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Maternal Thyroid Hormone Status and Feto-Maternal Outcomes in Preeclampsia and Normal Pregnancy During Third Trimester: A Comparative Observational Study.

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Abstract:
Background: *Changes in thyroid function in normal pregnancy are well – documented but in complicated pregnancy like preeclampsia, very little is known. Although pregnancy is usually associated with mild hypothyroidism, preeclamptic patients have higher incidence of hypothyroidism that might correlate with the severity of the condition. Maternal hypothyroidism is the most common disorder of thyroid function in pregnancy and is associated with fetal effects such as fetal loss, preterm birth, low birth weight, increased neonatal respiratory distress, low intelligence quotient (IQ) of off-springs and adverse maternal outcomes such as pregnancy induced hypertension, postpartum haemorrhage and placental abruption. Studies have shown evidences of hypothyroidism in preeclampsia necessitating thyroid function tests to be done in preeclampsia.*
Aims : *The present study was undertaken to evaluate the maternal thyroid hormone status and feto-maternal outcomes in preeclamptic women and compare to normotensive pregnant women. Therefore this study shows that there is a need to consider the thyroid hormones (serumT3, T4, TSH) in preeclampsia in its development & management and also to prevent its complications.*
Materials and Methods :
This comparative observational study was carried out in the Department of Obstetrics and Gynaecology at Bankura Sammilani Medical College and Hospital, Bankura, West Bengal, India. During the study period from 1st May 2019 to 31st October 2020; ***total 118 mothers,*** *among them* ***59 normotensive pregnant women*** *and* ***59 cases of preeclampsia*** *in third trimester of pregnancy were evaluated. After proper counseling and informed consent from each antenatal mother selected in the study population; detailed clinical history, clinical examination and necessary investigations were done. They were compared for serum levels of* ***total T3(TT3), total T4(TT4)*** *and* ***thyroid stimulating hormone (TSH)*** *and subsequently for feto-maternal outcomes. Data had been summarized as mean and standard deviation for numerical variables; count and percentage for categorical variables. The data was analyzed by SPSS software (version 27.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5 with the use of t-student, Chi-square, Independent sample T-test. p-value ≤ 0.05 was considered for statistically significant.*
Results: The mean TSH level and mean TT4 level *were significantly higher* ***(p<0.0001, p=0.005)*** *and* ***mean TT3 level*** *was significantly lower* ***(p=0.054)*** *in preeclamptic mothers compared with normotensive mothers (though TT3 and TT4 were within the normal range in both group). Oligohydramnios(mean AFI-less), preterm delivery(mean gestational age at birth-less), caesarean section rate were statistically higher* ***(p<0.0001, p=0.009, p<0.0001)*** *among preeclamptic mothers. Mean birth weight and Apgar score at 5 minutes were statistically lower* ***(p=0.0267, p=0.038)*** *among preeclamptic mothers.*
Conclusion: *In the present study a positive association was found between thyroid hypofunction and preeclampsia and it was found to be statistically significant. Hypothyroidism may be a modifiable risk factor for preeclampsia. With regards to the results of the present study, thyroid screening early in pregnancy may be helpful in predicting the occurrence of preeclampsia and timely thyroid hormone administration can reduce the maternal and perinatal morbidity and mortality associated with preeclampsia.*

Keywords: *Pregnancy, Preeclampsia, Thyroid hormone status, Total T3, Total T4, TSH, Hypothyroidism, Feto-maternal outcomes.*

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I. Introduction, Review of Literature, Aims & Objectives :

Pregnancy is a physiological process to supply adequate nutrition to the growing fetus. Many maternal physiological adjustments of different organ systems occur in pregnancy, which include circulatory, metabolic and hormonal changes **(1)**. During normal pregnancy, there is an increased thyroid demand and increased iodine uptake and synthesis of thyroid hormones. Thyroid hormone plays a role in placental development and is an important regulator of various metabolic and inflammatory processes. Changes in thyroid functions are well documented in normal pregnancy but the information about thyroid function in pregnancy complicated with preeclampsia is scanty.

