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Full length article

sCEACAM-1 levels in maternal blood in case of threatened preterm birth

Bora Zaimi [a,*], Maria Victoria Bazzano [a,b], Maximilian Rauh [a], Maria Emilia Solano [a,b], Maurice Kappelmeyer [a,b], Angela Köninger [a]

[a] University Department of Obstetrics and Gynaecology, Clinic St. Hedwig of The Order of St. John, University of Regensburg, Steinmetzstr. 1-3, D-93049 Regensburg, Germany

[b] Laboratory of Translational Perinatology, University of Regensburg, Biopark 1-3, D-93053 Regensburg, Germany

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ABSTRACT

Introduction: This study aims to investigate the role of CEACAM1 in preterm birth. Preterm birth is a phenomenon with numerous triggers, with the immune system hypothesized to play a significant role in the process, aligning with the concept of 'birth as an immunological rejection phenomenon'. There are several approaches to predict preterm birth, and the determination of sCEACAM1 levels, a member of the carcinoembryonic antigen family, may serve as a potential candidate biomarker.

Methods: A single-center prospective case series study included 67 pregnant women aged 18 years or older who presented before 37 weeks of gestation with signs of preterm birth in the years 2021–2023. At the time of admission, CEACAM1 was determined in maternal blood.

Results: The median sCEACAM1 levels were significantly higher in women who delivered preterm compared to those who delivered at term respectively, 5014 pg/ml (IQR: 3592–8826) vs. 3353 pg/ml (IQR: 2354–5049) ($p = 0.016$).

The median sCEACAM1 level in the group with PPROM (premature preterm rupture of membranes) at 34 weeks' gestation was 7001 pg/ml (IQR: 5683–13509), while the median sCEACAM1 level in the group without PPROM at 34 weeks' gestation was 3884 pg/ml (IQR; 2461–4985) ($p < 0.001$).

Conclusions: Pregnant women with preterm birth and/or PPROM before 34 weeks' gestation have higher CEACAM1 levels compared to women with threatened preterm labor who finally had labot at term. The results suggest early activated immune system as a potential pathomechanism of preterm delivery.

Introduction

Preterm birth, defined as birth before 37 weeks' gestation affects 5–18 % of pregnancies worldwide [1]. It is one of the leading causes of neonatal death [1] and of child death before the age of five years, while also contributing to child morbidity [2]. Around 15 million premature babies are born each year [3], highlighting the severity of this problem.

Preterm infants face a higher risk of various health complications compared to those born at term.

Maternal and fetal risk factors for preterm birth include demographic characteristics, nutritional status, maternal age [4], pregnancy complications, psychosocial characteristics, infections, clinical signs of preterm labor, premature rupture of membranes (PROM) and cervical insufficiency [5].

Methods for predicting preterm birth include measuring cervical length and various tests to detect specific biomarkers associated with preterm birth, including fetal fibronectin, insulin-like growth factor-binding protein-1, interleukin-6 and placental alpha-macroglobulin-1 [6,7]. These methods have limited positive predictive value and are primarily used to rule out imminent preterm birth [6]. A potential new candidate for predicting premature delivery could be the determination of the concentration of soluble CEACAM1 in maternal blood.

CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) is a protein encoded by the CEACAM1 gene. It is a member of the immunoglobulin superfamily and the carcinoembryonic antigen (CEA) family [8].

CEACAM1-distribution

What distinguishes CEACAM1 from other CEA family members is its broad tissue distribution. It is expressed on granulocytes, myeloid cells, in placentás endothelium, thyroid gland, adrenal gland, endometrium,

* Corresponding author.
E-mail address: Bora.Zaimi@stud.uni-regensburg.de (B. Zaimi).

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in the cell membrane of esophageal glands, uterine glands, pancreas, bile ducts of the liver, goblet cells as well as prostate and cervical epithelia [9]. CEACAM1 is also found in extravillous trophoblasts (EVT), macrophages, T cells, B cells, natural killer (NK) cells and thrombocytes [10–13].

CEACAM1-structure

CEACAM1 is composed by a transmembrane domain, either long or short cytoplasmic domains and a variable number of Ig-like extracellular domains. The highly glycosylated [14] extracellular domains consist of a membrane-bound immunoglobulin (Ig)V-like N region and a variable number of alternating IgC1- and IgC2-like proximal regions [8]. There are 11 isoforms of CEACAM1, resulting from the different combinations of the 9 exons that CEACAM1 gene contains [14].

In addition to the membrane-bound isoforms, soluble variants of human CEACAM1 (sCEACAM1) have been identified [15]. These isoforms are mainly generated by alternative splicing of the CEACAM1 gene [16]. It has been shown that the presence of soluble CEACAM1 protein has the capacity to alter the functional activity of CEACAM1 [17].

CEACAM1 can dimerize and form a homodimer or a heterodimer with other CEACAM family members, influencing biological processes including cell–cell adhesion, signal transduction, and immunomodulation [18,19]. CEACAM1 is also associated with the development and progression of various pathologies such as cancer [20], infectious [21] and autoimmune diseases [22]. In addition, CEACAM1 plays a role in the regulation of insulin sensitivity by promoting hepatic insulin clearance [23]. CEACAM1 sets itself apart from other family members through its expression in activated T cells [9].

