Differentiating Lymphocytic Adenohypophysitis from Pituitary Adenoma in the Peripartum Patient

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Lymphocytic adenohypophysitis (LAH) is an autoimmune disorder of the pituitary gland with a predilection for the peripartum period and often mimics a pituitary adenoma. We sought to define the clinical, endocrinologic and radiographic characteristics differentiating peripartum LAH from pituitary adenoma to enable the use of noninvasive diagnosis and appropriate therapy. From published reports and our own case, the clinical histories and laboratory and radiographic studies of 45 patients fulfilling the diagnosis of peripartum LAH were reviewed. History of infertility or menstrual irregularity, symptomatology, endocrinologic evaluation, diagnostic imaging and associated medical conditions were analyzed. For comparison, 806 patients with pituitary adenoma and pregnancy from published series were evaluated. The spontaneous pregnancy rate in pituitary adenoma patients was 2.4% vs. 100% in LAH patients. Visual disturbances and headaches were significantly more frequent in patients with LAH. Prolactin levels were significantly lower in patients with LAH than in those with pituitary adenomas (34.6 ± 46.3 [SD] vs. 393.0 ± 300.4, P < .0001). Abnormalities in thyroid and/or adrenal function were also more common in patients with LAH (57.5% vs. 2.5%, P < .001). There were no distinguishing characteristics on radiographic studies. History and endocrinologic evaluation can differentiate between LAH and pituitary adenoma in the peripartum patient. (J Reprod Med 1995;40:251-259)

Keywords: adenohypophysis; pituitary adenoma, prolactin-secreting; pregnancy complications.

Introduction
Severe headache and visual disturbance during pregnancy or the puerperium elicit a differential di-
agnosis ranging from preeclampsia to intracranial lesions. The etiology of sellar lesions in the pregnant or postpartum patient is most commonly enlargement of a prolactin-secreting pituitary adenoma. However, lymphocytic adenohypophysitis (LAH) should be considered in the differential diagnosis. LAH is a nonneoplastic, presumably autoimmune disorder of the anterior lobe of the pituitary gland that produces pituitary enlargement and has a predilection for late gestation and the postpartum period. It was first described by Goudie and Pinkerton in 1962 when it occurred in a 22-year-old woman who developed postpartum hypothyroidism and amenorrhea and ultimately died of adrenal insufficiency.

Recent advances in imaging, including high-resolution computed tomography (CT) and magnetic resonance imaging (MRI), have improved diagnostic accuracy but cannot precisely define the pathology of sellar lesions. As recently as 1988, utilizing modern imaging modalities, including MRI, Levine et al considered preoperative differentiation of a pituitary adenoma from LAH to be “extremely difficult, if not impossible.” Differentiation is imperative because of the unique diagnostic protocol, therapeutic regimen and surgical plan mandated by each of these entities. Standard transsphenoidal hypophysectomy with failure to specifically tailor preoperative and postoperative management, anesthetic protocol and surgery itself can result in negative and avoidable consequences for the patient. Indeed, the mortality rate from LAH has been reported to be as high as 30%, presumed secondary to adrenal insufficiency.

A recent case of LAH at our institution reemphasized the differential diagnosis of pituitary lesions in pregnancy and prompted this review of peripartum sellar masses. Comprehensive retrospective analysis of reported cases in addition to our recent experience, including precise definition of historical, clinical, endocrinologic and radiographic characteristics of each patient, was undertaken to determine which factors were most important in reaching the preoperative diagnosis of LAH and in differentiating this entity from pituitary adenoma. This should allow more specific, directed and efficient management of these complex and difficult patients and provide maximal patient benefit while minimizing associated morbidity.

**Materials and Methods**

Review of the literature revealed 44 reported cases of peripartum LAH. Of these, 77.8% were based on pathologic diagnosis and the remainder on clinical course. Information on the clinical history, laboratory data and radiographic studies was com-

![Figure 1](image_url)

**Figure 1**
Percentage of patients with pituitary adenoma or lymphocytic adenohypophysitis and selected historical attributes. *P < .001.
compiled from these cases as well as from our patients. Specifically, a history of infertility or menstrual irregularity, galactorrhea, agalactia and associated medical conditions, especially other autoimmune processes, were tabulated and analyzed. When available, hormonal assays for prolactin, growth hormone, follicle stimulating hormone, luteinizing hormone, ACTH, cortisol and thyroid function (obtained prior to treatment) were likewise assessed. The results of diagnostic imaging studies, including CT, MRI or both, were reviewed when available.

Corresponding data from 806 patients with pituitary adenomas in pregnancy were tabulated from previous reports. Only patients with pituitary adenomas not previously treated with radiation or surgery were included, and patients without viable pregnancies were excluded from evaluation. The overwhelming majority of pituitary tumors were diagnosed prior to conception. Only 3 of the 806 patients with pituitary adenoma had their initial diagnosis made during gestation.

Statistical analysis was performed by Fisher's exact test for dichotomous variables and χ² for continuous variables. A P value <.05 was considered significant.

