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ORIGINAL ARTICLE

Prevalence of Subclinical Hypothyroidism in Pregnant Females in Three Trimesters: A Cross-Sectional Study

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Abstract

Background: Subclinical hypothyroidism (SCH) in pregnancy is associated with multiple adverse obstetrical and fetal outcomes i.e. preterm labor, miscarriage, fetal distress& preterm birth. The present study was therefore planned to identify the high occurrence rate of SCH-positive cases (Pregnant females coming to ANMC & Hosp for antenatal care) & to highlight that TSH screening should be included in routine antenatal screening.

Objective: To identify SCH cases in pregnancy, coming for antenatal workup in Al Nafees Medical College & Hospital Islamabad, Pakistan.

Material and Methods: In this study random screening of 150 pregnant females for serum TSH levels was done. Females were divided into three equal groups i.e. 50 females in each trimester. Serum TSH levels were done by ELISA and American Thyroid Association Guidelines (ATA) for TSH levels were taken as reference values.

Results: The data obtained from this study indicated that 34.7% of positive SCH cases. Mean and SD of study variables i.e. age, parity, and Hb were also compared in three trimesters which showed insignificant variation.

Conclusion: It was evident from our study results that SCH is prevalent in our local population. This study reinforces that TSH screening should be included in routine antenatal screening. This will help us to avoid maternal and fetal adverse outcomes associated with SCH as documented in various studies on thyroid disorders.

Keywords: Subclinical hypothyroidism, serum TSH levels, Obstetrical outcomes, Miscarriages, ATA guidelines

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Introduction

Subclinical hypothyroidism (SCH) is principally a biochemical disorder intensified more during pregnancy. Diagnosis of SCH is established when thyroid stimulating hormone (TSH) levels are elevated with a normal free thyroxin (FT4) level.[1]There is an increased production of thyroxin (T4) and triiodothyronine (T3) by up to 50% owing to several physiological and hormonal changes during pregnancy.[2]Physiological changes during pregnancy.

Results in both an increase in the size of the thyroid gland as well as in the iodine requirement. The fetal thyroid gland is not functional after 18-20 weeks of gestation and the fetus is entirely dependent on maternal thyroid hormones after that period. 3Pregnancy intensifies the demands on the hypothalamic-pituitary-thyroid axis. As a consequence, thyroid dysfunction is

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common during gestation. Therefore, timely screening and management of both overt and subclinical hypothyroidism are very crucial. This will dramatically reduce the risk of adverse obstetric outcomes including fetal loss.[4] although the effects of overt hypothyroidism on pregnancy are well documented. Certain studies reported adverse outcomes with SCH as well. These adverse obstetrical outcomes are associated more so with overt hypothyroidism like gestational hypertension and miscarriages.[5] Due to the role of thyroid hormone on cardiovascular physiology and blood pressure regulation, the likelihood of gestational hypertension is more when compared with euthyroid women [6] multiple adverse obstetrical and fetal outcomes reported with SCH includes preterm labor, miscarriage, gestational hypertension, placental abruption, fetal distress, preeclampsia, gestational diabetes, and preterm birth. This fact highlights the role of healthcare professionals working in antenatal care for the early identification of thyroid disorders.ATA guidelines recommend trimester-specific reference ranges of TSH levels for making a diagnosis i.e. TSH range, first trimester >0.1mIU/L and <2.5mIU/L, second trimester <0.2mIU/L and >3.0mIU/L and third trimester >0.3 and <3.0 mIU/L.7The present study was therefore planned to ascertain the prevalence of Subclinical hypothyroidism amongst pregnant females

Material and Method:

Study Settings: This study was conducted in ANMC & H Islamabad, Pakistan in collaboration with the Pathology and Gynecology/Obstetrics departments of the same hospital. The laboratory tests were conducted at the multi-disciplinary laboratory (MDR) at ANMC & H Islamabad.

Duration of study:
Carried from20th Oct, 2020 to 20th Oct, 2021

Study design:
Comparative Cross-sectional study

Sampling Technique:
No probability of Convenience sampling

Sample selection: pregnant ladies in any trimester of pregnancy visiting the Obstetric Department of ANMC & H for antenatal care.

