

Risk Factors for Preterm Delivery in Asymptomatic Singleton Pregnant Women with a Sonographic Short Cervix

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Abstract

Objectives: Although an asymptomatic short cervix is a risk factor for spontaneous preterm birth (SPTB), the risk factors for SPTB among those with short cervix remain unknown. We herein investigated risk factors for preterm delivery (PTD) at <34 weeks of gestation in pregnant women with a short cervix. **Methods:** This was a retrospective study. Seventy-three asymptomatic pregnant women with a sonographic short cervix (excluding visible bulging fetal membranes) were selected, and the relationship between clinical or biochemical risk factors and preterm delivery (PTD) at <34 weeks was examined. **Results:** Thirteen cases (17.8%) had PTD at <34 weeks. A univariate analysis showed that a history of SPTD, gestational weeks on admission, cervical length, cervical mucus interleukin (CM-IL)-8 and amniotic fluid interleukin (AF-IL)-8 in PTD at <34 weeks significantly differed from those in delivery at ≥ 34 weeks ($p < 0.05$, respectively). A multiple logistic regression analysis identified CM-IL-8 ≥ 803.5 ng/mL [21.3 (3.0 - 260), $p = 0.002$] and cervical length ≤ 15 mm [17.1 (1.9 - 517), $p = 0.008$] as independent risk factors for PTD at <34 weeks. **Conclusions:** Evaluation for cervical inflammation may be necessary for appropriate treatment strategies in asymptomatic pregnant women with a short cervix. Cervical inflammation warrants further study.

Keywords

Amniotic Fluid, Cervical Mucus, Interleukin-8, Preterm Delivery, Sonographic Short Cervix

1. Introduction

A sonographic short cervix ≤ 25 mm in the second trimester of pregnancy is a pre-sign of spontaneous preterm birth (SPTB) [1]. Regarding the clinical cha-

racteristics of SPTB and its problems; 1) since it is just a sonographic sign, a short cervix is only detected in asymptomatic pregnant women using ultrasonography; 2) the positive predictive value of SPTB before 35 weeks was previously reported to be 17.8% [1], however, the majority of pregnant women delivered after 36 weeks; 3) it may be a pre-sign of cervical ripening with bag formation of visible bulging fetal membranes (cervical insufficiency) without clinical symptoms [2] [3], but does not necessarily develop visible bag formation, it might be a pre-sign of preterm labor (PTL) [4] or preterm premature rupture of membranes (pPROM) [5]; and 4) the etiology of a sonographic short cervix may be multifactorial [6], such as vaginal [7] [8], cervical [6] [9] [10], and intra-amniotic [6] [11] [12] [13] [14] [15] inflammation/infection, a history of cervical surgery [6] [16], low cervical collagen concentrations [17], and uterine anomalies [6] [18]. Therefore, the individualized management of asymptomatic pregnant women with a short cervix is needed. However, further studies are needed to clarify which risk factors for SPTB are important.

Intra-amniotic inflammation/infection has been strongly implicated in SPTB [19] [20] [21], and is more severe in the earlier gestational weeks of SPTB [22] [23] [24]. The cause of intra-amniotic inflammation/infection is mainly considered to be an ascending bacterial infection from the vagina through the cervix into the uterine cavity [4] [19] [25]. Therefore, a short cervix may be one of the conditions caused by vaginal, cervical, and/or intra-amniotic inflammation/infection. However, in clinical settings, it currently remains unclear which inflammation/infection is the most important risk factor for SPTB in asymptomatic pregnant women with a short cervix.

In our hospital, when a pregnant woman at risk of SPTB is hospitalized, clinical or chemical risk markers of SPTB, such as the preterm labor index (PLI) [26], maternal body temperature, white blood cell count (WBC), C-reactive protein (CRP), cervical length, Nugent score of vaginal secretions [27], fetal fibronectin (fFN) in vaginal secretions, cervical mucus interleukin (CM-IL)-8, amniotic fluid interleukin (AF-IL)-8 (amniocentesis was administered to asymptomatic pregnant women with a short cervix until March 2008), AF glucose, and AF granulocytes are measured. We previously identified PLI, AF-IL-8, AF glucose, and fFN in vaginal secretions as independent risk factors for PTD at <34 weeks in preterm labor (PTL) patients [28].

