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Incidence of Miscarriage in Pregnant Women due to TORCH Co-Infection in Erbil City/ Iraq

Safin Tahsin Kakayi[1], Hangaw Omer Haji[2], Ahmed Akil Khudhair Al-Daoody[1]

1Department of Medical Microbiology, College of Health Sciences, Hawler Medical University, Erbil, *:* safin.tahsin@gmail.com Kurdistan Region, Iraq.
2Department of Clinical Biochemistry, College of Health Sciences, Hawler Medical University, Erbil, *:* hangawhajii88@gmail.com Kurdistan Region, Iraq.

Safin Tahsin Haias: safin.tahsin@gmail.com
Hangaw Omer Haji: hangawhajii88@gmail.com
Ahmed Akil Khudhair Al-Daoody: ahmed.akil@hmu.edu.krd

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Abstract

Background: TORCH infections in pregnant women can result in serious effects, such as miscarriages, stillbirths, intrauterine growth retardations and congenital anomalies. TORCH infections caused by *Toxoplasma gondii*, rubella virus, cytomegalovirus and herpes simplex virus, and these organisms can transmit from mother to fetus through the placenta. The study aimed to investigate TORCH infection in pregnant women.

Materials and Methods: A cross-sectional and analytical study was conducted on 268 pregnant women (21-45 years) with miscarriage history. Blood samples were taken from all participants for screening TORCH infection. The screening was performed via Cobas e411 and using ROCH test kits manufactured by ROCH Company, Germany.

Results: *Toxoplasma gondii* was found in the highest percentage of TORCH infection (45.1%), followed by Cytomegalovirus CMV (21.6%), then Rubella (18.3%), which was found in the lowest percentage of infection. Non-significant differences were observed among age groups concerning Toxoplasmosis and Rubellosis, but significant differences were observed with CMV infection. Toxoplasma infections were observed with a high rate of infection (61.2%) in house wife, but there were no significant differences in Rubella and CMV infection based on occupation. The highest rate of toxoplasmosis (63.6%) was recorded in the first trimester of gestational age, with a significant difference, whereas there were no significant differences between gestational age with Rubella and CMV infections. Correlation was recorded between toxoplasmosis and the number of miscarriages with the highest rate (68.9%) in the number of miscarriages, whereas a non-significant correlation was recorded between Rubella or CMV infection and the number of miscarriages.

Conclusions: In TORCH infection, Toxoplasmosis are observed in high rate (45.1%) among pregnant women suffered from previous miscarriages, and significant correlation between toxoplasmosis and the number of miscarriages was found but this correlation was non-significant with Rubella and CMV infection.

Keywords: Miscarriage, Pregnant women, TORCH, *Toxoplasma gondii*, Rubella virus, Cytomegalovirus.

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حدوث الاجهاض لدى النساء الحوامل بسبب الاصابة بعدوى TORCHفي مدينة اربيل/العراق

سفين تحسين كاكيي[1]، هنكاو عمر حاجي[2]، احمد عقيل خضير الداودي[2]

1 كلية العلوم الصحية، جامعة اربيل الطبية، info@hmu.edu.krd، اربيل، العراق
2 كلية العلوم الصحية، جامعة اربيل الطبية، info@hmu.edu.krd، اربيل، العراق

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الخلاصة

الخلفية: يمكن أن تؤدي عدوى TORCH عند النساء الحوامل إلى آثار خطيرة ، مثل الإجهاض وولادة الجنين ميتا، وتأخر النمو داخل الرحم ، والتشوهات الخلقية. عدوى TORCH تسببها كل من التوكسوبلازما جوندي ، وفيروس الحصبة الألمانية ، والفيروس المضخم للخلايا وفيروس الهربس البسيط ، ويمكن لهذه الكائنات أن تنتقل من الأم إلى الجنين عبر المشيمة. هدفت الدراسة إلى التحقيق في عدوى TORCH عند النساء الحوامل.

الطريقة: أجريت دراسة مقطعية وتحليلية على 268 امرأة حامل (45-21 سنة) لهن تاريخ إجهاض. أخذت عينات الدم من جميع المشاركات لفحص عدوى TORCH. تم إجراء الاختبار عبر Cobas e411 وباستخدام عدة اختبار ROCH المصنعة من قبل شركة ROCH ، ألمانيا.

