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Observational Study of Subclinical Hypothyroidism in Pregnancy

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ABSTRACT

Introduction: *Maternal thyroid dysfunction is the second common endocrine disorder during pregnancy. Prevalence of subclinical hypothyroidism during pregnancy is increasing. It is associated with adverse maternal and foetal outcomes like pre-eclampsia, GDM, preterm, IUGR and miscarriage, anaemia, IUD.*

Objective: *To study the prevalence of Subclinical hypothyroidism during pregnancy and its relation with adverse maternal and foetal outcomes.*

Methods and materials: *It was an observational study undertaken at RRMCH from May-2013 to Feb 2014. Pregnant women were screened for thyroid dysfunction irrespective of gestational age. Women with raised Thyroid stimulating Hormone (TSH) were included in the study. Pregnancy outcome of women with raised TSH was compared with euthyroid pregnant women.*

Results: *Study group included 1663 pregnant women. Among them 168 women had hypothyroidism, women with subclinical and overt hypothyroidism were 156 and 12 respectively. Prevalence of hypothyroidism in this study was 10.1%, Subclinical Hypothyroidism and Overt hypothyroidism was 9.3% and 0.72% respectively. Overall prevalence of autoimmunity was 19.04% (n=32) in women with hypothyroidism. Prevalence of autoimmunity in SCH and OH was 17.9% (n=28) and 33.3% (n=4) respectively. In women with SCH 81.4% developed complications like Pre-eclampsia (21.8%), GDM (6.4%), Preterm labor (7.1%) and IUGR (7.7%) anemia (5.8%) compared to euthyroid women (p value <0.001).*

Conclusions: *Increasing prevalence of Subclinical Hypothyroidism during pregnancy and its association with adverse maternal and foetal outcome makes it a high risk factor. Subclinical hypothyroidism is like the bottom of the iceberg, hence prompt screening for thyroid dysfunction and early initiation of treatment can prevent adverse maternal and fetal morbidity.*

Keywords: *Subclinical Hypothyroidism, overt hypothyroidism, Pre-eclampsia, GDM, Preterm, IUGR*

INTRODUCTION

Thyroid dysfunction is the second common endocrine disorder in reproductive age women[1].The prevalence of thyroid dysfunction during pregnancy is estimated to be 2-5%[2].Thyroid autoantibodies and iodine deficiency are the etiological factors for hypothyroidism. Autoantibodies are found in 10-20% of women of reproductive age[7]. Prevalence of hypothyroidism in India ranges from 6.47%-14.3%[4]. During pregnancy incidence of Subclinical hypothyroidism ranges from 2-7%[18]. Subclinical Hypothyroidism is associated with maternal and foetal complications like pre-eclampsia, GDM, anaemia, IUGR, SGA, IUD. In view of increasing prevalence of Subclinical Hypothyroidism and its association with maternal and foetal complications this study was conducted.

Physiological changes of Thyroid during Pregnancy

Pregnancy has a significant effect on maternal thyroid physiology. Beta-HCG has a thyrotrophic activity and shares 85% homology with beta subunit of TSH. As a result of this TSH level decreases in early pregnancy in comparison to non-pregnant women[5,6]. Oestrogen mediated increase in thyroid binding globulin levels causes increase in Total T3 and T4 levels by 30-40%, this alters the equilibrium between bound and free thyroxine causing decrease in FT4 levels leading to rise in TSH level. Iodine is an important substrate for Thyroxine synthesis. During pregnancy there is increased demand for iodine. But the increased renal clearance of iodine during pregnancy leads to its reduced bio-availability[30]. Deficiency of iodine causes rise in TSH. Foetus is dependent on the mother for production of thyroid hormone for 10-12 weeks of pregnancy. Foetal thyroid begins functioning by the end of first trimester, however foetus is dependent on maternal iodine intake. Thyroid hormones are very essential for foetal brain development. Maintaining Thyroid homeostasis is essential for maternal and foetal wellbeing[5, 6].

