





RESEARCH ARTICLE

REVISED Soluble FMS-Like Tyrosine Kinase-1: Role in placenta accreta spectrum disorder [version 4; peer review: 2 approved]

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Abstract

Background: Placenta accreta is a pregnancy condition where the placenta's blood vessels attach too deeply to the uterine wall. Incidence of placenta accreta is increasingly seen today as the rate of cesarean section increases, however, the exact pathophysiology of this condition is still not fully understood. Soluble fms-like tyrosine kinase-1 (sflt-1) as a protein produced by the placenta was found to be decreased in placenta accreta, Therefore we aim to see if sfltsFlt-1 has a role in the development of placenta accreta.

Methods: This study involved 40 samples from patients that had been diagnosed with placenta accreta spectrum disorder (case group), and 40 samples from patients with normal pregnancies (control group) at Rumah Skit Umum Pusat H.Adam Malik (RSUP) Haji Adam Malik Medan, in Indonesia. Diagnosis of placenta accreta syndrome was based on Placenta Accreta Spectrum Score (PAS), and International Federation of Gynecology and Obstetrics (FIGO) classification of placenta accreta spectrum disorder. Analyses were performed by independent t-test, man Mann-Whitney U test, and Kruskal-Wallis analysis test, with a P-value <0.05 considered as statistically significant (95%CI).


Results: Based on this study, we found that the sFlt-1 level in the case group was lower than the control group. Data analysis using the Kruskal-Wallis test showed that there was a difference in sFlt-1 levels

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Any reports and responses or comments on the

in this study group ($p = 0.02$), which was further evaluated with post hoc analysis using Mann-Whitney U test. The results indicated that there were significant differences between the control and PAS 0, PAS1, and PAS 2 ($p = 0.043$; $p = 0.002$; $p = 0.03$).

Conclusion: sFlt-1 levels decreased in placental invasive pregnancies compared to normal pregnancies, however, this still needs to be investigated further in a multi-center study, considering that sFlt-1 levels are also influenced by ethnicity and other conditions that cannot be excluded in this study.

Keywords

Placenta Accreta, Pregnancy, FIGO, PAS Score, sflt-1

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article can be found at the end of the article.

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REVISED Amendments from Version 3

In this manuscript i add some explanation about protocol we use to determine time of termination in case group and control group.

Any further responses from the reviewers can be found at the end of the article

Introduction

Placenta accreta is a serious pregnancy condition that can develop when all or part of the placenta adheres to the uterine wall.¹ As the cesarean delivery rate increases, it has been noted that placenta accreta cases are on the rise.^{2,3} In 2019, at the Haji Adam Malik general hospital, Indonesia, the incidence of this complication had a sharp increase, which resulted in the increased costs of patient care. In 2016 at Adam Malik General Hospital, Medan, Indonesia, placenta accreta mortality rate was very high, as were its complications, such as bleeding, hysterectomy, and pelvic organ injuries.^{2,4-9} Until recently, the diagnosis of placenta accreta spectrum depended on ultrasonography. However, the American College of Obstetricians and Gynecologists (ACOG) and the International Federation of Gynecology and Obstetrics (FIGO) have issued a new terminology for this condition called placenta accreta spectrum, and they have divided the degree of this spectrum according to the ultrasonography, and the depth of invasion at the time of surgery.¹⁰⁻¹³ Diagnosis by ultrasonography has many weaknesses as this examination requires expertise and a good standard of ultrasonography equipment. As Indonesia is an archipelagic country, the distribution of doctors with proficient ultrasound expertise in all regions, especially in remote areas, is uneven. In several previous studies, it was reported that several biomarkers can be associated with the placenta accreta spectrum, namely soluble fms-like tyrosine kinase-1 (sFlt-1). As a protein, sFlt-1 is produced by the placenta and it has anti-angiogenetic properties.¹⁴ sFlt-1 plays a role in regulating the depth of invasion of the placenta. Previous studies have reported that there was a decrease in sFlt-1 levels in the placenta accreta spectrum.¹⁵ Therefore, we aim to investigate the use of sFlt-1 as a diagnostic biomarker for placenta accreta spectrum in the Indonesian population, as an effective replacement for the ultrasound examination.

