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PUBLISHED PAPER'S TITLE : INFLUENCE OF MATERNAL DIABETES MELLITUS AND MATERNAL ANEMIA ON CORD BLOOD TSH

Authors : **Author's name: Kulshrestha R[1], Bhadra J[2], Kulshrestha MR[3], Bansal P[4], Dokwal S[5], Dhupper V[2]**

[1]Senior resident, Department of obstetrics and gynecology, Modern Institute of Medical Sciences, Indore, Madhya Pradesh, India.
Email: rupita.kulshrestha@gmail.com, +918349162390.

[2]PG resident, Department of biochemistry, Pt BDSPGIMS, Rohtak, India.
Email: drjayeetabhadra@gmail.com, +919034709032; drvasudha659@gmail.com; +919813504035.

[3]Assistant Professor, Department of biochemistry, Modern Institute of Medical Sciences, Indore, Madhya Pradesh, India.
Email: drmrkul@gmail.com, +918349161504, +918607184136.

[4]Assistant Professor, Department of biochemistry, BPS Govt. Medical College for Women, Khanpur Kalan, Khanpur, India.
Email: piyushmamc03@gmail.com, +919671530885.

[5]Assistant Professor, Department of biochemistry, Pt BDSPGIMS, Rohtak, India.
Email: drsumitdokwal80@gmail.com, +919812643666.

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Research Paper

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Influence Of Maternal Diabetes Mellitus And Maternal Anemia On Cord Blood Tsh

Kulshrestha R[1], Bhadra J[2], Kulshrestha MR[3], Bansal P[4], Dokwal S[5], Dhupper V[2]

Declaration

The Declaration of the authors for publication of Research Paper in Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772) : Kulshrestha R[1], Bhadra J[2], Kulshrestha MR[3], Bansal P[4], Dokwal S[5], Dhupper V[2]the authors of the research paper entitled Influence Of Maternal Diabetes Mellitus And Maternal Anemia On Cord Blood Tsh declare that , we take the responsibility of the content and material of my paper as we ourself have written it and also have read the manuscript of our paper carefully. Also, we hereby give our consent to publish our paper in ajmams , This research paper is our original work and no part of it or it's similar version is published or has been sent for publication anywhere else. we authorise the Editorial Board of the Journal to modify and edit the manuscript. we also give our consent to the publisher of ajmams to own the copyright of our research paper.

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Abstract

Introduction: The cord blood TSH (CBTSH) levels may be elevated because of antenatal complications. This can lead to false positives in screening of congenital hypothyroidism. Thus, this study is aimed to evaluate the effect of maternal anemia and maternal diabetes mellitus on cord blood TSH.

Materials and methods: This cross sectional study included 734 term newborns. Neonates who were born preterm (<37week) or weighed <2.5Kg, those with major life threatening malformation or antenatally detected central nervous system malformations and those whose mothers were on any antithyroid drugs or had pre eclampsia were excluded from the study. Information about mother's health status was noted from hospital records. Depending upon the profiles of the newborns and their mothers, 4 groups were formed. Group 1 served as the control (n=306), group 2 (n=74), group 3 (n=333) and group 4 (n=21) had newborns whose mothers had diabetes mellitus only, anemia only and diabetes mellitus and anaemia both respectively. Cord blood samples were analyzed for TSH using sandwich immunoassay on Elecys 2020.

Results: The median CBTSH (IQR) value for group 1, 2, 3 and 4 were 6.72 mIU/ml (3.6), 7.0 mIU/ml (4.9), 7.9 mIU/ml (6.0) and 8.7 mIU/ml (5.5) respectively. CBTSH levels was significantly raised in newborns of diabetic mothers (p =0.030), anaemic mothers

(p=0.001) and mothers with both diabetes & anaemia (p=0.004) in comparison to those born to mothers without these diseases (controls; group1).

Conclusion: Our results show that cord blood TSH is significantly affected in presence of maternal anemia and gestational diabetes mellitus. This may be due to placental insufficiency and fetal hypoxia associated with these conditions, which results in intrauterine fetal stress.

