

Maternal Serum Fractalkine Concentrations in Pregnancies Complicated by Fetal Growth Restriction

Ecem Berfun TOPRAK SAGER¹, Ibrahim KALE¹, Hakan SAGER², Aysegul OZEL³, Murat MUHCU³

Istanbul, Türkiye

ABSTRACT

OBJECTIVE: Fractalkine is a newly discovered chemokine that is expressed in placental tissue during pregnancy and is subsequently shed into the maternal serum. Although there are a few studies examining the relationship between fractalkine and preeclampsia, its role in isolated fetal growth restriction has not been investigated yet. In this study, we aimed to investigate the relationship between isolated fetal growth restriction and maternal serum fractalkine concentrations.

STUDY DESIGN: This cross-sectional study was conducted on 86 pregnant women, 25 of whom were diagnosed with fetal growth restriction in the third trimester, 23 were small for gestational age, and 38 were healthy controls. These three groups were compared in terms of maternal serum fractalkine concentrations.

RESULTS: While the highest mean maternal serum fractalkine concentration was found in the small for gestational age group at 23.31 ng/mL, it was determined as 18.06 ng/mL in the fetal growth restriction group and 16.03 ng/mL in the control group. We did not find a statistical difference between the groups in terms of fractalkine concentrations ($p=0.258$). When the patients with fetal growth restriction and small for gestational age were evaluated as a single group and compared with the control group, the mean fractalkine concentration in the fetal growth restriction+small for gestational age group was higher than the control group, but this difference was not statistically significant ($p=0.214$).

CONCLUSION: Maternal serum fractalkine concentration was higher in both fetal growth restriction and small for gestational age groups compared to healthy controls, but this difference was not statistically significant. The role of the fractalkine molecule in the development of fetal growth restriction remains to be clarified in future studies with larger series.

Keywords: Fetal growth restriction, Fractalkine, Small for gestational age

Gynecol Obstet Reprod Med. 2023;29(2):79-85

¹ Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Türkiye

² Bursa Yuksek Ihtisas Research and Training Hospital, Department of Obstetrics and Gynecology, Bursa, Türkiye

³ Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology, Maternal Fetal Unit, Istanbul, Türkiye

Address of Correspondence: Ibrahim Kale
Umraniye Training and Research Hospital,
Elmalikent, Adem Yavuz Street,
34764 Umraniye Istanbul, Türkiye
dribakale@hotmail.com


Submitted for Publication: 09.07.2022 Revised for Publication: 15.07.2022

Accepted for Publication: 13.09.2022 Online Published: 26.09.2022

ORCID IDs of the authors: EBTS: 0000-0001-5528-3472

IK: 0000-0001-7802-7199 HS: 0000-0002-6947-5245

AO: 0000-0002-0283-1049 MM: 0000-0001-7039-375X

Quick Response Code:	Access this article online
	Website: www.gorm.com.tr e-mail: info@gorm.com.tr DOI:10.21613/GORM.2022.1342

How to cite this article: Toprak Sager EB, Kale I, Sager H, Ozel A, Muhcu M. Maternal Serum Fractalkine Concentrations in Pregnancies Complicated by Fetal Growth Restriction. *Gynecol Obstet Reprod Med.* 2023;29(2):79-85



Copyright© 2023. Toprak Sager et al. This article is distributed under a Creative Commons Attribution 4.0 International License.

Introduction

Fetal growth depends on many maternal, placental, and fetal factors, including the fetus's genetic background, hormones, growth factors, and nutrient supply (1). Fetal growth restriction (FGR) is known as the failure of the fetus to reach its genetically determined growth potential before birth and occurs in 10% of all pregnancies (2,3). A fetus can be considered small for gestational age (SGA) when the estimated fetal weight (EFW) or abdominal circumference (AC) falls below the 10th percentile of the predefined reference ranges for gestational age but, there is currently no gold standard for the diagnosis of FGR (4). Fetuses with AC or EFW below the 3rd percentile, fetuses with a decrease of more than 2 quarters or more than 50% in AC or EFW during follow-up, and also unfavorable findings detected in the uteroplacental and fetoplacental circulation are generally considered as FGR (4). The most important difference between FGR and SGA is that fetuses with FGR have an increased risk of adverse perinatal outcomes (5).

