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The mechanisms of seizures in eclampsia

Daniela Moura Guedes Santana

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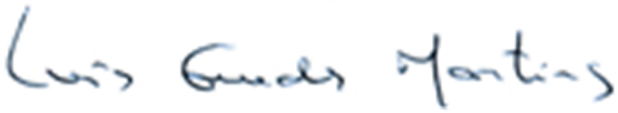

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RESUMO

A eclâmpsia é uma doença com alta morbimortalidade e impacto considerável a longo prazo na saúde das mulheres.

Pouco ainda se sabe sobre os mecanismos inerentes às convulsões eclâmpticas. Deste modo, o nosso objetivo é rever a literatura disponível sobre o assunto, expondo as teorias formuladas sobre esse tema e possibilitando a reflexão sobre possíveis estratégias terapêuticas.

Verificou-se que o comprometimento da autoregulação do FSC (fluxo sanguíneo cerebral) e a interrupção da BHE (barreira hematoencefálica) desempenham um papel essencial no desenvolvimento de convulsões na eclâmpsia. Vários fatores parecem afetar esses dois mecanismos, como a sobreexpressão de aquaporinas, libertação de citocinas pró-inflamatórias e a hipomagnesemia. Além disso, apesar de ser amplamente utilizado, o efeito do sulfato de magnésio é de facto pouco compreendido e a real contribuição da hipertensão para a patogénese da doença continua por determinar.

Várias questões ainda carecem de respostas e estudos de alta qualidade sobre este tema são escassos. É necessária uma investigação mais aprofundada para alcançar uma compreensão profunda desta doença perigosa, de modo a desenvolver estratégias terapêuticas adequadas.

Palavras-chave

Eclâmpsia; Gravidez; Convulsão; Encefalopatia; Sulfato de magnésio; Vasodilatação, Barreira hematoencefálica.

ABSTRACT

Eclampsia is a disease with high morbidity and mortality and a long-term impact on women's health.

Little is known about the mechanisms of eclamptic seizures. We aim to review the literature available on this subject, exposing the theories formulated regarding this theme and enabling reflection about possible therapeutic strategies.

CBF autoregulation impairment and BBB disruption have been found to play an essential role in development of seizures in eclampsia. Several factors seem to affect these two mechanisms, such as overexpression of aquaporins, release of pro-inflammatory cytokines and hypomagnesemia. Additionally, despite being widely used, the effect of magnesium sulfate is in fact poorly understood and real contribution of hypertension for disease pathogenesis remains to be determined.

Multiple questions remain to be answered and high quality studies on this theme are scarse. Further investigation is needed to achieve a profound understanding of this dangerous disease and to develop adequate therapeutic strategies.

KEYWORDS

Eclampsia; Pregnancy; Seizure; Encephalopathy; Magnesium sulfate; Vasodilation, Blood-brain barrier

ABBREVIATIONS

ACA – Anterior middle artery

AR – Autoregulation

BBB – Blood brain barrier

BHE – Barreira hematoencefálica

CBF – Cerebral blood flow

CH – Chronic hypertension

CVR **–** Cerebrovascular resistance

FSC – Fluxo sanguíneo cerebral

GHT – Gestational hypertension

MAP – Mean arterial pressure

MCA **–** Middle cerebral artery

MCAvmean – Mean velocity middle cerebral artery

NO **–** Nitric oxide

PCA **–** Posterior cerebral artery

PE – Preeclampsia

SiPE – Superimposed pre-eclampsia

SVR **–** Systemic vascular resistance

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INTRODUCTION

Eclampsia is a serious multisystem hypertensive disorder of pregnancy and a major cause of maternal morbidity and mortality [1-4]. In the last decades, there has been a marked increase in hypertensive disorders of pregnancy, being responsible for 10% of all maternal deaths. However, the incidence of eclampsia has been decreasing and is, in fact, a rare complication of preeclampsia [3, 4]. On the other hand, it accounts for approximately 50% of maternal mortality in poor and underdeveloped countries [4-10] due to underdiagnosis of hipertensive disorders and inadequate antenatal care [6, 7, 11]. In fact, most deaths can be prevented with timely treatment of the condition and early delivery in high-risk women [12, 13].

Eclampsia is characterized by new on-set generalized tonic-clonic seizures in a pregnant woman with preeclapmsia, with no other cause identifiable [4, 5, 7, 9, 12, 14]. It is related with encephalopathy caused by underperfusion of the brain [2, 12]. Severe headaches and other neurological impairments as cortical blindness and haemorrhagic stroke may also be present. It is considered an obstetric emergency and prompt delivery is the only definitive treatment [3, 7, 15-17]. Because a considerable percentage of patients develop this disorder in the post-partum period, these women should be under close monitoring after delivery. [6, 8] Prophylactic perfusion with magnesium sulfate is a common practice and it seems to be an efficient way to prevent major eclamptic adverse outcomes from happening. However, there is a lot of controversy about this topic in literature [2, 4, 6-9, 12]. In fact, either its preventive role, neither the mechanism of seizure in eclampsia are completely understood [5, 6, 8, 9, 12].

The pathophysiology of eclampsia is controversial and discussed since its was first diagnosed. Some pathophysiological mechanisms of pre-eclampsia are well established, such as the role of ischemia and endothelial dysfunction in end-organ disease. These changes contribute to an irreversible cardiovascular dysfunction and, therefore, for the high risk of cardiovascular disease, such as stroke, ischaemic heart disease and chronic hypertension in these women later in life [3, 4, 14, 18].

To accurately prevent eclampsia, it is imperative to understand its mechanisms. This systematic review pretends to highlight the facts already known about this clinical entity, and to collect useful knowledge and evidence in literature, that might be used to prevent this serious disorder, that still has negative impact all over the world.