In the present study, we retrospectively investigated which risk factors correlate with PTD at <34 weeks of gestation in asymptomatic pregnant women with a short cervix.

2. Materials & Methods

2.1. Study Population

In total, 378 pregnant women before 28 weeks of gestation at risk of SPTB were hospitalized at Toyama University Hospital between April 2000 and March 2008. We excluded patients with multiple pregnancies, fetal growth restriction (less

than -1.5 S.D.), congenital fetal anomalies, an abnormal fetal karyotype, preeclampsia, gestational diabetes mellitus, a history of cervical surgery, uterine anomalies, and steroid users. We also excluded patients with PTL and pPROM.

Cases in which bag formation of visible bulging membranes was detected in a digital speculum (Cuzco) examination were also excluded. In the present study, cervical insufficiency was defined as visible bulging fetal membranes from the cervix in asymptomatic pregnant women with or without a previous history of SPTB [2]. And “asymptomatic” was defined as a pregnant woman who visited hospital for routine pregnancy check-up. Therefore, the study population was considered to be normal pregnant women without an evaluation by a sonographic examination.

2.2. Management of Asymptomatic Pregnant Women with a Short Cervix

Cervical length was routinely measured every 2 weeks between 20 and 28 weeks of gestation with or without clinical symptoms, such as genital bleeding. The length between the internal and external os was assessed by transvaginal ultrasonography.

When asymptomatic pregnant women with a sonographic short cervix were identified in the outpatient clinic, hospitalization for physical rest was recommended. Generally, hospitalization is an exaggerated management (overtreatment), however, our treatment policy was to perform cervical cerclage immediately, when the cervix is suddenly shorter. After hospitalization, we evaluated cervical length every day for first week, and one or two times per week after the first week. Cardiotocogram (CTG) monitoring was also performed one or two times per day. Management strategies, such as therapeutic cerclage (McDonald’s cerclage), and maintenance tocolysis [29] [30] were carried out in each case at the discretion of the attending obstetricians. Vaginal progesterone was not administered because it was not covered by the national health insurance system of Japan. Patients were hospitalized from admission to 28 - 30 weeks of gestation. Cases without clinical symptoms, such as regular uterine contractions, were discharged from the hospital and managed in the outpatient clinic.

Transabdominal amniocentesis for research purpose was performed within 2 days of admission after informed written consent had been obtained. The Ethics Committee (No.187) of Toyama University Hospital approved amniocentesis for patients at risk of SPTB to evaluate the AF-IL-8 and infection. Intra-amniotic microbes were evaluated by culture system. Approximately 5 - 10 mL of amniotic fluid (AF) was obtained. Amniocentesis was only performed on asymptomatic pregnant women with a sonographic short cervix until March 2008 because of the rarity of asymptomatic cases with severe intra-amniotic inflammation and/or infection.

2.3. Study Procedures and Statistical Analysis

Demographic and clinical data [maternal age, nullipara, a history of SPTB, pre-

pregnancy body mass index (BMI), smoking during pregnancy, gestational weeks on admission, maternal body temperature, WBC, CRP, cervical length, Nugent score, fFN in vaginal secretions, CM-IL-8, AF-IL-8, AF-glucose, AF-WBC, AF-microbes, tocolysis, cerclage, gestational weeks at birth, neonatal birth weight, still birth, Apgar scores, and admission to the NICU] were collected and compared between delivery at <34 weeks and \geq 34 weeks [31].

Risk factors associated with preterm delivery at <34 weeks of gestation (PTD at <34 weeks) were assessed using a univariate analysis, which was performed using the χ^2 -test or Mann-Whitney *U* test, where appropriate. Cut-off values for risk factors were analyzed using a receiver operating characteristics (ROC) curve, and independent risk factors were investigated using a multiple regression logistic analysis. All analyses were performed using statistical analysis software (JMP, version 11.2.0; SAS Institute Inc., Tokyo, Japan). A *p*-value < 0.05 was considered to be significant.

We also discussed the pathology and management strategy for asymptomatic pregnant women with a short cervix based on the results of this retrospective study.

