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Decreased placental and maternal serum TRAIL-R2 levels are associated with placenta accreta

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ABSTRACT

Objectives: TNF-related apoptosis-inducing ligand receptor-2 (TRAIL-R2) is produced both by decidual and trophoblast cells during pregnancy and known to participate in apoptosis. In this study, we aimed to determine and to compare maternal serum and placental TRAIL-R2 levels in patients with placenta accreta, non-adherent placenta previa and in healthy pregnancies. We also aimed to analyze the association of placenta accreta with the occurrence of previous C-sections.

Study design: A total of 82 pregnant women were enrolled in this case–control study (27 placenta accreta patients, 26 non-adherent placenta previa patients and 29 age-, and BMI-matched healthy, uncomplicated pregnant controls). TRAIL-R2 levels were studied in both maternal serum and placental tissue homogenates. Determining the best predictor(s) which discriminate placenta accreta was analyzed by multiple logistic regression analyses. Adjusted odds ratios and 95% confidence intervals were also calculated.

Results: Both placental and serum TRAIL-R2 levels were significantly lower in placenta accreta group (median 34.82 pg/mg and 19.85 pg/mL, respectively) when compared with both non-adherent placenta previa (median 39.24 pg/mg and 25.99 pg/mL, respectively) and the control groups (median 41.62 pg/mg and 25.87 pg/mL, respectively) ($p < 0.05$). Placental TRAIL-R2 levels and previous cesarean section were found to be significantly associated with placenta accreta (OR: 0.934 95% CI 0.883–0.987, $p = 0.016$ and OR:7.725 95% CI: 2.717–21.965, $p < 0.001$, respectively). Placental and serum TRAIL-R2 levels were positively correlated.

Conclusion: Decreased levels of placental TRAIL-R2 and previous history of cesarean section were found to be significantly associated with placenta accreta, suggesting a possible role of apoptosis in abnormal trophoblast invasion.

1. Introduction

In a normal, healthy pregnancy, there is a perfect organisation of trophoblastic invasion, maternal decidual defence barrier and placental angiogenesis. An imbalance within these well-designed processes may cause inadequate or excessive trophoblastic invasion leading to many pregnancy associated disorders. The most common examined risk factor of abnormal placental invasion is the disturbance of the fine balance between the pro- and anti-invasive factors at the placentation site [1,2]. Previous reports indicated that the most important risk factor for placenta accreta is placenta previa in the presence of an uterine scar, and the remaining risk factors reported are multiparity, maternal age, any prior uterine surgery or curettage, uterine irradiation, endometrial ablation, Asherman syndrome or other uterine anomalies [1]. When all these associated risk factors are considered, it is clear that the common feature is the disruption of the fetal–maternal interface by the alterations in the local microenvironment [2]. Because abnormal placental invasion is commonly located in the area of the previous hysterotomy, and because the incidence of placenta accreta appears to be increasing parallel to the increasing number of cesarean deliveries, the scarring of the uterine wall, particularly by previous cesarean deliveries, is hypothesized as the most important risk factor leading to placental hyperinvasiveness [1,2].

Extravillous trophoblast cell (EVT) invasion of the maternal decidua is critical for the maintenance of a successful pregnancy.

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During normal placental development, EVT invade maternal tissues via two routes, the interstitial route, which proceeds through the decidua to the inner third of the myometrium, and the endovascular route, which includes the invasion of decidual spiral arteries [3]. EVT invasion is tightly regulated, unlike the uncontrolled invasion of neoplastic cells [4]. Deficient invasion of EVT has been shown to be related with miscarriage, preeclampsia, intrauterine growth restriction and preterm delivery [5–7]. Conversely, excessive trophoblast invasion together with decidual deficiency are the main mechanisms proposed for the pathophysiology of morbidly adherent placenta, placenta accreta [8]. A number of fetomaternal mechanisms work together in the regulation of trophoblastic invasion, and one mechanism is the balance between EVT proliferation and cell death, mediated through apoptotic mechanisms [9]. Apoptosis, programmed cell death, is a crucial factor in normal placental development and also for mediating immune privilege of the fetus during pregnancy [10,11]. Any disturbance of the balance between cell proliferation and apoptosis may also cause alterations in trophoblastic invasion. Although a number of mechanisms have been proposed, the molecular basis of trophoblast invasion remains poorly understood.

