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Review

Gestational pituitary apoplexy: Case series and review of the literature

Manel Jemel[a,*], Hajer Kandara[a], Mariem Riahi[a], Radhouane Gharbi[a], Sonia Nagi[b], Ines Kamoun[a]

[a] National Institute of Nutrition and Food Technology Department of Endocrinology, Manar University Tunis, Tunisia
[b] National Institute Of Neurology Department of Neuroradiology, Manar University Tunis, Tunisia

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ABSTRACT

Pituitary apoplexy is an uncommon but potentially life-threatening emergency due to abrupt ischemic infarction or hemorrhage of the pituitary tumor. In many instances, pituitary apoplexy is the initial presentation in patients who were not previously diagnosed to have pituitary adenomas. Variety of precipitating factors have been linked to the occurrence of pituitary apoplexy, which include pregnancy. However, pituitary apoplexy related to pregnancy is limited to isolated case reports and very small case series. The main symptom is headache of sudden onset associated with visual disturbances, signs of meningeal irritation, and/or endocrine dysfunction. In the context of pregnancy the diagnosis of pituitary apoplexy can be challenging and confused with other complex conditions such as pre-eclampsia. Magnetic resonance imaging is the most sensitive sequence to confirm the diagnosis by revealing a pituitary tumor with hemorrhagic and/or necrotic components. Corticotropic deficiency with adrenal insufficiency is a potentially life-threatening disorder for both mother and the fetus if left untreated. The choice between conservative management with dopamine agonists and glucocorticoid, this "wait and see approach" and trans-sphenoidal resection depend on the severity of neuro-ophtalmic signs and the gestational week.

In this article, we present three cases of pituitary apoplexy related to pregnancy. Pituitary apoplexy occurred in the third trimester in the three cases. It was the first presentation of an unknown pituitary adenoma in two cases, and complicated a preexisting macroprolactinoma in the other case. All three cases of our patients had sudden onset of severe headache and deterioration of the visual field in two cases. The pituitary MRI performed in our patients was the essential tool confirming the diagnosis of pituitary apoplexy. In all the patients was prompt replacement of deficient hormones especially glucocorticoids with close surveillance. The trans-sphenoidal resection was indicated in two pregnant women; as the first choice treatment in one case presenting with papillary edema, and as the second line after the deterioration of the visual field in one case. In the lack of guidelines of management pituitary apoplexy in case of pregnancy, we review the existing literature with pertinent clinical presentation, radiological findings, management and maternal/fetal outcomes of this rare pathology. The aim is to provide a rational framework for therapeutic management of pituitary apoplexy during pregnancy.

Contents

* Corresponding author.
E-mail addresses: maneljemel@gmail.com (M. Jemel), hajer.kandara@yahoo.fr (H. Kandara), riahi.mariem89@gmail.com (M. Riahi), g_radhouane@yahoo.com (R. Gharbi), Nagi.sonia5@gmail.com (S. Nagi), Ines.kamoun@planet.tn (I. Kamoun).

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Introduction

Pituitary apoplexy is originating from Greek means “sudden attack” with haemorrhage and/or infarction in pituitary tumor or, less commonly, the surrounding normal gland tissue. The first index case was, described by Bailey, in 1898 [1].The true incidence and prevalence of pituitary apoplexy is difficult to establish either because the majority of the studies are retrospectives or because the diagnosis of pituitary apoplexy is usually misdiagnosed. It seems to occur in 0.65–10.5%; this proportion increases up to 25% of surgical series [2].

Apoplexy represents the first clinical manifestation of previously unknown pituitary adenoma in 60%–80% of cases [3–5]. It remains the rare problems that is diagnostically and therapeutically challenging. The clinical spectrum of presentation does vary, commonly characterized by sudden and severe onset of cephalalgia, nausea, vomiting, visual disturbance, and decreased consciousness. The precise physiopathology is not completely clear. Although in most cases it occurs spontaneously, pituitary apoplexy can be precipitated by many risk factors such as hypertension, medications, major surgeries, coagulopathies, dynamic testing of the pituitary, or pregnancy [4]

However, pituitary apoplexy is a rare event during pregnancy, and few cases have been reported to date. It is potentially life-threatening endocrine emergency to booth the mother and the fetus, if misdiagnosed.