Diagnosing thyroid dysfunction during pregnancy is complicated due to the impact of pregnancy on thyroid homeostasis that makes interpretation of thyroid function difficult. Symptoms of hypothyroidism can be masked by hyper metabolic state of pregnancy. Hence use of trimester specific and assay specific TSH is recommended. In the first trimester of pregnancy TSH value $\leq$ 2.5mIU/l and in second and third trimester $\leq$3mIU /l[6, 7, 8] are considered normal.

Overt hypothyroidism (OH) is defined as an increase in serum TSH >10mIU/l with low free T3 and T4 levels. Subclinical hypothyroidism (SCH) is

defined as serum TSH >2.5mIU in first trimester, >3mIU in second and third trimester with normal free T3 and T4 levels[19].

OBJECTIVES

- To study the prevalence of subclinical hypothyroidism in pregnant women.
- To study the effect of subclinical hypothyroidism on maternal and foetal outcome.

METHODS AND MATERIALS

It was an observational study conducted at RRMCH, over a period of ten months. Study group included pregnant women attending antenatal clinic at RRMCH from May-13 to Feb-14.They were subjected to thyroid screening irrespective of gestational age.

Women with raised TSH were included in the study group. Women with raised TSH were screened for anti TPO antibodies and free T3 and free T4. Pregnant women with raised TSH (TSH>2.5mIU in first trimester,>3mIU in second and third trimester) and normal free T3 and T4 were diagnosed as subclinical hypothyroidism. Pregnant women with TSH > 10mIU and low free T3 and T4 were diagnosed as Overt hypothyroidism. Levothyroxine treatment history of the patient was collected. Pregnancy outcome of women with Subclinical Hypothyroidism and Overt Hypothyroidism was compared with euthyroid pregnant women.

Women with other autoimmune disorders, chronic hypertension, and overt diabetics were excluded from the study. TSH was done by using ultra-sensitive sandwich chemiluminescent immunoassay. T3 and T4 was done by competitive chemiluminescent immunoassay. Anti TPO antibodies was done using fully automated chemiluminescent immunoassay.

Trimester specific TSH values as per ATA 2011 and ES 2012 were taken into consideration. First trimester 0.1-2.5mIU, second trimester 0.2-3mIU and third trimester 0.3-3mIU were considered normal reference range[26]. The study was approved by ethical committee of RRMCH.

STATISTICAL METHODS

Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements were represented on Mean ± SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5 % level of significance. Chi-square/ Fisher Exact test were used to find the significance of study parameters on categorical scale between two or more groups.

RESULTS

A total of one thousand six hundred sixty three (1663) pregnant women were included in the study. Hypothyroidism was detected in One hundred and sixty eight (168) women. Pregnant women with Subclinical Hypothyroidism (SCH) were 156. Overt hypothyroidism (OH) was detected in 12 women. Prevalence of hypothyroidism in this study was 10.1%. Prevalence of Subclinical Hypothyroidism and Overt hypothyroidism was 9.3% and 0.72% respectively. Overall prevalence of autoimmunity was 19.04% (n=32) in women with hypothyroidism. Women with SCH and OH had 17.9% (n=28) and 33.3% (n=4) prevalence of autoimmunity.

Table 1 shows maternal demographic variables. Most women in the study group belonged to 20-30yrs age group (93%). Women in the study were primigravida (56%). Most of them were overweight 23-25 kg/m^2 (45%).Around 65% women were detected to have hypothyroidism at 17-20 weeks of gestation.

Table 2 shows the maternal complications in women with subclinical and overt hypothyroidism. Women with overt hypothyroidism had higher incidence of preeclampsia, 41.7% women with overt hypothyroidism had preeclampsia in comparison to 21.8% of women with subclinical hypothyroidism with a significant pvalue of <0.001. Incidence of GDM was 16.7% in women with overt hypothyroidism in comparison to 6.4% in women with SCH with a significant p value <0.001. Incidence of oligohydramnios was same in both groups 8.3% with a significant p value. Polyhydramnios was present in 1.3% of women with SCH. Women with overt hypothyroidism had higher incidence of anemia 16.7% in comparison to 5.8% of women with SCH. Women with SCH had 5.1% incidence of breech presentation with a significant p value of 0.01.

