



## **Association between Maternal Thyroid Hormone Level and Fetal Weight**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author ZM had done all the experimental work as well as drafted the manuscript. Authors PKR and AKJ have validated and analyzed the data. Author RD had initiated the thought and finalized the manuscript. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Aims:** Present study is aimed to find out the association between maternal thyroid hormone at delivery and weight of delivered fetus.

**Study Design:** This is a case-control study in which low birth weight was cases and appropriate for gestational age were considered as control.

**Place and Duration of Study:** Study was conducted at National Institute of Pathology (ICMR), New Delhi and Department of Biotechnology, Invertis University, Bareilly from July 2018 to July 2020.

**Subjects and Methods:** A total of 193 maternal blood samples were collected and fetal parameters were recorded as per inclusion criteria. Quantitative estimation of Triiodothyronine (T3), Thyroxine (T4), and Thyroid Stimulating Hormone (TSH) was done in the separated serum samples by pre-coated ELISA kits and data analysis was performed using SigmaStat. Cases include women having full-term deliveries with birth weight < 2.5Kg i.e. Low Birth Weight (LBW) and Controls includes women having Appropriate for Gestational Age (AGA) delivery with birth weight > 2.5Kg.

**Results:** No significant difference was observed in maternal age as well as age at marriage and other demographic parameters, while maternal weight and BMI is significantly less in LBW as

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compared to AGA i.e.  $49.62 \pm 5.34$  &  $53.96 \pm 6.92$  and  $21.32 \pm 4.01$  and  $22.66 \pm 1.57$  respectively having  $P < 0.001$ . Pearson correlation coefficient also revealed a significant negative correlation of T4 with both fetal weight and fetal length and a positive correlation of T3 with fetal weight, fetal length, and fetal head circumference, whereas TSH did not show any significant association with fetal parameters.

**Conclusion:** It was concluded that maternal T3 and T4 affects the fetal development during gestational period, TSH did not show any significant association with fetal parameters.

*Keywords: Thyroid; hypothyroidism; hyperthyroidism; low birth weight; appropriate gestational weight.*

## 1. INTRODUCTION

Neonatal and perinatal mortality has long been considered a matter of extreme concern worldwide. As per reports published by World Health Organization (WHO), around 10 million infants die yearly out of 130 million born worldwide [1]. This condition is even more frightful in developing countries and multifarious causes may be attributed to it. However, the most plausible reason behind this is considered to be the low birth weight (LBW) of the delivered fetus, which eventually results in the death of infants. LBW has been described by WHO as the weight of a baby at the birth of less than, 5.5 pounds or 2500 gm [2]. The most crucial stage of human life is antenatal development usually lasting for about 280 days before the actual birth of a fetus. During this time, a myriad of factors including environmental, social, genetic, physiological, nutritional, hormonal, etc. are known to influence the gestational period that directly affects the development of the fetus [3].

During pregnancy, diversified hormonal changes occur in response to increased metabolic demands of the growing fetus. However, these changes may sometimes result in multitudinous complications, endocrine disorders, being the most common. These endocrine disorders especially the thyroid dysfunction is most likely to cause deleterious effects on both the mother as well as the fetus. Previously, it has been contemplated that thyroid dysfunction results in miscellaneous pregnancy disorders namely maternal hypothyroidism and hyperthyroidism which in turn adversely affects fetal development resulting in intrauterine fetal death, impaired neurodevelopment, and low birth weight [4,5]. In 2015, a research group concluded that 2.5 - 6.5% of pregnant women suffer from Gestational Diabetes Mellitus and hypothyroidism [6]. The low birth weight of the infant is an indicator of impaired fetal growth and development, which accounts for neonatal mortality and morbidity [7-12]. Many researchers have investigated the

effects of maternal thyroid dysfunction during pregnancy on fetal growth with contradictory results [13,14]. Thus, the present study aimed at finding the association between maternal thyroid hormone level and fetal weight outcome after excluding all other factors that may lead to LBW.

## 2. MATERIALS AND METHODS

### 2.1 Study Design

The present study is a case-control study, designed to assess the association between maternal thyroid levels and fetal birth weight after deliveries via several known and/or unknown factors.

### 2.2 Questionnaire

A detailed questionnaire form was drawn and filled as accurately as possible, after detailed informed consent about the research to the patient, to record the information about the mother and the delivered fetus. The patient parameters recorded were maternal age and gestational age (based on the last menstrual period), menstrual history (regularity of menstrual cycle, bleeding, etc.), obstetrics history (including gravidity, parity, and abortions), and medical history. All the essential information about the delivered fetus was also noted.

