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# Recurrent pituitary apoplexy in pregnancy

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## SUMMARY

Pituitary apoplexy is caused by haemorrhage or infarction of the pituitary gland. Presenting signs and symptoms often include severe headache, visual disturbance, ophthalmoplegia, altered consciousness and impaired pituitary function. The management of pituitary apoplexy has very rarely been described during pregnancy and there is no existing data for further pregnancies of affected women. We present a case of a woman with a recurrent pituitary apoplexy due to haemorrhages in a pituitary adenoma in her third and fourth pregnancies. In both pregnancies, the pituitary apoplexy was managed conservatively, but due to therapy-resistant headaches, a preterm delivery was implemented.

## BACKGROUND

Pituitary apoplexy is a rare but potentially life-threatening reason for a pregnant woman to present with a sudden onset headache. Early diagnosis is important because it can result in a neuroendocrine emergency with acute central hypoadrenalism, hyponatremia, hypotension and neuro-ophthalmological deficits.<sup>1</sup> Especially for obstetricians, it is rarely a differential diagnosis, and the treatment in pregnancy represents a clinical challenge. During normal pregnancy, the pituitary gland volume increases up to 120% of its original size due to hyperplasia of the prolactin cells, and the metabolism of the pituitary gland undergoes significant changes as a result of placental hormone secretion.<sup>2,3</sup> Pituitary apoplexy results from an acute bleeding into a pre-existing pituitary adenoma or in the physiologically enlarged gland.<sup>1,3,4</sup> Occurrence and treatment of pituitary apoplexy during pregnancy have only been described in case reports. Owing to the rarity of the event, there are no randomised clinical trials available. In addition, there are no existing recommendations for the following pregnancies of the affected women. This is the first case report describing a recurrent pituitary apoplexy in a separate pregnancy of the same patient. It underlines pregnancy as a risk factor for pituitary apoplexy and adds knowledge to the body of literature regarding conservative management of pituitary apoplexy and for consulting prior to conception.

## CASE PRESENTATION

A 27-year-old gravida 3 para 0 at 34 weeks and 4 days of gestation presented at the emergency obstetrical department with a sudden onset headache and visual disturbances. She described a pulsating pain starting with an occipital headache, which spread to the forehead. The visual disturbances were described as repetitive flashes of light. Her medical history

