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Prevalence and Impact of Subclinical Hypothyroidism on Pregnancy- Prospective study From Apex Institute of North India

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Dr Neelam Aggarwal	Dr Vanita Suri	Dr Bharti Joshi
Assistant Professor(MBBS,MD) , Deptt of Obstetrics and Gynecology Post Graduate Institute of Medical Education and Research Chandigarh	Professor (MBBS,MD) Deptt of Obstetrics and Gynecology Post Graduate Institute of Medical Education and Research Chandigarh	(MBBS, MD, DNB) Research Officer, Deptt of Obstetrics and Gynecology, Post Graduate Institute of Medical Education and Research Chandigarh

Dr Pinaki Dutta	Dr Anil Bhansali	Dr kanya Mukhopadhyay
Assistant Professor(MBBS,MD,DM) , Deptt of Endocrinology , Post Graduate Institute of Medical Education and Research Chandigarh	Professor & Head (MBBS, MD, DM), Deptt of Endocrinology, Post Graduate Institute of Medical Education and Research Chandigarh	Assistant professor (MBBS, MD, DM), Deptt of Neonatology, Post Graduate Institute of Medical Education and Research Chandigarh

ABSTRACT *Subclinical hypothyroidism is one end of the spectrum of thyroid disorders with reported incidence of 2-5%. The data on prevalence and impact of subclinical hypothyroidism on pregnancy is restricted from north India; therefore we prospectively evaluated cohort of 1791 pregnant women for thyroid dysfunctions in apex institute of north India. Some important findings in this prospective analysis were 1) high prevalence of subclinical hypothyroidism (10.9%) in pregnancy and 59 % of these women had autoimmunity as cause of hypothyroidism. 2) Subclinical hypothyroidism was associated with significant increase in the rate of cesarean section (p=0.001) and neonates born to these women had lower birth weight as compared to neonates of euthyriod women which was statistically significant (p=0.002). Conclusion: Subclinical hypothyroidism has high prevalence in pregnancy in India and is associated with adverse maternal and fetal outcomes*

Introduction: Thyroid disorders commonly affect women of reproductive age group, so it is obvious to encounter these disorders during pregnancy. Subclinical hypothyroidism is one end of spectrum of thyroid disorders characterized by elevated serum thyrotropin levels (TSH) and normal free serum thyroxine (T4) concentration [1, 2]. The estimated prevalence of subclinical hypothyroidism in pregnancy is 2-5% [3, 4] and iodine deficiency remains the most common cause worldwide. Impact of subclinical hypothyroidism on pregnancy is not clear and well studied. Increased risk of obstetrical and perinatal complications like first trimester abortions, placental abruption, gestational hypertension, preterm labor and low birth weight has been cited in few studies[5,6].The infants born to pregnant women with subclinical hypothyroidism reported to have low birth weight, increased risk of respiratory distress syndrome, reduction in intelligent quotient and impaired cognitive and psychomotor child development[7,8].The need of screening for subclinical hypothyroidism before or during pregnancy is a controversial issue. In a resource limited settings like India the question of universal screening seems to be unfeasible, but few hold the view that the long term repercussions on the child and the family are worth the cost of screening. In order to assess the cost effectiveness of any screening protocol it is important to know the impact of that particular condition in that region. So to enlighten the observations related to the impact of subclinical hypothyroidism we prospectively evaluated and compared the maternal and perinatal outcome of pregnant women who were diagnosed with subclinical hypothyroidism in the present pregnancy in comparison to those with normal thyroid levels.

Material and methods

This study was conducted in one of the apex institute of north India for a period of one year and included prospective evaluation of 1791 pregnant women. All women with singleton pregnancy presenting to antenatal clinic and willing to participate for study were enrolled after receiving ethical clearance from institute's committee. Women with multiple pregnancies, co-morbid illness, previous history and positive family history of thyroid disorders were excluded from the study. After recruitment detailed history including demographic data were recorded in predesigned proforma. A complete physical and obstetrical examination was performed. Apart from recommended routine antenatal investigations a 5 ml of venous blood was collected for the estimation of tri-iodothyronine (T3) thyroxine (T4), thyrotropin (TSH) and thyroid peroxidase antibodies (TPO) for screening and all these levels were calculated with the help of Immunochemiluminiscence analyzer .Reference range used for T3, T4, TSH and TPO were 0.8-2.0 ng/ml 4.8-12.7 µg/ml, 0.27-4.5uIU/ml and 34IU/ml respectively. These women were then followed throughout their pregnancy and delivery. Maternal outcome variables included were the occurrence of preterm premature rupture of membranes, preterm labor, gestational hypertension or severe preeclampsia and obstetrical complications like cesarean section and abruption. Neonatal outcomes i.e. low birth weight, respiratory distress and neonatal hyperbilirubinemia were meticulously recorded. Preterm delivery included births less than 37 weeks of gestation and preeclampsia was defined as persistently elevated blood pressure of ≥140/90 with protenuria. Gestational diabetes was defined according to the IADPSG criteria with 75 gm glucose. Pregnancy was allowed to continue till 40 weeks of gestation, unless termination was indicated for maternal or fetal indications. The neonatal status at birth and at six

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weeks was assessed. The neonates whose birth weight was less than 1 standard deviation from the mean birth weight for gestational age as per our institutes growth were classified as small for gestational age. Low Apgar score was considered if score was < 7 at 1 minute. Thyroid function tests of all neonates were done at 72 hours of age and babies were followed up until discharge. The reference range used for neonatal TSH was < 20 uIU/ml at 72 hours of life. The pregnancy outcome was then compared to the thyroid status at screening.

Statistical analysis:
The data were analyzed using SPSS version 15 statistical package Variable measured in interval scales as the mean plus or minus the standard deviation (SD). Variables were compared by Fischer exact test and associations were considered statistically significant at the $p<0.05$ level.