Although pregnancy is usually associated with mild hypothyroidism, preeclamptic patients have higher incidence of hypothyroidism that might correlate with the severity of the condition**(2).** Maternal hypothyroidism is the most common disorder of thyroid function in pregnancy and is associated with fetal effects such as fetal loss, preterm birth, low birth weight, increased neonatal respiratory distress, low intelligence quotient (IQ) of off-springs and adverse maternal outcomes such as pregnancy induced hypertension, postpartum haemorrhage and placental abruption**(3).** Moreover hypothyroidism has been listed as one of the causes of high blood pressure in pregnancy i.e. the physiological changes in thyroid gland during pregnancy have been suggested as one of the pathophysiological causes of preeclampsia**(4)**.

The above incidence may justify screening for thyroid function during pregnancy **(1)**. Although there are limited number of studies on the levels of thyroid hormones in preeclampsia and it is suggested that there may be mutual influence between preeclampsia and thyroid function **(5)**.

Pregnancy is associated with profound modifications in the regulation of thyroid function. These changes are the result of the various factors like an increase of thyroid-binding globulin(TBG) due to elevated estrogens and human chorionic gonadotropin production from growing placenta which is leading to an increase in thyroxine (TT4) levels; increased renal losses of iodine due to increased glomerular filtration rate, modifications in the peripheral metabolism of maternal thyroid hormones, and modifications in iodine transfer of placenta**(6,7,8).**

Thyroid hormone production is regulated by the pituitary through the action of thyrotropin (thyroid-stimulating hormone, TSH). TSH comprises of two subunits and it has one alpha-subunit in common with luteinizing hormone, follicle stimulating hormone and human chorionic gonadotropin (hCG)**(9).** Human chorionic gonadotrophin hormone which is secreted by the placenta stimulates thyroid gland during pregnancy as there is structural similarity with thyrotropin. So cross-reactivity at the receptor stimulates thyroid hormone release and suppresses serum TSH levels. During the second trimester, serum hCG level decreases and increases serum TSH. During the 1st trimester, Tri-iodothyronine (TT3) and TT4 reach a concentration of 30-100% of pre-pregnancy levels. Changes in the free hormone levels are however controversial (**FIGURE 1.**).

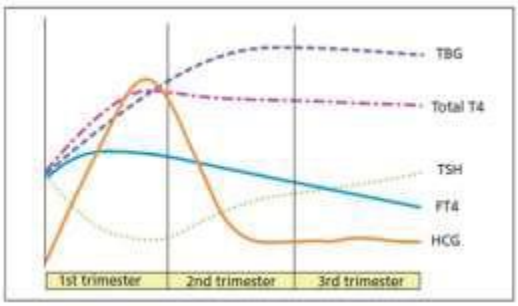

FIGURE 1 : Thyroid physiology during pregnancy.

Increasing evidence suggests that oxidative stress and altered endothelial cell function may have a role in preeclampsia (**10,11,12**). In preeclampsia, an increase in the superoxide anion, which may inactivate nitric oxide(NO), leading to reduced relaxation and increased vasoconstriction (**12,13**). In Preeclampsia, there is an increase in anti-angiogenic factors i.e. placental soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin (sEng) may contribute to endothelial dysfunction which in turn decreases nitric oxide production. This leads to decreased thyroid capillary flow which could lead to hypothyroidism which is reflected as high TSH level in preeclampsia**(14).**

Preeclampsia is a state of decreased estrogen, may be due to placental dysfunction. This decreased estrogen leads to decrease in synthesis of thyroid binding globulin(TBG). There is also excess loss of TBG and protein bound thyroid hormones due to proteinuria in preeclampsia. As thyroid binding globulin is decreased it might be the reason for lowering of serum T3 and T4 levels in preeclampsia along with growth retardation of the fetus **(15,16).**

As preeclampsia is multisystem disorder, the most affected organs are kidney, liver and brain. In liver and kidney peripheral conversion of the T4 to T3 occurs. Thus due to involvement of kidney and liver in preeclampsia no conversion of T4 to T3 occurs. This might be the main factor for decreased serum T3 concentration in preeclamptic patients**(17,18).**

The risks posed by preeclampsia to the mother include placental abruption, cerebrovascular accidents, postpartum hemorrhage, pulmonary edema etc. and those to the fetus include intrauterine growth restriction, intrauterine fetal demise, preterm birth (iatrogenic or spontaneous) and birth asphyxia**(19).**

The aim of the study is to examine the relation between maternal thyroid hormone function during later weeks of gestation with preeclampsia in a peripheral tertiary hospital in West Bengal, India where out of every 100 antenatal mothers attending per day (including both outdoor and indoor) , 5 of them are preeclamptic.

