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Original Article

Biochemistry Section

Thyroid Dysfunction among Pregnant Women during Different Trimesters of Pregnancy: A Tertiary Care Hospital Based Observational Study

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ABSTRACT

Introduction: Normal thyroid function in pregnancy is important for the health of the mother as well as for the development and growth of the foetus. If pregnancy is associated with any endocrine problems like hypothyroidism, the prospective for maternal and foetal adverse outcomes can be huge.

Aim: To find out the prevalence of thyroid dysfunction among pregnant women during different trimesters of pregnancy and to find out an association between Body Mass Index (BMI) and thyroid hormones in pregnancy.

Materials and Methods: This was an observational cross-sectional study conducted between 15th April 2019 to 14th June 2019 by enrolling 100 normal healthy pregnant women in the Department of Medical Biochemistry in collaboration with Department of Obstetrics and Gynaecology, Sultania Zanana Hospital associated with Gandhi Medical College, Bhopal Madhya Pradesh, India. Five milliliter of fasting blood sample was used for estimation of serum total T_3, total T_4 and Thyroid Stimulating Hormone (TSH) levels by Enzyme Linked Immuno Sorbent Assay (ELISA) method. Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS version. 16.0) software and the p-value <0.05 was considered as significant level.

Results: The mean age of the study subjects were found to be 23.76±3.80, 24.05±3.18 and 23.8±3.25 years in the first, second and third trimester, respectively. A total of 35% prevalence of thyroid dysfunction was found among pregnant women. Out of this 24% had hypothyroidism, 1% had hyperthyroidism and 10% had euthyroid hyperthyroxinemia. A significant negative correlation was found between BMI and T_4 levels in underweight category and a significant positive correlation between BMI and total T_3 in third trimester was observed.

Conclusion: A high prevalence of hypothyroidism was observed particularly in the second trimester of pregnancy. This study lay the background for further large scale studies that should be conducted in Bhopal as such a high prevalence of thyroid dysfunction in iodine sufficient population is alarming and the results have deteriorating effect on both the maternal and foetal health.

Keywords: Body mass index, Endocrine disorders, Hormones, Prevalence

INTRODUCTION

Thyroid disease is one of the most common endocrine disorders worldwide. Thyroid disorders are also common problem in pregnancy and hypothyroidism is widely prevalent in pregnant women. If pregnancy is associated with hypothyroidism, the prospective for maternal and foetal adverse outcomes can be huge [1,2]. Maternal hypothyroidism occurs in 2-5% of pregnant women and associated with the adverse pregnancy outcomes [3]. Prevalence of hypothyroidism was found to be more prominent in the Asian countries than that in the west [4]. In the west, the prevalence of hypothyroidism in pregnancy is 2.5%, Overt Hypothyroidism (OH) and Subclinical Hypothyroidism (SCH) is 0.3-0.5% and 2-3%, respectively [5,6], whereas the prevalence of OH (3-4%) and SCH (4.8 to 12%) is much higher in the East [7]. Therefore, the Indian Thyroid Society recommends screening of TSH levels in all pregnant women during the first antenatal check-up [8].

Very few studies have reported the prevalence of thyroid problems in pregnant women of Central India especially from Madhya Pradesh, India. Agrawal U et al., have reported 31.81% thyroid dysfunction in pregnant women belongs to Bhopal, Madhya Pradesh, India [9] and Pokhanna J et al., have reported the prevalence of hypothyroidism and hyperthyroidism 13% and 4%, respectively in pregnant women belongs to Indore, Madhya Pradesh, India [10]. In other regions of India, Sahasrabuddhe A and Pitale S have reported 41% prevalence of hypothyroidism in first trimester pregnant women at Nagpur, Maharashtra, India [11] and 23% prevalence of hypothyroidism in first- and second- trimester pregnant women have been reported in a study of Manipur, India [12]. Panda J et al., have reported prevalence of SCH and OH in first trimester pregnant women belongs to Bhuvneshwar, Orissa 33.7% and 7.7%, respectively [13]. A large Indian cohort study have also reported that 12.9% first trimester pregnant women of different regions of India have hypothyroidism [14]. Most of the studies have included the first trimester pregnant women to find out the prevalence of thyroid dysfunction; thus, in the present study, it is a need to find the prevalence of hypothyroidism in pregnant women in all trimesters. Various population characteristics such as ethnicity, BMI, social status and smoking have been known to influence thyroid hormones measurements and associated with differences in serum thyroid levels. During pregnancy, BMI is increased due to normal weight gain with progression of pregnancy. Han C et al., have reported that high BMI is an indicator of thyroid dysfunction during early pregnancy [15]. However, a causal relationship between BMI and thyroid function has not been established by this study and suggested for the further large scale studies.