Fractalkine (CX3CL1) also known as neurotactin was first described in 1997 and it is encoded on chromosome 16 in humans (6,7). Fractalkine, a new member of the chemokine family, is a low molecular weight protein and consists of two isoforms; soluble and membrane-bound form (8). The membrane-bound form mediates the adhesion of leukocytes to endothelial and epithelial cells via its receptor (CX3CR1), while the soluble form results from metalloprotease-induced shedding and carries chemoattractive activity for leukocytes (9).

In the literature, it has been revealed that fractalkine as a chemokine plays a role in the pathogenesis of some inflammatory diseases such as allergic asthma, atherosclerosis, rheumatoid arthritis, and Crohn's disease (10,11). Fractalkine has also been shown to be expressed in the endometrium, placenta, and amniotic epithelial cells (10,11). This knowledge has led scientists to investigate the role of fractalkine in pregnancy, and studies have shown that fractalkine is up-regulated in chorioamnionitis, gestational diabetes mellitus, and preeclampsia (12-14).

Data from studies on the role of fractalkine in pregnancy are still accumulating. A study published in 2014 showed that placental fractalkine is expressed in the apical microvillous plasma membrane of syncytiotrophoblasts, from which it is released into the maternal circulation by shedding due to metalloprotease enzymes (15). It has also been demonstrated in an in vitro study that the fractalkine/CX3CR1 system plays an effective role in the adhesion of THP-1 monocytes to villous trophoblasts (16). Other studies revealed that fractalkine, together with some other cytokines, is involved in the processes of implantation, invasion of trophoblast to spiral uterine arteries, and placental angiogenesis at the uteroplacental interface (17,18).

When we searched the studies on fractalkine in the literature, we found that no data was evaluating the relationship between fetal growth and fractalkine. Encouraged by previous studies, we hypothesized that fractalkine might play a role in the pathogenesis of FGR. In this context, we aimed to investigate the fractalkine concentrations in the serum of pregnant women diagnosed with isolated FGR.

Material and Method

This cross-sectional study was conducted with 86 pregnant women who applied to the Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey, between March 2020 and March 2021 and had their pregnancy follow-up and delivery in our hospital. Twenty-five pregnant women diagnosed with isolated FGR in the third trimester, 23 pregnant women diagnosed with SGA, and 38 healthy pregnant women matched for age, body mass index (BMI), and the gestational week were included in the study.

Gestational age was calculated according to the last menstrual period and confirmed with fetal crown-rump length in

the first trimester. Since all the pregnancy follow-ups of the participants were carried out in our clinic, fetal biometric measurements and percentiles were recorded in ultrasound examinations until delivery. FGR was diagnosed in pregnant women whose fetal AC or EFW values were below the 3rd percentile according to the gestational week, and whose fetal AC or EFW was below the 10th percentile with increased resistance in umbilical artery blood flow or loss of end-diastolic flow in the umbilical artery. SGA was diagnosed in pregnant women whose fetal AC or EFW values were between the 3rd and 10th percentiles according to the gestational week, who did not have oligohydramnios, and whose umbilical artery was Doppler velocimetry values were normal.

Since we think that serum Fractalkine concentrations may vary depending on maternal age, BMI, and gestational week, three groups were formed by matching these variables. Smokers, multiple pregnancies, a history of any pregestational or gestational systemic disease, pregnant women with known vascular disease, thrombophilia or autoimmune disease, congenital uterine anomaly, and those using aspirin or low molecular weight heparin were not included in the study. Pregnant women diagnosed with FGR and developing gestational hypertension, preeclampsia, or HELLP syndrome during pregnancy were not included in the study. In addition, pregnant women with known chromosomal or structural abnormalities in themselves, their partners, or fetuses, and pregnant women who were found in the high-risk group in fetal chromosomal anomaly screening tests were not included in the study.

Age, BMI, total weight gained during pregnancy, and obstetric history of the pregnant women who participated in the study were recorded. A single obstetrician performed the fetal ultrasound examination on the same ultrasound device (Voluson E6 Ultrason Device) on all participants. Fetal biometry, amniotic fluid, and umbilical artery Doppler velocimetry values were evaluated.

To investigate fractalkine concentrations, approximately 5 ml of blood samples were drawn from the participants at any time of the day during the third trimester. The samples taken from each participant were stored in biochemistry tubes. After waiting for approximately 20 minutes at room temperature, the samples were centrifuged at 3500 rpm for 10 minutes. After centrifugation, the supernatant was separated from the sediment and stored at -80 degrees. Fractalkine concentrations were studied with the Fractalkine Elisa Kit (BT LAB, Suraige Biotechnology, Pendik, Istanbul, Turkey) by Enzyme-Linked Immunosorbent Assay (ELISA) method by the manufacturer's recommendations.