METHODS

To compose this review, thorough literature searches were repeatedly conducted in PubMed and Medline with a limitation of articles written in the English language. The search terms used were Doppler, placenta, umbilical artery, fetal surveillance, and placental insufficiency. Additionally, the references of all analysed studies were searched to obtain necessary information.

EFFECT OF PREGNANCY ON CEREBRAL BLOOD FLOW

I. General considerations about Cerebral Blood Flow (CBF)

Brain is a novel organ, with a high metabolic demand, accounting for about 20% of the total body energy consumption in a normal adult at rest [19, 20]. Cerebral blood flow (CBF), defined as the blood supply to the brain at every given time is, therefore, of the outmost importance for brain viability and function [21].

CBF autoregulation (AR) allows blood flow to be constant despite considerable changes in the perfusion characteristics over time [12, 22]. In normotensive adults, CBF is maintained at a practically constant value of around 50mL/100g/min, with cerebral perfusion pressure (CPP) between 60 and 160mmHg [23]. When out of these limits, autoregulation can be completely threatened and the CBF is then totally dependent on mean arterial pressure (MAP) [24, 25].

In order to understand how CBF is shapped, Poiseuille's law must first be noticed, whose representation is in the image below (Figure 1):

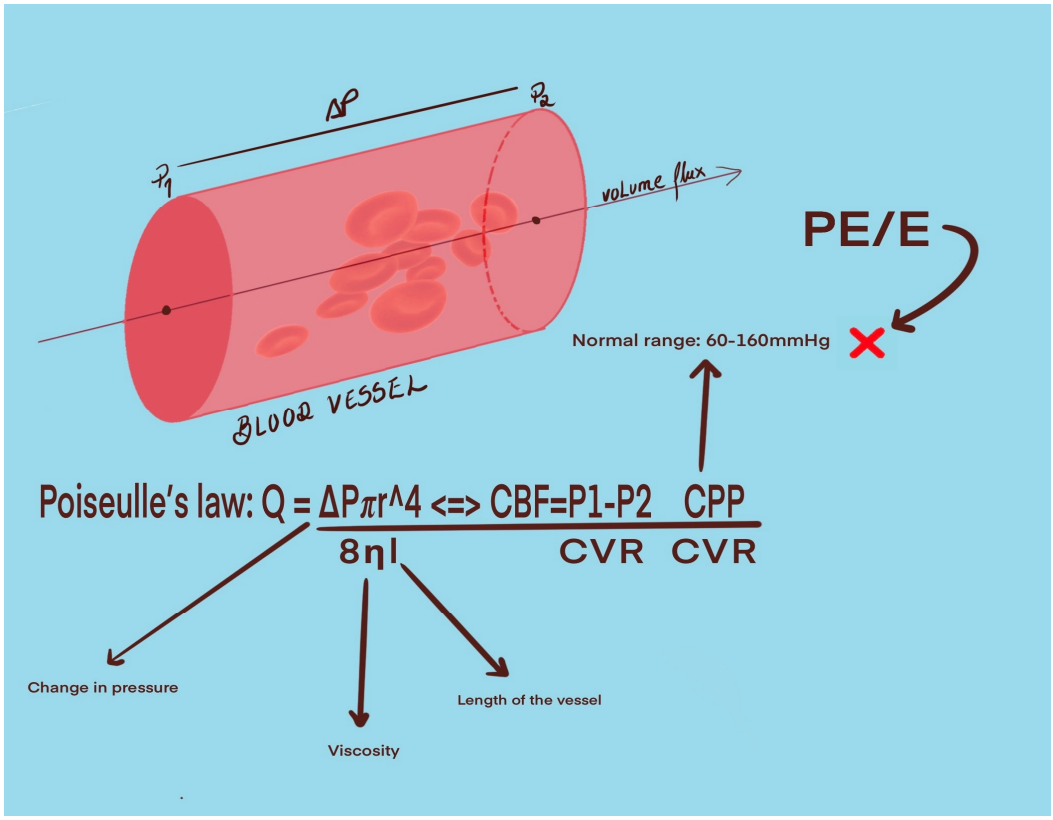

Figure 1. Poiseulle's law: adapting this law specifically to CBF, driving pressure will be cerebral perfusion pressure (CPP) and resistance represented by cerebrovascular resistance (CVR). The latter will vary according to angiogenic changes in the entire cerebral vascular system. Those who contribute most to it are small arteries and pial arterioles, which have the ability to regulate their lumen, by regulating its radius (r), through vasoconstriction or vasodilation. Finally, CPP can be defined as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP), while ICP refers to the pressure of the cerebrospinal fluid (CSF) in the subarachnoid space.

Four types of CBF regulatory responses are recognized: myogenic, metabolic, neurogenic and endothelial [20, 26].

Myogenic control regulates the smooth muscle contraction, altering vessels diameter according to blood pressure changes, a phenomenon called cerebral autoregulation (AR). Metabolic control is trigerred by chances in C02, 02 and protons: hypercapnia increases CBF due to vessel dilation whereas hypocapnia causes the opposite effect; hypoxia modulates cerebral perfusion only when below ≈50mmHg; hemodilution and anaemia, which are common during pregnancy, are known to increase CBF [20, 21]; nitrite, a product of NO metabolism, seems to have the vasodilator capacity [27]. Neurogenic control, also known as functional hyperemia or neurovascular coupling, refers to the alterations in local perfusion that occur in response to neuronal activation, throw dilation or contraction of the microvessels coupled to neurons [20, 28-30]. At last, endothelial regulation occurs in response to a number of substances produced

by the endothelial cells, which may be vasodilators (nitric oxide) or vasoconstrictors (endothelin-1) [26].

