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ON THE HISTOPATHOLOGICAL PATTERNS OF THE PLACENTA IN WOMEN WITH COVID-19 DURING PREGNANCY: CROSS-SECTIONAL STUDY

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Background. The COVID-19 pandemic has led to an active surge of studies devoted to the course of pregnancy under conditions of this infection, perinatal outcomes and long-term results, morphohistological features of the placental complex. In case of COVID-19, the placenta can be both a target organ for damage and a barrier between the mother and the fetus.

Materials and methods. 58 women with a confirmed (real-time PCR) moderately severy COVID-19 during pregnancy (the main group) and 40 healthy pregnant women (the control group) took part in a case-control study. The study was conducted from November 1, 2021 to December 31, 2022 from on the basis of the Communal Non-Profit Enterprise "Maternity Hospital No. 2" (Odesa).

Socio-demographic data and perinatal outcomes have been analyzed. The placentas were subjected to histological examination and described in accordance with the recommendations of the Amsterdam Consensus of the Placental Working Group. Statistical analysis was performed on the platform https://www.socscistatistics.com/tests/.

Results. The study and control groups were comparable in terms of demographic and anthropometric data. The incidence of COVID-19 was higher in the 2nd and 3rd trimesters of pregnancy (F=148.38358, p<0.00001). Significantly more often in "post-COVID" placentas, hemodynamic disorders were detected in the form of plethora and hemorrhages (53.45% vs 15%, OR= 6.506, 95% CI 2.370 17.858), maternal vascular malperfusion – villi infarctions (53.45% vs 12.5%, OR=8.037, 95% CI 2.758 23.423), agglutination of villi with an increase in the number of syncytial nodules (79.31% vs 15%, OR=21.722, 95% CI 7.409 63.684), vascular malperfusion of the fetus – hypovascularisation of the villi (only in 8.62% in the main group), and lymphoid infiltration of fetal membranes (17.24% vs 12.5%, OR=1.458, 95% CI 0.458 81.777).

Conclusion. The histopathological patterns found in post-COVID placentas indicate a significant impact of coronavirus infection on placental structure, but these changes are not specific and further research is needed to provide an evidence base.

Key words: COVID-19, pregnancy, histopathology of the placenta.

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ДО ПИТАННЯ ПРО ГІСТОПАТОЛОГІЧНІ ПАТТЕРНИ ПЛАЦЕНТИ У ЖІНОК, ЯКІ ПЕРЕХВОРІЛИ НА COVID-19 ПІД ЧАС ВАГІТНОСТІ: *CROSS-SECTIONAL STUDY*

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Пандемія COVID-19 через її високу контагіозність та летальність призвела до активного сплеску досліджень, присвячених вивченню перебігу вагітності в умовах такої інфекції, перинатальних результатів та віддалених результатів, а також морфогістологічних особливостей плацентарного комплексу. Зокрема, відомо, що у разі інфекції COVID-19 плацента може бути як органом-мішенню для ураження, так і бар'єром між матір'ю та плодом. Проведено гістологічне дослідження 58 «постковідних» (основна група) та 40 здорових плацент жінок (контрольна група). В основній групі частіше знаходили некротичні зміни трофобласту (у 4,27–5,28 раза), гемодинамічні порушення (у 3,54 раза) та ознаки гострого запалення плодових оболонок (в 1,37 раза). Плодову судинну мальперфузію виявлено лише у 8,62% плацент в основній групі. Захворюваність COVID-19 була вищою у 2-му та 3-му триместрах вагітності (F=148,38358, p<0,00001). Знайдені гістопатологічні патерни в «постковідних» плацентах свідчать про достовірний вплив інфекції COVID-19 на структуру плаценти, проте вони не є специфічними, отже, необхідні подальші дослідження.

Ключові слова: COVID-19, вагітність, гістопатологія плаценти.

Introduction. Throughout the entire period of intrauterine development, the fetus is completely dependent on a temporary organ – the placenta, which, on the one hand, separates the blood circulation of the mother and the fetus, and on the other hand, provides interaction and adaptation between the two organisms, as well as fetal protection [1; 2]. One of the mechanisms for preventing vertical transmission of pathogens from mother to fetus is the special structure of the epithelial covering of the placental villi, the syncytiotrophoblast, which reaches 12–14 m^2, and multinuclear syncytium has no intercellular spaces [1].