Keywords: Cord blood TSH, Congenital hypothyroidism screening, maternal anemia, gestational diabetes mellitus

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Introduction

Congenital hypothyroidism (CH) is the commonest cause of preventable mental retardation and developmental delay in neonates, with its incidence in India to be 1:1131.(1) More than 95% of infants with congenital hypothyroidism have few, if any clinical manifestations. The treatment for this condition is simple, inexpensive and highly effective, so the key to ensure normal growth and development in the affected children is early detection. In view of paramount importance of early diagnosis and treatment various screening programs have been initiated in developed countries were which proved to be extremely successful, both in terms of cost-effectiveness and impact on clinical outcome.(2) Cord blood TSH (CBTSH) estimation has the advantages of being easy to collect, non invasive and low rates of follow up loss as the results would be available before the mother leaves the hospital, enabling repeat sampling if needed at the earliest, which is critical for early institution of treatment if necessary.(3) Indian council of medical research (ICMR) introduced congenital hypothyroidism screening program for neonates at various centers in 2007.(4,5) Some countries use T4 while others prefer TSH as the tool since maternal diseases affecting placental dynamics influenceT4 levels. Few others use both T4 and TSH. Technically, using both T4 and TSH will be superior but would increase the cost of screening. Most of the countries have accepted TSH either through heel prick or through cord-blood as the screening method for congenital hypothyroidism.(6)

TSH has been recommended as the primary screening test because it detects not only permanent sporadic congenital hypothyroidism, but also compensated or transient primary hypothyroidism whose main cause is iodine deficiency.(7) The Indian Academy of Pediatrics recommends the use of cord blood samples for screening for CH.(8)

However, a major disadvantage of cord blood TSH assay is that it is affected by various maternal and perinatal factors such as maternal age, gestational age, maternal illnesses during pregnancy, gender of the baby, perinatal insults etc and is associated with a high number of false positives.(4) The present study aims to analyze the effect of two such maternal factors, anemia and gestational diabetes mellitus, on cord blood TSH.

Materials and methods:

This cross sectional study was performed at Christian Medical College & Hospital, Ludhiana. Cord blood samples obtained from 1500 term newborns over a period of 1 year for screening of congenital hypothyroidism after obtaining an informed consent from parents were taken for study. Informations regarding

antenatal and perinatal complications were obtained from hospital records. Neonates who were born preterm (<37 wk) or weighed <2.5Kg, those with major life threatening malformations or later diagnosed as case of congenital hypothyroidism or those with antenatally detected central nervous system malformations and those whose mothers were on any antithyroid drugs or had thyroid disorders or preeclampsia or eclampsia were excluded from the study group. . Thus, a total of 734 term newborns were included in this study after satisfying the exclusion criteria. Maternal anemia and gestational diabetes mellitus diagnosed as per hospital protocol and hemoglobin (Hb) and fasting blood glucose or post oral glucose tolerance test levels noted from records. Maternal anemia defined as Hb level <11g/dL (WHO criteria). Gestational diabetes mellitus defined as fasting blood glucose ≥126 mg/dL and/or 2 hour blood glucose ≥200 mg/dL post 75g oral glucose load (ADA criteria).

2 ml Cord blood sample was collected in a sterile container drawn from the umbilical cord while severing it at the time of birth of the baby. The sample thus collected was kept at room temperature of around 25°C and was transported to laboratory within one hour. Serum separation was done by centrifugation at 3000 rpm for 10 minutes and the sample was analyzed for TSH within 3 hours by electrochemiluminescence using sandwich principle (kit from Roche diagnostics) on Elecys 2020.

Depending upon the profiles of the newborns and their mothers, 4 groups were formed:
Group 1: Composed of (306) term newborns. The newborns had not suffered any asphyxia and their mothers had normal pregnancy with none having diabetes mellitus or anemia. This served as the control group.

Group2: Composed of (74) term newborns from mothers with diabetes mellitus but no anemia. The newborns had not suffered any asphyxia.

Group 3: Composed of (333) term newborns from mothers with anemia but no diabetes mellitus. The newborns had not suffered any asphyxia.

Group 4: Composed of (21) term newborns from mothers with both anemia and diabetes mellitus. The newborns had not suffered any asphyxia.

Data analysis was done using SPSS 20. Results were expressed as median & interquartile range. The level of significance was taken as $P < 0.05$ to assess the correlations.