3. Results

Seventy-three asymptomatic pregnant women with a sonographic short cervix \leq 25 mm were selected in the present study (Figure 1), and 13 cases delivered at <34 weeks (17.8%: 13/73)

Table 1 shows a comparison of clinical characteristics between asymptomatic pregnant women with a sonographic short cervix with PTD at <34 weeks and delivery at \geq 34 weeks. A history of PTB (57.1%), CM-IL-8 [803.5 (26.9 - 2785.9) ng/mL], AF-IL-8 [6.4 (0.3 - 138) ng/mL], and tocolytis (100%) in PTD at <34 weeks were significantly higher than those [15.8%, 154.8 (1.9 - 2229.5) ng/mL, 2.2 (0.1 - 30.8) ng/mL, and 60%, respectively] in Delivery at \geq 34 weeks. On the other hand, gestational age on admission [21 (19 - 26) weeks] and cervical length on admission [13 (5 - 24) mm] in PTD at <34 weeks was significantly lower than those [25 (16 - 28) weeks and 17 (5 - 25) mm, respectively] in Delivery at \geq 34 weeks.

Gestational weeks on admission \leq 23 weeks (AUC = 0.762), AF-IL-8 \geq 2.4 ng/mL (AUC = 0.706), CM-IL-8 \geq 803.5 ng/mL (AUC = 0.729), and cervical length \leq 15 mm (AUC = 0.726) were cut-off values that correlated with PTD at <34 weeks using the ROC curve (Figure 2).

Table 2 shows independent risk factors for PTD at <34 weeks identified by a multiple logistic regression analysis. CM-IL-8 \geq 803.5 ng/mL [21.3 (3.0 - 260), *p* = 0.002] and CL on admission \leq 15 mm [17.1 (1.9 - 517), *p* = 0.008] were independent risk factors.

Diagnostic values for predicting PTD at <34 weeks were sensitivity of 53.8% and specificity of 93.3% for CM-IL-8 (\geq 803.5 ng/mL), and 76.9% and 63.3%, respectively, for CL on admission (\leq 15 mm) (Table 3). Positive predictive values

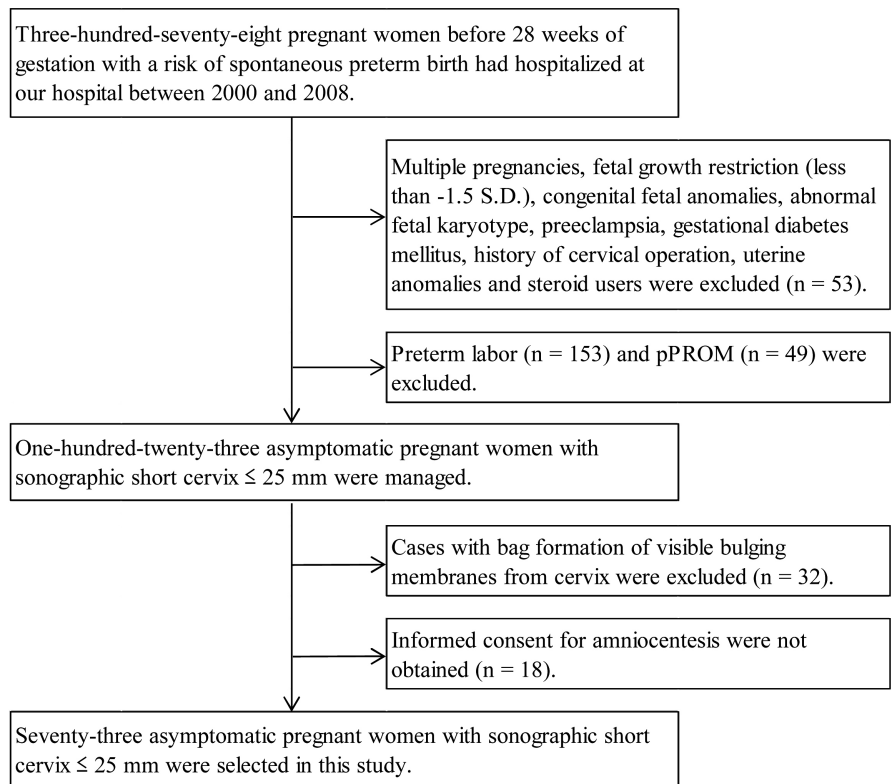


Figure 1. Study profile.