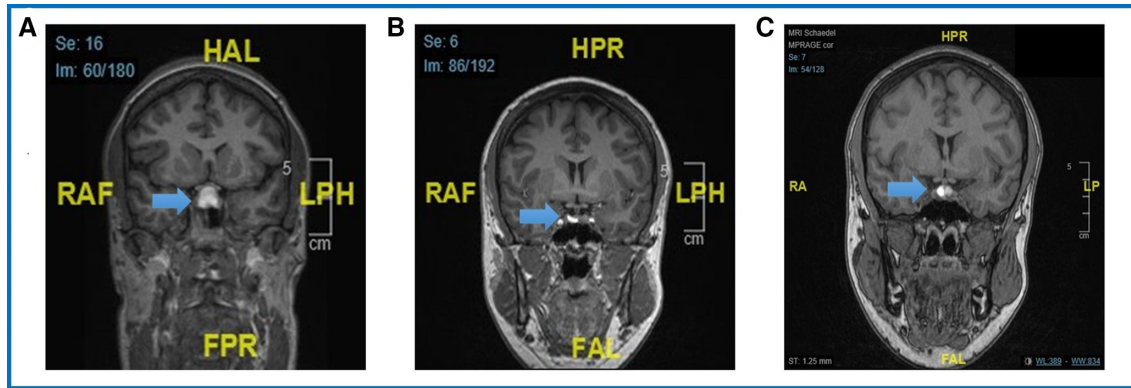
reported two miscarriages, laparoscopic ovarian cyst removal and a laparoscopic appendectomy. Besides insulin-dependent gestational diabetes, the pregnancy was unremarkable. First-trimester screening for thyroid abnormalities was normal. At the time of counselling, the gestational diabetes was treated with a dose of 22IE long-acting insulin (Lantus) and the patient showed a fasting blood sugar level of 6.2 mmol/L and a postprandial level of 14.6 mmol/L. On examination, the patient had an elevated blood pressure, but the rest of her neurological examination was normal. Cardiotocography indicated fetal well-being. Pre-eclampsia was ruled out and the patient was sent home. After recurrent visits because of persistent headaches and elevated blood pressures, a cranial MRI was implemented 2 weeks after the initial consultation. The MRI demonstrated an enlargement of the pituitary gland of 14×12×20 mm with an area of hyperintensity in T1 and hypointensive signal in T2 suggesting a subacute haemorrhage of an undiagnosed macroadenoma with contact to the optic chiasma ([figure 1](#)). At this time, pituitary hormone profile testing showed normal pituitary gland function except for the thyroid values ([table 1](#)). Haematology, biochemistry and coagulation profiles were unremarkable. An ophthalmological check-up revealed no abnormalities. The neurosurgical workup showed no need for a resection of the adenoma. An interdisciplinary round table was held with a team of obstetricians, neurosurgeons, endocrinologist and ophthalmologist. Primary caesarean section was recommended as the safest mode of delivery due to the following reasons: unclear evidence of a potential risk of recurrent haemorrhage caused by high venous pressure while pushing during labour and sonographic findings of a macrosomic fetus. The caesarean section was conducted at 36 weeks and 6 days of gestation. A healthy girl with a weight of 4100 g (>95 percentile) was born. The postpartum period was uneventful and the maternal neurological symptoms disappeared without further treatment after 1 day. An MRI 7 months after delivery showed a decreased size of the pituitary gland and the hormonal assessment confirmed a normal pituitary function ([table 1](#)). The following gynaecology check-ups were conducted at a private gynaecology practice. The patient was scheduled for an endocrinology appointment and a follow-up MRI at 12 months but did not show up for her appointment due to the reason that she was in the early stages of her next pregnancy and refused imaging without symptoms.

11 months after the last MRI follow-up, the patient was once again transferred to our department with an occipital headache and an episode of blurred vision. At this time, the patient was in



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**Figure 1** (A) Coronal view of T1-weighted imaging of first event, (B) coronal view of T1-weighted imaging postpartum, (C) coronal view of T1-weighted imaging of second event.

32 weeks of gestation. Her pregnancy was only complicated by gestational diabetes, without evidence of any deficiency in pituitary hormone secretion. The brain MRI demonstrated a subacute haemorrhage in the pituitary macroadenoma, which was smaller in size compared with the first event but larger compared with the postpartum check-up. Due to the untreatable headaches and the rising maternal distress, the caesarean section was conducted at 34 weeks and 5 days of gestation after lung maturation. A girl weighing 2750 g was born without any signs of fetal distress. The postpartum period was uneventful with spontaneous disappearance of neurological symptoms. Despite the sufficient prolactin value measured at the first event, breast feeding was not possible for the patient, due to a lack of milk production after both pregnancies.

### INVESTIGATIONS

The MRI in the first event demonstrated an enlargement of the pituitary gland of 14×12×20 mm with 14×9 mm area of hyperintensity in T1 and hypointense signal in T2 suggesting a subacute haemorrhage of an undiagnosed macroadenoma. The optic chiasm was elevated (figure 1A). An MRI after 7 months postpartum showed a significant size reduction of the pituitary gland to 8 mm with no contact to the optic chiasm as well as a reduction of the area of haemorrhage to 7×4 mm (figure 1B). The MRI in the second event showed fluid levels at T1-weighted image consistent with recent bleeding but no compression of optic chiasm.

