



Original Research Article

Gestational diabetes –Does it influence the thyroid hormone levels of the foetus in utero?

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ABSTRACT

Introduction: Babies born of mothers with gestational diabetes tend to develop obesity and diabetes in later life. This occurs in spite of good control of gestational diabetes. It was decided to study whether the maternal hyperglycemia produces any alteration in thyroid function of the foetus which could account for the development of insulin resistance and obesity in later years. The present study was done to find the level of thyroid hormones in the cord blood of infants of mothers with gestational diabetes.

Materials and Methods: The study included 32 pregnant women who were suffering from gestational diabetes mellitus and their newborn babies. The severity of maternal diabetes was assessed by the fasting and postprandial blood sugar levels and the glycated haemoglobin levels. The glycated haemoglobin was estimated during the third trimester of pregnancy. The thyroid hormone levels and blood sugar was estimated in cord blood. The birth weight of the baby was also noted.

Result: In our study, the serum T₃ levels in cord blood was very much increased as compared to the normal range. The cord blood T₃ levels also showed a statistically significant positive correlation with the maternal postprandial glucose levels and the glycated haemoglobin levels. The T₃ levels in cord blood of babies were much higher in those mothers who required insulin than the mothers who were controlled with diet alone.

Conclusion: The increased T₃ levels in cord blood may be an indicator of the hyperglycemia to which the foetus is exposed during intrauterine life.

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1. Introduction

Gestational diabetes is the term used when glucose intolerance is noticed for the first time during pregnancy. A known diabetic woman who becomes pregnant is not included in this category. Routine screening for diabetes is carried out in all pregnant women between the 24 -28 weeks of gestation. The fasting blood sugar in a pregnant woman should be less than 92mg/dl. After ingestion of 75 grams of glucose 1 hour postprandial should be less than 180 mg/dl and the 2 hour postprandial should be less than 153 mg/dl. Diabetes complicating pregnancy is associated with complication both for the mother and the foetus. The mother may develop diabetes after delivery. An oral glucose

tolerance test has to be done postpartum to rule out diabetes. The babies of mothers with gestational diabetes tend to be large. This leads to complications during delivery. Preterm delivery and respiratory distress syndrome are more commonly seen in offspring of mothers with GDM. The newborn may develop neonatal hypoglycaemia since their insulin levels are high but the glucose levels become normal when separated from the mother. These children have a greater risk of developing obesity and type II diabetes in later life.

The serum triiodothyronine levels are lower in the foetus and newborn when compared to the adult. The levels in cord blood range between 5-141ng/dl whereas in the adult the range is 77-207ng/dl. T₄ levels in cord blood are 7.4-13 mg/dl almost the same range as that in the adult. The TSH levels are 0.4-4.2 mIU/ml. (same range as in

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the adult). This low concentration of T_3 in the foetal blood may protect the developing organs against undue exposure to thyroid hormone. Children born to mothers suffering from gestational diabetes have an increased chance of developing childhood and adolescent obesity, diabetes mellitus and subtle neurological dysfunction.^{1,2} These may be related to the severity of maternal hyperglycemia during pregnancy which causes foetal hyperglycemia and foetal hyperinsulinism. Uncontrolled or poorly controlled maternal diabetes commonly results in foetal hyperglycemia. This stimulates the release of insulin from the foetal pancreas. This foetal hyperglycemia and hyperinsulinaemia result in increased foetal growth especially in those tissues that are insulin sensitive.^{3,4} It was decided to study whether this altered intrauterine environment would produce any alteration in the thyroid function of the foetus. It is a well established fact that serum T_3 levels fall during starvation and uncontrolled diabetes mellitus in spite of normal thyroid function.^{1,5} This is due to a decrease in the intracellular glucose concentration causing decreased conversion of T_4 to T_3 by the deiodinase enzyme. In the foetus of a mother with gestational diabetes, there is hyperglycemia and hyperinsulinaemia which might facilitate the entry of more glucose into the foetal cells. How this intracellular metabolic milieu affects the conversion of T_4 to T_3 by deiodinase is not known. In the present study, we have estimated the thyroid hormone level in the cord blood of babies born to mothers with GDM and correlated the levels with the severity of maternal diabetes. We have also made an attempt to compare the cord blood T_3 levels of babies of GDM mothers who were controlled with diet alone with those who required insulin therapy.

