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Case Reports

Microparticles hyperactivity in a case of intrauterine growth restriction

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Summary

A case of a residual intrauterine fetal growth is described in a primiparous woman, aged 33 years, undergoing the 37th week of pregnancy. The patient was admitted to the outpatient department of the present clinic complaining of decreased fetal movement in the past few days. The cardiotocography (CTG) was non reactive, with reduced variability for a period of more than 30 minutes. The evaluation of the activity of microparticles (MPs) showed a value of 48.90 nM, which was 21.26 times higher than the mean of normal women of comparable pregnancy age (2.31 ± 1.95 nM) and 18.11 times higher than that of the average women who had intrauterine growth retardation (2.70 ± 2.63 nM). The reasons for this increase in the activity of the MPs are discussed in this case report.

Key words: Microparticles; Pregnancy complications; Intrauterine growth restriction.

Introduction

The term intrauterine growth restriction (IUGR) refers to a fetus, who presents a lower growth rate than normal. The development of the fetus is considered restricted when the fetal weight is below the 10th percentile for the pregnancy age. The frequency of IUGR ranges from 4% to 7%. The diagnosis of IUGR, which is divided into symmetrical and asymmetrical, is done via ultrasound, by assessing the biparietal diameter (BPD), the head circumference (HC), the abdomen circumference (AC), the femur length (FL), and by estimating the fetal's weight EFW [1-3].

The microparticles (MPs) are vesicles with a diameter less than one mm, which derive from the cytoplasmic membrane of various cells (endothelial, monocytes, platelets) during the activation or their programmed cell death. Women during pregnancy show an increase in the activity of the MPs, compared with healthy non-pregnant women [4, 5]. Complications of pregnancy such as premature rupture of fetal membranes, pre-eclampsia, miscarriage, and IUGR, are believed to be associated with placental dysfunction and could provoke significant maternal and fetal morbidity and mortality, resulting in increased activity of the MPs [6].

The presentation of this case was motivated by the unusual finding of very high potency of MPs and its possible correlation with the pathogenesis of this complication.

Materials and Methods

A primiparous woman, 33-years-old, in the 37th week of pregnancy, after spontaneous conception, attended to the present authors' obstetric outpatient clinic complaining of reduced fetal movements the past few days. She had a free obstetric and medical history, and mentioned allergy to penicillin. A non-stress test (NST) was conducted, and for a period of 30 minutes showed reduced variability of the fetal's heart rate (< 10 beats / min), without any uterine contractions.

The physical examination showed an able-bodied person with a body mass index of 22,66 kg/m^2. The patient's blood pressure was 110/70 mmHg, her pulse was 68/min, and her temperature was 36.7 C°. On clinical examination there were no signs of uterine contractions or of ruptured membranes.

The patient was admitted to the present department for further assessment. A second NST was conducted after an hour, and showed similar findings to the first. On the ultrasound examination, it was revealed that the fetal's weight (2,173 g) was below the tenth percentile, BPD 31 weeks, HC 30 weeks and one day, AC 28 weeks and one day, and FL 33 weeks and two days. The placenta was in high anterior position, grade 2. Based on biometrics features, the fetus was three weeks restricted. The control of the umbilical artery via Doppler showed palm index (PI) 1.22 and resistance index (RI) 0.72 which were within normal range. The middle cerebral artery Doppler was also normal (PI 1.70 and RI 0.81). Her blood test results were also satisfactory (hematocrit 37.8%, hemoglobin 12.30 g/dl, platelets 272 x 103 /ml, white blood cells (WBC) were 18.4 x 103 /ml, with 82.0% neutrophils, whereas (CRP) 79 mg /L (normal range < 5 mg/L)).

An emergency cesarean section was conducted because of the non-reassuring NST and a living female infant was delivered, weighing 1,955 g with Apgar score: 7 at five minutes. The placental weight was 400 gr and its microscopic inspection showed the presence of micro infarcts and decalcification in the uterine surface.

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The measurement of procoagulant activity of MPs (platelet, leukocytes, endothelial) in plasma was carried out after exposure of amniotic phospholipids, with main representative the phosphatidyl - serine, bounded by the annexin V (Zymuphen MP - Activity).

Results

The measurement of procoagulant activity of MPs showed that their levels were 21.26 times higher than the mean of women with comparable age normal pregnancy (2.31 ± 1.95 nM) and 18.11 times higher than the mean of women with IUGR (2.70 ± 2.63 nM). The list of the pregnant women with asymmetrical type of IUGR included eight patients with mean (3.27).

Discussion

IUGR is related to considerable maternal and fetal morbidity and mortality. Etiology is partly understood and it is widely known that during the first half of pregnancy, trophoblastic invasion participates to the remodeling of the spiral arteries into dilated, inelastic vessels, converting them to low-resistance vessels capable of supplying large amounts of blood to the placenta and the developing fetus. Consequently, a functional uteroplacental circulation is the result of this physiological process [7-9].

Impaired remodeling due to deficient trophoblastic invasion is associated with maintenance of high resistance and low flow spiral arteries, related to possible subsequent development of IUGR. Various studies have been reported, connecting restricted invasion of the trophoblastic cells to the decidual segments leaving the myometrial segment of the spiral arteries unchanged [10, 11]. IUGR is a multi-system disorder and may be identified as symmetrical or asymmetrical. Causes of symmetrical IUGR are: genetic including chromosomal, constitutional and single gene defects, inborn errors of metabolism, smoking, heroine, therapeutic irradiation and/or accidental exposure, sickle cell anemia, and infections (toxoplasma, rubella, cytomegalovirus, herpes - T.O.R.C.H.).