CBF can be assessed by transcranial Doppler ultrasound (TCD) giving a non-invasive global index of CBF in static and dynamic conditions. TCD measures blood velocity rather than blood flow. Blood velocity is indeed representative of blood flow when vessel diameter is constant. However, because CBF in under regulation of four different mechanisms acting independently, TCD should be interpreted with caution.

II. Global physiologic adaptations in pregnancy

Most adaptations occurring during pregnancy, aim to create a favorable environment to the development of the fetus and occur in various body systems [20]. These adaptations may affect CBF regulation during pregnancy.

Maternal blood volume increases by around 50%, increasing cardiac output [20, 29, 31] and leading to cardiac remodeling by the end of pregnancy. Despite the increased cardiac output, mean arterial pressure (MAP) decreases over the second trimester, returning to normal at the end of pregnancy [20, 31]. This MAP behavior reflects a number of cardiovascular physiologic adaptations. Changes in the proportion of vasoconstrictors and vasodilators in plasma and alterations in vascular response to them mediate structural and physical changes in blood vessels. There is a significant reduction in systemic vascular resistance (SVR) and, therefore in cerebral vascular resistance (CVR) [29], due to a reduced response to vasoconstrictor factors [20, 32], and an increased release of NO, causing general vasodilatation [20, 32, 33]. Thus, at the end of pregnancy vasoconstriction, namely in cerebral territory, will be impaired due to the remodeling that will have occurred throughout pregnancy [33]. Consequently, a deregulation of CBF may occur in the presence of an insult [26], as seen in Figure 2.

Other maternal adaptation of pregnancy influencing CBF is the higher sensitivity to CO2 caused by progesterone, decreasing the threshold of the ventilator chemoreflex response, which results in a net decrease in PaCo2 and an increase in PaO2 and eventually in an altered CBF metabolic regulation.

Finally, although an increase in circulating permeability and vasoactive factors occurs in pregnancy, the blood-brain barrier does not seem to be affected by these changes.

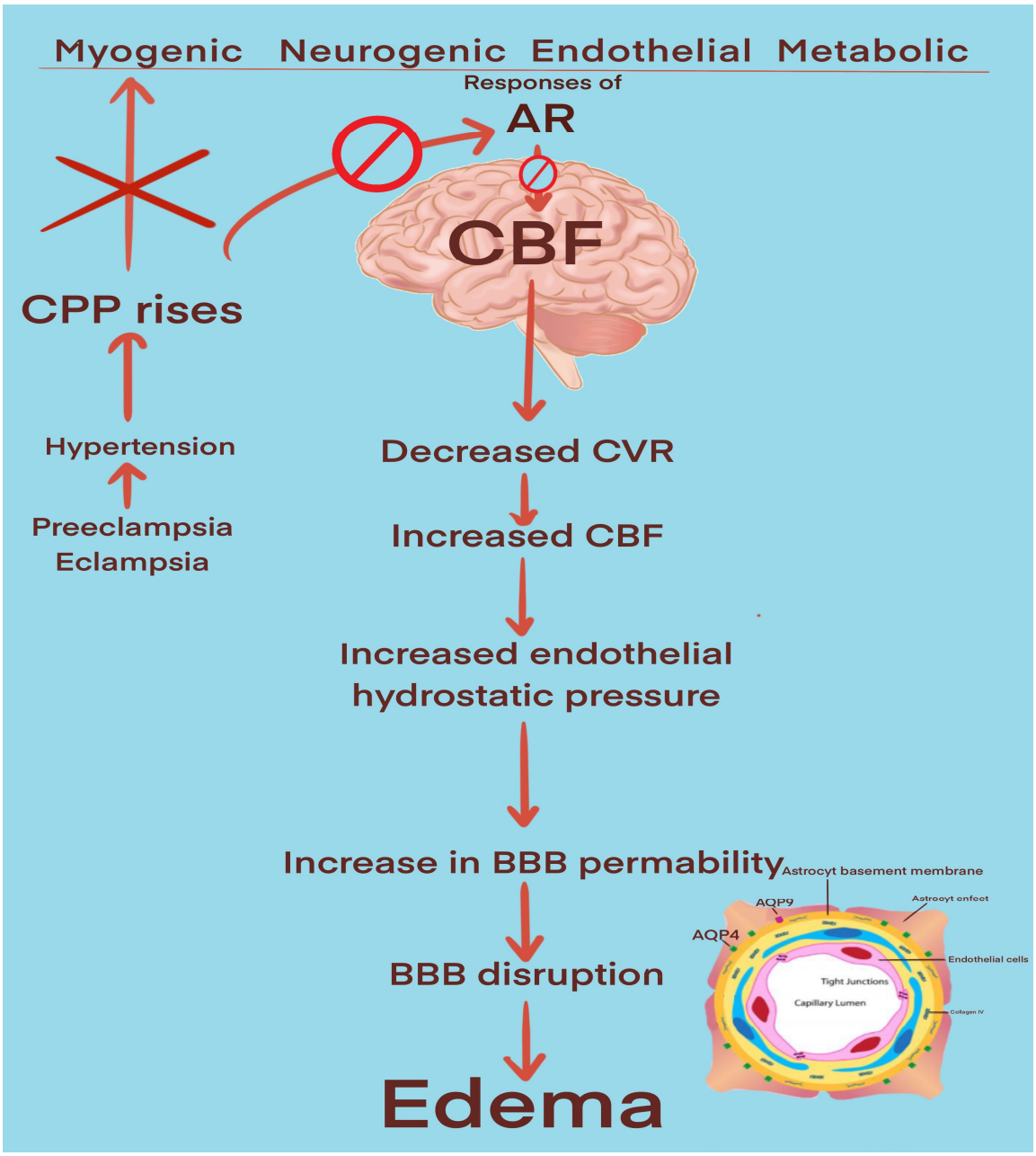

Figure 2. Consequences of loss of cerebral blood flow autoregulation

III. CBF in Pregnancy

During pregnancy, physiologic changes in cardiac output, blood pressure and blood gases influence in CBF regulation mechanisms. In normal circunstances, CBF velocity decreases, CBF volume increases and vascular resistance decreases. Those mechanisms are altered by hypertensive disorders and CBF may eventually be compromised due to loss of autoregulation capacity, although this alterations remain poorly understood [21, 26, 32].

