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Decreased oxidative stress may contribute to the disease process in placenta accreta

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Background/aim: The main aim of this study was to investigate serum total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), and arylesterase levels in pregnant women with placenta accreta and to compare those with age-matched healthy pregnant women.

Materials and methods: A total of 27 pregnant women who had clinically and pathologically proven placenta accreta and 30 age- and BMI- matched healthy pregnant women were enrolled in this case control study. Maternal serum TOS, TAS, OSI, and arylesterase levels were evaluated using logistic regression analysis to determine if there was an association with abnormal placental invasion or not.

Results: Decreased OSI (OR= 0.999, 95%CI: 0.998–1.000, P = 0.035) and increased arylesterase levels (OR= 0.981, 95%CI: 0.970–0.993, P = 0.001) were significantly associated with the presence of placenta accreta. Maternal serum TOS, TAS, OSI, and arylesterase levels were not predictive for adverse perinatal outcomes (P > 0.05).

Conclusions: Decreased OSI and increased arylesterase levels are significantly associated with placenta accreta and may contribute to the abnormal invasion process.

Key words: Arylesterase, oxidative stress index, total antioxidant status, total oxidant status, placenta accreta

1. Introduction

Placenta accreta is defined as complete or partial adhesion of the placenta to the myometrium and its incidence has increased up to 3 per 1000 deliveries and seems to be parallel with the increasing rate of cesarean delivery (1). Placenta accreta is a catastrophic clinical condition that threatens survival, due to intrapartum and postpartum bleeding and warrants a multidisciplinary approach. The rates of maternal mortality and morbidity with placenta accreta have been reported to be as high as 7% and 60 %, respectively (2). While increasing cesarean sections seem to be responsible for the increased incidence and deficiency of decidualization, increased angiogenesis, and overinvasiveness of the trophoblasts are implicated in the pathophysiology of placenta accreta, the molecular basis of this condition remains unclear (1,3). Placental angiogenesis and trophoblastic invasion are balanced during pregnancy. On the other hand, deterioration of the balance between angiogenic and antiangiogenic factors and also an imbalance between proinvasive and antiinvasive factors might cause abnormal uteroplacental vascularization and subsequently abnormal placental invasion (4).

Previous studies have widely studied the impaired growth of placental vasculature in pregnancy-associated pathologies that lead to placental insufficiency, including preeclampsia, intrauterine growth restriction, intrauterine fetal demise, and miscarriage (5–8).

Additionally, it has already been proposed that as placental circulation is established in human pregnancy, it results in a dramatic increase in placental oxygen levels, and thus causes an increase in reactive oxygen species (ROS) and oxidative stress (9,10). Moreover, this systemic oxidative damage continues until the end of pregnancy, and so it is suggested that certain amounts of ROS and oxidative stress are crucial for placental vascular development throughout pregnancy (11). However, it has been proposed that excessively increased oxidative stress due to placental hypoxia may limit placental angiogenesis, leading to pathologies such as IUGR and

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preeclampsia (12,13). As increased oxidative stress is already shown to contribute in limited angiogenesis, we suggest that increased angiogenesis in placenta accreta may also be associated with an imbalance between oxidant and antioxidant mechanisms.

In the current study we aimed to investigate maternal serum TOS, TAS, OSI, and arylesterase, and antioxidant enzyme levels in pregnant women with placenta accreta, and to determine whether any changes in their levels are useful in predicting adverse pregnancy outcomes in placenta accreta.

2. Materials and methods

A case-control study was carried out between June 2013 and May 2014 in the Obstetrics and Gynecology Department of Zekai Tahir Burak Women's Health Education and Research Hospital. A total of 86 participants were included in the study. Twenty-seven patients included in the study were diagnosed with placenta accreta during cesarean section and all cases were histologically confirmed according to previously established criteria as the abnormal adherence of placenta involving all degrees to the underlying uterine wall (14). Thirty age- and body mass index (BMI)-matched uncomplicated healthy pregnant women with normal placental location were also recruited. Adverse neonatal outcomes included low birthweight (<2500 g), preterm delivery (<37 weeks), low 1- and 5-min Apgar scores (Apgar score < 7), and neonatal intensive care unit admission. Neonatal intensive care unit admission criteria in our hospital are standard for all neonates and the neonatologists did not have any information about the present study.

