ABSTRACT

Pre-eclampsia is a multisystem disease that occurs in 2 to 8% of pregnant women and is a leading cause of maternal and perinatal morbidity and mortality. It is classically defined by new-onset hypertension and proteinuria after 20 weeks of gestation. In recent years, we have witnessed a substantial advance in the understanding of the pathogenesis of this condition. All disease subtypes are characterized by a disruption of vascular remodelling and a systemic antiangiogenic response that leads to hypertension, proteinuria, glomerular endotheliosis, HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome, and cerebral oedema—the clinical signs of pre-eclampsia and eclampsia. In the clinical practice, there is currently no reliable screening method in the first trimester of pregnancy with sufficient accuracy to identify women at high risk of developing pre-eclampsia, and only two interventions are strongly recommended by the World Health Organization for prevention of pre-eclampsia: calcium supplementation in all women with low dietary calcium intake and low-dose aspirin. Delivery is the only known cure. The treatment of pre-eclampsia and its complications is usually carried out by obstetricians but the role of nephrologists can be crucial, particularly when the condition is complicated by acute kidney injury. Several recent studies have shown an association between early-onset or severe pre-eclampsia and an increased risk of cardiovascular and/or renal disease later in life, suggesting that these women deserve a more careful monitoring programme, including clinical evaluation by nephrologists.

Keywords: Diagnosis; pre-eclampsia; pregnancy; prevention; treatment; vascular endothelial growth factor.

RESUMO

A pré-eclâmpsia é uma doença multissistémica que ocorre em 2 a 8% das gravidezes e é a principal causa de morbidade e mortalidade materna e neonatal. Classicamente é definida pelo desenvolvimento de hipertensão e proteinúria após a 20ª semana de gestação. Nos últimos anos, temos assistido a um avanço substancial na compreensão da patogénese deste distúrbio. Todos os tipos de doença caracterizam-
INTRODUCTION

Pre-eclampsia (PE) is a human pregnancy-specific disease defined by the onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman. This multisystem disorder complicates 2-8% of pregnancies in developed countries and is an important cause of maternal/perinatal morbidity and mortality. Worldwide, PE is responsible for approximately 50,000 maternal deaths annually.

In this review, the authors describe the pathogenesis, epidemiology, diagnosis, prevention and management of PE.

PATHOGENESIS

There are many theories, and disagreements, about the final event that precipitates PE. It seems that several different initial insults converge into a common pathophysiology pathway (or two common pathophysiologicals, if considering early- and late-onset PE). However, it appears clear that all subtypes of disease are characterized by a disruption of vascular remodelling and a systemic antiangiogenic response. The underlying mechanisms contributing to these changes still remain to be elucidated and might overlap.

At the beginning of a successful pregnancy, cytotrophoblast cells of fetal origin migrate through the decidua and part of the myometrium and invade maternal spiral arteries. This invasion is regulated by several factors, including the cytotrophoblast differentiation from an epithelial to endothelial phenotype (pseudovasculogenesis) and the immunological interaction between HLA molecules C, E and G and uterine natural killer cells. The maternal spiral arteries become larger vessels of low resistance and are responsible for maintaining blood flow to the developing fetus and placenta. In pre-eclamptic women, cytotrophoblast cells do not express specific adhesion molecules of the endothelial phenotype and are unable to penetrate the myometrium. The maternal spiral arteries do not turn into larger vascular channels, leading to a decrease in uteroplacental blood flow and an increase in uterine vascular resistance. The mechanical constriction of uterine arteries induces placental hypoperfusion and ischaemia. Poor trophoblast invasion of maternal spiral arteries is an early event in disease progression. However, this phenomenon is not unique to PE, since it also occurs in intrauterine growth restriction in the absence of hypertension, suggesting that it alone is unable to trigger the disease.