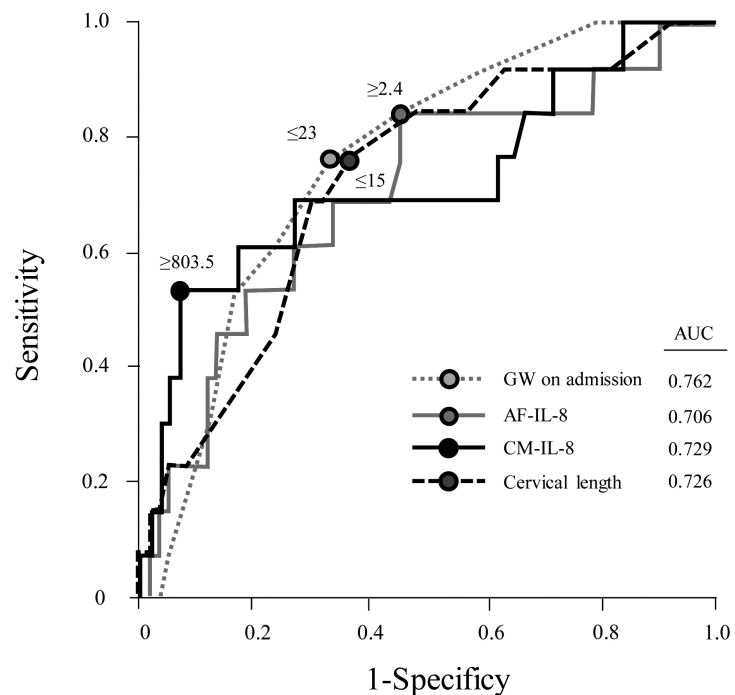


Figure 2. Receiver operating characteristic curves of each risk factor for preterm delivery at < 34 weeks of gestation in asymptomatic pregnant women with a short cervix ≤ 25 mm. The cut-off values were ≤ 23 weeks of gestational weeks on admission [area under the curve (AUC) 0.762] ≥ 2.4 ng/mL of AF-IL-8 (AUC 0.706), ≥ 803.5 ng/mL of CM-IL-8 (AUC 0.729), and ≤ 15 mm of cervical length (AUC 0.726), respectively.

Table 1. Clinical characteristics of asymptomatic pregnant women with sonographic short cervix between PTD at < 34 weeks and Delivery \geq 34 weeks of gestation.

	PTD at < 34 weeks (N = 13)	Delivery at \geq 34 weeks (N = 60)	(N = 73) <i>p</i> -value
Age (years old)	32 (27 - 40)	31 (20 - 39)	0.171
Nullipara (%)	46.1 (6/13)	36.7 (22/60)	0.524
History of SPTB (%)	57.1 (4/7)	15.8 (6/38)	0.016
Prepregnancy BMI	20.2 (17.4 - 34.0)	22.3 (17.0 - 35.5)	0.820
Smoking (%)	0 (0/13)	6.7 (4/60)	0.338
GW on admission	21 (19 - 26)	25 (16 - 28)	0.005
MBT ($^{\circ}$ C)	36.8 (35.9 - 37.4)	36.9 (35.6 - 37.6)	0.487
WBC (/mm ³)	8840 (4800 - 11,930)	9260 (4600 - 15,640)	0.320
CRP (mg/dL)	0.2 (0.1 - 0.5)	0.1 (0.1 - 1.6)	0.454
CL on admission (mm)	13 (5 - 24)	17 (5 - 25)	0.009
Nugent score (points)	1 (0 - 8)	0 (0 - 9)	0.553
fFN in VS (ng/mL)	41 (4 - 145)	14 (0 - 873)	0.133
CM-IL-8 (ng/mL)	803.5 (26.9 - 2785.9)	154.8 (1.9 - 2229.5)	0.011
AF-IL-8 (ng/mL)	6.4 (0.3 - 138)	2.2 (0.1 - 30.8)	0.029
AF-glucose (mg/dL)	38 (19 - 84)	42 (10 - 127)	0.366
AF-WBC (/mL)	6000 (800 - 49,000)	5000 (500 - 100,000)	0.302
AF-microbes by culture (%)	7.7 (1/13)	1.7 (1/60)	0.227
Tocolysis (%)	100 (13/13)	60.0 (36/60)	0.005
Cerclage (%)	69.2 (9/13)	53.3 (32/60)	0.295
GW at birth	27 (21 - 33)	37 (34 - 40)	<0.001
neonatal BW (g)	1158 (326 - 2249)	2966 (1916 - 3680)	<0.001
Still birth (%)	23.1 (3/13)	0 (0/60)	<0.001
APS (1 min) (points)	6 (3 - 8)	9 (5 - 9)	0.001
APS (5 min) (points)	8 (5 - 9)	9 (9 - 10)	0.002
Admission at NICU (%)	100 (10/10)	10.0 (6/60)	<0.001