2. Materials and Methods

This study was conducted in SAT hospital, Trivandrum. This descriptive study included 32 women who were suffering from gestational diabetes mellitus and their newborn babies. These women did not have any other systemic diseases. Women who were known to have diabetes prior to conception were excluded from the study. In the group of women suffering from gestational diabetes the following parameters were estimated and recorded, glucose challenge test, fasting and postprandial blood sugar, glycated haemoglobin estimated during the third trimester, mode of treatment and dosage of insulin. The following investigations were done in the cord blood of babies born to mothers with GDM, blood sugar and thyroid function tests – T_3 , T_4 and TSH. The birth weight of the newborn was also noted. Glucose challenge test (GCT) was done by estimation the fasting blood sugar and testing the urine by the benedict's test. 50 gm of glucose was administered to the patient and again blood sugar was estimated after 1 hour and benedict's test done on the urine sample. If the sugar in the 1 hour postprandial sample was more than 140

mg% an oral glucose tolerance test was done. The patient was put on a carbohydrate rich diet. The fasting blood and urine samples were collected. Then 75 gm of glucose was administered. Blood and urine samples were collected at hourly intervals for 3 hours. The blood sugar was estimated in all the samples and Benedict's test was done on the urine samples. For the diagnosis of GDM at least 2 values must exceed the following.

- Fasting blood sugar-105 mg%
- 1 hour postprandial -190 mg%
- 2 hour postprandial -165 mg%
- 3 hour postprandial -145 mg%

This study was conducted in 2003 when these were the criteria for the diagnosis of GDM. Currently, the values have been updated. The cord blood was collected and blood sugar and thyroid hormone levels were estimated in the serum. The serum for thyroid hormone estimation was stored in the deepfreeze and estimation was done within a week. The thyroid function tests were done by the ELISA method, the blood glucose by the glucose oxidase- peroxidase method and the glycated haemoglobin by the cation exchange resin method. TSH and serum T_4 levels were in the normal range but serum T_3 levels were increased in cord blood. The results were tabulated and analysed using SPSS software. A p value of < 0.05 was taken as statistically significant.

3. Results

32 women suffering from gestational diabetes and their newborn babies were analysed in the present study. The patients studied were in the age group 20 to 40 years. Of the 32 patients, 14 were between 20 and 25 years, 8 were between 25 and 30 years, 7 were between 30 and 35 years and 3 patients were more than 35 years old.

The weight of the women in the third trimester of pregnancy ranged between 50 kg and 80 kg. 7 women had body weight between 50 and 55 kg; 7 women between 55 and 60 kg; 12 were between 60 and 65 kg; 4 were between 65 and 70 kg and 4 were between 75 and 80 kg.

Table 1: Weight of mothers with GDM estimated during the third trimester of pregnancy

| No of mothers | Weight of the mother |
|---------------|-----------------------------|
| 7 | Weight between 50 and 55 kg |
| 7 | Weight between 55 and 60 kg |
| 12 | Weight between 60 and 65 kg |
| 4 | Weight between 65 and 70 kg |
| 4 | Weight between 75 and 80 kg |

Among the women included in the study, 15 were primigravida, 6 women were second gravida, 9 women were 3rd gravida and 2 women were 4th gravida. Both the 4th gravida had only 1 live child. Both these women had bad obstetric history and T_3 levels in the cord blood of their

babies were very high 620.76 ng/dl and 313ng/dl.

The glycated haemoglobin levels estimated during the third trimester of pregnancy was elevated and ranged between 8 and 15.4 mothers had glycated haemoglobin levels between 8 and 9, 19 mothers had between 9 and 10, 8 between 10 and 11, 2 between 11 and 12 and 1 >12.

