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REVIEW

Inflammation, Gestational Hypertension, and Preeclampsia – a Dangerous Association

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ABSTRACT

Gestational hypertension and preeclampsia complicate 2–8% of pregnancies, with a great impact on the fetuses, as well as on maternal well-being. Preeclampsia is considered a major cardiovascular emergency due to its potential to evolve to severe eclampsia, a devastating life-threatening condition. Worldwide, preeclampsia is considered to be one of the major factors that lead to maternal and fetal death. On average, hypertensive disorders are responsible for approximately 16% of maternal deaths, and every year, preeclampsia is estimated to cause more than 500,000 deaths of the fetus and 70,000 maternal deaths all over the world. While different studies published so far have not succeeded in identifying the exact mechanisms that cause preeclampsia, ischemic vascular phenomena, immunological disorders, and inflammation have been reported as important factors involved in its pathogenesis. The current review aims to provide updated, relevant literature data regarding the potential link between elevated inflammatory status and preeclampsia, at the same time underlining the role of emerging imaging techniques for the early detection of preeclamptic risk.

Keywords: preeclampsia, gestational hypertension, maternal and fetal mortality, inflammation, pregnancy-related cardiovascular emergency

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INTRODUCTION

Gestational hypertension and preeclampsia complicate 2–8% of pregnancies, with a great impact on the fetuses as well as on maternal well-being.[1] Preeclampsia is considered a major cardiovascular emergency due to its potential to evolve to severe eclampsia, a devastating life-threatening condition. These disorders usually appear de novo after 20 weeks of gestation and represent one of the major factors that result in maternal and perinatal mortality worldwide. On average, hypertensive disorders are responsible for approximately 16% of maternal deaths, and every year, preeclampsia is estimated to cause more than 500,000 deaths of the fetus and 70,000 maternal deaths around the world.[2]

Gestational hypertension was first described by Hippocrates, who reported that headache followed by convulsions and heaviness determined an unhealthy pregnancy.[3] This condition is characterized by hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) appearing de novo after 20 weeks of pregnancy, without proteinuria. Hematological and biochemical ab-

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normalities are also absent. It is approximated that in a quarter of cases, gestational hypertension will progress to preeclampsia, usually without fetal growth restriction.[4]

Preeclampsia is a pregnancy disorder characterized by new-onset hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure > 90 mmHg occurring at least twice within 4 hours, in a woman who presented normal blood pressure before pregnancy) after 20 weeks of gestation, usually with new-onset proteinuria (>300 mg/24 h) and other symptoms. In the absence of proteinuria, preeclampsia can include: thrombocytopenia (platelets reduced by >100,000), reduced liver function (liver transaminases double than normal), renal insufficiency (serum creatinine >1.1 mg/dL or twice the normal value), new-onset headache neutral to treatment, or pulmonary edema.[5]

Preeclampsia has been categorized according to fetal age at the time of diagnosis as early-onset (<34 weeks) and late-onset preeclampsia (≥34 weeks). Early-onset preeclampsia is related to faulty placentation, while late-onset preeclampsia seems to be related to the discrepancy between fetoplacental demands and maternal perfusion, together with a tendency of the mother for developing cardiovascular disease.[6]

The risk factors for preeclampsia are well-known and include: nulliparity, a previous pregnancy complicated with preeclampsia, history of chronic hypertension, multiple gestation, advanced maternal age (35 years or older), gestational diabetes, systemic lupus erythematous, thrombophilia, a body mass index before pregnancy >30, kidney disease, assisted reproductive technology, antiphospholipid antibody syndrome, or obstructive sleep apnea.[1] Other reported risk factors are: maternal infections such as urinary tract infection and periodontal disease, fetal diseases such as Ballantyne or mirror syndrome, twin-to-twin transfusion syndrome, or selective fetal growth restriction. A 5-fold increased risk of preeclampsia was shown to occur when a low vitamin D concentration is present in early pregnancy. Recently, SARS-CoV-2 infection during the COVID-19 pandemic has been incriminated as one of the serious risk factors for preeclampsia.[6]