CEACAM1 during pregnancy and its association with (preterm) birth/ preterm labor

We hypothesize that CEACAM1 plays a role in pregnancy, labor and delivery. During the first trimester of pregnancy, sCEACAM1 serum levels are higher than in the second trimester, possibly due to a transient immune activation associated with implantation and placentation [24]. sCEACAM1 serum levels reach their lowest level in the second trimester. In this pregnancy phase intricate endocrine-immune crosstalk results in the amelioration of e.g. T cell and macrophage inflammatory responses, promoting maternal immune tolerance to the fetus and placenta [25,26]. Hence, reduced sCEACAM1 levels may result from or contribute to reduced inflammatory responses in the second trimester [24]. In the third trimester, levels increase even further as the mother's immune system is activated to induce labor. After delivery, sCEACAM1 levels decrease (although levels are higher than in the second trimester), indicating the restoration of homeostasis of the mother's immune system [24].

Materials and methods

Study design

The study is a single-center prospective case series study recruiting a number (series) of clinical cases presenting at the St. Hedwig University Clinic, Perinatal Center Level 1, Regensburg, Germany, between 2021 and 2023. The study protocol was approved by the Ethic Commission of the University of Regensburg, Germany (21–2427–101).

Study population

The population included in this study consisted of a contingent of 67 cases of pregnant patients who presented with signs of preterm birth before 37 weeks' gestation and met the following conditions:

Inclusion criteria

Pregnant women aged 18 years or older, who are less than 37 weeks pregnant, were included in the study if they met one or more of the following criteria: a cervical length of less than 25 mm on vaginal ultrasonography, the presence of uterine contractions or premature rupture of membranes as reason for admission in the hospital.

Exclusion criteria

Pregnant women with intrauterine growth retardation (IUGR) or pre-eclampsia were excluded from the study.

The gestational age was confirmed by early measurement of the crown-rump-length between the 9th and 12th weeks of gestation, according to German maternal care guidelines.

Preterm contractions were characterized as painful contractions that led pregnant women to the hospital.

All participants in the study provided written consent, confirming their understanding and agreement to participate.

Sample and data collection

At presentation in the clinic a blood sample was collected from the study participants. Serum was separated after clotting and centrifugation at 2000*g* for 10 min, and stored at −80 °C until further use.

Information on the demographic and clinical data of the patients was retrieved from the database of the St. Hedwig University Clinic, Regensburg, Germany. Patient data was documented using programs Viewpoint 6.0 (GE Healthcare) and SAP.

Soluble CEACAM1 determination

Soluble CEACAM1 (Human sCEACAM1 CD66a) was quantified in serum samples using commercial sandwich ELISA kits, according to the manufacturer's instructions (R & D Systems, Catalog Number: DY2244). The optimal dilution was determined, and each sample was tested in duplicate. Optical density was determined using a microplate reader set to 450 nm, with wavelength correction at 540 nm. No cross-reactivity with human recombinant CEACAM3, CEACAM4, CEACAM5, CEACAM6, CEACAM7, and CEACAM- has been reported by the manufacturer.

Data analysis

We analyzed the data using SPSS 25.0 (Statistical Package for Social Sciences, Version 25.0).

Normally distributed data were expressed as mean and standard deviation; for non-normally distributed data, median and interquartile range were also included. Comparison between groups for continuous variables was performed using the Mann-Whitney *U* test. The chi-square test was used to compare proportions. Kendall's correlation coefficient was used to analyze correlations between variables. A p-value ≤ 5 % was considered as significant. The graphs were created using GraphPad Prism software (version 10.2.3).

Results

The study included 67 pregnant women with characteristics shown in Table 1. In 59 cases a singleton pregnancy and in 8 cases multiple pregnancy was present.

Among the 67 women analyzed, 61.2 % (n = 41) gave birth prematurely (< 37 weeks of gestation) and 38.8 % (n = 26) gave birth at term (≥37 weeks of gestation).

The most common reasons for women presenting on the day of blood collection were preterm premature rupture of membranes (PPROM) (52.2 %), contractions (32.8 %), cervical shortening (37.3 %) and

Table 1
Characteristics of the study population.

Variables	n	Mean ± SD	Median (IQR)
Age in years	67	31.2 ± 4.7	31 (29–35)
BMI before pregnancy (kg/m2)	66	24.3 ± 5.2	23.1 (20.5–27.2)
GA at the time of blood sampling (days)	66	221.6 ± 32.4	231.5 (212.8–223.3)
sCEACAM1-value at the time of blood sampling (pg/ml)	67	6639 ± 6529	4407 (3031–6564)
Leukocytes at the time of blood sampling (/nl)	64	12.2 ± 3.8	11.9 (9.95–13.6)
CRP at the time of blood sampling (mg/l)	64	7.04 ± 10.06	4 (2.0–8.0)
GA at birth (days)	67	251.5 ± 23.6	251 (243–266)

GA – Gestational age; BMI- Body-Mass-Index; CRP- C-reactive protein; IQR-Interquartile range;
SD- Standard Deviation; n- number of cases.

vaginal bleeding (11.9 %). There were more cases of PPROM (80.5 % vs.7.7 %; $p < 0.001$) in preterm births compared to term births, while cervical shortening was more common in term births than in preterm births (80.8 % vs. 9.8 %; $p < 0.001$) [Table 2].

