



A case of eclampsia complicated by cerebral haemorrhage and iatrogenic hypopharyngeal oedema and haemathoma

Eklampsija komplikovana cerebralnom hemoragijom, jatrogenim hipofaringealnim edemom i hematomom

Marija Kutlešić*, Tatjana Mostić-Ilić^{†‡}, Dragana Ilić[§], Ranko Kutlešić^{||¶}

Clinical Center Niš, *Center of Anaesthesia, [§]Institute of Radiology, ^{||}Clinic of Gynaecology and Obstetrics, Niš, Serbia; University of Niš, [¶]Faculty of Medicine, Niš, Serbia; Clinical Center of Serbia, [†]Center of Anaesthesia, Belgrade, Serbia; University of Belgrade, [‡]Faculty of Medicine, Belgrade, Serbia

Abstract

Introduction. Eclampsia, serious complication of preeclampsia, can further be complicated by intracranial haemorrhage. Cesarean section under general anesthesia represents an additional risk factor. **Case report.** We present a case of 22 years old primipara in the 38th gestational week who after a sudden occurrence of a headache, within one hour developed eclampsia. Emergent Caesarean section was undertaken; she was intubated after several attempts. Severe tongue and hypopharyngeal edema and haemathoma made the extubation impossible; she remained intubated, sedated, mechanically ventilated, on anti-oedematous, anticonvulsive, antihypertensive therapy. On the third postoperative day, tracheostomy was performed. On the sixth day, she complained of a headache and visual disturbances. Neurological examination revealed left-sided hemiparesis. Multislice computed tomography showed intracranial hemorrhage. It was not until the closure of tracheostoma (eleventh day) that her blood pressure normalized and the headache ceased. Four days later she was dismissed from the hospital with improved clinical state. **Conclusion.** In order to avoid sudden and unexpected, but serious complications of preeclampsia/eclampsia, we emphasize the need of searching for more subtle signs of the disease, of prompt radiologic diagnosis and aggressive blood pressure control, with a prepared strategy for difficult airway management.

Key words:

eclampsia; intubation, intratracheal; treatment outcome; intracranial hemorrhages; iatrogenic disease.

Apstrakt

Uvod. Eklampsija, teška komplikacija preeklampsije, i sama može imati komplikacije; intrakranijalna hemoragija je jedna od najozbiljnijih. Carski rez je dodatni faktor rizika. **Prikaz bolesnika.** Prikazali smo dvadesetdvođodišnju prvorotku, u 38. nedelji trudnoće, kod koje je, nakon iznenadne pojave glavobolje, unutar jednog sata došlo do razvoja eklampsije. Urađen je hitan carski rez. Pacijentkinja je intubirana nakon više pokušaja. Zbog izraženog traumatskog edema i hematoma hipofarinksa i jezika, po završetku operacije ekstubacija je bila nemoguća; ostala je intubirana, sedirana, na mehaničkoj ventilaciji, uz antiedematoznu, antikonvulzivnu i antihipertenzivnu terapiju. Trećeg postoperativnog dana načinjena je traheostoma. Šestog dana pacijentkinja se požalila na glavobolju i smetnje vida. Utvrđena je levostrana hemipareza. Multislajnsnom kompjuterizovanom tomografijom utvrđena je intrakranijalna hemoragija. Tek po zatvaranju traheostome, jedanaestog dana, arterijski pritisak se normalizovao i glavobolja je prestala. Četiri dana kasnije otpuštena je sa Klinike u poboljšanom opštem stanju. **Zaključak.** Da bismo predupredili iznenadni nastanak teških komplikacija preeklampsije/eklampsije, potrebno je tragati za suptilnijim znacima bolesti, obaviti brzu neurološku dijagnostiku, agresivno lečiti hipertenziju i pripremiti strategiju za slučajevne otežane intubacije.

Ključne reči:

eklampsija; intubacija, endotrahejna; lečenje, ishod; krvarenje, intrakranijalno; jatrogena bolest.

Introduction

Eclampsia, defined as the presence of new-onset grand mal seizures in a women with preeclampsia, that cannot be explained by another cause^{1,2}, is one of the most serious complications of hypertensive disorders of pregnancy³⁻⁵.