Placentation also requires an extensive angiogenesis to establish an appropriate vascular network to supply fetal needs. The placenta produces a wide...
and circulating levels of sEng and the development of endothelial dysfunction. Similarly, studies have found an association between the increased placental expression of sFlt-1 and soluble endothelial nitric oxide synthase (eNOS) and promotes endothelial phosphorylation of endothelial nitric oxide synthase (eNOS) and promotes endothelial receptors on the cell surface, which reduces phosphorylation of endothelial nitric oxide synthase (eNOS) and promotes endothelial dysfunction. Similarly, studies have found an association between the increased placental expression and circulating levels of sEng and the development of PE. Furthermore, Venkatesha et al. showed a positive correlation between increased levels of sEng and disease severity.

Several experimental models have explored the role of oxygen deprivation and hypoxia-reperfusion injury in the pathophysiology of PE. Some in vitro models suggest that hypoxia is not only a consequence of abnormal trophoblast invasion of maternal spiral arteries, but also a cause of it. Hypoxia-inducible factor-1α (HIF-1α) is a transcription factor that plays a key role in mediating cellular and systemic responses to hypoxia. Different methods of inducing excess HIF-1α in mice (Tal et al., and Kanasaki et al.) showed incomplete remodelling of maternal spiral arteries, fetal and placental growth restriction, hypertension, and proteinuria. By contrast, HIF-1α suppression reverses these symptoms. Burton and Jauniaux showed that pre-eclamptic placentas have multiple markers of oxidative stress, which would not be predicted by hypoxia alone, suggesting a causal role for hypoxia-reperfusion injury in PE pathogenesis. According to this theory, high-resistance maternal spiral arteries create alternating periods of hypoxia and normal oxygenation as the vessels contract and relax. An in vitro model showed that reoxygenation of hypoxic tissue results in the production of pro-inflammatory cytokines and sFlt-1.

Some articles highlight the role of a maternal immune response in the pathogenesis of PE. Several immune-associated conditions (for example, autoimmune diseases) increase the probability of a woman developing PE. Primiparity and a change of sexual partner are risk factors for PE, suggesting that the response to paternal antigens also plays a role. Some authors consider that PE arises from an exaggerated maternal vascular inflammatory response with a preponderance of Th1-type (cytotoxic) reaction. This hypothesis is supported by some studies that show an abundance of soluble markers of neutrophil activation in PE and activation of the complement system. The cytokines TNFα and interleukin 6 (IL-6) are elevated in pre-eclamptic women while the placental production of the anti-inflammatory cytokine IL-10 is decreased. Three of these cytokines have been used to create animal models that demonstrate the role of inflammation in PE. La Marca et al. and Sunderland et al. showed that TNFα-infused pregnant rats and baboons exhibit high blood pressure, increased urinary protein and elevated circulating levels of sFLT-1. Orshal and Khalil showed that IL-6 administration causes similar increases in blood pressure and proteinuria in pregnant rats, although sFLT-1 levels in these animals were not assessed. Additionally, exposure of an IL-10-knockout mouse to a hypoxic environment during pregnancy resulted in PE symptoms, whereas only fetal growth restriction occurred in wild-type mice exposed to hypoxia (Lai et al.). Inhibition of IL-10 by passive immunization (i.e., with a monoclonal antibody to IL-10) during early gestation increases blood pressure in baboons. Autoantibodies to angiotensin II type I (AT1) receptors and phospholipids have been verified in some women with PE and these might increase disease risk (Redman and Sargent and Abou-Nassar et al.). In rats, the injection of anti-AT1-receptor antibodies during pregnancy induces hypertension, proteinuria and defects in vascular remodelling. Moreover, it also increases HIF-1α expression, suggesting a potential pathophysiological link between hypoxic and immune factors (Wenzel et al.).