In terms of risk factors, differences were found between the preterm and term births with regard to the diagnosis of PPROM before 34 weeks of pregnancy, which was significantly more common in pregnant women with preterm birth, than in pregnant women with term birth (43.9 % vs. 3.8 %; $p < 0.001$)), and cervical length (CL) less than 25 mm before 34 weeks of pregnancy, which was significantly more common in pregnant women with term birth than in pregnant women with preterm birth (92.3 % vs. 31.7 %; $p < 0.001$). The percentage of women in whom cerclage was performed was significantly higher in pregnant women with term births than in pregnant women with preterm births (50.0 % vs. 19.5 %; $p = 0.009$) [Table 3].

sCEACAM1 concentrations (pg/ml) were found to be elevated in pregnant women who underwent preterm delivery compared to those with term delivery. The median value of sCEACAM1 in the group with preterm birth was 5014 pg/ml (IQR: 3592–8826), while the median value of sCEACAM1 in the group with term birth was 3353 pg/ml (IQR: 2354–5049) ($p = 0.016$) [Fig. 1].

When analyzing the correlation between sCEACAM1 and the time from blood collection to birth, no significant correlation was found ($p = 0.09$, Kendall-Tau-b coefficient = -0.145).

We also analyzed the associations between sCEACAM1 values and the time from blood collection to delivery in each subgroup separately. No significant correlation was observed between sCEACAM1 levels and

Table 2
Reasons for presentation at the hospital.

Reason for presentation at the hospital		Total n = 67 (%)	Birth		p-value*
			Preterm birth n = 41 (%)	Term birth n = 26 (%)	
Premature rupture of membranes	yes	35 (52.2)	33 (80.5)	2 (7.7)	<0.001
	no	32 (47.8)	8 (19.5)	24 (92.3)	
Contractions	yes	22 (32.8)	14 (34.1)	8 (30.8)	0.774
	no	45 (67.2)	27 (65.9)	18 (69.2)	
Vaginal bleeding	yes	8 (11.9)	5 (12.2)	3 (11.5)	0.936
	no	59 (88.1)	36 (87.8)	23 (88.5)	
Shortening of the cervix < 25 mm	yes	25 (37.3)	4 (9.8)	21 (80.8)	<0.001
	no	42 (62.7)	37 (90.2)	5 (19.2)	

*Chi-Square test.

Table 3
Risk factors by time of birth (premature birth/term birth).

Risk factors		Total n = 67 (%)	Birth		p-value*
			Preterm birth, n = 41 (%)	Term birth, n = 26 (%)	
Obesity	yes	5 (7.5)	3 (7.3)	2 (7.7)	0.955
	no	62 (92.5)	38 (92.7)	24 (92.3)	
Age of women over 35 years	yes	18 (26.9)	10 (24.4)	8 (30.8)	0.566
	no	49 (73.1)	31 (75.6)	18 (69.2)	
PPROM before 34 weeks of pregnancy	yes	19 (28.4)	18 (43.9)	1 (3.8)	<0.001
	no	48 (71.6)	23 (56.1)	25 (96.2)	
Cerclage	yes	21 (31.3)	8 (19.5)	13 (50.0)	0.009
	no	46 (68.7)	33 (80.5)	13 (50.0)	
CL < 25 mm before 34 weeks of pregnancy	yes	37 (55.2)	13 (31.7)	24 (92.3)	<0.001
	no	30 (44.8)	28 (68.3)	2 (7.7)	
Two or more previous miscarriages/ abortions	yes	8 (11.9)	6 (14.6)	2 (7.7)	0.393
	no	59 (88.1)	35 (85.4)	24 (92.3)	
Gestational diabetes	yes	10 (14.9)	5 (12.2)	5 (19.2)	0.431
	no	57 (85.1)	36 (87.8)	21 (80.8)	
COVID19 infection during pregnancy	yes	9 (13.4)	5 (12.2)	4 (15.4)	0.709
	no	58 (86.6)	36 (87.8)	22 (84.6)	
Vaginal bleeding	yes	1 (1.5)	1 (2.4)	0 (0.0)	0.422
	no	66 (98.5)	40 (97.6)	26 (100.0)	
Previous infertility treatment	yes	8 (11.9)	7 (17.1)	1 (3.8)	0.104
	no	59 (88.1)	34 (82.9)	25 (96.2)	
Previous preterm delivery	yes	4 (6.0)	2 (4.9)	2 (7.7)	0.636
	no	63 (94.0)	39 (95.1)	24 (92.3)	
Previous Sectio caesarea	yes	5 (7.5)	3 (7.3)	2 (7.7)	0.955
	no	62 (92.5)	38 (92.7)	24 (92.3)	
Multiple pregnancy	yes	8 (11.9)	4 (9.8)	2 (15.4)	0.489
	no	59 (88.1)	37 (90.2)	22 (84.6)	

*Chi-Square-test.
PPROM-Preterm premature rupture of membranes; CL- Cervix length.
Obesity: BMI = 30–34.9 kg/m^2; Multiple pregnancy: pregnancy with more than one fetus.

