ORIGINAL ARTICLE

Cytokines in the Placenta of Pakistani Newborns with and without Intrauterine Growth Retardation

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ABSTRACT

Background: Intrauterine growth retardation (IUGR) is major risk factor for increased neonatal mortality and morbidity, with a considerable risk for permanent brain damage. The prevalence of IUGR in Pakistan[1] newborns has been reported as high as 15-24%. The mechanism behind this condition remains unclear. It has been shown that cytokines play an important role in reproductive events. In the present study, we analyse gene expression and gone polymorphisms for different cytokines comparing infants with and without IUGR in a Pakistani population. The study showed significantly decreased levels of mRNA in the decidua of IUGR placentas. This gives support to our interleukin (IL-10) proposal that reduced levels of IL-10 may be involved in the pathogenesis of IUGR.

Key words: IUGR (intrauterine growth retardation) cytokines.

INTRODUCTION

Intrauterine growth retardation (IUGR) is a major risk factor for increased neonatal mortality, morbidity and still birth[1]. This includes a considerable risk for permanent brain damage followed by a higher rate of failure in school[2]. The prevalence of the IUGR in newborns of Lahore, Pakistan was reported as 15-16% in rural and semi rural population in 1984-87[3]. In Karachi the prevalence was 24%[4], while in Swedish population IUGR was found in about 1-4% of pregnancies despite several studies on the subject, the mechanisms behind this condition remain unclear.

When malformations and genetic causes for impaired fetal growth are excluded, IUGR is characterized by placental insufficiency. Impairment in the invasion of foetal trophoblasts during implantation into the maternal decidua has been considered as a cause of insufficient remodeling of the spiral arteries into vessels of low resistance resulting in reduced utero-placental blood flow and IUGR in the foetus[6]. The distribution of the foetal and the maternal blood circulation in the placenta is important for efficient exchange of oxygen and nutrients and thus for the normal growth of the foetus[7]

A few studies on human pregnancy indicate that cytokines are also involved in the pathogenesis of IUGR and other pregnancy dysfunctions.

In a previous investigation[8] it was shown that the levels of IL-10 mRNA were decreased and of IL-8 mRNA increase in the deciduas of IUGR placentas from Swedish mothers. In the present study, we analyzed the gene expression for different cytokines from the maternal (decidual) and the foetal (trophoblast) side of the placenta from IUGR and non-IUGR pregnancies, in Pakistani population.

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MATERIAL AND METHODS

The study group consisted of 218 pregnant women registered at the antenatal clinic of Lady Willingdon Hospital, Lahore, Pakistan. All mothers had ultrasound examination before the 20th week of gestation. Only mothers certain of the date for the onset of pregnancy confirmed by the ultrasound examination were included in the study. Mothers with twin pregnancies, congenital anomalies diagnosed by ultrasound examination and infections diagnosed during or after deliveries, which could influence the placental configuration or expression of cytokines were excluded from the study. The IUGR was diagnosed at antenatal check ups. The fudal height in cm was measured at each visit and plotted on a graph from 24 weeks onwards. Growth was suspected to be abnormally restricted or retarded if it was les than 2Sd. In such cases the ultrasound examination was used to help to establish the diagnosis of IUGR. The definition of IUGR was the lack of increase in estimated foetal weight (<11% compared with standard curves, examination >15 days) and/or pathologic Doppler velocimetry in the umbilical artery[10]. In moderate or severe cases of IUGR, Doppler test of umbilical artery blood flow velocity was used for the decision about time and mode of delivery.

RESULTS

Out of a total of 218 mothers, 100 delivered at the hospital and 84 chose to delivery at home. Ten samples were not taken and 24 mothers dropped out during the study. In the present investigation we used placenta, from 45 IUGR and 55 non IUGR patients. .

Small tissue samples (10-100 mg) were taken from the placenta immediately after delivery, both from the decidua and the trophoblast part, rinsed in physiological saline (0.9% NaCl) and fixed in RNA latex (Ambion – Intermedica, Stockholm, Sweden). The placentas were handled on ice and time between the delivery of the placenta and fixation in RNA latex never exceeded 10 minutes. Samples were stored at -8^0C at the Lady Willingdon Hospital, brought on ice to King Edward Medical University where they were stored at -20^0C until analyzed.

There was no significant differences in the mRNA expression of IL-8, -IL-6 and TNF-x between any of the groups. There was a significant decrease of mRNA expression for IL-10 ($p<0.0001$) and IL-12 ($P=0.00071$) in the deciduas, and of IL-10) $P=0.028$) in the trophoblasts of the IUGR placentas compared with the non-IUGR.

DISCUSSION

Considering the fact that IUGR is a major risk factor for newborns in poor countries[3] it is important to search for the mechanisms behind this condition in the hope of finding methods for its prevention and /or treatment.

IL-10 is a pro-inflammatory cytokine. It is needed for differentiation of T cells to Th I cells, but its role in pregnancy is not known, studies in patients suffering from spontaneous abortions have shown down-regulation of IL-11 in peripheral leukocytes and monocytes. The same was true for pre-elcamaptic patients.

IUGR is complex problem with a number of risk factors. In this study we have excluded mothers showing external risk factors for IUGR like malnutrition, infections, drug abuse and twin pregnancies and mainly concentrated on placenta-related IUGR. However, one of the risk factors present in this study is consanguinity, which was in our material somewhat more prevalent in the IUGR group than in the non-IUGR group)64% and 58% respectively) but was not significantly different[12] it would be important to find more evidence for whether or not a deficiency of IL-10 in the decidua could be a pathogenic mechanism in IUGR , because then it might be possible to find a strategy for treatment. Recently it was shown in an animal model that without regulatory T cells producing IL-10, pregnancies ended in abortions[13,14]. That model might be used to further analyze the possibility that the amount of the IL-10 produced by maternal regulatory T cells in the placenta may be crucial for the normal growth and development of the fetus.

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