Results

Of the 734 newborns constituting the study population, 306 fitted the criteria for group 1, 74 for group 2, 333 for group 3 and 21 for group 4. Out of 734 newborns, 21 had CBTSH values> 20 mIU/mL, however all had normal day 3 TSH levels on follow up.(Table 1) The median of CBTSH for group 1, 2, 3 and 4 were 6.7 mIU/mL (IQR=3.6), 7.0 mIU/mL (IQR=4.9), 7.9 mIU/mL (IQR=6.0) and 8.7 mIU/mL ((IQR=5.5) respectively. (Table 1; Figure 1 & 2)

CB TSH was thus significantly raised in newborns born to diabetic mothers i.e group 2 (P =0.030), anemic mothers i.e. group 3 (P=0.001) and to mothers with both diabetes & anemia i.e group 4 (P=0.004) in comparison to those born of normal mothers i.e group 1 which served as control.(Table 1)

Therefore we can say that the rise in median CBTSH levels were significant statistically when comparing groups 2,3 & 4 with controls i.e. group 1.but this comparison among groups 2, 3 & 4 was statistically insignificant with p value =

0.465 for group 2 & 3, p value = 0.634 for group 3 & 4 and p value = 0.285 for group 2 & 4. This may be due to less number of subjects in group 2 & 4 as our study was retrospective cross sectional study based on data collected from hospital records of deliveries occurring over 1 year period.

The relationship, however, could be better defined in studies based larger number of subjects and in longer duration.

Discussion:

Thyroid function is dynamic during the perinatal period with many factors potentially influencing maternal, fetal and neonatal TSH and thyroid hormone levels.(9) Multivariate models identified a various variables that independently can influence the CBTSH levels such as higher birth order (lower CB TSH); gestational diabetes (higher CBTSH); sexually transmitted disease during pregnancy (lower CBTSH); alcohol use during pregnancy (lower CBTSH); male sex (higher CBTSH); C-section (lower CB TSH) and Gestational age (lower CB TSH).(9)

Our results show that CBTSH is significantly elevated in presence of maternal anemia and gestational diabetes. These findings are in agreement with those of Chan et al who found significant independent correlation between cord blood TSH and maternal conditions like pre-eclampsia, glucose intolerance and maternal medical diseases.(5) Similar results were also observed by Herbstman et al in a study of 300 newborns where several perinatal factors including gestational diabetes were found to affect the thyroid hormone status. (9)

Maternal anemia associated with decreased oxygen carrying capacity of blood. Hyperglycemia and hyperinsulinemia in fetus cause increased oxygen demand. Glycosylated Hb poorly delivers oxygen to tissues. Fetal hypoxia associated with an increase in endogenous catecholamines. Catecholamine mediated alpha adrenergic stimulation in turn causes peripheral vasoconstriction to preserve the blood supply to vital organs (brain sparing effect). In severe hypoxia, even the cerebral vessels show constriction leading to local hypothermia. TRH stimulated by hypothermia which consequently leads to rise in TSH. Oxidative stress present in gestational diabetes and maternal anemia also a potential cause of raised CBTSH.

In a retrospective study done by Lao TT, Lee CP (2002), maternal characteristics, infant outcome and cord blood thyrotropin (TSH) concentration were compared between 469 diet-treated GDM pregnancies diagnosed by the World Health Organization 75 g oral glucose tolerance test (OGTT) with 474 non-diabetic pregnancies with normal OGTT results. Hyperthyrotropinemia was found in 7.2% of the GDM pregnancies & in the same group, the hyperthyrotropinemic newborns had a higher incidence (p = 0.017) of neonatal jaundice and this could have reflected increased fetal in-utero hypoxic stress in these pregnancies.(10)

Data on the effect of maternal malnutrition and/or anemia on thyroid hormone regulation in human fetuses are scarce, and would be of great importance in examining the relevance of Barker's hypothesis, which proposes adaptation of fetuses to undernutrition leading to permanent metabolic and endocrine changes that form the basis of adult diseases.