The unique immunological response of the placenta to bacterial and/or viral infection is realized through the

activation of certain cytokines, including those directly involved in the regulation of the gestational process [3]. In pregnant women, aberrant expression of pro-inflammatory cytokines with a subsequent imbalance between pro– and anti-inflammatory cytokines leads to complications of the gestational process, and COVID-19 infection is most likely no exception. According to A. Tanacan et al. (2021), the cytokine profile in pregnant women with SARS-CoV-2 infection varies depending on the trimesters of pregnancy, and cytokine levels correlate with the severity of the disease [4].

The pathogenetic mechanisms of exacerbation of SARS-CoV-2 coronavirus infection are associated with a 'cytokine storm' and multiple organ failure syndrome, so the assumption of placental involvement in the inflammatory process has led to an active study of the histopathological features of the placental complex in women who recovered from COVID-19 during pregnancy. It is reported that in some cases of SARS-CoV-2 infection during pregnancy, such changes as placental vasculopathy, atheromas in the vessels of the decidua, reduced perfusion, foci of placental infarction, inflammatory infiltrates, and chorangiosis were detected in the placenta. It is suggested that these changes relate to the expression of the primary mediators of SARS-CoV-2 penetration, ACE2 and TMPRSS2. Histological features of the placenta may increase its susceptibility to COVID-19, leading to inflammatory response with vasoconstrictive, proliferative and angiogenic effects. These events can lead to placental dysfunction and adverse pregnancy outcomes such as preeclampsia, premature birth, and increased rates of stillbirth [5; 6].

According to the Amsterdam Placental Workshop Group Consensus Statement, when describing the results of a morphological and histological examination of placentas, it is recommended to use certain terminology [7].

Already since 2020, studies of 'post-COVID' placentas, maternal and fetal vascular malperfusion have been mentioned [8; 9]. Subsequently, similar data were obtained confirming the presence of maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), and inflammatory lesions of the placenta, but there is no specificity of morphological changes [10; 11].

So, the COVID-19 pandemic, due to its high contagiousness and lethality, has led to an active surge in researches concerning various aspects of this infection, including the problems associated with the course of pregnancy, perinatal outcomes and long-term results. The pandemic continues, but the data available are often contradictory, in particular, this also applies to the morphology of the placental complex, which was the rationale for the purpose of our study.

The purpose is to study the range of histopathological features of the fetoplacental complex in women who recovered from COVID-19 during pregnancy, and compare the data with the uninfected control group (placentas of apparently healthy women).

Materials and methods.

Population

A prospective single-center case-control study was conducted, the participants of which were 98 women who completed their pregnancy. Of them 58 women with a confirmed COVID-19 during pregnancy were included in the main group and 40 healthy women – in the control group. From November 1, 2021 to December 31, 2022 on the basis of the Communal Non-Profit Enterprise "Maternity Hospital No. 2" (Odesa), which was a hospital base in Odesa and Odesa region to provide medical care to pregnant women with COVID-19 infection, collected data on the course of pregnancy, maternal and fetal outcomes, and placental sampling for biometrics, macroscopic and microscopic evaluation.

Verification of COVID-19 infection

Primary verification of COVID-19 infection was performed by a rapid coronavirus test based on the detection of SARS-CoV-2 nucleocapsid protein (antigen) by ICA (immunochromatographic assay) in swabs taken simultaneously from the posterior wall of the oropharynx and anterior nasal cavity. To confirm the diagnosis, biomaterials from the posterior pharyngeal and nasal wall (working part of the swab) were placed in a disposable sterile tube with 1–1.5 ml of transport medium containing viral lysis medium (commercially prepared product) and taken to a certified laboratory for detection of SARS-CoV-2 virus RNA by real-time polymerase chain reaction (PCR). The collection of material for analysis and its transportation were carried out in compliance with the requirements of regulatory documents.