### 2.3 Study Population

The study population consisted of two groups:

- i. **Cases i.e. LBW:** includes women having full-term deliveries with birth weight less than 2.5Kg.
- ii. **Controls i.e. AGA:** includes women having appropriate for gestational age (AGA) delivery with birth weight more than or equal to 2.5Kg.

Patients were first investigated for inclusion and exclusion criteria. A total of 193 volunteer subjects were recruited for the study, in which

101 and 92 belong to LBW and AGA respectively.

## 2.4 Inclusion and Exclusion Criteria

### 2.4.1 Inclusion criteria

All the samples shall be from singleton full-term deliveries with birth weight less than 2.5Kg at delivery as case i.e. LBW and birth weight more than 2.5Kg at delivery as control i.e. AGA.

### 2.4.2 Exclusion criteria

All those LBW and AGA deliveries were excluded from the present study which were having any of the following clinical history, complications or diseases viz. pre-term delivery, under-weight mother before delivery, chronic diseases, diabetes, cardiac, renal, or pulmonary problems, infections, tuberculosis, Placenta praevia, Abruptio placentae, intrauterine death (IUD), twins and multiple deliveries, etc.

## 2.5 Sample Collection

Maternal Blood samples were collected from the recruited study population just after the delivery in clot activator vacutainer tube for serum separation, procured from BD Vacutainer® Plus Plastic Serum Tubes. After blood clotting, blood samples were centrifuged at 1000-1500 rpm for 15 minutes using REMI refrigerated centrifuge. Aliquots of 100µl were prepared from separated serum samples for thyroid profile estimation. The remaining aliquots were properly labeled and stored at -80°C.

## 2.6 Thyroid Profiling by ELISA

Thyroid profiling i.e. quantitative estimation of Triiodothyronine (T3), Thyroxine (T4) and Thyroid Stimulating Hormone (TSH) was done in the separated serum samples by pre-coated ELISA (Enzyme-Linked Immunosorbent Assay) kits procured from Weldon Biotech India Pvt. Ltd. India.

After the preparation of the microtiter (MT) plate layout, 50µl of different concentrations of thyroid calibrators (0-40µIU/ml) and serum samples were dispensed in duplicate into the assigned well. Then 100µl of enzyme reagent (T3 or T4 or TSH) was added to each well close to the bottom, and after that MT plate was stirred gently for 15-20 seconds and incubated for 60 minutes at room temperature. After incubation, the

content of the plate was discarded and the plate was tapped on to absorbent paper for the complete removal of content. MT plate was then washed 3 times with a 300µl wash solution phosphate buffered saline with tween 20 (PBST) and the content was completely removed by tapping and blotting the MT plate on an absorbent paper. 100µl of working substrate tetramethylbenzidine (TMB) in buffered H<sub>2</sub>O<sub>2</sub> solution was then added to each well and the plate was incubated for 15 minutes at room temperature. After incubation 50µl of stop solution (1N HCl) was added to each well and mixed gently for 15-20 seconds. Absorbance (OD) was taken immediately with an MT plate reader at 450 nm supplied by BioTek Plate Reader and the standard curve and calculations were performed by Gen5 Data Analysis Software.

## 2.7 Statistical Analysis

Data analysis was performed using Microsoft Excel and statistical software Sigma-stat. Mean, mode, median, Unpaired t-test, and Pearson product-moment correlation tests were applied to check the statistical significance. P-value ≤0.05 was considered statistically significant.

## 3. OBSERVATIONS AND RESULTS

### 3.1 Details of the Mother

The age of LBW mothers ranges from 19-36 yrs with an estimated average age of 23.44 years while that of the control group ranges from 18-36 yrs with an average of 24.96 years. The mean age at marriage and of childbearing in LBW mothers is 19.73 years and that of AGA mothers is 20.92 years. It is also noted that 14 women were married at an age below 18 years in the LBW group and 6 in the AGA group.

