When associated with pregnancy, Sheehan’s syndrome and lymphocytic hypophysitis predominate. The diagnosis of Sheehan’s syndrome requires significant hypotension at the time of parturition. Many cases of postpartum hypopituitarism have been labelled as Sheehan’s syndrome without any documented episode of hypotension, and it is likely that at least some of these cases represent undiagnosed lymphocytic hypophysitis. The definitive diagnosis of lymphocytic hypophysitis requires a pituitary biopsy, although presumptive diagnoses are increasingly being made on the basis of pituitary enlargement on scans accompanied by variable extent of hormone deficiency.1 The natural history of this disease is unclear, although full recovery of function both with3 and without surgery is well-documented. One case (diagnosed without biopsy) resulted in an empty sella after 5 years of follow-up.5

Lymphocytic hypophysitis was first described in 1962 by Goudie and Pinkerton.6 There have subsequently been approximately 50 further cases reported in the world literature.7-42 It is thought to be an autoimmune disease, possibly involving both humoral and cell-mediated mechanisms.1 Diagnosis...
may frequently be delayed, due to the non-specific nature of the presenting symptoms and relationship to pregnancy. It most commonly affects women during late pregnancy or in the puerperium. There may be pressure effects due to pituitary swelling or hormonal deficiencies of single or multiple anterior pituitary hormones. There is no definitive treatment although in one patient treated with high-dose corticosteroids had temporary improvement in visual symptoms.\(^{33}\) Hormone replacement is necessary, although there is increasing evidence of some recovery of function in the short-to-medium term. In the long term, there may be atrophy of the pituitary gland, possibly giving rise to at least some of the cases of empty sella syndrome in adults.

In this report, we describe five patients in whom we believe pregnancy-associated hypopituitarism was caused by lymphocytic hypophysitis. Attention should be given to this diagnosis in women with vague and non-specific symptoms in the puerperium.

Case reports

Patient 1

A 31-year-old primigravida presented to a rheumatologist 3 weeks postpartum. She had had an uncomplicated pregnancy with normal vaginal delivery at term. Prior to conception, which required clomiphene, her periods had been regular. She first noted pain in her thighs and knees, with swelling of her fingers, and subsequently developed joint stiffness and generalized myalgia. She was thought to have Raynaud's disease and an associated connective tissue disorder, although an autoantibody screen was negative.

Eleven months postpartum she remained generally tired and it was noted that menstruation had not resumed. Biochemical profile, full blood count, ESR, and autoantibody screen remained normal, although secondary hypothyroidism prompted referral to an endocrinologist one year postpartum. She had been unable to breast feed. Investigation revealed secondary hypothyroidism, hypopituitarism, and a low prolactin (see Tables). Thyroid microsomal (TPO) and thyroglobulin (TgA) antibodies have been negative throughout. Replacement therapy (thyroxine and hydrocortisone) was commenced with immediate resolution of symptoms. Menses resumed one month later. Four months later, she conceived spontaneously and delivered vaginally at term without complications. Thyroxine replacement was successfully withdrawn after four months of treatment and 5 months later thyroid function tests confirmed her euthyroid status (fT\(_4\)=16.4 pmol/l, TSH=0.6 mU/l). She has required hydrocortisone replacement (20 mg ann, 10 mg nocte) throughout. There was no family history of autoimmune disease. Her haplotype was A1, A9 (24), B8, B15 (62), DR5, DR9.

Patient 2

This 33-year-old primigravida became symptomatic 6 weeks postpartum. She developed low back pain, ankle swelling and dry skin. She felt generally weak and had difficulty rising from a seated position. She also complained of dysaesthesia in her fingers, hair loss and dry hair. She had been unable to lactate. She had had an uncomplicated elective caesarean section at 39/40 following the development of hypertension and oedema.

Investigation revealed secondary hypothyroidism and hypopituitarism (see Tables) for which replacement therapy with thyroxine and hydrocortisone was started. Her symptoms resolved within days, although amenorrhoea persisted for 9 months postpartum (6 months post replacement therapy). She initially had a normal prolactin both basally and in response to TRH, but 6 months later both the basal and stimulated prolactin levels were undetectable. She has continued to require hydrocortisone and thyroxine.

Autoantibody screen was repeatedly negative except for antinuclear antigen which was positive (1/40, diffuse) at the last assessment having been negative when previously tested. Her haplotype was A11, A28, B12 (44), B12 (45), DR2, DR7. She has a maternal grandmother with hypothyroidism and maturity-onset diabetes mellitus.