النتائج: ظهرت التوكسوبلازما جوندي في أعلى نسبة (45.1٪) من الإصابة بـ TORCH يليها الفيروس المضخم للخلايا (21.6 CMV٪) ثم الحصبة الألمانية (18.3٪) التي لوحظت في أقل نسبة إصابة. لوحظت فروق غير معنوية بين الفئات العمرية فيما يتعلق بداء المقوسات وداء الحصبة الألمانية ، ولكن لوحظت فروق ذات دلالة إحصائية مع عدوى الفيروس المضخم للخلايا. وجدت التوكسوبلازما باعلى معدل للاصابة (61.2٪) في ربات البيوت ، بينما لوحظت فروق غير معنوية في الحصبة الألمانية والفيروس المضخم للخلايا فيما يتعلق بالوظيفة. سجلت أعلى نسبة إصابة بداء المقوسات (63.6٪) في الثلث الأول من عمر الحمل مع وجود فرق معنوية ، بينما كانت الفروق غير معنوية بين عمر الحمل مع عدوى الحصبة الألمانية والفيروس المضخم للخلايا. سجلت علاقة ارتباط معنوية بين داء المقوسات وعدد حالات الإجهاض بأعلى نسبة (68.9٪) في حالتي إجهاضين ، بينما سجلت علاقة غير معنوية بين الإصابة بالحصبة الألمانية أو الفيروس المضخم للخلايا وعدد حالات الإجهاض.

الاستنتاجات: في عدوى TORCH ، لوحظ داء المقوسات بنسبة عالية (45.1٪) بين النساء الحوامل اللواتي عانين من الإجهاض السابق ، ووجدت علاقة ارتباط معنوية بين داء المقوسات وعدد حالات الإجهاض ولكن هذا الارتباط كان غير معنوي مع عدوى الحصبة الألمانية والفيروس المضخم للخلايا.

الكلمات المفتاحية: الإجهاض ، النساء الحوامل ، TORCH ، التوكسوبلازما جوندي ، فيروس الحصبة الألمانية ، الفيروس المضخم للخلايا.

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INTRODUCTION

TORCH is an acronym stands that is used for *Toxoplasma gondii*, Rubella virus, Cytomegalovirus CMV infection, and Herpes Simplex virus infection. These groups of infections are the major threats of serious congenital infection throughout pregnancy, which may eventually cause fetal damage or other anomalies [1]. In most cases, the infection would be severe sufficient to cause fatal damage to a fetus than the mother. These infections would

enter the blood circulation of the fetus through the placenta [2]. The gestational age of the fetus will affect the degree of severity as reported by [3-4]. One of the most complications faced the pregnant women is recurrent spontaneous abortion (RSA), the etiology of RSA is various with an incidence rate of approximately 0.5 - 1% in the world [5].

TORCH infections (Cytomegalovirus CMV, Rubella virus and Toxoplasmosis) are considered the common causes of congenital infections and bad obstetrics outcomes worldwide [6-7]. TORCH infections have been widely known to be associated with irregular and bad pregnancy outcomes. However, very little information is available about the effect of TORCH infections on pregnancy outcomes [8]. The primary infections of CMV, Rubella virus, and Toxoplasmosis throughout the pregnancy could bring broad ranges of clinical symptoms during the trimesters of pregnancy [7]. Furthermore, during the early stages of pregnancy; the result of TORCH infections may lead to fetal death, intrauterine growth restriction (IUGR) and malformations [9]. Whereas, during the later stages of pregnancy the infections either be latent (asymptomatic) or may cause signs, broad ranges of clinical symptoms could be caused by TORCH infections, for instance, intracranial calcifications, jaundice, lymphadenopathy, hepatosplenomegaly and skin rash [7].

Toxoplasma gondii is an intracellular obligate parasite which will be transmitted to human beings by ingesting contaminated food infected with oocytes which could be transmitted through feline feces [10]. Congenital toxoplasmosis usually occurs predominantly in the first trimester during the pregnancy stages [11]. According to [12] reported that the seroprevalence rates of toxoplasmosis in pregnant women range between “10% to 75%”. Furthermore, rubella virus infections during pregnancy appear to have a wide devastating outcome; which is known as congenital rubella syndrome (CRS). The most crucial complement of CRS is miscarriage and stillbirth [13]. The incidence rate of CRS is approximately 0.6 - 2.2 cases per 1000 live births [14].