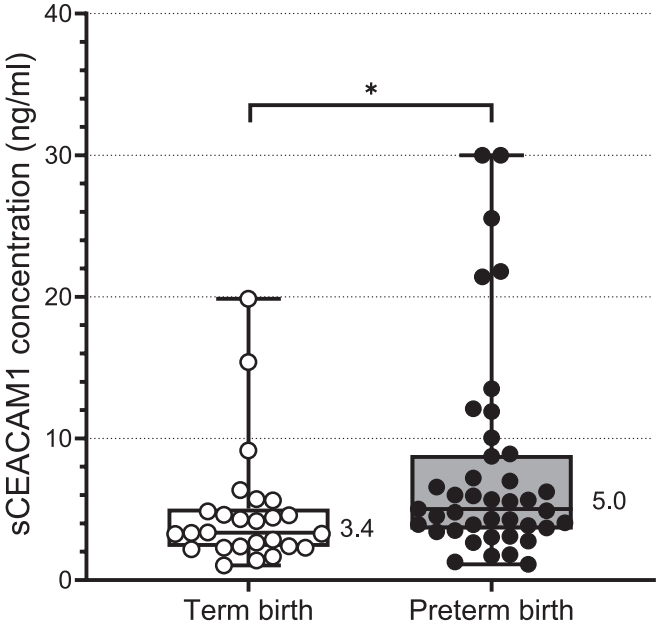

Fig. 1. Serum levels of sCEACAM1 among pregnant women were examined, distinguishing between those who experienced preterm delivery and term delivery. [*$p < 0.05$; Mann Whitney-U Test].

Table 4
Correlation values for sCEACAM1 levels (pg/ml) with the time between admission and delivery in different subgroups of pregnancy characteristics and outcomes.

Variables		Correlation indicators	Time from blood collection to birth (in days)
Birth	Preterm birth < 37 weeks of pregnancy	r*	0.026
		p-value	0.822
		n	40
	Term birth > 37 weeks of pregnancy	r*	0.074
		p-value	0.597
		n	26
PPROM	No PPROM before 34 weeks of pregnancy	r*	−0.167
		p-value	0.101
		n	48
	PPROM before 34 weeks of pregnancy	r*	0.166
		p-value	0.342
		n	18
Cervical length (CL)	No CL less than 25 mm before 34 weeks' gestation	r*	−0.049
		p-Wert	0.717
		n	29
	CL less than 25 mm before 34 weeks' gestation	r*	−0.137
		p-value	0.234
		n	37
Preterm labor	No preterm labor before 34 weeks gestation	r*	−0.123
		p-value	0.225
		n	48
	Preterm labor before 34 weeks gestation	r*	−0.219
		p-value	0.21
		n	18

*Kendall's Tau-b correlation coefficient.
PPROM-Preterm premature rupture of membranes; CL- Cervix length.
Time (in days) from blood collection to birth, analyzed depending on the time of birth; the diagnosis of PPROM before 34 weeks of pregnancy; the diagnosis CL less than 25 mm before 34 weeks of pregnancy and the diagnosis of preterm labor before 34 weeks of pregnancy.

the time from blood collection to delivery across the analyzed variables [Table 4].

No significant difference between multiple and singleton pregnancies was found [respectively median 6667 pg/ml (IQR: 2827–11443) vs. 4310 pg/ml (IQR: 3031–6229) (p = 0.486)].

Concentrations of sCEACAM1 (pg/ml) were found to be elevated in pregnant women with PPROM before 34 weeks of pregnancy compared to those without. The median value of sCEACAM1 in the group with PPROM before 34 weeks of pregnancy was 7001 pg/ml (IQR: 5683–13509), while the median value of sCEACAM1 in the group without PPROM before 34 weeks of pregnancy was 3884 pg/ml (IQR: 2461–4985) (p < 0.001) [Fig. 2].

Nine patients showed increased infection parameters (CRP (c-reactive protein) > 20 mg/l, Leukocytes > 16/nl). No significant correlation was found between sCEACAM1 and leukocytes in maternal blood (p = 0.868) or between sCEACAM1 and CRP in maternal serum (p = 0.196).

Discussion

The immune system differentiates between self and foreign structures [27]. The semi-allogeneic nature of the fetus, inheriting genetic material from both parents, may elicit inflammatory responses [28]. However, in physiological pregnancy immune attack to the fetus and placenta is prevented, which we refer to as maternal-fetal tolerance. In particular, the process of placentation requires maternal-fetal tolerance, which ensures that the fetus and mother can communicate efficiently via the placenta.

