Pituitary adenoma apoplexy in pregnancy: Case report and literature review

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Abstract. Gestational pituitary apoplexy is an extremely rare condition. It is characterised by an unexpected headache, vomiting, nausea, and visual disturbances. Pituitary apoplexy in pregnancy and postpartum is a challenging diagnosis with symptoms overlapping multiple conditions. There is a limited number of articles presenting cases or case series of gestational pituitary apoplexy. This is a potentially life-threatening emergency which requires a high index of suspicion for its diagnosis. This article presents a case of postpartum pituitary apoplexy and outlines the current stage of clinical, imagistic diagnosis and management options. A 26-year-old primipara was submitted to a Caesarean section, with no perioperative incidents. Forty-eight hours later she reported the apparition of frontal and temporal throbbing headaches, nausea, photophobia, and she was diagnosed with a pituitary tumor measuring 33x10.5x15.5 mm. Although initially conservative treatment was proposed, the clinical outcome was not favourable, thus the patient was submitted to endoscopic transsphenoidal resection. The histopathological studies demonstrated the presence of a pituitary macroadenoma. At the 2-year follow-up, the patient is free of disease. Although it represents an extremely rare condition, gestational pituitary apoplexy should be suspected whenever headache and neurological disorders such as nausea and photophobia are reported during the postpartum period.

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Introduction

Migraines are a common post-surgical and puerperal complaint, consistent with a myriad of etiologies, encompassing physiological changes, hormonal modifications, peri-surgical procedures and unknown prenatal conditions. The primary causes include tension-type headaches, cluster headaches and other trigeminal nerve cephalgia (1,2). Secondary headaches are are less common but can have severe consequences with significant mortality and morbidity if they are overlooked. Diagnosis of a secondary cause is a daunting task, taking into account that headache can be the only symptom of multiple conditions such as postdural puncture headache (PDPH), pneumocephalus, preeclampsia and eclampsia, meningitis, cerebral venous thrombosis, ischemic or hemorrhagic stroke, subarachnoid haemorrhage, reversible cerebral vasoconstriction syndromes, posterior reversible leukoencephalopathy syndrome and pituitary adenoma. Therefore, a high index of suspicion is required, and a low threshold for a neuroimaging investigation when dealing with postpartum headaches is needed (3,4). Needless to say, any suspicion of a secondary headache should be investigated by a multidisciplinary team due to the challenges posed by such wide-ranging conditions. Although pituitary adenoma is seldom a differential diagnosis in pregnancy and postpartum headache, it is part of a differential diagnosis when associated with visual loss. Ocular visual impairment is the next common symptom in pituitary adenoma after headache. We present the case of postpartum pituitary apoplexy, following an emergency Caesarean section.

Case report

After obtaining approval of the Ethics Committee of the National Institute of Mother and Child Care (Bucharest, Romania) (no. 25/2019), data of the patient were reviewed and presented in the current case report. A 26-year-old primigravida, 40 weeks gestation, was admitted to our maternity ward at the National Institute of Mother and Child Care, in