It complicates 0.05–0.3% of all pregnancies⁶ and 2–3% of cases of preeclampsia, with the maternal mortality of 1.8–14%^{2,7,8}. Eclampsia itself could be complicated by several serious conditions, like ischemic and hemorrhagic stroke, with estimated maternal mortality of 10–13%⁹. It has been shown that intracerebral haemorrhage occurs in 9 of

100,000 deliveries; 25–45% of that number is associated with preeclampsia/eclampsia, due to hypertension, endothelial damage and disturbed cerebral autoregulation^{9, 10}. The delivery by Caesarean section is also associated with 2–12 times increased risk of postpartum stroke⁹, partly because of intracranial pressure elevation, due to exaggerated neuroendocrine and cardiovascular stress response to endotracheal intubation and surgical incision^{11–13}.

We presented a case of eclampsia complicated by intracranial hemorrhage and hypopharyngeal edema and hematoma, as a consequence of intubation attempts during induction to anesthesia for the urgent Caesarean section.

Case report

A 22-year old primipara was admitted to our intensive care unit (ICU) sedated, intubated, mechanically ventilated, under the diagnosis: *Graviditas m.l. IX1/2. Status eclampticus. Haemorrhagio regio hypopharyngis traumatica. Status post sectionem caesaream isthmicotransversalis sec Dörfler*. Her family members claimed that she was healthy until the day of the delivery. She regularly visited her gynaecologist and her pregnancy passed uneventfully. At the beginning of pregnancy, her blood pressure (BP), was 90/65 mmHg, at the second trimester it was 100/60 mmHg and BP of 120/80 mmHg was measured two weeks before the delivery. During the pregnancy, she gained 20 kg. This morning she complained about a headache that was not taken seriously, so she was left alone in the house. After 30 min she was found unconscious on the floor and was immediately transferred to

her hometown hospital. At the admission, she was in *status eclampticus*. Emergent Caesarean section was indicated and within 10 min she was on the operating table. BP measured at that moment was 140/100 mmHg. Because of large facial, tongue and neck edema, endotracheal intubation was extremely difficult – she was intubated after five attempts. The rest of the operation passed uneventfully. The parturient gave birth to live female child, 3,500 g /55 cm. At the end of the operation the extubation was impossible, due to hypopharyngeal edema and hemorrhage (the consequence of intubation attempts), so she remained intubated, on controlled mechanical ventilation. Her state was additionally complicated by the rise in BP to 220/130 mmHg and it was decided to transfer the patient to our Clinic.

At the admission to our ICU the patient, although sedated, reacted to painful stimuli and responded to call. Physical examination showed no pathological signs other than large facial, tongue and neck edema. Neurological and ophthalmological examinations were also normal. The laryngological examination was impossible. BP was 140/100 mmHg. After those initial examinations, we enhanced the sedation and continued with pressure controlled mechanical ventilation, FiO₂ – 0.4, that provided satisfactory oxygen saturation (94–96%). The patient was continuously monitored: BP, heart rate, oxygen saturation, capnography, temperature, diuresis. Venous blood samples were immediately taken for hematological and biochemical analyses and were repeated every day during her stay at our hospital (Table 1).

Initial laboratory results out of reference ranges were as follows: white blood cells (WBC) $19 \times 10^9/L$, [94.1% neut-

Table 1

Laboratory results during hospitalization.

Analyses	day 1	day 2	day 3	day 4	day 6	day 15
Glycaemia (mmol/L)	7.3	4.5	3.6	5.3	5.1	4.1
BUN (mmol/L)	1.5	1.9	2.5	2.5	3.4	2.4
Creatinine (μmol/L)	55.5	71.2	79.3	65.7	52.6	51.0
Urate (μmol/L)	461	420	315	126	155	135
Bilirubin total (μmol/L)	8.0	7.0	5.2	7.4	8.1	6.0
Bilirubin direct (μmol/L)	1.7	1.3	1.2	1.4	1.7	0.8
Proteinaemia (g/L)	51.7	52.0	44.2	54.4	59.3	63.0
Albuminaemia (g/L)	26.9	26.2	24.2	31.5	31.8	32.0
AST (U/L)	43.8	58.6	25.2	27.7	30.1	29.2
ALT (U/L)	15.7	24.3	15.6	14.4	14.3	13.5
LDH (U/L)	866.2	990	811	833	1012	595
Fe (μmol/L)	18.8	17.2	10.2	10.9	7.66	18.6
Na (mmol/L)	136	136	141	140	141	140
WBC ($\times 10^9/L$)	19.0	20.2	15.7	16.4	14.8	9.9
Ne (%)	94.9	89	86	87	82	73.3
RBC ($\times 10^{12}/L$)	4.39	4.08	2.65	3.57	3.99	4.18
Hb (g/L)	137	126	81	106	115	126
Ht (%)	38	36	24	33	35	37
PLT ($\times 10^9/L$)	155	184	152	167	225	228
PT (s)	12.8	13.5	12.3	12.2	12.3	12.5
INR	0.913	0.968	0.897	0.865	0.916	0.899
APTT (s)	24.2	25.1	25.9	26.6	24.7	24.9
Fibrinogen (g/L)	7.2	6.8	5.9	6.6	7.3	5.9
D-dimer (ng/mL)	3,929	3,000	2,500	2,143	1,751	870
Proteinuria	ns	ns				