On the other hand, CMV is considered as the most common viral infections in adults with an overall 50% seroprevalence [15]; however, the seroprevalence rates of CMV are higher in low-income population compared with high income [6,16]. During the pregnancy stages; neonatal and congenital infections are estimated to be one of the most remarkable outcomes of primary CMV [17]. Some researchers demonstrated that the risk of primary infection in

seronegative mothers varies between 0.7 - 4.1% with an overall birth prevalence of approximately 0.64% [18].

Non-immune pregnant women are those who do not have pre-existing antibodies against TORCH infections and are at a higher risk of congenital infections. Also documented that congenital infections could occur predominantly in mothers who have acquired these infections in the first trimester during pregnancy stages [6-7]. Therefore, this study aims to illustrate the association between TORCH Co-infection with multiple miscarriages in pregnant women and also detection of infections according to gestational age, occupation and age.

Materials and Methods

Population study

A cross-sectional study was conducted from October 2019 to June 2020 at Hawler Private Hospital and Maternity General Hospital in Erbil City. A total of 268 reproductive age pregnant women were included for screening for TORCH infection. The mean age was 31 years old (range was between 21-45 years old).

Sample collection

Approximately 3ml of blood were taken from all patients by vein puncture under aseptic precaution and then all samples were transferred to Microbiology Department Laboratory for analysis. The samples were centrifuged at 3000 rpm for 5 minutes and the serum separated from whole blood and transported into a specific and sterile cuvette (Eppendorf tube). All serum samples were stored at −20°C until they were processed and screened for the presence of sero antibodies against Toxoplasmosis, Rubella and CMV. The screening was performed via Cobas e411 and using ROCH test kits manufactured by ROCH Company, Germany. The equivocal blood samples were retested again just for the confirmation of the result.

All data of this study were collected anonymously and safely stored, and the patients were interviewed in terms of a predefined questionnaire which was prepared by the researchers. In this study, patients with a bad obstetric history (BOH) had a previous history of unfavorable fetal outcome in the form of two or more miscarriages (abortion), early neonatal death, congenital anomalies, intrauterine fetal death, infertility, intrauterine growth retardation, and stillbirth.

Ethics approval and consent to participate

The Ethics Committee of the College of Health Sciences at Hawler Medical University approved this study, and verbal consent was obtained from pregnant women prior to their enrollment in this study. In addition, the details of all participants were kept confidential and pseudonymised data was stored.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 23, IBM Corporation, New York, NY, USA) for Windows 7 (Microsoft Corporation). Descriptive statistics were used to summarize the demographic variables. Demographics were categorized by age, occupation, gestational age, number of miscarriages and pathogenic agents of TORCH. The differences between the groups were analyzed with an independent t-test for categorical variables and either Chi-square tests or spearman coefficient was used to evaluate the correlations between TORCH agents and miscarriage. The *P*-value <0.05 was considered to be statistically significant.

Results and Discussion

TORCH infections are considering the common causes of congenital infections and can lead to an adverse outcome which are initially asymptomatic such as an embryo losing, stillbirth, and congenital defects of the child [19]. In other terms, microbial agents of TORCH can cross the placenta and infect the fetus during any trimester of pregnancy [20].

Sociodemographic properties of pregnant women

A total of 268 pregnant women enrolled in this study, which were suffered from previous miscarriages, their ages ranged from 21-45 years old with different gestational age as illustrated in Table 1. 56.7% (152/268) of these women were employed whereas the rest 48.1% (116/268) were unemployed (Housewife), for TORCH infection Toxoplasmosis appeared in the highest percentage 45.1% (121/268) of infection followed by CMV 21.6% (58/268), then Rubella 18.3% (49/268) that observed in the lowest percentage of infection "because of the scanty of IgM positive result for *Toxoplasma gondii* and there are no IgM for CMV and rubella, therefore we depended on the total (IgG+IgM) positive result to prepare our schedules".