Patient 3

A 31-year-old woman first noted haziness of vision in her left eye at 36/40 of her first pregnancy. The visual disturbance worsened for 6 weeks, by which time her right eye was also affected. She was noted to have a bitemporal upper outer quadrantanopia. Central vision was unaffected and she had not had headaches. Clinical examination was otherwise normal. Elective caesarean section for failed induction was uncomplicated.

Her visual disturbance spontaneously resolved over 6 weeks post-partum. Investigation revealed secondary hypothyroidism (see Tables). She did not lactate, and remained amenorrhoeic for 9 months postpartum (5 months post replacement thyroxine). She has been maintained on replacement thyroxine. She was not hypopituitaric.

Autoantibody screen was negative on two occasions. There is no family history of autoimmune disease.
Patient 4

A 41-year-old woman presented 2 weeks postpartum with headache, nausea, myalgia and visual blurring. She had had two previous uncomplicated pregnancies. She had first noticed visual disturbance at approximately 30/40 of pregnancy. Examination revealed an upper outer quadrantanopia and a hypothyroid appearance. She was unable to lactate, although menses resumed 6 weeks postpartum.

Investigation revealed secondary hypothyroidism and hypocortisolaemia (see Tables). Visual field testing confirmed an upper outer quadrantanopia. Visual fields returned to normal 2 months postpartum. She was started on thyroxine and hydrocortisone. Her thyroxine replacement has been successfully withdrawn over three years, but she remains hydrocortisone-dependent. One son has insulin-dependent diabetes, but there is no other family history of autoimmune disease. Her autoantibody screen was negative.

Patient 5

A 41-year-old woman first noticed increasing lethargy and anorexia one week after delivery of her sixth child. She subsequently developed myalgia and postural hypotension severe enough to cause loss of consciousness on four occasions. She had lost 16 kg in weight. At presentation she was noted to be mildly hypercalcaemic \((\text{Ca}^{++} = 2.6\text{--}3.0 \text{ mmol/l}}\) on several occasions \((\text{NR 2.1\text{--}2.6 mmol/l}}\), PTH \(\leq 1.5 \text{ pmol/l}}\), and hypocortisolaemic (see Tables). Replacement therapy resulted in a rapid resolution in her symptoms and normalization of serum calcium. The puerperium was further complicated by recurrent breast abscesses. She was able to lactate, but has remained amenorrhoeic to date. All six of her pregnancies were uncomplicated and resulted in six full-term healthy infants. After all five previous pregnancies, lactation had occurred and menses had resumed with 6 weeks of delivery.

Her autoantibody screen was negative, with the exception of a positive thyroid microsomal antibody titre of 1/100, which 2 months later rose to 1/1600. She had no goitre or thyroid tenderness. Her thyroid function tests at presentation were \(\text{FT}_4 = 21.5 \text{ pmol/l}}\) \((\text{NR 11\text{--}29}}\), \(\text{FT}_3 = 8.0 \text{ pmol/l}}\) \((\text{NR 3\text{--}8.6}}\), \(\text{TSH} \leq 0.02 \text{ mU/l}}\) \((\text{NR 0.3\text{--}4.8}}\). She subsequently developed florid hyperthyroidism, \(\text{FT}_4 = 61, \text{ FT}_3 = 29, \text{TSH} < 0.02\), at 6 months postpartum, presumably due to Graves’ disease. There is no family history of autoimmune disease. Her haplotype is A2, A3, B7, B14, DR2, DQ1.

### Methods

Short synacthen tests were performed either prior to starting hydrocortisone, or after omitting treatment for 48 h if on replacement therapy. A 250 µg intramuscular injection of Synacthen (tetraacosactrin acetate) was administered with blood sampling for cortisol at 0, 30 and 60 min. To assess pituitary ACTH reserve, 100 µg of human corticotrophin-releasing factor (hCRF, Shire Pharmaceuticals) was given intravenously, after withdrawal of hydrocortisone 3 days prior to the test, and blood samples for cortisol and ACTH were taken at 0, 5, 15, 30, 45, 60, 90 and 120 min. The adrenal response to 5 days of ACTH was determined by administering synacthen 0.5 mg intramuscularly twice daily on days 1 to 4 with plasma cortisol measurements at 0900 on days 1, 3 and 5. Insulin stress tests either preceded depot synacthen or were separated by at least 3 weeks. Patient 2 did not receive depot synacthen.