Case 1. A 32-year-old woman was admitted to at 37-weeks gestation (WG) because of, episodes of severe fronto-orbital headache with sudden blurring of vision, since the second trimester of pregnancy (at 20 weeks of gestation). Our patient had no comorbidities. The gravida 2, para 2, abortions 0 (G2P2A0) woman, had no history of preeclampsia or other pregnancy related complications. There was no trauma or loss of consciousness. She denied any prior similar episodes or history of migraine headache. She had no associated fever, chills, no neck pain. She has a low blood pressure at 9/6 mm Hg and the physical exam was otherwise normal. Glasgow coma score scale was 15/15. Cranial nerves were grosslyintact, extra-ocular movements were intact, and no nystagmus was noted. A complete neurological examination showed no signs of meningismus. Visual fields werenormal.The hormonal work-up (Table 1) and biochemical results including sodium, potassium, hematology and blood glucosewere normal.

A cerebral computed tomography (CT) scan without contrast showed a prominent and slightly hyperdense pituitary gland and pituitary apoplexy was suspected.

A magnetic resonance imaging (MRI) performed confirmed sellar central hemorrhagic infraction and pituitary hyperplasia, compatible with sub-acute pituitary apoplexy.

Hydrocortisone was immediately started intravenously 100 mg six-hourly. Labourwas induced and a healthy baby was born.

Physiological hydrocortisone supplementation and dopamine agonists (Bromochriptine) was commenced in postpartum.

Table 1
Laboratory results of three cases from our institute.

	Case 1	Case 2	Case 3
TSH (mU/L)		0.4	1.5
FT4 (pmol/L)	10.6	11	10.2
Prolactin (ng/ml)	866.7	50	–
Cortisol (nmol/L)	246	45	544

Reference range in general population: TSH: Thyroid Stimulating Hormon:0.35-5.5mUI/L, FT4: Free Thyroxine:10.0–23.0 pmol/L, PRL: 110–330 ng/ml in the second trimester [6], Cortisol: 275–685 nmol/l.

At 12 days post-partum, her endocrine work-up showed Prolactin at 208.6 ng/ml.

A repeat MRI ten weeks later showed regression of the pituitary mass with a central remnant cyst of 18 mm with no signs of invasion of optic chiasm, comparable with a preexisting pituitary tumor.

Case 2. A35-year-oldwomanpresentedwitha4-monthhistoryof-headachesandprimaryinfertilityof 4-year duration. Endocrine assessment revealed an elevated serum prolactin at 2448 μUI/L (normal: 40–530 μUI/L). A pituitary MRI revealed a well defined homogeneous lesion in sella on left side appearing hypo intense on TIW and mildly hyper intense on T2W images. The lesion measured 10 × 9 × 8 mm in size. No suprasellar extension of the lesion was seen.

She was commenced on Cabergoline, but unfortunately defaulted from endocrine follow up. Two years later, she represented at 22 weeks of pregnancy, with recent onset of severe headache nausea and vomiting. She have discontinued treatment following confirmation of pregnancy.

There was no neurological deficit, no trauma or loss of consciousness. On physical examination, there was no signs of meningismus. Ophthalmic examination showed preserved visual acuities and visual fields.

She received immediately hydrocortisone and recommenced on Cabergoline, 3 days later she presented secondary deterioration of the visual field. Ophthalmic examination showed papillary edema stade1. Her hormonal work-up showed a low cortisol and a lowprolactinlevel low for a woman in her first trimester.

A pituitary MRI was immediately performed and showed a pituitary mass of (14 × 8.8 × 13 mm) with a hyper intense signal T1, hypoT2 and a horizontal level in T2 compatible with a pituitary adenoma in apoplexy (Fig. 1).

She was transferred urgently to the neurosurgery department and she was operated by microsurgical transphenoidal route with simple operative follow-up.

It was a non-secretory adenoma with stalk compression, disconnected hyperprolactinemia and central adrenal insufficiency.

At 37 weeks of pregnancy, she delivered a healthy 3.5 kg baby girl.

Case 3. A 30-year-old woman was admitted at 24 weeks of gestation with sudden onset of severe headache and visual disturbance. She was well with no comorbidities.

The presented pregnancy had been uneventful until she reported a sudden and severe bilateral headache accompanied by blurry vision. No head trauma was reported and blood pressure and preeclampsy investigations were within normal.

A complete neurological examination showed no sign of meningeal irritation.

Ophthalmic examination showed a bitemporal hemianopia and a decrease in visual acuity but no ophtalmoplegic or diplopia was noted. MRI performed immediately showed an horizontal level with a sloping portion in iso signal T2 and hyper signal T1 surmounted by a spontaneous hypersignal in T1 and T2 evoking a bleeding within a macroadenoma.