Specific Objectives:

1. To estimate and compare maternal serum total T3, total T4, TSH level among preeclamptic and normotensive pregnant women.
2. To find out the relation between maternal serum thyroid profile with preeclampsia if any.
3. To determine feto-maternal outcomes among both groups.

II. Materials And Methods:

Study design: It is a comparative observational study.

Study area: Study has been carried out in the Department of Obstetrics and Gynaecology, Bankura Sammilani Medical College and Hospital , Bankura, West Bengal, India.

Study period: approximately 1 year 6 months. (1 st May 2019 to 31 st October 2020)

Sample size and sampling design: sample size is calculated based on formula used comparing to proportions

$n = (Z\alpha + Z\beta)^2 (S_1^2 + S_2^2) / (M_1 - M_2)^2$

where $Z\alpha$=2.58 at 99% confidence interval(two tailed).

$Z\beta$=1.28 with 90% power of test.

S_1 and S_2 are the SD for the event of interest in both groups (here it is assumed to be serum T4).

M_1 and M_2 means of event of interest on both groups .

For the proposed study the event of interest is assumed to be serum TSH level.

As per previous records, the value of S_1 , S_2 and M_1 ,M_2 are 2.30,1.18,4.52,2.67.

Putting the value in to the formula, sample size has been estimated to be 54 for each arm.

Considering 10% non response rate, sample size will be= 59 for each arm.

So, sample size= 59 for each arm.

In this study, **59 preeclamptic mothers** were compared with **59 normotensive mothers**. **Total study population was 118 mothers.**

Data Collection:

As per records, out of every 100 antenatal mothers attending our hospital per day (including both outdoor and indoor), 5 of them were preeclamptic and 95 were normotensive.

It was determined that data collection was done twice in a week .The days for data collection was selected via simple random sampling using lottery method at the start of each week. One mother was selected from the preeclamptic group of 5 with the help of simple random sampling by using lottery method.

One mother was selected from normotensive group of 95 such by using random number tables.

Inclusion criteria :

Diagnosed mothers of preeclampsia (BP ≥140/90 mm of Hg on at least two occasions, six hours apart and proteinuria ;300 mg/L in 24hrs or ≥ 1+ dipstick after 20 weeks of gestational age in previously normotensive and non proteinuric mothers) and normotensive mothers in third trimester with singleton pregnancy and no history of thyroid disease before and through pregnancy.

Exclusion criteria :

1)The patients with history of thyroid disorders, chronic hypertension, renal disorders, liver disorder, cardiovascular diseases.

2) Any metabolic disorders before or during the pregnancy.

3) Gestational diabetes mellitus.

4) Any history of treatment with drugs such as L-thyroxin that may affect thyroid function.

5) known hypertensive -essential or secondary.

6) women in labour.

7) fetal anomalies.

8) women with IUFD.

Parameters Studied:

1.Obstetrics parameters:

- Gestational age at birth. Term pregnancy was assessed in two ways -from the first day of LMP and from USG scan in 1st trimester, if there was discrepancy of more than 7days between two measurements, gestational age was assessed from USG scan. Gestational age was expressed in weeks.
- Measurement of blood pressure.
- Urine for protein.
- Amniotic fluid index (AFI) was calculated from ultrasound scan at term.
- Mode of delivery.

2. Thyroid parameters:

- Maternal serum total T3, total T4 and TSH level were measured in preeclampsia mothers and normotensive mothers at or after 28 weeks of gestational age.

  ELISA kit was used for total T3, total T4 and TSH estimation.

  Normal reference range for serum total T3: 0.6 -1.85 ng/ml.

  Normal reference range for serum total T4: 5 - 12 µg/dl.

  Normal reference range for serum TSH: 0.3-3 µIU/ml in 3rd trimester of pregnancy.

3. Fetal parameters:

- Measurement of birth weight of the baby and Apgar score at 5 minutes.