spontaneous labour. She delivered a 3,150 g female baby, Apgar score 9, through Category II Caesarean section for failure to progress. The anaesthetist performed spinal anaesthesia with bupivacaine and fentanyl. Caesarean section was routine and pain-free, with an estimated blood loss of approximately 400 ml. Pre-delivery haemoglobin was 11.5 g/dl and at post-delivery the value was slightly decreased at 10.2 g/dl. She had no prior medical history, and her antenatal care was uneventful. The immediate postpartum period was unremarkable. The patient remained alert and orientated with normal vital signs. The following day she was transferred to the postnatal ward. Approximatively 48 h post-delivery she presented frontal and temporal throbbing headaches, nausea, and photophobia, but no nuchal rigidity or backache. On examination, she presented left ptosis, anisocoria, incomplete 3rd cranial nerve paresis and normal fundoscopy. Vital signs were: temperature, 38˚C; blood pressure, 135/75 mmHg; heart rate, 68 beats per minute; and significant polyuria (3.9 cc/kg/h). An urgent neurological exam followed by an endocrinological appointment was required and indicated no signs of meningeal irritation or neurological deficiency. Consistent with her clinical examination, polyuria and polydipsia, pituitary apoplexy was a presumptive diagnosis and a magnetic resonance imaging (MRI) examination was performed. Head MRI showed a cystic pituitary tumour with a 33 mm transverse diameter, 10.5 mm anteroposterior, 15.5 mm craniocaudal. The tumour was bulging bilaterally in the cavernous sinus (into the sella turcica), encasing partially the right carotid artery. The tumour was in contact with the optic chiasm without signs of displacement or compression. The MRI diagnosis was of a pituitary macroadenoma, possible Rathcke cleft cyst (Fig. 1). Electrolytic and endocrinological tests were carried out, the results being displayed in Table I (day 4 post-delivery, 8 a.m.) showing hypopituitarism involving corticotrophin, lactotrophic and thyrotropin dysfunction with hyponatremia and hypochloremia.

Treatment with intravenous dexamethasone, thyroxin 50 μg, fluid and electrolyte replacement was initiated immediately. On the following day, a multidisciplinary meeting took place with obstetricians, anaesthesiologists, endocrinologists, neurologists and neurosurgeons in order to define a postpartum management plan. Initially, conservative management was started but as her condition worsened with a deteriorating level of conciseness, treatment was converted to surgical decompression. Endoscopic transsphenoidal pituitary surgery was performed to remove the 3x2x1 cm encapsulated tumour. Histopathology result showed a non-functional pituitary macroadenoma. Post-surgical clinical examination revealed normal neurological condition while the oculomotor paresis was wholly resolved. Two years after surgery, the patient is well under hormone replacement therapy. Currently, she is receiving oral medication, prednisolone 50 μg/day, thyroxine 75 μg and cycloprogynova (estradiol, norgestrel).

Table I. Electrolytic and endocrinological blood test results of the patients with pituitary apoplexy.

Parameter	Value	Normal range
Cortisol	43.1 nmol/l	123-626
Adrenocorticotropic hormone (ACTH)	25.14	7.0-63
Prolactine	162 nmol/l	64-395
Thyroid-stimulating hormone (TSH)	0.211 mIU/l	0.46-4.68
T3	1.19 nmol/l	1.49-2.60
Free T4	8.57 pmol/l	10.0-28.2
Cl	92.00	97-108
K	4.4 mmol/l	3.5-5.1
Na	122 mmol/l	136-145
Serum osmolality (mOs/kg)	269.9	280-300

Discussion

Pituitary adenomas represent approximatively 10-15% of all intracranial tumours. Microadenomas are tumours of less than 10 mm while macroadenomas include tumours larger than 10 mm. Giant adenomas are more than 40 mm in size. Between 14 and 54% are non-functional adenomas while the rest secrete excess hormones: 8-12% growth hormones, 2-6% release adrenocorticotropic hormone and less than 1% secrete thyrotropin (1-6). Despite solid research regarding pituitary adenoma, the pathogenesis remains unknown (5,6). Because of the associated hypertrophy of lactotrophic cells and the increase in normal pituitary volume, pregnancy is also considered a risk factor for pituitary apoplexy (7). Hereditary transmission is responsible for less than 5% of the cases (8). The pituitary gland also represents a location for metastatic deposits in 0.1-0.2% of cases, the most common primary tumours being represented by lung and breast (9-11). Pituitary apoplexy is a rare endocrinological emergency, which can occur without any eliciting factors. Nevertheless, in most cases, there are known risk factors such as major surgery, hypertension, coagulopathies or postpartum haemorrhage (Sheehan syndrome). Sheehan syndrome is the most common reason of postpartum pituitary insufficiency, which is caused by a massive blood loss during delivery or during the early postpartum period. Whenever Sheehan syndrome is suspected, two conditions should be part of the differential diagnosis, postpartum necrosis of a preexisting hypophyseal tumor and lymphocytic hypophysitis.

