ABSTRACT

Background: The thyroid status of mothers as well as neonates has a profound impact on neonatal brain development. Hypothyroidism at birth is one of the preventable causes of mental retardation in children. Low birth weight is an important cause of neonatal morbidity and mortality. Many factors responsible for low birth weight can be classified as fetal or maternal. Evidence-based interventions could save many newborns. For this, the knowledge has to be transformed into practice.

Method: This study was performed at a medical college and tertiary care hospital in western India’s Thane district of Maharashtra. Eligible female participants were those who have enrolled in the hospital over 5 months from February through June 2021. All statistical analyses were performed using Mystat statistical software version 12.0 or Statistical Package of Social Sciences version 20.0 for Windows (IBM Corp, Armonk, NY). The normality of the data distribution was determined using the Kolmogorov-Smirnov test.

Result: Maternal TSH and thyroxin are more than that of cord blood counterparts, while cord blood T3 levels were found to be more than maternal T3. Maternal TSH has a positive correlation with the birth weight of neonates. It shows a significant negative correlation between the birth weight of cord blood T3 (r = -0.563) and Thyroxin (r = -0.510), respectively. The higher the maternal thyroxin and T3, the lower the birth weight.

Conclusion: Present study shows the effect of thyroid status of mother and fetus both has an association with neonatal birth weight. More detailed analysis with sample collection as per trimester is required to know more about the impact of various confounding factors which have an impact on birth weight. Maternal TSH rather than thyroxin is a better predictor of neonatal birth weight.

KEYWORDS Birth weight, T3, T4, TSH.

INTRODUCTION

The thyroid status of a mother as well as a neonate has a profound impact on neonatal brain development. Hypothyroidism at birth is one of the preventable causes of mental retardation in children. Maternal thyroid disorders are known to have an association with pregnancy complications. During pregnancy, the production of thyroxine (T4) and triiodothyronine (T3) increases with an increase in the daily iodine requirement. These physiological changes may reflect hypothyroidism in the last trimester of pregnancy in women who were euthyroid in the first trimester. Screening for thyroid disorders in pregnancy is recommended in a few countries only due to a lack of resources and finances. In countries like Singapore, national screening for congenital hypothyroidism has been performed on umbilical cord serum since 1980. [1-3] Low birth weight is an important cause of neonatal morbidity and mortality. Many factors responsible for low birth weight can be classified as fetal or maternal [4]. Evidence-based interventions could save many newborns. For this, the knowledge has to be transformed into practice [5]. Many factors, including oxidative stress, contribute to all three trimesters, which are classified according to the duration of gestation. [6] Low birth weight is a product of various factors to
which both mother and fetus contribute. Among these factors, thyroid hormones play an important role. Thyroid hormones are essential for fetal growth and development [7], and several studies have demonstrated the association between maternal thyroid dysfunction and pregnancy outcomes. [8] Maternal hyper- and hypothyroidism have been associated with an increased risk of adverse pregnancy outcomes, but studies have led to inconsistent results. Gestational age at delivery and birth weight is an important predictor of neonatal mortality and morbidity, and literature reports that some of the complications associated with maternal thyroid disease may be secondary to preterm birth [9, 10].

Maternal hypo, as well as hyperthyroidism, is associated with preterm birth. Maternal hyperthyroidism is associated with a risk of low birth weight and small gestational age incidences. In the case of maternal hypothyroidism, there are diverse results as some mention incidences of small for gestational age (SGA) while some mention no correlation between maternal hyperthyroidism and birth weight. [11] Maternal thyroid disease is associated with an increased risk of obstetrical and labour complications such as fetal losses, hypertensive disorders during pregnancy, and preterm birth. Literature reports that effective and timely treatment can curtail the untoward effects. [12, 13]

MATERIAL & METHODS

Study population
This study was performed at a medical college and tertiary care hospital in western India’s Thane district of Maharashtra. Eligible female participants were those who have enrolled in the hospital over 5 months from February through June 2021. Written informed consent as per the Helsinki declaration has been obtained from subjects selected for the study. The sample size was calculated based on assuming a two-sided type I error α =5 %, power (1-β) 95% and correlation coefficient (ρ) 0.5, which provided the sample size required as 70. Every 10th term normal weight baby delivered in authors’ hospital was taken as control. Eighty neonates born in authors’ hospital, irrespective of the mode of delivery born at term, i.e., 37–40 week were included; 40 as cases and 40 as a control group. The maternal age group was 19–30 years, and weight was 52–68 kg. Those under treatment for hypo or hyperthyroidism were excluded. In addition, women who underwent in vitro fertilization had a twin pregnancy or fetal loss, used medication known to interfere with the thyroid, or had a history of thyroid disease, congenital abnormality or maternal events like pre-eclampsia, chronic diseases, addictions like smoking / tobacco chewing or any significant medical history were excluded. The Institutional Review Board and Institutional Ethics Committee approved this study protocol.

Data collection
During hospital visits, nurses, residents, and gynaecologists, with the use of the electronic patient file, prospectively collected all data. Maternal fasting blood samples were drawn from the median cubital vein. Cord blood sample (4 mL) was collected in sterile serum separating tubes (BD vacutainer SST II advance) immediately after the birth of babies, drawn from a 15-20 cm length of umbilical cord incised while severing it at the time of birth of the baby. Thus, a mixed umbilical cord blood sample containing blood from both umbilical artery and vein was obtained. Samples obtained were centrifuged at 3,000 RPM, and sera separated were analyzed immediately. According to the manufacturer’s protocol, TSH, T4, and T3 concentrations were measured with the SNIBE Biolumi 8000. The intra-assay and interassay coefficients of variation were 1.6% to 3.6% for TSH, and 1.9% to 4.0% for FT4. Birth weight was standardized for gestational age at birth. Information on birth weight, gestational age, and fetal sex was prospectively collected in the medical records.

