Cord Blood Levels of Insulin and Glucose in Full Term Pregnancies

Anagha Sahasrabuddhe*, Shailesh Pitale**, Dhananjay Raje***, MM Sagdeo*****

Abstract

Objectives: This pilot study was undertaken to know the normal values of cord blood insulin and glucose levels in full term normal pregnancies and pregnancies complicated with maternal conditions like pregnancy induced hypertension (PIH), thyroid dysfunction and Gestational Diabetes Mellitus (GDM).

Method: Full term pregnancies from Ketkar maternity hospital, Nagpur, since January 2011 were included in the study. A total of 121 cases have been studied. Demographic and clinical data of the included cases was obtained from the hospital records. Cord blood sample was analyzed for serum insulin and plasma glucose levels. These two metabolic parameters were used to derive (Homeostatic Model Assessment) HOMA index for insulin resistance and Glucose-to-Insulin Ratio (GIR). The data on physical and metabolic parameters was analyzed using parametric statistical significance tests for means and correlation using R-package

Result: The difference in glucose concentration was found insignificant (p > 0.05) across complicated and uncomplicated pregnancies. However, for the comparison ‘no complications’ vs PIH, the insulin levels differed significantly at 10% (p = 0.09). Accordingly, for the same comparison, GIR also indicated significant difference at 10% (p = 0.07) between the two maternal groups. The mean cord blood glucose level was higher in PIH cases compared to un-complicated maternal cases; while the mean insulin level was lower in PIH cases as compared to non-complicated cases, as a result mean GIR was higher in PIH category. HOMA did not show significant difference in any comparison. The relationship of metabolic parameters and the derived variables with birth weight in the two maternal groups showed insignificant relationships between birth weight and dependent variables (p > 0.05).

Conclusion: The levels of insulin and glucose in normal full term pregnancies was found to be 6.75 ± 2.96 mIU/ml and 91.69± 27.05 mg/dl respectively with GIR of 13.57±7.47 and HOMA 1.57± 0.83. Low serum insulin levels with normal or high GIR was noted in pregnancies complicated by PIH. Insulin resistance as measured by HOMA IR is increased in patients with hypothyroidism. Hyperinsulinemia is seen in babies with birth weight less than 2.5 kg or more than 3.5 kg.

Introduction

Size at birth and early growth rates are important predictors of development of obesity and other cardiovascular risk factors including insulin resistance later in life. Neonatal size and body composition are influenced by parental size, maternal food intake, physical activity and circulating concentrations of nutrients and metabolites (folate, glucose, triglycerides, cholesterol etc.). For a given BMI, Indians have a higher percentage of body fat and more visceral fat than members of other populations. This thin-fat phenotype is present at birth.1

Data regarding cord blood levels of insulin and glucose which represent exposure of fetus to various maternal conditions in utero is inadequate. Intrauterine growth restriction has an adaptive hormonal profile characterized by decreased levels of insulin and alteration in other factors like IGF (Insulin like growth factor)-1, IGF-2, IGFBP (Insulin like growth factor binding protein) -2, IGFBP-3 and altered IGFBP-1 and 2.2 Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) has shown that fetal growth is influenced by both fetal genes and maternal-uterine-placental factors. Important maternal factors include parity, smoking, weight gain, maternal complications and also maternal genetic factors in the mother or fetal placenta. The fetal gene effects are more evident in the absence of maternal uterine growth restraint. At birth, significant gene-environment interactions are seen. Rapid catch up early post-natal weight gain follows maternal uterine growth restraint and strongly predicts later childhood obesity and insulin resistance. Genetic factors that influence early growth may have conferred some early survival advantage in human history during times of under nutrition. With abundant nutrition and rising obesity rates these genetic factors and their interactions with maternal and childhood environmental factors that influence childhood growth may now contribute to early development of adult disease risk. Their recognition may help development of targeted early interventions to prevent progression towards adult disease.3 The effect of exposure of fetus to maternal stressful conditions like thyroid dysfunction, gestational DM, PIH on levels of insulin and glucose needs to be explored in detail. This study is ongoing and was undertaken with the following aims:

a. To know cord blood levels of insulin, glucose and insulin resistance in full term normal pregnancies,

b. To study the effect of maternal conditions like pregnancy induced hypertension (PIH), thyroid dysfunction and GDM on levels on these parameters
c. To correlate insulin resistance with birth weight.