Patients were excluded if any of the following disorders were present: multiple pregnancy, preterm premature rupture of membranes, previous pregnancy complicated with placenta previa, any previous complicated pregnancy, cervical or uterine surgery (myomectomy, metroplasty, uterine septal resection, conization, any intervention for previous pregnancy located in the lower uterine segment having settled in the uterine scar line), thyroid dysfunction, hypertension, epilepsy, gestational diabetes, type 1 or 2 diabetes, and patients using medication.

All participants included in the study were evaluated at their initial admission. A clinical examination was performed and anthropometric measurements as well as the previous obstetric and medical history were recorded. Gestational age was calculated from the last menstrual period and verified by ultrasonography. Blood samples were obtained after overnight fasting by venipuncture and processed within 1 h of withdrawal, and all serum samples were stored at –80 °C until the day of analysis. As oxidative stress markers can be easily affected by other factors, we took care that no additional factors such as concomitant uterine contractions, bleeding, and infection were present during the sample collection. All participants provided written informed consent. The study protocol was performed according to the principles of the Declaration of Helsinki and approved by the local Ethical Committee of our hospital.

Serum TOS and TAS levels were determined spectrophotometrically using a method previously described by Erel, and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 eqv./L) for TOS and as millimolar trolox equivalent per liter (mmol Trolox eqv./L) for TAS (15,16). The ratio of TAS to TOS represents the OSI, an indicator of the degree of oxidative stress. The OSI value is calculated according to the formula: OSI [arbitrary unit (AU)] = TOS (μmol H_2O_2 eqv./L)/TAS (mmol Trolox eqv./L) × 1002^5. Arylesterase activities results are expressed as kU/L serum.

2.1. Statistical analysis

IBM SPSS for Windows Version 20.0 (Armonk, NY, USA: IBM Corp.) was used for statistical analysis. Continuous variables were tested for normality by the Kolmogorov–Smirnov test. Normally distributed data were presented as mean ± standard deviations. Categorical comparisons were performed using the chi-square test. For data not normally distributed, median with data range (minimum to maximum) was used. We used the independent samples t-test and Mann–Whitney U test for parametric and nonparametric groups, respectively. The optimal cut-off points of laboratory parameters determining accreta were evaluated by ROC analyses, calculating area under the curve (AUC) as giving the maximum sum of sensitivity and specificity for the significant test. Sensitivity and specificity were alsocalculated at the best cut-off point for each clinical measurement. To determine if the oxidative stress markers are independently associated with the presence of accreta multiple logistic regression analysis was used. Odds ratios and 95% confidence intervals for each independent variable were also calculated. A P value less than 0.05 was considered statistically significant. Multivariate logistic regression analysis was also used to determine if a relationship between adverse neonatal outcomes and serum oxidative stress markers was present or not.

3. Results

Fifty-seven pregnant women were enrolled in the present case-control study: 27 patients with placenta accreta, and 30 age- and BMI-matched healthy pregnant controls. The baseline characteristics of the placenta accreta patients and controls are given in Table 1. There were no statistically significant differences in age, BMI, weight gain in pregnancy, or the percentage of smoking between the groups. Gravida, the percentage of preterm delivery, and prior cesarean section history were significantly higher in the accreta group. Maternal serum TOS and OSI were

Table 1. Baseline characteristics and laboratory parameters of the patients with placenta accreta and the controls.

	Placenta accreta n = 27	Control n = 30	P value
Age (years)	28.03 ± 5.28	30.56 ± 4.99	0.070
BMI (kg/m^2)	28.34 ± 4.47	28.07 ± 3.12	0.797
Smoking (%)	7 (25.9%)	3 (10.3%)	0.128
Prior cesarean delivery (%)	20 (74.1%)	7 (23.3%)	<0.001
TAS (mmol Trolox eqv./L)	0.223 ± 0.077	0.184 ± 0.069	0.049
TOS (μmol H_2O_2 eqv./L)	3.144 ± 0.689	4.179 ± 1.620	0.003
OSI (arbitrary unit)	1628.43 ± 785.63	2559.30 ± 1353.23	0.003
ARES (kU/L)	420.49 ± 141.82	256.56 ± 63.95	<0.001

P value: P < 0.05 statistically significant, BMI: body mass index, TAS: total antioxidant status, TOS: total oxidant status, ARES: arylesterase, OSI: oxidative stress index, H_2O_2: hydrogen peroxide

significantly lower, while TAS and arylesterase levels were significantly higher in the accreta group when compared with the controls (Table 1).