Methods

Population and sample

In this case control study, 80 patients enrolled from February 2020 until June 2020. The patients were divided into either the case group (placenta accreta spectrum), or the control group (normal pregnancy), with 40 patient in each group. Consecutive sampling was preformed for data collection. This research was conducted at the Haji Adam Malik Hospital in Medan, Indonesia, and the patients were selected from the outpatients at the obstetric outpatient polyclinic of this hospital. Patients gave informed consent before participating in this study. Patients in their third trimester of pregnancy who had been diagnosed with a spectrum of placenta accreta, and had planned to give birth by cesarean section, were included in this study. The diagnosis of placenta accreta spectrum was as per ACOG guidelines, based on the following ultrasound signs: (1) loss of the clear zone, defined as loss or irregularity of the hypoechoic plane in the myometrium underneath the placental bed; (2) placental lacunae, defined as the presence of numerous lacunae, often containing turbulent flow visible on grayscale or color Doppler ultrasound; (3) bladder wall interruption, defined as loss or interruption of the bright bladder wall (hyperechoic band or 'line' between the uterine serosa and bladderlumen); (4) uterovesical hypervascularity, defined as a striking amount of color Doppler signal seen between the myometrium and the posterior wall of the bladder, including vessels appearing to extend from the placenta, across the myometrium and beyond the serosa, into the bladder or other organs, often running perpendicular to the myometrium; and (5) increased vascularity in the parametrial region, defined as the presence of hypervascularity extending beyond the lateral uterine walls and involving the region of the parametria. Staging of PAS disorders based on the presence of ultrasound signs of PAS in women presenting with placenta previa: PAS 0, placenta previa with no ultrasound signs of invasion or placenta previa with placental lacunae but no evidence of abnormal uterus – bladder interface (i.e. no loss of the clear zone and/or bladder wall interruption); PAS 1, presence of at least two of placental lacunae, loss of the clear zone and bladder wall interruption; PAS 2, PAS 1 plus uterovesical hypervascularity; PAS 3, PAS 1 or PAS 2 plus evidence of increased vascularity in the inferior part of the lower uterine segment extending into the parametrial region. The last ultrasound examination prior to surgery was used to assess the presence and distribution of ultrasound signs of PAS. FIGO grade is divided into 6 grade. Grade 1: at Cesarean or vaginal delivery, there is complete placental separation at the third stage and normal adherence of the placenta. Grade 2: at Cesarean section/laparotomy, no placental tissue is seen invading through the surface of the uterus, there is incomplete separation with uterotonics and gentle cord traction, and manual removal of placenta is required for remaining tissue, and parts of the placenta are thought to be abnormally adherent; at vaginal delivery, manual removal of placenta is required and parts of the placenta are thought to be abnormally adherent. Grade 3: at Cesarean section/laparotomy, no placental tissue is seen invading through the surface of the uterus, there is no separation with uterotonics and gentle cord traction, and manual removal of placenta is required, and the whole placental bed is thought to be abnormally adherent; at vaginal delivery, manual removal of placenta is required and the whole placental bed is thought to be abnormally adherent. Grade 4: at Cesarean section/laparotomy, placental tissue is seen to

have invaded through the serosa of the uterus but a clear surgical plane can be identified between the bladder and uterus to allow non-traumatic reflection of the urinary bladder at surgery. Grade 5: at Cesareansection/laparotomy, placental tissue is seen to have invaded through the serosa of the uterus and a clear surgical plane cannot be identified.¹⁶ The examination was performed by two doctor from fetomaternal division who were trained and certified for the use of voluson P6 ultrasound system. Exclusion criteria in this study were patients who were not going to give birth at the Haji Adam Malik General Hospital, and patients who chose not to participate in this study. PAS score was made two days before the time of cesarean section. Blood sample was taken an hours prior cesarean section performed, and FIGO grade was assess during cesarean section. Patient characteristics data was obtained from the medical records (see underlying data: <https://data.mendeley.com/datasets/y6936wrfty/1>).¹⁷ Post birth, we assessed the degree of placental invasion of the uterus according to the FIGO criteria previously reported by ACOG, in the case group.