Among these pregnant women, the majority of the mothers included were housewives (LBW=98 and AGA=83). In LBW deliveries 76.23% of the women residing in the urban locality, 17.82% belongs to the rural area and the remaining 5.94% belongs to the industrial area, whereas in the case of AGA deliveries 89.13% were from urban, remaining 10.86% were from rural areas and no cases belonged to the industrial area. The patients were also categorized as per their socio-economic status and income but there is no notable difference found between LBW and AGA. The mean weight and height of mother having LBW deliveries were 49.62 kg and 152.92

cm respectively, whereas in the case of AGA deliveries these were 53.96 kg and 154.13 cm respectively. Thereby, the mean BMI observed in LBW cases was 21.32 kg/m<sup>2</sup> and that in normal pregnant females was 22.66 kg/m<sup>2</sup> which is significantly low in LBW cases as compared to AGA deliveries (P<0.0001). In basic clinical parameters, the mean hemoglobin content in the mother having LBW delivery was 9.55 gm% and in AGA delivery mothers it was 9.81 gm% (Table 1).

In LBW mothers, 96 patients had a regular menstrual cycle with 93 having moderate flow, whereas 03 patients had severe bleeding and 05 had decreased flow during menses. While in the control group, 85 patients had a regular cycle, 84 had moderate flow, 05 having severe bleeding and 03 had decreased flow during menses. 38 out of 101 patients i.e., 37.62% who had an LBW baby were Primi-gravida, and compared to this, only 36.95% of patients were Primi-gravida in the control group.

**3.2 Profile of the Newborn Fetus**

In the present study, full-term and singleton deliveries were recruited as per the inclusion criteria. Fetal weight, height, and head circumference were significantly less (P<0.0001) in the LBW group. Few caesarean cases were also reported in the LBW group while no caesarean case was observed in AGA (Table 2).

It was also observed that the mean birth weight of LBW and AGA deliveries was 1.90 kg and 2.88 kg respectively. The mean length of the fetus was found to be 43.05 cm and 50.08 cm in LBW and AGA groups respectively, whereas the mean head circumference was 31.24 cm and 34.53 cm in LBW and AGA groups respectively which is highly significant (Table 2; Fig. 1).

**3.3 Hormonal Profile of the Patients**

**3.3.1 T3 (Thyroid) hormone profile**

The range of T3 thyroid hormone in the maternal serum of LBW and AGA cases were 0.266 to

1.901 ng/ml and 0.519 to 1.739 ng/ml and the mean was 0.817 ng/ml and 0.938 ng/ml, respectively. The mean concentration of the T3 thyroid hormone was significantly high in AGA maternal sera samples in comparison to LBW maternal sera samples (Table 3; Fig. 2).

**3.3.2 T4 (Thyroid) hormone profile**

It was observed that the mean ± standard deviation and range of T4 in LBW and AGA deliveries were 9.12 ±1.49 ng/ml & 8.066 ±1.31 ng/ml and 5.205 to 12.335 ng/ml & 4.772 to 10.743 ng/ml respectively, the mean value of T4 was significantly high in case of LBW deliveries (Table 4; Fig. 2).

**3.3.3 Thyroid stimulating hormone profile**

The range of TSH thyroid hormone in the maternal serum of LBW cases and AGA cases were 0.834 to 13.566 and 1.359 to 12.383 uIU/ml as well as the mean was 5.41±2.97 and 6.125 ±3.04 uIU/ml. The mean concentration of the TSH thyroid hormone was high in AGA maternal sera samples in comparison to LBW maternal sera samples. But this difference is not considered to be statistically significant (Table 5; Fig. 2).

**3.4 Correlation Studies of Thyroid Hormones**

Pearson product-moment correlations between each thyroid hormone (T3, T4 &TSH) and fetal growth parameters as individual variable shows the correlation coefficients range between -1 to +1 and measures the strength of the linear relationship between the variables. P-values less than 0.05 was considered statistically significant at the 95.0% confidence level. By the following test, we have found that different pairs of parameters have found positive as well as a negative correlation. It has been found that the maternal thyroid hormone level (T4) is negatively correlated with the weight and length of the delivered fetus. T3 is positively correlated with fetal birth weight, length, and head circumference. No significant association was seen between TSH and any of the fetal

**Table 1. Details of mother’s having LBW and AGA deliveries**

Observation	LBW Deliveries	AGA Deliveries	P-Value
Sample Size	101	92	-
Weight : Mean + SD (Kg)	49.62±5.34	53.96±6.92	<0.001
Height : Mean ± SD (cm)	152.92±9.29	154.13±8.44	NS
BMI : Mean ± SD (kg/m <sup>2</sup> )	21.32±4.01	22.66±1.57	<0.001
Hb: Mean ± SD (gm%)	9.55±1.15	9.81±1.26	NS

growth parameters. The negative sign is two parameters and the yellow color indicates indicative of a negative correlation between the that the value is statistically significant (Table 6).

