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Effect of Maternal Hypothyroidism on Thyroid hormone status of fetus: A Hospital based study

Authors
Sanchayan Sinha[1], Arpita Mandal[2], Soma Gupta[3*], Chandana Das[4]
[1&2]Junior Resident, Department of Biochemistry, NRS Medical College, Kolkata
[3]Professor & Head, Department of Biochemistry, NRS Medical College, Kolkata
[4]Professor & Head, Department of Obstetrics & Gynaecology, NRS Medical College, Kolkata
Institute: Nil Ratan Sircar Medical College. Department of Biochemistry, 138 A.J.C Bose Road Kolkata- 700014, India
*Corresponding Author
Soma Gupta
Professor & Head, Department of Biochemistry, NRS Medical College, Kolkata
Address: 40A, Simla Street. Kolkata 700006, India

Abstract
Introduction: *Thyroid dysfunction is a common endocrinological disorder in pregnancy. It is important for normal development of placenta & early stages of neurodevelopment of foetus. Any deviation from normal activity of thyroid gland is known to be associated with adverse foetomaternal outcome.*
Aims & Objectives: *The study aims to find out thyroid hormonal status in pregnancy and thereafter to determine prevalence of hypothyroidism. Moreover, it aims to find out the effect of maternal hypothyroidism on fetal thyroid hormonal status.*
Materials & Methods: *The study included the estimation of TSH and fT4 level of 142 women during delivery. On the basis of thyroid hormonal status, the patients were divided into 2 groups, with hypothyroidism (n=41) & without hypothyroidism (n=101). Thyroid status of baby (TSH & fT4 level of cord blood) was measured. The data was tabulated & analysed using standard statistical method.*
Results: *Prevalence of hypothyroidism was 28.87%. Statistically significant positive correlation was found between thyroid status of mother & baby [p value >0.001].*
Conclusion: *maternal hypothyroidism adversely affects the thyroid hormonal status of the fetus; hence early detection of maternal hypothyroidism is very crucial.*
Keywords: *Thyroid autoimmunity, pregnancy, congenital hypothyroidism.*

Introduction

Thyroid, one of the endocrine glands in human body is important for maintaining homeostasis & basal metabolic rate. After diabetes, thyroid dysfunction is the second most common endocrinal disorder complicating pregnancy throughout the world.[1] India is a country where nutritional deficiency in pregnancy is more frequent than the developed countries. Iodine deficiency, one of the common nutritional deficiency is known to result thyroid dysfunctions especially hypothyroidism. This dysfunction is

found to be more prevalent in pregnancy. Not only subclinical variety but the overt cases of hypothyroidism are found to be present in pregnancy. The disease may be pre existing or present during pregnancy. Both the conditions remain neglected and undetected unless properly investigated. The conditions of those patients, who were hypothyroid before conception, become worse as the pregnancy advances if they remain undetected and untreated. Even some euthyroid women are often seen to develop hypothyroidism in the advanced weeks of pregnancy, especially in third trimester. The outcomes are adverse, even fatal as the thyroid hormones affect almost all systems in our body.

After conception, the thyroid hormones play very important function of maintaining the reproductive hormonal status (especially beta HCG and oestrogen) & growth & neurodevelop-ment of fetus.[2] Moreover, hypothyroidism in pregnancy has also been found to affect intelligence quotient (IQ) and neuropsychological development of fetus adversely.[3] This is because of the fact that maternal hypothyroidism during pregnancy raises the risk of insufficient placental transfer of maternal thyroid hormone to the developing fetuswhich have long lasting neuropsychological effects.[4]

The major circulating thyroid hormones are thyroxin (T4) and triiodothyronin (T3). Most T4 & T3 molecules are bound to the thyroid binding globulin (TBG) & only a little fraction of T4 &T3 are in the free form (fT4 & fT3) which is important for biological action. Thyroid stimulating hormone (TSH) is secreted from the anterior part of the pituitary gland. It also plays an important role in stimulating thyroid gland to synthesise & secrete thyroid hormones in the peripheral circulation. Low level of thyroid hormones as seen in hypothyroidism is known to send a feedback to secrete TSH from pituitary gland. Thus TSH level is found to be increased in hypothyroidism.