Table 3 shows fetal complications in women with overt and subclinical hypothyroidism. Fetal complications in women with SCH included IUGR (7.7%vs 2.7% p value <0.002), Small for gestational age (14.7% vs 5% p value <0.001), Preterm (7.1% vs2.7% p value <0.001), Intrauterine fetal death (3.2% vs 1.5% p value <0.001) as compared to euthyroid women.

Table 4 and Table 5 shows treatment details of the women in study group. Only 30.8% of women with `Subclinical Hypothyroidism were on treatment with Levothyroxine. All women with overt hypothyroidism (100%) were on treatment with levothyroxine. Despite on treatment all women with overt hypothyroidism had complications. Treatment of women with Subclinical Hypothyroidism showed no difference in relation to complications.

Table 1

Variables	Subclinical Hypothyroid	Overt Hypothyroid
Age (yrs)	20-30yrs (93%)	20-30yrs (95%)
Parity	Primi (56%)	Primi(58%)
BMI(Kg/m^2)	23-25 (45%0	23-24(43%)
Gestational age(of altered thyroid profile)	17-20wks (65%)	14-15wks (70%)

Table correlating Variable Parameters

Table 2

Maternal Complications	Euthyroid	Subclinical Hypothyroidism	Overt Hypothyroidism	p value
Preclampsia	122(8.2%)	34(21.8%)	5(41.7%)	<0.001
GDM	18(1.2%)	10(6.4%)	2(16.7%)	<0.001
Anaemia	13(0.9%)	9(5.8%)	2(16.7%)	<0.001
Oligohydramnios	38(2.5%)	13(8.3%)	1(8.3%)	<0.001
Polyhydramnios	15(1%)	2(1.3%)	0	0.890
Breech	19(1.3%)	8(5.1%)	0	<0.001
No complications	1136(76.2%)	29(18.6%)	0	<0.001

Table correlating Maternal Complications

Table 3

Neonatal Complications	Euthyroid	Subclinical Hypothyroidism	Overt Hypothyroidism	p value
IUGR	40(2.7%)	12(7.7%)	0	<0.002
SGA	75(5%)	23(14.7%)	2(16.7%)	<0.001
Preterm	41(2.7%)	11(7.1%)	2(16.7%)	<0.001
IUD	23(1.5%)	5(3.3%)	1(8.3%)	<0.001

Table correlating neonatal complications

Table 4

	On Treatment	No Treatment
Subclinical Hypothyroidism	48(30.8%)	108(69.2%)
Overt Hypothyroidism	12(100%)	0

Table on Levothyroxine Treatment

Table 5

	ON TREATMENT		NO TREATMENT	
	SCH	OH	SCH	OH
Complications	30(62.5%)	12(100%)	70(64.8%)	0
No Complications	18(37.5%)	0	38(35.2%)	0

Table correlating Effect of Levothyroxine in Subclinical Hypothyroidism.

DISCUSSION

Study group showed 10.1% prevalence of hypothyroidism. Similar studies of Dinesh Dhanwal et al, Sahu et al and Nambiar et al showed prevalence of 6.5%, 6.4% and, 4.8% respectively[3,4]. Prevalence of subclinical Prevalence of Subclinical Hypothyroidism and Overt hypothyroidism was 9.3% and 0.72% respectively. Overall prevalence of autoimmunity was 19.04% (n=32) in women with hypothyroidism. Women with SCH and OH had 17.9% (n=28) and 33.3% (n=4) prevalence of autoimmunity. Prevalence of thyroid autoimmunity and subclinical hypothyroidism was 18.5% in studies of Dhanwal et al[3].

Pregnant women with hypothyroidism had increased risk of pre-eclampsia in comparison to euthyroid women, 21.8% of women with Subclinical hypothyroidism (SCH) and 41.7% of women with overt hypothyroidism (OH) had pre-eclampsia in the study group in comparison to 8.2% of euthyroid women with P-value <0.001.Studies of Sahu. et al, Goel et al[4] showed women with Overt

hypothyroidism had Pre-eclampsia P value =0.04, P value=0.007 respectively. Studies of Wilson and Casey[19] showed 10.9% of women with SCH had Pre-eclampsia p value =0.16.Studies of Manissota et al showed association of hypothyroidism and pre-eclampsia[20]. Studies of Kharab et al showed similar relation[21].