**Table 2. Details of the newborn fetus**

Observation	LBW Deliveries	AGA Deliveries	P-Value
Sample Size	101	92	
Weight : Mean ± SD (Kg)	1.90±0.27	2.88±0.38	<0.001
Length : Mean ± SD (cm)	43.05±4.35	50.08±2.96	<0.001
Head Circ. : Mean ± SD (cm)	31.24±1.91	34.53±2.83	<0.001
Mode of Delivery	Vaginal	100%	-
	CS	7.92%	-

**Table 3. T3 concentration in LBW and AGA deliveries**

Observation	LBW Deliveries	AGA Deliveries
Sample size	101	92
Range (ng/ml)	0.266 to 1.901	0.519 to 1.739
Mean ± SD (ng/ml)	0.817 ±0.29	0.938 ±0.283
P Value	<0.001	

**Table 4. T4 concentration in LBW and AGA deliveries**

Observation	LBW Deliveries	AGA Deliveries
Sample size	101	92
Range (ng/ml)	5.205 to 12.335	4.772 to 10.743
Mean ± SD (ng/ml)	9.12 ±1.49	8.066 ±1.31
P Value	<0.001	

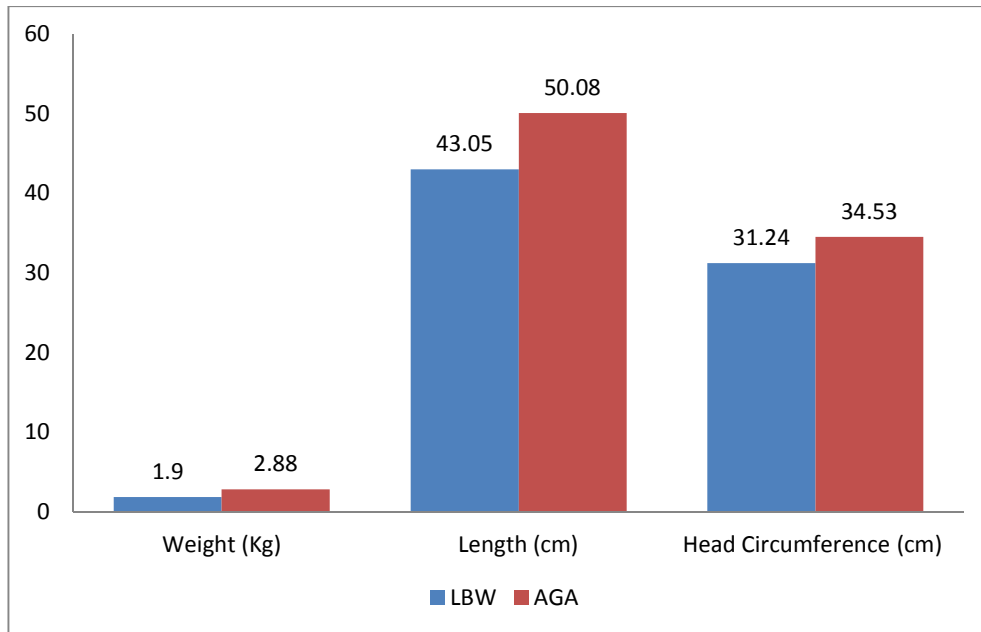
**Table 5. TSH concentration in LBW and AGA deliveries**

Observation	LBW Deliveries	AGA Deliveries
Sample size	101	92
Range (uIU/ml)	0.834 to 13.566	1.359 to 12.383
Mean ± SD (uIU/ml)	5.41 ±2.97	6.125 ±3.04
P-Value	NS	

