ISSN: 1343-4292
Volume 140, Issue 01, April, 2022

Measurement of maternal serum interleukin-33 level for the diagnosis of placenta previa accrete

Miami A. Ali Ficog[1*], Shaimaa Talib Gissab[2]

Iraqi board for medical specialization/Mustansiriyah university, college of medicine student[1]
Iraqi board for medical specialization AL Yarmouk Teaching Hospital Department of Obstetrics & Gynecology[2]

Corresponding Author: 1*

ABSTRACT— Placenta previa accreta is a life-threatening obstetric condition that is responsible for massive obstetric hemorrhage that is a leading cause of pregnancy-related death. Interleukin-33 is associated with the invasion, proliferation, and metastasis of various cancers. The trophoblast of the placenta previa accreta invades into the myometrium in a similar way to the invasion of cancers. We studied the role of interleukine-33 in placenta previa accreta as a biomarker for antenatal diagnosis. To determine the usefulness of serum Interleukin-33 as a sensitive biomarker of invasive placentation. Prospective cohort study, in the department of Obstetrics and Gynecology at Al-Yarmouk-Teaching Hospital. This study included 90 cases of pregnant women divided into 3 groups, (group 1) 20 pregnant women diagnosed to have placenta previa accreta (group 2) 30 pregnant women diagnosed to have placenta previa nonadherent, and (control group3) which comprised of 40 pregnant women with the normal placenta. Serum samples were collected for both groups to measure Interleukin-33 levels by ELIZA method then statistical analysis was performed to detect the association between the interleukin-33 concentration and placental invasion. The result of the present study showed that serum interleukine-33 was significantly higher in placenta previa accreta patients when compared with placenta previa non-adherent and control group with a p-value = 0.001 and the interleukin-33 in cases who require urologist interventions and bladder repair was significantly higher p value=0.001and interleukine-33 level was also higher in cases which revealed percreta by histopathological reports than in cases of increta and accreta with p value=0.001. Higher levels of maternal serum IL-33 have been linked to placenta previa accreta, and greater levels in patients with percreta compared to increta and accreta show that IL-33 may play a role in aberrant placental invasion.

KEYWORDS: Placenta Previa Accreta; Serum Interleukin-33(IL-33); Al-Yarmouk-Teaching Hospital

1. INTRODUCTION

Placenta accreta was first described in [1] as “failure of separation of the placenta from the uterine wall following delivery of the human fetus leading to the often-used term “morbid placental adherence”. Placenta accreta is defined as abnormal trophoblast invasion of part or all of the placenta into the myometrium that leads to the failure of placental separation partially or totally from the uterine wall which is associated with catastrophic hemorrhage [2]. Varied terminology has been applied to this condition; recent guideline suggested using the term “placenta accreta spectrum” (PAS)which include accreta, increta, and percreta [3]. The condition is unique to human pregnancy with no animal correlate reported in the literature [4].

The antenatal diagnosis of placenta accreta depends on:
1-Ultrasonography: ultrasound has been the primary diagnostic tool for PAS detection. The prenatal ultrasound has accuracy for the diagnosis of PAS in women with an anterior placenta previa and a previous Cesarean section, with a sensitivity of 91%and a specificity of 97% [5]. and Color Doppler signs suggestive

of PAS disorders are: Diffuse or focal lacunar flow; Vascular lakes with the turbulent flow (peak systolic velocity over15cm/s); hypervascularity of serosa -bladder interface; markedly dilated vessels over peritoneal sub-placental zone [5].

2- Magnetic Resonance Imaging (MRI), It is used especially if grayscale ultrasonographic and color Doppler are not satisfactory, when the placenta is posteriorly located and in obese patients [6].

3- Biochemical Markers. studies found a number of the marker were significantly higher in a woman with PAS like pregnancy-associated plasma protein PAPP-A [7]; Human Chorionic Gonadotrophin (HCG) [8] &Alpha-Fetoprotein (AFP) [9].