Myogenic control is essentially triggered by changes in CO2 concentration, through a NO-mediated dilation of cerebral blood vessels.[20] Despite being one of the fastest mechanisms of CBF regulation, this reaction appears to be delayed in pregnancy, which means that vasoconstriction only occurs at higher blood pressures compared with non-pregnant women [30]. However, studies evaluating cerebral auto-regulation and cerebrovascular reactivity in CO2 in pregnancy are scarce.

Despite controversial finding regarding neurogenic control, in fact, during pregnancy, a fastest response is recorded in the 2nd and 3rd trimesters by visual stimulation. However, there are no significant differences between pregnant and non-pregnant women regarding MCAvmean [29]. In severe preeclampsia there is an increased latency of visually evoked potentials, which solves in the postpartum period [29, 30].

Some studies found that mean velocities in medial cerebral artery (MCA) and posterior cerebral artery (PCA) are significantly lower in the last two trimesters, at rest, when compared with non-pregnant women. However, while MCA velocity decreases linearly throughout pregnancy, PCA velocity returns to normal at term [20]. Different mechanisms may regulate blood flow in these two main arteries evolved in the regulation of CBF. Such differences may result in an increase in CBF in early pregnancy, with subsequent involution at term [20].

REGULATION OF CEREBRAL BLOOD FLOW IN PREECLAMPSIA AND ECLAMPSIA

The effects of pre-eclampsia and eclampsia on CBF remain a matter of debate. In fact, evidence in literature is controversial [26, 34].

I. CBF in Hypertensive Disorders: Non-pregnant state

In non-pregnant women, arterial hypertension leads to important vascular remodeling, significantly reducing vascular diameter and increasing their stiffness and thickness [35]. Such alterations aim to protect cerebral blood vessels from sudden increases in blood flow. However, cerebral vasculature auto-regulation capacity becomes impaired at lower blood pressures and ischemia may occur and on a long term basis, dementia and cognitive impairment arise.

II. CBF in Hypertensive Disorders: Pregnancy

While pregnancy itself is expected to increase CBF in consequence of systemic a local physiologic alterations, conditions such as hypertensive disorders are thought to disrupt this adaptations and contribute to a net reduction in CBF. In fact, Van Veen et al. concluded a case-control study in women with preeclampsia and found an impairment in CBF auto-regulation, reporting higher resistance index and increased CPP than in healthy pregnant women, and impaired cerebrovascular reactivity to CO2. Furthermore, these findings seem to be even deeper in women with superimposed preeclampsia [12, 36].

In non-pregnant women, vascular remodeling caused by arterial hypertension leads to significantly reduced vascular diameters. Due to maternal hemodynamic adaptations these changes occur in an opposite direction during pregnancy. When hypertensive disorders occur in pregnant state, CBF is impaired at a degree determined by type and magnitude of hypertensive disorder and pre-existence of a hypertensive state before pregnancy. In any case, brain vascularity becomes susceptible to great elevation in blood pressure [35].

In hypertensive episodes of pregnancy, there is an increase in CBF and potentially, cerebral edema. An increase in BBB permeability has also been documented, with BBB leakage and

micro-bleeds when acute hypertension occurs. Such an insult activates and recruits glial cells and a process of neuroinflammation is initiated, with long-term consequences and possibly major clinical deficits [12, 26, 30, 37-40]. These may be some of the phenomena beside eclampsia [20, 26]. However, not only hypertension and BBB disruption are responsible for cerebral edema in eclampsia, since severe cases of eclampsia have also been reported in women without significant elevation of their blood pressure [1, 3, 8, 36, 41, 42]. Several studies in animal models used to study eclampsia, found that only pregnant rats have edema when acute hypertension occurs. Thus, it appears that brain in pregnancy is prone to injuries caused by variations in blood pressure [39, 43].

An increase in sympathetic activity above expected in hypertensive diseases is well documented [44, 45]. However, its impact on hypertension in pregnancy is questionable, since sympathetic activity declines after delivery but blood pressure only registers such a decrease in hypertensive women [45].

III. CBF behaviour in different hypertensive disorders of pregnancy

Although most hypertensive diseases of pregnancy share a common pathogenic origin and are often interconnected, some important differences concerning CBF regulation arise [26, 36].

Four different scenarios of hypertensive disorders in pregnancy must be considered: chronic hypertension (CH); pre-eclampsia (PE), gestational hypertension (GHT) and superimposed pre-eclampsia (SiPE).

Evidence shows that significantly impaired CBF regulation is seen in PE, siPE and CHT when compared with healthy pregnant women, while autoregulation in GHT seems to be spared. GHT and CHT have the closest to normal index of autoregulation (AR) [42]. On the other hand, women with SiPE show the lowest AR index among all [41, 46].

Accordingly, it was shown that women with PE and SiPE, have a considerable higher CPP and CVR and a critically lower AR index than women with chronic hypertension alone [26, 41]. Therefore, GHTN and PE appear to have substantial differences regarding their pathophysiology [42].

In PE, CPP in anterior cerebral artery (ACA), MCA and PCA is increased even when adequate antihypertensive medication is administrated [35, 37, 47-50]. On the other hand, the effect of PE specifically on parenchymal arterioles, responsible for vascularization of white matter, is not

yet explicit [30]. The high perfusion pressure recorded in preeclamptic women has often been associated with symptoms such as headache and it in those suffering from eclamptic seizure [51].

