

Association of Cord Blood Levels of Fetuin A and Insulin with Fetal Growth Parameters among Term Babies Born to Gestational Diabetic Mothers

Abstract

Introduction: Fetuin A is an emerging marker, which is known to have a function in occurrence of insulin resistance and diabetes among adults. GDM has been related with raised serum Fetuin A levels in diabetic mothers. There is need to study whether there is an relationship between placenta blood FA, insulin and growth in fetus parameters and if GDM intrauterine environment will modify this association.

Objective: The objective of this research is to estimate placental blood levels of FA, insulin among term infants born to GDM and euglycemic mothers. We also want to explore the relation between placental blood levels of FA, insulin with growth in fetus parameters.

Methodology- A case-control study was done among two centres in South India. The Case group had infants born to mothers with gestational diabetes and control group had infants born to healthy euglycemic mothers. A sample size of 84 in each group was recruited. Data was collected at 20, 28 and 32 weeks period of gestation and a term scan was also taken.

Results: Among cases, the correlations between fetuin A and foetal length and estimated foetal weight were significant at 28 weeks (p value= 0.001). In cases and controls, no significant correlation was found at 20, 28, and 32 weeks and term between insulin and various foetal growth parameters.

Conclusion: It is plausible that post-translational modifications of fetuin-A and insulin might be influenced in GDM mothers. There is a need of further research to establish the real association.

Keywords: Blood • Insulin • Fetal growth • Medical or surgical conditions • Babies • Gestational diabetic mothers

Introduction

Over the years, there is an increasing burden of syndromes related to insulin resistance like type II DM and cardiovascular diseases which continues to be a important and significant public health concern. Gestation Diabetes Mellitus (GDM) occurs when there is contra-insulin effect by various hormones of pregnancy leading to insulin resistance state along with impaired glucose tolerance. The raised glucose levels gets transferred from mother to fetus and is responsible for the fetal size increase. There is impaired growth (insulin-mediated) in the fetus in resistant states and will be more pronounced in GDM offspring. The predisposition to insulin resistance and type 2 diabetes may be developed in early life. There is limited knowledge of perinatal biomarkers that could predict insulin resistance and metabolic health in postnatal life [1].

Fetuin A (FA), predominantly a fetal glycoprotein synthesized by liver hepatocytes as multiple functions. The role of FA has been implicated in the regulation of insulin activity, osteogenesis, resorption of bone, inhibition of mineralization at ectopic sites and systemic inflammatory

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response. Its concentration increases in states of insulin resistance, low bone mass and atherogenesis. FA is an emerging marker, which is known to have a role in occurrence of insulin resistance and diabetes among adults. Its role in insulin resistance is said to be due to inhibition of phosphorylation of tyrosine kinase activity at insulin receptor level. GDM has been associated with raised serum FA levels in mothers when compared with controls. FA involvement in the GDM pathogenesis and predicting the risk of GDM from first trimester onwards has been studied [2].

Fetuin A also has been linked to calcium homeostasis, promotion of bone growth and linear growth along with prevention of pathological calcification. Fetuses have elevated FA levels and may have a role in fetal growth and development. Studies on mice with deficient FA levels demonstrated defects in growth plates and reduced femur length. In contrast clinical studies on cord blood FA levels in GDM mothers showed negative correlation with the birth length.

With limited studies in literature, it remains unclear, whether there is an association between these markers with fetal growth parameters / clinical markers of neonatal adiposity and if GDM intrauterine environment will modify this association.

Thus, this study aims to determine if cord blood FA levels would be different in euglycemic versus GDM pregnancies. Also, to find out if there's would be any association of cord blood FA levels with growth in fetus parameters and clinical markers of neonatal adiposity in pregnancies with or without GDM [3].

Methodology

A case control study was conducted among two hospitals, Neonatal intensive care units of Lady Goschen Hospital and Kasturba Medical College Hospital, Attavar, Mangalore in South India. The two groups were made with participants, case group with infants born to mothers with gestational diabetes and control group with infants born to healthy euglycemic mothers. Participants were excluded if any condition was present: Maternal history of smoking and substance abuse, Disorder affecting glucose metabolism (polycystic ovarian syndrome), uncontrolled thyroid, liver diseases, Prematurity (Gestational age less than 37 weeks), Previous exposure to dexamethasone, Neonatal sepsis, Maternal age > 45 years, Apgar score at 5th

min < 7, Pregnancies resulting from artificial reproductive techniques, Pregnancy induced hypertension, pre-eclampsia, Acute or chronic inflammation [4].