Serum TAS, TOS, PON, arylesterase, and OSI levels were again evaluated with ROC analysis; cut-off levels were determined and AUC values were calculated. The AUC, best cut-off values, sensitivity, and specificity for distinguishing the groups for each parameter are given in Table 2. All parameters except TAS were found to be statistically significant.

Multivariate logistic regression analysis was then used to determine if there was a relationship between groups and the defined cut-off levels of the laboratory parameters or not. Prior cesarean delivery (OR = 0.174, 95%CI: 0.041–0.744, P = 0.018), low OSI (OR = 0.999, 95%CI: 0.998–1.000, P = 0.035), and high arylesterase levels (OR = 0.981, 95%CI: 0.970–0.993, P = 0.001) were found to be statistically significant in the determination of placenta accreta (Table 3).

In addition, we examined if there were any changes in TOS, TAS, OSI, and arylesterase levels according to the management of placenta accreta. No significant changes were observed when the accreta patients were again evaluated by dividing them into 3 subgroups according to the management procedure: hysterectomy (n = 14), compression sutures (n = 6), and compression sutures + Bakri balloon tamponade (n = 7).

Further analysis was also performed to determine whether there was a correlation between oxidative stress markers and adverse neonatal outcomes (low APGAR, low birth weight, preterm delivery, and neonatal unit admission) or not. Multivariate logistic regression analysis, used to determine the predictive value of defined cut-off levels of the laboratory parameters and adverse perinatal outcomes, failed to determine such an association (P > 0.05).

Table 2. Cut-off levels of TAS, TOS, OSI, and arylesterase for the prediction of placenta accreta evaluated with ROC analysis.

	Cut off	Sensitivity %	Specificity %	AUC (95%CI)	P value
TAS (mmol Trolox eqv./L)	0.207			0.642 (0.494–0.790)	0.066
TOS (μmol H_2O_2 eqv./L)	3.568	70.37%	53.33%	0.659 (0.515–0.803)	0.040
OSI (arbitrary unit)	1623.38	66.67%	80.0%	0.726 (0.592–0.860)	0.003
ARES (KU/L)	338.73	92.59%	73.33%	0.859 (0.765–0.954)	<0.001

P value: P < 0.05 statistically significant, TAS: total antioxidant status, TOS: total oxidant status, ARES: arylesterase, OSI: oxidative stress index, AUC: area under the curve, CI: confidence interval, ROC: receiver operating characteristic, H_2O_2: hydrogen peroxide

Table 3. Multivariate logistic regression analysis of several factors for the prediction of placenta accreta.

	Univariate		Multivariate	
	OR (95%Cl)	P value	OR (95%Cl)	P value
Prior cesarean delivery	6.667 (1.342–33.125)	0.020	0.174 (0.041–0.744)	0.018
Prior curettage	7.000 (0.501–97.751)	0.148		
TAS (mmol Trolox eqv./L)	1.580 (0.809–3.813)	0.051		
TOS (μmol H_2O_2 eqv./L)	0.497 (0.295–0.835)	0.008	1.620 (0.597–4.395)	0.343
OSI (arbitrary unit)	0.999 (0.998–1.000)	0.009	0.999 (0.998–1.000)	0.035
ARES (kU/L)	0.983 (0.973–0.993)	0.001	0.981 (0.970–0.993)	0.001

P value: $P < 0.05$ statistically significant, TAS: total antioxidant status, TOS: total oxidant status, ARES: arylesterase, OSI: oxidative stress index, OR: odds ratio, CI: confidence interval, H_2O_2: hydrogen peroxide.