Inclusion/Exclusion Criterion

Criteria for inclusion in the main group were the following: a confirmed diagnosis of moderately severe COVID-19 at the time of admission for delivery or an indication to hospitalization due to confirmed coronavirus infection during pregnancy. The severity of the disease was established on the basis of the order of the Ministry of Health of Ukraine. According to the "Patient Pathway", developed by the Health Department of the Odesa City Council, pregnant women undergo X-ray examination or chest CT scan before hospitalization. The pregnant women with severe degree of the disease were hospitalized at the 3rd level of medical care – the perinatal center of the Odesa Regional Clinical Hospital.

The control group included women with a physiological course of pregnancy without a "COVID" history and severe extragenital pathology.

Morphometry and histological examination of placentas

Placentas were subjected to histopathological examination and described according to the Amsterdam Placental Workshop Group (2016) consensus recommendations [7]. For microscopic examination, after preliminary macroscopic evaluation and morphometry of the placenta, pieces of placental tissue were taken, viz. 1×1 cm, 2 sections each from the central, paracentral and marginal parts of the placenta, 8 cm long one strip of fetal membranes, 1 piece of umbilical cord – 8 'dots' from each placenta. The material was fixed in 10% formalin solution, dehydrated in 4 alcohol solutions of different concentrations, 2 chloroform solutions of different concentrations, then in 2 containers with paraffin-base. Sections 5 μm thick were prepared on a sledge microtome, stained with hematoxylin-eosin (H&E), covered with polystyrol and examined at magnifications of 10x10, 10x20 and 10x40; a LEICA DMIS No. 760 microscope was used. Placentas were not tested for SARS-CoV-2 using RT-PCR.

Ethical aspects of the study

On admission to the hospital all patients gave informed consent to participate in the study, which was approved by the Ethics Commission of the Odesa National Medical University and carried out in accordance with the guidelines of the Declaration of Helsinki. The work is a part of the scientific theme of the Department of Obstetrics and Gynecology of the Odesa National Medical University "The latest therapeutic, diagnostic and preventive approaches to diseases of the female reproductive system and high-risk pregnancy", registration number N 0117 U007494.

Statistical data analysis

Statistical analysis was performed by the licensed programs "Microsoft Excel" and "Social Science Statistics" (https://www.socscistatistics.com/tests).

Results

The investigated groups were homogeneous according to demographic and anthropometric indicators. All the women in both groups were covered by antenatal care.

A study of COVID-19 incidence as a function of gestational age showed that the longer the gestational age, the higher the likelihood of incidence (F=148.38358, $p<0.00001$). Most of the women in the main group became ill in the 3rd trimester of pregnancy – 65.51% (38 patients), in the 2nd trimester – 25.86% (15 patients), in the 1st trimester only 8.62% (5 patients). The average gestational age at the time of the disease was (29.6 ± 9.1) weeks.

Histological examination of 'post-COVID' placentas showed evidence of MVM and FVM and moderate inflammatory lesions. So, hemodynamic disorders in the form of congestion of the chorionic plate vessels (Fig. 1) and sclerotic changes in the terminal chorionic villi (Fig. 2) were found in 26 (44.82%) of "post-COVID" placentas. A frequent histological pattern was hemorrhage into the following placental structures: the intervillous subchorionic space (Fig. 3) – in 18 (31.03%), the fetal membranes (Fig. 4) – 19 (32.75%), the vessels of the basal plate (Fig. 5) – 11 (18.96%) placentas. The presence of hemorrhages in Wharton's jelly was also revealed in 12 (20.69%) placentas (Fig. 6). 15 (25.86%) placentas showed lymphoid infiltration of the fetal membranes (Fig. 7) with excessive fibrinoid deposition and lymphoid infiltration of the basal lamina (Fig. 8). In 79.31% (46 placentas), a significant number of syncytial nodules were found associated with placental risk factors for stillbirth. Other pathohistological patterns of the placenta were serous basal deciduitis, parietal amnionitis (20.69% – 12 placentas), compensatory villous angiomatosis (24.14% – 14 placentas) and calcium salt deposition (31.03% – 18 placentas).

The logistic regression models made it possible to establish the presence of a significant influence of the "post-COVID" status on the formation of maternal vascular malperfusion, namely such histological patterns as the presence of internal maternal chorionic villous infarctions and pseudoinfarctions, agglutination of the villous with an increased number of syncytial nodules, hemodynamic disorders in the form of congestion and hemorrhages in the placenta structures, hypovascularization of the villi of the fetal circulation, as well as a picture of acute and chronic inflammation of the fetal membranes (Table 1).