Interestingly, a markedly low maternal MCA Doppler resistance in the second trimester, measured by TCD can actually be predictive of the development of pre-eclampsia. While most patients who develop the disease prematurely have increased peripheral vascular resistance from an early state, those who develop the condition later have initially low vascular resistance [42].

IV. Transient and long term consequences of CBF changes for the hypertensive mother

Cerebral blood flow changes of pregnancy quickly return to non-pregnancy state within hours after delivery [20, 26, 46]. However, these post-partum reset is altered when hypertensive disorders are present [26].

When hypertension is present, CBF deregulation can lead to BBB disruption, cerebral vasogenic edema [12, 31, 39, 46, 52, 53] and neuronal injury [20, 21]. Recent studies show that consequences of these changes may remain over time, leading to neuronal degeneration and capillary rarefaction [21]. One of the most affected areas is the occipital lobe, which frequently presents cortical/subcortical lesions [30, 48, 54]. Using brain MRI, hyperintense T2 lesions are frequently found in posterior cerebral territories, usually regressing over time, a clinical situation called reversible posterior encephalopathy syndrome (PRES), a variant of hypertensive encephalopathy [40]. These cortical areas are rarely affected in healthy pregnancies, in which there is not even the expected increase in blood flow [20].

Pre-eclamptic/eclamptic women have a higher risk of developing long-term neurological consequences. Several studies found a permanent reduced cerebrovascular reactivity in women with history of hypertensive disorders when compared to normal pregnancies [12, 37, 55]. The risk of stroke increases by about 80% [12, 29, 31, 35, 53, 56], occurring at an earlier age. An association with dementia has been difficult to achieve [57]. However, some studies recorded a significant increase in the incidence of vascular dementia and Alzheimer's disease in these women [12, 58]. Cognitive impairment [12, 37, 46, 59-62] and a white matter lesions [12, 46, 53, 62, 63] have also been found in long-term follow-up.

The reversibility of cerebral changes during hypertensive disorders of pregnancy remains an important question yet to be answered, fostered by the divergence of results found.

V. Animal models and findings

Several animal models were built in order to more easily understand these disorders. One of the most used is the reduced uterine perfusion pressure model (RUPP). This model is based on the fact that reduction in utero-placental blood flow is observed in most patients with pre-eclampsia [53, 64]. In these rats, there is an altered myogenic control, both in passive and active circunstances. While non-pregnant rats adapt its vessel diameter to blood pressure changes, in RUPP rats the diameter does not change significantly, making it impossible for the organism to defend itself from changes in blood pressure [30, 38].

Other similar studies have been conducted. For example, plasma from preeclamptic women was injected into the brain veins of late pregnant rats, with a significant increase in the permeability of the animal's blood vessels, and an attenuated vascular reactivity was enhanced [65]. Thus, myogenic control appeared to be abolished [12, 38]. Another example is the genetic mousse model knocked-out for endothelial NO synthase. Also, eclamptic seizures were induced in some animal models to study complications of eclampsia [30].

Despite the effort to create a faithful model for hypertensive disorders of pregnancy, there are no animal models that mimic all characteristic symptoms of the different conditions of hypertension during pregnancy. Diagnosis of hypertensive diseases in pregnancy is, in fact, a matter of constant discussion and definitions have been recently changed. Also, various methodologies have been used to study CBF both in animal models and humans and CBF study in animal models measures only static autoregulation, making difficult to interpret the results.

MECHANISM OF SEIZURE IN ECLAMPSIA

There is a wide variety of biological stimuli potentially causing seizures. Normal and convulsive activities are separated by a seizure threshold. Neuronal reorganizations occurring under pathological conditions lower seizure threshold (Figure 3) [66].

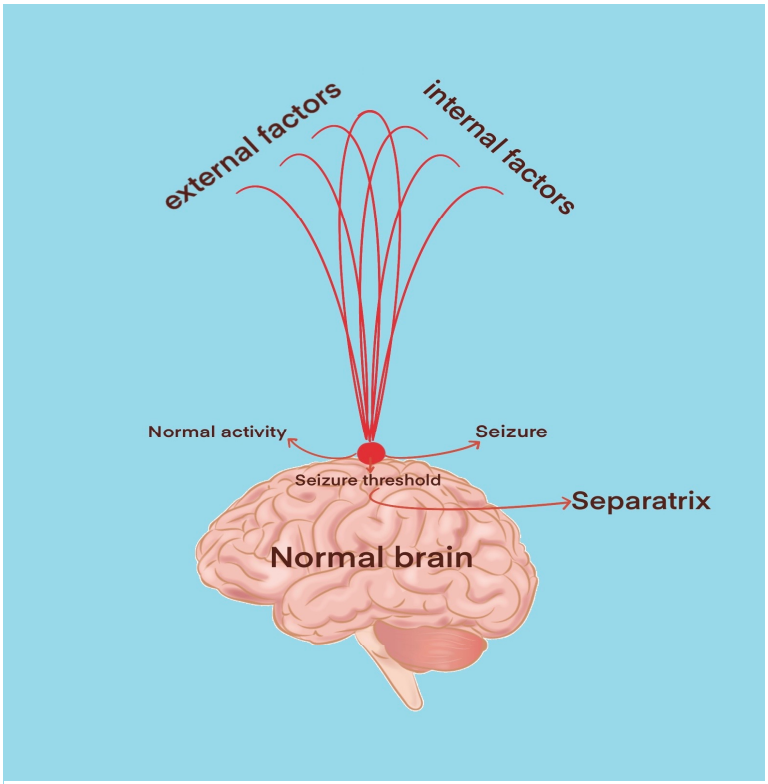

Figure 3. The impact of external and internal factors on the seizure threshold of a normal brain

A lot of theories and mechanisms of seizures in eclampsia have been studied and a variety of theories have been constructed. However, this remains a controversial theme and a lot is to be discovered.

