5 A STUDY ON RELATION OF SUBCLINICAL HYPOTHYROIDISM DURING PREGNANCY WITH ITS OUTCOMES IN GUJARAT.

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ABSTRACT

INTRODUCTION: Pregnancy is a period that places great physiological stress on both the mother and the fetus. When pregnancy compounded by endocrine disorders such as hypothyroidism, the potential for maternal and fetal adverse outcomes can be immense. Screening for subclinical hypothyroidism is essential in all pregnant women, especially in the Indian context, as Indian women have increased risk of developing iodine deficiency during pregnancy. Hence, this study planned to evaluate the effect of subclinical hypothyroidism on pregnancy outcomes.

METHOD: It was a prospective analytical study. Sample size consisted of 73 pregnant women attending antenatal OPD. Thyroid profile (serum TSH, FT3 and FT4) was done during first visit. The results analyzed and SCH decided as per trimester specific cutoffs: TSH >2.5mIU/L in 1st trimester, >3mIU/L in 2nd trimester and >3.5mIU/L in 3rd trimester. Information regarding general characteristics of participants recorded. The participants followed up to assess the mode of delivery, maternal and fetal outcome and any associated co-morbidities. Women with SCH treated accordingly.

RESULTS: Seventy-three antenatal women underwent thyroid screening, of them 24.7% had subclinical hypothyroidism. Proportion of SCH women having age less than 25 years was 55.6% compared to 72.3% in euthyroid women. No significant difference observed between SCH and euthyroid groups for iodized salt consumption, type of diet and BMI ($p>0.05$). Compared with euthyroid status, SCH was associated with higher rates of High blood pressure (HBP) (27.8% vs 7.3%, $p=0.02$) and Low birth weight among babies (38.9% vs 14.5%, $p=0.03$). Proportion of Anaemia and Poor APGAR score was also high in SCH women compared to euthyroid. However, the significance was only marginally high. (Anaemia- 72.2% vs 45.5%, $p=0.049$; Poor APGAR score- 27.8% vs 9.1%, $p=0.045$).

CONCLUSION: Prevalence of subclinical hypothyroidism among pregnant women is fairly high among Indians. Pregnant women with SCH had unfavourable maternal and fetal outcomes specifically there is an increased risk of high blood pressure and low birth weight babies. Thus, routine maternal thyroid function testing is necessary to improve maternal and

perinatal outcomes.

KEY WORDS: Subclinical hypothyroidism, Pregnancy, Maternal outcome, Fetal outcome

INTRODUCTION:

Thyroid dysfunction is the second most frequent endocrine disease among reproductive-aged women.[1] Pregnancy is a period that places great physiological stress on both the mother and the fetus. If pregnancy compounded by endocrine disorders such as hypothyroidism, the potential for maternal and fetal adverse outcomes can be immense. Hypothyroidism during pregnancy is usually asymptomatic, especially when subclinical.

Hypothyroidism during pregnancy increases the risk of abortion, gestational hypertension, anemia, abruptio placenta and postpartum hemorrhage.[2-4]Untreated maternal hypothyroidism can lead to preterm birth, low birth weight, and respiratory distress in the neonate. Enough evidence has accumulated over the years about the role of thyroxin in normal development of the fetal brain. Neurological deficits in infants and juveniles, including low intelligence quotient scores, cognitive delay, and psychomotor development impairment, are the main complications induced by maternal hypothyroidism during pregnancy.[5-7]

The prevalence of hypothyroidism in pregnancy varies from 0.4% to 11% worldwide.[8] In India, prevalence rates of hypothyroidism during pregnancy ranging from 4.8% to 11% and SCH is as high as 13.5%.[2, 9-10]The rate of detection, especially in a developing country like India, has not kept pace with the magnitude of the problem. Since hypothyroidism can be easily treated, timely detection and treatment of the disorder could reduce the burden of adverse fetal and maternal outcomes, which are very commonly encountered. Present study designed to find out the prevalence and impact of subclinical hypothyroidism.

MATERIALS AND METHODS

Design: Hospital based prospective analytical study.