Ethical approval

The study was conducted after obtaining approval from the research ethics committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital, Medan no: 273/KEP/USU/2020. Written informed consent was obtained from all the participants.

Data analysis

Before surgery, 3 cc of venous blood from 80 patient was taken and analyzed for serum levels of sFlt-1 in the laboratory of Haji Adam Malik General Hospital in Medan. To determine the termination time in the case group and the control group, we used the same method, by using the length of the cervix. In our population and according to our hospital protocol, case of placenta accreta spectrum disorder will be planned for cesarean section at > 37 weeks gestation according to the cervical length measured by transvaginal ultrasonography. when cervical length < 2.5 cm, and gestational age > 37 weeks, patient planned for cesarean section, but if the cervical length still above 2.5 cm, cesarean section performed at 39 weeks with monitoring, so to prevent bias, then we used the same protocol to determine termination time in the control group. We used human soluble fimosine like tyrosine kinase -1 ELISA Kit (Bioassay TL; MBS2601616) (see underlying data: <https://data.mendeley.com/datasets/y6936wrfty/1>).¹⁷ Serum levels of sFlt-1 was analysed and compared with the ultrasound-based placenta accreta spectrum disorder classification, and the postoperative FIGO scores of patients on the placenta accreta spectrum.

Statistical analysis

Analysis in this study was done with the use of SPSS version 26. All data are presented in Mean and standard deviation (SD). Independent Student t-test and Mann Whitney U test were used for the analysis of two variables, while for more than two variables ANOVA and Kruskal Wallis tests were performed. Post Hoc test was used if the ANOVA or Kruskal-Wallis analysis indicated a significant difference ($p < 0.05$). The results of the study were considered significant with a p-value < 0.05 (95).

Table 1. Patients characteristics.

	PAS (n = 40)	Control (n = 40)	P*
	Mean (SD)	Mean (SD)	
Age (years) Mean+sd	33 (4)	30 (5)	0.080
Bodyweight (kg)	54 (6)	54 (8)	0.720
Height (cm)	145 (20)	150 (5)	0.080
Mid upper arm circumference (cm)	24,8 (3.2)	25,9 (2.5)	0.360
Systolic BP (mmHg)	112 (10)	109 (12)	0.830
Diastolic BP (mmHg)	63 (8)	65 (10)	0.260
Mean arterial pressure	80 (4)	80 (5)	0.490
Gravida	3 (4)	3 (3)	0.090
Parity	2 (2)	2 (2)	0.500
Abortus	0 (0-3)	0 (0-2)	0.130
Gestational age (weeks)	36 (1)	37 (1)	0.680
History of cesarean section	2 (1)	1 (1)	<0.001
History of curretage	0 (0-2)	0 (0-0)	0.030
Last cesarean section (years)	4 (1-7)	1 (0-3)	<0.001

Result

Characteristics, proportions, and prevalence of patients

In **Table 1**, there were no significant differences between the case and control groups except for the number of previous cesarean sections ($p < 0.001$), history of curettage ($p = 0.03$) and the distance of previous cesarean section operations ($p < 0.001$). The comparison of the sFlt-1 levels between the case and control groups indicated that sFlt-1 levels decreased as the degree of placenta accreta spectrum increased. The levels of sFlt-1 based on the placenta accreta spectrum classification compared to controls resulted in a statistically significant difference among the groups ($p = 0.004$) (**Table 2**).

In **Table 3**, the level of sFlt-1 based on the postoperative FIGO score in the case group was analysed and compared to the control group. Our analysis indicated a difference in sFlt-1 levels, in that obtaining a high FIGO score showed a downward trend in the sFlt-1 level ($p = 0.004$).

Table 2. sFlt-1 analysis based on PAS.

	sFlt-1 (pg/ml) median (min-max)	p^*
Control	1246 (824-1636)	0.004
PAS 0	1711 (1367-2055)	
PAS 1	1474 (802-2270)	
PAS 2	1417 (835-2301)	

*Kruskal Wallis.