The kidney in pre-eclampsia

The VEGF plays a critical role in the maintenance of normal glomerular endothelial integrity and genetic glomerular VEGF deficiency has been shown to result in endotheliolysis with loss of fenestrae. The main production of VEGF within the glomerulus arises from the podocytes and, additionally, podocytes express VEGF-Receptor-1 in their membranes. The VEGF acts
as an autocrine factor on the podocyte, reducing apoptosis and promoting podocyte survival22. Circulating sFlt1, originating from the placenta, is able to bind and sequester VEGF, resulting in endothelial cell damage. Podocyte changes in PE include decreased expression and altered distribution of important podocyte proteins – synaptopodin, nephrin, GLEPP-1, podoplanin – and podocyte detachment in kidney biopsies and podocyturia. How VEGF-deficient states, such as PE, produce proteinuria is not entirely known. Nephrin is an essential component of the slit diaphragm, but it also signals within the podocyte, regulating the actin cytoskeleton and, thereby, the podocyte shape. VEGF interacts with the cytoplasmic domain of nephrin and through this binding reduces podocyte cell size, regulates the foot process structure and glomerular filter integrity23. Moreover, animals exposed to high levels of sEng had focal endotheliosis without significant proteinuria, whereas those exposed to both sEng and sFlt1 developed massive proteinuria and severe endotheliosis. The effects of sEng may be propagated through the disruption of transforming growth factor beta 1 (TGFβ) signalling with subsequent impairment of TGFβ1-mediated activation of eNOS24. Since eNOS is of prime importance in regulating vascular tone and also displays angiogenic properties, abrogation of eNOS as a result of elevated sEng levels induces endothelial cell injury and defects in vasodilation24.

**DIAGNOSIS AND RISK FACTORS**

The clinical manifestations of PE are non-specific even in severe disease. The most common symptoms are epigastric or right upper quadrant pain reported in 40-90% of patients. The diagnosis of PE depends on assessing blood pressure and proteinuria, typically by a 24-hour urine collection. The use of the urine protein to creatinine ratio is a more convenient method for the patient, however its use in pregnancy is controversial, and published studies are discordant25. The most widely accepted diagnostic criteria for PE are presented in Table I. Beyond proteinuria, the manifestations of renal damage may include acute decrease in effective renal plasma flow and glomerular filtration rate (in 30 to 40% of the patients), and podocyturia. Serum creatinine often remains normal or only slightly increased (1-1.5 mg/dL), except in severe PE, in which moderate/severe acute kidney injury (AKI) can develop. Renal tubular function is also impaired in PE, with an early dysfunction of uric acid tubular secretion. The urine sediment is usually benign. The histologic lesion associated with PE is glomerular endotheliosis26. The glomeruli are enlarged and solidified as a result of narrowed or occluded capillary lumens due to swollen native endothelial cells and, to a lesser extent, mesangial cells. Glomerular cellularity is not significantly increased and the endothelial changes are limited to the glomerular capillaries; arterioles are typically unaffected. Vascular thrombosis seen on light microscopy is unusual. In severe PE, particularly with the evolution/resolution of the lesions, mesangial interposition may be seen. Others changes, such as proeminent podocytes with protein reabsorption droplets and endocapillary foam cells, are secondary to proteinuria. Immunofluorescence may reveal the presence of fibrin deposits in glomeruli26. Some authors report low-level glomerular immunoglobulin deposition in severe PE that probably represents non-immunologic insudation23. Electron microscopy reveals endothelial cells with loss of fenestrations, cytoplasmic swelling owing to fluid and lipid accumulation and capillary occlusion. Mesangial cells may show similar changes. Podocytes show limited foot process effacement despite significant proteinuria26.