Pituitary hormone profile testing showed no significant deficiencies in both events (table 1). It was remarkable that after the first event, the TSH value was elevated in the context of pregnancy and fT4 was below the reference, which can be caused by the following reasons: low fT4 value can be a sign of a slight

central hypothyroidism, with an inadequate rising of TSH as a result of the pituitary apoplexy. Depending on the used laboratory assay, fT4 values can be measured inaccurately during pregnancy or low fT4 value and relatively high TSH value can be a sign of a pre-existing hypothyroidism. Because of the planned delivery, there was no indication for treatment of a potential hypothyroidism, and in the following clinical course, the values were normalised without substitution. Haematology, biochemistry and coagulation profiles were unremarkable. All conducted ophthalmological check-ups showed no abnormalities.

### DIFFERENTIAL DIAGNOSIS

Pituitary apoplexy is a rare differential diagnosis for a pregnant woman presenting with sudden onset headaches. It can be easily misinterpreted for pre-eclampsia, especially, since symptoms may also include visual disturbance, altered consciousness and hypertension.<sup>1</sup> Impaired pituitary function can be harder to detect because of the physiological change of pituitary hormone secretion in pregnancy.<sup>3</sup> One life-threatening differential diagnosis is subarachnoid haemorrhage, which would be visualised in the MRI by a hyperintensity in the subarachnoid space on fluid-attenuated inversion recovery sequences and could include meningism, syncope and seizures as clinical features. Other potential differential diagnoses are cavernous sinus thrombosis, meningitis and brainstem infarction.<sup>5</sup> More particularly lymphocytic hypophysitis has to be kept in mind as an important differential diagnosis for headaches with associated hypopituitarism, especially, as 55% of the cases occur during pregnancy or postpartum.<sup>6</sup> MRI features indicative of lymphocytic hypophysitis include a symmetric enlargement of the pituitary gland, a homogeneous appearance, a thickened pituitary stalk and an enlarged pituitary stalk in absence of a systemic infection.<sup>7</sup> Nevertheless,

**Table 1** Table of the laboratory parameters

Hormones	Range	Value (first event)	Value (7 months postpartum)	Value (second event)
TSH	0.33–4.490 mIU/l	4.510 mIU/l	1.830 mIU/l	1.870 mIU/l
Free T4	11.6–22.0 pmol/L	11.3 pmol/L	13.6 pmol/L	11.4 pmol/L
Prolactin	102–496 mU/l	12156 mU/l	258 mU/l	–
Cortisol	80–638 nmol/L	714 nmol/L	278 nmol/L	870 nmol/L
ACTH	<46.0 pg/mL	38.4 pg/mL	–	–
IGF-I	12.6–39.4 nmol/L	74.4 nmol/L	20.2 nmol/L	57.0 nmol/L
HGH	0.38–29.64 mIU/l	–	–	17.80 mIU/l
HbA1c	4.8%–5.9%	–	5.3 %	–

ACTH, adrenocorticotrophic hormone; HbA1c, haemoglobin A1c; hGH, human growth hormone; IGF-1, insulin-like growth factor-1; TSH, thyroid-stimulating hormone.

lymphocytic hypophysitis can be diagnosed with certainty, only histologically.

## OUTCOME AND FOLLOW-UP

In both pregnancies, the pituitary apoplexy did not contain pituitary gland function loss. The visual disturbance occurred only temporarily. There were no signs of compression of the optic chiasm by the pituitary mass and the ophthalmological examinations revealed no visual field defects or signs of an optic neuropathy. Conservative management with symptomatic treatment of the headache and close monitoring was conducted. Due to the therapy-resistant headaches, which occurred 2 weeks earlier, and even more pronounced in the second pregnancy and the enormous maternal distress a preterm delivery was implemented in both cases. Breast feeding was not possible for the patient after both pregnancies. In the majority of women, presenting with a pituitary apoplexy, the lack of breast milk indicates insufficiency of prolactin secretion. In our case, the measured prolactin level was normal in case of pregnancy (table 1), but a development of insufficient prolactin secretion in the postpartum period is conceivable. The neurological symptoms of the patient disappeared after delivery in both events. However, after the second delivery, the patient developed headaches coinciding with her menstruation.