Initial hormonal work-up and biochemical results were normal.

Urgent neurosurgical, endocrinology and obstetric team consultations were performed. Transsphenoidal surgery was indicated because of visual impairment.

High dose corticosteroids were administrated and she underwent endoscopic transsphenoidal excision of the pituitary adenoma within 48 h.

She reported a dramatic improvement in her vision.

Delivery after 38 weeks of pregnancy was uneventful and a healthy baby boy was born.

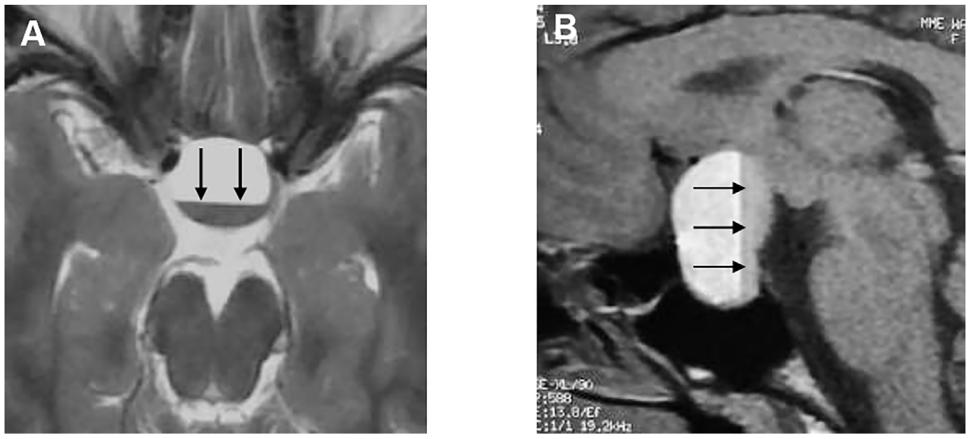

Fig. 1. Pituitary MRI: Sagittal (A) and coronal (B) T1-weighted MRI scans showing a fluid level inside the pituitary lesion, the upper compartment is hyper intense while the lower compartment is iso-intense.

Discussion

Pituitary apoplexy is a rare clinical syndrome, which develops as a consequence of acute hemorrhage and/or infarction in an underlying pituitary adenoma. It may occur spontaneously or precipitating by some factors. Rare cases occurring during pregnancy are reported in the literature. In 23 years, we encountered 3 cases of pituitary apoplexy accelerated by pregnancy in our institute.

In all the cases, the women presented with sudden headache at the third trimester. Apoplexy was the first presentation of an unknown adenoma in two cases and this highlights the importance to include pituitary apoplexy in the differential diagnosis of sudden headache in pregnant women even if there are not known to have a pituitary lesion. Pituitary apoplexy is a medical emergency because of endocrine disturbance including adrenal insufficiency which is life threatening. Thus, as soon as the diagnosis is suspected and radiological confirmed, intravenous hydrocortisone was started without waiting the result of the hormone work up. That's can explain our attitude even when cortisol was normal in the first and second case. The transfenoidal surgery was indicated in the second case owing to the visual disturbance and papillary edema. In the third case, surgery was indicated even in the lack of serious visual impairment and this can be explained by the old attitude when we considered pituitary apoplexy as a surgical emergency. In the lack of guidelines of management pituitary apoplexy in case of pregnancy, we review the existing literature. We performed a literature search using PubMed and Medline to identify relevant articles published between 1960 and2018. Our search was limited to articles in English and French, and we included abstracts only when enough data were available.The search was conducted using the MeSH terms 'pituitary apoplexy', 'pregnancy' and 'sudden headache'.

Pathogenesis

Pathogenesis of pituitary tumour apoplexy during pregnancy has been attributed to different hypotheses. In fact, during pregnancy pituitary gland undergoes major changes with altered anatomy and physiology. This include for instance, increase of volume and height of pituitary gland throughout gestation by approximately 30–45%, and this can persist even in post partum [7–10]. These changes are mainly due to an increased estrogen states, which causes lactotroph cells hyperplasia besides physiological elevation of prolactin [11]. Moreover, it has been demonstrated that estrogen is implicated in hemodynamic changes [12,13], and therefore contribute to the risk of apoplexy. These physiological changes lead to an imbalance between the stimulation of pituitary and the ability of increased blood flow at the level of the pituitary adenoma. This adenoma itself has a fragile vascularization [14–16].

