Screening of hypothyroidism in antenatal mothers and its feto-maternal outcome in tertiary care centre

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Abstract

Introduction: Over the past several years it has been proved that maternal thyroid disorders influence the outcome of mother and fetus, during and also after pregnancy. The most frequent thyroid disorder in pregnancy is maternal hypothyroidism. Overt hypothyroidism (low serum free T_4 & high TSH level) complicates from 2 to 3 pregnancies per 1000 whereas subclinical hypothyroidism (high serum TSH but normal free T_4 level) is seen in 2.3% cases.[2] Endemic iodine deficiency accounts for most hypothyroidism in pregnant women worldwide whereas chronic autoimmune thyroiditis is the most common cause of hypothyroidism in iodine sufficient parts of the world.

Objectives: (1) To detect cases of overt or subclinical hypothyroidism in antenatal mothers in early weeks of gestation by screening methods, (2) To start early treatment in positive cases for reduction of deleterious effects on maternal and fetal outcome, (3) To study the maternal complications during antenatal, intranatal and postnatal period in hypothyroid mothers in comparison to euthyroid pregnancy. (4) To note any difference in incidence of low birth weight babies and early neonatal complications in hypothyroid women.

Material and Methods: A prospective clinical study was conducted department of Obstetrics and Gynaecology, Calcutta National Medical College and Hospital, Kolkata, Study population included all pregnant mothers attending antenatal clinic in Calcutta National Medical College and Hospital, Study period was one year (June 2012-May 2013), Sample size is 500 in number.

Results: Cases (hypothyroid, TSH>2.3 µU/ml) constituted 4.4% of the screening population, in which the incidence of overt hypothyroid (free T_4<0.8 ng/dl) was 0.4% and that of subclinical hypothyroid (fT_4 within normal range) was 4.4%. Controls (euthyroid, TSH<2.3 µU/ml) were 95.6% of the study population. Most of the mothers both in cases (71.4%) and controls (89.8%) delivered between 37-40 weeks. Incidences of preeclampsia (36.4% vs. 8.4%), preterm labour (27.3% vs. 6.5%) and intrauterine growth restriction (13.6 vs. 1.3%) were significantly high in hypothyroid mothers than euthyroid group. Spontaneous vaginal deliveries (with or without episiotomy) were more common in controls (77.8%) than cases (45%). Hypothyroid mothers had caesarean section significantly more (50%) than the euthyroid group (20.9%). Among puerperal complications; only post partum haemorrhage was significantly more common in cases than controls (18.2% vs. 5%). Incidence of low birth weight babies (birth weight<2.5kg) were significantly higher in the hypothyroid mothers than the euthyroid group (35% vs. 8.1%). Majority of newborns of cases (65%) had Apgar score 5-7 at 1minute. Significantly increased number of neonates born to hypothyroid mothers had Apgar score<5 at one minute than euthyroid women in this study.

Keywords: Hypothyroid, Pregnancy.

Introduction

Thyroid diseases are the commonest endocrine disorders affecting women of reproductive age group and hence constitute the most frequent endocrine disorder in pregnancy also. It has long been recognized that maternal thyroid hormone excess or deficiency can influence the outcome for mother and fetus at all stages of pregnancy as well as interfere with ovulation and fertility.[1,2]

Maternal hypothyroidism is the most common disorder of thyroid function in pregnancy. Endemic iodine deficiency accounts for most hypothyroidism in pregnant women worldwide whereas chronic autoimmune thyroiditis is the most common cause of hypothyroidism in iodine sufficient parts of the world.[3]

Overt hypothyroidism is associated with maternal complications such as miscarriages, anemia in pregnancy, preeclampsia, abruptio placentae, postpartum haemorrhage and the off springs of these mothers have frequent complications

like premature birth, low birth weight, increased neonatal respiratory distress, more admissions to the neonatal intensive care unit and reduced intellectual function.[4,5] A threefold risk of placental abruption and twofold risk of premature birth were reported in mothers with subclinical hypothyroidism.[6,7]

Materials and Methods

Study Area: Department of Obstetrics and Gynaecology, Calcutta National Medical College and Hospital, Kolkata.

Study Population: Pregnant mothers attending antenatal clinic in Calcutta National Medical College and Hospital.

Study Period: One year (June 2012-May 2013).

