Screening of Subclinical Hypothyroidism in Antenatal Women and its Impact on Pregnancy Outcomes

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ABSTRACT

Objectives: To screen subclinical hypothyroid cases in antenatal checkups and to assess the impact of this condition on the fetomaternal outcome.

Study Design: Prospective cohort study.

Place and Duration of Study: Department of Gynecology and Obstetrics, Pakistan Naval Ship Shifa Hospital Karachi Pakistan, from Jun 2019 to May 2020.

***Methodology*:** During the study period, all singleton pregnant women with no comorbid, having booking visits during the first trimester of pregnancy were included. Three thousand four hundred fifty obstetric patients fulfilled the inclusion criteria. Their serum TSH and free T4 and T3 were sent along with routine antenatal investigations. Pregnancy specific first-trimester normal reference values of TSH (0.03-2.3µU/ml) and free T4 (0.8-1.8ng/dl) were used to classify pregnant women into euthyroid (controls) and overt and subclinical hypothyroid (cases). Comparison of antenatal complications (gestational diabetes, gestational hypertension, pre-eclampsia, and preterm labour), mode of delivery (vaginal delivery, cesarean section) and perinatal outcome (intrauterine growth restriction, intrauterine fetal death, low APGAR score at 5 min) was made among both the groups.

Results: Hypothyroid women had significantly increased risk of gestational hypertension (RR= 4.795% CI=2.902 to 7.773, p<0.0001), preeclampsia (RR=4.07, 95%CI=2.315 to 7.197, p<0.0001), preterm delivery (RR= 4.1, 95% CI=2.128 to 7.89, p<0.0001), cesarean section rate (RR=2.3611, 95% CI=1.7106 to 3.2591, p<0.0001) and risk of IUGR (RR=8.000, 95% CI= 1.869 to 34.227, p=0.005) as compared to euthyroid women.

Conclusion: Subclinical hypothyroidism is associated with gestational hypertension, pre-eclampsia, intrauterine growth restriction, preterm delivery and increased cesarean section rate.

Keywords: Outcome, Pregnancy, Subclinical hypothyroidism.

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INTRODUCTION

Thyroid disorder is the most typical endocrine disorder affecting women of reproductive age.[1] Excess or deficiency of thyroid hormone interferes with ovulation and fertility, and if the woman gets pregnant, it affects fetomaternal outcomes. The most common thyroid disorder seen in pregnancy is maternal hypothyroidism.[1]

Endemic iodine deficiency is the leading cause of hypothyroidism in pregnant women worldwide, whereas, in iodine insufficient parts of the world, chronic autoimmune thyroiditis is responsible for hypothyroidism.[2] Physiological changes during pregnancy increase the size of the thyroid gland.[3] Thyroid hormone production and iodine requirement both increase during pregnancy.[2] Women with iodine deficiency or with limited thyroid reserve develop hypothyroidism. Euthyroid status is important for both the mother and the fetus during pregnancy. The fetus is dependent on maternal thyroid hormones during the first trimester.[3] Impaired fetal neural development can occur with thyroxin deficiency at this stage. Maternal hypothyroidism can cause abortion, preterm birth and placental abruption.[4] However, clinical diagnosis is often missed due to pregnancy's hypermetabolic state, which causes nonspecific presentation of thyroid disorders. Serum TSH level plays a vital role in the evaluation of thyroid status.[5] Results of thyroid function tests of healthy pregnant women vary from those of healthy non-pregnant women due to physiological changes of pregnancy. Based on serum thyroidstimulating hormone (S.TSH) level, the diagnostic criteria of hypothyroidism during pregnancy have been changed. In the past, S.TSH value of 4.0-6.0 mIU/L was taken as normal. It is said that adverse fetomaternal outcome occurs if the first-trimester value of S.TSH is > 2.5m IU/L while the

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second and third-trimester value is >3m IU/L.[6] In the non-pregnant state, overt hypothyroidism in pregnancy is diagnosed based on increased serum TSH and decreased serum free thyroxin (FT4).[7] Subclinical hypothyroidism is diagnosed with increased TSH and normal thyroid hormone levels. Despite the well-known deleterious effects of overt thyroid dysfunction in women of reproductive age, the impact of subclinical hypothyroidism (SCH) on perinatal outcomes remains unclear. Before and during pregnancy, universal screening for thyroid dysfunction is controversial. American Association of Clinical Endocrinologists has recommended screening.[8] On the other side, the American College of Obstetricians and Gynecologists (ACOG) is against this.[9] At the same time, American Thyroid Association (ATA) recommends high-risk screening cases only.[3] However, Nazarpour *et al*. Say that >35% of pregnant patients with thyroid dysfunction will be overlooked if screening is done in high-risk cases only.[10]