Pituitary apoplexy is a potential life threatening for mother and fetus [17]. It may represent the first manifestation of apre-existing, un recognized adenoma in over 80% of cases in general [2].

The review of the few cases described in the literature ([18–47] and our cases Table 2) in pregnant women a known adenoma before apoplexy was diagnosed in: 9 macoadenomas (including 6 macroprolactinomas) and five microadenoma (including 4 microprolactinomas) (Table 2). Two patients were diagnosed with a macroadenoma during pregnancy because of severe headaches [20,21].

Non-functioning adenomas and large macroadenomas are the common subtypes of tumors prone to apoplexy [2]. However, these subtypes can lead to infertility in some extend; the hypothesis of possible tumor enlargement of a prior microprolactinoma during pregnancy is logical; this event can be explained by the expression of estrogen receptors by the prolactinoma [48]. In this review the tumor growth of a microadenoma prior to the pregnancy in apoplectic pregnant women was showed in 2 cases [39–46]. However, it has also occurred in normal pituitary [24,26], and in lymphocytic hypophysitis [41].

Clinical features

Based on the review of the literature the main and most earlier complaint is a sudden headache (81%). However it can be a challenging diagnosis and should be included in the differential diagnosis of severe and sudden headache even there is no prior history of pituitary adenoma. This symptom can be explained by meningeal irritation due to extravasation of blood and necrotic material into subarachnoid space, enlargement of sella turcica walls, dura mater compression, or involvement of the superior division of the trigeminal nerve inside the cavernous sinus [49,50].

Headache is commonly accompanied by signs of meningeal irritation nausea and/or vomiting (31%). This sign has been confound to preeclampsia in 2 cases [40,44]. Photophobia was noted in 14% in our review including our cases. Optic nerves, chiasma or optic tract can lead to visual field defects (47%), impaired visual acuity (41.2%) of cases of pituitary apoplexy related to pregnancy [44]. In our review visual disturbances was noted in 81% (including visual defects in 25%, impaired visual acuity in 40%, diplopia in 5%). Apoplectic pituitary can involve the oculomotor

Table 2
Summary of apoplexy cases during pregnancy from the literature review and our academic center.

Author [reference]	Age years	PriorLesion/WG at Treatmentpresentation		Clinical presentation	Pituitary imaging MRI/CT	Treatment			Evolution	Delivery week
						Hormonal/ Bromocriptine ReplacementCabergoline		WG, Surgery Histology		
Ohtsubo et al. [18]	29 (multi)	ADoma	24	Headache, vomiting, blurred vision DI	CT and MRI : a pituitary adenoma with hematoma			32 WG transsphenoidal approach during pregnancy Histo : acidophilic adenoma + hemorrhagic change.		Full term after the operation uneventuful
Kita et al. [19]	26 (G1)	–	26	Bitemporalhemianopsia, decreased visual	MRI: an 18 mm pituitary mass with a fluid–fluid level component displacing the optic chiasma upward.			27 WG endonasal endoscopic transsphenoidal surgery Histo: non functioning adenoma	Visual symptoms immediately improved, central DI	40 WG
Atmaca et al. [20]	33	MADoma (GH) initially diagnosed during pregnancy at 29 weeks	33	Sudden loss of vision and severe headaches.	MRI :pituitary apoplexy	+		33 WG transsphenoidal resection during which cesarian section		
Luliano et al. [21]	28	MADoma : discovered one week prior during a workup for headaches.	29	Bifrontal and retroorbitalheadach, Funduscopic subtle disk margin blurring with probable edema of the right optic disk.	MRI:pituitarymacroadenoma with hemorrhage into the tumor bed site and mild compression of the right optic nerve	+	BCP 2.5 mg × 3/day no significant improvement after 5 days	A transnasal operation rapidly indicated	The headaches resolved on postoperative day 1.	39 WG Uneventuful
Gheorghiu et al. [22]	33	ADoma (ACTH) (Nelson syndrome) Cushing's disease treated by adrenalectomy	22	Sudden onset of severe headache and nausea	MRI:1.6 cm intrasellar mass suggesting pituitary apoplexy	+			DI One month later	uneventfully
Freeman et al. [23]	22	MPRLoma Bromocriptine during 4 months stopped when she was pregnant	32	Headaches, diaphoresis bilateral superior quadrant anopsia photophobia, DI	CT scan: enlarged mass with prominent suprasellar extension. MRI : recent pituitary hemorrhage, impingement on the optic chiasm and non visualization of the neurohypophysis	+		Transsphenoidal evacuation	Prompt resolution of visual complaints and normalization of visual field defects.	39 WG spontaneous deliverery
Krull et al. [24]	28 (G1)	–	7	Headache, DI		+				
O'Donovan et al. [25]	37 (multi)	MPRLoma	8	Headache, left-sided ptosis, coma	Bromocriptine, left frontotemporal craniotomy		BCP	Left frontotemporal craniotomy	Left-sided 3rd cranial nerve palsy, slight ptosis	
Murao et al. [26]	35	-(HELLPsyndrome)	39	Nausea, vomiting, general fatigue DI	MRI: pituitary apoplexy without the presence of a preexisting pituitary mass	+				
Nagulesparan et al. [27]	34	–	31	Blurring of vision hazy vision for about three months.			BCP but 48 hours later the mother have a bitemporal hemianopia	Post partumcarniotomyHisto: haemorrhagic anterior pituitary tissue.		32 WG Caesarean section
Gondim et al. [28]	29	mPRLoma BCP (5 mg/ d)	30	Unilat headache, central scotoma, supero-temporal defect in the left eye	MRI: Macroadenoma with some inside hemorrhage	+	BCP 5 mg/day; 2 w later diplopia, progressive ptosis, complete third cranial nerve palse on the right	32 WG: Mini invasive pituitary surgery		39 WG spontanous delivery
Onesti et al. [29]	28	–	?	Headache, bitemporalhemianospsia		+		Transphenoidal decompression surgery		