Table 1: Some sociodemographic properties of pregnant women (n=268)

Properties	Variables	Number	%
Age groups (years)	21-25	38	14.2
	26-30	81	30.2
	31-35	92	34.3
	36-40	50	18.7
	41-45	7	2.6
Occupation	Housewife	116	43.3
	Employed	152	56.7
Gestational age (Trimesters)	1st Trimester	129	48.1
	2nd Trimester	65	24.3
	3rd Trimester	74	27.6
Miscarriage	One	39	14.6
	Two	167	62.3
	Three	62	23.1
Pathogenic agents (TORCH)			
Toxoplasma (IgG+IgM)	+ve	121	45.1
	-ve	147	54.9
Rubella (IgG+IgM)	+ve	49	18.3
	-ve	219	81.7
CMV (IgG+IgM)	+ve	58	21.6
	-ve	210	78.4

These findings contradicted the findings of a previous study which conducted in Serbia, which reported the highest seropositivity for CMV 96.2% and lowest for *T. gondii* 24.1% [21]. They also contradicted the findings of [22] in Northern part of India they reported positive cases of toxoplasmosis, Rubella virus and CMV which were 19.4%, 30.4% and 34.7%, respectively. Another study in Iraq reported lower rates of infection, (10.87%) for CMV, followed by *T. gondii* 4 (2.17%) and Rubella virus (1.09%) [23]. Dissimilar results were also obtained in some developed countries. For instance, [24] showed only 3.7% total seropositivity for toxoplasmosis in Korea and pointed out that in Europe and America relatively higher rates were recorded. According to Sahu *et al* [25] found that Rubella was the most predominant infection being positive in 69.1% of the cases, followed by CMV infection 66.7% and

Toxoplasma infection 39.8%. As it is clear from the results of this section, that different results were obtained from different investigations and may be due to the location or country in which study took place and the difference in the number of enrolled pregnant women. Furthermore, other reasons for different and similar seropositivity of TORCH infections in pregnant women from the area to area might be due to the hygienic habits, culture differences related to feeding habits, education level, primary health care program and early diagnosis of infections [23].

Distribution of Torch (*Toxoplasma gondii, Rubella virus, CMV*) with age group

The highest rate of *Toxoplasma gondii* infection was recorded at 57.1% (4/7) in the older age group (41-45) years and the lowest rate of infection was recorded at 37% (34/92) in the age group (31-35) years with non-significant ($P > 0.05$) differences were observed among age groups concerning Toxoplasmosis (Table 2). These results were consistent with previous results recorded by [26-27]. Also agreed with [21] who found the seropositivity of *T. gondii* increased with age. Increasing in toxoplasmosis with the age might be due to the lifestyle and afford to eat poultry which has been found to be one of the major sources for *T. gondii* transmission [28]. In addition, the introduction of modern farming systems and the increase in consumption of frozen meat as the main factors for *T. gondii* incidence reduction are particularly evident in young people [29].

Table 2: Distribution of Torch (*Toxoplasma gondii, Rubella virus, CMV*) with age group

Torch / Age	*Toxoplasma gondii*		Rubella		CMV	
	No.+ve (%)	No.-ve (%)	No.+ve (%)	No.-ve (%)	No.+ve (%)	No.-ve (%)
21-25	18 (47.4)	20 (52.6)	8 (21.1)	30 (78.9)	4 (10.5)	34 (89.5)
26-30	39 (48.1)	42 (51.9)	15 (18.5)	66 (81.5)	12 (14.8)	69 (85.2)
31-35	34 (37.0)	58 (63.0)	14 (15.2)	78 (84.8)	25 (27.2)	67 (72.8)
36-40	26 (52.0)	24 (48.0)	11 (22.0)	39 (78.0)	16 (32.0)	34 (68.0)
41-45	4 (57.1)	3 (42.9)	1 (14.3)	6 (85.7)	1 (14.3)	6 (85.7)
***p*-value**	0.950		0.918		0.014	

Additionally, the highest rate of Rubella infection was recorded at 22% (11/50) in the age group (36-40) years, while the lowest rate of Rubella infection was recorded at 14.3% (1/7) in the age group (41-45) years with non-significant ($P > 0.05$) differences were observed among

age groups concerning Rubellosis. These findings were in agreement with previous findings by [30] which observed the highest age-related seropositivity rate for rubella in the age group below 40 years. Another study suggested that women of this age group are sexually active and this may probably predispose them to a greater risk of exposure and infection [31]. In developed countries, the rate of susceptibility to rubella among women of childbearing age is low because of the scarcity of the rubella vaccine [32].