The theories formulated to explain how seizures occur in the setting of preeclampsia, resulting in eclampsia, are presented and discussed below.

I. Blood brain barrier

Blood brain barrier (BBB) limits the passage of bigger molecules to brain cells, having a protective role [12, 20, 46]. An adequate function of parenchymal arteries (PAs) and the integrity of neurovascular coupling is crucial to keep BBB healthy. This arteries are capable of upstream vasodilation, what ensures a decrease in CVR locally [30], a phenomenon that is impaired in PE women [30].

In hypertensive sidorders of pregnancy, the release of placental factors and the inscrease of substances potencially toxic to BBB, such as circulating oxidized LDL (oxLDL) binding to its receptor, LOX-1, leads to subsequent generation of peroxynitrite causing damage to BBB [12].

II. Immunogenic/cytotoxic theory

As previously discussed, maternal immunity changes during the gestational period. This theory states that seizures in eclampsia are related to these changes [32]. Through widespread inflammation, there is an increase in the release of pro-inflammatory cytokines leading to activation of glial cells [30]. Moreover, the upregulation of endothelin-1, produced by endothelial cells [67, 68], leads to hypoperfusion [68, 69]. This insult decreases the seizure threshold [12, 32, 68]. A representation of this theory is seen in Figure 4.

PRES (posterior reversible encephalopathy syndrome) supports this theory. It has various etiologies but all share an inflammatory state [67, 68, 70]. Accordingly, the increased activity of the VEGF has a crucial role in the establishment of PE/E [12, 29, 53, 65, 68].

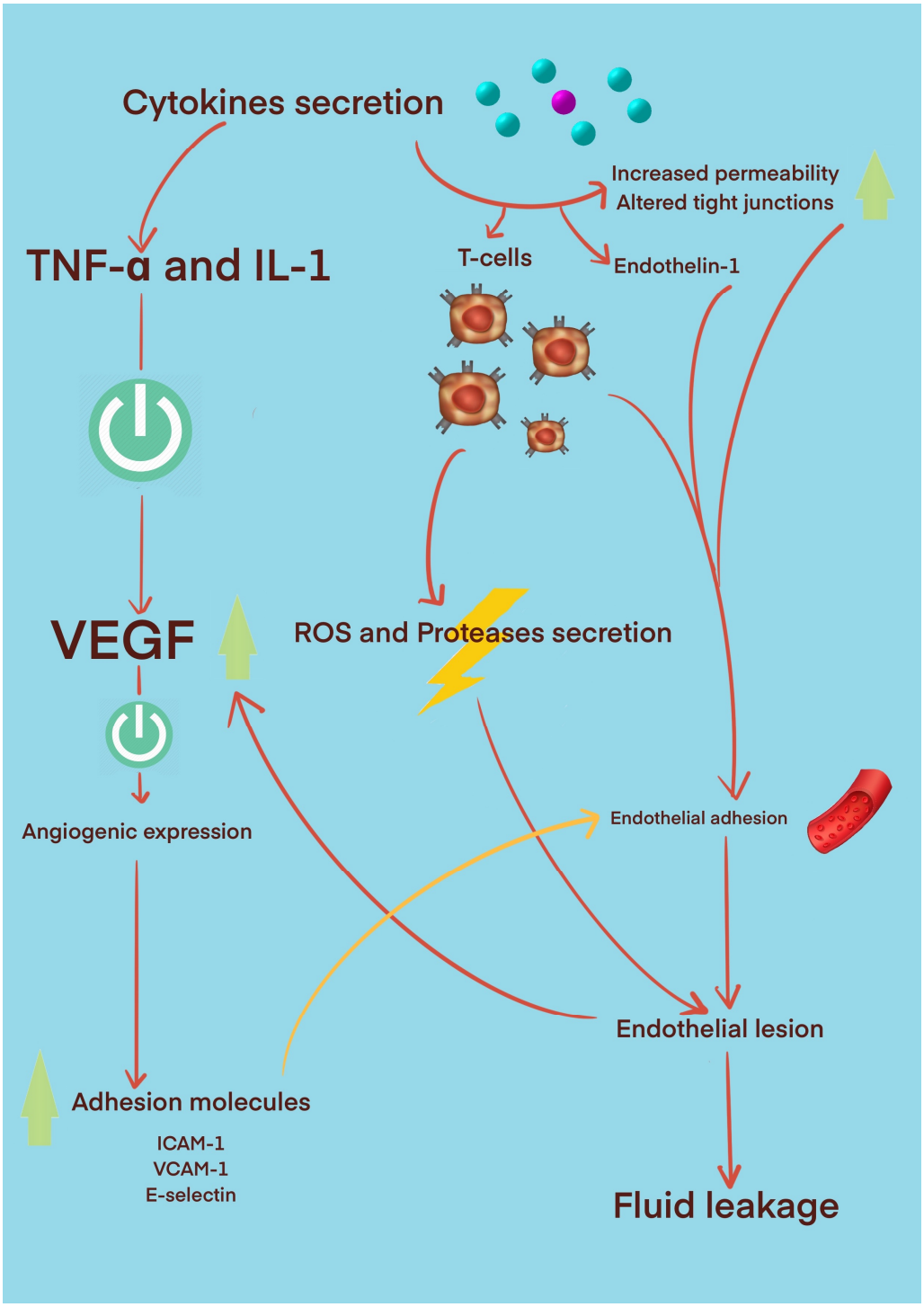

Figure 4. Cytotoxic theory visual scheme. Th cells and placental factors play an essential role in the release of pro-inflammatory cytokines.

III. The role of aquaporins in brain edema

Aquaporins 4 (AQP 4) and 9 (AQP9) are water transport channels and play an essential role in cerebral edema.