Mahajan SD et al (2005) studied thyroid hormone dysregulation in intrauterine growth retardation associated with maternal malnutrition and/or anemia and found that the effects of malnutrition or anemia on thyroid hormone profile are distinct and speculated that alterations in the pituitary-thyroid function result is beneficial adaptations to the hostile intrauterine environment in malnutrition related growth retardation and anemia.(11)

Although some studies have been performed in this field, the results being controversial and sometimes paradoxical. Moreover in contrast with our results is the study that performed by Herbstman et al, which evaluated a total number of 300 newborn. Thyroid hormone levels were measured and the association between various perinatal factors was assessed. They revealed that several perinatal factors such as maternal age, pregnancy induced hypertension, gestational diabetes, sexually transmitted disease during pregnancy, alcohol use during pregnancy and gestational age can affect thyroid hormone status in infants.(12)

However, results from other studies analyzing correlation between cord blood TSH and various adverse antenatal conditions are contradictory. Franklin et al studied the effect of maternal diabetes mellitus, toxemia, fetal distress and concluded that these factors did not affect cord blood TSH concentrations.(14) Only the delivery method influenced cord serum T_4. Another report from Fuse et al also found TSH values in cord blood TSH to be less influenced by perinatal factors than T_4 values. (15) Cord blood TSH is a marker of intrauterine stress faced by fetus.(14)
Raised CBTSH in presence of maternal anemia and gestational diabetes, as observed in our study, may be due to placental insufficiency and fetal hypoxia associated with these conditions, which can result in intrauterine fetal stress. Changes in TSH levels in response to T3 and T4 blood levels forms the basis of screening for congenital hypothyroidism through CB TSH estimation.(6)
Screening for congenital hypothyroidism (CH) is widespread for the last two decades. We have not been able to implement it in India because of several factors, like cost, lack of reliable laboratories on a large scale, and non-availability of baseline data in our population. Use of cord blood TSH as a screening tool is an attractive preposition because of its simplicity and accessibility.(6)

Conclusion:

Cord blood TSH is significantly affected by maternal anemia and gestational diabetes. In India where the set up is less favorable for patient recall, development of correction formula for various adverse antenatal factors can be useful to eliminate false positives detected by CBTSH assay. Larger elaborated studies exploring CBTSH variation in maternal anemia and gestational diabetes could help us to understand and formulate the connection between CBTSH, maternal Hb and HbA_1C.

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Table 1. Comparison of cord blood TSH among various groups

Group	Number	Median (IQR) mIU/mL	p value (in comparison to controls)	Neonates with CBTSH >20 mIU/mL
1	306	6.7 (3.6)	-	0 (0%)
2	74	7.0 (4.9)	0.030	6 (8.1%)
3	333	7.9 (6.0)	0.001	18 (5.4%)
4	21	8.7 (5.5)	0.004	2 (9.5%)

Figure 1. Distribution of cord blood TSH among various groups

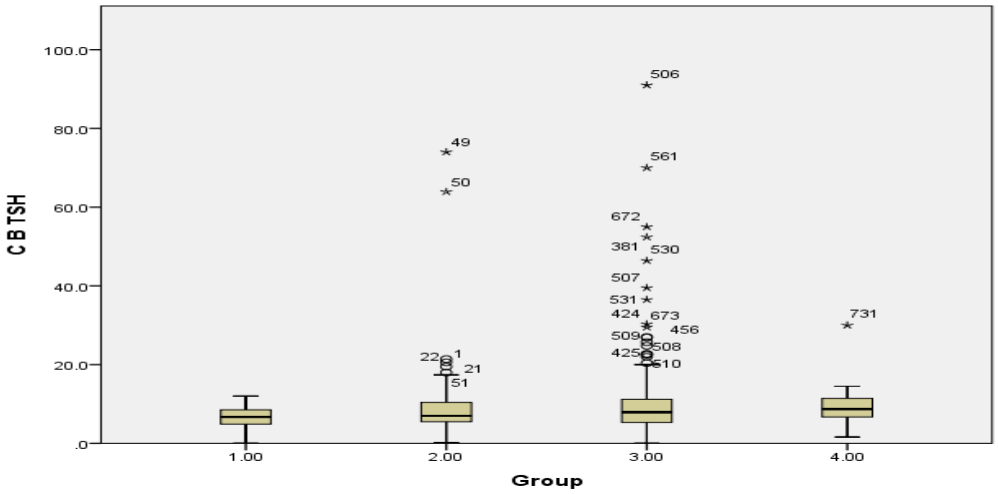

Figure 2. Line diagram of median cord blood TSH among various groups