Hervet et al. [30]	26	–	24	Headache						
Parihar et al. [31]	2**2**	MPRLoma BCP stopped as pregnancy was diagnosed	20	Headache, vomiting, vision loss	pituitary apoplexy and compression over optic nerve and chiasma			Transsphenoidal decompression of gland and removal of hematoma.	Relief of headache and restoration of ormal vision	full term Uneventful normal lactation
Witek et al. [32]	25 (G1)	MPRLoma BCP 2.5 mg × 2/day 8 months MRI: decrease in pituitary tumor size. Resolution of HPR degression of BCP when pregnancy was confirmed	14	Headaches, dizziness, visual abnormalities.	MRI features of tumor enlargement with optic chiasm displacement and focal hemorrhage within the tumor		BCP reinitiated 20th WG resistant headaches, deterioration of neurological condition and decreased visual-field	20 WG Selective transsphenoidaladenomectomy Histo: sparsely granulated lactothroph pituitary adenoma	Improvement of neurological condition Complete recovery of the visual acuity and visual field	38 WG caesarean section
Reference [33]	27	–	35	Severe fronto-orbital headache, photophobia, and blurring of vision of sudden onset.	MRI: an intra- and extrasellar mass, with suprasellar extension and compression of the optic chiasm, deviation of the pituitary stalk, and fluid levels at T1-weighted image consistent with recent bleeding			The day after delivery, endonasal endoscopic transsphenoidal surgery.	In the next few days, there was a marked mprovement of visual field and visual disturbances.	urgent cesarean section
Scherrer et al. [34]	?	MADoma	16	Headache, visual disturbance			BCP			
Scherrer et al. [34]	?	mADoma	28	Headache, visual disturbance			BCP			
Lunardi et al. [35]	21(multi) Acromegalic	–	24	Sudden, violent, left temporal headache, reduction of visual acuity, bitemporalhemianopsia	CT brain scan: intrasellar space-occupying lesion with a marked suprasellar extension, which was hyperdense in patches and enhanced little after intravenous injection of contrast medium.			Transphenoidal approach	Visual acuity recovered After 10 days, visual field had normalized., decresed GH. DI	normal delivery at tem
Fujimaki et al. [36]	23 (G1)	–	24	Retro-orbital pain, headache bitemporalhemianopsia, 32 WG her bitemporalhemianopsia worsened	MRI: large mass occupying the pituitary fossa and suprasellar cistern	+		Surgery was performed 1 month post partum Lymphocytic infiltration	Visual acuity improved, visual field widened after delivery, MRI: optic chiasm was compressed markedly by the pituitary mass	caesarean section was planned for the 34th gestational week
Ginath et al. [37]	31 (G1)	PRLomabromocriptine until confirmed pregnancy	39	Headache and nausea.			.BCB		Resolution of the headache and nausea	cesarean section
Heide et al. [38]	26 (multi)	–	23	Severe continuous headache, nausea, vomiting, photophobia, lowered consciousness diplopia and DI	MARI: 2 cm large pituitary tumour On the T1 weighted image the signal intensity was high and on T2 low, compatible with haemorrhage in a pituitary mass	+			Clinical improvement continued in the following days	38 WG uneventful
Janssen et al. [39]	27 (G1)	mPRLoma BCP 2.5 mg × 2/ay. Soon thereafter the patient became pregnant and BCP medication was ceased.	10	Headache, visual disturbance	MRI: tumour growth of the prolactinoma, suprasellar extension and a marked compression of the optic chiasm. Liquefaction was seen within the prolactinoma, indicating an apoplexy within the tumour	+	BCP 2.5 mg × 2/day		19 WG: headache disappeare, visual field defects improved At 33 W G, laboratory values and visual field examination returned to normal	40 WG Vaginal delivery uneventful