4. Discussion

In the present case-control study of oxidative stress markers in placenta accreta, increased levels of maternal serum arylesterase levels and decreased OSI were found to be associated with placenta accreta. Oxidative stress has already been suggested to contribute in the pathogenesis of placenta-related diseases of pregnancy such as preeclampsia and miscarriage (17). Various studies showed increased oxidant status in pregnancies with both preeclampsia and fetal growth retardation, and thus suggested that oxidative stress is a major contributor in preeclampsia- and fetal growth retardation-related endothelial dysfunction (18,19). Although, to the best of our knowledge, there are no studies comparing oxidative stress markers between placenta accreta and healthy pregnant women, we hypothesized that a mechanism just the opposite of preeclampsia might have contributed to the disease process in placenta accreta. In the present study, we found that oxidative stress was decreased, while antioxidant status and arylesterase, an antioxidant enzyme, were increased. Thus, it seems like there is an imbalance between oxidant and antioxidant mechanisms towards dominance in antioxidant status in placenta accreta. McMahon et al. recently demonstrated that lower levels of placental soluble fms-like tyrosine kinase-1 (sFLT-1) expression were associated with invasive placentation (20). sFLT-1 is a potent antiangiogenic growth factor and an association between increased levels and preeclampsia has been widely evaluated (21,22). Although sFLT-1 has been reported to be a predictive marker and important in the pathophysiology of preeclampsia, the mechanism of its involvement was recently demonstrated. Jiang et al. reported that in the serum of sFLT-1 treated preeclamptic mice, oxidant malonyl dialdehyde levels were higher and antioxidant superoxide dismutase levels were lower when compared with controls (23). Hence, they suggested that sFLT-1 promoted apoptosis by increasing oxidative stress. Since sFLT-1 levels were reduced in placenta accreta, it would not be inappropriate to suggest that reduced sFLT-1 resulted in decreased apoptosis of trophoblasts and increased angiogenesis, by implication of decreased oxidative stress. Our study is in agreement with the above-mentioned studies, since we found reduced oxidative stress in placenta accreta.

The antiangiogenic property of the placenta in preeclampsia and placenta accreta cases is known. Öztürk et al. observed significantly lower levels of TAS in the placenta of pregnant patients having preeclampsia when they were compared with healthy controls, and showed its significant relation with the maternal serum TAS levels (24). Moreover, Hilali et al. demonstrated significantly lower levels of TAS and increased levels of TOS and OSI in the maternal serum and cord samples of patients having mild preeclampsia (25).

Recently, Choi et al. suggested that alphafetoprotein (AFP) is a novel marker protein for the antioxidant effect of the placenta (26). In addition, it has been already proposed that unexplained elevated maternal serum AFP is associated with placenta accreta (1). These studies confirm the accuracy of our findings, since increased AFP may be responsible for the increase in antioxidant status in placenta accreta.

In conclusion, reduced OSI and increased arylesterase levels are associated with placenta accreta. Decreased oxidative stress might be either a cause of abnormal placental invasion or a consequence of increased AFP, and so this study needs to be validated with further studies investigating the causal relationship of oxidative stress in placenta accreta.