Hemodynamic disturbances: congestion of the villous vessels (26 – main group), hemorrhage in the intervillous space (18 – main group), hemorrhage in the basal plate (11 – main group, 1 – control group), hemorrhage in the fetal membranes (19 – main group, 4 – control group). Significance level $p<0.05$.

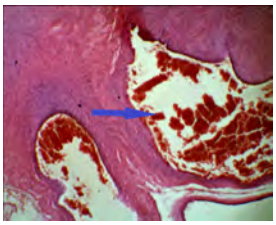

Fig. 1. (14504) Congestion of the vessels of the chorionic plate. H&E x40

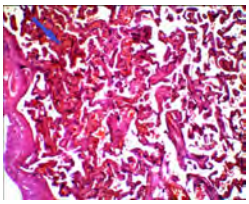

Fig. 2. (16267) Congestion of vessels of sclerotically changed terminal chorionic villi. H&E, x40

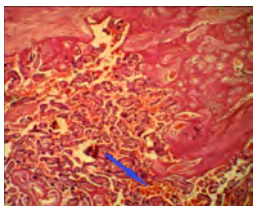

Fig. 3. (8968). Hemorrhages into the subchorionic intervillous space. H&E, x40

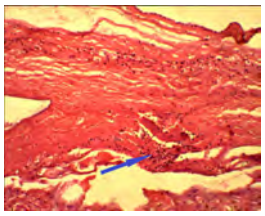

Fig. 4. (9938). Hemorrhage into fetal membranes H&E, x100

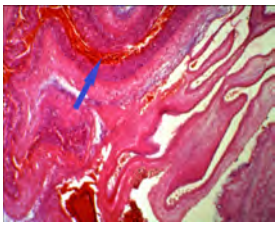

Fig. 5. (10455). Hemorrhage into the chorionic plate. H&E, x40

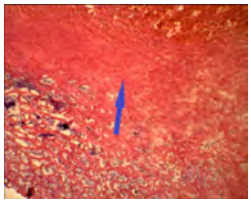

Fig. 6. (9937). Hemorrhage in Wharton's jelly of the umbilical cord. H&E, x40

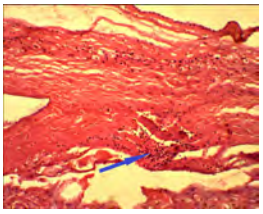

Fig. 7. (9938). Lymphoid infiltration of placental membranes. H&E, x100

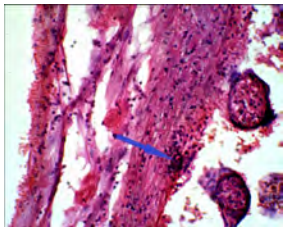

Fig. 8. (14503). Lymphoid infiltration of the chorionic membranes. H&E, x200

Highlights

The placentas of COVID-19 pregnant women are characterized by the presence of histopathological patterns in the maternal and fetal circulation and pronounced "silent" hemodynamic disturbances in the form of plethora or hemorrhages in the placental structures.

All histopathological patterns of 'post-COVID' placentas are not specific. Further studies are needed, in particular to determine the functional characteristics of these placentas.

Discussion. The complicated course of pregnancy and negative perinatal outcomes associated with COVID-19 are evidenced by the results of some studies. A. Tanakan et al. (2021) showed that pregnant women with COVID-19 infection have a higher levels of inflammatory markers in the blood than in the control group, and the course of pregnancy is characterized by a higher incidence of complications. In addition, cytokine levels differed by trimester of pregnancy, except for IL-6, and were significantly correlated with disease severity, except for IL-1. M. V. Surekha et al. (2023) suggest that COVID-19 infection during pregnancy, regardless of the presence of other problems, particularly anemia, may be associated with various abnormal histopathological changes in the placenta associated with placental hypoxia [6; 8].

The known theory of "cytokine" regulation of the gestational process to some extent may help to explain the pathological mechanisms of uteroplacental complex involvement in the systemic inflammatory response in COVID-19, as well as its impact on perinatal outcomes in general, including preterm labor, preeclampsia, intrauterine growth retardation, etc. [3; 4; 12].