**Methods**

In this pilot study, full term pregnancies from Ketkar Maternity hospital, Nagpur since January 2011 were studied. The inclusion criterion was – full term delivery; while the exclusion criterion was – premature delivery. Only those patients who signed the informed consent were recruited in the study. A total of 121 cases have been included in the study. A detailed history of each included case was recorded in a structured format. Height was measured on wall mounted stadiometer and weight was measured by calibrated Tainita scale. Birth weight and height of the newborn was obtained from the medical records. Data on ANC complications was also obtained from the history and review of medical records. Cord blood sample was analyzed for the two metabolic parameters - serum insulin and plasma glucose. Serum insulin was measured by radioimmunoassay using Diasorin kit. Plasma glucose level was estimated by GOD-POD method. The study was approved by the independent ethics committee, Nagpur.

**Statistical Methods**

The two metabolic parameters were used to derive HOMA index for insulin resistance and Glucose-to-Insulin Ratio (GIR). The significance of difference of these metabolic parameters between mothers with complication and without complications was analyzed using parametric statistical significance test (t-test).

Also, correlation and its significance between the birth weight and each metabolic parameter as well as the above two derived parameters were studied using Pearson’s correlation coefficient. All the analysis was performed using R programming language.

**Results**

The cases i.e., pregnant mothers, included in the study had either no complications or complications like Hypothyroidism, PIH and GDM. These two maternal categories were considered in the downstream analysis. The distribution of cases along with their mean age is shown in Table 1. The table also shows infant’s birth weight (BW) summarized according to maternal characteristics. The difference in the mean birth weight between the two maternal groups was found insignificant (p > 0.05).

In view of the study aims, GIR and HOMA insulin resistance derived from the two metabolic parameters, glucose and insulin, were referred as primary indicators of fetal insulin sensitivity. As regards the frequency distribution of these metabolic parameters, both indicated positive skewness, as a result the derived variables (GIR and HOMA) also indicated positive skewness. Since the statistical parametric tests are based on the assumption of normality of data, each data set (glucose, insulin, GIR and HOMA) on original scale was log-transformed. The mean and standard deviation for each data set was obtained according to maternal characteristics and shown in Table 2. The geometric mean on original scale (equivalent to arithmetic mean of log-transformed data) for each variable was obtained as a measure of central tendency. The pseudo-standard deviation was obtained for each variable on the original scale. The significance of difference for metabolic parameters and the derived variables was obtained between two maternal groups using t-test for independent samples. Also, the significance was tested between mothers with no complications and those with PIH (n=15), as well as between no complications and those with Hypothyroidism (n=10). The equality of variance across groups was ascertained by Levene’s test. The results are shown in Table 2. The difference in glucose concentration was found insignificant (p > 0.05) across both the comparisons. This result corroborated with the finding in some similar study. The difference in the mean insulin level between the two maternal groups was insignificant. However, for the comparison no complications – PIH, insulin levels differed significantly at 10% (p = 0.09). Accordingly, for the same comparison, GIR also indicated significant difference at 10% (p = 0.07) between the two maternal groups. The mean cord blood glucose level was higher in PIH cases compared to non-complicated maternal cases; while the mean insulin level was smaller in PIH cases as compared to non-complicated cases, as a result mean GIR was higher in PIH category. The GIR in other comparisons was found insignificant. HOMA also did not show significant difference in any comparison.

