Karolinska Institutet

**Department of Women's and Children's Health**

# Maternal and Neonatal Anthropometry and Growth Factor Expression and Apoptosis in Human Placenta: a comparison between two Populations.

AKADEMISK AVHANDLING
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## ABSTRACT

The insulin-like growth factors (IGFs), IGF-binding proteins (IGFBPs), and IGFBP proteases, are key endocrine regulators of somatic growth and cellular proliferation. IGFs are involved in growth both pre- and postnatally. Dysregulation of the IGF axis can lead to growth disorders such as intrauterine growth restriction (IUGR), prenatally, and small for gestational age (SGA), postnatally. This hormone axis is dependent on essential micronutrients and trace elements for proper growth and functioning of cells and organs. A deficiency in micronutrients may therefore lead to deficiencies in the axis. The IGFs have been further associated with anti-apoptotic activity with deficiencies in the axis possibly resulting in the activation of apoptosis and the subsequent inhibition of normal placental and foetal growth leading to babies being born small for their gestational age. Determining the aetiologies behind SGA may help our understanding of this vast clinical problem and may also help in suggesting possible interventions to improve pregnancy, and life, outcomes.

The aim of this study was to look in to the associations between the insulin-like growth factors and the regulation of apoptosis, looking at newborn and maternal anthropometric outcomes in the Swedish and Pakistani populations.

Human placental samples were obtained from 89 women at rural field sites in Pakistan (papers I, II, & IV). Furthermore, 33 samples were obtained from the Swedish population (papers III and IV). Maternal and neonatal anthropometric variables were noted at the time of delivery. Umbilical cord blood samples were also taken to assess levels of certain key micronutrients, namely zinc and iron. IGF mRNA expression levels were assessed using RT-PCR techniques. Oestrogen receptor (ER) and progesterone receptor (PR) expression levels were quantified using solution hybridization. Additionally, protein analysis was conducted using Western immunoblot analysis, ELISA, and radioimmunoassay studies. For the purposes of experimentation and analysis, samples were divided into small, appropriate, and large for gestational age groups (SGA, AGA, & LGA, respectively). TUNEL and immunohistochemical staining were also employed for the assessment of apoptotic proteins and factors.

In the Pakistani population, we have shown significantly lower expression levels of placental IGF-I and IGF-II in the SGA group. Furthermore, we have shown lower IGF-I protein levels and significant associations of maternal and newborn anthropometry to IGF expression and protein levels, as well as placental IGFBP-1 levels. These findings suggest the importance of the IGF-axis in birth weight outcomes. Significant correlations of maternal anthropometry and birth anthropometry may indicate the potential use of maternal anthropometry as a screening tool for low birth weight. We have also shown significant differences in cord blood haemoglobin, iron, and zinc levels in the two groups (though all values were within normal ranges), indicating the importance of an adequate nutritional status in pregnancy. In the Swedish population, we have shown similar significant differences in IGF-I expression, with lower levels in the SGA group. We have, in addition, shown significant correlations of PR and IGF-I expression, and ER and maternal anthropometry. These results further suggest the complex multi-factorial regulation of the IGF-axis and indicate the possible role of the ERs and PR in the pathogenesis of foetal growth restriction. Furthermore, placentas of Pakistani mothers have higher levels of placental apoptosis than their Swedish counterparts. Pakistani mothers were also significantly smaller than Swedish mothers in our population groups. These differences in apoptotic activity and anthropometry may thus be associated with the differences in birth weights between these populations.

In summary, this thesis adds to our overall understanding of the correlations between maternal anthropometric and newborn biometric measurements, along with placental levels of components of the IGF-axis and apoptosis. Our data supports previous data on the role of nutrient supplementation in pregnancy and offers an explanation to the possible mechanisms behind the complex problem of foetal growth restriction. Furthermore, our results appreciate the fine balance of growth promoting and growth inhibiting factors in foeto-placental growth and development.