Sample Size: Approximately 500 in number.

Study Design: Prospective clinical study- a cohort study.

At 1st visit after obtaining informed consent from the mother detailed history was taken in a prescribed proforma with emphasis on duration of marriage, any history of infertility and its treatment, past or family history of thyroid disorders, previous pregnancy complications and signs & symptoms attributed to hypothyroidism during this pregnancy.

Physical examination was done to look for thyroid enlargement and to ascertain the pregnancy.

The following inclusion & exclusion criteria were used:

Inclusion Criteria:
Pregnant women who first attended antenatal clinic within 12 weeks of gestation.

Exclusion Criteria:

Pregnant women visiting first antenatal clinic at >12 weeks of gestation.

Women with known hypothyroidism prior to this pregnancy.

Women with acute or chronic illnesses i.e. hypertension, diabetes, tuberculosis etc.or on any drugs that may alter pregnancy outcome.

Specific investigations i.e. serum TSH & free T_4 were done by ultrasensitive fully automated ADVIA centaur, Bayer USA chemiluminescent system using tow site sandwich, chemiluminescent immunoassay.

These tests were done in random blood samples as the variation in TSH secretion due to circadian rhythm with a peak at 01.00hrs and nadir at 11.00hrs is small and does not influence the timing of blood sampling.

Pregnancy specific 1st trimester normal reference values[8]: TSH (0.03-2.3 µU/ml), Free T_4 (0.8-1.8ng/dl)

These reference ranges were used to classify the mothers into euthyroid (controls) and hypothyroid (cases). Women with elevated TSH (>2.3µU/ml) and free T_4 <0.8ng/dl were considered as overt hypothyroid and mothers with elevated TSH (>2.3µU/ml) but free T_4 within normal range were diagnosed as subclinical hypothyroid.

As soon as the diagnosis was made, treatment was started with levothyroxine. Serum TSH was monitored 6-8weekly in the hypothyroid mothers and levothyroxine dosage was adjusted to keep the TSH level below 2.5µU/ml in the 1st trimester and less than 3.0µU/ml in the rest of pregnancy.[9]

All the pregnant women under this study were followed up regularly in antenatal clinic and trend of weight gain, blood pressure recording, development of anemia, any episode of per vaginal bleeding, any other medical or obstetric problem were studied in them.

Thorough obstetrical examination was done in each visit to determine lie, presentation, position, viability of fetus and any other obstetrical complication. The findings were confirmed by Trans Abdominal Sonography (TAS).

Routine laboratory investigations including blood for haemoglobin%, fasting & postprandial sugar, urea, creatinine, HbsAg, VDRL, HIV 1 & 2, ABO & Rh grouping, thalassemia screening, urine examination- routine (protein, sugar) & microscopic were attributed to these mothers.

At the onset of labour, duration of pregnancy and mode of onset were studied. Progress of labour was monitored and any deviation from normal course was managed accordingly. Mode of delivery and complication was noted.

After delivery of baby, all possible methods of resuscitation were undertaken. Apgar scoring was done on 1 minute and 5 minute. Any obvious congenital anomaly was noted. Weight of newborn was measured and early neonatal complication was noted & treated accordingly.

In puerperium, mother was observed for post-partum haemorrhage, sepsis, failing lactation, pyrexia, wound infection and other complications.

Data Analysis Method

Data entry was done right after capture of relevant data for a given subject was complete. Statistical evaluation was done by appropriate statistical method using 'SPSS software' for WINDOWS.

Result and Analysis

The present study has been conducted on 500 pregnant women attending antenatal clinic in CNMCH, G & O Department, within 1st trimester of pregnancy (1st visit).

Screening tests (serum TSH and free T_4) were done in all of them and the mothers were then classified into hypothyroid (cases) and euthyroid (controls) based on test results.

Distribution of Study Population

Table 1: Distribution of cases and controls in study population

Category	No	Percentage (%)
Euthyroid (controls) (TSH<2.3µU/ml)	478	95.6
Hypothyroid (cases) (TSH>2.3µU/ml)	22	4.4
Total	500	100

This table shows that 22 cases (hypothyroid) were found in the study population whose TSH values were >2.3µU/ml. So the prevalence of hypothyroidism in the screening population was 4.4%. The rest (478) were found as euthyroid (controls).