Recently, new proofs suggest the action of IL-33 in the decidual trophoblast proliferation and invasion. Interleukin-33member of the interleukin-1 (IL-1) family of cytokines that is expressed in multiple organs and cell types in humans play major roles in host defense and immune system regulation in infectious and inflammatory diseases. It also affects the proliferation and invasion of trophoblast cells [10].

In light of these findings, the present study aimed to investigate if there were any differences in maternal serum level of IL-33 of patients having PPA when they were compared to healthy controls.

2. Aim of study

To determine the usefulness of serum interleukin-33 as a sensitive biomarker for the prenatal diagnosis of placenta previa accrete.

Patients and methods: This are a prospective cohort study had been done at Al-Yarmouk Teaching Hospital for ten months period from March 2020- to January 2021.

2.1 Inclusion Criteria

For all groups (case& control): singleton viable pregnancy ≥ 28 weeks of gestation at the time of delivery, groups include first group patients with placenta previa accreta and Second group those patients with non-adherent placenta previa, as well as control group pregnant women with normal placentation.

2.2 Exclusion criteria

patients were excluded if any of the following conditions were present: -
Multiple pregnancies; non-viable fetus; Fetus with a gross congenital abnormality; Preeclampsia & hypertensive disorders; Preterm premature rupture of membranes (PPROM); Gestational diabetes, type 1&type 2 diabetes; Auto-immune disease; Gestational cholestasis; Acute trauma leading to oxidative stress; chorioamenities; Cigarette smoking; History of thromboembolic disease.

2.3 Method and Data collection

Detailed obstetric, gynecological & medical history was obtained from each patient then examination including (BMI) &vital signs & obstetric clinical examination was performed for all patients. The routine investigation was done such as blood group, Rh typing, full blood count and, renal function test. Ultrasound was performed by an experienced ultra-sonographer in AL Yarmouk Teaching Hospital using a medical system equipped with a convex probe 3.5 MHZ transducers using SIEMENS ACUSON. Grayscale B-mode U/S was first used to screen the placenta tissue in a systematic fashion and those suspected of having abnormal placenta were referred to color Doppler U/S for further evaluation of the uteroplacental vascular morphology for the possibility of placenta accreta.

ISSN: 1343-4292
Volume 140, Issue 01, April, 2022

Serum interleukin -33 assay: Blood samples were obtained by venipuncture and processed within 30 minutes -1 hour after withdrawal, by centrifugation at (2000-3000 RPM) for approximately 20 minutes. All serum samples were stored at -20 degrees Celsius until the day of analysis. All specimens were clearly labeled with the names of patients at the time of collection. Quantitative determination of interleukin-33 was measured by enzyme-linked immunosorbent assay (ELIZA) using interleukin-33 ELIZA kit (SHANGHAI Biological Technology, China) and the results are presented as pg. /ml.

3. Result

The mean level of interleukin-33 in the pregnant women with placenta previa accreta was (101.96±22.88) which is significantly higher than that in the pregnant women with placenta previa nonadherent (49.33±13.96) and normal placenta (24.99±7.86), with a p value=0.001.as shown in table (1).

Table no: 1 significance of differences between means of IL33 according to a group of studies by one-way ANOVA.

	No. Of patient	IL- 33 level(pg/ml) Mean ± Std. D.		P-value	Pairwise comparisons		
					1 - 2	2 - 3	1 - 3
1-Placenta previa accreta	20	101.964 ± 22.8802		0.001	0.001	0.001	0.001
2- Placenta Previa(non- adherent)	30	4 9.330 ± 13.9652					
3-Normal placenta	40	24.992	7.8662				
Total	90	50.209	33.0213				

Statistically significant difference was found in the level of interleukin-33 with the operative finding, the mean of IL-33 levels in cases of placenta accrete patients who ended with ceasrean hysterectomy was (106.78±21.05) while the mean of IL-33 levels in those who underwent local adherent area resection with oversewing of the defect was (74.66±10.61), p value=0.02.