INFLAMMATORY CHANGES IN PREECLAMPSIA

Preeclampsia is a dangerous hypertensive disorder associated with chronic inflammation and production of autoantibodies. It involves proteinuria, inflammation, endothelial dysfunction, thrombosis, and placental defects.[7] The main cause of preeclampsia is unknown. One hypothesis states that it is caused by placental ischemia as a result of shallow trophoblast invasion. Studies show the presence of an immune imbalance, with an increase in the number of pro-inflammatory CD4+ T cells and a decrease in the number of regulatory T cells (Tregs). As a consequence, chronic inflammation occurs, characterized by the presence of pro-inflammatory cytokines, autoantibodies, and oxidative stress.[8]

A recent hypothesis unifies these two concepts: the abnormal immune response and the ischemic vascular origin. According to this hypothesis, a modified immune response during pregnancy determines the abnormal early functioning of the placenta, with extensively damaged endothelial integrity because of syncytiotrophoblast ischemia.[9]

Studies suggest that a disturbance in the activity of the phagocytic system may be involved in the immune response of preeclamptic pregnancy.[10] The syncytiotrophoblast plays a critical role in the process, and the severity of preeclamptic pregnancy is reflected by the quantitative and qualitative profiles of circulating monocytes.[11]

Several pro-inflammatory cytokines (TNF-α, IL-6, and IL-8) are of major importance in normal pregnancy, while their presence is exaggerated in preeclampsia. The inhibition of anti-inflammatory cytokines also has a major role in preeclampsia.[12,13] Other factors involved in the development of preeclampsia include the cytotrophoblast-secreting interleukins 1β, 2, 4, 6, 8, 10, 12, and 18, tumor necrosis factor (TNF-α), intercellular adhesion molecule (ICAM) 1, interferon γ (IFN-γ), transforming growth factor β1 (TGFβ1), monocyte chemoattractant protein-1 (MCP-1), and vascular cell adhesion molecule (VCAM).[11] Cholesterol and uric acid may also augment the inflammatory response in the syncytiotrophoblast.[14]

It has been proven that in preeclampsia, pro-inflammatory cytokines are released into the circulation, and both monocytes and granulocytes are activated.[15] Increased cytokine levels may stimulate nicotinamide adenine dinucleotide phosphate oxidase activation, which determines an increase in superoxide generation, leading to increased oxidative stress in preeclamptic women.[16] Oxidative stress also seems to play a role in the inflammatory response in preeclampsia. This causes a disparity between reactive oxygen species and the antioxidant defense system and tissular response. Reactive oxygen species have a major contribution to the pathogenesis of preeclampsia, as they lead to the appearance of pro-inflammatory chemokines, cytokines, and cellular debris from apoptotic changes in the syncytiotrophoblast.[11] Reactive oxygen species lead to increased endothelin-1 expression and B cell production of autoantibodies against the angiotensin II (AngII) type

1 receptor (AT1-AA). This has a significant importance in triggering preeclampsia due to an immune imbalance, which creates an uncontrolled state of inflammation.[17] AT1-AAs activate the angiotensin II type 1 receptor, producing a biological response which leads to preeclampsia.[18] Lamarca *et al.* found that IL-6 infusion stimulates AT1-AA production, while the activation of AT1 receptors mediates hypertension in pregnancy.[19]

Generalized systemic inflammation is common in all pregnancies.[20] Redman *et al.* suggest that preeclampsia is not significantly different from normal pregnancies, being located at the extreme end of a continuous spectrum of inflammatory responses.[21] Germain *et al.* showed that during the first trimester of a normal pregnancy, monocytes were set to produce more IL-12p70 and TNF-α, while in pregnancies complicated with preeclampsia, more IL-18 was produced.[22] Mihu *et al.* showed that while in a normal pregnancy, serum CRP levels >1,000 ng/mL are normal, serum CRP values >3,000 ng/mL are distinctive for preeclampsia. They concluded that there is a marked systemic inflammatory reaction in preeclampsia, which may have consequences upon fetal status at birth, but inflammatory variables cannot be used to assess the severity of preeclampsia.[23] Greer *et al.* reported that preeclampsia is associated with increased plasma concentration of IL-6, but normal concentration of IL-8.[24] Olusi *et al.* reported significantly lower IL-6 and IL-8 levels in preeclampsia compared to normal pregnancy.[25]