Thyroid Status in Study Population

Distribution of study population according to thyroid status, Category is divided into Euthyroid (controls) (TSH<2.3 µU/ml) - 478(95.6%) out of which Overt (free T_4<0.8ng/dl)- 2, Hypothyroid (cases) (TSH>2.3 µU/ml) - 22(4.4%) out of which Subclinical (free T_4 0.8-1.8 ng/dl)- 20

So, depending upon the results of thyroid function tests (serum TSH and free T_4), the study population were divided into 3 categories:

Euthyroid – 478 mothers, which was the 95.6% of the study population.

Overt hypothyroid – 2 mothers, which constituted 0.4% of the screening population.

Subclinical hypothyroid – 20 mothers, which formed 4% of the study population.

Age Distribution of Study Population

Table 2: Age incidence of cases and controls

Age group (years)	Cases (n=22) (%)	Controls (n=478) (%)
18-20	1(4.5%)	69(14.4%)
21-25	10(45.5%)	175(36.6%)
26-30	9(40.9%)	172(36%)
31-35	2(9.1%)	62(13%)
Total	22(100%)	478(100%)

The tables show that there was no significant difference in the mean ages of cases and controls. In both cases and controls, maximum numbers of mothers were in the age group of 21-25 years followed by the age group of 25-30 years. The table shows that there was no significant difference in socio economic status of hypo and euthyroid mothers.

Most of the women included in this study belonged to lower socio-economic status and least no of mothers were in higher socio-economic status.

Most of the mothers in both case and control group were of Primi Gravida (59.1% vs. 53.1%). Least no of mothers had gravida >3 (4.5% in cases and 4% in controls).

Majority of the cases (95.5%) and controls (64%) had no living children because most of the women included in this study were of primi gravida (table 6).

But significantly more number of cases had no living issue than controls due to history of increased no of miscarriage or neonatal death in hypothyroid mothers.

Only 4.5% of cases had living children whereas 36% of controls had living issue within which 1.1% had >2 living children.

Gestational Age at Delivery:

Table 3: Duration of pregnancy in cases and controls at delivery

No. of children	Cases (n=21) (%)	Controls (n=473) (%)	Chi square test
<37 weeks	6(28.6%)	31(6.6%)	X^2=14.535
37-40 weeks	15(71.4%)	425(89.8%)	P=0.0007
>40 weeks	-	17(3.6%)	DF=2

(Abortion in cases and controls were excluded from the calculation of this table) (P value<0.05-statistically significant) The above table showed that significantly increased no of cases (28.6%) had preterm delivery (delivery before 37 completed weeks) than controls (6.6%).

Most of the mothers delivered between 37-40 weeks.

In 3.6% euthyroid mothers, pregnancy became postdated.

Complications during Pregnancy and Labour:

Table 4: Comparison of different antenatal complications in cases and controls

Complications	Cases (n=22) (%)	Controls (n=478) (%)	Relative risk and P value
Anaemia	7(31.8%)	140(29.3%)	RR-1.08 P value-0.7
Preeclampsia	8(36.4%)	40(8.4%)	RR-4.34 P value<0.0001
Eclampsia	1(4.5%)	3(0.6%)	RR-7.24 P value-0.08
APH	1(4.5%)	6(1.3%)	RR-3.62 P value-0.22
Diabetes	1(4.5%)	20(4.2%)	RR-1.09 P value-0.9
Preterm labour	6(27.3%)	31(6.5%)	RR-4.2 P value-0.0002
Abortion	1(4.5%)	5(1%)	RR-4.34

			P value-0.17
IUFD	1(4.5%)	3(0.6%)	RR-7.24 P value-0.08
Multifoetal pregnancy	1(4.5%)	5(1%)	RR-4.34 P value-0.17
Complications	Cases	Controls	Relative risk and p value
IUGR	3(13.6%)	6(1.3%)	RR-11.38 P value-0.003

(RR>1 and P value<0.05 = statistically significant)

The table shows different pregnancy complications in hypothyroid (cases) and euthyroid (controls) mothers. Chance of development of preeclampsia was more in hypothyroid mothers than euthyroid group, relative risk was 4.34 and it was statistically significant. Incidence of eclampsia, intrauterine foetal death, multifetal pregnancy and miscarriage were slightly more in hypothyroid cases, but not statistically significant.1 mother in hypothyroid group (4.5%) developed placental abruption. Incidence of antepartum haemorrhage was not significantly high in the cases.