They are particularly abundant in nervous tissue. Additionally, there is an important increase in AQP4 pregnant rats [71]. This water channel has been associated with greater neuronal excitability [72, 73]. Therefore, the dysregulation of these channels contributes to seizure [74]. Magnesium sulfate reverts this process inhibitting AQP4 expression [62, 75-77]. AQP9 is permeable to other substances, such as nucleic acids, glucose, and urea, having a potencial role in seizure mechanism in pathologic metabolic conditions [73].

An upregulation of both proteins is observed in the hippocampus of women after seizure, with consequent higher microglia activation [73].

IV. PRES theories

PRES can be identified in almost 100% of women with eclampsia and in PE women with neurological symptoms [13, 43, 67, 68, 70, 77-79]. The parieto-occipital region is the most affected [39, 43, 80]. This might be related to the distribution of the sympathetic innervation in the brain. The vasoconstriction that occurs due to sympathetic stimulation is greater in the anterior areas, protecting them from injury [95].

In MRI, vasogenic edema in white matter is present, as an area of low density [80]. At T2 MRI, hyperintensity is observed in the injured sites [81]. Eventually, some patients may also have cytotoxic edema, which may suggest some degree of ischemia [82].

Most women suffer from PRES as a consequence of previous PE/E. In most cases, a preceding peak of blood pressure can be identified [79]. Nevertheless, there is still a significant number of normotensive women that develop PRES [5, 12].

The loss of CBF autoregulation leads to PRES [67, 78]. Cerebral hyperperfusion occurs, due to forced vasodilation of blood vessels. However, other areas present reactive vasoconstriction (Figure 5). Endothelial lesion leads to vasogenic edema [12, 67, 68, 70, 77, 82]. Additionally, in

posterior cortex, there is an increased expression of nNOS, making it more sensitive to hyperperfusion [39, 43].

Despite this, the theory of hypoperfusion is gaining relevance [80, 81]. It states that vasoconstriction leads to critical ischemia and, subsequently, vasogenic edema [67, 79], as we can see in Figure 5. In fact, supporting this theory, areas of hypoperfusion and vasospasm are found in the posterior regions of the brain [67, 80]. Also, there is a reduction in the caliber of cerebral arteries [12], as well as an increase in the thickness of carotid arteries [35].

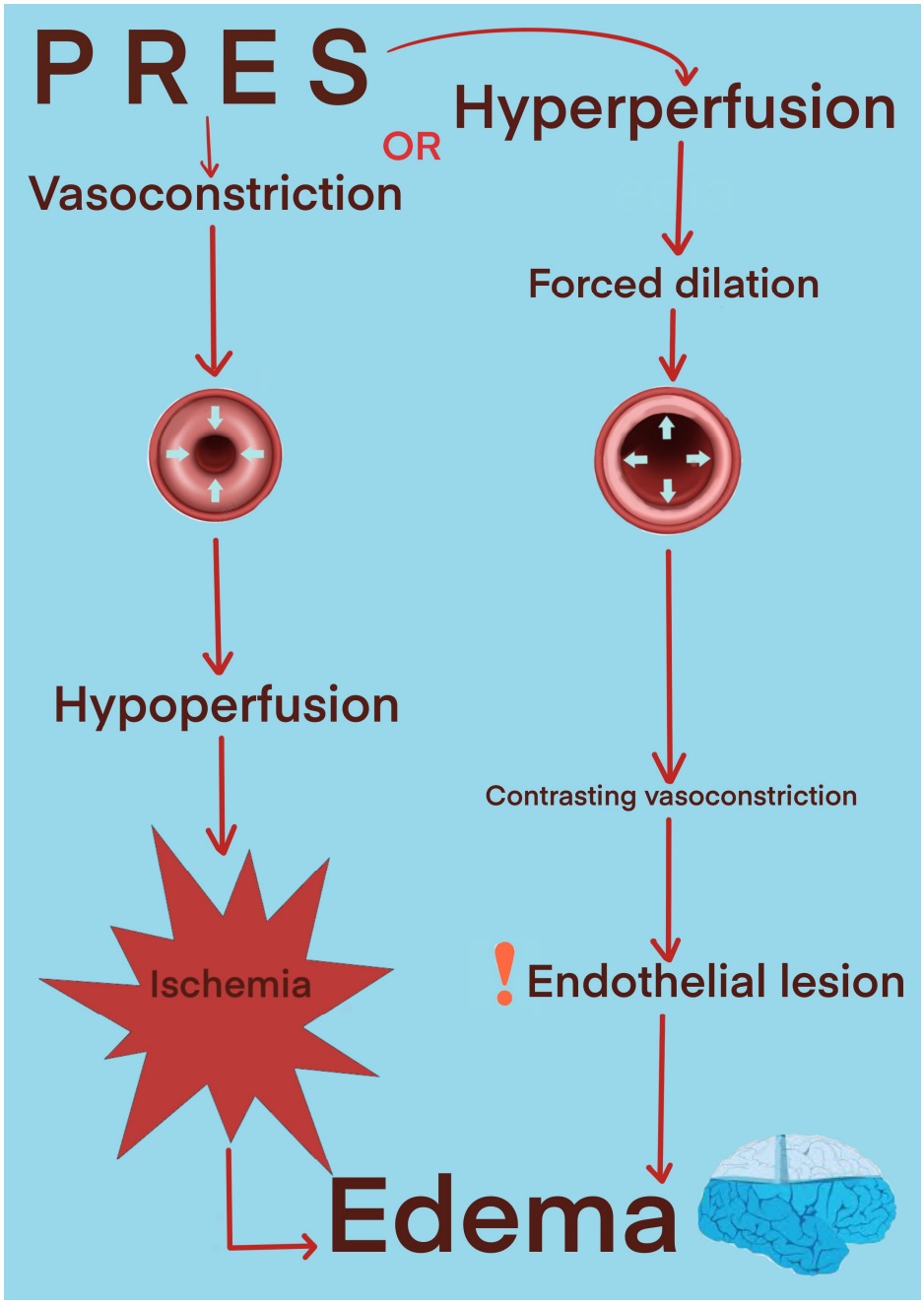

Figure 5. Hyperperfusion and Hypoperfusion theories on the development of PRES

V. Hypomagnesemia

MgSO4 (magnesium sulfate) is used worldwide in the prophylaxis and treatment of eclamptic seizures. However, little is known about its mechanism of action [62, 69, 75-77, 83, 84]. Its effect on lowering blood pressure is not very significant. Thus, further mechanisms might be involved [69].