Recent research tried to find a feasible screening tool for predicting preeclampsia, but relevant biomarkers during the first trimester have not yet been identified. Studies have shown that in the second and third trimesters, the measurement of angiogenic factors may present a high predictive accuracy for the evolution of preeclampsia and its assumed adverse outcomes. Low-dose aspirin administration in the first 16 weeks of gestation has been proven to decrease the incidence of early-onset preeclampsia by more than 60%.[26]

ENDOTHELIAL DYSFUNCTION, CARDIOVASCULAR RISK, AND PREECLAMPSIA

Normal pregnancy involves cardiovascular and hemodynamic transformations in the mother. Their role is to provide the nutrient and oxygen demands for the fetus through systemic vasodilatation, enlarged blood volume, enlarged cardiac output, decreased vascular resistance, and a slight decrease in blood pressure. These hemodynamic and vascular changes have several endothelial consequences, including redistribution of blood flow in different maternal organs and tissues, and the decrease of endothelium-derived vasodilators.[27]

The endothelial dysfunction of the mother can be caused by certain components of the placenta and is involved in the pathophysiology of preeclampsia. The first step in the pathogenesis of preeclampsia is abnormal placentation during the cytotrophoblast invasion of the spiral arteries. Endothelial dysfunction has an important role in preeclampsia.[28] Reduced placental perfusion leads to impaired remodeling of decidual vessels, which releases placental factors into the maternal circulation.[29]

Regarding patients with SARS-CoV-2 infection, the endothelial dysfunction caused by this acute inflammation may be connected to preeclampsia. Moreover, a recent study has proven that women with severe COVID-19 have a 5-fold greater risk to develop preeclampsia compared to those with asymptomatic COVID-19.[30]

The soluble FMS-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) have been shown to have a major significance in endothelial dysfunction that accompanies preeclampsia.[31] The sFlt-1 receptor is an antiangiogenic, free-circulating splice variant of the vascular endothelial growth factor receptor 1. The antiangiogenic sFlt-1 and the angiogenic PlGF are balanced in normal pregnancies and out of balance in preeclampsia, with decreased PlGF and increased sFlt-1.[32] In their study, Maynard *et al.* found that women presenting with preeclampsia had increased serum levels of placental sFlt-1, and they were able to induce preeclampsia-like symptoms in pregnant rats that were administered sFlt-1.[29] In another study, the excess production of sFlt-1 was involved in complete hydatidiform mole in women with preeclampsia, and sFlt-1 concentrations were 2- to 3-fold higher in patients with hydatidiform mole.[30] Another recent study reported that sFlt-1 decreased to less than 1% of its level before birth, but sFlt-1 levels and the sFlt-1/PlGF ratio were still higher at 1 and 5–8 years postpartum in women with preeclampsia.[29]

The increased production of agonistic autoantibodies against the angiotensin II type I receptor by mature B cells is also significant for preeclampsia. Vasoconstriction is increased by stimulation of the AT1 receptor by the autoantibodies of angiotensin II type I receptors.[33]

Excessive inflammation is considered a powerful mediator of maternal endothelial dysfunction, and increased triggering of NF-kB, an important regulator of the immune response, was discovered in women with preeclampsia. The arbitrators of endothelial triggering and dysfunction include tumor necrosis factor alpha (TNF-α) and IL-1.[34]

Maternal heart transformation in preeclampsia includes eccentric ventricular remodeling, improved metabolism, and enhanced function. Women with preeclampsia present impaired relaxation, increased signs of hypertrophy, decreased stroke volume index and cardiac index, as well as diastolic and systolic dysfunctions.[32] In normal pregnancies, ultrasound studies have shown an excessive increase in left ventricular mass and remodeling with diastolic dysfunction, which return to normal in the postpartum period.[35] Valensise *et al.* have shown that cardiac output was significantly decreased in early-onset preeclampsia compared to late-onset preeclampsia. Melchiorre *et al.* found that preeclampsia was also associated with diastolic dysfunction and abnormal cardiac geometry in the majority of women who developed preeclampsia.[35]