As the primary outcome of the study, FGR, SGA, and control groups were compared in terms of maternal serum fractalkine concentrations.

The Local Ethics Committee of Umraniye Training and

Research Hospital, Istanbul, Turkey has approved this study (Ethics Committee Approval No: B.10.1.TKH.4.34.H.GP.0.01/42, Date:15.02.2021)

The study protocol was maintained by the Declaration of Helsinki, and informed consent was obtained from all the participants.

Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 25.0. The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed or not. While evaluating the study data, descriptive statistical methods (mean, standard deviation, frequency, ratio) were used. An independent t-test was used for the comparison of two groups showing parametric distribution, and One-way ANOVA test analysis methods were used for comparing more than two groups. The Post-Hoc test was used to determine the difference obtained in the com-

parison of more than two groups. The Chi-square test was used in the evaluation of categorical data. Statistical significance was accepted at $p < 0.05$ for all values.

Results

When the FGR group, SGA group, and control group were compared in terms of demographic features, all three groups were similar in terms of age, BMI, and weight gained during pregnancy ($p=0.268$, $p=0.493$, $p=0.498$, respectively). Parity was found to be significantly higher in the control group than in the other groups ($p=0.015$) (Table I).

When the three groups were compared in terms of fetal umbilical artery Doppler velocimetry values, umbilical artery PI, RI, and S/D were found to be significantly higher in the FGR group, as expected ($p=0.000$, $p=0.000$, $p=0.000$, respectively) (Table II).

Table I: Comparison of groups in terms of demographic features

	FGR Group n=25	SGA Group n=23	Control Group n=38	<i>p</i>
Age (Years) mean± SD	26.20 ± 4.02	26.0 ± 5.33	27.95 ± 5.78	0.268*
BMI (kg/m ²) mean± SD	28.66 ± 3.25	27.46 ± 4.39	28.78 ± 5.0	0.493*
Weight gained during pregnancy (kg) mean± SD	12.80 ± 4.43	11.35 ± 4.78	12.55 ± 4.55	0.498*
Parity	Nulliparous n (%)	12 (48%)	16 (69.6%)	0.015**
	Multiparous n (%)	13 (52%)	7 (30.4%)	

*One-way ANOVA, **chi-square test, FGR: fetal growth restriction, SGA: small for gestational age

Table II: Comparison of the groups in terms of fetal umbilical artery doppler values and perinatal outcomes

	FGR Group (n=25) Mean±SD	SGA Group (n=23) Mean± SD	Control Group (n=38) Mean± SD	<i>p</i>
Umbilical artery Doppler PI Mean ± SD	1.32± 0.46 ^{ab}	0.75 ± 0.2	0.78 ± 0.13	<0.001
Umbilical artery Doppler RI Mean ± SD	0.72 ± 0.12 ^{ab}	0.51 ± 0.09	0.54 ± 0.07	<0.001*
Umbilical artery Doppler S/D Mean ± SD	3.45 ± 1.02 ^{ab}	2.12 ± 0.54	2.17 ± 0.29	<0.001*
Gestational age at birth mean± SD	37.44 ± 1.08 ^{ab}	38.48 ± 1.2	38.63 ± 1.22	<0.001
Birth weight Mean ± SD	2274.20 ± 379.48 ^{ab}	2634.13 ± 212.72 ^c	3242.11 ± 427.67	<0.001*
Mode of Delivery	Vaginal Birth n (%)	8 (32)	9 (39.1)	0.060**
	Cesarean Section n (%)	17 (68)	14 (60.09)	
1st minute APGAR Score Mean ± SD	8 ± 0.96	7.87 ± 1.01	8.34 ± 1.07	0.180*
5th minute APGAR Score Mean ± SD	9.28 ± 0.74	9.22 ± 0.74 ^d	9.63 ± 0.54	0.031*
NICU Admission	Yes n (%)	5 (20)	2 (8.7)	0.544**
	No n (%)	20 (80)	21 (91.3)	