Analysis of the relationship of metabolic parameters and the derived variables with birth weight in the two maternal groups was also done. A correlation of each dependent variable with birth weight was obtained using Pearson’s correlation coefficient. Figure 1 provides scatter plots of birth weight and four dependent

---

**Table 1 : Descriptive statistics for age of mother and infant birth weight according to maternal characteristics**

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Type of complication</th>
<th>No of cases</th>
<th>Mean age of mother (yr)</th>
<th>Mean birth weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No complications</td>
<td>-</td>
<td>89</td>
<td>28.12±3.2</td>
<td>2.82±0.48</td>
</tr>
<tr>
<td>Complications</td>
<td>Hypothyroidism</td>
<td>10</td>
<td>27.4±3.2</td>
<td>2.79±0.64</td>
</tr>
<tr>
<td></td>
<td>PIH</td>
<td>15</td>
<td>28.66±4</td>
<td>2.74±0.37</td>
</tr>
<tr>
<td></td>
<td>GDM</td>
<td>3</td>
<td>31±2</td>
<td>3.26±1.1</td>
</tr>
</tbody>
</table>

**Table 2: Metabolic parameters from cord blood classified according to maternal characteristics**

<table>
<thead>
<tr>
<th>Cord blood metabolic parameter</th>
<th>Maternal characteristic</th>
<th>No complications</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>All complications: 92.70 ± 42.47</td>
<td>PIH: 96.33 ± 30.94; Hypothyroidism: 93.41 ± 60.41; GDM: 68.61 ± 60.9; IUGR: 98.76 ± 44.14</td>
<td></td>
</tr>
<tr>
<td>Insulin (mU/ml)</td>
<td>6.75 ± 2.96</td>
<td>PIH: 5.64 ± 2.038; Hypothyroidism: 6.87 ± 4.18; GDM: 6.16 ± 1.92; IUGR: 6.223±2.50</td>
<td></td>
</tr>
<tr>
<td>HOMA</td>
<td>1.572 ± 0.837</td>
<td>PIH: 1.38 ± 0.475; Hypothyroidism: 1.631 ± 1.22; GDM: 1.073±0.404; IUGR:1.56 ± 0.448</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.1
than nineteen, was observed in 4 out of 121 (3.3%) samples. In birth weight. Hyperinsulinemia, defined as insulin levels greater with birth weight. HOMA did not show any relationship with

Contrary to this, the insulin levels were on higher side in low weight babies and lower in heavy weight babies, thereby leading to a significant positive correlation of 0.31 (p = 0.04). Overall incidence of low birth weight was more in complicated pregnancies 31.25% as against 20% in uncomplicated pregnancies. Our results showed HOMA insulin resistance was greater than 2.5 in 18% of the cases. Eighteen of them were normal pregnancies. Thirty percent of the fetuses born to hypothyroid mothers had HOMA insulin resistance greater than 2.5 and cord sample of one (out of 16) PIH patient had HOMA greater than 2.5.

Discussion

Human beings are plastic and able to adapt to their environment. During development, the organs and systems of the body go through critical periods when they are plastic and sensitive to the intrauterine environment. It enables production of phenotypes that are better matched to their environment than would be possible if the same type of phenotype was produced in all environments. Developmental plasticity is defined as the phenomenon by which one genotype can give rise to a range of different physiological or morphological states to different environmental conditions during development. The fetus responds to harsh intrauterine environment by adaptations like reduced body size and altered metabolism, which help it to survive shortage of food after birth.