Very few studies have been done about subclinical hypothyroidism among pregnant women in Pakistan. Moreover, the effects of subclinical hypothyroidism on maternal and fetal outcomes are largely unknown. That is why we analysed the thyroid function tests of pregnant women and detected cases of overt or subclinical hypothyroidism in antenatal mothers during early weeks of gestation by screening method. To reduce early treatment was started to reduce maternal and fetal adverse effects if any overt cases were found. We studied the maternal and fetal complications in subclinical hypothyroid ladies compared to euthyroid pregnancy.

Our study will help better understand the effect of subclinical hypothyroidism on gestation and fetal health. This will also aid in future research in our country.

METHODOLOGY

This prospective cohort study was done at the Obstetrics and Gynaecology Department of PNS Shifa Karachi Pakistan, from June 2019 to May 2020. PNS Shifa is a tertiary care referral hospital providing service to a large number of the army and civilian personnel. The Ethical Committee approved the study of the hospital (NO. ERC/2020/MED/32). Informed verbal and written consent was taken from all the participants, maintaining their confidentiality. Using the WHO sample size calculator, the Sample size was calculated. Taking the 4.4% prevalence of hypothyroidism in pregnant women,[11] a minimum sample size of 65 was calculated to provide the study 80% power in assessing the impact of subclinical hypothyroidism status on maternal and fetal outcomes. For recruitment, a non-probability, purposive sampling technique was used. Ladies were divided into two groups. One had subclinical hypothyroidism in Group-1, and others had normal, uncomplicated euthyroid pregnancy in Group-2.

Inclusion Criteria: Pregnant women who first attended antenatal clinics within 12 weeks of gestation were included.

Exclusion Criteria: Women having a first antenatal visit at > 12 weeks of gestation, multiple pregnancies, known thyroid disorder prior to pregnancy, a chronic medical disorder such as hypertension, diabetes, cirrhosis liver, or tuberculosis and bad obstetric history with a known cause were excluded.

A detailed history was taken. Physical examination was done to look for thyroid enlargement and to ascertain pregnancy. Specific investigations, i.e. serum TSH and free T4 and T3, were sent along with routine antenatal investigations such as blood for haemoglobin, random sugar level, HBsAg, Anti HCV, Blood group & Rhesus factor.

Pregnancy specific 1st trimester normal reference values are TSH (0.03-2.3μU/ml), free T4 (0.8-1.8 ng/dl).[11] This reference classified pregnant women into euthyroid (control) and subclinical hypothyroid (cases). Women with TSH ≤2.3μU/ml and free T4 >0.8 ng/dl were considered euthyroid. Women with elevated TSH (>2.3μU/ml) and free T4 <0.8 ng/dl were considered overt hypothyroid, while ladies with elevated TSH (>2.3μU/ml) and normal free T4 were diagnosed as subclinical hypothyroid. If any overt cause is found, treatment was started with levothyroxine. Serum TSH was monitored 6-8 weekly in the hypothyroid mother, and levothyroxine dosage was adjusted to keep TSH level below 2.5μU/ml in the first trimester and less than 3.0μU/ml in the rest of the pregnancy.[12]

All the studied pregnant women were followed up regularly in an antenatal clinic until delivery as per routine hospital protocol. The development of any medical or obstetric problems was also checked in them. The maternal outcomes compared between the study and control group were spontaneous abortion, gestational hypertension, pre-eclampsia, gestational diabetes mellitus and mode of delivery. The fetal out-

comes studied were intrauterine growth restriction, prematurity, fetal distress, low APGAR score at 5 minutes, NICU admission and intrauterine fetal death. The gestational age of pregnant women was calculated from the last menstrual period (LMP) and was confirmed with ultrasonography.

Blood pressure of 140/90 or more on two separate occasions after 20 weeks of gestation was taken as gestation hypertension. Pre-eclampsia was defined as gestational hypertension with proteinuria. Eclampsia was defined as tonic-clonic fits with increased blood pressure. Gestational diabetes mellitus (GDM) was defined as diabetes mellitus occurring during pregnancy. Delivery before 37 completed weeks of gestation was taken as preterm delivery. New borne weight <2,500g at term was considered a low birth weight.

Data was analyzed using statistical software SPSS version 19.0. For qualitative variables, frequency and percentage were calculated. For quantitative variables, mean and standard deviation were calculated. Differences in maternal and fetal outcomes variables were analyzed with the Pearson chi-square test. The *p*-value of ≤ 0.05 was considered significant.