*ONE-WAY ANOVA, **chi-square test, FGR: fetal growth restriction, SGA: small for gestational age, NICU: neonatal intensive care unit. Groups were compared by ONE-WAY ANOVA, followed by post hoc analyses for two group pairwise comparisons with the Bonferroni correction for multiple testing. a: Represents a comparison between FGR and SGA group, $p < .001$. b Represents a comparison between FGR and the control group, $p < .001$. c Represents a comparison between SGA and the control group, $p < .001$. d Represents a comparison between SGA and the control group, $p < .05$

When the three groups were compared in terms of perinatal outcomes, there was no difference between the three groups in terms of mode of delivery and 1st-minute Apgar score, while the 5th-minute Apgar score was significantly lower in the group with SGA ($p=0.060$, $p=0.180$, $p=0.031$, respectively). While gestational age at birth and birth weight were significantly lower in the FGR group, the rate of admission to NICU was similar in all three groups. ($p=0.000$, $p=0.000$, $p=0.544$, respectively) (Table II). None of the participants included in the study had a fetal loss in the prenatal, intrapartum, or postnatal period.

Maternal serum fractalkine concentrations of the three groups were compared. While the highest maternal serum fractalkine concentration was found in the SGA group at 23.31 ng/mL, it was determined as 18.06 ng/mL in the FGR group and 16.03 ng/mL in the control group. We did not find a statistical difference between the groups in terms of third-trimester maternal serum fractalkine concentrations ($p=0.258$) (Table III).

We evaluated the patients with FGR and SGA as a single group under the name of FGR+SGA and compared them with the control group in terms of third-trimester maternal serum fractalkine concentrations. Although the mean maternal serum fractalkine concentration was higher in the group with FGR+SGA (20.5 ng/mL) than in the control group (16 ng/mL), this difference did not reach statistical significance ($p=0.214$) (Table IV).

Discussion

In this study, we investigated maternal serum fractalkine concentrations in the third trimester in pregnant women with isolated fetal growth restriction. Although we detected higher maternal serum fractalkine concentrations in the FGR and SGA group compared to the normal healthy controls, this was not statistically significant.

In the literature, there is limited knowledge about the role of fractalkine in pregnancy. Studies with trophoblast cell lines have shown that fractalkine is involved in establishing the first contact between blastocyst and endometrium and then trophoblast migration to the maternal decidua in the early stage of pregnancy (18,19). Siwetz et al. stated that placental fractalkine expression and placental fractalkine release increase from the first trimester to the term. As a result of the fragmentation of membrane-bound form on the syncytiotrophoblasts by metalloproteases (ADAM10 and ADAM17), soluble fractalkine is occurred and is shed into the maternal circulation. They also noted another source of fractalkine is maternal endothelium and the maternal serum soluble fractalkine pool is consist of the sum of these two forms (15). The contribution of placental fractalkine to the pool of soluble fractalkine during pregnancy is difficult to estimate and is thought to represent a small amount compared to fractalkine shed from the endothelium of the maternal blood vessels (15).

After it was revealed that fractalkine mediates the migration of trophoblasts to the maternal decidua in early pregnancy, studies have been conducted to examine the role of fractalkine in preeclampsia. In a study conducted by Usta et al., it was found that the expression of fractalkine in the placental tissue of pregnant women complicated with preeclampsia, both in the trophoblast, decidua, and capillary endothelial cells, was increased, especially in severe preeclampsia, compared to normotensive pregnant women. Although they stated that fractalkine expression in the placenta in preeclampsia showed a positive correlation with the accompanying FGR, high blood pressure, and the amount of proteinuria (14).

In a study performed on placental explants, it was determined that the concentration of fractalkine expressed in placental tissue was incubated with a metalloprotease enzyme inhibitor that mediates shedding of soluble fractalkine increased, but soluble fractalkine decreased. The decrease in soluble fractalkine after metalloprotease inhibitor was much

Table III: Comparison of the groups in terms of maternal serum fractalkine concentrations

	FGR Group (n=25) Mean ± SD	SGA Group (n=23) Mean ± SD	Control Group (n=38) Mean ± SD	<i>p</i>
Gestational age at blood sampling (weeks)	35.80 ± 1.14	35.90 ± 1.02	36.11 ± 0.92	0.592*
Fractalkine concentration (ng/mL)	18.06 ± 16.07	23.31 ± 17.7	16.03 ± 16.46	0.258*

*ONE-WAY ANOVA, FGR: fetal growth restriction, SGA: small for gestational age

Table IV: Comparison of the group with FGR+SGA and the control group in terms of maternal serum fractalkine concentrations