Inclusion criteria: pregnant ladies with no signs or symptoms of thyroid disease or thyroid surgery

Exclusion criteria:

Known cases of hypertension and ischemic heart disease Symptomatic hypothyroidism 3. History of preterm births, fetal anomalies, or stillbirths in previous pregnancies

Sample Size Calculation:

One hundred fifty samples taking 11% prevalence of subclinical hypothyroidism in pregnancy. The sample size was calculated by using the following formula.8,9

n = t2p (1-p) /m2

n = Total sample

p = Prevalence of subclinical hypothyroidism (11% in Pakistan)

t = 95% Level of confidence (Standard value 1.96)

m = 5% margin of error. = (1.96) 2 (0.11) (1 – 0.11) / (0.05)2 = 0.34176/ 0.0025 = 139 Samples.

Data Collection Procedure:

One hundred and fifty pregnant females who came for antenatal care in the Obstetrics department were enrolled for the study based on history and clinical examination. History and examination findings were noted down on the bio-data Proforma of each patient after taking informed consent on the consent form. Serum TSH estimation was done by using generation ELISA10. (ELISA Reference corrected) Techno Diagnostic 3rd Generation ELISA Microplate Reader, Open system (USA Made) was a machine used for the ELISA Test, and Genway Biotech kits (China Made), were used for the estimation of TSH, ELISA. (ELISA machine and kit name added as said)Trimester-wise cut-off values of TSH for labeling a case of SCH as given by ATA guidelines were taken as reference. After sample processing for TSH, leftover samples were saved in the refrigerator of the biochemistry lab for use in the future.

Sample Processing:

The serum separation was done from the sample in a gel tube on the same day, at 3000rpm for 05 minutes, and preserved at -40C in aliquots for the estimation of TSH. The processing of TSH was done twice weekly by 3rd generation ELISA on microplate-based ELISA 10. The sample processing was done as per the recommended guidelines. The positive and negative quality controls were run with each batch for quality assurance. The results of serum TSH were documented on lab evaluation Proforma.

Statistical data analysis:

Data were analyzed using the Statistical Package for Social Sciences version 20 (SPPS 20). The numerical variables of TSH were used to assess statistical inference. Following statistical tests were used for qualitative and quantitative data analysis;

Quantitative Variables: Amongst the quantitative variables, mean values and the standard deviation were used to assess the accuracy of results amongst three trimesters of pregnancy. P-value < 0.05 was considered as statistically significant.

Qualitative Variables: The frequencies were calculated in terms of percentages for SCH in three trimesters of pregnancy.

Results:

The data obtained from this study indicates that 34.9% of females were found positive for SCH in our local population. Trimester-specific cut-off values of TSH as recommended by ATA guidelines were used for the diagnosis of cases of SCH.

Samples for TSH were taken and processed as explained in the methodology. Trimesters-specific cut-off values of TSH as described by ATA were taken as reference. Pregnant females having values of TSH greater than the cut-off values given by ATA were labeled as having SCH.

Frequency Distribution of SCH:

The overall distribution of SCH in three trimesters of pregnancy along with mean and standard deviations (SD) of TSH are shown in Table 1.

Table 1: Mean, SD, and Occurrence Percentage of TSH

Group (n=50)	TSH Normal Range (mIU/L)	Frequency (SCH)	Occurrence Percentage (%)	Mean (SCH)	Standard deviation
Trimester-I	(0.1-2.5)	18	36.73	3.5	±0.57
Trimester-II	(0.2-3)	19	38	3.85	±0.66
Trimester-III	(0.3-3)	15	30	4.05	±0.73
Cumulative Occurrence Percentage (%)					34.91 %

The mean and standard deviation (SD) of TSH in the first, second, and third trimesters were 3.5±0.57, 3.85±0.66 and 4.0±0.73 respectively. Regarding the frequency distribution of subclinical hypothyroidism out of the total 150 (N) participants, 34.91% (N=52) participants had found suffering from SCH. Percentages of SCH cases in individual groups were 36.7% (n= 18), 38% (n = 19), and 30% (n=15) in trimesters I, II, and III respectively as shown in Fig.1. Highest percentage of females positive for SCH was observed in the second trimester as shown in Fig.1 and Fig 2. Fig.3 is a representation of the total number of samples along with both SCH positive and SCH negative cases in each group

