CORD AND MATERNAL BLOOD LEVEL OF IGF-II IN NORMAL PREGNANCY, PREGNANCY INDUCED HYPER TENSION AND GESTATIONAL DIABETES MELLITUS

ABSTRACT
Cord and maternal blood levels of insulin-like growth factor (IGF)-II were studied in women with either pregnancy induced hypertension (PIH) \( (n=15) \), gestational diabetes mellitus (GDM, \( n=14 \)) and women with normal uncomplicated pregnancies \( (n=15) \). IGF-II levels were measured by enzyme linked immunosorbent assay. Maternal and cord blood levels of IGF-II were compared between three groups (Kruscal Wallis analysis of variance) and correlated (Spearman rank correlation) with neonatal anthropometric measurements (Birth weight, length and head circumference). Birth size did not significantly differ between the three groups studied. There was no significant difference in cord or maternal blood IGF-II levels between the three groups. In normal pregnancies cord blood IGF-II positively correlated with birth weight \( (r = 0.5676, P = 0.0273) \). In conclusion, maternal or cord blood IGF-II levels did not significantly differ between the groups. Correlation observed between cord blood IGF-II with birth weight in normal pregnancy. A larger number of subjects need to be studied to further clarify the association between cord blood IGF-II and infant anthropometric variables.

KEY WORDS: Insulin-like growth factor (IGF)-II, neonatal anthropometry, fetal growth
INTRODUCTION
Insulin like growth factor -II is a mitogenic polypeptide with a structure similar to proinsulin. It stimulates cell proliferation and differentiation effects on fetal growth. It is the major secretary growth factor in embryonic tissues and placenta. IGF-II is known to play a key role in fetal growth and development (Daughday and Rotwein, 1989).

Circulating level of IGF-II increases during second and third trimesters of pregnancy and it has been shown to be associated with size at birth (Jones and Clemmons, 1995; Lauszus et al, 2001).

In an elegant study in a mouse knockout model, the litter lacking IGF-II gene was shown to be only 60% in size compared to their wild-type littermates at birth but a normal postnatal growth rate was observed (DeChiara et al, 1990).

Pregnancy Induced Hypertension (PIH) and Gestational Diabetes Mellitus (GDM) are known to cause fetal growth retardation and macrosomia respectively. (Lala and Chakraborty,2003). These deviant fetal growths are associated with higher rates of mortality and morbidity (Cambel and Lees, 2000). In view of lack of any data on the circulating IG-II in pregnancies complicated by PIH or GDM for Sri Lankan women the present investigation was carried out.

MATERIALS AND METHODS

Subjects
This was a cross sectional study carried out on normal healthy pregnant mothers (n=15) and pregnancy with diabetes mellitus (n=15). Study was approved by the Institutional Review Board and written informed consent was obtained from the mothers and fathers. The subjects enrolled were women in para 1 or 2, aged 21-35 years who had naturally conceived and who delivered a singleton baby with no apparent congenital malformation or hereditary / genetic disorder. GDM were diagnosed by attending medical staff using following criteria GDM was defined as either a raised fasting blood glucose level of >7.8 m mol/L or a blood glucose level of >11.1 mmol/L 1 - 2 hours following a 75 g oral glucose load.

On admission to the study, socio-demographical and clinical data were recorded.

Samples
Maternal blood was collected either at the onset or after the delivery. Cord blood was collected at the delivery.

Measurements
Newborn anthropometry including birth weight (Seca baby weighing scale), crown-heel length (infantometer), and head circumference (standard measuring tape) were measured within 24 hours after delivery. Ponderal index was calculated as weight (Kg)/height (m^2)

IGF-II Assay
Maternal and cord blood IGF-II levels were measured by ELISA using commercially available kits (IGF-II active non-extraction ELISA - Catalog No: DSL-10-2600, Diagnostic System Laboratories, Inc. Webster, USA). All the kit reagents stored at 4°C were brought to room temperature before use. Standards, samples and controls were assayed in duplicates. All the assays were performed according to the manufacturer’s recommendations.