At the beginning of the pregnancy, between weeks 6 and 8, maternal blood volume begins to increase, the maximum being as much as 50% higher the non-pregnant volume. By increasing the heart rate and stroke volume, cardiac output increases by 30–50% during pregnancy.[36]

Women with preeclampsia are at an increased risk to develop a cardiovascular disease in the future.[29] A meta-analysis performed on 22 studies with over 258,000 women affected by preeclampsia found a 1.8 to 2.5 higher risk for coronary heart disease, stroke and death, and a 4-fold risk of heart failure, which was higher in the first 10 years after a pregnancy with preeclampsia.[37] In their study, Ahmed *et al.* revealed that the most frequent outcome of vascular condition was stroke, with a risk increased 14.5-fold after preeclampsia.[38]

Recently, it has been shown that pravastatin may influence the angiogenic balance, by increasing the release of PlGF and circulating PlGF levels, and decreasing the release of sFlt-1 from the placenta, with potential value in the prevention of preeclampsia.[32]

ECHOCARDIOGRAPHIC PATTERN OF LEFT VENTRICULAR DYSFUNCTION IN GESTATIONAL HYPERTENSION AND PREECLAMPSIA

Preeclampsia involves arterial stiffness, increased vascular resistance, and decreased cardiac output. Consequent to the raised left ventricular afterload in the absence of an acceptable preload, concentric hypertrophy may develop, with mildly/moderately damaged diastolic function due to myocardial stiffening.[39]

Speckle-tracking echocardiography is a new ultrasound technique that uses frame-by-frame tracking of acoustic reflections called speckles.[40] Compared to conventional echocardiography, speckle-tracking echocardiography is more sensitive in assessing subclinical left ventricular and right ventricular dysfunction. Global longitudinal strain, global circumferential strain, global area strain, and global radial strain are measured.[39,40] Two-dimensional speckle-tracking echocardiography enables an objective quantification of myocardial deformation in all spatial directions, independently from the angle of cardiac translational movements.[41] Before the introduction of speckle-tracking echocardiography, only magnetic resonance imaging was able to analyze several deformation components of myocardial dynamics including torsional dynamics and left ventricle rotational movements.[42] Myocardial strain, a parameter representing myocardial deformation, is more sensitive and more accurate for detecting cardiac dysfunction than conventional echocardiographic indices.[43]

According to Liu *et al.*, global longitudinal strain of all three myocardial layers decreased significantly in preeclamptic women, with early-onset preeclampsia causing more damage than late-onset preeclampsia.[44] In a study by Moors *et al.* speckle-tracking echocardiography was able to find dissimilarities between pregnant women with hypertensive pregnancy disorders and normotensive pregnant women, mainly in left ventricular global longitudinal strain, which was significantly reduced in pregnant women with hypertensive disorders.[40]

According to Orabona *et al.*, global longitudinal strain has a better prognostic value for predicting major adverse cardiovascular events than left ventricular ejection fraction. In another study by Mostafavi *et al.*, the mean global circumferential strain was significantly lower in women with preeclampsia. According to the authors, increased systolic diameters, increased right ventricular diameters, diastolic termination, and decreased global circumferential strain were all expected in patients with preeclampsia.[45]

The values of left ventricular and right ventricular global longitudinal strain were significantly lower in preeclamptic patients than in controls during pregnancy. In the postpartum period, left ventricular global longitudinal strain values of preeclamptic patients increased significantly, becoming similar to those of the controls at 6 months, while the right ventricular global longitudinal strain of preeclamptic patients decreased significantly.[46]

In their study, Buddeberg *et al.* reported diastolic, but not systolic, disturbances after preeclampsia. Using 2D-speckle tracking they observed a reduction in left ventricular global strain, epicardial strain, endocardial strain, and longitudinal strain.[47] Ajmi *et al.* reported no difference between preeclamptic and non-preeclamptic women in terms of peak global circumferential strain and global radial strain.[48] Shahul *et al.* found that women with preeclampsia suffered sig-

TABLE 1. The main findings of studies investigating the role of imaging biomarkers in preeclampsia