Table 2 (*Continued*)

Author [reference]	Age years	PriorLesion/WG at Treatmentpresentation		Clinical presentation	Pituitary imaging MRI/CT	Treatment			Evolution	Delivery week
						Hormonal/ Bromocriptine ReplacementCabergoline		WG, Surgery Histology		
Bamfo et al. [40]	31 (G1)	–	10	Severe vomiting, 16 weeks decreased vision in her left eye. An optician noted left -sided ptosis. 18 weeks diplopia	Cystic lesion within the pituitary fossa, representing haemorrhage into a preexisting solid or cystic lesion. Th e lesion was extending into the left cavernous sinus with evidence of compression of the optic chiasma	+			39 WG Delivery by caesarean section	
Lee et al. [41]	26 (G1)	–	24	Headache progressively worsened sudden “fog” in her left eye temporal visual field	MRI: 1.5 × 1.5 × 2.3 cm mass arising from the pituitary fossa and extending into the suprasellar cistern compressing the optic chiasm. A region of bright signal consistent with old hemorrhage	+		Transphenoidal surgery Histo : lymphocytic hypophysitis	Vaginal delivery 1 week after surgery	
Lamberts et al. [42]	30 (G1)	PRLoma	23	Headache, vomiting, left abducens paresis, fatigue		+			Uneventful pregnancy, complete recovery	
Rosen et al. [43]	32	–	22	Headache, nausea, vomiting, hyponatremia		+				
Grand'Maison S et al. [44] Case 1	33 (G6)	–	39	Headache, blurry vision, dizziness, neck stiffness	CT brain scan without contrast: prominent and slightly hyperdense pituitary gland of 12 mm in contact with the optic chiasm. (MRI): sellar central haemorrhagic infarction and pituitary hyperplasia without underlying lesion, compatible with sub-acute pituitary apoplexy.	–			40 WG Labour was induced at	
[44] Case 2	30 (G1)	MPRLoma CBG 0.5 mg/week 13 WG, CBG restarted (0.5 mg/week) for residual macroprolactinoma just before pregnancy and rapidly increased of PRL	20	Headache	MRI: recurrent pituitary mass of 17*22*14 mm with a hypointense signal compatible with acute bleeding and pituitary apoplexy.	–	CBG increased at 24 W G to 0.5 mg × 2/week		Spontaneous vaginal delivery at term	headaches was stopped at delivery
[44] Case 3	37 (G1)	mPRLoma CBG 0.5 mg/week during 1 year Stopped at 6 WG	16	Sudden onset of severe headache nausea, vomiting, blurred vision, photophobia		–	CBG restarted at 0.5 mg/week and later stopped at 36 WG		Improvement, regression of the sellar mass after 5 weeks	38 WG inducton for suspicion of preeclampsia and had a caesarean for failure of labour progression.
Tandon et al. [45]	27	PRLoma 19 weeks gestation	36	Severe onset headache, acute vision loss in the left eye.	MRI: suprasellar, hemorrhagic mass measuring approximately 2.1 × 1.3 cm in size with noted optic chiasm compression			Emergent endoscopic endonasaltranssphenoidal resection	Neurologic deficit resolved	Cesarean section one week after the endoscopic}