Keeping this in mind, the present study was designed to assess the prevalence of thyroid dysfunctions in pregnant women of all trimesters and also to find out the association of thyroid function with BMI during pregnancy in women from Bhopal, Madhya Pradesh, India.

MATERIALS AND METHODS

This was an observational cross-sectional study, carried out in the Department of Medical Biochemistry in collaboration with

Department of Obstetrics and Gynaecology, Sultania Zanana Hospital associated with Gandhi Medical College, Bhopal, Madhya Pradesh, India. Total 100 apparently healthy normal pregnant women who were attending anti-natal care clinic at Sultania Zanana Hospital and came for Thyroid Function Test (TFT) in Endocrinology Laboratory at Department of Medical Biochemistry between 15th April 2019 to 14th June 2019 were enrolled for the study. Sample size was 100 because it was an Indian Council of Medical Research-Short Term Studentship project (ICMR-STS) and the duration for the research project was only two months as per the ICMR-STS criteria. Normal pregnant women with first, second and third trimester, age between 20 to 40 years was considered as an inclusion criteria for the recruitment of pregnant women. The pregnant women having previous diagnosed thyroid problem, hypertension, gestational diabetes, urinary tract infection, renal disease or any history of obstetric or medical complications was excluded from the study. The enrollment of pregnant women was done after obtaining written informed consent and ethical approval. The Institutional Ethics Committee (IEC), Gandhi Medical College, Bhopal approved this research study by letter no.10027/MC/IEC/2018, dated 12/04/2019. After enrollment, all pregnant women were subjected to detailed clinical history, general physical examination; body temperature, pulse, Blood Pressure (BP), height, weight, BMI (weight in kilogram/height in meter square), Waist Circumference (WC), Hip Circumference (HC), Waist Circumference/Hip Circumference Ratio (WHR) and systemic examination; Cardiovascular System (CVS), Central Nervous System (CNS), respiratory system and all data noted in case proforma sheet. Enrolled pregnant women were further divided into four categories based on the World Health Organisation (WHO) BMI criteria [16]; underweight: <18.5 kg/m^2, normal: 18.5-24.9 kg/m^2, overweight: 25-29.9 kg/m^2, obese: ≥30 kg/m^2.

Assessment of thyroid dysfunction in pregnancy: The reference ranges of the TSH used in this study was based on the guidelines of American Thyroid Association (ATA) for the Diagnosis and Management of Thyroid Disease during Pregnancy [17], Endocrine Society [18] and National Guideline [8]. As per regulation 14.2. of ATA guideline, if trimester specific ranges for TSH are not available in the laboratory, then following trimester specific cut-off values of TSH were used for assessment of thyroid dysfunction during pregnancy. According to this criteria, a normal TSH value in first, second and third trimester should be between 0.1-2.5 mIU/L, 0.2-3.0 mIU/L and 0.3-3.0 mIU/L, respectively.

Lab Investigations and Methodology

Five milliliter fasting blood sample was collected under aseptic condition in a plain vial. After centrifugation of the blood samples at 4000 rpm for 10 minutes in a centrifuge machine, the serum was stored in refrigerator at 2°C to 8°C. Prior to use, all the serum samples were brought to room temperature and then used for the estimation of serum total T_3, total T_4 and TSH by ELISA method. The ELISA procedure was carried out using the commercially available ELISA kits (Rapid Diagnostic Pvt., Ltd.,). The absorbance was measured at 450 nm at automated micro-plate reader (Thermo fisher Scientific Pvt., Ltd.,). The analytical sensitivity for serum T_3, serum T_4, and serum TSH assay as ≤0.2 nanogram per milliliter (ng/mL), ≤1 microgram per deciliter (µg/dL), ≤0.08 micro International Unit per milliliter (µIU/mL), respectively. The intra-assay Coefficient of Variations (CV) for the assays was 2.25%, 5.54% and 5.46%, respectively. The inter-assay CV for the assays was 3.58%, 3.34% and 4.97%, respectively.