	FGR+SGA Group (n=62) Mean ± SD	Control Group (n=28) Mean ± SD	<i>p</i>
Gestational age at blood sampling (weeks)	35.90 ± 1.08	36.11 ± 0.92	0.343*
Fractalkine concentration (ng/mL)	20.50 ± 16.9	16.0 ± 16.4	0.214*

*Independent t-test, FGR: Fetal growth restriction, SGA: small for gestational age

higher in the third trimester than in the first trimester (15). This study revealed that if these metalloproteases are somehow overactive, the concentration of soluble fractalkine will increase, or vice versa, if there is a decrease in the activity of these metalloproteases, the concentration of soluble fractalkine will decrease.

In different studies, it has been shown that metalloproteases (ADAM10 and ADAM17) detected in syncytiotrophoblasts, which mediate the shedding, are interestingly increased in preeclampsia (20,21). Consistent with this information, it is not surprising that in subsequent studies, serum fractalkine concentrations were found to be higher in women whose pregnancy was complicated with preeclampsia than in normotensive healthy pregnant women (22,23).

In the ECLAXIR study conducted by Stephanian et al. about fractalkine receptor CX3CR1 polymorphisms, they found no difference in CX3CR1 polymorphisms in pregnant women whose pregnancy was complicated with preeclampsia compared to normotensive pregnant women in the third trimester; but found a higher concentration of fractalkine in maternal serum in the preeclampsia group. They stated that an increase in soluble fractalkine is a consequence of more proteolysis of the membrane-bound form. Therefore, they suggested that the change in fractalkine concentration rather than fractalkine receptor is most likely related to preeclampsia (22).

In all these studies conducted in preeclampsia cases, it was shown that the expression of fractalkine in the placental tissue increased, the metalloproteases that mediate the shedding of soluble fractalkine into the maternal circulation increased, and accordingly, the soluble fractalkine increased. However, considering that vasoactive substances released in preeclampsia affect the entire vascular system in the whole body, the contribution of fractalkine released from the endothelium to preeclampsia still awaits investigation.

Fetal growth restriction is seen in approximately 30% of pregnant women whose pregnancy was complicated by preeclampsia. The relationship between preeclampsia and FGR is not fully understood, both are thought to be associated with placental insufficiency (3). Just as FGR is not seen in all preeclamptic cases, hypertensive disorders are not the only cause in all FGR cases. Although the cause of FGR seen in pregnancies not accompanied by hypertensive disorders is unknown, it is thought to be a multifactorial effect (24).

At the beginning of this study, we hypothesized that maternal serum fractalkine concentrations would be higher in cases whose pregnancy was complicated by isolated FGR, as shown in preeclamptic cases. Consistent with this, we found that maternal serum fractalkine concentration was higher in the FGR group than in healthy controls. In previous studies, maternal serum fractalkine concentrations were found to be higher in cases with FGR secondary to preeclampsia during

pregnancy, and it was determined that the increase in placental fractalkine expression showed a positive correlation with the severity of FGR (14,23). However, we could not find a relationship between FGR severity and maternal serum fractalkine concentrations in our study. The highest mean fractalkine concentration (23.31 ng/ml) was found in the SGA group with a mean birth weight of 2634 g, while the fractalkine concentration in the FGR group with a mean birth weight of 2274 g was lower than that in the SGA group (18.06 ng/ml). Due to the small number of participants in the study groups, we think that we could not show a positive relationship between FGR severity and maternal serum fractalkine concentrations, as in the preeclampsia studies in the literature.

Limitations of this study are the small number of participants and the fact that the expression of fractalkine and its receptor in the placenta was not evaluated. Another limitation is that the fractalkine concentration detected in the maternal serum is the sum of the fractalkine shredded into the serum from the placenta and all other tissues expressing fractalkine. We couldn't determine how much of the fractalkine concentration detected in peripheral venous blood originates from the placenta and how much comes from other tissues.

To the best of our knowledge, this is the first study in the literature examining the maternal serum fractalkine concentration in the third trimester in pregnant women with isolated FGR.

In conclusion, we found that maternal serum fractalkine concentration was higher in the group with FGR and SGA compared to the healthy control group, but this was not statistically significant. Also but we did not detect any relationship between FGR severity or birth weight and maternal serum fractalkine concentrations. In isolated FGR cases, the state of placental fractalkine expression and the activity of metalloproteases that mediate the shedding of soluble fractalkine remain to be explored.