Statistical Methods
All statistical analysis was performed by using a statistical package GraphPad prism 2.01 (GraphPad Prism, San Diego, CA). Non parametric analysis of variance ( Kruskal Wallis test) was used to compare maternal and cord blood levels of IGF-I, IGF-II and IGFBP-1 between the three groups. Spearman Rank correlations test was used to examine the relationship between IGF-II IGF-I, IGF-II and IGFBP-1 levels with infant anthropometric indices within each group.. The level of significance was considered as p-value< 0.05.

RESULTS & DISCUSSION

The anthropometric variables at birth of infants of women with uncomplicated normal pregnancies, PIH and GDM are shown in Table 1. Though PIH was expected to result in lower birth weights and GDM higher birth weights, there was no significant difference in birth weights between PIH, GDM and normal pregnancy groups.

<table>
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<th>Table 1: Anthropometric variables of infants at birth</th>
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<td>Weight (Kg)</td>
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CC = Chest circumference  HC = Head circumference
Cord blood and maternal blood IGF-II levels (percentile distribution) in three studied groups are shown in Fig 1. Cord or maternal blood IGF-II did not differ between the three studied groups. A previous study reported that significantly lower cord IGF-II levels were found in intrauterine growth retardation compared to normal. They did not find any significant difference in cord blood IGF-II between LGA and normal infants (Guidice et al, 1995). In contrast, Hall et al (1986) reported higher cord serum IGF-II in newborns of diabetic mothers. In our study, no significant difference in cord blood IGF-II levels in PIH and in GDM groups, compared to normal pregnancies may result from the fact that there were only five low birth weight infants in PIH and three high birth weight infants in GDM groups. The fact that the total sample size was small may also have contributed.

![Cord blood IGF-II levels](image1)

![Maternal IGF-II levels](image2)

**Fig 1:** Percentile distribution of Cord (A) and maternal blood (B) IGF-II in normal pregnancies (n=15), pregnancy induced hypertension (PIH, n=15) and gestational diabetes mellitus (GDM, n=15). Line inside the box represents the median (50th percentile) and the box represents the interquartile range (25th to 75th percentile). Whiskers indicate the lower and upper quartiles.

Cord IGF-II levels in normal uncomplicated pregnancies, but not in PIH and GDM groups significantly correlated with birth weight (r = 0.5676; P = 0.0273). There were no significant correlations between cord blood IGF-II and other anthropometric variables in any of the three groups.

Conflicting results have been reported on the relation between IGF-II and fetal growth in previous studies. Ong et al., (2000) reported that cord IGF-II positively correlated with birth weight. Others have shown a weakly correlation or no correlation with birth weight (Susa et al., 1984; Hall et al., 1986; Samman et al., 1990; Lassarrec et al., 1991; Fant et al., 1993; Verhaeghe et al., 1993; Osorio et al., 1996; Klauwer et al., 1997).

IGF-II is the primary growth factor during early embryonic development where differentiation and proliferation of tissues and organogenesis take place (Daughday and Rotwein, 1989). It is also an angiogenic growth factor (Herr et al., 2003) increases placental function primarily by increasing placental (uterine and umbilical) blood flows, associated with increased placental vascularity and the migration of trophoblast cells. Therefore, transfer of glucose is increased and stimulates fetal insulin gene family...
including IGF-I and IGF-II subsequently increasing fetal size.

The associations between maternal IGF-II levels and fetal growth or infant birth size are inconsistence. (Wiznitzer et al, 1989, Olaussen et al, 2008, McIntyre et al, 2000, Zhong et al, 2012). However, we found Maternal IGF-II did not correlate with neonatal anthropometry in normal uncomplicated pregnancies, PIH or GDM groups.

CONCLUSION & SUGGESTION

We have observed correlation between cord blood IGF-II and birth weight in uncomplicated normal pregnancy. To refute or confirm these observations the present investigation should be expanded to include a larger number of subjects.

REFERENCE