STATISTICAL ANALYSIS

Statistical analysis of data was done using SPSS (version 16.0) software. Continuous variables were checked for normality and then results were expressed as Mean±Standard deviation (SD). One-way Analysis of Variance (ANOVA) test was used for comparison of data among the groups. Correlation analysis was done using Pearson's Correlation (r). The p<0.05 was considered as a significant level.

RESULTS

The number, percentage and mean±SD levels of both the anthropometric parameters as well as the clinical characteristics of the study subjects are mentioned in [Table/Fig-1]. Out of 100 pregnant women across all trimesters, the mean age of pregnant women was 23.76±3.80, 24.05±3.18 and 23.8±3.25 years in first, second and third trimester, respectively. The difference between ages among trimester wise was not found statistically significant (p=0.930). However, maximum numbers of study subjects were in age group of 25-29 years [Table/Fig-2]. BMI mean value of women in first, second and third trimester was 22.25+3.69, 22.38+3.77 and 22.84+2.99, respectively. No statistically significant difference was found for BMI among trimester as shown in [Table/Fig-3]. Out of 100 study subjects, 60% pregnant women were found in normal BMI category. However, 11% women showed underweight and 15% women were found in obese category as presented in [Table/Fig-4]. A statistically significant difference was found for serum total T_3 (p<0.001), serum total T_4 (p<0.01) and serum TSH (p<0.001) levels among trimester groups [Table/Fig-5]. The prevalence of hypothyroidism, hyperthyroidism, euthyroid-hyperthyroxinemia and euthyroid was 24%, 1%, 10% and 65%, respectively observed among 100 pregnant women as shown in [Table/Fig-6]. The highest prevalence of hypothyroidism (40.0%) was found in second trimester's pregnant women in comparison to first and third trimester women. No significant correlation was observed among pregnant women for BMI with serum T_3 and serum TSH levels. However, serum T_4 level of pregnant women showed significantly negative correlation with BMI in underweight category as compared to obese and normal category as mentioned in [Table/

Parameter (s)	N (%)	Mean±SD
Age (year)	-	23.90±3.41
Urban	77 (77%)	-
Rural	23 (23%)	-
Weight (Kg)	-	50.68±8.68
Height (m)	-	1.50±0.06
Waist (cm)	-	86.97±21.13
Hip (cm)	-	97.16±8.87
WHR	-	0.88±0.09
Trimester		
Ist	30 (30%)	-
IInd	40 (40%)	-
IIIrd	30 (30%)	-
SBP (mmHg)	-	109.58±10.58
DBP (mmHg)	-	74.32±9.57

[Table/Fig-1]: Anthropometric and clinical characteristics of among pregnant women.
Data are presented as Mean±SD; N; Number; %: Percentage; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; WHR: Waist hip ratio

Age (year)	First trimester (N)	Second trimester (N)	Third Trimester (N)	p-value
20-24	13	13	12	0.930 (NS)
25-29	12	21	12	
30-35	4	6	6	
36-40	1	0	0	
Total	30	40	30	
Mean±SD	23.76±3.80	24.05±3.18	23.8±3.25	

[Table/Fig-2]: Age wise comparison of study subjects among trimester groups.
Data are presented as Mean±SD; N: Number; %: Percentage; p<0.05 was considered as significant level; NS: Not significant

Fig-7]. No significant correlation was observed among trimester wise pregnant women for BMI with serum T_4 and TSH levels. However, serum T_3 level of pregnant women showed significant positive correlation with BMI during third trimester (r=0.498 and p=0.005) as compared to first and second trimester as shown in [Table/Fig-8].