Study population: Study setting selected was antenatal OPD at tertiary care hospital. Every week, Monday and Thursday chosen to enroll the participants. On each day of antenatal OPD, every 10th woman coming to the antenatal OPD was enrolled for the study. In case of non-response or any other reason, next woman enrolled for study, provided she fulfill the inclusion criteria. Total 73 antenatal women enrolled for the study.

Study variables:

Information regarding general characteristics of participants was recorded. The participants also subjected for clinical examination and laboratory investigations which general and systemic examination, height and weight measurement, blood pressure measurement, hemoglobin estimation, thyroid function tests etc.

Assessment of thyroid function performed by measurement of TSH, FT3 and FT4 levels. European Thyroid Association Guidelines used to classify thyroid function during pregnancy. As per these guidelines, antenatal woman diagnosed as having subclinical

hypothyroidism (SCH) if TSH >2.5mIU/L in 1st trimester, >3mIU/L and >3.5mIU/L in 2nd trimester and 3rd trimester respectively provided normal free T3 and T4. If the TSH was >10.0 mIU/L regardless of the FT4 level, the woman diagnosed as having overt hypothyroidism.

Study participants followed up to assess the maternal outcomes, fetal outcomes and any associated co-morbidities. Women with SCH were treated accordingly and babies born to SCH mothers screened for congenital hypothyroidism.

Exclusion criteria

- Pre-existing thyroid disorders
- Patients presenting with symptoms of overt hypothyroidism
- Women with multiple pregnancies

Ethics statements

- Ethical clearance was obtained from institutional human ethics committee to conduct the study.
- Study was conducted according to world medical declaration of Helsinki.
- Informed consents obtained from all enrolled subjects prior to the study.
- Privacy of all subjects guaranteed.

Statistical analysis

The results for continuous variables expressed as mean +/- SD and for categorical variables as percentages. To compare the means and proportions, chi-square and t-test used with 5% level of significance.

OBSERVATION AND RESULTS

In present study, out of 73 women, 55 (75.3%) had TSH and fT4 values within the normal reference ranges in the trimester of testing and were considered to be euthyroid, whereas 18 (24.7%) had high TSH levels coupled with normal fT4 levels and were considered to have sub clinical hypothyroidism (SCH). [Table 1]

TABLE 1

Subclinical Hypothyroidism	Number	Percentage
Present	18	24.7
Absent	55	75.3
Total	73	100.0

Table 2 shows maternal general characteristics. Proportion of age less than 25 years found to be 55.6% in women with SCH, and 72.3% in euthyroid women. Difference was not statistically significant (p=0.17). However, on comparing the mean age between two groups, the difference was statistically significant (p=0.02).

Out of 18 SCH women, 15 (83.3%) regularly taking iodised salt in their diet, whereas among euthyroid women (n=55), 45 (81.8%) taking iodised salt. Difference was

insignificant. There was no association between Vegetarian/Non-vegetarian diet and SCH (p=0.74). Of the 18 SCH women, 07 (38.9%) had vegetarian diet whereas in euthyroid women 19 (34.5%) had vegetarian diet.

Among SCH women (n=18), 02 (11.1%) were overweight, whereas in euthyroid women (n=55), 03 (5.5%) were overwight. Mean BMI was also more in SCH women (21.1 kg/m^2) compared to euthyroid women (21.4 kg/m^2). However, there was no association found between BMI and SCH (p>0.05).

TABLE 2 General characteristics of study population

Variable		Sub clinical hypothyroidism(n=18)	Euthyroid(n=55)	p- value
Age (years)	**< 25**	10 (55.6)	40 (72.3)	
	>=25	08 (44.4)	15 (27.7)	0.1736
	Mean ± SD	24.3 ± 4.3	22.1 ± 3.2	0.0233
Iodized salt consumption	**Yes**	15 (83.3)	45 (81.8)	
	No	03 (16.7)	10 (18.2)	0.8840
Diet	**Vegetarian**	07 (38.9)	19 (34.5)	
	Non-Vegetarian	11 (61.1)	36 (65.5)	0.7384
BMI (kg/m^2)	**< 25**	16 (88.9)	52 (94.5)	
	>= 25	02 (11.1)	03 (5.5)	0.4095
	Mean ± SD	21.1 ± 2.7	21.4 ± 3.1	0.7146