Diagnosis of postpartum apoplexy is a challenging one as many patients do not have any pituitary history. The most commonly encountered symptom is headache, which is frequently associated with various pathological conditions. Alongside headache, blurred vision, diplopia, photophobia, or bitemporal hemianopsiavision loss have all been reported in pituitary adenoma. Symptomatology in cases of known adenoma is due to a sharp increase in size, which is an estrogen-driven one (9). This will raise intrasellar pressure causing compression and necrosis of the pituitary gland with subsequent pituitary insufficiency. Increased intracranial pressure leads to neurologic symptoms such as nausea and vomiting. Quite often, patients can lose their consciousness or have at least a mild degree of lethargy (10). The clinical picture can mimic multiple neurological conditions, and this is why a high index of suspicion should prompt investigation for pituitary apoplexy.

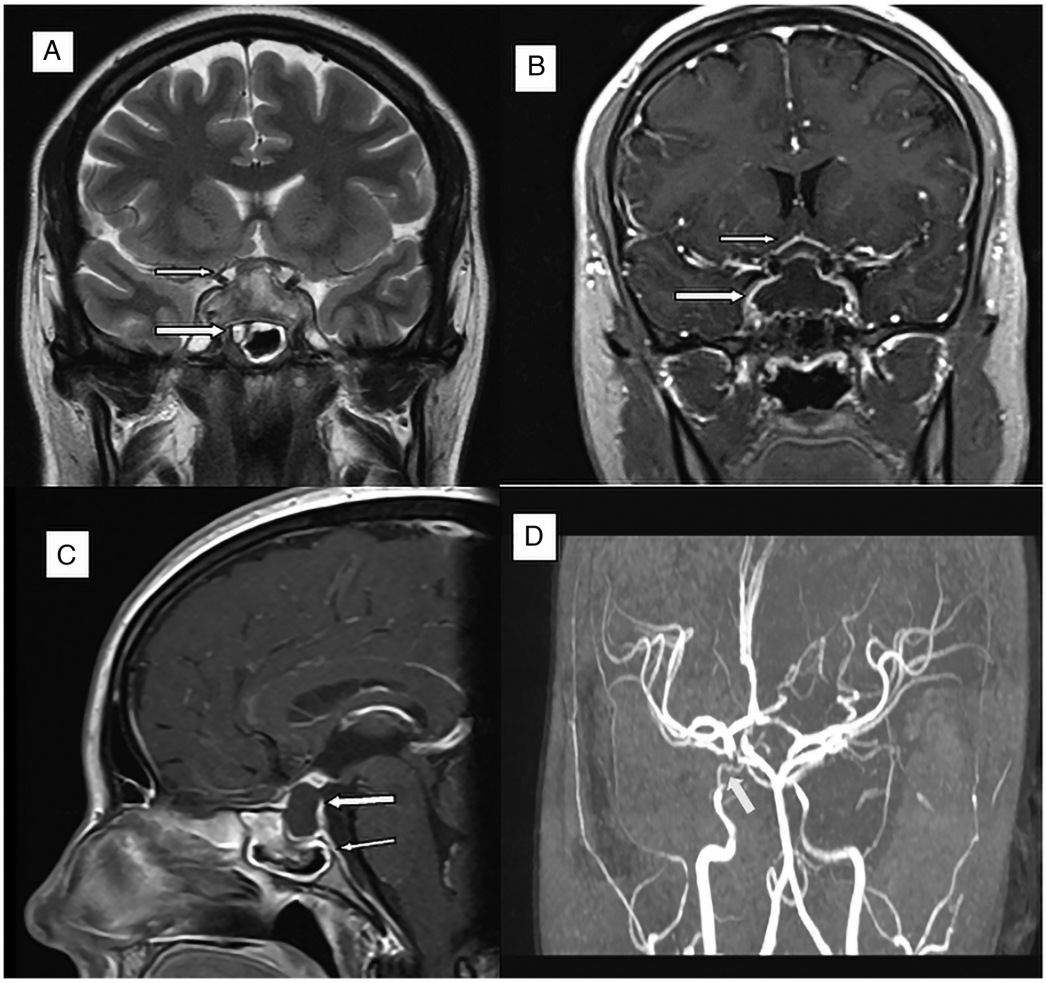

Figure 1. Magnetic resonance imaging (MRI) images of our case. (A) T2-weighted coronal image showing a cystic pituitary tumor (thick arrow) compressing the optic chiasm (thin arrow). (B) Post-contrast T2 showing a cystic pituitary mass (thick arrow) compressing the optic chiasm (thin arrow). (C) Sagittal-cystic mass (thick arrow), and thickened muscosa of the sphenoidal sinus (thin arrow). (D) Bilateral reduction of the intracavernous diameter of the carotidian artery, more prominent on the right side (arrow).

When it comes to the laboratory tests which are required in order to provide a positive diagnosis, it should be emphasized that pregnancy is a condition presenting with hormonal imbalance making interpretation of endocrine and dynamic tests more difficult. Increased levels of prolactin are normal during pregnancy, although low levels of prolactin can suggest pituitary insufficiency (11). Patients with pituitary apoplexy and low prolactin levels are the most affected and it is unlikely that they will have a successful post-surgical recovery (12). Adrenocorticotropic hormone (ACTH) deficiency is commonly present in pituitary apoplexy, but thyroid-stimulating