**Table I** Diagnostic criteria for pre-eclampsia

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<tr>
<th><strong>Pre-Eclampsia</strong></th>
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<td>Blood pressure: systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg, after 20 weeks of gestation in a previously normotensive woman AND</td>
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<td>Proteinuria: ≥ 300 mg in a 24-hour urine collection</td>
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<th><strong>Severe Pre-Eclampsia</strong></th>
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<tr>
<td>Blood pressure: systolic ≥ 160 mmHg or diastolic ≥ 110 mmHg, on two occasions at least 6 hours apart</td>
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<tr>
<td>Proteinuria: ≥ 5 g in a 24-hour urine collection</td>
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<td>Symptoms of target organ involvement:</td>
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<td>Cerebral and visual disturbances</td>
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<td>Pulmonary oedema</td>
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<td>Epigastric or right upper quadrant pain</td>
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<td>Impaired liver function</td>
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<td>Thrombocytopenia</td>
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<td>Acute kidney injury</td>
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Susana Machado, Marta Neves, Luís Freitas, Mário Campos
involvement. PE can also be classified into early-onset and late-onset and these subtypes may represent different forms of the disease. Early-onset PE (before the 34th week of gestation) is often associated with abnormal uterine and umbilical artery Doppler ultrasound waveforms, fetal growth restriction and adverse maternal and perinatal outcomes. Late-onset PE (after the 34th week of gestation) seems to be strongly associated with maternal features (for example, body mass index), normal or slightly increased uterine artery resistance index and minimal fetal involvement.

Several factors have been proven to increase the risk of PE, such as: age (pregnant women older than 40 years); maternal obstetric factors (nulliparity, multiple gestation pregnancy, previous PE and molar pregnancy); paternal obstetric factors (father born from a pre-eclamptic pregnancy); maternal comorbid conditions (chronic hypertension, renal disease, pregestational diabetes mellitus, obesity and rheumatic disease); maternal genetic factors (antiphospholipid antibody, factor V Leiden mutation and PE in a first-degree relative’s pregnancy).

**PREDICTIVE MODELS AND PREVENTIVE INTERVENTIONS**

Screening for PE attempts to identify high-risk pregnancies in an effort to modify antenatal care and institute preventive measures in order to reduce maternal and fetal complications. In the clinical practice, there is currently no reliable screening method in the first trimester of pregnancy with sufficient accuracy to identify women at a high risk of developing PE. Guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend routine screening for specific risk factors for PE (nulliparity, older age, high body mass index, family history of PE, underlying renal disease or chronic hypertension, multiple pregnancy, more than 10 years between pregnancies, and a personal history of PE). The expected rate of PE when any one of these risk factors is present ranges from 3% to more than 30% and, in prospective studies of general obstetric populations, the reported performance of a limited number of clinical risk factors to predict PE is modest. A prospective and multicentre cohort of “healthy” nulliparous women, the SCOPE (Screening for Pregnancy Endpoints) study, developed a multivariable predictive model for PE based on clinical risk factors present in early pregnancy in combination with ultrasound estimates of uteroplacental perfusion and fetal measurements at 19-21 weeks’ gestation. The proposed algorithm performed better than the NICE guidelines, predicting 34% of cases of PE and 53% of cases of preterm PE. Poon et al. recently published a prediction algorithm at 11-13 weeks of gestation that combine maternal characteristics, uterine artery pulsatility index, mean arterial blood pressure, median serum pregnancy-associated plasma protein-A and PI GF values. The detection rates of early-PE and late-PE were 95.3% and 45.6%, respectively. A systematic review studied the current literature on the predictive potential of first-trimester serum markers (ADAM12, fβ-hCG, Inhibin A, Activin A, PP13, PI GF, and PAPP-A) and of uterine artery Doppler velocity waveform assessment. Low levels of PP13, PI GF, and PAPP-A and elevated level of Inhibin A were found to be significantly associated with the development of PE later in pregnancy. The detection rates of single markers in the prediction of early-onset PE were relatively low, and ranged from 22% to 83%. Detection rates for combinations of multiple markers varied between 38% and 100% and show promise in identifying patients at high risk for PE development. Large scale prospective studies are, however, required to evaluate the power of this integrated approach in the clinical practice.