Several studies have highlighted hypomagnesemia in PRES, regardless of its underlying etiology. In fact, PRES women have lower magnesium levels [13, 43, 67].

Magnesium can have a neuroprotective role, inhibiting the inflammatory state of pregnancy. Thus, it reduces BBB permeability [76, 77]. After its administration, pro-inflammatory mediators [62, 68, 69, 75, 76] and process of pinocytosis decrease [77]. Moreover, it reduces neuroinflammation and microglial activation, increasing seizure threshold [43, 62, 69, 76, 77, 84]. By acting as an anti-oxidant, it reduces lipid peroxidation. Therefore, it fights the increasing osmotic fragility of erythrocytes [85]. Additionally, as an NMDA-R antagonist, reduces neuronal excitability [77, 84].

It also stabilizes blood pressure through its action on vascular function [77, 83], improving uteroplacental perfusion [77, 83]. Uterine and cerebral arteries are more sensitive to its action during pregnancy [2, 12, 77]. On the other hand, it antagonizes calcium channels [62, 67, 75-77, 83, 84], reverting endothelial dysfunction [86]. Consequently, it leads to vasodilation and smooth muscle relaxation [70, 84].

By this variety of roles, magnesium sulfate as an important role in stabilizing serious preeclampsia and in prevention of seizures and for now is one of the scares therapeutic weapons in hypertensive disorders of pregnancy.

DISCUSSION

Eclampsia and its mechanisms remain poorly understood. Defined as a hypertensive disorder of pregnancy, this disease appears to have a poor association with blood pressure. Thus, many researchers now consider hypertension to be a consequence of an already installed endothelial injury. Consequently, the reason why pregnant women, with blood pressure within the normal range of cerebral autoregulation develop neurological symptoms and/or eclampsia remains unexplained.

Several theories have been formulated and deepened: loss of CBF autoregulation, BBB disruption, immune overexpression, vasospasm and hypomagnesemia. Eclampsia is possibly a multifactorial disease, to which all these mechanisms contribute. There is a variety of scientific papers on this subject. However some limitations are evident: firstly, eclampsia is an exclusive disease of humans, and most studies are carried out on rats. Thus, interpretation of results should be cautious. Concerns also arise regarding methodology. Transcranial Doppler is frequently used to study CBF, but this technique has no sensitivity to assess true CBF. On the other hand, most studies carried out in humans are prospective and this could lead to patients' misclassification. Definition of preeclampsia is controversial and many of the neurological symptoms experienced are difficult to record and some cases of severe preeclampsia might be misdiagnosed. In this way, the development of eclampsia may seem more unexpected than it actually is.

Regarding the cytotoxic theory, it is known that some placental factors may have an essential role in the release of pro-inflammatory cytokines. However, they are yet to be identified. Other theories yet to be validated are the role of impairment of glucose metabolism and hyperlipidemia.

The reason why certain regions of the hippocampus are affected and others are not is unknown. Thus, it is questioned whether different mechanisms will affect different cerebral areas.

On the other hand, other theories have been formulated. However, the impact of these emerging mechanisms remains unknown. In-depth knowledge of the previous theories did not allow absolute prevention of eclampsia. Therefore, the search for other essential factors can be the key to its prevention and treatment. Further studies should be carried out for this purpose, with adequate samples and methodology.

The questioned role of hypertension in eclampsia lead to new definitions. Thus, severe PE is now PE with severe symptoms. The main objective of such a change is evident. Its severity should never be underestimated, regardless of blood pressure values. Despite this changes, very high blood pressures (160 / 110mmHg) continue to be universally recognized as an essential risk factor.

Eclampsia is associated with poor maternofetal outcomes and long-term consequences. Therefore, it should be prevented. Seizure prophylaxis with magnesium sulfate should be considered in all women suffering from pre-eclampsia, even with no severe hypertension or symptoms. On the other hand, some concerns arise regarding its administration and adverse effects. Therefore, it is imperative to establish protocols on this subject.

Studies to understand and fill in the gaps of knowledge regarding neurological complications in pre-eclamptic patients are being done for several years now. Nevertheless, there is still a lot to conclude. A better comprehension of eclampsia outcomes could decrease both morbidity and mortality.

On women who have died of eclampsia, it has been shown that cerebral edema is a recurrent finding. Improved education and awareness of the importance of antenatal care may not only improve maternal and neonatal outcomes. It will also assist in the enhanced characterization of eclampsia.

In conclusion, eclampsia is a very unpredictable and dangerous disorder. A better characterization of its risk factors and knowledge of its pathological mechanisms should be a priority.

ETHICS COMMITTEE APPROVAL

N/A

PEER-REVIEW

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AUTHOR CONTRIBUTIONS

Concept – D.S., L.G-M.; Design – D.S., C-M., L.G-M.; Supervision – L.G-M.; Literature Review – D.S., C-M., L.G-M.; Writer – D.S., C.M., L.G-M.; Critical Review- L.G-M.

CONFLICTS OF INTEREST

We have no conflicts of interest in this review.

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