Simultaneous administration of insulin (0.1 U/kg), thyrotrophin-releasing hormone (TRH) (200 µg), and

### Table 1 Thyroid, thyrotroph and lactotroph function

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date</th>
<th>TRH test (200 µg i.v.)</th>
<th>Thyroid function at presentation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>FT4 (pmol/l)</td>
<td>TSH (mU/l)</td>
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<tr>
<td></td>
<td></td>
<td>Basal</td>
<td>Max</td>
</tr>
<tr>
<td>1</td>
<td>7/7/93*</td>
<td>14.5</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>7/10/93*</td>
<td>16</td>
<td>0.03</td>
</tr>
<tr>
<td>3</td>
<td>18/4/94*</td>
<td>2.2**</td>
<td>3.9</td>
</tr>
<tr>
<td>4</td>
<td>11/3/94*</td>
<td>16.4</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>9/90</td>
<td>4.1</td>
<td>1.2</td>
</tr>
<tr>
<td>3</td>
<td>3/91*</td>
<td>3.9</td>
<td>10.2</td>
</tr>
<tr>
<td>5</td>
<td>5/3/94***</td>
<td>23.8</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*On thyroxine; **non-compliant; ***off thyroxine.

Normal response to TRH: TSH 2–8 x basal, PRL > 5 x basal.
luteinizing-hormone-releasing hormone (LHRH) (100 μg) was performed to assess anterior pituitary hormone reserve. Hydrocortisone had been stopped 3 days prior to the test. Adequate hypoglycaemia (plasma glucose <2.2 mmol/l) was achieved in all tests. Cortisol, growth hormone (GH) and prolactin were measured at -15, 0, 30, 45, 60, 90 and 120 min as well as basal insulin-like growth factor-1 (IGF-1), follicle-stimulating hormone (FSH), oestadiol, progesterone and free thyroxine (fT4). Thyroid-stimulating hormone (TSH) and luteinizing hormone (LH) were measured at 0, 30 and 60 min. Anti-pituitary and other organ-specific antibodies were sought by indirect immunofluorescence using monkey pituitary, adrenal cortex, ovary and testis, and a human non-functioning and GH-secreting

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Pituitary-adrenal function</th>
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<tr>
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<td>Short Synacthen test (SST) (250 μg im)</td>
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<td></td>
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<tr>
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<td>&lt;50</td>
</tr>
<tr>
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<tr>
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<td>&lt;50</td>
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<tr>
<td>5</td>
<td>&lt;50</td>
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</table>

SST normal response: cortisol peak > 550 nmol/l.
Long ACTH test normal response: cortisol > 700 nmol/l.
NP, not performed.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Gonadotroph function following LHRH (100 μg i.v.)</th>
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<tbody>
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<td>10/93</td>
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<tr>
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<td>5</td>
<td>5/93</td>
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<td>3/94</td>
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</table>

Normal response, LH > 5 x basal
Normal ranges: FSH 1–26 (varies with cycle); Oestradiol 160–2290 (varies with cycle); Progesterone 2–60 (varies with cycle).
NA, not available.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Insulin stress tests</th>
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<tbody>
<tr>
<td>Patient</td>
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<td>5/3/94</td>
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<td>5</td>
<td>5/3/94</td>
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</table>

Normal ranges: GH (fasting, unstressed, basal) < 5.5 mIU/l; IGF (age 31–45) 13–37 nmol/l.
Normal response (IST): GH > 20 mIU/l; cortisol > 550 nmol/l.
Patient 4 did not have this test performed.
adenoma as substrates. All sera were tested at a dilution of 1:5, and a positive control was included.

Results

The results of hormonal investigations are shown in Tables 1–4, with comments accompanying case descriptions. All sera were negative for anti-pituitary and other organ-specific autoantibodies.

Neuroradiology

Patient 1

MR scan of the pituitary (11 months postpartum) showed thickening of the right hemipituitary with an area of low signal in the right lateral part of the gland elevating the diaphragma sellae on that side.

Patient 2

MR scan of the pituitary (4 months postpartum) showed a normal-size fossa but general enlargement of the pituitary, producing convexity of the diaphragma sellae and shortening of the infundibulum. Contrast enhancement was homogeneous throughout the gland. The maximum height of the pituitary measured 11.5 mm. (normal <11 mm) Repeat MR scan 6 months later (10 months postpartum) showed that pituitary size had returned to normal.