References

1. Belfort MA, Publications Committee Society for Maternal-Fetal Medicine. Placenta accreta. Am J Obstet Gynecol 2010; 203: 430-439.
2. O'Brien JM, Barton JR, Donaldson ES. The management of placenta percreta: conservative and operative strategies. Am J Obstet Gynecol 1996; 175: 1632-1638.
3. Khong TY. The pathology of placenta accreta, a worldwide epidemic. J Clin Pathol 2008; 61: 1243-1246.
4. Al-Khan A, Aye IL, Barsoum I, Borbely A, Cebral E, Cerchi G, Clifton VL, Collins S, Cotechini T, Davey A et al. IFPA Meeting 2010 Workshops Report II: Placental pathology; trophoblast invasion; fetal sex; parasites and the placenta; decidua and embryonic or fetal loss; trophoblast differentiation and syncytialisation. Placenta 2011; 32: S90-99.
5. Myatt L. Role of placenta in preeclampsia. Endocrine 2002; 19: 103-111.
6. Barut F, Barut A, Gun BD, Kandemir NO, Harma MI, Harma M, Aktunc E, Ozdamar SO. Intrauterine growth restriction and placental angiogenesis. Diagn Pathol 2010; 5: 24.
7. Pinar H, Carpenter M. Placenta and umbilical cord abnormalities seen with stillbirth. Clin Obstet Gynecol 2010; 53: 656-672.
8. Manolea MM, Dijmarescu AL, Popescu FC, Novac MB, DiȚescu D. Evaluation of the implantation site morphology in spontaneous abortion. Rom J Morphol Embryol 2015; 56: 125-131.
9. Jauniaux E, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ. Onset of maternal arterial blood flow and placental oxidative stress. A possible factor in human early pregnancy failure. Am J Pathol 2000; 157: 2111-2122.
10. Myatt L, Cui X. Oxidative stress in the placenta. Histochem Cell Biol 2004; 122: 369-382.
11. Pereira RD, De Long NE, Wang RC, Yazdi FT, Holloway AC, Raha S. Angiogenesis in the placenta: the role of reactive oxygen species signaling. Biomed Res Int 2015; 2015: 814543.
12. Ahmed A, Kilby MD. Placental insufficiency: hypoxia or hyperoxia? Lancet 1997; 350: 826-827.
13. Ahmed A, Dunk C, Ahmad S, Khaliq A. Regulation of placental vascular endothelial growth factor (VEGF) and placenta growth factor (PIGF) and soluble Flt-1 by oxygen-a review. Placenta 2000; 21 Suppl A: S16-24.
14. Fox H. Placenta accreta 1945-1969. Obstet Gynecol Surv 1972; 27: 475-490.
15. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005; 38: 1103-1111.
16. Erel O. A novel automated direct measurement method for total antioxidant capacity using a new generation more stable ABTS radical cation. Clin Biochem 2004; 37: 277-285.
17. Jauniaux E, Poston L, Burton GJ. Placental-related diseases of pregnancy: involvement of oxidative stress and implications in human evolution. Hum Reprod Update 2006; 12: 747-755.
18. Mert I, Oruc AS, Yuksel S, Cakar ES, Buyukkagnici U, Karaer A, Danisman N. Role of oxidative stress in preeclampsia and intrauterine growth restriction. J Obstet Gynaecol Res 2012; 38: 658-664.
19. Schneider D, Hernandez C, Farias M, Uauy R, Krause BJ, Casanello P. Oxidative stress as common trait of endothelial dysfunction in chorionic arteries from fetuses with IUGR and LGA. Placenta 2015; 36: 552-558.
20. McMahon K, Karumanchi SA, Stillman IE, Cummings P, Patton D, Easterling T. Does soluble fms-like tyrosine kinase-1 regulate placental invasion? Insight from the invasive placenta. Am J Obstet Gynecol 2014; 210: 68.e1-68.e 4.
21. Thadhani R, Mutter WP, Wolf M, Levine RJ, Taylor RN, Sukhatme VP, Ecker J, Karumanchi SA. First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for preeclampsia. J Clin Endocrinol Metab 2004; 89: 770-775.
22. Hertig A, Berkane N, Lefevre G, Toumi K, Marti HP, Capeau J, Uzan S, Rondeau E. Maternal serum sFlt1 concentration is an early and reliable predictive marker of preeclampsia. Clin Chem 2004; 50: 1702-1703.
23. Jiang Z, Zou Y, Ge Z, Qing Z, Huang SY, Sun L. A role of sFlt-1 in oxidative stress and apoptosis in human and mouse preeclamptic trophoblasts. Biol Reprod 2015; 93: 73.
24. Öztürk E, Balat O, Acılmıs YG, Ozcan C, Pence S, Erel O. Measurement of the placental total antioxidant status in preeclamptic women using a novel automated method. J Obstet Gynaecol Res 2011; 37: 337-342.
25. Hilali N, Kocyigit A, Demir M, Camuzcuoglu A, Incebiyik A, Camuzcuoglu H, Vural M, Taskin A. DNA damage and oxidative stress in patients with mild preeclampsia and offspring. Eur J Obstet Gynecol Reprod Biol 2013; 170: 377-380.
26. Choi HY, Kim SW, Kim B, Lee HN, Kim SJ, Song M, Kim S, Kim J, Kim YB, Kim JH et al. Alpha-fetoprotein, identified as a novel marker for the antioxidant effect of placental extract, exhibits synergistic antioxidant activity in the presence of estradiol. PLoS One 2014; 9: e99421.