Table 3. Post-Hoc analysis of sFlt-1 level based on FIGO.

	sFlt-1 (pg/ml) median (min-max)	p^*
Control	1246 (824-1636)	0.002
FIGO 1	-	
FIGO 2	1482 (847-2270)	
FIGO 3	-	
FIGO 4	-	
FIGO 5	1466 (802-2301)	
FIGO 6	1259 (816-2139)	

*Kruskal Wallis.

Table 4. Correlation of PAS and FIGO on sFlt-1 serum levels in patients with placental accreta.

Variable	sFlt-1 serum (pg/ml) Median (min-max)	r^*	p^*
PAS			
PAS 0	1711 (1367-2055)	0.270	0.015
PAS 1	1474 (802-2270)		
PAS 2	1417 (835-2301)		
FIGO			
FIGO 1	-	0.251	0.025
FIGO 2	1482 (847-2270)		
FIGO 3	-		
FIGO 4	-		
FIGO 5	1466 (802-2301)		
FIGO 6	1259 (816-2139)		

*Spearman.

The analysis of the correlation between the sFlt-1 levels and the placenta accreta spectrum classification, based on ultrasonography and FIGO score showed a weak correlation between the groups ($r = 0.27, p = 0.015; r = 0.251, p = 0.025$) (Table 4).

Discussion

Placenta accreta is a life-threatening condition with an increasing incidence. History of cesarean section is a major risk factor for the placenta accreta spectrum. Diagnosis of this complication is currently by ultrasonography, with several recent studies reporting satisfactory results produced with this mode of diagnosis.¹⁸ However, in remote areas where there is a lack of ultrasound equipment and experienced operators, the use of biomarkers can be a solution to this challenge. Recently, studies have reported several proangiogenic and antiangiogenic markers associated with the incidence of placenta accreta spectrum.¹⁹ In this condition, there is an imbalance between proangiogenic and antiangiogenic factors, where proangiogenic factors are more dominant and have a significant increase in line with the depth of placental invasion of the uterus.¹⁵ The antiangiogenic factor that acts as a regulator is decreased so that the invasion of the placenta is uncontrolled. There are some studies that have established sFlt-1 as proangiogenic and antiangiogenic factors.¹⁵ In previous years, sFlt-1 was widely used as a predictor in cases of placenta-related disorders such as preeclampsia.²⁰ This is because in preeclampsia, implantation that occurs is usually superficial due to failure of the transformation of the spiral arteries, therefore there is usually an increase in sFlt-1 levels and decrease in placental growth factor (PLGF) level. sFlt-1 and PLGF as markers were chosen because they are specific to the placenta, although PLGF is also produced by other organs.²¹ In our study, comparison of the case group with the control group showed no significant difference in the patient characteristics, except for the history of the number of cesarean sections, the duration of the curettage and the length of the previous cesarean section (Table 1). We also found a decrease in sFlt-1 levels in the placenta accreta spectrum group compared to the control group. Increase in the degree of the spectrum was followed by a decrease in the sFlt-1 level (Table 2), as well as the FIGO score (Table 3). Based on Figure 1, we can see an increase in sFlt-1 levels in response to normal pregnancy. Serum sFlt-1 levels increased with increasing gestational age, but sFlt-1 levels in the PAS group tended to be lower than in the control group. Our results additionally showed a weak correlation between sFlt-1 with the accreta spectrum degree and FIGO score. This study is the first study to link sFlt-1 with the degree of placenta accreta spectrum based on ultrasonography and FIGO score. The concentration of sFlt-1 changes throughout the pregnancy, starting with a decrease at 8-12 weeks to 16-20 weeks, with a gradual increase at 26-30 weeks, and a rapid increase at 35-39 weeks. Hirashima et al. reported that the sFlt-1 concentration at 35-39 weeks of gestation was 2000 pg/ml.²² In this study we found lower levels of sFlt-1 (1246 pg/ml) in the control group, and even lower values were observed in the placenta accreta spectrum group (PAS 0, 1711; PAS 1, 1474; PAS 2, 1417).²² These results supports our hypothesis that sFlt-1 is decreased in the placenta accreta spectrum and therefore, it can not regulate placental invasion of the endometrium. Similarly, McMahon et al. had also reported that the lower expression of sFlt-1 in the placenta was associated with placental invasion.²³ Additionally, sFlt-1 may play a role in the regulation of cytotrophoblast invasion, so that lower sFlt-1 concentration is likely to lead to deeper placental invasion (acreta/increta/percreta). Shainker et al. It has been reported that sFlt-1 expression is reduced in the placental invasion, and non-deep invasion areas of placenta accreta spectrum cases when compared with normal placentas ($p = 0.003$ and $p = 0.001$ respectively). Whereas in the placenta from the accreta spectrum cases, the invasive placenta did not show a significant difference in sFlt-1 expression.²⁴