Factors like gene defects and chromosomal anomalies seem to be responsible for this complication. Fetuses with chromosomal disorders (trisomy 13, 18, and 21) and other autosomal abnormalities (various deletions and ring chromosome structure alterations) have suboptimal growth. Congenital malformations, and chromosomal disorders are responsible for approximately 20% of IUGR fetuses, and that percentage is substantially higher if growth failure is detected before 26 weeks gestation [12, 13]. Maternal nutritional abnormalities lead to reduced fetal growth if substrate deprivation is severe. IUGR fetuses are not common in heavier woman (> 68.03 kg prepregnancy weight).

Fetal infections consist 5%-10% of all causes of IUGR, like T.O.R.C.H. with cytomegalovirus, rubella, herpes (*H. Simplex*), syphilis, and also parvovirus has been reported to impair fetal growth. Cytomegalovirus seems to affect fetal development before 20 weeks of gestation. The viruses that infect the trophoblast alter trophoblast gene expression, and this alteration reduces trophoblast invasive activity, leads to apoptotic cell death, impairs trophoblast function and induces IUGR.

Maternal smoking and drugs reception such as cocaine, heroin, alcohol, anticonvulsants, and warfarin's derivatives may also influence fetal development. There are also reports that 15%-30% of multiple gestations, especially monochorionic twins with the fetal transfusion syndrome, are associated with IUGR [13-16].

Causes of asymmetrical IUGR are: preeclampsia, anemia, vasculopathies, hemoglobinopathies, chronic hypertension, extensive placental infarctions, abruptio placenta, multiple gestations, and severe renal and cardiovascular pathology.

Maternal vascular disease, with its deficiency in uteroplacental perfusion, is related to 25%–30% of all IUGR infants while chronic hypertension and superimposed preeclampsia usually have the most profound effect on fetal growth [17]. One more risk factor seems to be the thrombophylic disorders and preliminary evidence show that the prothrombin gene mutation may be a cause. The antiphospholipid syndrome has also been associated with IUGR and a wide spectrum of pregnancy complications [18]. There is also a relation between abnormal size and function of placenta and IUGR infants, such that when gestational age was used as a covariant, 24% were found to have smaller placenta [19].

The presented case had the characteristics of the asymmetrical type of IUGR. Specifically, the biometrical results of the fetus showed a restriction of abdominal circumference (AC: 28w+1d), which was significantly increased in relation to other biometrical measurements. Inflammatory markers like leucocytes, neutrophils, and C-reactive protein (CRP) were high, and this may be the evidence of involution of inflammation and placenta deficiency. The authors' previously described patient had pathological increased procoagulant activity of MPs. This finding may be the evidence of macroscopical appearance of calcifications at the uterine side and the low weight of placenta.

Cell-derived MPs are small vesicles released from cells upon activation or apoptosis. MPs seem to play a role in inflammatory processes by altering or activating the function of various cells types like monocytes, endothelial cells, or neutrophil granulocytes. This process is being conducted via the transfer of bioactive molecules, or ligand-receptor interactions. It has been shown *in vitro* by Nauta *et al*. and Gasser *et al*., that MPs may also play a role in complement activation via the classical pathway, (C1q binding to MPs and the deposition of C3, C4 components of the complement activating surfaces). Elevated platelet-derived MP/ (PDMP), monocyte-derived MP/ (MDMP), and endothelial cell-derived MP/ (EDMP) concentrations are documented in almost all thrombotic diseases including both arterial and venous beds. Conclusively, elevated levels of MPs have been found in a number of conditions associated with inflammation, cellular activation and dysfunction, angiogenesis and transport [20, 21].

During normal pregnancy multiple changes occur in the vascularization, and the balance of haemostasis shows an effect on procoagulant state. Coagulation factors are elevated in the preeclamptic state and recurrent pregnancy loss in comparison to normal pregnancy and uteroplacental thrombosis. Thus, haemostatic imbalance and vascular dysfunction may have a role in both these pregnancy complications [4,22]. There are not many studies (Pubmed and Medline) valuating the levels of MPs in IUGR and particularly the diversification between asymmetrical and symmetrical type of IUGR [23].

In the present case, very important point is the over increase of procoagulant activity of MPs. The levels of MPs were 21.26 times higher of the mean of normal women with comparable age pregnancy (2.31±1.95 nM) and 18.11 times higher of the mean of women with IUGR (2.70 ± 2.63 nM).

The interpretation of these findings may be strong evidence of inflammation confirmed by increased leucocytes, neutrophils, and CRP. In the present case, the macroscopical observation of placenta showed low weight and bold calcification on the uterine side of it. This may be connected with the elevation of MPs, which are released from the surface of cells following cell activation or apoptosis, including chemical stimuli, (cytokines, thrombin, and endotoxin), or physical stimuli (shear stress or hypoxia).

Following cell apoptosis, MPs formation depends on an elevation in the cytosolic calcium concentration, with consequent activation of calpain and protein kinases and inhibition of phosphatase. These changes may have a direct effect to cytoskeletal reorganisation, membrane blebbing, and the formation of MPs. Secondary activation of the coagulation mechanism may correlate MPs to the development of platelet and fibrin rich thrombi, through the recruitment of cells and the accumulation of tissue factor (TF), or via both factor VII (FVII)/TF which participates to dependent and independent pathways [4, 24].

Conclusion

It seems that there is a possible correlation between inflammation, placental insufficiency, and IUGR. In the present case, intrauterine inflammation seems to be the main cause of IUGR, followed by secondary activation of coagulation, while these warrant increased expression of MPs. Further studies are needed to clarify this correlation and the probable difference in expression of MPs in the two types of IUGR.

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