

LDH (Lactate Dehydrogenase): A Biochemical Marker for the Prediction of Adverse Outcomes in Pre-eclampsia and Eclampsia

Dave Anupama · Maru Laxmi · Jain Astha

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About the Author



Anupama Dave MS, DNB FICOG MNAMS FICS is working as an Associate Professor in , Obstetrics and Gynaecology Department, MGM Medical College, Indore. She has 17 years of teaching experience. She has 20 publications in national and international journals—14 publications in the Journal of Obstetrics and Gynaecology of India. She was awarded the prestigious FOGSI Chorion Award for the research work on LDH in AICOG 2013 Mumbai.

Abstract

Objective The aim of the study was to find out the role of Serum lactate dehydrogenase in prediction of adverse outcomes of PE & E i.e., severity of disease and occurrence of complications.

Materials and Methods This study was conducted in the Department of Obstetrics and Gynaecology, MGM Medical College, Indore. A total of 200 women were studied; they were divided into control ($n = 100$), severe pre-eclampsia ($n = 32$), eclampsia ($n = 68$). Demographic and hematological parameters were studied including LDH levels.

Results The incidence of severe pre-eclampsia—1.2 % & Eclampsia 2.7 %, PE & E patients were significantly younger, with low gravidity and parity. They had significantly increased systolic and diastolic pressure, liver enzymes, uric acid, urine albumin, and LDH levels. Serum urea and creatinine were normal in majority of cases. The symptoms and complications of PE along with perinatal mortality were increased significantly in patients with LDH >800 IU/l compared with those who had lower levels. Complications like Retinopathy, ARF, Abruption, DIC, CVA, MODS, Shock were also associated with high level of serum LDH >800 IU/L. Low birth weight of babies was also associated with high level of serum LDH levels in PE & E patients. The incidence of poor perinatal outcome was higher in PE & E patients with high serum LDH level (>600 IU/L).

Conclusion LDH is the earliest marker seen in blood during hypoxia and oxidative stress. It is a useful biochemical marker that reflects the severity of and the occurrence of complications of PE & E; these are

Dave A. (✉), Associate Professor ·
Maru L., Professor and Head of Department ·
Jain A., Resident
Department of Obstetrics and Gynaecology, M. Y. Hospital &
MGM Medical College, 314, Saket Nagar, Indore 452018,
Madhya Pradesh, India
e-mail: arvinddave10@yahoo.co.in

preventable if identified at an earlier stage and adequately managed at a higher center. Test is easily available, so screening of all cases of PE & E with LDH levels must be made mandatory.

Keywords Serum lactate dehydrogenase · LDH · Preeclampsia & eclampsia · Biochemical marker

Introduction

Pregnancy causes profound anatomical, physiological, and metabolic changes in maternal tissues. These well-orchestrated changes can go wrong at some stage of pregnancy resulting in various fetomaternal complications. One of the commonest and most dreaded complications is hypertension (preeclampsia (PE)/gestational hypertension (GHTN) which can further complicate into eclampsia (E). They are still the major killers in developing countries. 10 % of all pregnancies are complicated by hypertension. PE & E account for about half of these cases worldwide and have been recognized and described for years despite the general lack of understanding of the disease [1].

How pregnancy incites or aggravates hypertension remains unsolved despite decades of intensive research [2]. Defective placentation and endothelial dysfunction are considered to be the core features. Various factors including genetic, racial, immunological, dietary, increased insulin resistance, increased oxidative stress, hypoxia, and prostaglandin imbalance have been linked to these abnormalities.

Lactate dehydrogenase (LDH) is an intracellular enzyme which converts pyruvic acid to lactic acid during the process of glycolysis. Glycolysis is the major energy pathway in the placenta. Hypoxia in PE further enhances glycolysis and increases LDH activity. Studies have shown that LDH activity & gene expression are higher in placentas of PE than normal pregnancy [3–5]. Hypoxia induces LDH isoenzyme activity in trophoblasts resulting in higher lactate production. LDH has five isoforms and among all LDHA4 seen in placentae with PE is most responsive to hypoxia [6–9]. Elevated levels of LDH are indicative the cellular damage and dysfunction, so it can be used as a biochemical marker because it reflects the severity of the disease, occurrence of complications and fetal outcome. Its estimation would prove useful because these complications are preventable.