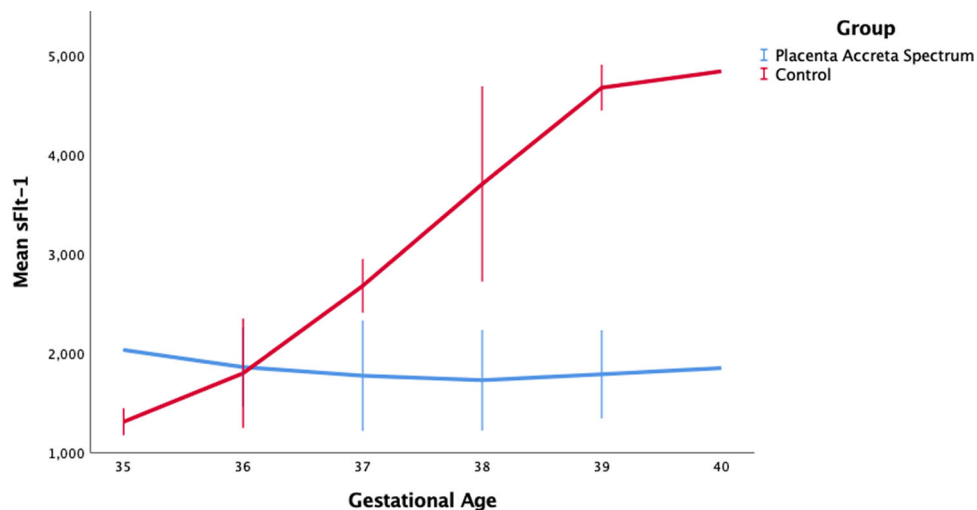


Figure 1. sFlt-1 level by gestational age between placentra accreta spectrum (PAS) and control group.

Ostaz et al. reported that there was a decrease in oxidative stress in placenta accreta, and an invasion of the raised placenta and a high oxidative stress in preeclampsia. However, on the placenta accreta spectrum, there was a decrease in the level of oxidative stress, which is probably related to a decrease in the concentration of antio-angiogenic factor, sFlt-1.²⁵ Su et al., reported that aspirin which is usually used as a preeclamptic prophylaxis, has a suppressive effect on sFlt-1.²⁶ Therefore from these findings it can be suggested that suppression of sFlt-1 will increase placental invasion and stimulate placental angiogenesis. Although, whether giving aspirin in normal pregnancy will increase the risk of placenta accreta spectrum incidence has not yet been studied. It can be beneficial to further investigate the effects of aspirin, in order to recognise whether sFlt-1 is a single factor that plays a role in the occurrence of placenta accreta spectrum, or there are other factors involved in placental invasion, such as a history of cesarean section or curettage, which can cause damage to the nitroabuzh layer of the endometrium. This study has several limitations, such as the small sample size. Additionally, we only measured the sFlt-1 levels in the third trimester before the cesarean section was performed. Therefore, we can not report on the effects of sFlt-1 in placenta accreta in the first and second trimesters. Furthermore, we can not rule out the possibility of bias in the assessment of FIGO scores.

Conclusions

sFlt-1 was found to be decreased in the placenta accreta spectrum, however this result requires further analysis as this correlation was not very strong. Further studies are needed to assess whether sFlt-1 can be used as a biomarker to replace ultrasonography in the diagnosis of the placenta accreta spectrum.

Data availability

Underlying data

Mendeley data: Data for Soluble FMS-Like Tyrosine.