There was no significant difference in incidence of anaemia and diabetes in the 2 groups.

There were more number of preterm deliveries, and intrauterine growth restriction (IUGR) in the cases, the relative risks were high (4.2 and 11.38 respectively) and statistically significant.

Mode of Delivery:

Table 5: Comparison of different modes of delivery in cases and controls

Mode of delivery	Cases (n=20) (%)	Controls (n=470) (%)	Relative risk and P value
Spontaneous Vaginal delivery	9 (45%)	366 (77.8%)	RR-0.58, P-0.03
Instrumental vaginal delivery	1(5%)	6 (1.3%)	RR-3.98, P-0.19
LSCS	10 (50%)	98 (20.9%)	RR-2.43, P-0.0002

(Abortion and IUFD in cases and controls were excluded from the calculation of this table) (RR>1 and P value<0.05 statistically significant)

The table thus shows Spontaneous vaginal deliveries (with or without episiotomy) were more common in the euthyroid group (77.8%) than hypothyroid mothers (45%). Hypothyroid mothers needed caesarean section significantly more (50%) than the euthyroid group (20.9%), relative risk being 2.43.

Instrumental vaginal delivery (forceps) was slightly more common in cases (5%) than controls (1.3%), but not statistically significant.2 assisted breech deliveries occurred in the control group.

Incidence of post-partum haemorrhage was more in hypothyroid mothers (18.2%) than the euthyroid group (5%), relative risk being 3.6, was statistically significant.

Puerperal pyrexia, wound infection, failing lactation- all these puerperal complications were slightly more prevalent in cases than controls (but not statistically significant).

Birth Weight Pattern of Babies

Table 6: Birth weight pattern of babies of cases and controls

Birth weight	Cases (n=20) (%)	Controls (n=470) (%)	Chi square test
<2.5 kg	7(35%)	38(8.1%)	X^2=17.034
2.5-3 kg	12(60%)	368(78.3%)	P=0.0002
>3 kg	1(5%)	64(13.6%)	DF=2

(Abortion and IUFD were excluded from the calculation in this table)
(P<0.05-statistically significant)

Incidence of low birth weight babies (birth weight<2.5kg) were significantly more in the hypothyroid mothers than the euthyroid group (35% vs. 8.1%).

In most of the mothers (both cases and controls), babies had birth weight between 2.5-3 kg.

5% of cases and 13.6% of controls had birth weight of babies>3kg.

5% of neonates born to hypothyroid mothers and 1.9% of babies of euthyroid mothers had Apgar score<5 at 1 minute.

Majority of babies of cases (65%) had Apgar score 5-7 at 1 minute.

Majority of newborns of controls (58.3%) had Apgar score 8-10 at 1 minute.

Early neonatal deaths among cases were higher (5%) than controls (2.1%), relative risk was 2.35 but it was not statistically significant.

Early neonatal morbid conditions were also more common in hypothyroid mothers (45%) than the euthyroid group (6.8%); relative risk was 6.9 being statistically significant.

4 euthyroid mothers had congenital anomalies-2 multiple, 1 cleft lip and cleft palate and 1 CTEV (congenital talipes equino varus), but no congenital anomaly in the babies of hypothyroid mothers found.

Discussion

There are many studies in support of universal screening for thyroid dysfunction during pregnancy, specifically subclinical hypothyroidism. While various aspects of hypothyroidism are analyzed in these studies, the main theme relating all is the support to screen all pregnant individuals, regardless of the presence of symptoms or risk factors. The most important aspects concerning hypothyroidism related to encourage screening are the adverse feto-maternal outcomes associated and long term sequelae of those outcomes.

Distribution of cases and controls according to thyroid status: (Tables 1, 2)

Depending upon the results of the thyroid function tests (serum TSH and fT_4); the study population was divided into:

Hypothyroid (cases) – constituted 4.4% of the study population (TSH>2.3µU/ml).

Euthyroid (controls) – were 95.6% of the screening population (TSH<2.3 µU/ml).

Hypothyroid women were further divided into 2 groups:

Overt hypothyroid – 0.4% of the study population (fT_4<0.8 ng/dl).