BUN – blood urea nitrogen; AST – aspartate transaminase; ALT – alanine transaminase; LDH – lactate dehydrogenase; Fe – ferrum; Na – sodium; WBC – white blood cells; Ne – neutrophils; RBC – red blood cells; Hb – hemoglobin; Ht – hematocrit; PLT – platelets; PT – prothrombin time; INR – international normalized ratio; APTT – activated partial thromboplastin time; ns – non significant.

roplies (Ne)]; lactate dehydrogenase (LDH) 866 U/L; proteinemia 51.7 g/L; albuminemia 26.9 g/L; fibrinogenemia 7.2 g/L; D dimmer 3,929 ng/mL.

We immediately started: antiedematous therapy (solution of Mannitol 20% 125 mL/6 h, Dexamethasone 4 mg/8h); anticonvulsive, sedative, analgesic therapy (solution MgSO₄ 1 g/h, slow midazolam infusion if needed, remifentanyl 100–200 µg/h); antihypertensive (urapidil 25 mg boluses and 10–100 mg/h infusion; followed by captopril 12.5 mg/8 h and Nifedipine 20 mg/12 h, when peroral application became possible); antibiotic, uterotonic, anticoagulant and substitutional therapy according to laboratory results (crystalloid and amino-acid solutions, 20% albumin solution, solutions for parenteral and enteral nutrition).

During the hospitalization, BP was 130/70 to 160/110 mmHg.

After partial reduction of the oedema, on the third day of hospitalization, laryngeal examination became possible. *Haemathoma et oedema radices linguae et hypopharyngis* was diagnosed and tracheostomy was indicated and performed. After that intervention we started weaning the patient

from the ventilator, so the next morning she was conscious, oriented, breathed spontaneously. Neurologic examination showed no pathological signs. During next three days we mobilized the patient and started enteral nutrition.

On the 6th postoperative day, the patient complained of a headache and visual disturbance, but ophthalmologic examination did not reveal any pathological changes. Since the symptoms persisted, the examination was repeated the next day. The diagnosis was *Oedema papillae nervi optici bill. Papilla stagnans*. Discrete left-sided hemiparesis was found on neurological examination. Endocranial multislice computed tomography (MSCT) was indicated and showed intracranial hemorrhage (46 × 23 mm) in right parietooccipital cortical brain area (Figure 1). Digital subtraction angiography (DSA) of the right carotid artery in anterior-posterior (AP) (Figure 2a) and latero-lateral (LL) (Figure 2b) projection revealed normal angiographic findings. A neurosurgeon advised the conservative treatment. During next two days, we continued with antiedematous, sedative and antihypertensive therapy. Our patient was very cooperative, but at the same time very tense, so it was not easy to control her BP. A headache persisted. On the

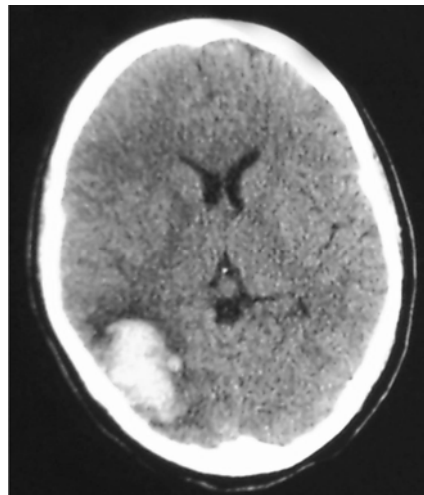


Fig. 1 – Computed tomography (CT) examination in axial cross-section showing intracerebral haematoma in the occipital lobe of the right cerebral hemisphere. Present oedema of the right cerebral hemisphere.