Apoptosis continues to increase throughout pregnancy and can be initiated either intrinsically by the mitochondrial pathway or extrinsically via membrane-associated death receptors [10,12]. In the extrinsic pathway, the members of the tumour necrosis factor (TNF) family, such as TNF-α, Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL), are the most relevant factors that trigger apoptosis by binding to receptors on the cell surface [13]. TRAIL belongs to the TNF superfamily and was first identified in 1995. TRAIL is a type II membrane protein and can also exist as a soluble fragment (sTRAIL) following proteolytic cleavage [14]. Both membrane-expressed TRAIL and the soluble form have been shown to induce apoptosis in various cell lines. TRAIL can interact with five different receptors. Among these five receptors, TRAIL-R1 (DR4) and -R2 (DR5) are also known as death receptors (DR) and induce apoptotic signalling [10,15]. EVT was previously shown to express both TRAIL and its receptors. Additionally, TRAIL-R1 and R2 can be detected in the placenta throughout pregnancy, and the immunohistochemical analysis by Chen et al. showed that staining of both these receptors was gradually increased parallel to placental development [15]. Therefore, it would not be wrong to say that as both apoptosis and the immunoreactivity of death receptors increase throughout gestation, TRAIL receptors may be implicated in altered trophoblastic invasion. In addition to the trophoblastic expression of TRAIL-R2, it has been shown that human decidual stromal cells also express TRAIL-R2, but not TRAIL and TRAIL-R1 [16]. So, as TRAIL-R2 is produced both by decidual and trophoblast cells during pregnancy and known to participate in apoptosis, we suggested that it may be associated with altered trophoblast invasion in placenta accreta.

In the present study, we aimed to determine and to compare maternal serum and placental TRAIL-R2 levels in patients with placenta accreta, non-adherent placenta previa and those with healthy pregnancies. We also aimed to evaluate whether the placental and serum levels of TRAIL-R2 are correlated. Another purpose of the study was to determine the other possible risk factors, such as scarring of the uterine wall by previous cesarean deliveries, which may be associated with placental invasion anomalies.

2. Materials and methods

2.1. Design and study population

A prospective case–control study was performed between August 2013 and September 2014 in the Perinatology Department of Zekai Tahir Burak Women's Health Education and Training Hospital. A total of eighty-two participants were included in the study. Twenty-seven patients were diagnosed as placenta previa prenatally by grey-scale ultrasonography and later histologically diagnosed as placenta accreta according to previously established criteria defined as the abnormal adherence of the placenta involving all degrees to the underlying uterine wall [17]. Twenty-six age- and body mass index- (BMI) matched patients with placenta previa diagnosed by ultrasonography and who were later confirmed to have no adhesion abnormalities during cesarean section were also recruited. Twenty-nine healthy, uncomplicated pregnant women with normal placental location were selected as the control group and were matched with the other groups for age, BMI and gestational age at the time of delivery. The patients in both the accreta and the previa groups were delivered by C-section because they were initially diagnosed as placenta previa by ultrasonography. None of the patients in either the accreta and non-adherent placenta previa groups had a previous history of placenta accreta or placenta previa. The reasons for previous C-sections based on the participant declarations were the malpresentation of the fetus, cephalopelvic disproportion, previous history of C-section and fetal distress during the course of vaginal delivery. All controls were delivered by cesarean section to standardise the placental sampling and to avoid possible factors, which may affect the results. The indications for cesarean section in the control group were either the history of previous cesarean deliveries or malpresentation of the fetus.

Patients were excluded if any of the following disorders were present: multiple pregnancy, preterm premature rupture of membranes, preterm labour, previous pregnancy complicated with placenta previa, any previous complicated pregnancy, cervical or uterine surgery, including myomectomy, metroplasty, uterine septal resection, conisation, or 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 medication usage.

All participants provided written informed consent. The study protocol was performed according to the principles of the Declaration of Helsinki and was approved by the local Ethical Committee of our hospital.

All participants included in the study were evaluated at the initial admission. 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 an overnight fasting by venipuncture and processed within 1 h after withdrawal by centrifugation at 5000 revolutions/minute (2236 × g) for 10 min. All serum samples were stored at - 80° until the day of analysis.

2.2. Placental sampling

All participants were followed until delivery and all placental samples were collected immediately after cesarean section. Placental samples were obtained by cutting near the central zone of the maternal surface villous lobule following the removal of amniotic membranes. Placental fresh specimens showing no signs of inflammation and/or necrosis macroscopically from the area of the distinct lesion were collected. Using a sterile scalpel, a quadrangular segment along the placental thickness, from the basal towards the chorionic surface, was excised. Placental tissue samples were immediately stored without treatment in sterile tubes at - 80° until the completion of participation.