Author	Year	N	GA cases	GA controls	LV-GLS	p value	LV-GRS	p value	LV-GCS	p value
Orabona *et al.*	2017	90	60	30	EO-PE ↓	<0.05	EO-PE =	>0.05	EO-PE =	>0.05
					LO-PE ↓	<0.05	LO-PE =	>0.05	LO-PE =	>0.05
Shahul *et al.*	2012	39	22	17	PE ↓	0.0009	PE ↓	0.007	PE ↓	0.04
Liu *et al.*	2019	86	45 EO-PE	86	GLS endo EO-PE ↓	0.000				
			44 EO-PE		GLS avg EO-PE ↓	0.000				
					GLS endo LO-PE ↓	0.000				
					GLS avg LO-PE ↓	0.000				
Mostafavi *et al.*	2019	100	60	40	PE =	0.164	PE ↓	0.028		
Paudel *et al.*	2020	90	55	35	PE ↓	0.001	PE ↓	0.002	PE ↓	0.002
Buddeberg *et al.*	2018	70	30	40	PE ↓	0.001				
Ajmi *et al.*	2018	60	30	30	PE ↓	<0.001	HD =	0.27	HD =	0.25

GA, gestational age in weeks; LV-GLS, left ventricular global longitudinal strain; LV-GRS, left ventricular global radial strain; LV-GCS, left ventricular global circumferential strain; PE, preeclampsia; EO-PE, early-onset preeclampsia; LO-PE, late-onset preeclampsia; GLS endo, the average value of global longitudinal strain in the endocardial layer at the basal, mid-ventricular and apical levels; GLS avg, the average value of GLS-endo, GLS-mid and GLS-epi; HD, hypertensive disorder; ↓, statistically significant decrease; ↑, statistically significant increase; =, no significant difference compared to the control group; empty cell, parameter not analyzed in the study

nificant reduction of the longitudinal, circumferential, and radial strain in contrast with pregnant women who presented nonproteinuric hypertension, and pregnant women who did not present a hypertensive disorder.[43] Table 1 lists the main findings of studies investigating the role of imaging biomarkers in preeclampsia.

INFLAMMATORY BIOMARKERS IN PREECLAMPSIA

Two functional subsets of T cells that are known to secrete cytokines are involved in different activities in preeclampsia: Th1 cells and Th2 cells. Th1 cells secrete TNF-β, IL-2, IFN-γ, IL-3, and GM-CSF, activating Tc and macrophages to stimulate cellular immunity and inflammation, and stimulating the bone marrow to produce more leukocytes.[49] During normal pregnancy, the production of Th1 cytokines is inhibited, studies showing that their excessive expression could induce preeclampsia.[50] Th2 cells produce IL-4, IL-5, IL-6, and IL-10, which stimulate antibody production by B cells.[49] Altered plasma concentrations of cytokines such as IL-1b, IL-6, IL-10, IL-18, and TNF-α were reported to be involved in defective placental invasion and endothelial damage in preeclampsia.[50]

Preeclampsia is thought to be a condition of exaggerated systemic inflammation. Inappropriate immune interaction at the beginning of pregnancy is thought to cause abnormal placentation and production of materials that are released into the maternal circulation, generating systemic inflammation, maternal disease, and endothelial dysfunction.[51]

Interleukin-6 (IL-6) is a cytokine with multiple functions that is generated by human trophoblasts. It adjusts immune response, acute phase reactions, hematopoiesis, and inflammation, and also increases trophoblastic proliferation invasion and differentiation.[50] IL-6 emerged as a marker for intraamniotic infection and obstetric infections, and is considered one of the most effective circulating markers of endothelial dysfunction.[49]

Interleukin-8, also known as CXCL-8, is a chemoattractant that has been demonstrated to influence pathological angiogenesis, metastasis, and tumor extension. This cytokine is one of the main chemoattractants for neutrophils and may also trigger the neutrophils. Increased IL-8 levels were found in several systemic inflammatory diseases.[53]