Patient 3

Unenhanced CT scan one month postpartum was reportedly normal, however, a later MR scan (3 months postpartum) showed a normal-sized fossa, with diffuse enlargement of the pituitary gland extending into the suprasellar cistern obliterating the infundibulum and elevating the optic chiasma. The maximum height of the pituitary was 15 mm. Repeat MR scan 4 months later (7 months postpartum) showed an 80% reduction in the size of the pituitary, now with only slight bulging into the suprasellar cistern and no elevation of the optic chiasma. (See Figure 1) By 12 months postpartum, pituitary size had returned to normal.

Patient 4

CT scan (1 month postpartum) showed a normal-sized fossa containing a homogeneously enhancing intrasellar mass extending into the suprasellar cistern. The infundibulum and optic chiasma could not be identified. The maximum height of the pituitary measured 17 mm. Repeat CT scan 3 months later (4 months postpartum) showed a 90% reduction in pituitary size with only slight convexity of the superior surface of the gland. The infundibulum and optic chiasma were identified as normal. An MRI scan of the pituitary, 2 years after presentation, showed that the size of the pituitary gland as well as its signal had returned to normal.

Patient 5

MR scan (8 months postpartum) revealed a normal sized fossa, containing a thin (2.8 mm thickness layer of pituitary tissue with deeply concave upper border, consistent with a partially empty sella. Homogeneous contrast enhancement was observed.

Discussion

Lymphocytic hypophysitis was first described as a pathological entity in 1962, although the first case diagnosed in life was not until 1980. In the intervening period, all reported cases were post-mortem findings in which secondary adrenal insufficiency was a presumed factor in the cause of death. There have subsequently been more than 30 histologically proven cases of lymphocytic hypophysitis, most diagnosed with the aid of a pituitary biopsy, but with some further post-mortem diagnoses. Definitive diagnosis requires a pituitary biopsy, although presumptive diagnoses are now made on the basis of the clinical and laboratory findings, without pituitary histology.

Lymphocytic hypophysitis is an increasingly diagnosed condition that occurs almost exclusively in late pregnancy or the puerperium. It can occur rarely in men and postmenopausal women. The clinical presentation is variable, and the spectrum is reflected in our patients. Two first had visual symptoms (due to pituitary enlargement) during the last trimester of pregnancy, without known antecedent pituitary disease, and the others first noticed symptoms within a few weeks of parturition. In other reported cases, visual disturbance or headache tend to be the presenting features during pregnancy, whilst symptoms of hormonal deficiency predominate in those cases presenting after parturition.

Four of our patients had secondary hypothyroidism, and in two of these (patients 1 and 4) thyroxine replacement has been successfully withdrawn. However, the most recently diagnosed patient developed postpartum hyperthyroidism presumably due to Graves disease, in addition to lymphocytic hypophysitis. Our patient shares two class I (A3, B7) alleles with the one other patient with lymphocytic hypophysitis and thyroiditis to be tissue-typed. In addition, she did not have the A1, B8, DR3 combination found in cases of isolated post partum thyroiditis in the UK.

In our patients, prolactin was undetectable in four and elevated in one. In previous cases of lymphocytic hypophysitis, normoprolactinaemia has been the exception with 85% of cases (approximately evenly
Figure 1. Serial MRI scans of patient 3. a 3 months post partum: diffuse enlargement with obliteration of the suprasellar cistern and stretching of the optic chiasm. b 7 months post partum. Optic chiasm now clearly normal and suprasellar cistern is visible, but the upper border of the pituitary is still convex, indicating enlargement. Pituitary stalk is not identified. Post-contrast scan on the right indicates homogeneous enhancement. c 12 months post partum. Pituitary now of normal size with slightly concave upper border. Pituitary stalk now clearly visible crossing the suprasellar cistern.
divided) reported as having hyper- or hypoprolactinaemia.\textsuperscript{1} Patient 4 has shown no recovery of lactotroph function over the 2.5 year period of follow-up. Patient 2 initially had a slightly subnormal prolactin response to TRH and this has significantly worsened with repeat testing. During the second pregnancy in Patient 1, the prolactin did not rise despite the physiological stimulus of pregnancy (PRL = 38 nU/mL, 20 weeks pregnant). In all reported cases of lymphocytic hypophysitis, prolactin is the only hormone whose levels have been raised. It is possible that this is due to the presence of a pituitary mass effect with stalk compression interrupting the flow of dopamine, although our cases with pituitary enlargement had subnormal prolactin levels. Alternatively, there may be an as yet undetected stimulatory antibody to lactotrophs. Previously reported cases have had surgery for a suspected prolactinoma on the basis of hyperprolactinaemia and/or a pituitary mass,\textsuperscript{20,24,42-44} although prolactin levels have spontaneously returned to normal without surgery. It is important to consider lymphocytic hypophysitis in the differential diagnosis of hyperprolactinaemia of pregnancy and the puerperium as surgery can be avoided. Furthermore, it has been suggested that pregnancy neither initiates formation of prolactinomas nor accelerates their growth,\textsuperscript{45} thus increasing the probability that the diagnosis, in such circumstances, is lymphocytic hypophysitis.