Results:
A total of 1791 were included in the study out of which 1594 (89.1%) of the women had a normal thyroid profile and the remaining 197 (10.9%) had hypothyroidism. None had clinical or biochemical evidence of hyperthyroidism. None of the patients who had biochemical evidence of hypothyroidism had any signs or symptoms suggestive of hypothyroidism.TPO positivity was seen in 112 (59%) of the hypothyroid women and the mean TSH were 6.81±1.1 µIU/ml in the study group as compared to 2.81±1.7 µIU/ml in the control group. The mean age of the woman in study group was comparable with control group and majority of the women in both groups were recruited before twenty weeks (Table I)

Selected pregnancy outcomes in women with subclinical hypothyroidism compared with controls are listed in table II. The incidence of preterm premature rupture of membranes, preterm labor, gestational hypertension or severe preeclampsia and gestational diabetes was similar in both groups (P =>0.05). Incidence of caesarean section was significantly increased in hypothyroid group as compared to euthyroid group (p=0.001) and fetal distress was the cause in 147 (75%) of hypothyroid cases.

Infant outcomes of both groups are listed in table III. Although mean gestational age at delivery was not statistically different in both groups (p=0.274), birth weight of neonates born to hypothyroid women was significantly lower than euthyroid group (p=0.002). Incidence of respiratory distress syndrome and neonatal hyperbilirubinemia was similar in both groups and neonates born to hypothyroid mother had normal TSH at 6 weeks of gestation.

Discussion:
There are some important observations in this prospective analysis of 1791 women who were screened for thyroid dysfunctions during pregnancy. First, high prevalence of subclinical hypothyroidism (10.9%) was found in this study which correlates well with data reported from India [9, 10, 11]. Study reported by Dhanwal et al [11] has cited high prevalence (14.3%) of hypothyroidism, especially subclinical in pregnant women from north India. Good numbers of these women (57%) were positive for thyroid peroxidase antibodies (TPO) suggesting autoimmunity as etiology of hypothyroidism [12]. Second, incidence of cesarean section was significantly higher in hypothyroid group and fetal distress was the most common indication. These findings support the study by Sahu et al [10] which showed that cesarean rate for fetal distress was significantly higher among pregnant women with subclinical hypothyroidism. Likely hood of increased caesarean rate and fetal distress in hypothyroid women may be attributed to the irreversible placental effect of abnormal thyroid status along with TPO antibodies [13, 14].Low birth weight in neonates born to clinical/overt hypothyroid women has been linked to the increased incidence of gestational hypertension and its related complications[15,16] .Our study differs from literature in view that despite similar incidence of gestational hypertension or severe preeclampsia in both groups birth weight of neonates born to hypothyroid women were significantly lower than euthyroid women.

The strong point of our study is appreciable number of subjects enrolled for screening. This also supports the secular trend of high prevalence of subclinical hypothyroidism in north India demonstrated by previous studies. Limitation of our study is that we have not analyzed the association of TPO positivity with adverse effects. Except autoimmunity no other causes of hypothyroidism were evaluated and we do not have long term follow up of babies born to hypothyroid group.

There is pertinent literature to say now that subclinical hypothyroidism has bad impact on pregnancy. However whether we should start screening all women for subclinical hypothyroidism is still debatable. How thyroid deficiency results in maternal complications is not clear and there is limited literature to support the beneficial effect of treating subclinical hypothyroidism in pregnancy [17, 18, 19].In a study by Negro et al, adverse outcomes did not significantly differ between case finding and universal screening group but, treatment of hypothyroid group identified by screening significantly lowered maternal and fetal complications [20]. Although our study has demonstrated high prevalence and adverse effect of subclinical hypothyroidism on pregnancy which may be an incentive to screen all pregnant women for same but paucity of interventional studies regarding the effectiveness of treatment of subclinical hypothyroidism in pregnancy do not allow us to recommend universal screening at this stage. As more evidence will be generated in future this view may be altered.

Tables

Table I: Baseline characteristics of the study group

Variables	Hypothyroids(n=197)	Euthyriod (n=1594)	P value
Mean age (years)	26.58 ± 2.1	26.47 ± 2.7	0.582
Trimester at inclusion			
≤ 20 weeks	130 (65.9%)	1020 (63.9%)	0.581
≥20 weeks	67 (34%)	574 (36%)	0.581
Primigravida	66(33.5%)	647(40.5%)	0.055
TPO positive	112(59%)	-	

Table II: Pregnancy outcomes

Outcome	Subclinical Hypothyroids (n=197)	Controls (n=1594)	P value
Mean gestation at delivery(weeks)	38. 41 ± 2.6	38.35 ± 2.2	0.724

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Mean birth weight (grams)	2.694 ± 648	2,805 ± 442	0.002
Preterm premature rupture of membrane	8 (4%)	96 (6%)	0.267
Gestation hypertension or Pre eclampsia	24 (12%)	160 (10%)	0.350
Gestational diabetes mellitus	4 (2%)	64 (4%)	0.169
Intrahepatic cholestasis of pregnancy	27 (14%)	255(16%)	0.425
Preterm labor	32 (16%)	287 (18%)	0.405
Abruption	2(1%)	5(0.3%)	0.174
Cesarean section	49 (24.8%)	243 (15.2%)	0.001

Table III=Neonates outcomes

Outcome	Subclinical hypothyroids(n= 197)	Controls (n= 1594)	P value
Small for gestational age	32 (16%)	303 (19%)	0.348
Neonatal hyperbilirubinemia	28 (14%)	175 (11%)	0.177
Neonatal Respiratory distress	3(1.52)	20(1.25)	0.733
Neonatal mean TSH	2.99±2.02	-	

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