

Effect of Oxidative Stress on Fetus Outcome in Hypothyroidism Associated Pregnancy in a Tertiary Care Hospital in Eastern Region of India

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Abstract

Introduction: Oxidative stress occurs due to the imbalance between reactive oxygen species generation & antioxidant defense which is more in pregnancy in comparison to normal population & it is also further augmented in hypothyroidism which is often detrimental for the fetus. We try to find the oxidative stress and its effect on mother and baby in the pregnant hypothyroid women.

Materials & Methods: we compared the total oxidative stress (TOS) by modified free oxygen radical test in 250 pregnant women (out of which 78 were hypothyroid & 172 euthyroid) compare the same in 250 non pregnant women from antenatal & G&O OPD of NRS Medical College, Kolkata. fT4 & TSH were estimated by ELISA method using standardized kit. Fetal outcome was measured in terms of birth asphyxia, neonatal hypothyroidism, low birth weight & early neonatal sepsis.

Result: Significantly higher levels of TOS ($p < 0.001$) has been found in hypothyroid pregnant population than euthyroid. One way ANOVA test done between nonpregnant, pregnant euthyroid & pregnant hypothyroid population, came statistically significant ($F=410.4$ & $p < 0.05$). posthoc ANOVA shows significant difference with each other between all the 3 groups. Significantly increased levels of neonatal hypothyroidism, birth asphyxia & low birth weight has been found with babies of hypothyroid mothers.

Discussion: oxidative stress has been proved here to be augmented in pregnancy which is further worsen in hypothyroidism causing poor fetal outcome.

Keywords: oxidative stress, hypothyroidism, pregnancy, birth asphyxia.

Introduction

The thyroid dysfunction is the second most common endocrinal disorder complicating pregnancy

throughout the world after diabetes.^[1] In pre-existent undiagnosed hypothyroid cases, pregnancy worsen the load of disease, even can turn fatal if remains untreated.^[2] Hypothyroidism in pregnancy affect

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intelligence quotient (IQ) and neuropsychological development of fetus adversely.^[3]

The term oxidative stress refers to the imbalance between generation of reactive oxygen species (ROS) and the ability of antioxidant defence mechanisms.^[4-5] They oxidize fats, proteins, and DNA and thus can cause a cytostatic effect on the cell, damage cell membranes, and activate the apoptotic pathway.^[6]

During pregnancy, increase in basic metabolism and "consumption" of oxygen and the use of fatty acids as the primary source of energy for most maternal retro-placental tissues lead to increased production of hydrogen peroxide^[7-8]. Studies have shown that there is increased oxidative stress in pregnant women with hypothyroidism but effect on fetal outcome is not established properly.^[9]

Objectives: So we design the study to compare the total oxidative stress in hypothyroid pregnant women along with its effect over the fetal outcome

Materials and Methods

The study was done at NRS Medical College & Hospital, Kolkata, West Bengal, in the Department of Biochemistry, from April 2020 to march 2021.

Ethical permission: permitted by institutional ethics committee of NRS medical college.

After exclusion a total of 250 pregnant women attending antenatal OPD were included as case

alongwith 250 age matched non pregnant women as control. Out 250 pregnant women 78 were detected to have hypothyroidism & the rest 172 were euthyroid.

Serum fT4 & TSH was measured by ELISA method using standardized kit for all the collected samples. Total oxidative stress (TOS) was measured from serum by Modified FORT test, standardized in our laboratory using N, N-dimethyl-p-phenylenediaminesulphate as chromogen^[19-20]. The test is based on the ability of transition metals, such as iron, to catalyse the breakdown of hydroperoxides into derivative radicals, which are then preferentially trapped by the buffered chromogen (N, N-dimethyl-p-phenylenediamine-sulphate) and develop a coloured product which can be colorimetrically measured.^[10-11] Standardization and assay of total oxidative stress (TOS): Standard curve was prepared using different dilutions of hydrogen peroxide (H₂O₂) (in milli-mole per liter) at 505nm

Fetal outcome were measured in terms of thyroid hormonal status of the baby at birth (fT4 & TSH), birth asphyxia (APGAR score) & birth weight.

Result

Results shows there is a significant increase in oxidative stress in pregnancy which is further aggravated by hypo-thyroid status. Fetus outcome along with fetal hypothyroid status is also directly correlated with maternal thyroid status.