Fetal thyroxin is almost always obtained from maternal source in first trimester of pregnancy as fetal thyroid gland becomes functional in the second trimester of gestation.

Studies have shown that despite sufficient iodine intake during pregnancy, the women are still having hypothyroidism as the pregnancy advances. The most important cause of it is autoimmune thyroid diseases. Elevated levels of thyroid autoantibodies are detected in the peripheral circulation in autoimmune thyroid diseases. Anti thyroid peroxidase (anti TPO) antibody and anti thyroglobulin (anti TG) antibodies are two most frequently found autoantibodies.

Though it has been found in various studies that hypothyroidism is a very serious issue regarding complications related to pregnancy, its true prevalence is still debatable.

So, it is very important to find out the prevalence of hypothyroidism in pregnancy in our population. Early diagnosis and proper management of the above mentioned conditions can prevent or reduce fetal demise in future. But, still we do not have any concrete data for these facts. So, there is a need of future study to address these issues. There is very little data available on these conditions in West Bengal. To fill up the gap, this study was carried out with the following objectives:

1. To measure serum TSH and fT4 levels of the samples taken from the women of 3rd trimester of pregnancy & find out the prevalence of hypothyroidism
2. To measure TSH &fT4 levels in the cord blood taken from the same women during delivery

Materials and Methods

The study was carried out in the Department of Biochemistry of a tertiary care Hospital after obtaining necessary permission from Institutional Ethics Committee. The study period was from January 2017 to December 2017. A total of 142 pregnant women were included in the study. All women irrespective of their parity who were admitted for delivery were included in the study. Women under antithyroid medication or having

other endocrinal disorders like diabetes mellitus, or known to suffer from any autoimmune disease or malignancy, or giving any history of pregnancy induced hypertension or preeclampsia were excluded from the study.

An amount of 5 ml blood was collected from the median cubital vein of all study subjects by disposable plastic syringe. The needle was detached from the Nozzle & the blood was transferred in a clotted vial and was allowed to clot. Then the clotted vials were centrifuged. Separated serums were labelled appropriately and were stored in -20^{0}C & analysed within 7 days.

Immediately after delivery, 5ml of blood collected from umbilical cord with all aseptic precautions and transferred into a clotted vial and allowed to clot. Then the serum was separated and stored and analysed within 7 days.

Serum fT4 &TSH levels in maternal blood samples as well as in cord blood were measured by ELISA method using standard kits.

Statistical Analysis

The results obtained were tabulated in excel sheet& analysed by standard statistical methods using SPSS 20.

Result

The present study was conducted in the department of Biochemistry in collaboration with the department of Obstetrics and Gynaecology in N.R.S. Medical College, Kolkata, India. A total of 142 pregnant women admitted for delivery in the labour room of NRS Medical College & Hospital were taken as study subjects by applying inclusion and exclusion criteria after clearance of Institutional Ethics Committee (NMC/6543, Dated 26/12/2016). The patients were enrolled in the study after obtaining informed consent. The patients were divided according to their thyroid hormone status into 2 groups: mother with and without hypothyroidism. The prevalence of hypothyroidism is shown in Fig. 1.

Among total 142 pregnant women 41 patients were revealed to be hypothyroid. Hypothyroidism was considered when TSH level was equal to or above 3µIU/ml. Rest 101 patients were found to have no hypothyroidism.

The level of TSH and FT4 in cord blood of the baby was distributed in mothers with and without hypothyroidism, expressed in Mean and SD and presented in Table 1. The levels were found to be statistically significant for both the parameters.

Correlation of TSH and FT4 level in mother and baby has been depicted in Fig. 2a and 2 b respectively. In both the cases the parameters were found to be positively and significantly correlated.