TNF-α and IL-6 are pro-inflammatory cytokines secreted mainly by neutrophil granulocytes and macrophage cells, with harmful effects on pregnancy. In the acute phase response, TNF-α and IL-6 are involved as main mediators.[54] TNF-α is involved in the immune response and acts as a multipotent modulator having the function of a strong pyrogen. It circulates in the body responding to stimuli (infectious agents or tissue damage), regulating the metabolic activities of other tissues, triggering neutrophils, and transforming the characteristics of vascular endothelial cells.[53] According to Mtali *et al.*, interleukin-6 (IL-6) levels were significantly ($p < 0.001$) higher in pregnancies with hypertensive disorders than in normal pregnancies, and IL-6 levels increased with the gravity of the hypertensive disorder.[55] Freeman *et al.* reported that IL-1β, TNF-α, IL-6, intercellular adhesion molecule-1, E-selectin, and C-reactive protein polymorphisms were not associated with any risk of developing preeclampsia.[56] Taylor *et al.* found that circulating TNF-ß, IL1-ß, IL4r, and IL-6 levels were associated

TABLE 2. Association of cytokines with the risk of developing preeclampsia

Author	Year	N	GA cases	GA controls	IL-1β	IL-6	IL-8	IL-10	TNF-α	p value
Taylor *et al.*	2016	707	410	297	↓					0.006
Sharma *et al.*	2007	131	54	77		↑	↑	↓	↑	<0.001
Mtali *et al.*	2019	153	76	77		↑				<0.001
Xiao *et al.*	2012	179	104	75		↑				0.002
Rezavand *et al.*	2016	240	120	120		↑				<0.001
Afshari *et al.*	2005	42	24	18		↑				0.02
Luppi *et al.*	2006	46	15	31	↑	↑	↑			<0.05
Mihu *et al.*	2008	110	40	70					↑	<0.001

GA, gestational age in weeks; IL, interleukin; TNF, tumor necrosis factor; ↓, statistically significant decrease; ↑, statistically significant increase; empty cell, parameter not analyzed in the study

with preeclampsia, but the results were not significant statistically.[51] Sharma *et al.* reported that IL-6, IL-8, and TNF-α were increased significantly in preeclamptic subjects compared with pregnant and non-pregnant healthy controls (p <0.001), suggesting that the modified levels of these molecules could be employed as markers of pro-inflammation and endothelial dysfunction in preeclamptic pregnancies.[53] In the study of Xiao *et al.*, serum IL-6 levels were significantly increased in women with early- and late-onset preeclampsia compared to women with a healthy pregnancy. They also found that IL-6 levels were significantly increased in severe preeclampsia.[57]

Based on the findings of Rezavand *et al.*, inflammatory factors and cytokines, especially IL-6, may be viewed as a risk factor for preeclampsia. Serum IL-6 levels were significantly higher in patients with preeclampsia compared to the control group (p <0.001).[58] The results of a study conducted by Afshari *et al.* showed that IL-6 was present in higher concentration in women with preeclampsia,[59] while Stonek *et al.* found that the presence of IL-6 G174C, TNF-α G308A, and IL-10 G1082A polymorphisms was not associated with preeclampsia in a population of Caucasian women.[60] At the same time, Luppi *et al.* found that the level of expression of IL-1β, IL-6 and IL-8 in monocytes of preeclamptic women was significantly increased compared to normal pregnant women.[61] Mihu *et al.* found significantly increased serum TNF-α concentrations (p <0.001) in pregnant patients with preeclampsia compared to normotensive pregnant women,[62] while Lau *et al.*, in a systematic review and meta-analysis, found elevated maternal circulating TNF-α, IL-6, and IL-10 levels in preeclampsia.[63] Another study by Nath *et al.* discovered that women with preeclampsia had significantly lower IL-10 levels compared with normotensive pregnant women (p = 0.0004), which supports the role of decreased IL-10 levels in the pathophysiology of preeclampsia.[64] Table 2 lists the most important findings of the main studies investigating the role of cytokines in preeclampsia.

CONCLUSIONS

Gestational hypertension and preeclampsia are hypertensive disorders with an increased incidence, responsible for increased maternal and perinatal mortality worldwide. The exact mechanisms of preeclampsia progression are still unknown; however, the ischemic vascular origin and the abnormal immune response seem to be significantly associated with this devastating condition. The measurement of inflammatory markers, markers of endothelial dysfunction, and imaging biomarkers associated with ventricular dysfunction can lead to early identification of pregnant women at high risk for major cardiovascular events, guiding the preventive strategy and antihypertensive therapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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