Thyroid hormones have an effect on cardiovascular physiology and blood pressure regulation, which are mediated by genomic mechanism that cause ventricular remodelling. Studies have proven that hypothyroidism causes endothelial dysfunction characterized by diminished nitric oxide production, which in turn causes impaired vasorelaxation[19]. Studies have also shown that altered functions of liver and kidney during pre-eclampsia causes decreased peripheral conversion of T4 to T3 leading to T3 hypothyroxiemia and raised TSH levels. Loss of proteins and protein bound hormones may also contribute to hypothyroxiemia[21].

In our study 7.1% and 16.7% of women with SCH and OH had preterm delivery respectively in comparison to 2.7% of euthyroid women, p value <0.001. Studies of Wang et al and Stagnaro Green showed increase in the risk of preterm delivery in women with SCH with significant p value. Studies of Cleary Goldmann showed similar results[9, 10].

In our study 6.4% and 16.7% of women with SCH and OH had GDM in comparison to 1.2% euthyroid women, with a p value of <0.001. Studies of Oliveria et al, Agarwal et al, Karkosta et al, T.Izzo et al showed 16% and 20.2%, 8.8%, 10% of women with SCH developed GDM[11,12,8,23]. Studies of Maratou and colleagues has shown decreased rate of insulin stimulated glucose transport inside cells of hypothyroid patient[15].Studies of Tudela .et al showed 1.9-4.9% of women with SCH had GDM[22].Women with subclinical hypothyroidism have increased insulin resistance. Studies of Cleary Goldmann showed similar results[31].

Present study showed increased prevalence IUGR and SGA babies in women with SCH. IUGR was present in 7.7% women with SCH in comparison to 2.7% euthyroid women.14.7% of women with SCH had SGA babies in comparison to 5% of euthyroid women. Studies of Idris et al, Sahu et al and Liang Miao et al[25] showed increased prevalence of IUGR in women with SCH. Studies of F.Saki et al showed 13.7% of women with SCH had IUGR[24]. Thyroid hormone is essential for growth of all vital organs, deficiency of thyroid hormone can cause negative effect on pituitary thyroid axis of newborn and interferes with the normal vascular responsiveness and cardiovascular homeostasis of the fetus[16].

This study showed increased incidence of Intra Uterine Death in women with hypothyroidism. Women with SCH and OH had 3.2% and 8.3% incidence of IUD in comparison to 1.5% of euthyroid women, With a p value <0.001.Studies of Allan et al showed 3.8% of women with hypothyroidism had IUD. Studies of Masamao Ohasi et al showed similar results[17].

This study showed increased incidence of anaemia in pregnant women with hypothyroidism. 5.8% and 16.7% of pregnant women with SCH and OH had anaemia respectively. p value being significant <0.001.

Thyroid hormones have an effect on haematopoiesis. It effects haematopoiesis by increasing Erythropoietin production or by increasing haematopoietic factors production by non-erythroid cells. Hypothyroidism causes decrease in red cell mass and hypo proliferation of erythroid progenitors. It has effect on iron absorption, it causes decrease in acid secretion there by impairing iron absorption[18,27].

In this study pregnant women with SCH had 5.1% incidence of breech presentation in comparison to 1.3% of euthyroid pregnant women, with a significant p value of 0.001.Studies of Kuppens et al have shown similar results of 11% of women with SCH had breech presentation with a p value of 0.06.Studies of Victor J. Pop showed similar results[28].

Maternal hypothyroxiemaia is a risk factor for motor and cognitive delay. Thyroid hormone are essential for normal brain development. Fetal thyroid becomes functional after 12 weeks of gestation. It is hypothesised that fetal movements are essential for cephalic presentation. Maternal hypothyroxieamia in early gestational age affects fetal presentation at birth due to an effect on intrauterine development and activity[28,29].

In this study 8.3% of women with SCH and Overt hypothyroidism had oligohydramnios respectively in comparison to 2.5% of euthyroid women with a p value of < 0.001.Probably placental insufficiency may be the cause of oligohydramios in women with hypothyroidism. More RCTs are needed in this regard.