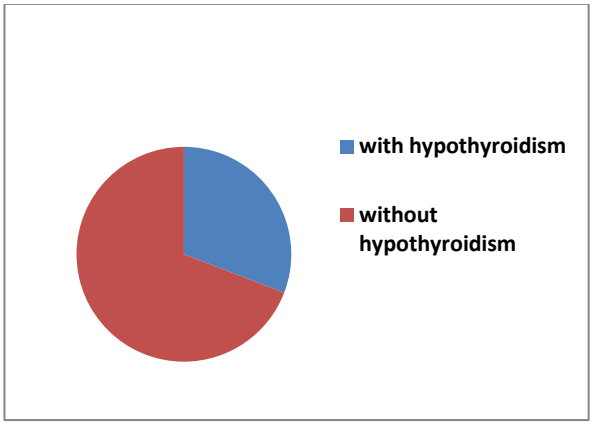

Fig. 1: Thyroid status in study population

Table 1: Thyroid status of the baby as measured by cord blood (mean ± SD)

Cord blood	Mother with hypothyroidism (n = 41)	Mother without hypothyroidism (n=101)
TSH (µIU/ml)	14.13 ± 8.18*	9.3 ± 6.14
fT4 (ng/dl)	1.08 ± 0.37**	1.23 ± 0.42

*t value: 3.84, p<0.05. ** t value: 1.99, p<0.05

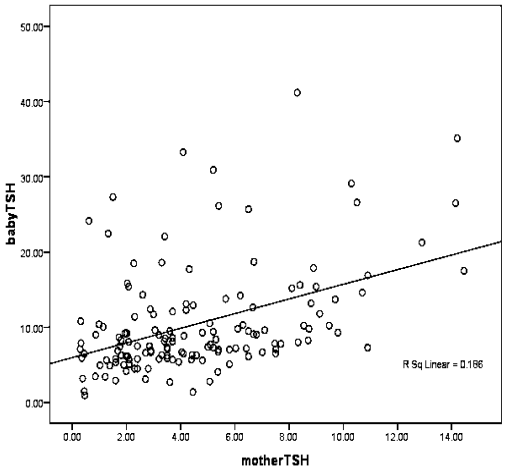

Fig 2a: Correlation of TSH among mother & baby (r = 0.428, p< 0.001)

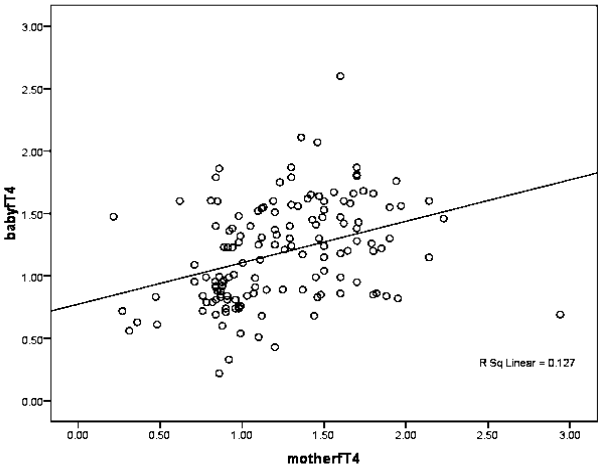

Fig 2b: Correlation of T4 among mother & baby ($r = 0.354$, $p < 0.001$)

Discussion

India is presently having high prevalence of hypothyroidism among the pregnant women through last few decades. Though several etiological background of this non-communicable disease has been well explained, a number of recent literatures suggest that nutritional deficiency & autoimmune thyroid disease are very important factors for hypothyroidism complicating the pregnancy resulting adverse fetomaternal outcome.