Study Techniques and Statistical Analysis:

After proper counseling and informed consent from each antenatal mother selected in the study population; detailed clinical history, clinical examination and necessary investigations were done. They were compared for serum levels of total T3(TT3), total T4(TT4) and thyroid stimulating hormone (TSH) and subsequently for feto-maternal outcomes. Data had been summarized as mean and standard deviation for numerical variables; count and percentage for categorical variables. The data was analyzed by SPSS software (version 27.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5 with the use of t-student, Chi-square, Independent sample T-test. p-value ≤ 0.05 was considered for statistically significant.

III. Result & Discussion :

TABLE 1: COMPARISON OF THE MEAN LEVELS OF THYROID HORMONES IN THE STUDY POPULATION.

Thyroid Hormones	Preeclamptic mothers (n=59) Mean ±SD	Normotensive mothers(n=59) Mean±SD	p- value
Serum TT3(ng/ml)	0.8949±0.1195	0.9356±0.1079	0.054 (significant)
Serum TT4(µg/dl)	9.0559±0.6717	8.7458±0.4925	0.005(significant)
Serum TSH(µIU/ml)	4.9864±1.3222	1.6186±0.3679	<0.0001(significant)

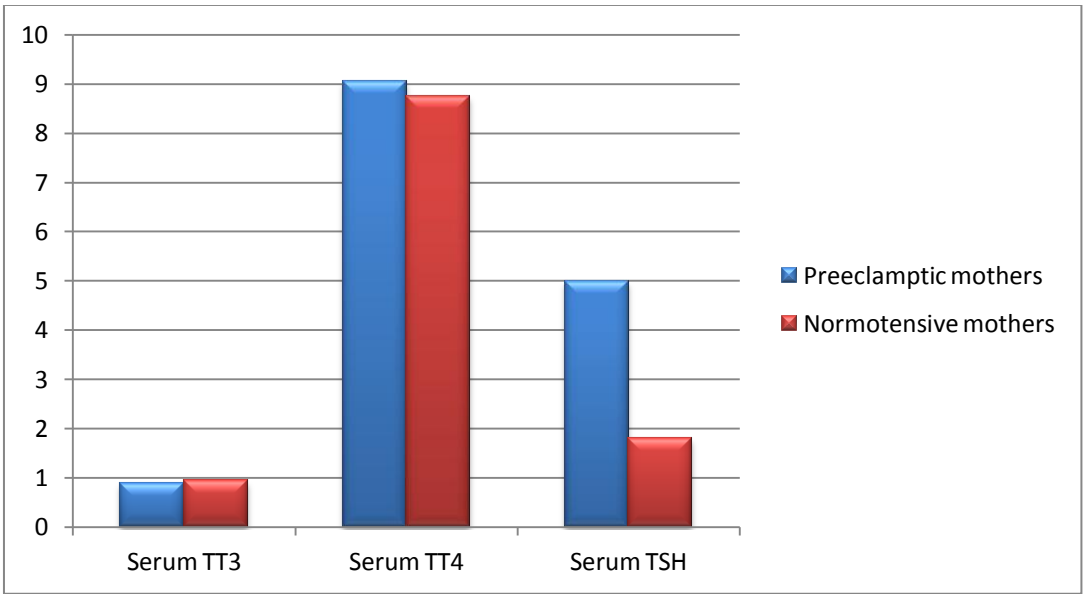

FIGURE 2: SHOWING COMPARISON OF THE MEAN LEVELS OF THYROID HORMONES IN THE STUDY POPULATION.

Preeclampsia is a multisystem disorder of unknown etiology unique to human pregnancy. It may be associated with hypothyroidism that carries a higher risk of adverse obstetric outcomes. A number of biochemical markers have been proposed to predict preeclampsia but with inconsistent reliability and poor

predictive value for routine use. Understanding the frequency of thyroid dysfunction in preeclampsia and its impact on feto-maternal outcomes may be helpful in predicting the occurrence and severity of preeclampsia.