Table 2: The glycated haemoglobin levels estimated during the third trimester of pregnancy

| No of mothers | Glycated haemoglobin levels |
|---------------|-----------------------------|
| 4 | Between 8 & 9 |
| 19 | Between 9 & 10 |
| 8 | Between 10 & 11 |
| 2 | Between 11 & 12 |
| 1 | Greater than 12 |

The serum T₃ levels in cord blood range from 5-141 ng/dl (normal range) the mean value being 68ng/dl. In the present study, the T₃ levels ranged from 98.4-620.76, the mean value being 182.77ng/dl.

15 patients with GDM were controlled with diet alone and 19 patients required insulin therapy. The mean T₃ levels in the cord blood of babies of mothers on diet control were 163.74ng/dl whereas the mean T₃ values for mothers requiring insulin was significantly higher 197.8ng/dl.

Table 3 Comparison of Mean T₃ levels in cord blood of babies of mothers with GDM with babies of normal mothers and comparison of mean T₃ levels in cord blood of babies of mothers with GDM who were treated with diet alone and those who required insulin therapy

The T₃ levels in the cord blood of newborns of gestational diabetic mothers showed a statistically significant positive correlation with the postprandial blood glucose of the mother the correlation coefficient being +0.3451 (p value < 0.025). The dependant variable serum T₃ levels in cord blood may be predicted from the independent variable the post prandial blood sugar regression equation $T_3 = 47.69 + (0.73 \times \text{PPBS of the mother})$

The T₃ levels in the cord blood of newborns of gestational diabetic mothers showed a statistically significant positive correlation with the glycated haemoglobin levels in the mother. The correlation coefficient being +0.3717 (p value < 0.025) the T₃ levels may be predicted from the regression equation $T_3 = 93.84 + 28.01 \times \text{glycated haemoglobin of the mother}$. The estimation of glycated haemoglobin was estimated during the third trimester of pregnancy.

15 patients with GDM were controlled with diet alone and 19 patients required insulin therapy. The mean T₃ levels in the cord blood of babies of mothers on diet control were 163.74ng/dl, whereas the mean T₃ value for those requiring insulin was significantly higher 197.8ng/dl.

There was a statistically significant positive correlation between the dose of insulin required to control the maternal gestational diabetes and serum T₃ levels in the cord blood

of their infants. There was no correlation between the cord blood T₃ levels and maternal fasting blood sugar, cord blood sugar levels or the birth weight of the baby.

On correlating the serum T₃ levels with the parameters of control of maternal gestational diabetes there was a positive correlation between the T₃ levels in cord blood and the postprandial blood sugar of the mother (p value < 0.025), cord blood serum T₃ levels and glycated haemoglobin levels in the mother (p value < 0.025). There was also a positive correlation between the dose of insulin required for the control of diabetes in the mother and T₃ levels in cord blood. (p value < 0.005).

4. Discussion

Pregnancy is associated with increased insulin resistance. In mothers suffering from gestational diabetes, the increased insulin resistance combined with a decreased pancreatic beta cell reserve triggers impaired glucose tolerance. The uptake of glucose by the foetus across the placenta takes place entirely by facilitated diffusion. The normal blood sugar in the foetus ranges between 60 -90 mg/dl (about 2/3 of the maternal blood sugar level). The foetal blood glucose concentration is controlled primarily by the maternal blood glucose concentration. Afzal et al have reported a positive correlation between cord blood insulin and glucose levels and the birthweight of the baby and the weight of the placenta in normal term infant.⁶ Pederson's hypothesis states that the maternal hyperglycemia in women with gestational diabetes leads to foetal hyperglycemia and foetal hyperinsulinism.^{7,8} Increased glucose and insulin together with the lack of insulin resistance in the foetal cells might favour the entry of more glucose into the foetal cells which in turn might increase the Type I deiodinase activity resulting in increased T₃ levels in the foetal circulation. In hepatocytes grown in tissue culture, when excess glucose is added to the culture medium, T₃ levels are increased.⁹

Children born to mothers suffering from gestational diabetes have an increased chance of developing childhood and adolescent obesity, diabetes mellitus and subtle neurological dysfunction.¹ These may be related to the severity of maternal hyperglycemia during pregnancy which results in foetal hyperglycemia and foetal hyperinsulinism. This may cause disturbance in the metabolism of lipids especially in the third trimester of pregnancy. Intensified management of gestational diabetes mellitus can normalize birth weight of the baby. Tight control is achieved by maintaining the glycated haemoglobin levels at less than 6.2.¹⁰ Newborn infants of women with GDM have increased adiposity and reduced fat-free mass even if they are not macrosomic. It is not clear whether intrauterine exposure to maternal diabetes is a risk factor for the development of insulin resistance in these infants.