The phenomenon of maternal-fetal tolerance is enabled by several

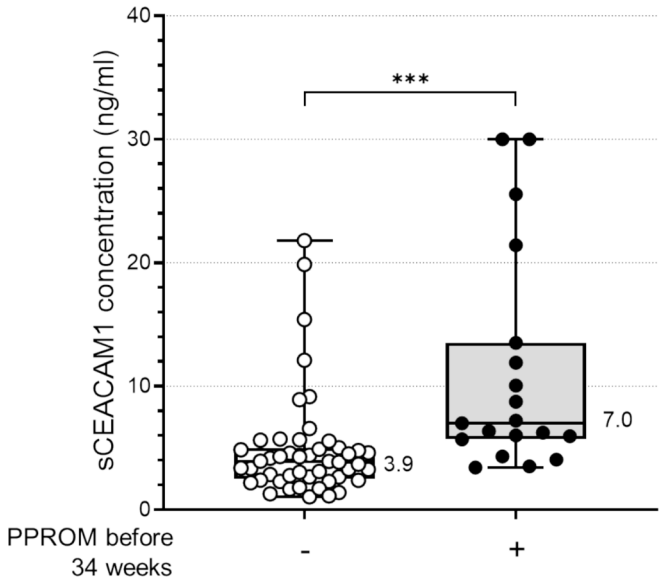

Fig. 2. Serum levels of sCEACAM1 among pregnant women were examined, distinguishing between those who experienced preterm premature rupture of membranes (PPROM) before 34 weeks of pregnancy and those who did not (No PPROM before 34 weeks of pregnancy). [***p < 0.001; Mann Whitney-U Test].

complex mechanisms. Among many others, maternal decidual macrophages have the ability to inhibit NK cell-mediated killing of cytotrophoblast cells [29], while Foxp3 + CD4 cells maintain a protective regulatory memory for the fetal antigen [30]. In addition, silencing chemokine genes plays an important role in preventing the accumulation of activated T cells [31], ensuring stable maternal-fetal tolerance throughout pregnancy.

This tolerance comes to an end in the third trimester, when reactivation of maternal inflammatory responses triggers uterine contractions and thus the delivery of the child [32,33].

Considering CEACAM1's interaction with activated T cells, corticotropin-releasing hormone, estrogen, osteopontin, and cytokines, the changes in its concentration during pregnancy and its presence in EVT cells and the placenta's endothelium it is plausible to postulate that CEACAM1 could also contribute to the occurrence of preterm birth as a surrogate parameter for preterm immune activation [34–38].

In our study we found that the median value of sCEACAM1 in the group with preterm birth was almost one and a half times higher than the median value of sCEACAM1 in the group with term birth at the moment of presentation with signs of threatened preterm birth.

As mentioned in section 1.3, an increase in the level of sCEACAM1 is observed as the maternal system prepares for the onset of labor [24]. Therefore, it is not surprising that higher sCEACAM1 values were identified in women experiencing premature births.

It is also interesting to compare sCEACAM1 levels among various clinical signs of threatened preterm birth. Therefore, our study design included different subgroups, which were compared with each other. As a result, we found that the median value of sCEACAM1 in the group with PPROM before 34 weeks of pregnancy was 1.8 times higher than the median value of sCEACAM1 in the group without PPROM before 34 weeks of pregnancy.

The occurrence of programmed cell death, also known as apoptosis, has been shown to be a crucial factor in PPROM [39]. Concurrently, CEACAM1 is able to trigger the cellular apoptosis machinery [40,41], which may explain the elevated levels of sCEACAM1 we detected.

Kim et al. conducted a study examining the levels of Vascular Endothelial Growth Factor (VEGF) to assess their predictive value for spontaneous preterm birth in singleton pregnancies, finding significantly higher mean VEGF levels in the preterm group compared to the

term group [42]. Ergun S et al. on the other hand demonstrated that VEGF can upregulate the expression of CEACAM1 in endothelial cells [43]. This might once again provide a possible explanation for the higher sCEACAM1 levels we observed.

CEACAM1 is highly expressed by activated decidual lymphocytes and has been demonstrated to hinder the proliferation, cytokine secretion, and killing mechanism of IL-2-activated CD4+T, natural killer T (NKT), and NK cells, respectively [10]. Local bacterial or viral infections can trigger changes in decidual lymphocytes, altering their composition, cytotoxicity, and cytokine profile. Without proper regulation, such activation poses the risk of causing damage to placental or fetal tissues [10]. Therefore maintaining immune balance in the decidua is crucial to eliminate pathogens without the developing fetus. The mentioned activity of CEACAM1 is one of the mechanisms that allows for the maintenance of this balance [10]. Given that infections can be associated with PPROM [44], it is tempting to hypothesize (despite our results showing no significant correlation between CEACAM1 and leukocytes/CRP) that (subclinical) infections are one of the reasons that high sCEACAM1 levels are found in pregnant women who develop PPROM. This does not imply that every instance of PPROM is necessarily the result of an infection; however, it does underscore a potential association between CEACAM1, PPROM, infection and inflammation.

Although our inclusion criteria, such as cervical length < 25 mm, uterine contractions, and membrane rupture, are associated with different risk degrees for threatened preterm birth, we included all parameters simultaneously, as clinical practice also uses them to indicate intensified maternal care.

Conclusion

We found higher values of sCEACAM 1 in women with PPROM before 34 weeks of pregnancy compared to those without, as well as in women who gave birth prematurely, compared to those who gave birth on time. These findings support the hypothesis that CEACAM1 contributes to the processes of labor and delivery.