Elevated levels of LDH have also been seen in cases of HELLP syndrome. Many authors have used elevated total LDH (usually more than 600 U/L) as a diagnostic criterion for hemolysis [10–12]. Among all five isoforms, only two of them (LDH1 and LDH2) are released from ruptured red blood cells [13].

We conducted a research with an aim to study the role of Serum lactate dehydrogenase as a predictor of adverse fetomaternal

outcomes in cases of pre-eclampsia and eclampsia. Various demographic and hematological variables were also assessed in this study.

Materials and Methods

The present study was carried out in the Department of Obstetrics and Gynaecology, M.G.M. Medical College and Associated M.Y. Hospital, Indore. It was a prospective study which extended from August 2011 to January 2012 (last 3 months for follow-up).

Selection of cases The cases were selected from those admitted as emergency cases in labor room, taken at random, irrespective of age and parity. On a specially designed proforma, the patient particulars were recorded; 100 cases were studied and 100 cases were taken as control.

The cases with hypertension which were excluded from the study were those with

1. Coincidental hypertension in pregnancy. Essential hypertension as suggested by: (i) history or documentation of hypertension in the pre-pregnant state; (ii) hypertensive present before 20 weeks of gestation
2. Renal diseases
3. Coincidental seizures in pregnancy
 - I. History or documentation of epilepsy in pre-pregnant state.
 - II. Space occupying lesion in brain like tuberculoma, or brain tumor.
 - III. Trauma to brain
 - IV. Hyperpyrexia.

Various demographic and laboratory parameters were evaluated. Lactate dehydrogenase levels were done for all cases; depending on the values obtained, the cases were divided into three groups: Group 1—levels of LDH <600, Group 2—levels between 600 and 800, Group 3—levels >800.

Total of 200 cases were studied they were divided into pre-eclamptic, eclamptic and control groups containing 32, 68 and 100 patients respectively.

Statistical analysis was done with SPSS-17 program. Variables are described first and then compared with three groups using ANOVA and Chi-square test. A *P* value of < 0.05 was considered significant.

Results

In the study of 200 cases, PE & E cases were significantly younger, with low gravidity and parity. They had increased systolic and diastolic pressure ($P < 0.000$) and liver

enzymes, uric acid, urine albumin, and LDH levels compared to controls. Serum urea and creatinine were normal in majority of cases. It was seen that *S bilirubin*, SGOT, and SGPT were significantly raised in PE & E cases compared to controls ($P < 0.000$); also low platelet count < 1 lac/cu mm was seen in majority of PE & E cases P value < 0.000 which is significant. LDH level > 600 IU/L was seen in 84.375 % of PE & 97.03 % of E cases; this was found to be statistically significant ($P < 0.000$). The symptoms and complications of PE along with perinatal mortality were increased significantly in patients with LDH > 800 IU/l compared to those who had lower levels. Incidence of low birth weight babies and poor perinatal outcome was also associated with high level of serum LDH in PE & E cases. Group I (LDH < 600 IU/L) comprised 82.97 % of healthy baby, 10.63 % were sick and required admission in nursery and 6.38 % of babies were IUD/SVD. Group II (LDH 600–800 IU/L) comprised 50 % of healthy baby, 30.33 % were sick and required admission in nursery and 16.66 % of babies were IUD/SVD. Group III (LDH > 800 IU/L) comprised 33.33 % of healthy baby, 38.88 % were sick and required admission in nursery and 33.33 % of babies were IUD/SVD. This finding was statistically significant ($P < 0.000$). Complications like retinopathy, acute renal failure (ARF), abruptio, disseminated intravascular coagulation (DIC), cerebrovascular accidents (CVA), multiple organ disorder syndrome (MODS), and shock were also associated with high level of serum LDH > 800 IU/L. *Abruptio* was seen in 2.2 % of Group I, 5.5 % of Group II, and 14.03 % of Group III. Retinopathy was seen in 30.5 % of Group II and 63.15 % of Group III. ARF was seen in 8.77 of Group III. CVA was seen in 2.7 % of Group II and 7.017 % of Group III. MODS was seen in 15.7 % of Group III. DIC was seen in 7.017 % of Group III. Shock was seen in 8.77 % of Group III. 19.2 % of Group III died.