All of our patients had abnormal short synacthen tests, although in patient 3, only marginally so, and the cortisol response to hypoglycaemia was normal. It has been impossible to withdraw hydrocortisone successfully in the four patients on replacement therapy, although patient 4 has had her replacement dose of hydrocortisone reduced.

When pituitary tumours cause hypopituitarism, GH secretion is often lost first, followed by the gonadotrophic hormones, ACTH, TSH, and lastly prolactin. It has been suggested by some authors that GH levels are not reduced in lymphocytic hypophysitis,\textsuperscript{1} but this is not the case in our patients. In all four women who had an insulin stress test, the GH response to hypoglycaemia was subnormal; in patient 2 it remained so with repeat testing. Most authors report subnormal GH responses to hypoglycaemia\textsuperscript{14,16,25,42} although the response may be normal.\textsuperscript{44} It is possible that the growth hormone response to hypoglycaemia may be blunted by hypogonadotrophism and therefore the growth hormone response in the patient with hypogonadotrophism was almost absent. The serum IGF-1 level remained in the normal range, which may imply a normal pattern of pulsatile GH secretion, despite subnormal levels on provocative testing.

Four of our patients were initially amenorrhoeic. All now have normal LH responses to LHRH, although it was initially subnormal in patient 4. In patient 1, menses resumed following commencement of replacement therapy (thyroxine and hydrocortisone). Patients 2 and 3 remained amenorrhoeic for 6 and 5 months, respectively, following replacement therapy, but then resumed spontaneous regular menstruation. Patient 5 remains amenorrhoeic 6 months post partum, but has an elevated prolactin.

It is known that the normal pituitary gland swells during pregnancy due to an increase in the number of lactotrophs.\textsuperscript{45} Hyperplasia of these cells (‘pregnancy cells’) is visible after 4 weeks of pregnancy, and the gland returns to normal over several months post partum. Magnetic resonance imaging during pregnancy has been reported to show a mean increase in size of the pituitary gland of 2.6 mm in each standard orthogonal view,\textsuperscript{46} with a progressive increase in size as pregnancy advances. In this series, the pregnant pituitaries imaged had a convex upper border, with no chiasmal compression, and a homogeneous signal intensity. Physiological pituitary enlargement in pregnancy is not accompanied by hormone deficiency syndromes. Therefore, presence of pituitary hypothyroidism or hypoadrenalism accompanied by pituitary enlargement indicates that the latter is pathological rather than physiological.

Of our patients, four out of five had abnormal scans with enlarged pituitary glands. In the one with a normal pituitary, the scan was not done until 8 months post partum, and it then showed a partially empty sella. Over the duration of follow-up, four of the patients have had more than one scan, and in all of these there has been a return of the gland size to normal. At presentation, patient 3 had a normal CT scan despite having a visual field defect consistent with chiasmal compression. An MRI scan 2 months later showed an enlarged pituitary, although by this time her visual fields were normal. Normal CT findings with an abnormal MRI has been previously reported in this condition.\textsuperscript{43} It is increasingly recognized that pituitary masses found in association with pregnancy may be due to lymphocytic hypophysitis and may spontaneously regress. There are no pathognomonic features of lymphocytic hypophysitis available using current imaging techniques. Masses may be homogeneous\textsuperscript{16,25,43} or heterogeneous.\textsuperscript{29} The sella turcica may be normal in size, or enlarged\textsuperscript{13,32} and there may be demineralization of the dorsum sellae.\textsuperscript{13}