Table II: Comparison of TSH using ANOVA in three Trimesters-Value of < 0.05 was considered significant

Variable	Groups	Mean and SD	f-Value	p-Value
TSH	1st Trimester	3.51± 0.57	1.572	*>0.05
	2nd Trimester	3.85± 0.66		
	3rd Trimester	4.05± 0.73		

Table -II shows the results of ANOVA applied to the mean and SD of TSH values when applied to three groups. Analysis of variance (ANOVA) applied between SCH positive and negative cases was proved to be insignificant as shown in Table II. It wasn't therefore followed by the post Hoc Tukey test. This comparison also showed that there is no significant variation in TSH levels when taken in three trimesters. A single TSH value irrespective of gestational age/trimester can be used to label a case as having SCH.

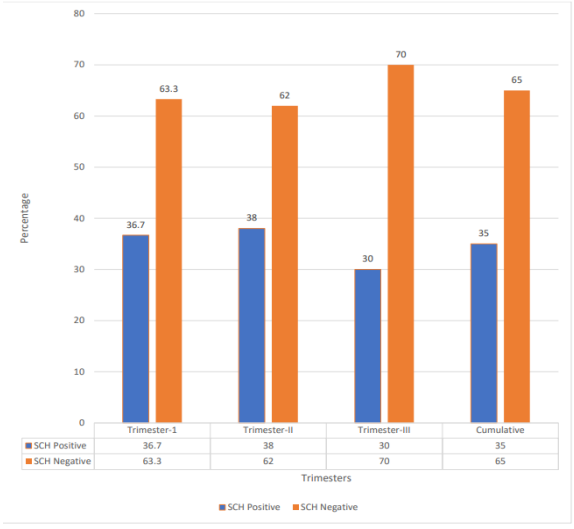

Fig.1: Percentage Distribution of SCH in three trimesters.

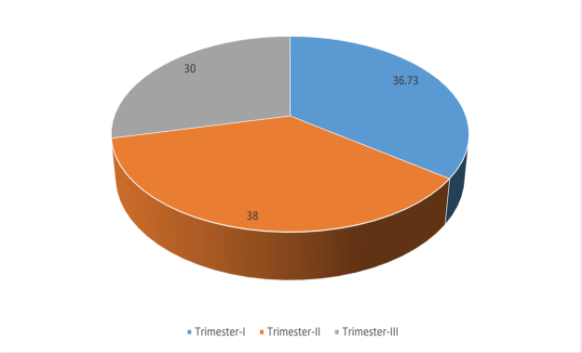

Fig. 2: Percentage Distribution of SCH in three trimesters.

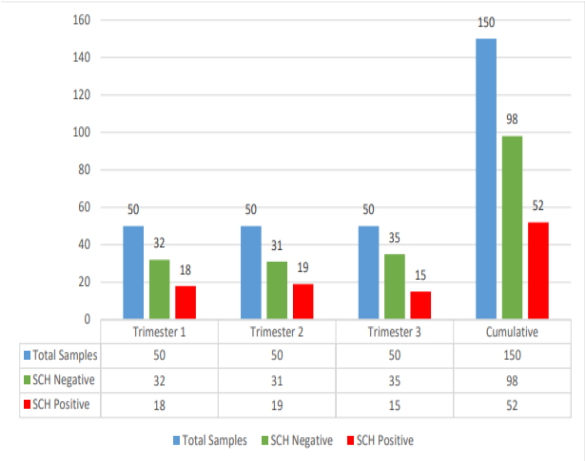

Fig.3: Frequency distribution of SCH positive and negative cases

According to the results, 52 females were found to have raised TSH levels whereas 98 females showed normal TSH levels out of 150 females in our study population. When further analyzed for individual trimesters, 18 positive cases of SCH while 32 negative cases were found in the first trimester. In the second trimester, there were 19 positive cases of SCH while 31 negative cases were found. In the third trimester, 15 positive cases of SCH were found out of a total of 50 subjects. These results showed that on random screening of pregnant females, we found a high percentage of females positive for SCH. The screening of SCH should be done on a larger sample size to get the prevalence of this disease preferably on a provincial level. This will help us to establish a strategy for early screening followed by management if needed. All these measures will reduce maternal and fetal adverse outcomes associated with SCH.