To the best of our knowledge no studies have been done to show the effect of gestational diabetes in thyroid hormone

Table 3: Comparison of study variables in two groups studied

| | Number of samples (n) | Mean T3 levels in cord blood |
|------------------------------------|-----------------------|--|
| Mothers with GDM | 32 | 182.77ng/dl (Range 98.4ng/dl - 620.76 ng/dl) |
| Normal mothers as per textbook ref | | 68ng/dl (Normal range:- 5-14 ng/dl) |
| Mothers controlled with diet alone | 15 | 163.74 ng/dl |
| Mothers requiring insulin | 19 | 197.8 ng/dl |

Table 4: Correlation of cord blood T3 with various parameters

| Parameters | Correlation coefficient | 95% confidence limit | P value | Regression equation |
|----------------------------------|-------------------------|----------------------|-----------------|---|
| GCT | 0.1253 | -0.968, +2.014 | not significant | |
| FBS | 0.2325 | -0.406, +2.008 | not significant | |
| PPBS | 0.3451 | +0.015, +1.452 | <0.025 | $T_3 = 47.69 + (0.73 \times PPBS)$ |
| Glycated Hb in the 3rd trimester | 0.3717 | +2.817, +53.212 | <0.025 | $T_3 = 93.84 + (28.01 \times \text{glycated Hb 3rd trimester})$ |
| Dose of insulin | 0.5797 | 1.533, +9.39 | <0.005 | $T_3 = 98.63 + (5.46 \times \text{dose of insulin})$ |
| Cord blood sugar | 0.0311 | -1.057, +1.258 | not significant | |
| Birth weight of the baby | -0.0914 | -98.14, +58.28 | not significant | |

levels in cord blood of their offspring. In the present study there was no significant difference between the mean TSH and T_4 levels in cord blood of babies

born to mothers with GDM as compared to the normal range. But the mean T_3 levels in the cord blood of babies born to mothers with GDM was much higher than normal range (182.77ng/dl). The T_3 levels in cord blood also showed a statistically significant correlation with the parameters of diabetic control like the postprandial blood sugar levels (p value <0.025) and the glycated haemoglobin levels (p value <0.025). 15 patients with GDM were controlled with diet alone and 19 patients required insulin therapy. The mean T_3 levels in the cord blood of babies of mothers on diet control were 163.74ng/dl, whereas the mean T_3 value for those requiring insulin was significantly higher 197.8ng/dl. There was a statistically significant positive correlation between the dose of insulin required to control the maternal gestational diabetes and serum T_3 levels in the cord blood of their infants. There was no correlation between the cord blood T_3 levels and maternal fasting blood sugar, cord blood sugar levels or the birth weight of the baby.

Further studies will have to be done to follow up these children to find out if children with increased T_3 levels in cord blood develop obesity and insulin resistance in later years.

5. Conclusion

In our study the T_3 levels in cord blood of neonates of diabetic mothers were higher than the normal range and the increase in T_3 levels correlated with the severity of maternal diabetes as judged by the postprandial glucose levels and the glycated haemoglobin levels the serum T_3 levels in cord blood were much higher in those mothers who

required insulin therapy as those who were controlled with diet alone. This may be due to the exposure to maternal hyperglycemia which in turn causes foetal hyperglycemia and foetal hyperinsulinism. Further studies will have to be done to see if T_3 levels in cord blood can be a marker for the extent of hyperglycemia to which the foetus is exposed during intrauterine life.

6. Source of funding

None.

7. Conflict of interest

None.

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