hormone (TSH), growth hormone (GH), and gonadotropin deficiency have also been reported. Adrenal insufficiency is the most serious complication as it is life-threatening (10). Hyponatremia complicates pituitary apoplexy as it is a sign of adrenal insufficiency or of the syndrome of inappropriate antidiuretic hormone (ADH) secretion (13). Therefore, whenever pituitary apoplexy is part of a working diagnosis, a full endocrine (cortisol, ACTH, prolactine, follicle-stimulating hormone, luteinizing hormone, insulin-like growth factor 1, free T4, TSH) and blood assessment (full blood count, glycemia, electrolytes (serum sodium and potassium), and renal and liver function) should be performed urgently.

The gold standard for pituitary apoplexy diagnosis is MRI as it confirms the diagnosis in over 90% of cases. On T1-weighed images, haemorrhage typically manifests with hyperintensity related with the rest of the brain (14). MRI and MR angiogram techniques also help to differentiate an aneurism from pituitary apoplexy. MRI is safe during pregnancy, and to date no damaging fetal effects have been reported. MRI is the investigation of choice compared with any other ionising technique. The majority of radiologist avoid using gandolinum in pregnancy as it crosses the placenta, enters fetal circulation, is eliminated by kidneys and secreted in amniotic fluid. To date, no deleterious effects have been reported regarding using gandolinum in pregnancy (15).

Based on the review of the literature [Table II (4,7,10,13,16-50)], we found 48 cases of pregnancy-related pituitary tumour apoplexy. Statistical analysis of the gestational age at diagnosis showed an average value of 27.9 weeks (range 10-39 weeks) with the caveat that three of these cases, including ours, occurred during the postpartum period. Extremely rare, pituitary apoplexy can occur even in the first trimester as reported by Janssen *et al* at 10 weeks of gestation (16). Prolactinoma (21 cases) was the most common tumor encountered and in many occasions in patients who

Table II. Outcomes of pregnancy-related pituitary tumour apoplexy cases submitted to surgical decompression during pregnancy.