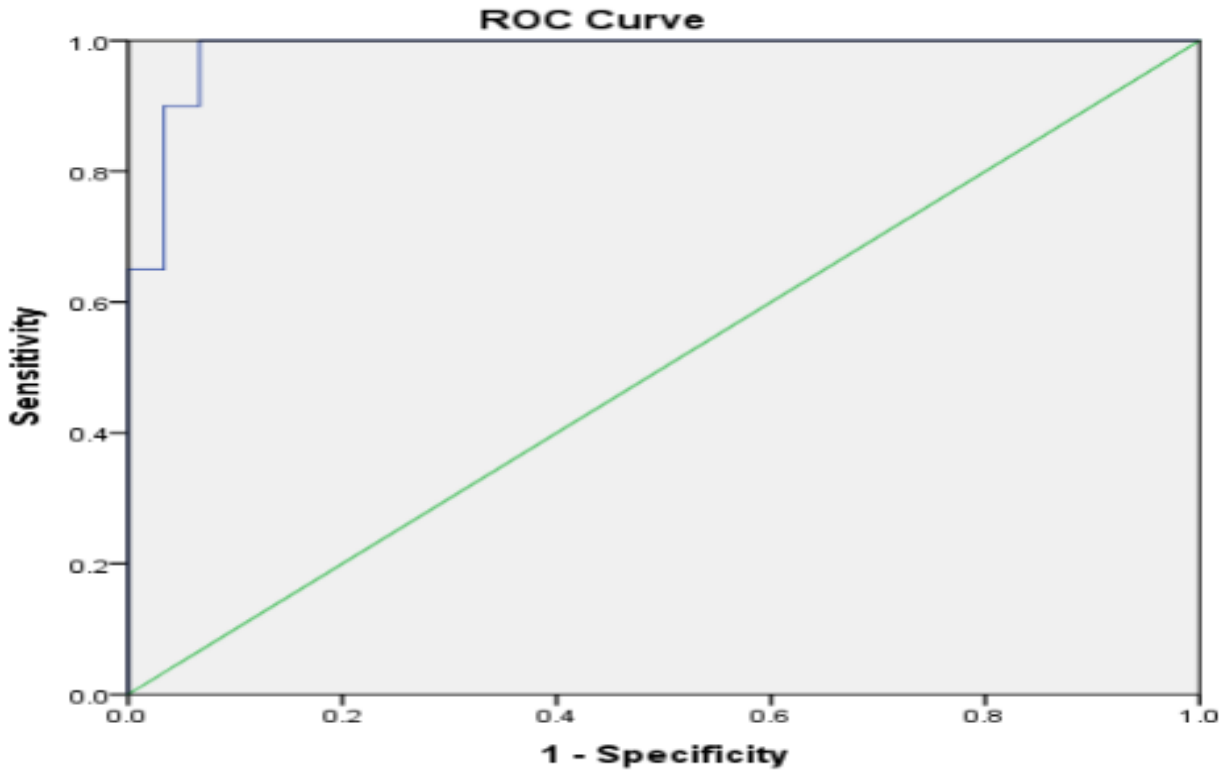
The mean of IL-33 levels in the cases that required urologist interference and bladder repair was (115.93±17.53) which also shows statistical significance, p value=0.001.

The mean of IL-33 level was higher in cases who requires blood transfusion (113.69_+15.57), p value =0.001 as shown in table (2).

Table (2); Description of IL33 level means according to operative finding, bladder injury and blood transfusion in PPA by two-sample T-test

	No. of patients	**Level of IL-33 (pg/ml) (Mean ±Std.**	**P-value**

			D.)	
Operative finding	Cesarean hysterectomy	17	106.781 ±21.0526	0.02
	Adherent area resection	3	74.667 ± 10.6157	
Bladder injury	Yes	12	115.939 ± 17.5335	0.001
	No	8	81.000 ± 10.0380	
Blood transfusion	Yes	14	113.693 ± 15.5721	0.001
	No	6	74.595 ± 8.6476	



The ROC curve of IL-33 levels to detect Placenta previa accreta from Placenta Previa non-adherent, Total Area Under the Curve=0.985, p value=0.001, at IL33 cutoff point =72, the sensitivity=90% and specificity= 96.7%.