Discussion

In our hospital, there were 3,395 obstetric admissions during the period of the study (Aug. 2011–Oct. 2011) in which 42 and 92 patients were diagnosed as PE & E, respectively. This indicates a frequency of 1.2 % for PE and 2.7 % for E, but in this study 140 cases were included which were then further investigated and their LDH levels were done.

It is known that hypertensive disorders in pregnancy are commonly associated with certain high risk factors and depict changes in certain hematological parameters also. Demographic variables were studied and it was seen that –81.25 % of PE and 72.1 % of E cases were < 25 years of age. 73.5 % of E and 43.75 % PE patients were unbooked.

50 % of PE and 61.76 % of E patients were nulliparous. Ali et al. [14], Demir et al. [15], and Qublan et al. [16] also reported similar data in their respective studies as these are the known risk factors.

On further analysis of the hematological tests, Hb % value was less than 10 g/dl in 43.15 % of PE and 35.3 % of E cases. Platelet count was < 1 lac/cu mm in 9.375 % of pre-eclampsia and 26.47 % of eclampsia patients. ($P < 0.000$) Total bilirubin was > 1.2 mg/dl in 21.875 % of pre-eclampsia and 35.3 % of eclampsia patients. ($P < 0.008$) These values were significant.

Liu et al. [17] in a study reported that 20.6 % of patients with severe pre-eclampsia had abnormal liver function tests, mainly the elevation of SGPT. The increase in serum bilirubin was rarely seen. In our study also SGOT was > 72 IU/L in 9.37 % of PE and 22.06 % of E patients. ($P < 0.004$) SGPT was > 72 IU/L in 9.375 % of pre-eclampsia and 17.65 % of eclampsia patients. ($P < 0.000$) 20.6 % of patients with PE had abnormal liver function tests, mainly the elevation of SGPT. If we look at the renal function tests, serum urea was more than 50 mg/dl in 9.3 % in PE cases and 10.2 % of E cases. Serum creatinine was more than 1.5 mg/dl in 3.125 % in PE cases and 5.88 % of E cases.

Regarding the mode of delivery, Aali et al. [13] had found that Cesarean section was performed in 57.5 % of E and 66.4 % of PE cases, respectively, and that 34.1 % of PE & 24.2 % of E cases had low birth weight babies. In our study, on the contrary 28.1 % of PE cases & 14.7 % of E cases delivered by Cesarean Sect. 75 % of PE cases and 79.4 % of E cases, had birth weight of their babies < 2.5 kg.

Sudden IUD is one of the major problems seen in these cases. Qublan et al. [15] had found IUD seen in 4.8 % of cases; intrauterine growth retardation in 33.9 % and prematurity in 77.9 % cases of PE. Aali et al. [13] had found that 6.6 % of PE & 15.5 % of E cases had IUD. In the analysis of perinatal outcome in our study, 34.3 % of PE cases and 35.9 % of E cases, respectively, had had poor outcome of pregnancy (baby admitted to nursery). 18.75 % PE & 27.94 % of E cases had had SVD/IUD (Table 1).

The main objective of our study was to estimate the levels of serum lactate dehydrogenase. LDH level > 600 IU/L was seen in 84.375 % of PE & 97.03 % of E cases; this was found to be statistically significant ($P < 0.000$) Table 2.

Demir et al. [15] had found that in complicated cases of pre-eclampsia and eclampsia, LDH level was significantly higher. Qublan et al. [16] reported that LDH is a biochemical marker predicting adverse pregnancy outcomes in severe pre-eclampsia patients. In his study, an LDH level > 600 IU/L was seen in 54.8 % of severe pre-eclampsia and 12.2 % of mildly pre-eclampsia cases.

The cases were divided into three groups on the basis of LDH levels as seen in Table 3. Group I (LDH level <600 IU/L) had 10.63 % of PE cases and 24.25 % of E cases and 85.10 % of normal cases. Group II (LDH level 600–800 IU/L) had 22.22 % of pre-eclampsia and 77.77 % of eclampsia cases. Group III (LDH level >800 IU/L) had

33.33 % of pre-eclampsia and 66.66 % of eclampsia cases. These data were statistically significant ($P < 0.000$) All normal or cases taken as control had levels of LDH <600. Group II with LDH >600 had PE & E cases and no normal cases. Group III LDH >800 had majority of eclampsia cases. Therefore, it is clearly seen that there is a significant rise in LDH levels with increasing severity of disease. A recent study by Jaiswar et al. [18] also reported similar findings (Table 4).