RESULTS

During the study period, a total of 9526 patients had antenatal visits. Out of these, 6076 were excluded because of non-fulfilling inclusion criteria. Three thousand four hundred fifty fulfilled the inclusion criteria. Out of 3450 women, 158 women were diagnosed with subclinical hypothyroidism with a frequency of 4.58%, and 2(0.05%) women were diagnosed with overt hypothyroidism (158+2=160 cases). The mean age of women with subclinical hypo-thyroidism was slightly higher than the mean age of control (26.92 ± 3.9) years vs 25.96 ± 3.4years). Women with subclinical hypothyroidism had slightly higher BMI than control (25.2 ± 0.8 kg/m² vs 22.8 ± 0.9 kg/m²). Table–I showed the demographic characteristics of cases and control.

Table-I: Demographic characteristics.

Characteristics	Cases n=160 (100%)	Control n=160 (100%)
Age (Years)	26.92 ± 3.95	25.96 ± 3.49
Parity		
-Nulliiparous	63 (39.37%)	87 (54.37%)
-Multiparous	97 (60.62%)	73 (45.62%)
Body Mass Index at first visit (kg/m²)	25.2 ± 0.8	22.8 ± 0.9

Women with subclinical hypothyroidism had significantly increased risk of gestational hypertension (RR=4.7, 95% CI=2.902-7.773, *p*<0.0001), preeclampsia (RR=4.07, 95%CI=2.315-7.197, *p*<0.0001) and preterm delivery (RR= 4.1, 95% CI=2.128-7.89, *p*<0.001) as compared to control. Table-II showed the comparison of antenatal complications in cases and control.

Table-II: Comparison of antenatal complications in cases and control.

Complications	Cases n= 160 (100%)	Control n=160 (100%)	Relative Risk, 95% CI and *p*-value
Spontaneous Abortion	7 (4.3%)	2 (1.25%)	RR=3.5 95% CI=0.738 to 16.591 *p*=0.1146
Gestational Hypertension	76 (47.5%)	16 (10%)	RR=4.7 95% CI=2.902 to 7.773 *p*<0.0001
Preeclampsia	53 (33.125%)	13 (8.125%)	RR=4.07 95%CI=2.315 to 7.197 *p*<0.0001
Gestational Diabetes Mellitus	7 (4.37%)	7 (4.37%)	RR=1 95% CI=0.359 to 2.785 *p*=1.000
Preterm Labor	41 (25.6%)	10 (6.25%)	RR= 4.1 95% CI=2.128 to 7.89 *p*<0.0001

Women with subclinical hypothyroidism had a significantly high cesarean section rate (RR=2.3611, 95% CI=1.7106 to 3.2591, *p*<0.0001) compared to control. Table-III showed the comparison of mode of delivery in cases and control.

Table-III: Comparison of mode of delivery in cases and control.

Mode of Delivery	Cases n (%)	Control n (%)	Relative Risk, 95% CI and *p*-value
Vaginal Delivery	75 (46.87%)	124 (77.5%)	RR=0.6048 95% CI=0.5027 to 0.7277 *p*<0.0001
Lower Segment Cesarean Section	85 (53.125%)	36 (22.5%)	RR=2.3611 95% CI=1.7106 to 3.2591 *p*<0.0001

Table-IV: Comparison of fetal outcome in cases and control.

Fetal Variables	Cases n (%)	Control n (%)	Relative Risk, 95% CI and *p*-value
Intrauterine Growth Restriction	16 (10%)	2 (1.25%)	RR=8.000 95% CI=1.869 to 34.227 *p*=0.005
Intrauterine Fetal Death	1 (0.625%)	-	RR=3.00 95% CI=0.123 to 73.099 *p*=0.5001
Low APGAR Score at 5 Minute	3 (1.875%)	1 (0.625%)	RR=3.00 95% CI= 0.3154 to 28.5367 *p*=0.3391
Neonatal Intensive Care Unit dmission	7 (4.37%)	4 (2.5%)	RR= 1.75 95% CI= 0.5225 to 5.8615 *p*=0.3642

A significantly increased risk of IUGR was found in women with subclinical hypothyroidism compared to euthyroid (RR=8.000) 95% CI=1.869 to 34.227, *p*= 0.005). Table-IV showed the comparison of fetal outcomes in cases and control.