Authors (ref.)	Year	Age (years)	Diagnosis	Onset	Treatment	Outcome
Oguz *et al* (17)	2020	26	Macroprolactinoma	22 weeks	Surgical	Hypothyroidism
Jemel *et al* (27)	2019	37	Prolactinoma	32 weeks	Surgical	Hypothyroidism
Bachmeier *et al* (4)	2019	30	Macroadenoma	36+5 weeks	Surgical decompression	Full recovery
Annamalai *et al* (36)	2017	25	Microprolactinoma	37+4 weeks	Conservative treatment	Full recovery
O'Neal (32)	2017	27	Macroadenoma	29 weeks	Surgical decompression	Diabetes insipidus
Galvao *et al* (46)	2017	30	Macroprolactioma	28 weeks	Conservative treatment	N/A
Abraham *et al* (22)	2016	32	Enlarged pituitary	23 weeks	Surgical decompression	N/A
Grand'Maison *et al* (7)	2015	33	Macroadenoma	39 weeks	Conservative	Full recovery
Watson (42)	2015	33	Macroadenoma	37+4 weeks	Conservative	Full recovery
Querol Ripoll *et al* (34)	2015	37	Cystic microprolactinoma	24	Surgery	Panhypopituitarism
De Ycaza *et al* (47)	2015	26	Macroprolactinoma	28 weeks	Conservative	Partial hypopituitarism
Bedford *et al* (48)	2015	35	Adenoma	N/A	N/A	N/A
Piantanida *et al* (9)	2014	27	Adenoma	35 weeks	Surgery	Central hypothyroidism
Hayes *et al* (26)	2014	41	Microprolactinoma	18 weeks	Surgery	Full recovery
Tandon *et al* (49)	2014	27	Prolactinoma	36 weeks	Surgery	Temporary diabetus insipidus (DI)
Chegour and El Ansari (38)	2014	29	Prolactinoma	19 weeks	Conservative	Resolution of visual visual symptoms
Mathur (51)	2014	34	Pituitary apoplexy spinal anaesthesia	Postpartum	Surgical decompression	Reversible cerebral vasoconstrictive syndrome; Full recovery
Kita *et al* (28)	2012	26	Macroadenoma	26 weeks	Surgical decompression	Diabetus inspidus
Witek *et al* (35)	2012	25	Macroprolactinoma	19 weeks	Surgical decompression	Full recovery
Janssen *et al* (16)	2012	27	Prolactinoma	10 weeks	Conservative	Partial recovery; Adrenal insufficiency
Couture *et al* (39)	2012	37	Microprolactinoma	19 weeks	Conservative	Full recovery
Tonda and Rizvi (45)	2011	22	Hypophysitis	36 weeks	Conservative	Panhypopituitarism
Murao *et al* (44)	2011	35	Normal pituitary	39 weeks	Conservative	Panhypopituitarism
Bamfo *et al* (37)	2011	31	Macroadenoma	23 weeks	Conservative	Full recovery
Iuliano and Laws (40)	2011	28	Acroadenoma	29 weeks	Conservative	Full recovery
Ginath and Golan (24)	2010	31	Prolactinoma	39 weeks	Surgery	Full recovery
Perotti and Dexter (33)	2010	29	Pituitary macroadenoma	Postpartum	Surgery	Panhypopituitarism
Parihar *et al* (41)	2009	20	Macroprolactinoma	20 weeks	Surgical decompression	Full recovery
Okafor *et al* (21)	2009	30	Macroprolactinoma	33 weeks	Conservative	Death
Gheorghiu *et al* (50)	2009	33	Nelson syndrome	22 weeks	Conservative	Diabetus inspidus
Krull *et al* (13)	2010	7	Normal pituitary	7 weeks	Conservative	Miscarriage 9th week; Ischemic encephalopathy whichwas resolved; Persistent panhypopituitarism and DI

Table II. Continued.