Parameter		First trimester (N=30)	Second trimester (N=40)	Third trimester (N=30)	p-value
BMI (kg/m^2)	Mean±SD	22.25±3.69	22.38±3.77	22.84±2.99	0.933 (NS)
	range	(16.79-29.37)	(16.23-31.46)	(18.56-27.98)	

[Table/Fig-3]: Comparison of BMI of pregnant women among trimester groups.
Data are presented as Mean±SD; BMI: Body mass index; p<0.05 was considered as significant level; NS; Not significant

Category	BMI (kg/m^2)	N	%
Under weight	<18.5	11	11%
Normal	18.5-24.9	60	60%
Over weight	25-29.9	14	14%
Obese	>30	15	15%

[Table/Fig-4]: Distribution of among pregnant women according to BMI category.
BMI; Body mass index; n: Number; %: Percentage

Parameter (s)	First trimester (N=30)	Second trimester (N=40)	Third trimester (N=30)	p-value
Serum total T_3 (ng/mL)	2.35±0.55	2.97±0.77	3.07±0.96	<0.001 (S)
Serum total T_4 (µg/dL)	10.46±1.83	10.59±1.94	11.99±2.90	<0.01 (S)
Serum TSH (µIU/mL)	1.47±0.93	3.09±1.89	2.80±1.11	<0.001 (S)

[Table/Fig-5]: Status of thyroid profile parameters among pregnant women trimester wise.
Data are presented as Mean±SD; p<0.05 was considered as significant level; S: Significant

Thyroid disorder	Trimester wise pregnant women			
	Total (n=100) n (%)	First trimester (n=30) n (%)	Second trimester (n=40) n (%)	Third trimester (n=30) n (%)
Euthyroid	65 (65.0%)	26 (86.6%)	22 (55.0%)	17 (56.6%)
Hypothyroidism	24 (24.0%)	01 (3.33%)	16 (40.0%)	07 (23.3%)
Hyperthyroidism	01 (1.0%)	01 (3.33%)	00 (0.0%)	00 (0.0%)
Euthyroid-hyperthyroxinemia	10 (10.0%)	02 (6.66%)	02 (5.0%)	06 (20.0%)

[Table/Fig-6]: Trimester wise prevalence of thyroid dysfunction among pregnant women.
n: number, %: Percentage

Parameter (s) category	Serum total T_3 (ng/mL)		Serum total T_4 (µg/dL)		Serum TSH (µIU/mL)	
	r	p	r	p	r	P
BMI (kg/m^2) (Underweight)	-0.411	0.209	-0.665	0.025	0.350	0.291
BMI (kg/m^2) (Normal)	0.121	0.357	0.094	0.474	0.154	0.240
BMI (kg/m^2) (Overweight)	-0.023	0.937	-0.131	0.655	-0.145	0.620
BMI (kg/m^2) (Obese)	-0.266	0.337	-0.234	0.401	0.134	0.633

[Table/Fig-7]: Correlation between BMI and thyroid hormones among pregnant women as per the BMI category.
BMI: Body mass index; r: Pearson's correlation coefficient; p: significant level; p<0.05 was considered as significant level

Parameter (s) trimester	Serum total T_3 (ng/mL)		Serum total T_4 (µg/dL)		Serum TSH (µIU/mL)	
	r	p	r	p	r	p
BMI (kg/m^2) (First trimester)	0.330	0.074	0.268	0.151	0.322	0.082
BMI (kg/m^2) (Second trimester)	-0.088	0.589	-0.286	0.073	-0.071	0.663
BMI (kg/m^2) (Third trimester)	0.498	0.005	-0.071	0.709	0.116	0.541

[Table/Fig-8]: Correlation between BMI and thyroid hormones among pregnant women trimester wise.
BMI: Body mass index; r: Pearson's correlation coefficient; p: Significant level; p<0.05 was considered as significant level

DISCUSSION

This study was conducted to find out the prevalence of thyroid dysfunction in pregnant women of all trimesters attending antenatal care clinic in the Bhopal, Madhya Pradesh, Central India.