Area Under the Curve

Test Result Variable(s): IL-33result

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.985	.013	.000	.959	1.000

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

ISSN: 1343-4292
Volume 140, Issue 01, April, 2022

Coordinates of the Curve		
Test Result Variable(s): IL-33result		
Positive if Greater Than or Equal To[a]	Sensitivity %	1 — Specificity%
27.200	100%	0%
33.750	100%	16.7%
34.550	1.00%	20%
47.150	100%	43.3%
58.800	100%	76.7%
68.885	90%	93.3%
72.000	90%	96.7%
73.500	85%	96.7%
78.430	80%	96.7%
92.170	60%	0%
123.000	25%	0%
135.700	0%	0%

4. Discussion

In the present study a significant difference between the serum Interleukin-33 level in patients with placenta previa accreta when compared to patients with a placenta previa non-adherent (mean 101.96±22.88 vs. 49.33±13.96), p-value 0.001 and this may be related to the significant trophoblastic invasion, These results were also reported by [10]. An additional finding of this study is that serum IL-33 was higher among pregnant women with placenta previa non-adherent when compared to pregnant women with the normal placenta and this may be explained by what was demonstrated in [11], in which IL-33 is a novel cytokine that signals through the ST2 surface receptor which is like high mobility group box protein1(HMGB1), both are" alarmin "that provides a danger signal as a result of tissue damage and necrosis with the release of intracellular content and [12] study who hypothesized that increased expression of high mobility group box protein 1 (HMGB1) in placenta previa may be associated with the pathogenesis of placenta previa by regulating the expression of the proangiogenic factor VEGF, so the mRNA expression level of HMGB1 &VEGF were significantly increased in placenta previa group when compared to the normal placental group. This explain the increase in IL-33 level in patients with placenta previa non adherent group when compared to patients with normal placenta group.

Regarding the intraoperative findings, in the current study, 85% of patients with placenta previa accreta ended with cesarean hysterectomy a procedure commonly performed on patients with massive hemorrhage that cannot be controlled by other conservative management. This percentage was considered high when compared to another study while [13], [14] the percentage of hysterectomy was 78.4-80% due to the availability of different methods including uterine artery embolization, balloon tamponade, and interventional radiology

Which are lacking in our country.

Bladder injury occurred in about 60%(12/20 cases) in patients with placenta previa accreta group who had a cesarean hysterectomy which is comparable with [15] in which 59.7%(43/72cases) of patients were reported to have bladder injury in the placenta accreta group which is the higher percentage when compared to another study like [16] in which the bladder injury was 39.5% may be attributed to the differences of management options for placenta accreta group between the studies.

Further, a serum level of IL-33 of cutoff 72 pg/ml was specifically associated with placenta previa accreta and stratified them from those of placenta previa non-adherent with sensitivity=90% and specificity=96.7%, with p-value 0.001. However, a study by [10] which investigate the role of Interleukin-33 in placenta previa

accreta found Interleukin-33 at a cutoff value of 47.26pg/ml had a sensitivity of 51% and specificity of 79%, with a p-value of 0.02.

5. Conclusion

A higher level of maternal serum interleukin-33 was positively correlated with the degree of placental invasion so it can be used as a potential biomarker for the antenatal diagnosis of placenta previa accreta. as well as increased IL-33 levels were related to cesarean hysterectomy, massive blood transfusion, and bladder injury in placenta previa accreta patients, so increased interleukin-33 levels can be used to anticipate the risk of such complications in placenta previa accreta patients.