Declarations

All participants signed informed written consent before being enrolled in the study.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request. / The datasets and code used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: The authors received no funding or grants.

Conflict of interest statements: Authors declare no conflict of interest in this study.

Acknowledgments: We thank all participants who voluntarily participated in this study.

Authors' contributions: Ecem Berfun Toprak Sager is responsible for the data collection. İbrahim Kale is responsible for

the application for ethical approval and the writing of the manuscript. Hakan Sager is responsible for the statistical analysis of the study, graphic, and figure design. Aysegul Ozel is responsible for the study design and final revision before publication. Murat Muhcu is responsible for data collection and supervision.

References

- Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. *Am J Obstet Gynecol.* 2018;218(2S): S745-S761. Doi: 10.1016/j.ajog.2017.11.577. PMID: 29422210.
- Resnik R. Intrauterine growth restriction. *Obstet Gynecol.* 2002;99(3):490-6. Doi: 10.1016/s0029-7844(01)01780-x. PMID: 11864679.
- McKinney D, Boyd H, Langager A, Oswald M, Pfister A, Warshak CR. The impact of fetal growth restriction on latency in the setting of expectant management of preeclampsia. *Am J Obstet Gynecol.* 2016;214(3):395.e1-7. Doi: 10.1016/j.ajog.2015.12.050. PMID: 26767794.
- Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol.* 2020;56(2):298-312. Doi: 10.1002/uog.22134. PMID: 32738107.
- Lees CC, Romero R, Stampalija T, Dall'Asta A, DeVore GA, Prefumo F, et al. Clinical Opinion: The diagnosis and management of suspected fetal growth restriction: an evidence-based approach. *Am J Obstet Gynecol.* 2022;226(3):366-378. Doi: 10.1016/j.ajog.2021.11.1357. PMID: 35026129; PMCID: PMC9125563.
- Bazan JF, Bacon KB, Hardiman G, Wang W, Soo K, Rossi D, et al. A new class of membrane-bound chemokine with a CX3C motif. *Nature.* 1997;385(6617): 640-4. Doi: 10.1038/385640a0. PMID: 9024663.
- Pan Y, Lloyd C, Zhou H, Dolich S, Deeds J, Gonzalo JA, et al. Neurotactin, a membrane-anchored chemokine up-regulated in brain inflammation. *Nature.* 1997;387(6633): 611-7. Doi: 10.1038/42491. Erratum in: *Nature* 1997 Sep 4;389(6646):100. PMID: 9177350.
- Kim KW, Vallon-Eberhard A, Zigmund E, Farache J, Shezen E, Shakhar G, et al. In vivo structure/function and expression analysis of the CX3C chemokine fractalkine. *Blood.* 2011;118(22):e156-67. Doi: 10.1182/blood-2011-04-348946. PMID: 21951685; PMCID: PMC4507037.
- Imai T, Hieshima K, Haskell C, Baba M, Nagira M, Nishimura M, et al. Identification and molecular characterization of fractalkine receptor CX3CR1, which mediates both leukocyte migration and adhesion. *Cell.* 1997;91(4):521-30. Doi: 10.1016/s0092-8674(00)80438-9. PMID: 9390561.
- D'Haese JG, Demir IE, Friess H, Ceyhan GO. Fractalkine/CX3CR1: why a single chemokine-receptor duo bears a major and unique therapeutic potential. *Expert Opin Ther Targets.* 2010;14(2):207-19. Doi: 10.1517/14728220903540265. PMID: 20055718.
- Ruze A, Zhao Y, Li H, Gulireba X, Li J, Lei D, et al. Low shear stress upregulates the expression of fractalkine through the activation of mitogen-activated protein kinases in endothelial cells. *Blood Coagul Fibrinolysis.* 2018;29(4):361-8. Doi: 10.1097/MBC.0000000000000701. PMID: 29406386; PMCID: PMC5965924.
- Szukiewicz D, Kochanowski J, Mittal TK, Pyzlak M, Szewczyk G, Cendrowski K. Chorioamnionitis (ChA) modifies CX3CL1 (fractalkine) production by human amniotic epithelial cells (HAEC) under normoxic and hypoxic conditions. *J Inflamm (Lond).* 2014;11:12. Doi: 10.1186/1476-9255-11-12. PMID: 24851083; PMCID: PMC4029884.
- Szukiewicz D, Kochanowski J, Pyzlak M, Szewczyk G, Stangret A, Mittal TK. Fractalkine (CX3CL1) and its receptor CX3CR1 may contribute to increased angiogenesis in diabetic placenta. *Mediators Inflamm.* 2013;2013: 437576. Doi: 10.1155/2013/437576. PMID: 23956503; PMCID: PMC3730155.
- Usta A, Turan G, Sancakli Usta C, Avci E, Adali E. Placental fractalkine immunoreactivity in preeclampsia and its correlation with histopathological changes in the placenta and adverse pregnancy outcomes. *J Matern Fetal Neonatal Med.* 2020;33(5):806-15. Doi: 10.1080/14767058.2018.1505854. PMID: 30049235.
- Siwetz M, Blaschitz A, Kremshofer J, Bilic J, Desoye G, Huppertz B, et al. Metalloprotease dependent release of placenta derived fractalkine. *Mediators Inflamm.* 2014; 2014:839290. Doi: 10.1155/2014/839290. PMID: 24771984; PMCID: PMC3976874.
- Siwetz M, Sundl M, Kolb D, Hiden U, Herse F, Huppertz B, et al. Placental fractalkine mediates adhesion of THP-1 monocytes to villous trophoblast. *Histochem Cell Biol.* 2015;143(6):565-74. Doi: 10.1007/s00418-014-1304-0. PMID: 25566740; PMCID: PMC4487366.
- Hannan NJ, Salamonsen LA. CX3CL1 and CCL14 regulate extracellular matrix and adhesion molecules in the trophoblast: potential roles in human embryo implantation. *Biol Reprod.* 2008;79(1):58-65. Doi: 10.1095/biolreprod.107.066480. PMID: 18367676.
- Hannan NJ, Jones RL, White CA, Salamonsen LA. The chemokines, CX3CL1, CCL14, and CCL4, promote human trophoblast migration at the feto-maternal interface. *Biol Reprod.* 2006;74(5):896-904. Doi: 10.1095/biolreprod.105.045518. PMID: 16452465.
- Cammass L, Reinaud P, Dubois O, Bordas N, Germain G, Charpigny G. Identification of differentially regulated genes during elongation and early implantation in the ovine trophoblast using complementary DNA array screening. *Biol Reprod.* 2005;72(4):960-7. Doi: 10.1095/biolreprod.104.034801. PMID: 15616222.