In this study we found the mean TSH level and mean TT4 level were significantly higher **(p<0.0001, p=0.005)** and mean TT3 level was significantly lower **(p=0.054)** in preeclamptic mothers compared with normotensive mothers (though TT3 and TT4 were within the normal range in both group)**(Table1, Figure2)** that is in line with those found by Kharb S et al, Kumar CA et al, Roberts JM et al, Kadono M et al, Thangaratinam S et al **(10-14,17,18).** Thus, thyroid hormone level might be correlated with the occurrence of preeclampsia.

TABLE 2 : FETO-MATERNAL OUTCOMES IN THE STUDY POPULATION.

Parameters	Preeclamptic mothers (n=59)	Normotensive mothers(n=59)	p- value
1.Gestational age at birth (wks) :Mean ±SD	**37.0678±1.1427**	**39.0339±5.5646**	**0.009(significant)**
2.AFI:Mean±SD	**5.7458±0.9394**	**7.8305±1.2198**	**<0.0001(significant)**
3.Mode of delivery: **Vaginal delivery(n=82)** **LSCS(n=36)** **Total(n=118)**	 **27(32.93%)** **32(88.89%)** **59(50%)**	 **55(67.07%)** **4(11.11%)** **59(50%)**	**<0.0001(significant)**
4.Apgar score at 5 mins :Mean±SD	**7.2881±0.7668**	**7.5932±0.8120**	**0.038(significant)**
5.Birth weight (kg):Mean±SD	**2.6644±0.1436**	**2.7271±0.1596**	**0.0267(significant)**

In this study we noticed that oligohydramnios(mean AFI-less),preterm delivery(mean gestational age at birth-less),caesarean section rate were statistically higher **(p<0.0001, p=0.009, p<0.0001)** among preeclamptic mothers**(Table2, Figure3)**. Sravani M et al, also found higher incidence of preterm deliveries (10%) in patients with hypothyroidism complicated with hypertension**(20).** This may be secondary to the increased severity of preeclampsia associated with raised thyrotropin levels as found in the above-mentioned study and thus increasing the neonatal morbidity due to prematurity. The most frequent mode of delivery for women suffering from preeclampsia is elective caesarean section(88.89%)**(Figure4)**.

Mean birth weight and Apgar score at 5 minutes were statistically lower **(p=0.0267, p=0.038)** among preeclamptic mothers in the present study**(Table2, Figure3)**. Similarly, Sardana D et al, found a significant negative correlation between birth weight and TSH level (p<.001) in patients with preeclampsia**(21).** Kharb S et al, found that birth weight was significantly lower in preeclamptic women having high TSH levels as compared to euthyroid preeclampsia patients (p<.001) and commented that this might be explained by placental dysfunction in preeclamptic patients causing failure in estrogen production, leading to a decrease in TBG, total T3 and total T4 levels with simultaneous growth failure of the fetus**(22).** These findings showed the unfavourable outcomes of preeclampsia complicated with thyroid dysfunction. Sunanda K et al, also found that preeclamptic patients with raised TSH had increased perinatal mortality and morbidity in terms of abnormal Apgar score at birth and NICU admissions compared with euthyroid preeclamptic patients**(2).**