Kinase: Role in placenta accreta spectrum disorder <https://data.mendeley.com/datasets/y6936wrfty/1>.¹⁷ This project contains the following underlying data: Data file 1. (sFlt and PLGF ELISA result), Data file 2. (Patient raw data) Data are available under the terms of the [Creative Commons Attribution 4.0 International License](#).

Consent statement

Written informed consent for publication of the patients' details was obtained from the patients/a guardian of the patient.

Author contributions

Sarma N Lumbanraha, role: conceptualization, funding acquisition, resources, supervision, visualization; M Rizki Yaznil, role: investigation, methodology, supervision, visualization; Andre M Siahaan, role: investigation, methodology, supervision, writing – original draft preparation; Berry E P Bacin, role: formal analysis, resources, writing – review and editing.

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Version 4

Reviewer Report 15 September 2022

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Ferdinando Antonio Gulino 

Department of Obstetrics and Gynecology, Azienda di Rilievo Nazionale e Alta Specializzazione (ARNAS) Garibaldi, Catania, Italy

The authors made all the modifications requested and now it could be accepted for indexing

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Obstetrics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 14 September 2022

<https://doi.org/10.5256/f1000research.138138.r149778>

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Akihide Ohkuchi 

Department of Obstetrics and Gynecology, Jichi Medical University School of Medicine, Tochigi, Japan

The authors appropriately performed revision. I do not have any more queries

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Obstetrics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 3

Reviewer Report 04 January 2022

<https://doi.org/10.5256/f1000research.77677.r115268>

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Ferdinando Antonio Gulino 

Department of Obstetrics and Gynecology, Azienda di Rilievo Nazionale e Alta Specializzazione (ARNAS) Garibaldi, Catania, Italy

The manuscript "Soluble FMS-Like Tyrosine Kinase-1: Role in placenta accreta spectrum disorder" is original and well structured, gives important novelty to scientific literature but its immediate clinical practice is still limited. The statistical analysis is well conducted and the language is acceptable. It represents an interesting work and it allows focusing the attention on placenta previa when there are some risk factors. The main concern is related to the cesarean section of the patients with PAS disorders: were all planned cesarean sections? how many urgent cesarean sections did you have in your statistics?

If we consider also the control group we had a mean gestational age at delivery of 37 weeks, is it normal for your population? When was performed the blood sample in the control group considering that we don't know the right time for delivery in a normal pregnancy? A reply by the authors could be interesting. Otherwise, the manuscript is well performed and there are no critical points.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Obstetrics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 13 Mar 2022

Sarma Lumbanraja, Universitas Sumatera Utara, Medan, Indonesia

Thank you for your review

I would like to answer some question from your analysis

1. In this study, we did not include an emergency case of placenta accreta, because, contraction can change sFlt-1 level in blood, so to minimize bias in our study, case of emergency c-section was excluded.
2. In our population and according to our hospital protocol, case of plasenta accreta spectrum disorder will be planned for cesarean section at > 37 weeks gestation according to the cervical length measured by transvaginal ultrasonography. when cervical length < 2,5 cm, and gestational age > 37 weeks, patient planned for cesarean section, but if the cervical length still above 2,5 cm, cesarean section performed at 39 weeks with monitoring.
3. In the control grup, we do the same protocol as the case group. blood was taken 1 hours before the cesarean section performed. we only limited the case to patient that will performed cesarean section because obstertic indication, for patients with a spontaneous vaginal delivery was excluded from this study, because we cannot predict the time of delivery.

thank you
best reagards

Competing Interests: No competing interests were disclosed.