Ethical considerations and official approvals: Approval of the proposal was obtained from the Scientific Council of Obstetrics and Gynecology, Council of Iraqi Board of Medical Specialization. A verbal agreement was obtained from each participant before their enrolment in the study.

6. References

[1] C. Irving and A. T. Hertig, "A study of placenta accreta," Surgery, Gynecology & Obstetrics, vol. 38, no. 6, pp. 1088–1200, 1937.

[2] Usta IM, Hobeika EM, Musa AA, Gabriel GE, Nassar AH. Placenta previa-accreta: risk factors and complications. Am J Obstet Gynecol. 2005

[3] E. Jauniaux, F. Chantraine, R. M. Silver, J. Langhoff-Roos, andss for the FIGO Placenta Accreta Diagnosis and Management Expert Consensus Panel, "FIGO consensus guidelines on placenta accreta spectrum disorders: epidemiology," International Journal of Gynecology & Obstetrics, 2018 vol. 140, no. 3, pp. 265–273.

[4] E. Chuong, "Evolutionary perspectives into placental biology and disease," Applied & Translational Genomics, vol. 2, pp. 64–69, 2013.

[5] Florrie N.Y.Yu, K.Y.Leung," Antenatal diagnosis of placenta accrete spectrum(PAS) disorders, Best practice & Research Clinical Obstetrics and Gynecology,2020.

[6] W.Christopher Baughman ,MD. JaneE,Corteville,MD.rAJIVr.Shah,MD. "Placenta Accreta: Spectrum of US and MR Imaging Finding" November- 2008 volume 28.Number 7.

[7] D.Lyell,A.Faucett,R.Baer et al.,"Maternal serum marker,characteristics and morbidly adherent placenta in women with previa" journal of perinatology,vol.35,no.8.pp.570-574,2015.

[8] B.Buke, H.Akkaya, S. Demir et al."Relationships between first trimester aneuploidy screening test serum analysts and placenta accrete," The Journal of Maternal – Fetal &Neonatal Medicine,vol.31,no. 1,pp.59-62,2017.

[9] A.Sekizawa,M.Jimbo,H.Saito et al.," Increased cell-free fetal DNA in plasma of tow woman with invasive placenta" Clinical Chemistry ,Vol.48,no.2,pp.353-354,2002.

[10] Sibel Ozler , Efser Oztas ,Basak Gumus Guler &Ali Turhan Caglar "Increased level of serum interleukin-33 is associated with adverse maternal outcomes in placenta previa accrete ,The Journal of

maternal-fetal &neonatal medicine,2019.

[11] Gray S. Firestin , Ralph C. Budd,…James R. Odell," Kelley and Firestines Textbook of Rheumatology", interlukin-33 and other Alarmins, Tenth edition,2017 .

[12] Han Xie, ;Ping Qiao, Yi Lu, Ying Li et al. "Increased expression of high mobility group box protein 1 and vascular endothelial growth factor in placenta previa" 2017(1)..

[13] Eller AG, Porter TF, Soisson P, Silver RM. Optimal management strategies for placenta accrete .British J. of Obstetrics and Gynecology.2009;(116):648-54.

[14] Sentilhes L,Ambroselli C, Kayem G,et al .Maternal outcome after conservative treatment of placenta accrete. J Obestet Gynecol 2010;115:526- 34.

[15] Jaafer, Zainab A. ;Reshed Z. Obeid , Dina A. Salman," Serum Zinc: A Noninvasive Biomarker for the prediction of Invasive Placentation "International Jornal of Women Health and Reproduction Science, vol. 8, No.4, October 2020.

[16] Saad El. Gelany, Mohammed, H.Mosbeh, Ahmed R.Abdelraheim" Placenta Accreta Spectrum(PAS) disorders :incidence, risk factors and outcomes of different management strategies in a tertiary referral hospital in minia, Egypt: a prospective study"BMC Pregnancy and Childbirth 19,2019.