In this study analysis related to treatment with Levothyroxine was done. In this study 30.8% of women with SCH were on treatment with levothyroxine, 69.2% of women were not on treatment. All women with overt hypothyroidism were on treatment.

In this study all women with overt hypothyroidism had complications despite on treatment with levothyroxine. In this study 64.8% of women with SCH not on treatment had complications. Most women (62%) on with levothyroxine who had complications were Anti TPO antibodies positive .No statistical difference was noted. Our study lacks adequate research on treatment for hypothyroidism during pregnancy.

Studies of Muttukrishna Jayaram showed similar results[14]. Studies of Ablovich et al and Negro et al shows women with hypothyroidism should be treated with levothyroxine to have better maternal and fetal outcomes[26,32]. Studies of Velkeniiers showed reduced fetal loss in women treated with thyroxine[33]. More RCTs are needed with regard to treatment of women with subclinical hypothyroidism.

CONCLUSION

Subclinical hypothyroidism is like the bottom of iceberg because diagnosing thyroid dysfunction during pregnancy is difficult due to physiological changes in thyroid homeostasis and most symptoms of thyroid dysfunction mimic pregnancy symptoms. Use of trimester specific TSH values aids in diagnosing hypothyroidism in pregnancy. SCH is increasing in prevalence during pregnancy and is associated with maternal and foetal morbidity. Universal screening for thyroid dysfunction should be recommended for all pregnant women. This will help diagnosing SCH at the earliest, and early initiation of treatment with Levothyroxine can prevent complications like Pre-eclampsia, GDM, anaemia, IUGR, and IUD.