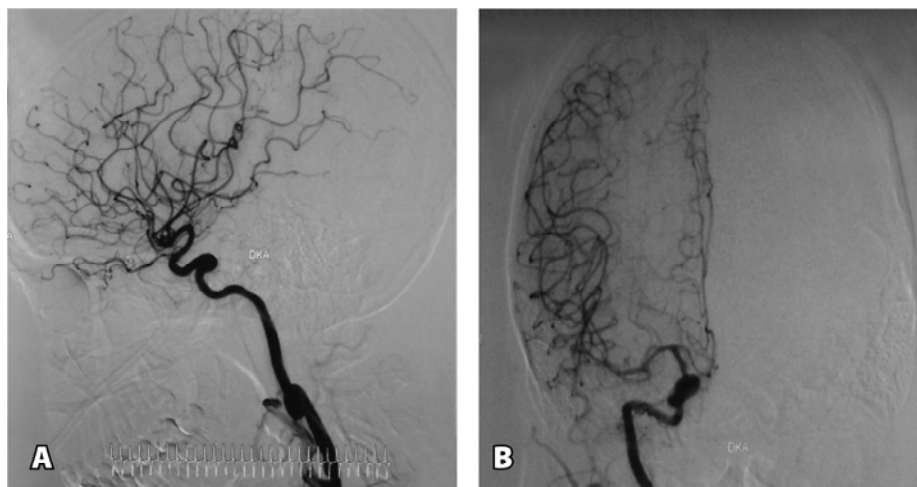


Fig. 2 – A) Digital subtraction angiography (DSA) of the right carotid artery in anterior-posterior (AP) and B) latero-lateral (LL) projection reveal normal angiographic findings.

8th postoperative day, after a termination of gynecological treatment and normalization of laboratory parameters, she was transferred to the Clinic for the Neurological Diseases. The same therapeutic regime was applied, but it was not until the closure of tracheostoma (11th postoperative day) that her BP returned to normal values and headache ceased. On the 15th postoperative day, she was dismissed from the hospital with improved clinical state but with persistent discrete left-sided hemiparesis.

Discussion

Besides the cases of eclampsia with the typical clinical course (occurring between the 20th gestational week and 48 h after delivery, and progressing from mild to severe preeclampsia, culminating in eclamptic seizures), there is growing evidence of atypical forms of the disease regarding the time of onset and clinical course^{5, 14, 15}. Hypertension is the hallmark of the disease (systolic BP more than 140 mmHg or diastolic BP more than 90 mmHg on two occasions at least 4 hours apart after 20 weeks of gestational age, or systolic BP more than 160 mmHg or diastolic BP more than 110 mmHg confirmed within a short interval^{1, 13}), but BP elevation over 160/110 mmHg was registered in only 25–54% of eclampsia cases; proteinuria was absent in 16–40% of cases; there were cases without both hypertension and proteinuria, where the diagnosis was made based on symptoms of increased capillary leak (ascites, pulmonary oedema, pleural effusions, large facial and hand edema) or disturbed hemostasis^{4, 7, 16–19}. In 2013 the American Congress of Obstetricians and Gynecologists (ACOG) Task Force Report proteinuria was excluded as necessary sign for the diagnosis of preeclampsia; the diagnosis can be made based on a presence of high BP and any of following severe features: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary oedema or cerebral/visual symptoms^{1, 13}. Persistent occipital /frontal headache, sudden BP elevation, visual disturbances, nausea, vomiting, restlessness, hyperreflexia, altered mental status, sudden development of facial and hand edema, right upper quadrant and epigastric pain are typical symptoms and signs that precede the occurrence of eclampsia, but in 20% of cases eclampsia starts suddenly, without prodromal signs^{4, 14, 17, 18, 20–22}.

According to anamnesis, our patient was always healthy; her pregnancy was controlled and passed uneventfully. The highest BP value, measured two weeks before the delivery, was 120/85 mmHg, which is below the threshold value for the diagnosis of a hypertensive disorder of pregnancy¹. The only thing that could arouse suspicion was the elevation of systolic and diastolic pressure from the baseline value measured before the 20th week of gestation of 30 and 15 mmHg respectively, which are also the criteria that could refer to a hypertensive disorder of pregnancy^{23, 24}. There was a weight gain of 20 kg, much greater than recommended in pregnancy (12 kg). It seems that we have to be aware, in our clinical practice, of the existence of those rather subtle changes and signs; searching for them could help us avoid more serious complications. In case of our patient, progression from first complain of a headache to eclampsia was indeed very fast. It is emphasized in the literature that

the rapidity of BP elevation could be of great clinical relevance. A headache, a typical prodromal symptom of eclampsia as well as a symptom of stroke, should not be neglected. Transcranial Doppler ultrasound examinations of the mild cerebral artery revealed a strong association between a headache and abnormal cerebral perfusion pressure².