More comprehensive studies involving a larger cohort, wherein blood samples are collected from all pregnant participants (with or without signs of preterm birth) at specific time points during gestation, and subsequent analysis correlating CEACAM1 levels with the duration until childbirth, could reveal a precise predictive capacity of CEACAM1 in determining the timing of delivery. In this manner, the determination of CEACAM1 values could enable us to precisely determine the expected outcome in pregnant women showing signs of preterm delivery, thus providing us with knowledge that can help prevent or treat premature births under distinct conditions.

Ethical statement

The study was approved by the Ethic committee of the Medical Faculty, University of Regensburg (21-2427-101). Every participant gave written informed consent before study inclusion.

CRediT authorship contribution statement

Bora Zaimi: Writing – original draft, Formal analysis, Data curation. **Maria Victoria Bazzano:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Maximilian Rauh:** Writing – review & editing, Supervision, Resources. **Maria Emilia Solano:** Writing – review & editing, Resources, Project administration. **Maurice Kappelmeyer:** Writing – review & editing, Visualization. **Angela Köninger:** Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] O'Reilly P, Dakin A, Keating N, Luethe L, Corcoran S. Does the use of gestation-specific centiles for cervical length change the management of pregnancies at risk of recurrent spontaneous preterm birth? Eur J Obstet Gynecol Reprod Biol 2021: 264349–52. https://doi.org/10.1016/j.ejogrb.2021.07.052. Cited in: PubMed; PMID 34385081.

[2] World Health Organization. Preterm birth [Internet]. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/preterm-birth.

[3] Liu T, Xu Y, Gong Y, Zheng J, Chen Z. The global burden of disease attributable to preterm birth and low birth weight in 204 countries and territories from 1990 to 2019: an analysis of the Global Burden of Disease Study. J Glob Health 1990;2024: 144109. https://doi.org/10.7189/jogh.14.04109. Cited. In: PubMed; PMID 38991211.

[4] Esposito G, Mauri PA, Cipriani S, Franchi M, Corrao G, Parazzini F. The role of maternal age on the risk of preterm birth among singletons and multiples: a retrospective cohort study in Lombardy, Norther Italy. BMC Pregnancy Childbirth 2022;22(1):234. https://doi.org/10.1186/s12884-022-04552-y. Cited. In: PubMed; PMID 35317757.

[5] Goldenberg RL, Culhane JF, Iams JD, Romero R. Preterm birth 1: epidemiology and causes of preterm birth. Obstet Anesth Dig 2009;29(1):6–7. https://doi.org/10.1097/01.aoa.0000344666.82463.8d.

[6] Oskovi Kaplan ZA, Ozgu-Erdinc AS. Prediction of preterm birth: maternal characteristics, ultrasound markers, and biomarkers: an updated overview. J Pregnancy 2018. https://doi.org/10.1155/2018/8367571. 20188367571, Cited in: PubMed; PMID 30405914.

[7] Pirjani R, Moini A, Almasi-Hashiani A, Farid Mojtahedi M, Vesali S, Hosseini L, et al. Placental alpha microglobulin-1 (PartoSure) test for the prediction of preterm birth: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2021;34 (20):3445–57. https://doi.org/10.1080/14767058.2019.1685962. Cited. In: PubMed; PMID 31736399.

[8] Tsugawa N, Yamada D, Watabe T, Onizawa M, Wang S, Nemoto Y, Oshima S, Tsubata T, Adachi T, Kawano Y, Watanabe M, Blumberg RS, Okamoto R, Nagaishi T. CEACAM1 specifically suppresses B cell receptor signaling-mediated activation. Biochem Biophys Res Commun 2021:53599–4105. https://doi.org/10.1016/j.bbrc.2020.11.126. Cited in: PubMed; PMID 33352461.

[9] Thomas J, Klebanov A, John S, Miller LS, Vegesna A, Amdur RL, Bhowmick K, Mishra L. CEACAMS 1, 5, and 6 in disease and cancer: interactions with pathogens. Genes Cancer 2023:1412–29. https://doi.org/10.18632/genesandcancer.230. Cited in: PubMed; PMID 36741860.

[10] Markel G, Wolf D, Hanna J, Gazit R, Goldman-Wohl D, Lavy Y, et al. Pivotal role of CEACAM1 protein in the inhibition of activated decidual lymphocyte functions. J Clin Invest 2002;110(7):943–53. https://doi.org/10.1172/JCI15643 Cited. In: PubMed; PMID 12370272.

[11] Huang Y-H, Yoon CH, Gandhi A, Hanley T, Castrillon C, Kondo Y, et al. High-dimensional mapping of human CEACAM1 expression on immune cells and association with melanoma drug resistance. Commun Med (Lond) 2024;4(1):128. https://doi.org/10.1038/s43856-024-00525-8. Cited. In: PubMed; PMID 38956268.

[12] Götz L, Rueckschloss U, Balk G, Pfeiffer V, Ergün S, Kleefeldt F. The role of carcinoembryonic antigen-related cell adhesion molecule 1 in cancer. Front Immunol 2023. https://doi.org/10.3389/fimmu.2023.1295232. 141295232, Cited in: PubMed; PMID 38077351.