A sample size of 84 in each case and control group was recruited in the study, based on mean cord blood Fetuin A, insulin concentrations in diabetic newborns when compared to babies born to healthy mothers. (16) Non probability purposive sampling was used to recruit the participants.

Relevant data on study and comparison groups was collected with structured proforma. Assessment of in utero biometric variables (femur length, EFW) at 20, 28, 32 weeks, term scan (beyond 37 weeks) and assessing trends of growth by plotting on WHO fetal growth monitoring charts was done. Estimation of FETUIN-A was done through Elisa Kit manufactured by Bioassay technology laboratories, China. Insulin levels were estimated using ELISA kit manufactured by Epitepe diagnostics, inc, USA Birth Weight was recorded through digital weighing scale by Moon Belt & Co. Model:BE-EQ22 (max capacity – 20 kgs, graduation 10gms with 1.2 in LCD display). Birth Length was measured by infantometer by Indosurgical Company. (Acrylic base, sliding side adjustable, dual scale reading in cm/inches up to 90 cm; Size 18*5). Interpretation of Z scores for birth weight and birth length by standard WHO anthropometric Z score charts. Birth Weight and weight/length as markers of neonatal adiposity [5].

Statistical analysis

Data was entered in MS Excel. Data was analyzed using IBM Statistical Package for Social Sciences (SPSS) for Windows version 25. The data was analyzed with descriptive statistics like mean, mode and median. Chi square test was done to assess the association between categorical variables, Pearson's correlation coefficient was used to see the correlation between continuous variables, and P value of less than 0.05 was considered statistically significant [6].

Results

The socio-demographic and behavioral profile of the cases are described. The Mean (SD) age of the mothers in the case, control group was 30.3 (4.6) years and 27.04 ± 4.8 respectively. Among cases around 69% (n=58) had delivery in LGH and two third (64%, n=54) underwent LSCS mode of delivery whereas among controls all

women had delivery in LGH and 58.3% (n=49) underwent NVD mode of delivery Among cases, 9 (10.7%) women had a history of GDM.

It describes about the values of various lab parameters assessed in cases and controls. The Mean (SD) value of Glucose Challenge Test in cases was 172.6 (29.9) mg/dL whereas in controls was 115.9 (18.9) mg/dL. The Mean (SD) of Glucose Tolerance Test in cases was 155.7 (14.0) mg/dL. The mean (SD) cord fetuin level among cases was 17.09 (43.4) ng/ml whereas in control group it was 12.33 (20.0) ng/ml. This change was not significant statistically ($p=0.36$). The Mean (SD) insulin level among cases was 9.98 (14.05) IU/ml whereas in control group it was 8.99 (12.72) IU/ml. This change was significant statistically ($p=0.63$). The Mean (SD) birth weight of new born among cases was 3.11 (0.39) kg and among controls it was 2.96 (0.41) kg and this change in values was significant statistically ($p=0.02$). The Mean (SD) birth length of newborn was almost similar in both the groups, cases 49.2 (2.0) cm and controls 48.8 (2.1) cm, with no statistical difference ($p=0.13$). Looking at the gender variation across the case and control group. Among the case group 55.9% (n=47) were females however among control group 51.2% (n=4) were male.

It shows various parameters assessed at 20 weeks, 28 weeks, 32 weeks and at term through ultrasound among the case and control groups. The Mean (SD) fetal length at 28 weeks among the cases was 5.47 (0.44) cm and in controls it was 4.93 (0.56) cm. This change was significant statistically ($p=0.01$). Mean (SD) abdominal circumference at 32 weeks among the cases was 28.87 (1.65) mm and in controls it was 28.05 (1.60) mm. This change was significant statistically ($p=0.01$). The Mean (SD) head circumference at 32 weeks was also found to be statistically ($p=0.04$) among the two groups. It also depicts correlation of various fetal parameters in cases with cord blood fetuin concentration at different periods. After adjusting for various maternal characteristics, cord blood fetuin concentration among cases at 28 weeks was negatively correlated to foetal length ($r=-0.88$, $p=0.001$) and estimated foetal weight ($r=-0.82$, $p=0.001$). And the correlation with both the parameters was strong. While the correlation with other parameters such as abdominal circumference, circumference of head and biparietal diameter was non-significant ($p>0.05$). Correlation of various fetal parameters in controls with cord blood fetuin concentration

at different time periods is described. None of the foetal parameters were found to be significantly correlated with fetuin levels among the controls at different time periods ($p>0.05$). Correlation of various fetal parameters in controls with insulin concentration at different time periods found none of the foetal parameters were found to be significantly correlated with insulin levels among the controls at separate time ($p>0.05$) [7].