In eclamptic patients, according to the treatment protocol, we immediately started antioedematous therapy (solution Mannitol, dexamethasone). For the treatment and prevention of new eclamptic seizures, we used MgSO₄, as it is the first choice medication, useful also as sedative and antihypertensive agent^{7, 14, 16, 17, 25–32}. Our main problem was BP regulation, complicated by the need for mechanical ventilation and, later, by fear, anxiety in awoken patient with tracheostomal cannula.

BP control is crucial in the treatment of eclamptic patients, not in removing the cause of the disease, but in preventing numerous complications: cardiac decompensation, pulmonary oedema, retinal ablation, ischemic or haemorrhagic stroke with subsequent neurologic and cognitive disturbances^{14, 16, 22, 27, 33, 34}. In pregnancy, during BP elevation, there is reduced vascular resistance in small cerebral vessels, that raises blood-brain barrier permeability and enables the development of oedema and seizures; this is even more pronounced in cases of generalized endothelial injury, as in preeclampsia^{14, 18, 35, 36}. This is why it is believed that in pregnancy, the acute BP elevation over 160/110 mmHg, persisting more than 15 min, represents hypertensive emergency³⁷, which demands a prompt intravenous antihypertensive treatment. Since the sudden reduction in BP could compromise fetoplacental perfusion, only 10% of BP reduction is recommended during the first hour and another 15% gradually over next 2–3 h^{8, 14, 17, 38–42}. The long-term goal should be to keep BP at 140–150/85–90 mmHg.

In our hospital we do not have first choice medications for the treatment of hypertensive disorders of pregnancy (labetalol, hydralazine, nicardipine) and since we wanted to avoid nitroglycerine because of supposed elevation of intracranial pressure after the eclamptic attack, we chose urapidil. This arteriolar and venous α_1 -receptor blocking agent reduces systemic vascular resistance and preload without reflex tachycardia and elevation of intracranial pressure^{8, 29, 42}. When our patient woke up and was able to swallow, we started using nifedipine and captopril (as all angiotensin-converting enzyme (ACE) inhibitors, it is contraindicated in pregnancy, but allowed during lactation period)^{8, 33, 43–47}. BP was not easy to control; in spite of our patient's patience and cooperation, together with sedative and analgesic support (although reduced, because of fear of respiratory depression), every manipulation (i.e. aspiration through tracheostomic cannula) led to significant BP elevation.

One explanation for the failure of antihypertensive therapy in certain patients with preeclampsia/eclampsia (that goes up to 42%), might be the existence of polymorphisms in genes that influence pharmacokinetics and pharmacodynamics of antihypertensive medications and lead to the resistance to conventional therapy. Individualized pharmacogenomic approach to the therapy could be the solution⁴⁸. The understand-

ding of underlying pathophysiological mechanisms of preeclampsia should help to identify novel therapeutic targets. For example, it is well known that placental dysfunction provokes excessive production of antiangiogenic proteins, soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, and a decrease of proangiogenic placental growth factor (PlGF). This imbalance, that leads to endothelial dysfunction, precedes the clinical manifestation of preeclampsia by weeks or even months, so measurement of serum (and urinary) concentrations of these proteins or, even more accurate, circulating sFlt-1/PlGF ratio or PlGF/soluble endoglin ratio in early pregnancy could predict the development of preeclampsia and adverse maternal and fetal outcome. sFlt-1/PlGF ratio could serve as a useful biomarker for diagnosis and differential diagnosis of preeclampsia in uncertain and atypical cases, aid the management of such pregnancies and monitor the new options for the treatment (administration of proangiogenic or removal of antiangiogenic factors)^{1,49,50}. However, because of limited clinical experience, these biomarkers are still not included in most guidelines^{1,49}.