Statistical Analysis
All analyses adjusted for potential confounders such as gestational age at blood sampling, maternal age, BMI, parity, education level, fetal sex, hypertension, and diabetes based on biological plausibility, identification of a variable as a confounder in previous studies, change of the effect estimates of interest, or reduction in the residual variability of the outcome. All statistical analyses were performed using Mystat statistical software version 12.0 or Statistical Package of Social Sciences version 20.0 for Windows (IBM Corp, Armonk, NY). The normality of the data distribution was determined using the Kolmogorov–Smirnov test.

RESULTS

As shown in Figure 1, there is a significant difference between the cord blood and maternal blood thyroid profile. Maternal TSH and thyroxin are more than cord blood counterparts, while cord blood T3 levels were found to be more than maternal T3. The lipid profile also reports (Table 1) the significant difference between maternal and cord blood. Levels of all the lipid profile parameters are higher in the maternal serum than in cord blood. Maternal TSH positively correlates with the birth weight of neonates, as shown in Fig.2 (r = 0.224). Trends toward lower maternal TSH levels and lower birth weight were observed but reached negligible statistical significance. Fig.3 shows maternal T3 (r = -0.451) and Fig.4 shows maternal thyroxin (r = -0.505) respectively, having significant negative correlation with neonatal birth weight. In Fig.5, the correlation of birth weight is shown with cord blood T3 and Thyroxin. It shows significant negative correlation of cord blood T3 (r = -0.563) and Thyroxin (r = -0.510) respectively, with the birth weight. The higher the maternal thyroxin and T3, the lower the birth weight. The same is applicable to cord blood thyroxin and T3. Higher thyroxin levels can be associated with low birth weight. Our study shows that as maternal TSH increases, neonatal birth weight increases, but as maternal T3 and thyroxin increase, birth weight shows a declining trend. The same is applicable to cord blood T3 and Thyroxin; as they increase, birth weight tends to decrease. Fig.6 shows the receiver operator characteristic (ROC) curve for T4 and TSH. The area under the curve (AUC) gradually increases from 0.623 to 0.896. This shows the contribution of T4 & TSH to neonatal birth weight. T3 has a very negligible contribution with an AUC of < 0.5.

DISCUSSION

Some reports are showing maternal hypothyroidism in pregnancy is associated with lower birth weight, whereas hypothyroxinaemia is associated with higher birth weight. An inverse association of maternal TSH (even within the normal range) with birth weight was reported in the literature. [16] Our study showed the inverse association between maternal thyroxin and

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Table 1 Lipid profile (Maternal Vs Cord Blood)

|                      | Mother        | Child         | p-value |
|----------------------|---------------|---------------|---------|
| Total cholesterol    | 234.71 ± 72.51| 76.87 ± 38.58 | <0.05   |
| Triglycerides        | 191.04 ± 65.90| 40.91 ± 16.73 |         |
| HDL                  | 64.79 ± 17.53 | 29.49 ± 19.31 |         |
| LDL                  | 116.84 ± 39.86| 27.11 ± 7.66  |         |
| VLDL                 | 38.24 ± 13.16 | 8.39 ± 3.34   |         |

birth weight, but with increased maternal TSH, the birth weight tends to increase. Some studies have mentioned that high maternal TSH is associated with a higher risk of prematurity and respiratory distress syndrome. [17]

At birth, term infants experience a surge in TSH that peaks
around 30 minutes post-delivery. In preterm infants of 24–27 weeks, the hypothalamic-pituitary-thyroid axis development is more immature, and the TSH surge is smaller. [18-19] There are contradictory reports regarding the association between birth weight and cord blood TSH. [20, 21] Our study observed no such correlation between birth weight and cord blood TSH.

Various metabolic pathways and processes throughout the gestational period are controlled by thyroid hormones in the mother as well as the fetus. By facilitating placental implantation, thyroid hormones control the growth of the fetus. Another way to regulate the growth is by regulating various metabolisms, oxygen and glucose consumption and various other factors, which are the part of skeletal growth, tissue differentiation and accretion. A meta-analysis reported the inverse association between thyroxin and birth weight. Similar results are obtained in our study. Thyroid hormone crosses the placenta to reach the fetus. Maternal thyroxin has a direct effect on the developing fetus. It is hypothesized that the effects of thyroxin are mediated by increased catabolism of lipids and proteins in the fetus. This causes depletion of energy available. At the same time, vascular resistance in the placenta is also high. This adds to the effect of maternal thyroxin. [22, 23] Effect of thyroxin is amplified by an increased fetal nutritional demand and increased fetal growth rate associated with the progression of pregnancy. A recent trial showed that thyroxin supplementation is associated with the increased risk of small for gestational age infants. [24] Our results displayed an inverse correlation between birth weight and T3. It is not clear that T3 crosses the placenta; hence, further studies are necessary to study the actual effect of T3 on neonatal birth weight.

The present study shows that maternal thyroid and TSH have a profound effect on neonatal birth weight. Cord blood thyroxin and TSH also contribute to a certain extent. However, one of the study’s limitations can be mentioned as there is no trimester pattern followed for the sample collection. That could provide a more detailed picture of the effects of thyroid status in various trimesters.

CONCLUSION

The present study shows the effect of thyroid status of mother and fetus both has association with neonatal birth weight. More detailed analysis with sample collection as per trimester is required to know more about the impact of various confounding factors which have impact on birth weight. Maternal TSH rather than thyroxin is better predictor of the neonatal birth weight.

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CONFLICT OF INTEREST

There are no conflicts of interest to declare by any of the authors of this study.

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