Maternal and Fetal outcomes are compared in Table 3. Cut –off of 11 gm% was taken to determine anemic status in pregnant woman as per the WHO criteria. Significantly higher proportion of SCH women had anemia (72.2%) compared to euthyroid women (45.5%) [p< 0.05]. Mean Hb level was also lower in SCH women (9.7 gm%) compared to euthyroid women (10.0 gm%). Proportion of high blood pressure was significantly higher in women with SCH than in euthyroid women (27.8% vs 7.3%, p=0.02)

More low birth weight babies delivered in SCH group than euthyroid group (38.9% vs 14.5%). There was a strong association between SCH and LBW (p=0.03). However, difference of mean birth weight of babies was not significant (2.6 kg vs 2.7 kg, p=0.43)

Poor APGAR score (< 7) was more in SCH women (27.8%) than euthyroid women (9.1%) at 1 minute after delivery of baby. There was significant association between SCH in mother and

poor APGAR of baby (p<0.05)

Table 3 Maternal and Fetal outcomes

Variable		Sub clinical hypothyroidism(n=18)	Euthyroid (n=55)	p- value
Hb (gm%)	**<11**	13 (72.2)	25 (45.5)	0.0485
	11 or more	05 (27.8)	30 (54.4)	
	Mean ± SD	9.7 ± 1.3	10.0 ± 1.2	0.3701
High Blood Pressure (SBP>140 and/or DBP>90)	**Yes**	05 (27.8)	04 (7.3)	0.0216
	No	13 (72.2)	51 (92.7)	
Birth Weight (kg)	**< 2.5**	07 (38.9)	08 (14.5)	0.0265
	2.5 or more	11 (61.1)	47 (85.5)	
	Mean ± SD	2.6 ± 0.5	2.7 ± 0.3	0.4312
APGAR Score (at 1 minute)	**< 7**	05 (27.8)	05 (9.1)	0.0454
	7 or more	13 (72.2)	50 (90.9)	

DISCUSSION

Subclinical hypothyroidism (SCH) is the commonest form of hypothyroidism in pregnancy; it comprises of high thyroid-stimulating hormone (TSH) with thyroxin (T4) levels in normal or low normal range.

If the TSH is greater than 2.5 at any time during pregnancy, T4 levels should be checked to determine whether the hypothyroidism is overt or subclinical. If T4 is low, the diagnosis is overt hypothyroidism, which can impair the infant's neurocognitive development. There are also increased risks for premature birth, low birthweight, and miscarriage. Overt hypothyroidism must be treated. If TSH is high and the T4 is normal, the diagnosis is subclinical hypothyroidism. In this case, the next step is to check for antithyroid peroxidase antibodies. Women who are antibody positive should be treated. The effect of subclinical hypothyroidism on fetal neurocognitive development is not clear. But one large study showed lower IQ tests in the children of untreated women. Treatment is necessary when TSH is 10 or more, regardless of the T4 level. In addition, TSH should be monitored every 4 weeks during the first 20 weeks of gestation, then once again between 26 and 32 weeks.[11]

The current study performed to gain insight into the impacts of SCH on maternal and perinatal outcomes. In our study sample, 24.7% of pregnant women were diagnosed with SCH.

Forough et al[12] in the year 2012 conducted a study on 600 pregnant women in Iran and showed 11.3% prevalence of SCH. Sannaboraiah A et al[13] in their study of 200 antenatal

women found 9.5% prevalence of subclinical hypothyroidism. Dhanwalet al[14] in his study showed an SCH prevalence of 4.3% among the pregnant women in north India. Abalovichet al[15] in the year 2007 estimated subclinical hypothyroidism appears to occur in 2-3% of pregnancies. Gayathri et al[16] in the year 2007 analyzed the prevalence of SCH among 495 pregnant women attending Government hospitals in South India and showed that prevalence was 2.8% in her study. Subclinical hypothyroidism identified in 2.3% of the 25,756 antenatal women tested by Brian et al[17] in their study in Texas in year 2000. Liang-Miao Chen et al.[18] in their prospective study on 8012 pregnant women at Third Hospital Affiliated of Wenzhou Medical University, Zhejiang, China, reported that 371 (4.63%) had high TSH levels coupled with normal fT4 levels and were considered to have SCH.