Table 1 Distribution according to demographic variables

Demographic variables	Pre-eclampsia		Eclampsia		Normal	
	No.	%	No.	%	No.	%
<20 years	6	18.75	15	22.05	12	12
21–25 years	20	62.5	34	50	40	40
26–30 years	5	15.625	11	16.17	35	35
>30 years	1	3.125	8	11.76	13	13
Gravida 1	16	50	42	61.76	40	40
Gravida 2	6	18.75	14	20.5	37	37
Gravida 3	7	21.875	4	5.88	20	20
Gravida 4	1	3.125	5	7.35	0	0
Gravida 5	1	3.125	1	1.47	3	3
Gravida 6	1	3.125	1	1.47	0	0
Gravida 7	0	0	1	1.47	0	0
Booked cases	18	56.25	18	26.47	80	80
Unbooked cases	14	43.75	50	73.52	20	20

If we look at the perinatal outcome according to LDH Level, Group 1 (<600 IU/L) had 82.97 % of healthy baby, 10.63 % were sick and required admission in nursery, and 6.38 % of babies were IUD/SVD; Group II (600–800 IU/L) had 50 % of healthy baby, 30.33 % were sick and required admission in nursery, and 16.66 % of babies were IUD/SVD; and Group III (>800 IU/L) had 33.33 % of healthy baby, 38.88 % were sick and required admission in nursery, and 33.33 % of babies were IUD/SVD. This finding was statistically significant ($P < 0.000$). Qublan et al. [16] in his study had found that 61.5 % of perinatal deaths were found in cases having LDH level more than 800 IU/L.

In the analysis of birth weight according to LDH level (Table 5), Group 1 (<600 IU/L) had 51.06 % of babies with weight less than 2.5 kg and 48.93 % of babies with weight more than 2.5 kg. This group had all the normal cases; still

Table 2 Distribution of case according to hematological variables and blood pressure

Variable	Pre-eclampsia			Eclampsia			Control			P value
	No.	%	(Mean ± SD)	No.	%	(Mean ± SD)	No.	%	(Mean ± SD)	
SBP (mm Hg) >150	20	62.5	151.87 ± 17.31	50	73.53	156.62 ± 0.63	00	00	116.75 ± 26.80	0.000
SBP (mm Hg) <150	12	37.5		18	26.47		100	100		
DBP (mm Hg) >110	15	46.88	104.06 ± 13.65	31	45.59	104.12 ± 16.7	0	0	74.75 ± 8.16	0.000
DBP (mm Hg) <110	17	53.12		37	54.41		100	100		
Hb % (gm %) <10	14	43.15	9.96 ± 2.06	24	35.3	10.34 ± 2.86	70	70	9.22 ± 1.06	0.053
Hb % (gm %) >10	18	56.85		44	64.7		30	30		
PC (lac/mm) >1	3	9.37	1.92 ± 0.774	18	26.47	1.62 ± 0.86	40	100	2.53 ± 0.65	0.000
PC (lac/mm) <1	29	90.63		50	73.53		0	0		
S.Bilirubin mg/dl) >1.2	7	21.87	1.32 ± 1.44	24	35.3	1.32 ± 0.90	5	5	0.75 ± 0.309	0.006
S.Bilirubin mg/dl) <1.2	25	78.12		44	64.7		95	95		
S.SGOT (IU/l) >72	3	9.3	41.7 ± 33.33	15	22.06	53.1 ± 30.55	0	0	32.23 ± 4.85	0.004
S.SGOT (IU/l) <72	29	90.6		53	77.9		100	100		
S.SGPT (IU/l) >72	3	9.37	44.75 ± 36.0	12	17.65	47.34 ± 29.01	0	0	33.8 ± 6.3	0.000
S.SGPT (IU/l) <72	29	90.6		56	82.35		100	100		
S.LDH (IU/l) >600	27	84.3	1,024.94 ± 64.28	66	97.03	1,064.99 ± 758.27	0	0	393.4 ± 65.7	0.000
S.LDH (IU/l) <600	5	15.62		2	2.97		100	100		
S. Urea (mg/dl) >50	3	9.37	29.44 ± 12.92	7	10.29	32.47 ± 21.43	0	0	25.63 ± 7.1	0.121
S. Urea (mg/dl) <50	29	90.62		61	89.71		100	100		
S.Creatinine (mg/dl) >1.5	1	3.12	0.87 ± 0.25	4	5.88	1.11 ± 0.9	3	3	0.98 ± 0.33	0.20
S.Creatinine (mg/dl) <1.5	31	96.87		64	94.12		97	97		