Subclinical hypothyroid – 4% of the screening population (fT_4 0.8-1.8 ng/dl).

In comparison to other studies (Abalovich et al in 2002,[9] Cleary-Goldman et al in 2008[10]), the incidence of overt hypothyroidism was almost same in this study (0.2-0.5% *vs.* 0.4%). But the incidence of subclinical hypothyroidism was slightly higher in this study (4%) compared to above mentioned studies (2.3-2.5%). Casey et al[6] reported an overall incidence of hypothyroidism to be 2.5 percent. But in an Indian population survey in 2013, the prevalence of subclinical hypothyroidism was much higher (8.02%) and female gender and older age were found to have significant association with hypothyroidism.[11]

The age distribution was comparable in both cases and controls. Most of the mothers (45.5% in cases and 36.6% in controls) were in the age group of 21-25 years. The mean age of cases at presentation was 26 ± 3.9, which was comparable to western studies 27 ± 6 (Bijay Vaidya et al.[12]), 29 ± 5 (Negro et al.[13]).

Socio-economic Status: Most of the mothers included in this study (59% in cases and 51% in controls) were of lower socio-economic status, as patients visiting this govt. tertiary hospital are mainly of lower economic status. Iodine deficiency disorders are main cause of hypothyroidism in Indian mothers of lower socio economic status.[14]

Obstetric History: Most women of this study both in case (59.1%) and control (53.1%) group were of primi gravida. But history of miscarriages and neonatal deaths were more common in hypothyroid mothers. So 95.5% of hypothyroid mothers in this study had no living children.

In a study by Ramachandra Rao V et al.[15] to know the prevalence of hypothyroidism in recurrent pregnancy loss in first trimester, the prevalence of hypothyroidism was 4.12%. Negro et al. in a recent study also mentioned that mild hypothyroidism had an increased risk of pregnancy loss (miscarriage & fetal death).[16] A different study in 2005 by Casey et al. found that subclinical hypothyroidism could mean an increased risk of placental abruption and of preterm delivery, both of which can result in later pregnancy loss.[6]

Gestational Age at Delivery: Most of the mothers in both case and control group delivered between 37 to 40 weeks. Incidence of preterm labour was significantly more in hypothyroid mothers than euthyroid women (28.6% vs. 6.6%). In 3.6% of controls, pregnancy became postdated whereas no postdated pregnancy noted in cases.

In literature, Glinoer et al found that preterm birth was associated with thyroid autoimmunity and subclinical hypothyroidism during pregnancy.[17] Another study reported that the incidence of subclinical hypothyroidism was high in cases who had very preterm delivery (between 32 weeks).[7] Comparing to these previous studies, the incidence of preterm birth was lower in the present study which shows the efficacy of screening and treatment of hypothyroidism in antenatal mothers in early weeks of gestation.

Complications during Pregnancy and Labour: The most important complications; incidences of which were significantly higher in hypothyroid mothers than controls, were preeclampsia (36.4% vs. 8.4%), preterm labour (27.3% vs. 6.5%) and intrauterine growth restriction (13.6 vs. 1.3%). Incidences of eclampsia, antepartum haemorrhage, multifoetal pregnancy, abortion and intrauterine death- all were 4.5% in hypothyroid cases and not significantly more than controls. Incidences of anaemia and diabetes were comparable in both groups.

Davis LE et al.[5] (1988) in a study of hypothyroidism complicating pregnancy found that maternal complications were more common in hypothyroid women and included anaemia(31%), preeclampsia(44%), placental abruption (19%), postpartum haemorrhage (19%). In comparison to other previous studies,[6,7] the complications were reduced in this study probably due to treatment of hypothyroid mothers with levothyroxine. Abalovich et al[9] demonstrated that adequate LT_4 replacement during pregnancy minimizes the risk of miscarriage and preterm delivery. In a study of Tan et al[18] pregnancy related complications of the mother and the fetus/neonate were compared between 419 women with treated hypothyroidism and 20,080 without hypothyroidism. The study concluded that treated hypothyroidism was not associated with an increased risk of maternal or neonatal

complications. Similar results were reported in a study by Matalon et al.[19]

Mode of delivery: Spontaneous vaginal deliveries (with or without episiotomy) were more common in the euthyroid group (77.8%) than hypothyroid mothers (45%). Hypothyroid mothers had caesarean section significantly more (50%) than the euthyroid group (20.9%), mostly due to either IUGR with oligohydramnios or fetal distress in labour. Incidence of instrumental vaginal delivery (forceps) was 5% in cases and 1.3% in controls.