Discussion

No difference in terms of FA and insulin between cases and controls was found. This could be because, in our tertiary care setting, hyperglycemia in GDM mothers was well-managed and most of these mothers with GDM would have reached a euglycemic state towards the late gestational period. In this study, a significant difference in birth weight but not in birth length between the two groups. No significant difference in terms of fetal length, estimated fetal weight, AC, HC, and BPD between the two groups at 20 weeks and term. However, at 28 weeks, the fetal length; and at 32 weeks, AC and HC were significantly different between the two groups.

In cases, the correlations between FA and length of fetus and estimated fetal weight was significant at 28 weeks; however, no significant correlation was found at 20, 32, and term. It may be inferred that the role of FA and insulin on growth in fetus GDM could be executed through mechanisms and pathways independent of growth in fetus factors and hepatokines. Similarly, like our results, in a previous study, it was found that GDM does not significantly affect the concentrations of Insulin-Like Growth Factor (IGF)-1, -2, IGF-Binding Protein (IGFBP)-3 in the umbilical cord blood and the blood in periphery. The role of IGF-1 in fetal developmental process was also strengthened by a positive correlation between IGF-1 concentration in the placental blood and the newborn length [8].

In another two studies, the authors demonstrated negative correlations of placental blood FA and insulin levels with growth in fetus parameters. Mechanistically, it was found in a pre-clinical study in knockout mice that FA is important for bone growth longitudinally. Additionally, fetuin-A may also exert its action as a calcification inhibitor. This role could explain the negative correlation between cord blood FA level and growth in fetus parameters in GDM mothers. However, it has not been studied whether and how maternal FA could penetrate the placental

barrier. Poor correlation between fetuin-A and insulin levels with fetal growth parameters in euglycemic pregnancies in study implies under normal conditions, FA and insulin might not affect growth of fetus [9].

It was found in a study that FA may be involved in excessive growth. This relation was found to be independent of fetal growth factors. Thus, FA may be involved in more growth and the mechanism is independent of growth factors (insulin, IGF-I, IGF-II). In another nested case-control study involving infants of mothers with GDM and euglycemic pregnancies, the authors evaluated the correlation between blood fetuin-A level with GDM and fetal growth. It was exhibited that GDM was not associated with cord blood fetuin-A levels. FA level was negatively correlated with growth in GDM but not in euglycemic pregnancies. This interesting finding implies a conditional negative correlation between FA level and growth in fetusparameters.

In another previous study, the authors saw adipose tissue, concentrations of plasma, and placental RNA expression of FA, FB, and FGF-21 in pregnant women who are healthy, pregnant women (GDM), and healthy non-pregnant women. Elevated FA and FB levels were found during pregnancy which was independent of GDM. On the contrary, the FGF-21 level was significantly different between healthy pregnant mothers and GDM mothers implying a possible role in the pathogenesis of GDM [10].

Conclusion

The regulation of the fetal growth mechanism is entirely different from the growth process postnatally. Placenta and maternal-related variables influence the growth in fetus, especially towards late gestation. On the other hand, postnatal growth is hugely influenced by genetic factors. It is still unclear how FA and insulin influence growth in GDM mothers. The role of FA and insulin might be modified in GDM mothers depending on the hormonal milieu inside the uterus. A previous case-control study has further demonstrated that fetal insulin and IGF-1 levels were significantly higher among macrosomic neonates as compared to those in normal neonates. Thus, some studies might influence post-translational modifications of FA and insulin might be influenced in GDM mothers, and this hypothesis may further explain

the negative association between FA and fetus growth in GDM in some studies. However, there are sparse data on protein modifications (post-translational), and this hypothesis needs to be proved in future studies.

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Conflict of Interest

None

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