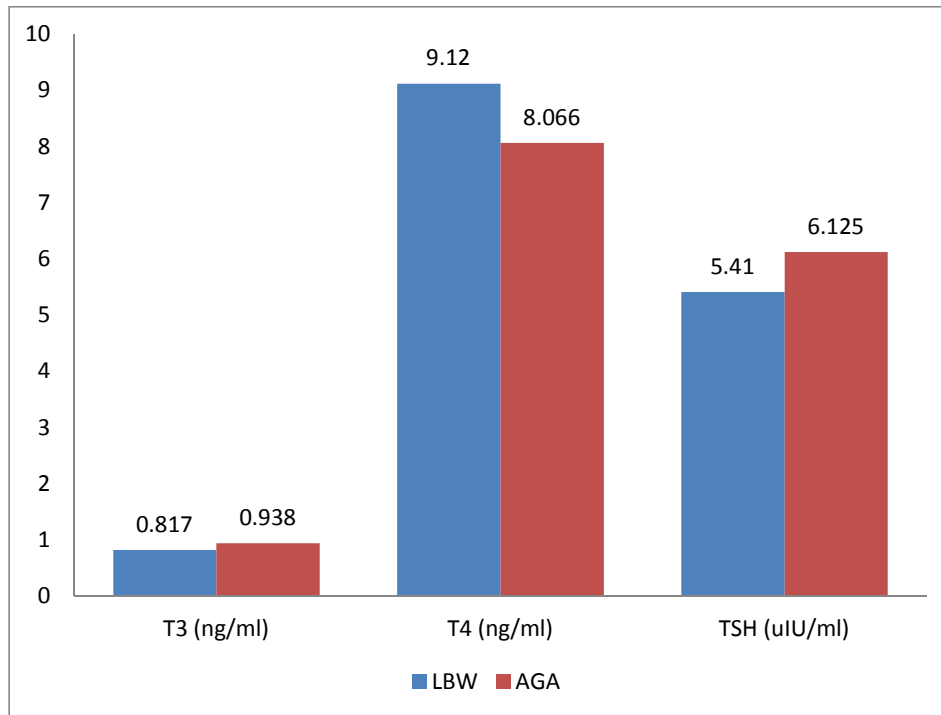
**Table 6. Correlation studies of maternal thyroid on fetal growth**

		MB T3	MB T4	MB TSH	FL	HC	FW
MB T3	R	1	0.110	-0.142	0.206	0.161	0.171
	P	0	0.127	0.0491	0.00401	0.0257	0.0172
MB T4	R	0.110	1	-0.135	-0.171	-0.122	-0.265
	P	0.127	0	0.0611	0.0175	0.0923	0.001
MB TSH	R	-0.142	-0.135	1	-0.009	-0.0173	0.424
	P	0.0491	0.0611	0	0.901	0.811	0.559
FL	R	0.206	-0.171	-0.009	1	0.735	0.749
	P	0.00401	0.0175	-0.901	0	4.710	4.680
HC	R	0.161	-0.122	-0.0173	0.735	1	0.560
	P	0.0257	0.0923	0.811	4.707	0	2.611
FW	R	0.171	-0.265	0.0424	0.749	0.560	1
	P	0.0172	0.00019	0.559	4.680	2.611	0

MB-Maternal Blood; FL-Fetal Length; HC-Head Circumference; FW-Fetal Weight; R-Coefficient of Correlation; P- P Value



**Fig. 1. Bar-graph showing significantly less birth weight, length & head circumference of LBW and AGA fetus (P<0.001)**



**Fig. 2. Mean T3, T4 and TSH levels in maternal serum having LBW and AGA deliveries**

#### 4. DISCUSSION

The thyroid profile of the mother during pregnancy has been known to manifest a great

impact on fetal development since the fetus is completely dependent on maternal thyroid hormones during its initial stages. Any abnormality in maternal thyroid levels during

pregnancy hampers fetal growth since thyroid hormones are critical for the normal growth and development of the human fetus [15]. Thus, maintaining an optimum concentration of thyroid hormones is a requisite for ensuring a healthy pregnancy as aberrant changes in thyroid levels negatively affects the fetal development particularly the development of the central nervous system and neurocognitive development of offspring as well [16]. Several studies have indicated that both hypothyroidism and hyperthyroidism have been associated with abortions, stillbirths, preterm delivery, LBW, and pregnancy-induced hypertension thereby increasing incidences of neonatal morbidity and mortality [17-19]. Prematurity and Intrauterine growth retardation are the two main inducing factors for LBW deliveries and one of the main driving forces behind these two is thyroid hormonal imbalance [20].

Both overt and subclinical hypothyroidism poses a risk of placental abruption, preterm delivery, and LBW [21,22] However, the risk for LBW deliveries is lower in mothers suffering from subclinical hypothyroidism as compared to those affected with overt hypothyroidism [23,24]. This has been confirmed by a study by Blazer et al. [25] stating that the women affected with hypothyroidism gave birth to LBW infants [25].