The general term prevention can have three different connotations: primary, secondary, or tertiary. Primary prevention of PE involves avoiding pregnancy in women at high risk, lifestyle modification or improving nutrient intake in the entire population. Secondary prevention, in the context of PE, implies breaking off the disease process before clinically recognizable disease emerges. Tertiary prevention relies on the use of treatment to avoid PE complications. A number of trials, reviews, and protocols evaluating strategies for the prevention of PE are available in the scientific literature. Despite the variety of possible prophylactic interventions described, studies have produced disappointing results. Interventions such as rest, exercise, reduced salt intake, garlic, marine oil, daily supplementation with magnesium, vitamin C, D or E, diuretics, progesterone and nitric oxide showed insufficient evidence to modify the outcomes of PE. Two interventions are strongly
recommended by the World Health Organization (WHO) for prevention of PE: (1) Calcium supplementation at doses of 1.5 – 2.0 g of elemental calcium/day in all women, but especially those at high risk of developing PE, if dietary calcium intake is low (< 600 mg/day); (2) Low-dose aspirin (75 mg/day) in women at high risk of developing this condition.

**TREATMENT**

The treatment of PE depends essentially on illness severity, gestational age and fetal wellbeing. Delivery is the best treatment for PE, but an expectant approach is also recognized in specific situations. Worsening maternal condition (such as AKI), eclampsia or signs of fetal compromise, are considered indications for prompt delivery regardless of gestational age. Figure 1 represents a proposed algorithm for PE management.

The role of the nephrologist is crucial in the treatment of AKI related to PE. Administration of intravenous fluids should be started as soon as possible, not only to restore or maintain renal perfusion, but also to prevent hypovolemia and ensure an adequate uteroplacental perfusion and fetal wellbeing. However, fluid balance should be monitored closely to avoid overload, since women with severe disease are at risk of pulmonary oedema and significant third-spacing. Maintenance fluids at a perfusion rate of 80 mL/hour are often adequate.

Antihypertensive drugs should be used for emergency treatment of severe hypertension (systolic

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**Figure 1**

Proposed algorithm for the management of pre-eclampsia.

**AKI** – acute kidney injury; **BP** – blood pressure; **HELLP** – haemolysis, elevated liver enzymes and low platelet count; **MgSO4** – magnesium sulphate.
blood pressure (SBP) > 160 mmHg and/or diastolic blood pressure (DBP) > 110 mmHg). The goal of antihypertensive treatment is to maintain SBP between 140 mmHg and 155 mmHg, and DBP between 90 and 105 mmHg. Some of the antihypertensive drugs commonly used in the general population (angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists) are contraindicated in pregnancy. Diuretics are not recommended because of the high risk for volume depletion and are only indicated for treatment of pulmonary oedema. There are some controversies regarding the best drug for the treatment of hypertension during pregnancy. The most commonly used drugs are methyldopa, β-blockers and dihydropyridine calcium channel blockers (such as nifedipine). Methyldopa is regarded as a first-line drug for the maintenance treatment of hypertension in pregnancy, because it is safe, effective and the subject of many studies. It is an α-agonist agent that decreases central vascular resistance without decreasing cardiac output. Dosing is started at 750 mg/day, with a maximum dose of 3 g/day. Intravenous hydralazine and labetalol are recommended for the treatment of hypertensive emergencies. However, some authors associate the use of hydralazine with a higher risk of persistent hypertension, hypotension, caesarean delivery, oliguria, abruptio placentae, abnormal fetal heart rate, and low Apgar scores. These authors consider that the results are not robust enough to guide clinical practice but do not support the use of hydralazine as a first-line drug for the treatment of hypertensive crises in pregnancy.

Other complications of AKI can arise in PE, particularly hyperkalemia, metabolic acidosis and anaemia. The administration of insulin, glucose and ion exchange resin are recommended for the treatment of hyperkalemia. There are no published data regarding the use of resin in pregnant women, but this drug has a local action within the gastrointestinal tract, therefore, there is no reason for a fetal deleterious effect. In the healthy pregnant woman, a 4 mEq/L decrease in bicarbonate concentration is common. This fact has to be taken into account when correcting metabolic acidosis with sodium bicarbonate. Regarding anaemia associated with AKI, blood transfusion is recommended in acute therapy. The erythropoiesis-stimulating agents are safe in pregnancy, but higher doses are usually required to obtain the desired therapeutic effect.