Lymphocytic hypophysitis is thought to be an autoimmune disease involving both humoral and cellular arms of the immune system. It has been associated with other classical immune diseases\textsuperscript{5,6,12,20,24} with organ-specific autoantibodies. The most frequent association is with thyroiditis.\textsuperscript{3,15,23,24,47} However, thyroiditis may occur in 4–7% of patients post partum, with a positive anti-thyroid microsomal antibody titre being noted in even more women in the postpartum period,\textsuperscript{47} and therefore any association may be fortuitous.
Adrenalitis has been found in two cases, suggestive of Addison's disease, but none of the present patients had adrenal antibodies or antibodies against other steroid-producing cells in testis or ovary. Other reported autoantibodies include antimitochondrial antibodies, anti-parietal cell antibodies, anti-smooth-muscle antibodies, and antithyroid antibodies. None of our patients had these. Anti-pituitary antibodies have been sought by a number of authors using immunofluorescence on a variety of substrates including adult monkey pituitary, human foetal pituitary and rat and mouse preparations. Mayfield reported a case with antibodies against all anterior pituitary cell types in which there was an abnormal response of growth hormone, cortisol, TSH and prolactin to stimulation testing, although there was no evidence of antibody bound to the resected pituitary after immunohistochemical staining. Ochiwa and Shishib proved that antibodies against rat pituitary cytosol in one patient which were only present during the period of hypopituitarism. Other authors have reported negative results. All five patients in this report were negative by indirect immunofluorescence assays on sections of monkey pituitary and human pituitary adenomas. Normal human pituitary is not easily used for immunofluorescence, as corticotrophs have FL receptors, which cause non-specific binding of immunoglobulins. One possible explanation for the absence of pituitary antibodies confirmed in this study is that their level decreases during the third trimester of pregnancy, in line with thyroid auto-antibodies, and related to the immune suppressive effects of pregnancy. Alternatively, lymphocytic hypophysitis may be a cell-mediated immune process, with little or no humoral immunity being generated.

Antinuclear antibodies have been found in previous patients with lymphocytic hypophysitis. Guay et al. reported a case in which a maximum titre of 1/80 became negative 3 months after transphenoidal resection of a pituitary mass subsequently diagnosed as lymphocytic hypophysitis. Our patients had autoantibody titres measured serially from diagnosis. In patients 1 and 2, the antinuclear antibody titres first became positive 19 and 9 months post partum, having been negative earlier. The significance of this change in status is not known, although it may indicate a continuing stimulus to the immune system. At 25 months post partum, an autoantibody screen, including ANA, was negative in patient 1. Patient 2 also developed antibodies to dsDNA.

Pregnancy has been reported after the diagnosis of lymphocytic hypophysitis without evidence of further pituitary destruction in subsequent pregnancies. One woman had a radiologically empty sella at the time of her third pregnancy. After her second pregnancy, she developed a pituitary mass and became and remained deficient in thyroxine and cortisol. Classically, a primary empty sella shows an enlarged sella turcica with hormonal abnormalities being demonstrated in less than 50% of cases. Whilst in lymphocytic hypophysitis, almost all cases show endocrine abnormalities. It is possible that prior lymphocytic hypophysitis may be the cause of a subgroup of cases of the adult empty sella syndrome, particularly those with hormonal loss and normal-sized fossae.

Two of our patients had visual field defects, and in both of them fields returned to normal without the use of immunosuppressive doses of corticosteroids or surgical decompression. The use of corticosteroids has been reported to improve the pressure effects due to pituitary enlargement in lymphocytic hypophysitis. It is not yet established whether corticosteroids affect the outcome in cases of lymphocytic hypophysitis, but in suspected cases in whom there are visual field defects, there may be a place for a short trial of steroids until such time as spontaneous resolution is observed on repeat imaging.

In conclusion, we believe that lymphocytic hypophysitis is more common than previously thought, but that the non-specific nature of symptoms and tendency to recovery make the diagnosis difficult unless it is specifically considered. The presentation is variable and may be to neurosurgeons, neurologists, ophthalmologists, rheumatologists, obstetricians, or endocrinologists. The entity should be thought of in women with persistent malaise post partum, in whom hypocortisolaemia and/or hypothyroidism may be found on testing. Patients presenting with visual disturbance or amenorrhoea tend to be investigated earlier due to their more specific symptoms. The presence of a mass in the pituitary fossa is not an absolute indication for surgery, as there is frequently regression of the mass with time. All patients in whom this diagnosis is suspected should have long term endocrinological and radiological follow-up.

Acknowledgements
We are grateful to Sister M. Brown and staff of the Metabolic Unit, North Staffs Royal Infirmary, and Sister A. Holmes, Programmed Investigation Unit, Royal Shrewsbury Hospital, for performing the dynamic tests. We are grateful to the North Staffordshire Hospital Trust for support.

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