Results
The rate of spontaneous conception was significantly higher in patients with LAH than in those with pituitary adenomas (100% vs. 2.4%, P<.001). The percentage of patients with headache or visual symptoms was also significantly greater in patients with LAH (Figure 1). Agalactia was more common in patients with lymphocytic adenohypophysitis, whereas galactorrhea prior to pregnancy or postpartum/postlactation was more frequent in patients with pituitary adenomas (Figure 1). Symptoms of thyroid and adrenal dysfunction, such as weakness and fatigue, were reported to occur in 37.8% of patients with LAH. Corresponding data on patients with pituitary adenomas was not reported.

Hormonal profiles for these two groups of patients differed in a number of ways. Prolactin levels were lower in patients with LAH both antepartum and postpartum (Table I). Adrenocortical and thyroid function was abnormal in a significantly

![Figure 2](image-url)

Figure 2
Percentage of patients with pituitary adenoma or lymphocytic adenohypophysitis and normal hormonal values. *P<.001.
larger percentage of patients with LAH than with pituitary adenomas (Figure 2). No significant differences in proportion of patients with abnormal growth hormone and gonadotropin levels were noted.

The prevalence of other autoimmune diseases, including thyroiditis, adrenalitis, parathyroiditis and retroperitoneal fibrosis, in patients with LAH was 24.4%. Thyroiditis accounted for the overwhelming majority (81.8%) of the associated autoimmune conditions. The presence or absence of autoimmune disease was not commented on in any of the pituitary adenoma reports.

Thirty-three patients with LAH underwent CT, and 10 received MRI scans. Twenty-seven of the CT scans showed pituitary abnormalities, 21 had evidence of suprasellar extension, and 6 scans had no detectable abnormality. The most common CT finding was diffuse pituitary enlargement with contrast enhancement. MRI studies of patients with LAH showed homogeneous pituitary enlargement. The signal intensity was isointense with brain parenchyma on the T1-weighted images and increased on T2-weighted images; Gd-DTPA enhancement was noted (Figure 3A). Pituitary adenomas can appear as focal lesions or total pituitary enlargement with the same CT and MRI characteristics as LAH has. No radiographic features distinguishing LAH from pituitary adenomas were noted (Figure 3B).

**Discussion**

It has been asserted that a pituitary mass discovered during pregnancy should be considered a prolactinoma until proven otherwise; however, as shown in this report, alternative etiologies, including...
ing LAH and nonsecretory pituitary adenomas, should also be considered.

Prolactin-secreting adenoma is the most common cause of an expanding pituitary lesion during pregnancy; the enlargement is postulated to be due to estrogen. The incidence of pituitary adenomas in pregnancy is unknown. Autopsy series have documented an incidence of 9–27% of pituitary adenomas in unselected patients. The incidence increases with age, reaching a peak in the sixth decade. By some estimates, as many as 33% of patients with secondary amenorrhea and 50% of patients with amenorrhea and galactorrhea suffer from pituitary adenomas.

Pituitary adenomas are slowly growing tumors that typically manifest as reproductive irregularities years before presenting with symptoms of chiasmal compression. Rapid prolactinoma enlargement during pregnancy is a rare but well-described entity. Although pregnancy is associated with lactotroph hyperplasia and possibly also an increased incidence of hemorrhage into a preexisting pituitary adenoma, a patient with new-onset headache or visual disturbance from a pituitary adenoma generally has some history of menstrual or endocrine dysfunction prior to pregnancy. Indeed, a history of reproductive dysfunction is the strongest indicator of the etiology of the peripartum pituitary mass. In the absence of signs or symptoms indicative of an antepartum prolactinoma, including irregular menses, a history of galactorrhea or difficulty becoming pregnant, the diagnosis of prolactinoma is unlikely.

Definitive diagnosis of a pituitary mass during gestation is complicated by the normal elevation of prolactin during pregnancy. Lactotroph stimulation by elevated estrogen levels causes a 30–400% increase in pituitary mass, as verified by MRI and autopsy studies. This increase in gland size and lactotroph number is paralleled by an increase in prolactin to approximately 35, 175 and 210 ng/mL in the first, second and third trimesters, respectively.

LAH is being increasingly recognized as a cause of hypopituitarism in women during late pregnancy or the postpartum period. The hormonal profile associated with LAH is quite distinct from that characterizing the majority of pituitary adenomas. Prolactin elevation does occur with LAH but to a much lesser degree, and the majority of patients have prolactin levels within the accepted normal range for gestation. Prolactin levels in a patient with LAH may be elevated as a result of residual lactotroph hyperplasia or compression of the pituitary stalk by the inflammatory mass. Similarly, nonsecretory pituitary adenomas can also be associated with hyperprolactinemia secondary to pituitary stalk compression.

Abnormalities in ACTH, cortisol and thyroid function are much more common in LAH patients, reflecting involvement and consequent dysfunction of the entire anterior pituitary rather than just one adenomatous cell type. Since adrenal or thyroid insufficiency can be fatal, the diagnosis of these conditions is particularly important. If LAH is suspected, cortisol levels and thyroid function tests must be obtained to allow prompt hormone replacement when indicated.