Authors (ref.)	Year	Age (years)	Diagnosis	Onset	Treatment	Outcome
Atmaca *et al* (18)	2006	33	Macroadenoma (GH-oma)	29 weeks	Surgical decompression	Panhypopituitarism
Paech (20)	2006	21	Macroadenoma	Postpartum	Conservative	Full recovery
Fujimaki (43)	2005	23	Hypophysitis	34 weeks	Conservative	Adrenal insufficiency
De Heide *et al* (10)	2004	26	Macroprolactinoma	23 weeks	Conservative	Panhypopituitarism
Gondim *et al* (25)	2003	29	Macroadenoma	30 weeks	Surgical decompression	Full recovery
Lee and Pless (30)	2003	26	Hypophysitis	28 weeks	Surgical decompression	Full recovery
Freeman *et al* (23)	1992	22	Prolactinoma	32 weeks	Surgical decompression	Diabetus inspidus
Lunardi *et al* (19)	1991	21	Macroadenoma (GH-oma)	24 weeks	Surgical decompression	Full recovery
O'Donovan *et al* (31)	1986	37	Macroprolactinoma	8 weeks	Left frontotemporal craniotomy	Left-sided cranial nerve palsy
Lamberts *et al* (29)	1979	N/A	Prolactinoma	23 weeks	Surgical decompression	Resolution of visual symptoms
Our case	2020	26	Macroadenoma	Postpartum	Surgical decompression	Panhypoituitarism

DI, diabetus insipidus; N/A, not available.

were under treatment. This is in line with published literature where prolactinoma is present in approximately 50% of all cases (17). There were 17 cases of non-secreting adenoma, 2 cases of GH-oma, 3 cases of hypophysitis, one case of Neslon syndrome, one case of enlarged pituitary gland, one case of pituitary apoplexy followed by reversible cerebral vasoconstrictive syndrome and one case of normal size pituitary gland but with a histopathological diagnosis of adenoma post-surgery (Table II). In many hospitals, current practice is to halt cabergoline/bromocriptine, although there is no robust evidence for this decision (17). Onset of symptoms in a patient with a known adenoma should trigger imagistic investigations that will clarify if this is a case of progressive adenoma or a different aetiology. A real challenge is the diagnosis of pituitary apoplexy in patients with unknow adenomas. Precious time can be lost by interpreting a headache as a migraine type. There are several cases, including ours, where pituitary apoplexy was the main cause (9,10,18,19,51). Migraine is rather an exclusion diagnosis, and for this reason, failure to consider a different diagnosis can cause significant mortality and morbidity. Only a small proportion of these cases were diagnosed during the postpartum period. Symptoms such as dizziness, headache, nausea and vomiting are thought to be connected to surgery and anaesthesia and not necessarily to neurological or endocrinological conditions. This is why it is important to pay attention to 'red flags' to avoid diagnostic errors.

Mathur *et al* described a case of postpartum pituitary apoplexy following spinal anaesthesia which was treated conservatively. Ten days later, continuous thunderclap headache prompted computed tomography (CT) angiography and contrast-enhanced MRI. Images were suggestive of stenoses in the anterior and right middle cerebral arteries as well as of the vertebrobasilar segments. Based on the clinical picture, history and imagistic investigation, the final diagnosis was of reversible cerebral vasoconstrictive syndrome (RCVS). The patient's condition improved after treatment with nimodipine and lamotrigine (51). Perotti and Dexter described a postpartum pituitary apoplexy after a spontaneous delivery. The mother presented with headache, nausea and photophobia. A contrast CT scan showed a 6.1x3.9x5.2 cm giant macroadenoma which required trans-sphenoidal craniotomy (33). Paech *et al* published a case of a 15x13x12 mm macroadenoma, which was diagnosed post-delivery. Similar to our patient, this case presented initially with drooping eyelid and dilated left pupil. She reported no headaches, facial weakness or any other neurological symptom. She was managed conservatively and 14 months after her first presentation she delivered a second baby. Pregnancy course and postpartum period were unremarkable (20). We only found one case of pregnancy pituitary adenoma, which ended with the demise of the patient. A 30-year-old patient diagnosed with pituitary adenoma at 24 weeks of gestation was prescribed bromocriptine with a plan for a postnatal neurosurgery. Following a preterm delivery at 35 weeks through Caesarean section she developed hypertension, acute encephalopathy and fatal cardiac arrest on day three postpartum (21).