Table 1: Demographic and Biochemical characteristics of the study

	Non pregnant (n=250) (mean± SD)	Pregnant (n=250)	T value	P value
TOS (mmol/L - equivalent of H ₂ O ₂)	31.09± 3.1	65.9± 2.9	134.5	<0.001
fT4 (ng/ dl)	0.97± 1.3	0.5± 1.6	3.33	<0.0013
TSH (mU/L)	2.7± 1.9	5.1±2.4	16.8	<0.001

Table 2: One way ANOVA & post hoc ANOVA test (Tukey HSD) for TOS in 3 groups (non pregnant, pregnant euthyroid & pregnant hypothyroid)

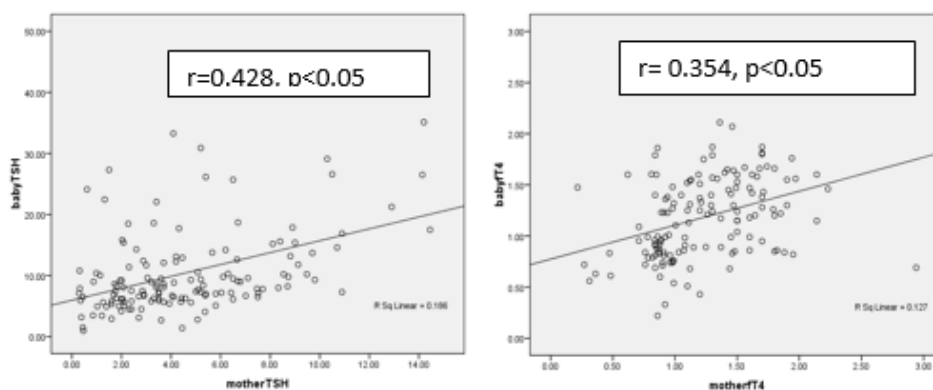
	Mean square	F value	significance
Between group	28923.3	410.04	0.000
Within group	3068.35		

Table 3: Post hoc (Tukey HSD) for TOS in 3 groups

Pairwise comparison	Mean values	Mean differences	Q value	P value
T1:T2	M1: 31.09 M2: 53.39	22.29	20.37	0.000
T1:T3	M1: 31.09 M3: 77.02	46.02	42.05	0.000
T2:T3	M2:53.39 M3:77.02	23.73	21.68	0.000

Table 4: The fetal outcomes were measured at the time of delivery of both euthyroid & hypothyroid mothers

	Hypothyroid mother	Euthyroid mother
Baby TSH (mU/L) (mean±SD)	14.13±8.18	9.3±6.14
Baby fT4 (nd/dl) (mean±SD)	1.08±0.37	1.17±0.31

**Fig 1: Correlation curves of thyroid status of mother & baby****Table 5: APGAR score at 5 minute of birth& lowbirth weight in hypothyroid & euthyroid mother**

	Hypothyroid mother	Euthyroid mother	Odds ratio	P value
APGAR score (<5 at 5 min)	42%	5%	14.25	<0.05
Birth weight (<2.5 kg)	38%	24%	2.37	<0.05

Discussion

In this study there is significantly increased level of TOS & TSH level in pregnant population than the non-pregnant. [table 1] similar finding has been found in the study of P. Santulli et al.^[12]

In thyroid dysfunction there is chance of more production of ROS and decreased glutathione can increase the oxidative stress also. ^[13-14]

Correlation of thyroid hormonal status of the mother and the baby shows statistically significant positive correlation between maternal and baby TSH levels with correlation coefficient (r value) is +0.428 and p value is <0.05. The fT4 levels of mothers and the babies were also significantly positively correlated with correlation coefficient (r value) is +0.354 and p value is <0.05.

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. [15]

The incidence of adverse fetal outcome was found to be statistically significant in hypothyroid state for the Low birth weight(<2.5 kg) [odd ratio 2.37, p value= 0.026]similar finding has been found in the study of Leuang AS et al^[16]&Low APGAR score [odd ratio 14.25, p value < 0.0001] Similar finding has been found in the study of La Franchi AS et al.^[17]

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) ^[18].Moreover, modified iodine metabolism can also has its effect in pregnant hypothyroid status.Studies done on pregnancy complicated with hypothyroidism have confirmed that the reactive oxygen species are working efficiently along with reducing the levels of oxidants, e.g., vitamin E or C. A significantly lower antioxidant effect of trolox—a substance derived from vitamin E on lipid peroxidation processes in the placenta of women suffering from hypothyroidism — has been proven. ^[19]This increased oxidative stress effect the mother and fetus outcome by damaging various organs.Oxidative stress causes abnormalities in the structure of DNA that can lead to early miscarriages, preeclampsia, fetal growth restriction, fetal abnormalities, and birth defects ^[20-21].

Summary: Our study has brought forth a baseline idea of increase oxidative stress in pregnancy which is further augmented in hypothyroidism. It also shows that if it is diagnosed late in pregnancy or remain undiagnosed causes grave prognosis to the baby.

Limitations: The sample size is not large enough. long term followup of the new born was not possible in the study.

Conflict of interest: There is no conflict of interest

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