[13] Ye Y, Leng M, Chai S, Yang L, Ren L, Wan W, et al. Antiplatelet effects of the CEACAM1-derived peptide QDTT. Platelets 2024;35(1):2308635. https://doi.org/10.1080/09537104.2024.2308635. Cited. In: PubMed; PMID 38345065.

[14] Gray-Owen SD, Blumberg RS. CEACAM1: contact-dependent control of immunity. Nat Rev Immunol 2006;6(6):433–46. https://doi.org/10.1038/nri1864. Cited. In: PubMed; PMID 16724098.

[15] Singer BB, Scheffrahn I, Heymann R, Sigmundsson K, Kammerer R, Obrink B. Carcinoembryonic antigen-related cell adhesion molecule 1 expression and signaling in human, mouse, and rat leukocytes: evidence for replacement of the short cytoplasmic domain isoform by glycosylphosphatidylinositol-linked proteins in human leukocytes. J Immunol 2002;168(10):5139–46. https://doi.org/10.4049/jimmunol.168.10.5139. Cited. In: PubMed; PMID 11994468.

[16] Beauchemin N, Arabzadeh A. Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) in cancer progression and metastasis. Cancer Metastasis Rev 2013;32(3–4):643–71. https://doi.org/10.1007/s10555-013-9444-6. Cited. In: PubMed; PMID 23903773.

[17] Markel G, Achdout H, Katz G, Ling K-L, Salio M, Gruda R, et al. Biological function of the soluble CEACAM1 protein and implications in TAP2-deficient patients. Eur J