Pathologically, LAH is characterized by diffuse lymphocyte, plasma cell and eosinophil infiltration of the anterior pituitary, with resultant destruction of parenchymal cells and fibrosis (Figure 4A). This is in direct contrast to the uniform sheets, cords or nests of pituitary cells seen with pituitary adenomas (Figure 4B). The differential diagnosis of LAH by light microscopy includes sarcoidosis, syphilis, tuberculosis and granulomatous hypophysitis. These can be differentiated by the absence of granulomas in LAH as well as by clinical manifestations.

LAH often has a progressive clinical course: the pituitary initially becomes edematous, inflamed and enlarged, producing a mass effect with its consequent symptomatology, including visual disturbance, headache and hormonal dysfunction. The preliminary disease is occasionally subclinical, with no mass effect. Pituitary destruction and fibrotic replacement, resulting in an atrophic gland, typically follow with regression of the sellar mass and postpartum hypopituitarism.

Postpartum panhypopituitarism can also result from Sheehan’s syndrome, in which pituitary insufficiency is hypothesized to result from infarction of the gland secondary to arterial spasm in small vessels supplying the hypertrophied pituitary gland of pregnancy, as occurs during hypovolemic shock. Postpartum hypopituitarism after a delivery without hypotension or excessive blood loss is unlikely to be due to Sheehan’s syndrome.

Although previous reports have recommended surgical intervention with open biopsy to confirm the diagnosis of LAH, this may be unnecessary. Surgical intervention carries the inherent risks of any intracranial procedure, and routine transsphenoidal hypophysectomy can result in panhypopitu-
Hematoxylin and eosin staining of a postpartum pituitary biopsy of (A) lymphocytic adenohypophysitis and (B) a pituitary adenoma. Note the dense infiltration of lymphocytes, plasma cells and eosinophils with rare nests of residual pituicytes in LAH and the monotonous proliferation of pituitary cells in the pituitary adenoma (×100).

Pituitarism. Because this disorder may be self-limited, an accurate preoperative diagnosis could avoid the need for surgery entirely, allowing the greatest degree of pituitary preservation.

Patients with presumed LAH causing mild headaches or visual symptoms during pregnancy or the puerperium can be closely observed with serial visual field examinations and CT or MRI scans or both as an alternative to surgical intervention. Initial laboratory results and sella imaging should direct further evaluation and initiation of corticosteroid and hormone replacement.

Corticosteroid therapy has been suggested, but no prospective, controlled study supports the efficacy of this treatment. Theoretically, corticosteroid therapy can induce remission and protect remaining viable pituitary tissue during acute inflammation. Pestell et al. reported an improvement in visual symptoms with corticosteroid and bromocriptine therapy and proposed that the inhibitory effect of bromocriptine on lactotroph hyperplasia induced by pregnancy may contribute to the improvement in vision. Reusch et al. described a 29-year-old woman with LAH during pregnancy who was treated unsuccessfully with a course of high-dose dexamethasone and subsequently required surgical decompression. At least five patients have been treated with corticosteroids in anticipation of surgical resection, with an improvement in signs or symptoms. Feigenbaum postulated that with improved knowledge of the pathophysiologic characteristics and natural history of LAH and the ability to make a prospective diagnosis among symptomatic peripartum women, a trial of medical therapy prior to routine neurosurgical exploration could be warranted. Indeed, resolution of symptomatology and diminution of tumor mass in response to medical therapy may make surgery unnecessary.

Feigenbaum et al. advocate a comprehensive diagnostic evaluation, including immediate initiation of bromocriptine treatment, in order to exclude pituitary adenoma. They recommend initiation of corticosteroid therapy only with failure of response to bromocriptine. It is our contention, based upon analysis of the data from this review, that historical and endocrinologic information can establish the diagnosis of LAH. In a patient fulfilling the diagnostic criteria for LAH, corticosteroid therapy can be initiated immediately, without a trial of bromocriptine. Response to medical therapy, as assessed by changes in visual fields, changes in lesion size on diagnostic imaging studies and recovery or progression of endocrine deficits, direct subsequent management. Corticosteroid therapy may not obviate the need for neurosurgical intervention in all cases of pregnancy-associated LAH, but surgery...
should be reserved for patients with acute chiasmal compression unresponsive to pharmacotherapy. In addition, alteration in surgical technique is recommended with decompression and biopsy or subtotal resection in lieu of complete adenohipophysectomy.

Perturbations of the immune system associated with pregnancy typically resolve following delivery and may enable withdrawal of steroid therapy with careful assessment of residual function. Repeat pituitary testing is required because hypopituitarism may be transient, and long-term hormone replacement therapy may be unnecessary. Such patients should be closely monitored for chronic or acute pituitary insufficiency and for occurrence of features of other autoimmune disorders.

This review has revealed many distinguishing characteristics between LAH and pituitary adenomas that should facilitate differentiation of these two entities. The clinical history and endocrinologic profile characterizing LAH are distinct from those of a prolactin-secreting adenoma and should permit a prospective diagnosis. Presumption of LAH warrants a trial of medical therapy utilizing high-dose corticosteroids. This may avert surgical intervention and allow maximal residual pituitary function with minimal morbidity and long-term sequelae.

References