BIBILIOGRAPHY

1. Van den Boogaard E, Vissenberg R et al. Significance of (sub) clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Human reproduction update.vol 17, issue 5, sep 2011,pg no 605-619. PMID No. 21622978
2. Unnikrishnan AG, Kalra s, et al. Prevalence of hypothyroidism in adults: an epidemiological study in eight cities of India: Indian J of endocrinology and metabolism.2013;32(192):397-403.PMID:23961480[PubMed] PMCID:PMC3743364
3. Dhanwal DK, Prasad S, Agarwal AK ET al. High prevalence of subclinical hypothyroidism during first trimester of pregnancy in North India:Indaian J of endocrinology Metabolism 17(2):281-4.PMID: 23776903 [PubMed] PMCID: PMC3683205
4. Sahu MT, Das V, Mittal S. Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome: Archieves of gynaecology and obstetrics. 2010 Feb; 281(2):215-20. PMID:19437026
5. Khalid A El Baba, Sami T Azar. Thyroid dysfunction in pregnancy: International journal of internal medicine.2012;5:227-30.PMCID:PMC 3302764
6. Pietro cignini, Ester Valentina Cafa et al. Thyroid physiology and common diseases in pregnancy: review literature: Journal of prenatal medicine 2012; 6(4):64-71. PMID:23272277,PMCID : 3530964
7. Donny L.F. Chang and Elizabeth N. Pearce. Screening for maternal Thyroid dysfunction in pregnancy: A review of the clinical evidence and current guidelines: Journal of Thyroid research,vol 2013PMID: 23762776 [PubMed] PMCID:PMC3671674
8. Karakosta P,Alegakis D et al. Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes: J clinical endocrinology metabolism. 2012 Dec; 97(12):4464-72. PMID:23015651
9. Wang.S et alClinical or subclinical hypothyroidism and thyroid antibodies before 20 weeks of pregnancy and risk of Preterm birth: A systematic Review. Zhonghua Fu Chan Za Zi nov2014; 49(11):816-22. PMID: 25603905
10. Alex Stagnaro Green, Maternal Thyroid Disease and Preterm delivery. JCEM; vol 94: issue 1
11. Agarwal MM, Dhatt GS et al. Thyroid function abnormalities and antithyroid antibody prevalence in pregnant women at high risk for gestational diabetes mellitus: Gynaecological Endocrinology 2006 May;22(5):261-6.PMID:16785147
12. Olivieri A, Valensise H et al. High frequency of antithyroid autoantibodies in pregnant women at increased risk of gestational diabetes mellitus: European J of endocrinology 2000 Dec;143(6):741-7. PMID:11124856
13. Mecacci F, Parretti E et al. Thyroid autoimmunity and its association with non-organ-specific antibodies and subclinical alterations of thyroid function in women with a history of pregnancy loss or preeclampsia: J Reproductive Immunology. 2000 Feb; 46(1):39-50. PMID:10708243
14. Muthukrishnan Jayaraman, Abhyuday Verma et al. Pregnancy outcomes with thyroxine replacement for subclinical hypothyroidism: Role of thyroid autoimmunity: Indian J Endocrinology Metabolism. 2013 Mar-Apr; 17(2): 294–297. PMID:23776906 PMCID:PMC3683208
15. Lambadiari, V, , Mitrou, P, , Maratou, E, , Raptis, AE, , Tountas, N, , Raptis, SA, , Dimitriadis, G, 2011 Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes: *Endocrine* 39:28–32
16. Blazer S, Moreh -Waterman Y et al. Maternal hypothyroidism may affect fetal growth and neonatal thyroid function. Obstetrics gynaecology 2003 Aug; 102(2):232-41. PMID:12907094
17. Masanao Ohashi et al.Risk based Screening for Thyroid Dysfunction during Pregnancy.J of Pregnancy, vol 2013(2013): article ID 619718
18. Mohammedreza Ravanbond,kamya et al.Treatment of iron deficiency anaemia in patients with subclinical hypothyroidism. The American journal of Medicine,may 2014: volume 126,issue 5:pg no.420-424.
19. Wilson, Karen, Casey et al. Subclinical thyroid disease and the incidence of hypertension in pregnancy. Obstetrics Gynecology journal 2012; 119: 315-20
20. Tuija Mannisto. Thyroid disease during pregnancy, Expert rev of endocrinology; 2013;339 :b4336
21. Kharb s,Sardana D, correlation of Thyroid function with severity and outcomes of pregnancy.Annals of medical and health science research. Jan-mar 2013; vol3: issue1
22. Tudela CM,Casey BM,Relation of subclinical thyroid disease to the incidence of gestational diabetes.Obste Gynaecology journal;2012;119(15) :983-8
23. T.Izzo et al, pregnancy, gestational diabetes. Thyroid functions: our experience. Giom.int obst. Gin giomale Itaiano di obstetrician ginecologia, 2013; may-june: 355(3):466-470
24. F.Saki, Mohammed Hossein et al.Thyroid function in pregnancy and its influence on maternal and fetal outcomes. International endocrinol metabolism 2014 oct;12(13):e19378

25. Liang Miao Chen et al .Effects of subclinical hypothyroidism on maternal and perinatal outcomes during pregnancy: A single cohort study of Chinese population. PLoS one. 2014;9(10) : e 109364
26. Robert Negro and Stagnaro Green et al. diagnosis and management of SCH in pregnancy.BMJ 2014;349
27. Ritu Rana, Kejal Joshi et al .Screening of pregnant women for Iodine deficiency and Iron deficiency during early gestation in vadodara.
28. Kuppens and Kooist et al, Maternal thyroid function during early gestation is related to breech presentation at term. clinical endocrinology vol72,issue 6,820-24; june 2010
29. William.G.R, Neurodevelopmental and neurophysiological actions of thyroid hormones. J of neuroendocrinology 2008, 20: 784-94.
30. Joanna.Klubo, Kennet D. Burman, Levothyroxine Treatment in Pregnancy: indications, efficacy & therapeutic regimen. J of Thyroid Research, Vol 2011(2011), article ID 843591
31. Jane Cleary Goldmann et al. Subclinical Hypothyroidism in Pregnancy outcomes. AJOG 2005,vol 193,issue 6,pg s_3
32. Ablovich et al, Overt and Subclinical Hypothyroidism complicating Pregnancy, Thyroid 2002 jan; 12(1):63-68.
33. B.Velkeniers et al, Levothyroxine Treatment and pregnancy outcome in women with Subclinical Hypothyroidism undergoing ART: Systemic Review and Meta-analysis. Human Reproduction Update, vol 19,issue 3,Pg 251-58.