Hypothyroidism has adverse effects on the course of pregnancy and the development of the fetus [26]. Grave's disease is a prime cause behind the occurrence of maternal hyperthyroidism during pregnancy. Being an autoimmune disorder, a woman suffering with this produces an antibody called thyroid-stimulating immunoglobulin (TSI) that mimics TSH. This antibody binds to the TSH receptor instead of TSH. However, this binding is not regulated and thus women start producing a large quantity of thyroid hormone [27].

During the prenatal stage, the development of the fetus is completely dependent on the mother in terms of nutrients and hormones, the exchange of gases, and the removal of toxic substances. All these functions are well played by the placenta. There has been evidence that during the first semester, the thyroid hormones in the fetus are of maternal origin whereas after that the onset of fetal TH production starts in the mid-second trimester [28]. Thus it becomes extremely important that maternal thyroid hormone levels and their transport across the placenta are highly regulated. The concentration of maternal free T4

is seen to increase moderately during the first trimester. In contrast, the fetal concentration of free T3 remains lower than the maternal free T3 throughout gestation [29].

In the present study increased maternal T4 concentration was found to be associated with LBW deliveries. This is in the agreement of the previous study by Phoojaroenchanachai et al. [30], in which maternal hyperthyroidism was shown to increase the risk of LBW deliveries [30]. Vrijkotte et al. [31], in 2017 also demonstrated similar results. They proclaimed that an inverse relationship exists between maternal T4 and the weight of the delivered fetus. They further added that this association was more prominent for boys as compared to girls [31]. However, in a study by Pop et al. [32], children of women with hypothyroxinaemia at 12 weeks of gestation had delayed mental and motor functions compared with matched controls and this data suggest that low maternal plasma free T4 concentration during early pregnancy is an important risk factor for impaired development [32]. Additionally, as per the results, maternal serum levels of T4 were also found to be negatively associated with fetal length apart from the birth weight ( $p < 0.001$ ). T4 was also found to be negatively correlated with a head circumference of the delivered fetus; however, this correlation was not statistically significant. This study also demonstrated a positive correlation of T3 with fetal weight, length, and head circumference, which was found to be statistically significant. Additionally, no significant association was observed between TSH and fetal growth as per our study. In accordance with our results, Johns et al. [33], in their research study suggested that there occurs an inverse association of fetal growth with T4 and a positive association with T3. They further added that no significant association was observed for TSH and fetal growth [33]. Different researches have proposed varied results about the association between maternal thyroid levels and fetal growth. A study by Kilby showed serum concentrations of free T3 and free T4 levels were lower in fetuses affected by LBW, although serum TSH levels were not significantly different [34]. A study by Zhang et al. [35] proclaimed that increased value of TSH or T4 and a decreased value of T3 was found to be associated with LBW deliveries [35].

The most widely accepted hypothesis for thyroid disorders during pregnancy and reduced fetal weight is that due to defective expression of thyroid receptors, the action and functioning of thyroid hormones within trophoblast function is

altered, inhibiting the proper development of the placenta [34]. Since the placenta is the only source for getting nutrition and gaseous exchange between mother and fetus, the failure of the placenta in performing its regular and normal functions directly hampers the growth and development of a fetus resulting in LBW infants. Furthermore, increased binding of thyroid hormones to TRs within the nucleus of trophoblast cells lowers the TH available for transport to the fetus resulting in LBW deliveries [34]. Thus the assessment of expression of thyroid hormone receptors and transporters in both normal as well as LBW pregnancies may help in predicting the LBW deliveries. Studies using hypothyroid animal models have provided further evidence for the importance of THs in placental development [36-38]. Thus, it becomes extremely important that pregnant mothers should be kept under medical supervision and routine prenatal care to ensure healthy fetal growth and development.

## 5. CONCLUSION

This study indicates the association between maternal thyroid hormone levels (T3,T4,TSH) with fetal weight. We found that T3 hormone is significantly low while the T4 is significantly high in the maternal blood samples LBW in comparison to AGA. Further correlations studies validated that the maternal T4 hormone level is negatively correlated with the weight and length of the delivered fetus. T3 is positively correlated with fetal birth weight, length, and head circumference. This proves the hypothesis that thyroid dysfunction is associated with fetal development during gestational period.

## CONSENT

As per the inclusion criteria patients were recruited in the study after explaining about the research and written consent.

## ETHICAL APPROVAL

Ethical approval was taken before collecting of the samples from the concerned ethical committee.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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