PTD; preterm delivery, SPTB; spontaneous preterm birth, BMI; body mass index, GW; gestational weeks, MBT; maternal body temperature, WBC; white blood cell count, CRP; C-reactive protein, CL; cervical length, fFN; fetal fibronectin, VS; vaginal secretions, CM; cervical mucus, IL; interleukin, AF; amniotic fluid, BW; body weight, APS; Apgar score, NICU; neonatal intensive care unit.

were 63.6% for CM-IL-8 and 31.2% for CL on admission. On the other hand, negative predictive values were 90.3% for CM-IL-8 and 92.7% for CL on admission.

Table 2. Independent risk factors for PTD at <34 weeks of gestation by multiple logistic regression analysis.

Factor	Odd Ratio	95% CI	(N = 73)
			p-value
History of PTB	11.1	0.76 - 400	0.079
GW on admission (≤ 23 weeks)	5.8	0.92 - 57.8	0.062
AF-IL-8 (≥ 2.4 ng/mL)	5.7	0.90 - 61.1	0.065
CM-IL-8 (≥ 803.5 ng/mL)	21.3	3.0 - 260	0.002
CL on admission (≤ 15 mm)	17.1	1.9 - 517	0.008

PTD; preterm delivery, PTB; preterm birth, CI; confidence interval, GW; gestational weeks, AF; amniotic fluid, IL; interleukin, CM; cervical mucus, CL; cervical length.

Table 3. Diagnostic values for predicting PTD at < 34 weeks of gestation (n = 73).

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CM-IL-8 (≥ 803.5 ng/mL)	53.8 (7/13)	93.3 (56/60)	63.6 (7/11)	90.3 (56/62)
CL on admission (≤ 15 mm)	76.9 (10/13)	63.3 (38/60)	31.2 (10/32)	92.7 (38/41)
CM-IL-8 & CL	38.5 (5/13)	95.0 (57/60)	62.5 (5/8)	87.7 (57/65)

PTD; preterm delivery, PPV; positive predictive value, NPV; negative predictive value, CM; cervical mucus, IL; interleukin, CL; cervical length.

4. Discussion

4.1. Clinical Significance

We generally examine cervical length using ultrasonography in the outpatient clinic between 22 to 24 weeks of gestation because a short cervix is a pre-sign of SPTB. The early detection of this pre-sign before the appearance of clinical symptoms, such as cervical insufficiency (visible bag formation), PTL, or pPROM, looks to be beneficial.

Management strategies for asymptomatic pregnant women with a short cervix include the administration of progesterone [32] [33] [34], therapeutic cerclage [35] [36] [37], a vaginal pessary [38] [39] [40]. However, these treatment strategies had not been administered according to each etiology. The strategy based on the pathological condition may improve the prognosis. On the other hand, previous studies pointed out that the pregnant women with a short cervix had delivered at term without treatment in most cases [41] [42] [43]. Therefore, observation without treatment would be better choice in some cases.

In the present study, the following 5 risk factors for PTD at <34 weeks were identified in the univariable analysis; a history of SPTB, gestational weeks on admission ≤ 23 weeks, AF-IL-8 ≥ 2.4 ng/mL, CM-IL-8 ≥ 803.5 ng/mL, and cervical length ≤ 15 mm. Therefore, management strategies according to each risk factor are possible. In particular, CM-IL-8 and cervical length were identified as independent risk factors.

Although there was a significant difference in amniotic inflammation by univariable analysis, the level of inflammation was extremely low [24]. It is clinically important that the intra-uterine environment is still maintained in asymptomatic pregnant women with short cervix.