Hayes AR et al. [46]	41	mPRL CBG 500 mg weekly stoped when pregnancy was confirmed	18	Subtle bitemporal, visual field deficits	Non-contrast MRI: pituitary haemorrhage with a significant increase in the size of the adenoma compared with 7 months before	+		second trimester :stereotactic endoscopic transsphenoidal excision Histo: prolactinoma		at term vaginal delivery
Abraham RR et al. [47]	32	–	23	Photophobia and right-sided numbness blurriness, diplopia decreased right V1-V2 facial	MRI: enlargement of the pituitary (1.7 cm), with layering haemorrhage posteriorly, and compression of the optic nerve	–		emergent endoscopic endonasalHisto: pituitary parenchyma with haemorrhage and fibrosis		
Our case series Case 1	32 (multi)	–	37	Severe fronto-orbital headache, sudden blurring of vision, since the second trimester of pregnancy	(CT) scan without contrast: prominent and slightly hyperdense pituitary gland and pituitary apoplexy was suspected. (MRI) sellar central hemorrhagic infraction and pituitary hyperplasia, compatible with sub-acute pituitary apoplexy	+				37 WG Labour was induced
Case 2	35 (G1)	MPRLoma MRI was performed and revealed a macro adenoma with an initial size tumor of ($10 \times 9 \times 8$ mm). She was commenced on Cabergoline	22	Severe headache, nausea, vomiting deterioration of the visual field. Ophthalmic examination showed papillary edema stade 1	A pituitary MRI a pituitary mass of ($14 \times 8.8 \times 13$ mm) with a hyper intense signal T1, hypoT2 and a horizontal level in T2 compatible with a pituitary adenoma in apoplexy	+		Microsurgical transphenoidal Non functionningMacroadénoma		37 weeks of pregnancy, she delivered
Case 3	30	–	24	Sudden onset of severe headache, visual disturbance, a bitemporal hemianopia, a decrease in visual acuity	MRI performed immediately showed an horizontal level with a sloping portion in iso signal T2 and hyper signal T1 surmounted by a spontaneous hypersignal in T1 and T2 evoking a bleeding within a macroadenoma.	+		Endoscopic transsphenoidal excision of the pituitary adenoma within 48 hours. .	Improvement in her vision	Delivery after 38 WG
Total of cases 36 cases	Mean age 29,5 years	9 MAD (6 MPRoma + 3 MADoma) 5 mAD (4 mPRLoma + 1 mADoma) 5 AD (3 PRL oma)	1stT: 5 2ndT: 20 3rdT: 10	Headaches: 29/36 Vomitting and/or nausea: 11/36 Visual disturbance: 29/36 Photophobia: 5/36 Ophtalmoplegia: 3/36 Altered consciousness: 2/ 36 DI: 5/36		18/ 36	Dopamine agonist: 11/36 (9 BCP + 2 CBG) Associated with surgery in 6/ 20 cases	19/ 36		

WG: week gestation, ADoma: Adenoma non specified, MADenoma: Macroadenoma non specified, mAD: microadenoma non specified, PROLoma: Prolactinoma, MPRLoma: Macroprolactinoma, mPRLoma: microprolactinoma, DI: Diabtesinsipidus, CBG: Cabergoline, BCP: Brompcriptinr, NFA: non functioning adenoma, GH: Growth Hormon, T: trimester.

nerves resulting in ptosis (8%). Altered level of consciousness may occurs, to varying degrees ranging from lethargy to stupor or even coma as consequence of blood or necrotic tissue leaking into the subarachnoid space, eventual arterial hypotension and/or hypoglycemia due to adrenal insufficiency [25,38]. In our review, it was noted in5%.

Hyponatraemia as an electrolyte disturbance was noted in 5%in our review, which is often multifactorial and the most likely pathogenetic mechanism proposed of hyponatraemia is adrenal insufficiency. Other etiologies can include the syndrome of inappropriate ADH secretion (SIADH) resulting either from adrenal insufficiency itself or from hypothalamus irritation [51]. Posteriorpituitaryinvolvementisnotcommoninpaanddiabetesinsipidus-was reported in 3% of cases despite frequent and significant suprasellar extension in many cases [52]. In this review including our cases, it was noted in 14% [18,23,24,26,38].

This may be attributable to the preservation of the posterior pituitary as result of its different blood supply from the inferior hypophyseal artery rather than the superior hypophyseal artery that supplies the anterior pituitary and usually the tumor.

Reviewing the series of patients with PA, one or more endocrine deficiencies can be present at the onset and urgent evaluation of hormonal levels is mandatory [4].

The most relevant deficit is that of adrenocorticotroph hormone (ACTH) resulting in life- threatening acute central hypoadrenalism. [38].