An undernourished baby may establish a thrifty way of handling food. Insulin resistance, which is associated with low birth weight, may be viewed as persistence of fetal response by which blood glucose concentrations were maintained for the benefit of the brain but at the expense of glucose transport into the muscles and muscle growth. The thinness of Indian babies is due to poor muscle and small abdominal viscera. The small Indian babies are programmed to deposit more fat from their intrauterine life. Exaggeration of this tendency in later life is associated with insulin resistance syndrome. Low birth weight has been linked to visceral adipose tissue (VAT) accumulation, insulin resistance and cardiovascular risk factors in middle aged and elderly individuals, many of whom may be classified as metabolically obese normal weight with metabolic syndrome. It has been suggested that increased activity of the hypothalamic-pituitary-adrenal axis may link low birth weight with subsequent development of cardiovascular risk factors and disease. It is imperative to recognize that insulin resistance becomes apparent during infancy, probably because of IUGR in pregnancy and catch up growth in early infancy result in metabolic programming leading to higher risk of various components of metabolic syndrome in adult life. Increasing evidence links maternal malnutrition, low birth weight and nutritional programming in early life with the development of constellation of metabolic syndrome in adult life, with common denominator of insulin resistance.

For better understanding of the pathophysiology of the process, it is necessary to generate a normative data of the insulin and glucose levels and establish cut off value of insulin resistance at birth. Fetal insulin concentrations reflect the intrauterine glucose load given to the fetus by the mother. In fetus, blood glucose levels are determined by placenta- the fetal levels reflecting maternal levels with no endogenous glucose production.

This is a pilot study and so far we have included 121 full term pregnancies. Of these, 89 were normal uncomplicated pregnancies, 10 with antenatal maternal hypothyroidism, 15 had pregnancy induced hypertension, 3 with Gestational diabetes. Low birth weight (< 2.5 kg) was seen in 25 newborns and birth weight more than 3.5 kg was noted in 6 babies, of which 2 had GDM.

The levels of insulin and glucose in normal full term pregnancies was found to be 6.75 ± 2.96 mIU/ml and 91.69± 27.05 mg/dl respectively with GIR of 13.57±7.47 and HOMA 1.57± 0.83. Glucose level was lower in low weight babies and higher in heavy weight babies, while insulin levels were on higher side in low weight babies and lower in heavy weight babies.
and consequently GIR showed positive correlation with birth weight in complicated pregnancies. It can be hypothesized that harsh intrauterine conditions in complicated pregnancies could alter the fetal programming and may affect development and functioning of beta cells. Higher incidence of low birth weight in complicated pregnancies reflects effect of such complications on fetal development. Significantly lower insulin levels (5.25±2.81) and higher insulin sensitivity (11.02±1.85) was seen in some other studies done on IUGR newborns.13,14 Both the studies reported higher TSH levels. Insulin sensitivity was noted to have negative association with T4 and positive association with TSH and concluded that thyroid hormones may play a role in fetal development.14 The change of early hypothyrosis that decrease in growth hormone might be the pathogenesis of IUGR. The decreased GH and insulin might compromise the basic metabolism of the fetus.14 The high Glucose- Insulin Ratio (GIR) showed that hyperglycaemia in IUGR newborns may be associated with reduced glucose tolerance in Indian children, glucose tolerance tests were carried out on 379 four year old children in Pune, India. Among 201 children who were followed for the routine postnatal wards at birth, those with lower birth weights had higher plasma glucose and insulin concentrations, thirty minutes after an oral glucose load, independently of their current size (p = 0.01 and 0.04, respectively). Mean glucose and insulin concentrations were 8.1 mmol/l and 321 pmol/l in children whose birth weight had been 2.4 kg or less, compared with 7.5 mmol/l and 289 pmol/l in those who weighed more than 3.0 kg. Among 178 children who were observed in the Special Care Baby Unit, those with lower birth weights also had higher plasma insulin concentrations at thirty minutes but there were no trends with plasma glucose. The findings suggest that Indian children with reduced intra-uterine growth have reduced glucose homeostasis after a glucose challenge. This is consistent with the hypothesis that Type 2 diabetes mellitus in India may be programmed in fetal life.15

Since there is no data available on cord blood normal GIR as well as HOMA resistance, the findings of various groups have been compared with the levels of normal full term pregnancies in our study.