In a study by Idris et al in 2005, it was found that the caesarean section rates were higher in the study cohort compared with the local rate (28.7% vs. 18%).[20] A separate study reported a markedly increased use of cesarean section because of fetal distress among women who were severely hypothyroid (56%) at their initial antenatal visit compared with women who were mildly hypothyroid or euthyroid (3%).[21]

Puerperal Complications: Incidence of postpartum haemorrhage was significantly more in hypothyroid mothers than euthyroid women in this study (18.2% vs. 5%); relative risk was 3.6. Puerperal pyrexia, wound infection and failing lactation were also noted in a small percentage of hypothyroid mothers (4.5% each).

Postpartum haemorrhage in hypothyroidism is produced both through uterus hypo tony and coagulation problems, with plaque adhesiveness problem. Various studies (Leung, Buckshee, and Davis) from the literatureindicate a percentage between 7% and 19%.[22]

Birth weight pattern and Apgar score of newborns: Incidence of low birth weight babies (birth weight<2.5kg) were significantly more in the hypothyroid mothers than the euthyroid group (35% vs. 8.1%). In most of the mothers, babies had birth weight between 2.5-3 kg (60% in cases and 78.3% in controls). 5% of cases and 13.6% of controls had birth weight of babies>3kg.

Majority of newborns of cases (65%) had Apgar score 5-7 at 1minute, while most of newborns of controls had Apgar score 8-10 at 1 minute. Significantly increased number of neonates born to hypothyroid mothers had Apgar score<5 at one minute than euthyroid women in this study.

In a study by Davis et al,[5] increased prevalence of fetal complications such as low birth weight (31%) and fetal death (12%) have been reported. Another study by Sharma Partha P[23] showed that most common cause of fetal morbidity was low birth weight (27.03%).

Neonatal mortality and morbidity including congenital anomalies:

Incidence of early neonatal deaths among cases was slightly higher (5%) than controls (2.1%). But neonatal morbid conditions were significantly more common in hypothyroid mothers (45%) than the euthyroid group (6.8%); relative risk was 6.9 and rate of admission of newborns of cases in neonatal intensive care unit was high. 4 babies born to control mothers had congenital anomalies but no congenital anomaly in the babies of hypothyroid mothers was found.

Casey et al[6] in 2005 reported that admission to the neonatal intensive care nursery and respiratory distress were twice as likely in infants delivered of women with subclinical hypothyroidism (RR 1.8). Fetal death rates were the same (5/1,000 births) in both groups, and the neonatal death rates, although higher in infants of women with subclinical hypothyroidism (5/1,000 compared with 2/1,000 live births), were not significantly different. There does not appear to be an increased risk of major congenital anomalies associated with hypothyroidism in literature.[24]

Conclusion

Therefore, it can be concluded from the present study that-

1. Treatment of thyroid dysfunction during pregnancy whether it be overt or subclinical has shown to be effective in reducing the amount and severity of deleterious pregnancy outcomes. Even when inadequate, treatment has proven to be more beneficial than no treatment.
2. So, this study supports universal screening of pregnant women for thyroid dysfunction by serum TSH and free T_4 values in early weeks of gestation to diagnose hypothyroid mothers. Without the diagnosis of a thyroid condition, the proper prevention and treatment steps cannot be implemented.
3. Though levothyroxine usage during pregnancy is cheap, cost effective and safe during pregnancy, the cost of screening and treatment in contrast to the cost of adverse pregnancy complications and potential of chronic developmental delays is one that must be analyzed and evaluated when deciding if a screening protocol should be implemented.
4. D. The notion of gestation age-specific reference ranges are of special interest concerning screening; otherwise there may be a significant amount of missed diagnoses of thyroid disorder, specifically that of subclinical hypothyroidism.
5. Additionally, the status of education regarding women's health specifically related to pregnancy regarding prenatal and early antenatal care needs to be furthermore evaluated and improved.

Conflict of Interest: None.

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