There is a wide variation in prevalence of SCH during pregnancy in different studies with higher prevalence in current study.

Age and SCH In present study, SCH women had significantly higher mean age compared to euthyroid (p=0.02).Sannaboraiah A. et al[13] also observed positive correlation between subclinical hypothyroidism and higher maternal age (p=0.018). The study by Kalpeshet al[19] had similar results i.e., increased maternal age was associated with higher incidence of thyroid dysfunction. Higher mean age among SCH group may be due to that SCH shown to increase with age.

High blood pressure and SCH The results of our study suggest an association between subclinical hypothyroidism and increased blood pressure levels (27.8% vs 7.3%, p=0.02). Several mechanisms could explain why subclinical hypothyroidism has an adverse effect on blood pressure. Clinical hypothyroidism known to increase blood pressure levels, and the main underlying cause of this thought to be the degree of systemic vascular resistance present in patients with clinical hypothyroidism.[20] Luboshitzky et al found that the prevalence of hypertension in the subclinical hypothyroidism group was significantly higher than that in the normal control group, supporting our findings.[21] YunfeiCai et al[22] also found association between SCH and increased blood pressure in their meta-analysis of subclinical thyroid dysfunction patients. Similarly Liang-Miao Chen et al[18] also found significantly higher proportion of high blood pressure in women with SCH than in euthyroid women (3.504% vs. 1.819%, P= 0.02).However, Duanet al[23] and Walsh et al[24] in their cross-sectional study not found significant association between subclinical hypothyroidism and an increase in blood pressure.

HB and SCH Hypothyroidism can cause certain forms of anemia, which are usually macrocytic hypochromic, and/ or normocytic. In this study, proportion of anemia was significantly higher in SCH women compared to euthyroid women [72.2% vs 45.5%, p=0.048]. Akteret al[25] reported anemia among 17.2% of SCH patients whereas Sannaboraiah A et al[13] found 31.6% anemic patients among SCH group in their studies.

BMI and SCH In current study, overweight proportion was more in SCH women compared to euthyroid women. However, mean BMI was lower in SCH group than euthyroid group. There

was no association found between BMI and SCH (p=0.41). Karthicket al[26] found that patients with SCH represent lower BMI when compared to euthyroid control group.On the contrary, Knudsen et al[27] in the year 2005 found a positive association between BMI and serum TSH (P < 0.001). The study by Solanki et al[28] found that individuals with higher BMI had higher levels of serum TSH and that this trend continued from the underweight to the obese group (p <0.001). Hypothyroidism is associated with a moderate increase in weight gain, and it has been described recently that changes in TSH could be result of excess weight[29].

LBW and SCH Incidence of LBW in our study was found to be significantly higher in SCH group compared to euthyroid (38.9% vs 14.5%, p=0.03). In Akteret al[25] study also, low birth weight babies were common in patients with subclinical hypothyroidism (27.6%). In Liang et al[18] study, more LBW infants were delivered in the SCH group than in the euthyroid group (4.582% vs. 1.885%, P<0.001). Same association reported by Leung et al[30].These findings suggest that the increased rate of LBW in infants born to women with SCH is related to this thyroid disorder. Because LBW is reported risk factor for subnormal neurobehavioral performance and intellectual development[31-33]possible links between LBW in infants born to mothers with SCH and impaired psychological development have been proposed[34-35].

APGAR Score and SCH In present study, incidence of low APGAR Score at 1 minute was significantly higher among SCH women compared to euthyroid women (27.8% vs 9.1%, p=0.045).In a study by Sannaboraiah A et al[13], 9 out of 19 babies had APGAR score less than 7 (47.36%). Foroughet al[12] reported that subclinical hypothyroidism had a significant association with low Apgar score at first minute (P = 0.022). It increased the risk of low Apgar score by 2.15 times. Goelet al[36] also showed a higher risk of fetal distress in mothers with subclinical or clinical hypothyroidism. It seems that hypothyroidism exerts irreversible influences on the placenta and fetus during pregnancy and decreases the fetal ability to tolerate stress and therefore, neonates present with low Apgar scores at birth[37]. **Limitation of the study**Thyroid peroxidase antibodies (TPO antibodies) was not determined.