Hyperinsulinemia was observed in 4 out of 121 pregnancies. In three of these four cases, birth weight was not normal. Three had low birth weight (< 2.5 kg), while the fourth had more than 3.5 kg. A very high insulin level (40 mIU/ml) was seen in one of the four IUGR newborns. This high level in IUGR could be the result of immaturity of the beta cells, which is well documented in literature. Immaturity of normal homeostatic mechanisms may therefore result in hypoglycaemia in IUGR and SGA babies. Whether hyperinsulinemia is a result of insulin resistance in high birth weight is not known. However our study reports significant low levels of insulin in PIH as compared with normal resulting in high Glucose- Insulin Ratio (p < 0.1). In women whose pregnancies are complicated due to hypertension, there appears to be an exaggeration of insulin resistance and associated metabolic changes.16 In our study too, we found higher levels of glucose as compared with the normal. Comparatively, insulin levels were lower which again speaks of immaturity of fetal beta cells in handling glucose. Although it remains uncertain as to what extent these factors are pathogenic in hypertensive pregnancy, the available data suggests that some may play a role in disease evolution, whereas others may be markers of the underlying disease process. Exaggerated hyperinsulinemia relative to normal pregnancy is well described in women with established preeclampsia.16,17

Increased oxidative stress has been reported in fetuses born to mothers with established PIH. Also there is a report of decreased antioxidant protective mechanism in such babies.18 Whether this stress has any impact on developing beta cells of the fetus is unknown but possibility cannot be ruled out.

Singleton infants with intrauterine growth restriction have an adaptive hormonal profile characterized by decreased levels of insulin like growth factor IGF-1, IGF-2, insulin like growth factor binding protein-3(IGFBP-3) and insulin according to one study.3,18,19

Size at birth and early postnatal growth rates are important determinants of human perinatal survival. They also predict the tempo of growth, adult height and long term risks of obesity, type-2 DM and cardiovascular disease. Results of Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) show that fetal growth is influenced by both fetal genes and maternal-uterine-placental factors. With abundant nutrition and rising obesity rates, these genetic factors and their interactions with maternal and childhood environmental factors that influence childhood growth may contribute to the early development of adult disease risk.20

Results of our study match with findings of a few other studies which show no evidence of increased metabolic risk at birth.21,22 Studies have reported high insulin levels in macrosomic infants than controls (with normal birth weights) but glucose levels did not differ in both groups.22

Comparative studies indicate that metabolic responses to obesity may be greater in South and East Asians than their Western counterparts at given Body mass Indexes (BMIs). Higher percentage of body fat in Asians at given BMIs and over responsiveness to obesity may in part explain the phenomenon for which the underlying causes are not clear.11 Low birth weight is at least partly responsible for hyperactivity of hypothalamic – pituitary- adrenal axis, which leads to a state of functional hypercortisolism with increased circulating cortisol levels and greater responsiveness of the hypothalamic – pituitary- adrenal axis which might play a role in development of metabolic syndrome at both central and peripheral level later in life.23 Our preliminary data shows significant correlation of cord blood glucose and GIR with birth weight, in pregnancies with complications like maternal hypothyroidism, IUGR and PIH. Long term longitudinal studies are required to know as to how intrauterine conditions lead to permanent changes in fetal programming and plasticity.

Conclusion

In our pilot study, levels of insulin and glucose in normal full term pregnancies was found to be 6.75 ± 2.96 mIU/ml and 91.69± 27.05 mg/dl respectively with GIR of 13.57±7.47 and HOMA 1.57± 0.83.

Low serum insulin levels with normal or high GIR was noted in pregnancies complicated by PIH. Insulin resistance
as measured by HOMA IR is increased in patients with hypothyroidism.

Hyperinsulinemia is seen in babies with birth weight less than 2.5 kg or more than 3.5 kg.

Acknowledgements

The authors would like to thank Dr. Mangala Ketkar, Ketkar Hospital, Nagpur for providing access to hospital records for this study.

References