Short Communication

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Placental delayed villous maturation is associated with evidence of chronic fetal hypoxia

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Abstract

Background: Normal development of the human placenta, referred to as villous tree maturation, entails formation of the vasculosyncytial membranes. These structures develop by the approximation of syncytiotrophoblasts with the villous capillary endothelium and constitute the most efficient sites of gaseous exchange in the placenta. Defective maturation of the villous tree can lead to deficient vasculosyncytial membranes, implicated in the high incidence of hypoxic complications. Hypoxia, in turn, can stimulate production of erythropoietin, whereby increased fetal plasma or amniotic fluid concentrations of this hormone reflect fetal hypoxemia. The current study was undertaken to determine whether delayed villous maturation is associated with changes in amniotic fluid erythropoietin concentrations.

Methods: Placental histologic examination was performed using hematoxylin and eosin. Subsequent to histologic assessment of delayed villous maturation, the diagnosis was

confirmed with CD-15 immunohistochemistry. The controls (n=61) were pregnancies without villous maturation abnormalities, and cases (n=5) were pregnancies with delayed villous maturation. Amniotic fluid erythropoietin concentrations were measured using a specific immunoassay.

Results: Concentrations of erythropoietin in the amniotic fluid (1) of controls were less than the limit of detection and (2) of cases with delayed villous maturation were significantly higher than those of controls (P-value = 0.048).

Conclusion: Delayed villous maturation is associated with higher concentrations of amniotic fluid erythropoietin.

Keywords: amniotic fluid; CD-15; disorders of villous maturation; erythropoietin; human placental maturation disorders; vasculosyncytial membranes.

Introduction

Vasculosyncytial membranes are unique structures of the human placenta [1], which include the apposition of the trophoblasts (syncytio- and cyto-) with the fetal chorionic villous endothelium (Figure 1). These structures are

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Figure 1: Term placentas: Normal histology (A–C) and Delayed villous maturation (D–F).

Normal term placenta (A) Normal chorionic plate with subchorionic villi that are mature and appropriate for gestational age. (B) Terminal villi with vasculosyncytial membranes (arrows); (C) Chorionic villous capillary endothelium negative for CD-15 staining. Delayed villous maturation in term placenta. (D) Chorionic villi exhibiting monotonous immature villous population recapitulating the histology of early pregnancy with substantially more villous stroma, more centralized vessels, and fewer and less well-formed vasculosyncytial membranes than that of normal pregnancy for gestational age; (E and F) CD-15-positive immature endothelium considered as a diagnostic marker of persisting villous immaturity and chronic placental dysfunction. (E) 100× and (F) 200× magnification; brown stain CD-15 positive villous endothelium.

essential for the normal oxygen and nutrient exchange between the maternal and fetal circulations. The formation of the vasculosyncytial membranes is part of normal development of the human placenta and is specifically referred to as villous tree maturation. Defective villous tree maturation can lead to deficient vasculosyncytial membranes that, in turn, have been implicated in nutritional disorders such as fetal growth restriction, respiratory failure of the placenta or fetal hypoxia. We previously reported that 20.7% of placentas of structurally normal cases of fetal death have delayed villous maturation, a condition in which there is insufficient development of the terminal villi, reduced vascularization of the chorionic villi and deficiency of vasculosyncytial membranes [2].

Chronic fetal hypoxemia can stimulate production and secretion of erythropoietin [3]. As erythropoietin does not cross the placenta and is not stored, increased fetal plasma or amniotic fluid concentrations of this hormone are considered to reflect chronic fetal hypoxemia. The current study was designed to determine whether delayed villous maturation is associated with changes in amniotic fluid erythropoietin concentrations.

Study design

This was a retrospective observational study of singleton pregnant women without pre-eclampsia, gestational hypertension, abruption or gestational diabetes mellitus who (a) underwent an elective cesarean section at 37–42 weeks of gestation; (b) had amniotic fluid retrieved at the time of cesarean delivery; (c) had a live-birth newborn; (d) had a placental histologic examination at Hutzel Women's Hospital, Detroit, MI, USA; and (e) provided written informed consent and agreed for such information to be used for research purposes. Controls (n=61) were pregnancies without villous maturation abnormalities, and cases (n=5) were pregnancies with delayed villous maturation. The collection of data was approved by the Human Investigation Committee of Wayne State University.

Placental histologic examination was performed using hematoxylin and eosin and CD-15 immunohistochemistry by a perinatal pathologist (SJ) blinded to clinical information, except gestational age at delivery. Histologic assessment of delayed villous maturation was made by the presence of a monotonous immature villous population (at least 10 such villi), constituting up to at least

Amniotic fluid erythropoietin concentrations were measured using a commercially available specific immunoassay [American Laboratory Products Company (ALPCO), Salem, NH, USA]. The sensitivity of the assay was 1.8 mIU/mL, and coefficients of variation for intra- and inter-assays were 6.1% and 9.2%, respectively. For statistical analysis, a result that was below the limit of detection was replaced by 99% of the minimum observed value.

(1) Concentrations of erythropoietin in the amniotic fluid were measurable only in 41% (25/61) of controls (25th percentile and 50th percentile of amniotic fluid erythropoietin were less than the limit of detection; 75th percentile of amniotic fluid erythropoietin = 4.2 mIU/mL). (2) Patients who had delayed villous maturation (n = 5) had a significantly higher concentration of amniotic fluid erythropoietin than those in the control group (n = 61) (Wilcoxon rank sum test P-value = 0.048) (Figure 2).

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