Immunol 2004;34(8):2138–48. https://doi.org/10.1002/eji.200425021. Cited. In: PubMed; PMID 15259011.
[18] Helfrich I, Singer BB. Size matters: the functional role of the CEACAM1 isoform signature and its impact for NK cell-mediated killing in melanoma. Cancers (Basel) 2019;11(3). https://doi.org/10.3390/cancers11030356. Cited in: PubMed; PMID 30871206.
[19] Kim WM, Huang Y-H, Gandhi A. Blumberg RS. CEACAM1 structure and function in immunity and its therapeutic implications. Semin Immunol 2019. https://doi.org/10.1016/j.smim.2019.101296. 42101296, Cited in: PubMed; PMID 31604530.
[20] Yu J, Cai W, Zhou T, Men B, Chen S, Tu D, Guo W, Wang J, Zhao F, Wang Y. CEACAM1 increased the lymphangiogenesis through miR-423-5p and NF- kB in Non-Small Cell Lung Cancer. Biochem Biophys Rep. 2024;40101833. doi:10.1016/j.bbrep.2024.101833 Cited in: PubMed; PMID 39398537.
[21] Khairnar V, Duhan V, Patil AM, Zhou F, Bhat H, Thoens C, et al. CEACAM1 promotes CD8+ T cell responses and improves control of a chronic viral infection. Nat Commun 2018;9(1):2561. https://doi.org/10.1038/s41467-018-04832-2 Cited. In: PubMed; PMID 29967450.
[22] Matsumoto H, Fujita Y, Onizawa M, Saito K, Sumichika Y, Yoshida S, Temmoku J, Matsuoka N, Yashiro-Furuya M, Asano T, Sato S, Suzuki E, Machida T, Watanabe H, Migita K. Increased CEACAM1 expression on peripheral blood neutrophils in patients with rheumatoid arthritis. Front Immunol. 2022;13978435. doi:10.3389/fimmu.2022.978435 Cited in: PubMed; PMID 36591283.
[23] Horst AK, Najjar SM, Wagener C, Tiegs G. CEACAM1 in Liver Injury, Metabolic and Immune Regulation. Int J Mol Sci. 2018;19(10). doi:10.3390/ijms19103110 Cited in: PubMed; PMID 30314283.
[24] Mach P, Gellhaus A, Prager S, Moore T, Wennemuth G, Kimmig R, Köninger A, Singer BB. Soluble CEACAM1 and CEACAM6 are differently expressed in blood serum of pregnant women during normal pregnancy. Am J Reprod Immunol. 2017;78(4). doi:10.1111/aji.12700 Cited in: PubMed; PMID 28593707.
[25] Morelli S, Mandal M, Goldsmith LT, Kashani BN, Ponzio NM. The maternal immune system during pregnancy and its influence on fetal development. RRBS 2015;171:doi:10.2147/RRB.S80652.
[26] Chatterjee P, Chiasson VL, Bounds KR, Mitchell BM. Regulation of the Anti-inflammatory cytokines interleukin-4 and interleukin-10 during pregnancy. Front Immunol. 2014;5253. doi:10.3389/fimmu.2014.00253 Cited in: PubMed; PMID 24904596.
[27] Chaplin DD. Overview of the immune response. J Allergy Clin Immunol 2010;125 (2 Suppl 2):S3–. https://doi.org/10.1016/j.jaci.2009.12.980 Cited. In: PubMed; PMID 20176265.
[28] Wegorzewska M. Maternal immune recognition of the semi-allogeneic fetus during fetal intervention in mice [Internet]: UCSF. 2014. Available from: https://escholarship.org/uc/item/6k2754w1#main.
[29] PrabhuDas M, Bonney E, Caron K, Dey S, Erlebacher A, Fazleabas A, et al. Immune mechanisms at the maternal-fetal interface: perspectives and challenges. Nat Immunol 2015;16(4):328–34. https://doi.org/10.1038/ni.3131 Cited. In: PubMed; PMID 25789673.
[30] Rowe JH, Ertelt JM, Xin L, Way SS. Pregnancy imprints regulatory memory that sustains anergy to fetal antigen. Nature 2012;490(7418):102–6. https://doi.org/10.1038/nature11462 Cited. In: PubMed; PMID 23023128.
[31] Lissauer D, Eldershaw SA, Inman CF, Coomarasamy A, Moss PAH, Kilby MD. Progesterone promotes maternal-fetal tolerance by reducing human maternal T-cell polyfunctionality and inducing a specific cytokine profile. Eur J Immunol 2015;45(10):2858–72. https://doi.org/10.1002/eji.201445404 Cited. In: PubMed; PMID 26249148.
[32] Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. Ann N Y Acad Sci 2011;1221(1):80–7. https://doi.org/10.1111/j.1749-6632.2010.05938.x. Cited. In: PubMed; PMID 21401634.
[33] Mor G. Pregnancy Reconceived: What keeps a mother's immune system from treating her baby as foreign tissue? A new theory resolves the paradox. [Internet]. 2007. Available from: https://www.researchgate.net/profile/Gil-Mor-2/publication/291468070_Pregnancy_reconceived/links/56f54eea08ae95e8b6d1d51c/Pregnancy-reconceived.pdf.
[34] Kalantaridou SN, Zoumakis E, Weil S, Lavasidis LG, Chrousos GP, Makrigiannakis A. Reproductive corticotropin releasing hormone, implantation, and fetal immunotolerance. Crit Rev Clin Lab Sci 2007;44(5–6):461–81. https://doi.org/10.1080/10408360701548468 Cited. In: PubMed; PMID 17943493.
[35] Meakin C, Barrett ES, Aleksunes LM. Extravillous trophoblast migration and invasion: Impact of environmental chemicals and pharmaceuticals. Reprod Toxicol. 2022;10760–8. doi:10.1016/j.reprotox.2021.11.008 Cited in: PubMed; PMID 34838982.
[36] Zhu Y, Song D, Song Y, Wang X. Interferon gamma induces inflammatory responses through the interaction of CEACAM1 and PI3K in airway epithelial cells. J Transl Med 2019;17(1):147. https://doi.org/10.1186/s12967-019-1894-3. Cited. In: PubMed; PMID 31072323.
[37] Briese J, Oberndörfer M, Niemann J, Schulte HM, Makrigiannakis A, Löning T, et al. Osteopontin (OPN) is colocalized with the adhesion molecule CEACAM1 in the utero-placental system and enhances with its receptor Integrin ß3 the invasion of extravillous trophoblast cells. Exp Clin Endocrinol Diabetes 2006;114(S:1). https://doi.org/10.1055/s-2006-932977.
[38] Briese J, Schulte HM, Bamberger CM, Löning T, Bamberger A-M. Expression pattern of osteopontin in endometrial carcinoma: correlation with expression of the adhesion molecule CEACAM1. Int J Gynecol Pathol 2006;25(2):161–9. https://doi.org/10.1097/01.pgp.0000189243.49522.ae. Cited. In: PubMed; PMID 16633066.
[39] Menon R, Richardson LS, Lappas M. Fetal membrane architecture, aging and inflammation in pregnancy and parturition. Placenta. 2019;7940–5. doi:10.1016/j.placenta.2018.11.003. Cited in: PubMed; PMID 30454905.
[40] Nittka S, Böhm C, Zentgraf H, Neumaier M. The CEACAM1-mediated apoptosis pathway is activated by CEA and triggers dual cleavage of CEACAM1. Oncogene 2008;27(26):3721–8. https://doi.org/10.1038/sj.onc.1211033. Cited. In: PubMed; PMID 18278069.
[41] Nittka S, Günther J, Ebisch C, Erbersdobler A, Neumaier M. The human tumor suppressor CEACAM1 modulates apoptosis and is implicated in early colorectal tumorigenesis. Oncogene 2004;23(58):9306–13. https://doi.org/10.1038/sj.onc.1208259. Cited. In: PubMed; PMID 15568039.
[42] Kim A, Lee ES, Shin JC, Kim HY. Identification of biomarkers for preterm delivery in mid-trimester amniotic fluid. Placenta 2013;34(10):873–8. https://doi.org/10.1016/j.placenta.2013.06.306. Cited. In: PubMed; PMID 23953866.
[43] Ergün S, Kilik N, Ziegeler G, Hansen A, Nollau P, Götze J, et al. CEA-related cell adhesion molecule 1: a potent angiogenic factor and a major effector of vascular endothelial growth factor. Mol Cell 2000;5(2):311–20. https://doi.org/10.1016/s1097-2765(00)80426-8. Cited. In: PubMed; PMID 10882072.
[44] Shivaraju P, Purra P, Bheemagani N, Lingegowda K. Vaginal infections and its relation to preterm labour, PPROM, PROM and its outcome. Int J Reprod Contracept Obstet Gynecol 2015:1422–6. https://doi.org/10.18203/2320-1770.ijrcog20150723.