Hyperprolactinemia is a physiological condition in pregnancy [6], but the level of prolactin can be inappropriately low in pregnant women presenting pituitary apoplexy. In contrast the PRL level can be inappropriately higher raising the possibility of a prolactinoma [32,33,39, our first case].

Imaging findings

The diagnosis of pituitary tumor apoplexy is based on imaging evaluations, mainly using magnetic resonance imaging. Pituitary MRI is the radiological investigation of choice [4].

It is possible to find a fluid intralesionnel level (Fig. 1).

In the acute stage of pituitary apoplexy, the MRI signal is isointense or slight hypointense on T1-weighted imaging with hypointensity on T2-weighted imaging (T2W1). A “brushed” specific pattern of alternating subtle T1-hyperintense and -hypointense areas within the sellar mass may suggest apoplexy at the earlier stage [53].

Pregnancy is not an absolute contraindication to MRI, with no special consideration for the first trimester versus any other trimester of pregnancy [54]. However, it seems prudent to avoid MRI in pregnant women during the first 3 months of gestation, unless necessary. Only essential sequences should be performed, possibly without contrast injection (gadolinium), unless essential for diagnosis and management [54].

Treatment

The initial management includes fluid and electrolyte replacement, alongside prompt replacement of deficient hormones and close observation. It is important to note that the assessment of pituitary function in pregnancy is complicated by the major physiological

changes in anterior pituitary hormones in normal pregnancy, because of changes in pituitary secretion, placental hormones and changes in hormone binding globulins [55]. Total cortisol increases two to three times by the third trimester of pregnancy so that cortisol may appear to be normal or above the normal reference range in a patient with adrenal insufficiency; usual diagnostic criteria cannot be used [56]. At present, due to the difficulties to confirm adrenal insufficiency in pregnancy, low threshold is recommended for treatment and would give initial presumptive steroid replacement in any case of pituitary apoplexy in pregnancy [55]. Glucocorticoids allow to treat both adrenal insufficiency and the effect of edema on suprasellar structures [2,38].

The latest guidelines [4] suggest the use of hydrocortisone100–200 mg as an intravenous bolus, followed either by continuous intravenous infusion (2–4 mg per hour) or by six-hourly intramuscular injection (50–100 mg).

After initial treatment and for the present, there are no clear recommendations regarding treatment of pituitary apoplexy in pregnant women, especially whether to choose between a conservative approach with dopamine agonists and neurosurgical intervention by transphenoidal resection. Prolactin is difficult to interpret during pregnancy, therefore intervals references in pregnant women were established according to trimester, days postpartum [6]. In case of prior prolactinoma or hyperprolactinemia concomitant to pituitary apoplexy conservative medical treatment with dopamine agonists should be the first choice of treatment followed by a strict a close observation [37,39,44].

Bromocriptine is the dopamine agonist of choice in the setting of pregnancy because of a greater safety record. Some authors [44] suggested that dopamine agonists therapy, even in the setting of a low prolactin level, may help prevent the normal increase in pituitary gland size during pregnancy.

Transsphenoidal surgery under general anesthesia does not appear to present teratogenic risk to the fetus. Moreover, according to the previous reports and our own experience 19 cases underwent urgent decompressive pituitary and have good outcomes in terms of symptoms and deliveries, suggesting that pituitary surgery for pregnant women is a feasible option. Most studies indicate that surgical treatment, usually within 7 days after the apoplectic event, leads to higher rates of visual impairment recovery [4,57].

Surgery approach was indicated in these pregnant women who presented with a deteriorating level of consciousness or a significant or progressive neuro-ophthalmological deficit (Table2). The pituitary surgery commonly by endocropic transphenoidal approach was preceded by bromocriptine in 6 patients. The final decision should result from a multidisciplinary approach taken in to account the severity of clinical presentation and the gestational week [4].

Conclusion

The view of the existing literature underlines that pituitary apoplexy, even it is a rare disorder, it is potentially life-threatening in both pregnant women and the fetus. It should be born in mind in pregnant women either with known or undiagnosed prior pituitary adenoma. It has an unpredictable clinical course and, in the absence of more evidence-based data and guidelines the choose between conservative vs surgical approach depend on clinical judgment from multidisciplinary team including neurosurgeons, endocrinologists, neuro-radiologists, neurologists and gynecologist. The decision should take into consideration the presence and severity of neurological signs and their stability on the one hand and the term of pregnancy on the other.

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