4.2. Cervical Inflammation

Based on our previous findings, CM-IL-8 ≥ 803.5 ng/mL indicates severe cervical inflammation (cervicitis >360 ng/mL) [44], which may be strongly associated with SPTB. In the pathology of asymptomatic short cervical cases, cervical inflammation may play a crucial role in shortening mechanisms.

Progesterone exerts anti-inflammatory effects [45] [46], and natural progesterone is often used in the treatment of asymptomatic short cervical cases to prevent SPTB [8] [34] [47]. Therefore, the present results may indicate its efficacy against local severe inflammation in the cervix.

4.3. Short Cervix ≤ 15 mm

Decreases in cervical length may increase the risk of SPTB [48]. In the present study, cervical length ≤ 15 mm was identified as an independent risk factor for PTD at <34 weeks with or without a history of SPTB. Previous studies reported a correlation between a short cervix ≤ 15 mm and SPTB [49] [50], which is consistent with the present results.

The efficacy of therapeutic cerclage has been suggested for patients with a short cervix ≤ 15 mm [51] [52] [53]. Therapeutic cerclage was recently shown to significantly reduce PTD at <35 weeks of gestation in patients with a short cervix <10 mm and no history of SPTB, who are at a high risk of SPTB [37]. Considering these reports and our results, the therapeutic cerclage is not necessary for cases with cervical length more than 16 mm.

4.4. Strengths and Limitations of the Present Study

The present study had the following strengths: 1) Although the etiology of or risk factors for SPTB in asymptomatic short cervical pregnant women have been extensively examined, there is no report that which factors associated with SPTB is more important by a multiple regression analysis. 2) This is the first study to clarify whether cervical or intra-amniotic inflammation is more important using inflammatory markers, such as IL-8. 3) The present results advocate the clinical concept that manages patients with a short cervix according to each individual cause. Therefore, the present results may lead to be a new logical and novel management strategy. For example, hospitalization, progesterone, and cerclage may not be necessary in asymptomatic short cervical cases at a low risk of SPTD. We previously reported that elevated CM-IL-8 in cerclage cases was an indicator of SPTD [35].

The present study had the following limitations: 1) The number of patients examined was small (73 cases), the 95% confidence interval (CI) was larger, and

clinical data were gathered from a single hospital; however, further studies with a large number of patients will increase its significance. 2) Although severe cervicitis is significant risk factor for PTD at <34 weeks, the cause of cervicitis was not identified in the present study. Vaginal microbes, such as bacteria and/or *Ureaplasma/Mycoplasma* [54], which have recently been reported to correlate with SPTB [55] [56], may contribute to severe cervicitis; however, the Nugent score was not related in this study. 3) Although the rate of therapeutic cerclage for a short cervix was high, a significant difference was not observed between the two groups (PTD at <34 weeks vs. Delivery at \geq 34 weeks).

4.5. Proposals for Future Research

In the management of asymptomatic pregnant woman with a short cervix, we propose the selection of suitable strategies based on each etiology. Therefore, the mechanisms contributing to cervical shortening without clinical symptoms need to be elucidated. Furthermore, large clinical studies, such as randomized controlled trials, are needed to clarify the ascending mechanisms of vaginal, cervical, and intra-amniotic inflammation and/or infection.

5. Conclusion

Risk factors for SPTD at <34 weeks in asymptomatic pregnant women with a sonographic short cervix include a history of SPTD, a shorter cervix (\leq 15 mm), and cervical and/or amniotic inflammation. However, the value of AF-IL-8 was very low in most cases. Appropriate treatment strategies need to be planned according to each risk factor. Especially, severe cervical inflammation and shorter cervix (\leq 15 mm) were independent risk factors. It is clinically important that the inflammation in cervix rather than in amnion was more significant. Further studies are also needed to assess cervical inflammation.

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Date Availability Statement

The data used to support the present results are available from the corresponding authors on reasonable request.

Authors' Contributions

Satoshi Yoneda conceptualized the study design. Satoshi Yoneda and Noriko Yoneda gathered and statistically analyzed clinical data. Satoshi Yoneda wrote the first draft of the manuscript. Shigeru Saito provided further technical and editorial inputs. The manuscript was reviewed and approved by all authors be-

fore its submission.

Conflicts of Interest

There is no financial or other relationship that may lead to a conflict of interest.

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