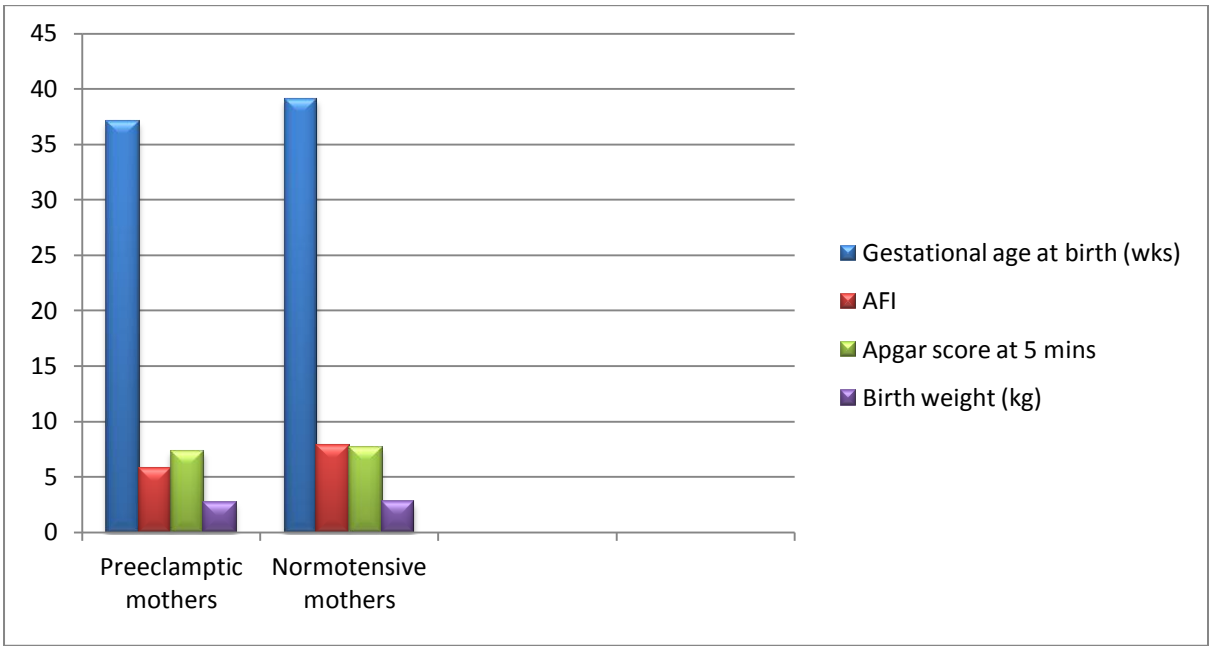

FIGURE 3: SHOWING FETO-MATERNAL OUTCOMES IN THE STUDY POPULATION.

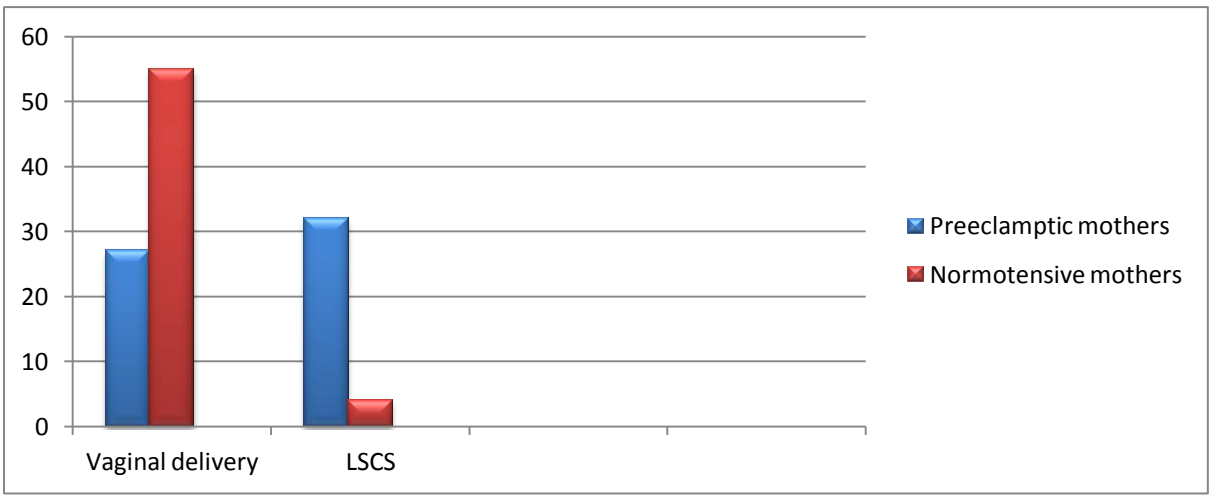

FIGURE 4: SHOWING MODE OF DELIVERY IN THE STUDY POPULATION.

IV. Conclusion:

In the present study a positive association was found between thyroid hypofunction and preeclampsia and it was found to be statistically significant. Hypothyroidism may be a modifiable risk factor for preeclampsia. With regards to the results of the present study, thyroid screening early in pregnancy may be helpful in predicting the occurrence of preeclampsia and timely thyroid hormone administration can reduce the maternal and perinatal morbidity and mortality associated with preeclampsia. However, to conclusively prove the hypothesis of our study, randomized controlled trials with larger sample size are required without any hospital bias.

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