Concerning CMV infection, significant ($P < 0.05$) differences were observed among age groups concerning CMV infection, with the highest rate of infection at 32% (16/50) in the age group (36-40) and the lowest rate of infection was recorded at 10.5% (4/38) in the age group (21-25) years. These results were relatively agreed with the results of a previous study [25], which declared that the rate of CMV infection was highest in the age group above 31 years**.** While disagreed with the finding of a study by [33], which concluded that CMV infection was common in most middle-aged women (36 years and older). Moreover, Among the United States population in the age group of (12–49) years, the force of infection was 1.6 infections per 100 susceptible persons per year and the average age of CMV infection was 28.6 years[34]. These features could be explained by more recent primary infections in the youngest women and the boosting of the immune response following viral reactivation [35] or natural exposure to multiple CMV strains in older women, who therefore may have had more intense and prolonged antibody response to the cumulative viral reactivation or exposure over time [36].

Prevalence of TORCH (*Toxoplasma gondii, Rubella virus, CMV*) infection according to occupation

As seen in Table 3. Statistically, the significant difference ($P < 0.05$) was observed in toxoplasmosis concerning occupation with a high rate of infection at 61.2% (71/116) in the unemployed women (Housewife). Vas versa non-significant differences ($P > 0.05$) were observed in Rubella and CMV infection concerning occupation with a high rate of infection at 21.1% (32/152) and 23.7% (36/152) respectively in the employed women.

Table 3: Prevalence of TORCH (*Toxoplasma gondii, Rubella virus, CMV*) according to occupation

Torch / Occupation	*Toxoplasma gondii*		Rubella		CMV	
	No.+ve (%)	No.-ve (%)	No.+ve (%)	No.-ve (%)	No.+ve (%)	No.-ve (%)
Housewife	71 (61.2)	45 (38.8)	17 (14.7)	99 (85.3)	22 (19.0)	94 (81.0)
Employed	50 (32.9)	102 (67.1)	32 (21.1)	120 (78.9)	36 (23.7)	116 (76.3)
***p*-value**	0.000		0.174		0.351	

The previous study concluded that the overall prevalence of TORCH infection seems to be a little less but non-significant in women with higher educational status (employed women) than those engaged in the agriculture or others a large part of which consists of daily laborers (Housewife) [25], these findings were consistent with our observations. Regarding toxoplasmosis lack of knowledge significantly increased the risk of infection, most of the employed women (educated people) who have heard about the disease knew the association of the infection with undercooked meat, unwashed vegetables and recognize cats as a source of infection [37]. As well as, the findings of this study agreed with other studies [38-39], which have shown the seroprevalence of CMV is higher among employed groups. This might be due to an association between employed women and workplaces which may increase their risk of exposure to CMV and Rubella. As the relation between maternal occupation and congenital malformation was mentioned by [40].

Distribution of TORCH (*Toxoplasma gondii, Rubella virus, CMV*) infection concerning gestational age

As illustrated in Table 4, the highest rate of toxoplasmosis was 63.6% (82/129) recorded in the first trimester of gestational age with a significant difference ($P < 0.05$). While the highest rate of infection by Rubella and CMV were 24.3% (18/74) and 28.4% (21/74) respectively recorded in the third trimester of gestational age with non-significant differences ($P > 0.05$).