Depending on the stage of pregnancy, women in the 3rd trimester are the most vulnerable and susceptible to infection. This is explained by physiological features of changes in the ratio of organs of the thoracic and abdominal cavity, high diaphragm position and restricted respiratory excursion, decreased amplitude of chest movements against the background of increased metabolic processes and increased oxygen demand, as well as increased body weight [8; 13; 14]. Our study also showed that the longer the pregnancy, the greater the likelihood of COVID-19 morbidity ($F=148.38358$, $p<0.00001$).

Histopathological examination of placentas in our work showed the presence of a certain spectrum of non-specific changes, but their frequency was statistically significant compared to the control group. The most frequent (typical) 'post-COVID' placentas were described as follows:

A) Pathological immaturity. The variant of hypovascular chaotic sclerotic villi; small fibrin thrombi in the intervillous space; moderate compensatory villous angiomatosis, numerous syncytial nodules. Acute hemodynamic

Table 1

Association of the "post-COVID" status of women with histopathological features of the placenta

	Histological pattern (dependent variable)	Independent variable: COVID-19	N (%)	OR	95% CI	p value
MVM	Villous infarctions (pseudoinfarcts, anemic infarcts)	Control group	5 (12.5)	8.037	2.758 23.423	F=0 p<0.05
		Main group	31 (53.45)			
	Villi agglutination with increased number of syncytial nodules	Control group	6 (15)	21.722	7.409 63.684	F=0.00001, p<0.05
		Main group	46 (79.31)			
FVM	Chorangiosis	Control group	6 (15)	1.803	0.627 5.183	F=0.3164 p>0.05,
		Main group	14 (24.14)			
	Avascular / hypovascular villi crowding	Control group	0	–	–	F=0.0097, p <0.05
		Main group	5 (8.62)			
AIP	Serous basal deciduitis Parietal amnionitis	Control group	4 (10)	2.348	0.698 7.895	F=0.1789, p>0.05
		Main group	12 (20.69)			
CIP	Lymphoid infiltration of Fetus membranes	Control group	5 (12.5)	1.458	0.458 81.777	F=0.5807, p<0.05
		Main group	10 (17.24)			
OTHER	Hemodynamic disturbances	Control group	6 (15)	6.506	2.370 17.858	F=0.0001, p<0.05.
		Main group	31 (53.45)			
	Hemorrhage in the Wharton's jelly of umbilical cord	Control group	1 (2.5)	10.174	1.266 4.645	F=0.0129, p<0.05
		Main group	12 (20.69)			
	Deposition of calcium salts in the villi	Control group	10 (25)	1.35	0.545 3.342	F=0.65 p>0.05
		Main group	18 (31.03)			
	Intervillous thrombosis	Control group	5 (12.5)	1.826	0.589 5.665	F=0.41692, p>0.05.
		Main group	12 (20.69)			
	Increase in perivillous fibrin	Control group	5 (12.5)	1.826	0.589 5.665	F=0.08184, p>0.05
		Main group	12 (20.69)			

Note: AIP – acute inflammatory process; CIP – chronic inflammatory process; MVM – maternal vascular malperfusion: FVM – fetal maternal vascular malperfusion; OTHER – other pathological patterns of the placenta.

disturbance: congestion of the villous vessels, blood in the intervillous space, focal hemorrhages in the chorionic plate of the placenta, fetal membranes, Wharton's jelly of the umbilical cord.

B) Dissociated development and maturation of the chorion. Along with normal terminal villi there are zones of embryonic villi, zones of hypovascular villi and fields of compensatory capillary hyperplasia. Acute haemodynamic disorder: occlusion of villous vessels, blood in the intervillous space, focal hemorrhages in the chorionic and basal lamina of the placenta; irregular lymphoid infiltration of the basal lamina, fetal membranes.

The described histological patterns are presented in photographs.

It is known that impaired maturation of placental villous tissue is associated with negative perinatal outcomes for both the fetus and the mother [14]. MVM was supported by a significantly higher frequency of internal maternal infarctions, pseudoinfarctions (53.45% vs 12.5%) and variants of hypo/avascular villi with an increase in the number of syncytial nodules (79.31% vs 15%), as well as hemodynamic disturbances in "post-COVID" placentas (53.45% vs 15%) compared to the control group.