CONCLUSION AND SUMMARY

The major finding of this study was that SCH, a relatively common disorder in pregnant women, has pronounced effects on maternal and fetal outcomes. Specifically, SCH can lead to HBP in mothers, and higher incidences of LBW in infants. If the condition detected early, it is easy to treat, with very little detriment to the mother and the fetus. Thyroxine replacement in pregnant women suffering from overt or SCH does prevent obstetric and fetal complications and shows no harmful effects of thyroxine therapy. However, without a matched untreated control group, we cannot conclude that all pregnant women with SCH should be treated with thyroxine.

Therefore, until studies are done to demonstrate that thyroxine supplementation will obviate any of these maternal and fetal morbidities, widespread serum TSH screening and

treatment of women with subclinical hypothyroidism during pregnancy is unjustified.

REFERENCES

1. Rashid M, Rashid M H. Obstetric management of thyroid disease. ObstetGynecolSurv. 2007; 62: 680–688
2. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid. 2002; 12: 63–6
3. E Van den Boogaard, R Vissenberg, J A Land et al. Significance of subclinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Human Reproduction Update. 2011; 17: 605–619
4. T Mannisto, P Mendola, J Grewal, Y Xie, Z Chen, S K Laughon. Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. Journal of Clinical Endocrinology and Metabolism. 2013; 98(7): 2725–2733
5. Pop V J, Kuijpens J L, van Baar A L, Verkerk G, Van Son M M, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. ClinEndocrinol (Oxf). 1999; 50: 149–155
6. Haddow J E, Palomaki G E, Allan W C, Williams J R, Knight G J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999; 341: 549–555
7. Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forns J, et al. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. Epidemiology. 2013; 24: 150–157
8. P E Patton, M H Samuels, R Trinidad, and A B Caughey. Controversies in the management of hypothyroidism during pregnancy. Obstetrical and Gynecological Survey. 2014; 69(6): 346–358
9. Lazarus J H. Screening for thyroid dysfunction in pregnancy: is it worthwhile? J Thyroid Res. 2011; 3: 97-112
10. Garber J R, Cobin R H, Gharib H, Hennessey J V, Klein I, Mechanick J I, et al. Clinical practice guidelines for hypothyroidism in adults: co-sponsored by American Association of Clinical Endocrinologists and the American Thyroid Association. EndocrPract. 2012; 18(6): 988-1028
11. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011; 21: e10811125
12. Saki F, Dabbaghmanesh M H, Ghaemi SZ, Forouhari S, Omrani GR, Bakhshayeshkaram M. Thyroid function in pregnancy and its influences on maternal and fetal outcomes. Int J EndocrinolMetab. 2014; 12(4): e19378
13. Sannaboraiah A, Upadhyaya R, Garag S, Krishnappa S. Subclinical hypothyroidism in pregnancy and outcomes. Int J ReprodContraceptObstet Gynecol. 2017; 6(4): 1-7
14. Dhanwal D K, Prasad S, Agarwal A K, Dixit V, Banerjee A K. High prevalence of subclinical