Table 4: Distribution of TORCH (*Toxoplasma gondii, Rubella virus, CMV*) concerning gestational age

Torch / Gestational Age	*Toxoplasma gondii*		Rubella		CMV	
	No.+ve (%)	No.-ve (%)	No.+ve (%)	No.-ve (%)	No.+ve (%)	No.-ve (%)
1st Trimester	82 (63.6)	47 (36.4)	22 (17.1)	107 (82.9)	20 (15.5)	109 (84.5)
2nd Trimester	30 (46.2)	35 (53.8)	9 (13.8)	56 (86.2)	17 (26.2)	48 (73.8)
3rd Trimester	9 (12.2)	65 (87.8)	18 (24.3)	56 (75.7)	21 (28.4)	53 (71.6)
p-value	0.023		0.133		0.623	

These results were in agreement with the results of a previous study which found out that the prevalence of toxoplasmosis seems to be higher in the first trimester of pregnancy in comparing with other trimesters [41], which may be due to the persistence of encysted forms of Toxoplasma in chronically infected uteri, and their subsequent rupture during placentation lead to infection of the baby in the first trimester and often to recurrent miscarriages [42]. In contrast, [43] reported that toxoplasma is more likely to get through the placental barrier in later trimesters than in earlier pregnancy, which may be due to the placental trophoblast that is not conductive to the propagation of *T. gondii* and could prevent the parasite from crossing the placenta in early gestation [44].

Concerning CMV and Rubella infections. Similarly, another study observed that the high prevalence rate of CMV and rubella virus infections were found in those women in the third trimester of gestation [45]. While, this result is not in line with the previous finding by [46] the virus will adversely affect which reported that approximately, 30% to 50% of fetuses of women who contact with Rubella during the first 3 months of pregnancy. About CMV a study in Iran by [47] indicated that a majority of CMV-positive cases were in the second trimester of pregnancy. The dissimilarity of obtained results may be due to the absence of baseline data, the presence of IgG without IgM in women undergoing their first screening in the third trimester raises doubts as it may be the result of a previous infection occurring at any time in life before the pregnancy. However, statistical data confirmed that the possibility of an

infection occurring in the first trimester with the subsequent loss of IgM cannot be excluded [48].

Distribution of TORCH (*Toxoplasma gondii, Rubella virus, CMV*) infection according to miscarriage

A significant correlation ($P < 0.05$) was recorded between toxoplasmosis and the number of miscarriages with the highest rate of 68.9% (115/167) in case of two number of miscarriages. Whereas non-significant correlation ($P > 0.05$) was recorded between Rubella or CMV infection and the number of miscarriage (Table 5).

Table 5: Prevalence of Torch (*Toxoplasma gondii, Rubella virus, CMV*) according to miscarriage

Torch / No. of Miscarriage	*Toxoplasma gondii*		Rubella		CMV	
	No.+ve (%)	No.-ve (%)	No.+ve (%)	No.-ve (%)	No.+ve (%)	No.-ve (%)
One	3 (7.7)	36 (92.3)	11 (28.2)	28 (71.8)	12 (30.8)	27 (69.2)
Two	115 (68.9)	52 (31.1)	17 (10.2)	150 (89.8)	27 (16.2)	140 (83.8)
Three	3 (4.8)	59 (95.2)	21 (33.9)	41 (66.1)	19 (30.6)	43 (69.4)
X^2	0.012*		0.094		0.546	

*Correlation is significant at the 0.05 level using Chi-Square (Spearman Correlation)

A study in Basra was in agreement and declared that most of the miscarriages due to TORCH infection caused by *T. gondii* 60% [49]. While these results were in disagreement with a study performed by [50], which investigated to determine the effect of TORCH agents on pregnancy outcome, and recorded 102 (55.4%), 50 (27.2%), 27 (14.7%) and 5 (2.7%) for the number of single, twice, triple, four and more miscarriages, respectively. *T. gondii* caused abortion either inhibits or triggers the apoptosis with excessive levels of Th1 cytokines, particularly IL-18 and IFN- γ [51], and Rubella virus can reach the placenta and cause primary infections, which lead to spontaneous abortion [52]. Whereas the mechanism by which CMV lead to miscarriage is not clear [53].

Conclusion:

The prevalence of *Toxoplasma gondii* infection is high among TORCH infections, causes a high rate of abortion than others, and carries a substantial risk of infection during pregnancy. These results support the need for TORCH screening among reproductive-age women as a general and particularly during early pregnancy. Early diagnosis and timely action will help to treat these cases effectively and will reduce the risk of morbidity and mortality.

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Conflict of interests.

There are non-conflicts of interest.

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