In the present study, the mean age of pregnant women was lower as compared to Western countries [19,20] and the mean age difference was not significant among the trimesters. A South Indian study have reported 27.4±4 years mean age of pregnant women belongs to Chennai [21]. The possible reason for this finding in Bhopal might be an early marriage and early conception rate that is more prevalent in Central India. In the present study, no statistically significant difference was observed for BMI in pregnant women as trimester wise. Overall mean BMI was lower and only 15% women was in obese category which is also less percentage than other study [21]. This lower BMI indicates the less risk of pregnancy related complications in women.

Mandel SJ et al., have suggested that TSH should be used as a marker for diagnosis of hypothyroidism in pregnancy [22] and the effect of the thyroid dysfunction on the obstetric outcomes appear to manifest when TSH cut-off >2.5 mIU/L in the first trimester. Therefore, National guideline (2014) and American Thyroid Association (2011) have suggested >2.5 and >3 mIU/L cut-off range of TSH for the diagnosis of hypothyroidism in the first and second-third trimester, respectively [8,17]. In the present study, the serum total T_3, T_4 and TSH levels were found statistically significant in all trimesters of pregnancy. In this study, trimester wise raised total T_3 and total T_4 values were observed during pregnancy and in third trimester maximum rise was observed for total T_3 and total T_4. Another interesting finding was that TSH cut-off >3 mIU/L observed in the second trimester only. The slight decrease in the values of TSH in the third trimester might be a reflection of proper clinical screening and management done by the clinician. In support to present results, Nepalia R and Verma AK, have also observed high serum T_3 and T_4 values during pregnancy [23]. In contrast to the present findings, Kumar A et al., have observed a rise in mean value of T_4 levels in second trimester and after that decline in third trimester and gradual increase in TSH levels during all trimesters of pregnancy [24]. Zarghami N et al., have also observed the declining mean FT_3 and FT_4 levels during the pregnancy [25].

The important finding in the present study was the highest prevalence of hypothyroidism (40.0%) found in second trimester's women in comparison to first and third trimester, when the trimester specific TSH cut-off values were used. The overall prevalence of hypothyroidism in this study was 24% which is higher than the Western studies [5,6] as well as previous published Indian studies [10,26,27]. The difference in the prevalence rate of various studies in India because of different cut-off values of TSH level were used in these studies. Most of the studies had much higher prevalence of hypothyroidism in first trimester when compared to the present study results [10,13,26-28]. In this study, the prevalence of hypothyroidism in second trimester was higher in comparison to previous published Indian studies. Very few Indian studies have reported the prevalence of hypothyroidism in second trimester [13,27,29]. In third trimester, 23.31% prevalence of hypothyroidism was observed among pregnant women which was lower as compared to the Panda J et al., and Rajput R et al., study prevalence 75% and 25.8%, respectively [13,27]. In first trimester, 3.33% prevalence of hyperthyroidism observed in the present study which was similar to the other studies [10,26,30]. Based on trimester-specific TSH cut-off values, a trimester wise comparative prevalence of thyroid disorders in pregnant women of different studies of India is shown in [Table/Fig-9] [9-11,13,26-30]. There may be various possible

Study	Year and Place	Thyroid disorders	First trimester TSH Cut-off (0.1-2.5 mIU/L)	Second trimester TSH Cut-off (0.2-3.0 mIU/L)	Third trimester TSH Cut-off (0.3-3.0 mIU/L)
Present study	2019, Bhopal	Hypothyroidism	3.33%	40%	23.3%
		Hyperthyroidism	3.33%	00%	00%
Panda J et al., [13]	2018, Bhubaneswar	Hypothyroidism	36.7%	37%	75%
		Hyperthyroidism	-	-	-
Pahwa S and Mangat S [30]	2018, Amritsar	Hypothyroidism	6.0%	-	-
		Hyperthyroidism	2.0%	-	-
Pokhanna J et al., [10]	2017, Indore	Hypothyroidism	13%	-	-
		Hyperthyroidism	4.0%	-	-
Dubey S and Pradhan A [26]	2017, Sikkim	Hypothyroidism	8.0%	-	-
		Hyperthyroidism	2.0%	-	-
Rajput R et al., [27]	2016, Rohtak	Hypothyroidism	21.5%	15.8%	25.8%
		Hyperthyroidism	-	-	-
Mandal RC et al., [28]	2016, Southern West Bengal	Hypothyroidism	32.94%	-	-
		Hyperthyroidism	-	-	-
Agrawal U et al., [9]	2016, Bhopal	Hypothyroidism	31.8%[#]	-	-
		Hyperthyroidism	-	-	-
Sahasrabuddhe A and Pitale S [11]	2012, Nagpur	Hypothyroidism	41%	-	-
		Hyperthyroidism	-	-	-
Sahu MT et al., [29]	2010, New Delhi	Hyperthyroidism	-	6.47%	-
		Hyperthyroidism	-	-	-