Such clinical course raises another question: did intracranial haemorrhage occur during patient's hospitalization at our clinic, or was it a consequence of initial events? If we had done MSCT initially, at the day of the admission, we would perhaps have known the answer, but on the basis of initial examination, the neurologist did not think there was the reason to indicate radiologic imaging. Having in mind that therapeutic approach (based on clinical experience) is usually the same with and without radiologic examination (in majority of cases it turns to be posterior reversible encephalopathy syndrome with vasogenic oedema^{14,36}, we have a dilemma – should every eclamptic patient undergo MSCT or magnetic resonance imaging (MRI), or should it be reserved for atypical forms of eclampsia, or for differential diagnosis in dubious cases, where it could help choosing appropriate therapeutic regime⁴.

According to the recommendations in the literature, cerebral imaging should be performed in patients with sensory or motor deficits or prolonged coma^{14,51}. Hemiparesis and visual disturbance in our patient might have been masked by deep sedation during the period on mechanical ventilation (although neurologic examination did not reveal any pathological sign at that time). We reacted as soon as she was able to complain. The finding on MSCT posed diagnostic dilemma: was this initially haemorrhagic stroke or intracranial haemorrhage superimposed on eclampsia. Eclampsia and stroke share numerous risk factors (hypertension, coagulopathy, tobacco abuse, maternal age over 35) as well as signs and symptoms (a headache altered consciousness, seizures, focal neurologic or visual disturbances)^{2,52,53}. Having hypertension and *grand mal* seizures (preceded by a headache), our patient met the criteria for preeclampsia with severe features¹, although her laboratory results revealed only mild elevation in serum concentrations of lactate dehydrogenase (LDH) and uric acid, without proteinuria and coagulation screen disturbances (except elevated D-dimer concentration). Our patient's clinical symptoms overlap with many clinical

conditions, like idiopathic seizure disorder, cerebral venous or arterial thrombosis, cerebral vasculitis, angiomas, previously undiagnosed brain tumors, metabolic/toxic encephalopathy, thrombophilia, hemolysis, elevated liver enzyme levels, low platelet levels (HELLP) syndrome, thrombotic thrombocytopenic purpura^{1,51,52,54}. On a basis of anamnestic, laboratory and cerebral imaging findings we excluded these possibilities. On the other hand, cerebral aneurysms and arterio-venous malformations, as the most common causes of intracranial haemorrhage^{1,2,53,54}, were not confirmed in MSCT. Having in mind that eclampsia represents the most common cause of intracerebral haemorrhage in pregnancy (89% of eclampsia related strokes were hemorrhagic^{2,55}), we presume that our case was the case of eclampsia complicated by haemorrhagic stroke. Since intracranial haemorrhage is one of the most important causes of eclampsia related maternal mortality^{2,10,11,54} and that uncontrolled acute hypertension is usually the trigger of disease; we emphasize again the importance of prompt and aggressive BP control^{2,9,52,53}.

Presented case also illustrates already well known fact that pregnancy enhances the risk of difficult (1–6%) and failed (0.13–0.6%) intubation. Large airway edema, weight gain, enlarged breasts, changed Mallampati score, should always be kept in mind⁵⁶. The situation is additionally complicated by reduced tolerance to apnea – a consequence of pregnancy induced reduction in functional residual capacity on the one hand, and raised metabolic rate and oxygen consumption on the other^{56–60}. Besides that, there is exaggerated neuroendocrine stress response to endotracheal intubation and surgical incision under relatively light anesthesia during induction to delivery period of Caesarean section; BP could rise by 40–50% even in otherwise healthy patients, so it is obvious how dramatic can induction to anesthesia be in eclamptic patient^{60–63}. Unstable hemodynamic during the induction to anesthesia is one of the reasons that made Caesarean Section an independent risk factor for stroke^{10,11,64–66}. That is why it seems reasonable in vulnerable cases to pharmacologically attenuate hypertensive response to surgical stress (antihypertensives, magnesium sulphate, lidocaine, low-dose opioids) and to have protocols for situations of difficult endotracheal intubation^{13,59,62,67–74}.

Conclusion

We emphasize the need of more careful examination and search for more subtle signs and symptoms of preeclampsia in pregnant patients, in order to avoid sudden, unexpected, but serious complications. Initial radiologic examination of severe cases, especially those transferred from other hospitals, should help us make the right diagnosis and choose adequate therapeutic regime. In cases of severe preeclampsia, the need for endotracheal intubation should always be anticipated and difficulties expected, so we need to have protocols for cases of difficult intubation and to pharmacologically attenuate cardiovascular stress response in such situations.

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