DISCUSSION

During pregnancy, thyroid-binding globulin increases under the influence of estrogen, and iodide decreases due to increased renal clearance and placental loss. This leads to thyroid abnormalities. Thyroid function depends upon nutritional intake, genetic predisposition and environmental factors. That is why thyroid dysfunction has a different prevalence in different populations. We found a 0.05% frequency of overt hypothyroidism and 4.58% of subclinical hypothyroidism.

In contrast, Roy *et al*, found a 0.4% incidence of overt hypothyroidism and 4% of subclinical hypothyroidism in pregnant ladies.[1] Another Indian study showed a 2.3-2.5% prevalence of subclinical hypothyroidism and 4.8-11% of overt hypothyroidism.[12] Kiran *et al*, studied cases of diagnosed hypothyroidism before conception and during the antenatal period. They found subclinical hypothyroidism in 37% of total hypothyroid pregnant ladies.[11] Asian subcontinent has a variable prevalence of 4.8-13.3%.[14,13] Ezzeddine *et al*, found a 17% prevalence of hypothyroidism in pregnant women of Lebanon.[15] At the same time, 2-10% of the western population have hypothyroidism.[16]

In our study, the age distribution was comparable in both cases 26.92 ± 3.95 years and controls, 25.96 ± 3.49 years. Roy and his colleagues,[1] observed similar findings. This was also comparable to western studies.[16]

We observed 63 (39.37%) cases and 87 (54.37%) controls were primiparas. Priyanka Roy,[1] observed similar findings. The miscarriage rate in the study and control group was the same (*p*=0.1146). Similar findings were observed by Hiriyur *et al*,[17] and Joshi *et al*.[18] As thyroid hormones have many effects on cardio-vascular physiology and blood pressure regulation, there is a high prevalence of gestational hypertension in hypothyroid women compared to euthyroid women. We observed 53 (33.125%) cases of pre-eclampsia in the study group compared to 13 (8.125%) cases in the control group. A similar finding was observed by studies done in China,[7] and India.[1] However, Hiriyur *et al*,[17] and Dima Ezzeddine,[15] observed no statical difference in preeclampsia in cases and controls.

In our study, the frequency of GDM in subclinical hypothyroid and euthyroid was the same (*p*=1.000). Roy *et al*, Ezzeddine *et al*, and Joshi *et al*,[1,15,18] observed similar findings. Sarojamma *et al*, reported a high incidence of gestational diabetes mellitus (GDM) in hypothyroid women, but this study was not case-control.[2]

Maternal thyroid hormone regulates trophoblastic proliferation and invasion during early placental development. Inadequate trophoblastic cell invasion may result in abnormal placentation, a risk factor for preterm delivery.[15] We observed that 41 (25.6%) cases had a preterm delivery, and 10 (6.25%) controls had preterm delivery. However, Hiriyur *et al*,[17] observed no significant difference in the number of preterm deliveries in hypothyroid and euthyroid women.

We observed a higher cesarean section rate in subclinical hypothyroid women (53.125%) compared to euthyroid women (22.5%). Roy *et al*, also observed a high cesarean section rate in hypothyroid women and an increased rate of spontaneous vaginal delivery in euthyroid women.[1] Nevertheless, Hiriyur *et al*,[17] and Joshi *et al*,[18] found a similar cesarean section rate in both cases and control. A study done in Agha Khan showed that ladies with preconception TSH >2.5 µIU /ml had significantly high cesarean section rate.[11] The study from China also showed that preconception TSH >2.5µIU/ml is associated with adverse pregnancy outcomes, including a high cesarean section rate.[7]

We observed that low birth weight babies (birth weight <2.5 kg) were significantly more in subclinical hypothyroid mothers (10%) than in the euthyroid group (1.25%). Similar findings were observed by Roy *et al*,[1]

We observed that newborns of subclinical hypothyroid women (1.875%) and euthyroid women (0.625%) had no significant difference in APGAR scores. Roy *et al*, observed majority of the newborn cases (65%) had an APGAR score of 5-7 at one minute, while most newborns in control had an APGAR score of 8-10 at one minute.[1] However, one study found no statistical difference in perinatal outcomes in both groups.[18]

The strength of this study was that it was a prospective study. We analyzed the relationship between subclinical hypothyroidism and pregnancy outcomes.

CONCLUSION

To conclude, subclinical hypothyroidism during pregnancy, mainly when detected in the first trimester, is associated with an increased hypertensive disorder, preterm delivery, cesarean section and IUGR. To improve pregnancy

outcomes, screening and treatment of thyroid disorders are important.

Conflict of Interest: None.

Author's Contribution

KR: Conception, main work, RA: Conception, analysis, NN:, AT:, AI:, BI:, SA: Facilitation.

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