20. Yang Y, Wang Y, Zeng X, Ma XJ, Zhao Y, Qiao J, et al. Self-control of HGF regulation on human trophoblast cell invasion via enhancing c-Met receptor shedding by ADAM10 and ADAM17. *J Clin Endocrinol Metab.* 2012; 97(8): E1390-401. Doi: 10.1210/jc.2012-1150. PMID: 22689693.
21. Zhao S, Gu Y, Fan R, Groome LJ, Cooper D, Wang Y. Proteases and sFlt-1 release in the human placenta. *Placenta.* 2010;31(6):512-8. Doi: 10.1016/j.placenta.2010.03.014. PMID: 20434767; PMCID: PMC3257833.
22. Stepanian A, Benchenni S, Beillat-Lucas T, Omnes S, Defay F, Peynaud-Debayle E, et al; ECLAXIR study group. Search for an association between V249I and T280M CX3CR1 genetic polymorphisms, endothelial injury and preeclampsia: the ECLAXIR study. *PLoS One.* 2009;4(7):e6192. Doi: 10.1371/journal.pone.0006192. PMID: 19587779; PMCID: PMC2702686.
23. Szewczyk G, Pyzlak M, Pankiewicz K, Szczerba E, Stangret A, Szukiewicz D, et al. The potential association between a new angiogenic marker fractalkine and a placental vascularization in preeclampsia. *Arch Gynecol Obstet.* 2021;304(2):365-376. Doi: 10.1007/s00404-021-05966-3. PMID: 33496844; PMCID: PMC8277623.
24. Crovetto F, Triunfo S, Crispi F, Rodriguez-Sureda V, Roma E, Dominguez C, et al. First-trimester screening with specific algorithms for early- and late-onset fetal growth restriction. *Ultrasound Obstet Gynecol.* 2016;48(3):340-8. Doi: 10.1002/uog.15879. PMID: 26846589.