Table 3 Distribution according to LDH level in various groups

Various groups	<600 (Group 1)		600–800 (Group 2)		>800 (Group 3)	
	No.	%	No.	%	No.	%
Pre-eclampsia (1)	5	10.63	8	22.22	19	33.33
Eclampsia (2)	2	4.25	28	77.77	38	66.66
Normal (3)	100	100	0	0	0	0
Total cases	107		36		57	

Table 4 Distribution according to Mode of delivery and birth weight

Variables studied	Pre-eclampsia		Eclampsia		Normal	
	No.	%	No.	%	No.	%
Vaginal delivery	23	71.875	58	85.29	75	75
Cesarean section	9	28.125	10	14.7	25	25
Birth weight <2.5 kg	24	75	54	79.4	45	45
Birth weight >2.5 kg	8	25	14	20.6	55	55

Table 5 Distribution of birth weight and perinatal outcome according to LDH level

Birth weight & perinatal outcome	<600 (Group 1)		600–800 (Group 2)		>800 (Group 3)	
	No.	%	No.	%	No.	%
Birth weight <2.5 kg	55	51	27	75	45	78.94
Birth weight >2.5 kg	52	49	9	25	12	21.05
Healthy baby (1)	89	83	18	50	18	31.57
Sick baby (2)	11	10.6	12	33.33	21	36.84
SVD/IUD (3)	7	6.4	6	16.66	18	31.57

birth weight of majority was <2.5 kg, and they were perhaps constitutionally small. Group II (600–800 IU/L) had 75 %, Group III (>800 IU/L) had 78.94 % of babies with weight <2.5 kg and 21.05 % of babies with weight >2.5 kg. ($P < 0.006$) Similarly, Qublan et al. [16] had found that cases having LDH level >800 IU/L had mean fetal weight of 1,821 + 656 in comparison to 1,849 + 563 in 563 in Group II having LDH level 600–800 IU/L and 1,891 + 498 in Group I having LDH level <600 IU/L.

It is important to analyze the complications as prediction would help in averting them, thereby preventing a lot of associated morbidity and mortality. As shown in Table 6, the % of complications in PE & E cases, respectively, are as follows: Abruption 18.75 and 7.3 % and retinopathy 31.25 and 54.4 %. Acute renal failure occurred in 7.3 % and DIC in 5.88 % of eclampsia patients. CVA was seen in 4.4 % of eclamptics. MODS was seen in 13.3 % of eclamptics. Shift to ICU was seen in 14.70 % of eclampsia patients (which was due to aspiration, development of pulmonary edema and acute respiratory distress in these cases). Shock was seen in 3.125 % of PE cases and 5.88 %

of E cases. 3.125 % of PE cases and 14.7 % of E cases died due to multiple complications, MODS, DIC, and sudden cardiac arrest.

Ali et al. [14] had found that 5.4 % of PE and 24.25 % of E cases had ARF. DIC in 3 % PE and 18.2 % E. 3 % of pre-eclampsia in 27.3 % of eclampsia had classic HELLP syndrome. 6 % of pre-eclampsia and 6 % eclampsia had partial HELLP syndrome. 4.8 % of pre-eclampsia and 21.2 % eclampsia had acute respiratory distress syndrome. 9.6 % of pre-eclampsia 18.2 % of eclampsia had abruption. 4.8 % of pre-eclampsia and 6 % eclampsia had PPH. 3.6 % of pre-eclampsia and 9 % of eclampsia had pulmonary edema. 0.6 % pre-eclampsia and 6 % of eclampsia had aspiration pneumonia. 0.6 % of pre-eclampsia and 30.3 % of eclampsia had neurological complications. 2.4 % of pre-eclampsia and 36.3 % eclampsia were transferred to ICU. 18.2 % of eclampsia had died.