At this moment, there is no robust evidence regarding the best management. This is a matter of debate between surgical vs. a conservative method. Whenever pituitary

apoplexy occurs in pregnancy, initial treatment consists of fluid, electrolyte, and hormonal replacement. In a normal pregnancy, cortisol levels are two to four times above the average values due to placental function, pituitary production, and changes in hormone-binding globulin. Criteria that are used outside pregnancy cannot be used during gestation or early puerperium. Meanwhile, it should be emphasized that adrenal insufficiency is a life-threatening condition. Therefore, glucocorticoid input is vital and should be started as soon as pituitary apoplexy is suspected. UK guidelines for pituitary apoplexy recommend 100-200 mg hydrocortisone as intravenous bolus, followed by 2-4 mg/h intravenous continuous administration or by 50-100 mg every six hours by intramuscular injection. Once the acute episode is overcome, the steroid regimen should be reduced to a standard maintenance dose of 20-30 mg (52).

After stabilization of the patient, the critical question is whether surgery is necessary or medical treatment is an option. Due to the rarity of this condition, there are no randomized control trials only case reports and case series being reported to date. It is practical to carry on with medical treatment, and if there is no improvement or a deterioration in clinical condition then surgery must be performed. In seriously ill patients, the current literature and expert opinion favors surgical decompression. Analysis of 22 cases from Table II showed that surgical decompression in pregnancy is safe without any teratogenic effects (4,9,17-19,22-35,51). The majority of cases were able to deliver in the late 3rd trimester as was exemplified by Oguz *et al* and Querol Ripoll *et al*; the authors showed that surgery performed even in the second trimester does not alter pregnancy course (17,34). Analysis of cases treated conservatively showed that this is a viable and safe option in a patient without visual field defects. Overall, in 16 cases there was full recovery of endocrinological function and in 21 cases, various degree of insufficiency ranging from diabetes insipidus to panhypopituitarism and cranial nerve palsy being encountered (4,7,9,19,24,26,29,30,35-42,51). For 11 cases, long-time consequences were not noted. Most patients, while they were receiving multiple medications, reported a good quality of life (9,10,16,18,31-34,43-45).

In conclusion, to the best of our knowledge, this is the third case reported of postpartum gestational pituitary apoplexy arising in the context of a previous macroprolactinoma which shows the rarity of this condition. To date, there are no clear guidelines regarding the most efficacious treatment for pituitary apoplexy. This issue is more complex in pregnancy. As pituitary apoplexy is unpredictable, it is imperative to inform patients with known adenoma about apoplexy symptoms. Antenatal care should be individualised with urgent MRI and visual field test if the situation requires. A high index of suspicious, a multidisciplinary approach and good clinical judgement can ensure the best decision in terms of management and patient counselling.

In pregnancy and puerperium alike, headache is common and although it is usually benign can herald serious and detrimental intracranial issues.

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Availability of data and materials

Further information regarding the case presentation is available upon request.

Authors' contributions

NB contributed to the conception of the study, collected, analyzed and interpreted data from the literature and critically revised the manuscript. IB contributed to the conception of the study, performed the literature research, drafted the manuscript and is responsible for confirming the authenticity of all the raw data. LGP contributed to the conception of the study, performed the literature research, drafted the manuscript and is responsible for confirming the authenticity of all the raw data; ODT and TG contributed to the interpretation of the data from the literature, collected, analyzed and interpreted the data corresponding to the patient and critically revised the manuscript. AI collected, analyzed and interpreted the data corresponding to the patient and critically revised the manuscript. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

The Ethics Committee of the National Institute of Mother and Child Care (Bucharest, Romania) (no. 25/2019) approved the study.

Patient consent for publication

Patient consent for publication was obtained and signed by the patient on 11/05/2019.

Competing interests

The authors declare that they have no competing interests.

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