## DISCUSSION

Overall data of pituitary apoplexy associated with pregnancy is limited to case reports and small case series. The majority of incidents appeared in the second or third trimester. A current search in the PubMed database for the Medical Subject Headings (MeSH) terms pituitary apoplexy, pituitary disease and pregnancy shows 98 results, including 35 case reports and series. Retrospective literature studies found that the principal symptoms of pituitary apoplexy in non-pregnant women and pregnant women are sudden headache (97% respectively 94%), nausea (80% respectively 30%) and loss of visual fields (71% respectively 61%).<sup>3,8</sup> The symptoms are caused by an increase in pressure within the sella turcica produced by haemorrhage into the pituitary gland and its expansion into the cavernous sinus with compression of the optic and other cranial nerves, the optic chiasm, the brain stem and of the pituitary tissue itself. Around 20% of patients will have a change in mental status varying from a mild encephalopathy to coma as consequence of the compression or in cases of hypopituitarism because of life-threatening acute central hypoadrenalism, hyponatremia or hypotension.<sup>1,8</sup> Most frequently reported precipitating factors for a pituitary apoplexy are pituitary stimulation, surgery, coagulopathy and hypertension.<sup>1,4,9</sup> Pregnancy itself is discussed as a precipitating factor due to the physiological changes in the pituitary gland. Recently, Chan *et al* reported a case of a near-full-term gravid patient presenting with pituitary apoplexy and acute SARS-CoV-2 infection. It is unclear whether the COVID-19 infection was a contributing factor in the apoplectic event, or if these events were coincidental.<sup>10</sup> Nevertheless, the minority of patients will have precipitating factors.<sup>9</sup> The diagnostic modality of choice for pregnant women is MRI without contrast.<sup>1,3,8</sup> There are few treatment recommendations and they are often based on the approach used to treat non-pregnant women.<sup>5,11</sup> Treatment consists of immediate fluid and electrolyte replacement following a conservative management with replacement of deficient hormones or a surgical management with transsphenoidal resection.<sup>1,5,9,11</sup> Indications for a surgical intervention are significant neuro-ophthalmic signs or reduced level of consciousness. The decision between a conservative and a surgical

approach should be made by an interdisciplinary team based on the clinical situation.<sup>11</sup> Symptoms like visual deficits have been demonstrated to resolve in most cases with operative and conservative treatment, but full recovery of pituitary function is less common.<sup>1,12</sup> Therefore, a long-term hormone replacement therapy can be required in some patients. For all patients with pituitary apoplexy follow-up appointments with annual endocrine assessments and cranial MRI scans should be considered for 5 years to detect possible tumour regrowth and recurrent apoplexy.<sup>11</sup> Most data of obstetrical and fetal outcomes as well as for following pregnancies of affected patients are missing in the reported literature. The available data show that both, conservative as well as operative treatment, have small impact on delivery and fetal well-being. Regarding the delivery mode, vaginal birth and caesarean section have been reported.<sup>8</sup> Our case report indicates that affected women have a higher probability of reoccurrence of a pituitary apoplexy in the following pregnancies. Thus, these women need close monitoring with repeated visual field and vision examination and hormonal workup in further pregnancies. Moreover, the higher risk should be kept in mind in the situation of precipitating factors, for example, hypertension or the use of anticoagulation. The diagnosis and treatment of pituitary apoplexy associated with pregnancy remains a clinical challenge. Given the complexity of the disease pregnant women with pituitary disorders should be treated in specialised centres involving a multidisciplinary team.

## Learning points

- ▶ Treatment approach of pituitary apoplexy during pregnancy is close observation combined with adequate substitution of the deficient hormone axis or primary neurosurgical therapy for patients with neuro-ophthalmological symptoms.
- ▶ In some cases, urgent delivery by caesarean section can be indicated, but caesarean section is not the mandatory delivery mode.
- ▶ Affected patients are at higher risk in further pregnancies.
- ▶ Before planning a pregnancy patients with any processes in the pituitary region should receive additional obstetrical and neurosurgical counselling

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