The indications for dialysis are the same as for the general population with severe AKI: uraemic symptoms (encephalopathy, pericarditis or neuropathy), volume overload, hyperkalemia and/or metabolic acidosis unresponsive to initial medical treatment. Notwithstanding, many authors recommend starting dialysis earlier, when GFR falls to below 20 ml/min per 1.73 m². Despite the absence of randomized trials showing benefits of a specific dialysis modality, in most cases the choice falls on intermittent haemodialysis. Some aspects must be considered when prescribing dialysis in pregnant women. Increasing the dialysis dose leads to an increase in fetal survival and decrease in prematurity. A daily dialysis program (more than 20 hours/week) should thus be established in order to: (a) improve the uraemic environment, a high risk factor for prematurity and polyhydramnios, and (b) minimize haemodynamic fluctuations during haemodialysis that adversely affect uteroplacental perfusion and increase the risk of placental oxidative stress. When establishing a dry weight, it is important not to forget the normal weight gain (0.3-0.5 kg/week) in the second and third trimesters. Some dialysate parameters should be tailored in pregnant women, such as bicarbonate to 25 mEq/L and sodium to 135 mEq/L. Heparin and low-molecular-weight heparin are safe in pregnancy since they do not cross the placental barrier. Both can be used during haemodialysis treatment.

### MATERNAL AND PERINATAL OUTCOMES

The maternal and perinatal outcomes in PE depend on gestational age at onset, disease severity, maternal comorbid conditions and type of care provided to the pregnant woman. In mild PE, the prognosis is usually favourable, whereas severe PE is associated with maternal and neonatal complications.

The major fetal complication is growth restriction, reported in 10 to 25% of cases of severe PE. Hypoxaemic neurologic damage (< 1%) or perinatal death (1.2%) can seldomly occur.

Severe PE may trigger early and late complications in pregnant women. The most frequent immediate maternal complications are disseminated coagulopathy/
haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome (10%-20%), pulmonary oedema (2%-5%), AKI (1%-5%) and abruptio placenta (1%-4%)\(^3\). After delivery, the hypertension and proteinuria of PE disappears within a few days to weeks. Exceptionally, proteinuria may still be detected until 6 months after delivery. A renal biopsy should be performed if proteinuria persists for more than 6 months and whenever it is accompanied by an active urine sediment and/or rapidly deteriorating renal function.

Long-term epidemiologic studies point to an increased risk of cardiovascular diseases (chronic hypertension, ischaemic heart disease, stroke and venous thromboembolism) in women who developed PE, especially those with early-onset or recurrent PE\(^1,2,27\). In two large studies conducted by Mongraw-Chaffin et al.\(^22\) and Fraser et al.\(^23\), these women had an eight- to nine-fold increased risk of death from cardiovascular events compared with women without history of PE. Several studies have shown that women with a history of early-onset/ severe PE exhibit impaired endothelial function, vaso-dilation, higher levels of fasting glucose, insulin and dyslipidaemia many years after pregnancy\(^27,22,23\). This late cardiovascular morbidity may reflect an underlying predisposition in the women for both disorders and/or permanent arterial damage caused by mechanisms behind PE. Some authors advocate that increases insulin resistance, sympathetic and pro-inflammatory overactivity, endothelial dysfunction, and the abnormal lipid profile in PE constitute an early manifestation of the metabolic syndrome, thereby putting affected women at an increased risk for cardiovascular disease\(^4,44\).

Pre-eclamptic women may be at increased risk of developing end-stage renal disease (ESRD) later in life\(^4,45\). This data is supported by a Norwegian study that demonstrated a four-fold increase in risk of ESRD compared with women without PE\(^46\).

In conclusion, despite being known as a pregnancy-specific disease, recent data show that pre-eclampsia can determine the prognosis of these women, increasing the risk of cardiovascular disease and end-stage renal disease. Consequently, pre-eclamptic women deserve a monitoring programme beyond 6 months after childbirth, which may benefit from the collaboration of nephrologists.

**Conflict of interest statement.** None declared.

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