Demir et al. [15] had found that in 13.2 % of pre-eclampsia had HELLP syndrome. 3.5 % pre-eclampsia had acute tuber necrosis. 18 % of pre-eclampsia became eclampsia. 2.8 % of pre-eclampsia cases had maternal mortality due to

Table 6 Distribution according to complications and LDH level

Complications	Pre-eclampsia		Eclampsia		Normal	<600 (Group 1)		600–800 (Group 2)		>800 (Group 3)	
	No.	%	No.	%		No.	No.	%	No.	%	No.
Abruption	6	18.75	5	7.3	0	1	2.127	2	5.56	8	14.03
DIC	0	0	4	5.88	0	0	0	11	30.55	36	63.157
ARF	0	0	5	7.3	0	0	0	0	0	5	8.77
MODS	0	0	9	13.23	0	0	0	1	2.77	4	7.02
CVA	0	0	3	4.4	0	0	0	0	0	9	15.79
Retinopathy	10	31.25	37	54.4	0	0	0	0	0	4	7.01
Shock	1	3.125	4	5.88	0	0	0	0	0	5	8.77
Shift to ICU	0	0	10	1.47	0	–	–	–	–	–	–
Died	1	3.125	10	1.47	0	0	0	0	0	11	19.29

complications including eclampsia. 0.7 % of pre-eclampsia had DIC. 0.7 % pre-eclampsia patients had intracranial hemorrhage. 0.7 % pre-eclampsia cases had hypertensive retinopathy. 9 % pre-eclampsia patients had abruptio placentae. 61.8 of 0.7 % pre-eclampsia patients were uncomplicated.

If we further analyze these complications according to LDH level (IU/L) (Table 6), Abruptio was seen in 2.2 % of Group I, 5.5 % of Group II, and 14.03 % of Group III. Retinopathy was seen in 30.5 % of Group II and 63.15 % of Group III. ARF was seen in 8.77 of Group III. CVA was seen of 2.7 % of Group II, 7.017 % of Group III. MODS was seen of 15.7 % of Group III. DIC was seen in 7.017 % of Group III. Shock was seen of 8.77 % of Group III. 19.2 % of Group III died.

Qublan et al. [16] had found that eclampsia was a complication in 4.7 % of Group II patients and 30.8 % of Group III. Abruptio placenta was seen in 15.4 % of Group III patients. Intracranial hemorrhage was seen in 7.7 % of Group III. HELLP syndrome was seen in 15.4 % of Group III patients. Acute renal failure was seen in 7.7 % of Group III patients. Pulmonary edema was seen in 7.7 % of Group III patients. DIC was seen in 7.7 % of Group III patients.

However, more research is required in this field. It would be more specific to estimate levels of LDH-A (4) isoenzyme activity in cases of preeclampsia [3]. Testing for other markers (LFTs) in addition would help in better prediction. In a study by Kozic et al. [19], it was reported that adverse maternal outcomes were more common in women with abnormal AST, ALT, LDH, total bilirubin, and INR results ($P < 0.05$). Therefore, LFTs and LDH should be studied in all cases of PE & E.

Sonagra et al. [20] have concluded in their study that regular estimation of LDH, ALP (alkaline phosphatase), and UA (uric acid) is advisable for pregnancy diagnosed with hypertensive disorders in order to detect and prevent the morbidity and mortality in mother as well as in the fetus. It may give an idea regarding the disease severity and functioning of liver and kidney in these patients. Progressive

increase in their levels should be considered as a signal for prompt intervention to improve pregnancy outcome.

Conclusions

Serum LDH is the earliest marker seen in blood during hypoxia and oxidative stress. It is raised in cases of PE & E. It is a useful biochemical marker as it reflects the severity of and the occurrence of complications of PE & E; these are preventable if identified at an earlier stage and adequately managed at a higher center. The test is easily available.

Detection of high-risk patients with increased levels of LDH mandates close monitoring, prompt and correct management to decrease both maternal and fetal morbidity and mortality. Therefore, we conclude from this study that screening of all cases of Preeclampsia and Eclampsia with LDH levels should be made mandatory.

Compliance with ethical requirements and Conflict of interests

Study was done after taking consent from the cases enrolled and also permissions were taken from Institutional Ethical committee and the authors declare that they have no conflict of interest.

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