Pregnancy is state of significant changes in the steroid hormonal metabolism and function which in turn affects the synthesis & metabolism of thyroid hormones. Changes in maternal thyroid function during pregnancy result from a combination of increased metabolic demands, increased serum TBG concentrations, stimulation of the TSH receptor by human chorionic gonadotropin (hCG)[5]. Moreover, transfer of thyroxin transplacentally, increased maternal renal clearance of iodine and changes in thyroid binding globulin disturb thyroid homeostasis in pregnancy. Thyroid hormone production which is iodine dependant gradually declines if the increase on iodine demand placed by the pregnant state is not met. The reference range for serum thyroid stimulating hormone (TSH) and free thyroxine (FT4) are different during pregnancy, reflecting the physiological changes. The reference range for TSH is lower than non-pregnant state, while FT4 levels are high due to the stimulatory effect of serum beta hCG on the TSH receptors.

Maternal TSH is usually within normal limits during pregnancy but it can be decreased in the first trimester due to the increased hCG levels and the cross-reactivity of this hormone on TSH receptors[6]; both are glycoprotein hormones with a common α subunit and a considerable homology between their β subunits. Therefore hCG has a weak thyroid stimulating activity[6] As the gestational age increases, the percentage of women with subclinical hypothyroidism is doubled. Hence there is a need for screening subclinical hypothyroidism and thyroid autoimmunity in pregnancy.[6] The role of routine screening becomes relevant in these patients as they are asymptomatic and symptoms, if any are ascribed to pregnancy itself. There is a wide range in the prevalence of thyroid dysfunction worldwide. In the USA which is considered an iodine replete country, 2%–3% of apparently healthy, non pregnant women of childbearing age have an elevated serum TSH with the majority in the subclinical range as per the study done by Negro R. et al.[7] In southern Iran, in a study done by Saki F et al, the prevalence of hypothyroidism among pregnant women was shown to be 13.7%.[8] In a study carried in South India, the prevalence of thyroid dysfunction was high with subclinical hypothyroidism found in 6.47% and overt hypothyroidism found in 4.58% of pregnant women.[9] In our study, the prevalence of hypothyroidism was found to be 28.87%.

Maternal hypothyroidism can also be associated with significant impairment of physical and mental development of fetus. In human fetal brain, thyroid hormone receptors, TRα1 and TRβ1 isoforms are present by 8-10 weeks. TRα1 isoforms increase 8-10 folds by 16-18 weeks[12]. Study done by S Chan & Kilby suggests that, children of even marginally iodine deficient mothers show psychomotor and cognitive impairment. Such data indicates sensitivity of the developing CNS to maternal thyroid metabolism in utero.[13]

In a study done by Man EB et al showed that there was up to 60% of surviving children having evidence of impaired mental and physical development.[14]

Various studies are available to establish the fact that the babies of hypothyroid mothers are having more incidence of congenital hypothyroidism than the babies of euthyroid mothers. In the study of Kris Poppe et al in 2003 the deficiency of maternal thyroid hormones may increase the chance of insufficient placental transfer of thyroid hormones which in turn increases the chances of congenital hypothyroidism.[16]

For the present study, thethyroid hormonal status of the mother and baby has been given in table no 1. It shows that TSH level of the babies of the mothers with hypothyroidism was 14.13 ± 8.18 (mean ± SD), whereas the TSH levels of the babies of mothers without hypothyroidism was 9.3 ± 6.14 (mean ± SD). The fT4 level of the babies of mothers with hypothyroidism was 1.08 ± 0.37 (mean ± SD) & of the babies of mothers without hypothyroidism was 1.23 ± 0.42(mean ± SD).

Correlation of thyroid hormonal status of the mother and the baby has been given in Fig 2a & 2b. It shows statistically significant positive correlation between maternal and baby TSH levels with correlation coefficient (r value) is +0.428 and p value is <0.001. The fT4 levels of mothers and the babies were also statistically significantly positively correlated with correlation coefficient (r value) is +0.354 and p value is <0.001.

Conclusion

The prevalence of hypothyroidism in pregnancy was found to be 28.87%. Statistically significant positive correlation has been found between thyroid status of mother and baby (as measured by TSH & f T4 in both maternal serum and cord blood). Though the study population is less in respect to an epidemiological study, and most of the patients were from apparently low socio economic status, which did not represent the whole population, still it can be inferred that, early identification of maternal hypothyroidism is crucially important for proper growth and development of fetus.

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