hypothyroidism during first trimester of pregnancy in North India. Indian J EndocrinolMetab. 2013; 17(2): 281-4
15. Abalovich M, Amino N, Barbour L A, Cobin R H, De Groot L J, Glinoer D. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J ClinEndocrinolMetab. 2007; 92(8): S1-47
16. Gayathri R, Lavanya S, Raghavan K. Subclinical hypothyroidism and autoimmune thyroiditis in pregnancy- a study in South Indian subjects. J Assoc Physicians India. 2009; 57: 691-3
17. Brian M Casey, Jodi S Dashe, C Edward Wells, Donald D McIntire, William Byrd, Kenneth J Leveno et al. Subclinical Hypothyroidism and Pregnancy Outcomes. The American College of Obstetricians and Gynecologists. 2005; 105(2): 239-45
18. Liang-Miao Chen, Wen-Jun Du, Jie Dai, Qian Zhang, Guang-Xin Si, Hong Yang, et al. Effects of Subclinical Hypothyroidism on Maternal and Perinatal Outcomes during Pregnancy: A Single-Center Cohort Study of a Chinese Population. PLOS ONE. 2014; 9(10): e109364
19. Kalpesh K, Alpesh P, Harshid L. High prevalence of thyroid dysfunction among pregnant women in Ahmedabad City, Gujarat, India. Int J Adv Res. 2015; 3(8): 676-82
20. Ojamaa K, Klemperer J D, Klein I. Acute effects of thyroid hormone on vascular smooth muscle. Thyroid 1996; 6: 505–512
21. Luboshitzky R, Aviv A, Herer P, Lavie L. Risk factors for cardiovascular disease in women with subclinical hypothyroidism. Thyroid 2002; 12: 421–425
22. YunfeiCai, YongkuiRen, Jingpu Shi. Blood pressure levels in patients with subclinical thyroid dysfunction: a meta-analysis of cross-sectional data. The Japanese Society of Hypertension. Hypertension Research. 2011; 34: 1098–1105
23. Duan Y, Peng W, Wang X, Tang W, Liu X, Xu S, Mao X, Feng S, Feng Y, Qin Y, Xu K, Liu C. Community-based study of the association of subclinical thyroid dysfunction with blood pressure. Endocrine. 2009; 35: 136–142
24. Walsh J P, Bremner A P, Bulsara M K, O'Leary P, Leedman P J, Feddema P, Michelangeli V. Subclinical thyroid dysfunction and blood pressure: a community-based study. ClinEndocrinol (Oxf). 2006; 65: 486–491
25. Akter S N, Tarannum R, Kabir M S. Pregnancy in overt and subclinical hypothyroidism and its feto-maternal outcome. J Med Today. 2013; 25:02
26. Karthick N, Dillara K, Poornima K N, Subhasini A S. Dyslipidaemic changes in women with subclinical hypothyroidism. J ClinDiagn Res 2013; 7(10): 2122-5
27. Knudsen N, Laurberg P, Lone B R, Bülow I, Perrild H, Ovesen L, et al. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J ClinEndocrinolMetab. 2013; 90(7): 4019-24
28. Solanki A, Bansal S, Jindal S, Saxena V, Shukla U S. Relationship of serum thyroid stimulating hormone with body mass index in healthy adults. Indian J EndocrinolMetab. 2013; 17(Suppl1): S167-S9

29. Sanyal D, Raychaudhuri M. Hypothyroidism and obesity: An intriguing link. Indian J EndocrinolMetab. 2016; 20(4): 554-7
30. Leung A S, Millar L K, Koonings P P, Montoro M, Mestman J H. Perinatal outcome in hypothyroid pregnancies. Obstet Gynecol. 1993. 81:349–353
31. Lipper E, Lee K, Gartner L M, Grellong B. Determinants of neurobehavioral outcome in low-birth-weights infants. Pediatrics. 1981; 67: 502–505
32. Leitner Y, Fattal-Valevski A, Geva R, Eshel R, Toledano-Alhadef H, et al. Neurodevelopmental outcome of children with intrauterine growth retardation: a longitudinal, 10-year prospective study. J Child Neurol. 2007; 22: 580– 587
33. Fattal-Valevski A, Leitner Y, Kutai M, Tal-Posener E, Tomer A, et al. Neurodevelopmental outcome in children with intrauterine growth retardation: a 3-year follow-up. J Child Neurol. 1999; 14: 724–727
34. Haddow J E, Palomaki G E, Allan W C, Williams J R, Knight G J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999; 341: 549–555
35. Idris I, Srinivasan R, Simm A. Maternal hypothyroidism in early and late gestation: effects on neonatal and obstetric outcome. ClinEndocrinol (Oxf). 2005; 63: 560–565
36. Goel P, Radotra A, Devi K, Malhotra S, Aggarwal A, Huria A. Mater¬nal and perinatal outcome in pregnancy with hypothyroidism. Indian J Med Sci. 2005; 59(3): 116–7
37. Mannisto T, Vaarasmaki M, Pouta A, Hartikainen A L, Ruokonen A, Surcel H M, et al. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective popula¬tion-based cohort study. J ClinEndocrinolMetab. 2009; 94(3): 772–9