Version 2

Reviewer Report 13 September 2021

<https://doi.org/10.5256/f1000research.76853.r93502>

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Akihide Ohkuchi 

Department of Obstetrics and Gynecology, Jichi Medical University School of Medicine, Tochigi, Japan

Please answer the following queries:

1. Table 1: Is the “Gestational age” at blood sampling or at delivery? You should show both gestational age at blood sampling and at delivery, because the serum levels of sFlt-1 steeply increased even if the difference age is only one week at 36-40 weeks of gestation.
2. Table 4: The values of sFlt-1 in Table 3 and Table 4 are not matched. You should re-check the results.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Obstetrics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 13 Sep 2021

Sarma Lumbanraja, Universitas Sumatera Utara, Medan, Indonesia

thanks for the correction

1. Gestational age in patient characteristics data is gestational age at the time of blood sampling. Blood samples were taken 1 hour before surgery. enforcement of the PAS score accreta based on ultrasound was carried out 1 day before the cesarean section. Blood collection to assess sFlt-1 levels was carried out 1 hour before the patient underwent a cesarean section and the diagnosis of accre based on FIGO was performed during the duration of the operation.

2. Sorry for the error in inputting data in this table. we will fix this writing error soon. thanks

best regards

Competing Interests: there is no conflict of interest in this reaseach

Author Response 27 Nov 2021

Sarma Lumbanraja, Universitas Sumatera Utara, Medan, Indonesia

Hello,

I have clarified the question you asked me and I am currently making improvements to my article. Are there any further objections or questions regarding the first question you asked in my research so that I can make further improvements to improve my article? I'm very grateful for your input.

Thanks

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 22 July 2021

<https://doi.org/10.5256/f1000research.58225.r90029>

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Akhide Ohkuchi

Department of Obstetrics and Gynecology, Jichi Medical University School of Medicine, Tochigi, Japan

General comments:

The most important matter is the no-adjustment of gestational age at blood sampling. Without adjusting for gestational age, you never conclude that sFlt-1 levels in cases were significantly decreased compared with those in controls.

Other comments:

1. Title: "Soluble FMS-like tyrosine kinase-1: Role in placenta accreta spectrum disorders" may be better.
2. Abstract: Line 6: sflt-1 should be sFlt-1. Please reflect this modification in the whole manuscript.
3. Abstract: Line 6, and Introduction: Line 14: "produced by the placenta" should be changed to "mainly produced by the placenta".
4. Abstract: Line 17: "man Whitney" and Line 23: "Mann. Whitney" should be changed to "Mann-Whitney".
5. Methods: PAS 0, PAS 1, and PAS 2 should be defined briefly in the Methods. In addition, the FIGO score should be briefly defined in the Methods.
6. Methods: Statistical analysis: You wrote, "Post Hoc test was used if the ANOVA analysis indicated a significant difference ($p < 0.05$)." However "Post Hoc test was used if the ANOVA analysis or Kruskal-Wallis tests indicated a significant difference ($p < 0.05$)." may be a better expression. In addition, you should write how to analyze correlation.
7. Results: Table 1: Is the "Gestational age" at blood sampling or at delivery? You should show both gestational age at blood sampling and at delivery because the serum levels of sFlt-1 steeply increased even if the difference age is only one week at 36-40 weeks of gestation.
8. Results: Table 1: P-value should be shown till three decimal places, for example, 0.08 should be shown as one of the following numbers: 0.075, 0.076, ..., 0.084.
9. Results: Table 2: Because the levels of sFlt-1 were strongly affected by the gestational age, you should analyze statistics including not only the levels of sFlt-1, but also gestational age (weeks of gestation). One possible statistical method may be generalized linear model which is included in SPSS advanced model. Instead, you can compare sFlt-1 levels after logarithmic transformation using two-way ANOVA.
10. Table 4: The values of sFlt-1 in Table 3 and Table 4 are not matched. You should re-check the results.
11. Discussion: Line 28-29: "Shainker *et al.* It has been reported that" Is a grammatical error.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Obstetrics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 21 Aug 2021

Sarma Lumbanraja, Universitas Sumatera Utara, Medan, Indonesia

Thank you for the suggestions and input on my research. me and the team have made some improvements according to the comments you gave on my research. For linear analysis, I tried to include a new chart showing the differences in sFlt-1 levels in the case group and the control group in our patients according to gestational age. for the PAS score assessment, the value we took was 2 days before the patient's cesarean section. For blood collection, it is done 1 hour before cesarean section. I hope this fix can answer all your questions. Thank you for the suggestions and input to improve this article.

Competing Interests: there is no conflict of interest in this study. thank you

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