An increase in the number of internal maternal placental infarctions and syncytial nodules is associated with placental hypoperfusion/hypoxia and negative perinatal outcomes, including stillbirths. With COVID-19-induced maternal hypoxia, it is the maternal part of the circulation that is primarily involved in the systemic pathological process, an assumption consistent with many authors. Mother's viral invasion and hypoxia can promote ischemia of the placenta and lead to necrotic changes in the villous tree (infarction, distal villous hypoplasia, decidual arteriopathy, etc.) [5; 6; 9; 14].

In addition, cytokines play a leading role in COVID-19 pathophysiology, which also determine and regulate the interaction between the blastocyst and the endometrium during implantation and subsequent placentation. Under certain conditions (preterm birth, preeclampsia, intrauterine growth retardation, etc.), the expression of cytokines changes. In particular, under conditions of hypoxia and reoxygenation, the synthesis of TNF-α and IL-6, which are among the most aggressive cytokines with marked proinflammatory capacity, is increased in placental villi. In this situation, the effects of both COVID-19-induced hypoxia and immunopathological effects of cytokines are cumulative [12].

About the FVM was evidenced by cases of chorangiosis (24.14% vs 15%) detected in our study and aggregated avascular/hypovascular chorionic villi, which were determined only in "post-COVID" placentas (8.62%). R.N. Baergen et al. (2020) showed that signs of impaired perfusion or fetal vascular thrombosis are observed in 50% of "post-COVID" placentas, and M.V. Surekha et al. (2023) – that COVID-19 is an independent risk factor for severe chorangiosis (ad OR 8.74, 95% CI 3.51–21.76, $p<0.0001$) [6, 8]. S. Magawa et al (2023), evaluating placentas by MRI in pregnant women with COVID-19, found that placental oxygenation in these patients remained reduced even after recovery, but no changes in fetal development were observed [15].

According to C. Milot et al. (2023), signs of FVM are detected in 44.9%, and MVM in 89.8% of "post-COVID" placentas. These authors argue that SARS-COV-2 causes placental lesions that develop after recovery. Chronic villitis was more common in women who gave birth later than 14 days after infection than in the group who gave birth earlier than 14 days after infection (26.9% vs 4.4%, $p=0.05$) [10]. J.E. Patiño Escarcina et al. (2023) identified chorioamnionitis, chronic villitis and focal perivillositis in 11.8%, L. Bertero et al. (2021) also indicated a higher incidence of chronic villitis and deciduitis compared to the control group [5; 16].

According to our data, signs of the chronic inflammatory process were detected in the main and control groups in 17.24% vs 12.5% ($F=0.5807$, $p<0.005$), and acute amnionitis and serous basal deciduitis – in 20.69% vs 10% ($F=0.1789$, $p>0.05$).

We found no significant difference between the groups in terms of incidence such as calcium salt deposition in placenta (31.03% vs 25%), increased perivillous fibrin deposition (20.69% vs 12.5%, intervillous thrombosis (20.69% vs 12.5%), which is in agreement with S.K. Lad et al. (2023) [2].

The present literature data on the frequency of MVM, FVM and the incidence of acute or chronic inflammatory damage to the placental complex in COVID-19 infection suggest that the placenta, as an independent organ with a self-regulating metabolism and hormonal status, may be at risk of developing "long COVID" with all its characteristics. Nevertheless, it is likely that there are certain metabolic (biochemical) or hormonal (most likely combined) mechanisms directly in the placenta that may shape the resistance of the placental barrier to coronavirus infection. These assumptions require further research.

So, the results of a comparative histopathological study of "post-COVID" placentas and placentas of healthy women allow us to draw the following conclusion.

Conclusions.

Histopathological patterns found in "post-COVID" placentas a significant effect of coronavirus infection on the structure of the placenta and these changes may reflect the presence of placental hypoperfusion and ischemia.

All histopathological patterns of "post-COVID" placentas are not specific. Further research is needed, in particular, to determine the functional characteristics of these placentas and the immunohistochemical substantiation of the mechanisms involved in the development of adverse perinatal outcomes.

Conflict of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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