[Table/Fig-9]: Trimester wise comparison of prevalence of thyroid disorders among pregnant women of India [9-11,13,26-30].
[#]trimester was not defined in study

reasons for the higher prevalence of hypothyroidism in the second trimester and low prevalence in first trimester of the present study, but among that one of the possible reason might be that most of the women had lack of the awareness to visit the ANC clinics for routine check-ups and thyroid test and thus they might have ignored the presence of thyroid dysfunction in the first trimester. Also, various physiological changes take place in the second trimester which can lead to hormonal imbalances. Though this study was conducted in an iodine sufficient population, therefore, the overall higher prevalence of hypothyroidism in this study can be attributed to various reasons. Most of the women followed the non-vegetarian diet pattern and one of the study has reported that vegan diets are associated with reduced risk of hypothyroidism. Therefore, it can be assumed that since vegan diets are linked with lower body weight and thus the normal BMI, it may offer protection against hypothyroidism [31].

In the present study, no significant correlation was found between BMI and serum total T_3, T_4 and TSH levels in different BMI category however, a significant negative correlation between serum total T_4 levels and BMI was found in underweight category. Haddow JE et al., have also reported no association between TSH value and body weight but showed negative correlation between body weight and T_4 during pregnancy [32]. On the contrary, Bestwick JP et al., have showed a statistical significant correlation between TSH and body weight [33]. Previous studies that also been reported negative correlation between T_4 and BMI during pregnancy [34,35]. The present study also find out correlation between BMI and serum total T_3, T_4 and TSH in various trimesters of pregnancy and found no statistical correlation between them. However, a significant positive correlation was observed between serum total T_3 and BMI in third trimester. This result is similar to Ashoor G et al., study who reported increased T_3 levels with higher BMI [36]. MannistoT et al., have also observed a positive correlation between T_3 level and BMI in pregnant women which further strengthens present study result [37]. Another astonishing result from this study is the occurrence of euthyroid-hyperthyroxinemia in about 10% of the pregnant women. As per our knowledge, there is no study in Central India which has reported the prevalence or occurrence of euthyroid-hyperthyroxinemia in pregnant women. Thus, it can said that the study is the first in the Central India to the very best of our knowledge to have reported the aforementioned data.

Limitation(s)

This study consists of small sample size. In this study, medical and radiological thyroid examinations were not performed and urinary iodine level and thyroid peroxidase (TPO) antibodies among pregnant women were not evaluated. This study, however is small but, it does throws light on the alarming need for large scale research to determine the effectiveness of thyroid disorders during different trimesters of the pregnancy in India.

CONCLUSION(S)

The overall prevalence of thyroid dysfunction among pregnant women was found to be 35% in Bhopal District. Among the thyroid dysfunctions, the prevalence of hypothyroidism was 24% which was found to be high in the pregnant women from Bhopal. The clinical relevance of this study showed that the cases of hypothyroidism were found to be increased particularly in second trimester during the pregnancy. The overall prevalence of hyperthyroidism was 1% and 10% euthyroid-hyperthyroxinemia was also observed among pregnant women of Bhopal. In the present study, a significant negative correlation was observed between BMI and T_3 in underweight category and in third trimester a significant positive correlation was seen between BMI and T_4 levels. However, these results couldn't expressed a significant link between BMI and thyroid hormones during pregnancy. This is a study from a single tertiary care hospital, therefore, representation of the sample may not be for whole population. So, large scale multi-centric studies are required in future.

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