Discussion:

Thyroid disorders are the second most frequent endocrine conditions in women of childbearing age. Subclinical hypothyroidism (SCH) with high levels of serum thyroid-stimulating hormone (TSH) despite normal levels of serum free thyroxin (FT4) is amongst them.[10]. These disorders are associated with the likelihood of various adverse outcomes and complications. Maternal thyroid hormones are essential for fetal brain development, especially during gestational weeks 1–20. Thyroid disorder more so SCH during pregnancy, results in fetal neurodevelopmental defects.[11]It's been documented in certain studies that adverse pregnancy outcomes are observed in both spontaneous pregnancies and those achieved using assisted reproduction technologies .[12]

Considering the prevalence of SCH, one of the important observations is that SCH in contrast to overt hypothyroidism commonly reverts to euthyroidism. So, the prevalence of SCH has been overestimated. The annual rate of progression to overt disease is about 2% to 4% in such patients. [13] Several studies reported the association of SCH and overt hypothyroidism with complications such as gestational diabetes (GDM), hypertension, and pre-eclampsia. Females with SCH were twice as likely to deliver prematurely compared to euthyroid subjects. These women also had a 3 times higher incidence of miscarriage (especially during the first 20 weeks) and placental abruption. SCH affects not only the mother during pregnancy but also has proven neonatal outcomes. Intrauterine growth restriction, small for gestational age, low birth weights, and low Apgar scores were all reported in neonates of SCH mothers. In the general population, the prevalence of SCH among pregnant women is estimated to be 2% to 3 %.14. Keeping in mind the adverse obstetrical and neonatal outcomes with SCH, administration of levothyroxine (LT4) is still a questionable option. In the 2019 Chinese Medical Association (CMA) guideline, LT4 therapy is recommended for pregnant women with SCH whereas the 2017 American Thyroid Association (ATA) guidelines strongly recommend LT4 therapy for TPOAb-positive women with SCH during pregnancy. In contrast American College of Obstetricians and Gynecologists (ACOG) guideline in 2020, LT4 therapy is not recommended for pregnant women with SCH, [15]. It has been documented in multiple studies conducted that SCH has recognized

poor outcomes in pregnancy. A study conducted in Lebanon showed that 17% of 920 pregnant women had hypothyroidism during pregnancy and these women also showed associations with miscarriage and morbid obesity during pregnancy. Subclinical hypothyroidism in pregnancy is related to a higher risk of recurrent miscarriage, intrauterine growth restriction, preterm birth, low birth weight, perinatal mortality, and pre-eclampsia. This association becomes more significant when taken along with the higher prevalence of the disease.

Another multicenter study conducted locally in Riyadh; Saudi Arabia (SA) showed that the prevalence of subclinical hypothyroidism in pregnant women was 13%. An epidemiological study from 11 cities in nine states of India showed that 13.13% of pregnant women have hypothyroidism (n = 388), using a cutoff TSH level of 4.5 μIU/ml. Hence, it is important to recognize and establish a thyroid function test profile as a baseline to monitor the levels during pregnancy to avoid these bad consequences during and after pregnancy. 16 In the United States and Europe, the prevalence of SCH among pregnant women is estimated to range from 2% to 18%. In India and other iodine-deficient countries, the prevalence of SCH among pregnant women was as high as 13.5%-15.1%. Consequently, there is an unmet need to assess the risk of SCH in pregnant women in high-risk areas, which will help in the proper planning of a universal screening program for all pregnant women. Pakistan is also on the list of severely iodine-deficient countries. Certain studies conducted by the World Health Organization (WHO) provided a startling rise in iodine deficiency disorders in the past few years. Data regarding pregnant women with hypothyroidism in Pakistan is very limited. Since hypothyroidism can devastate both the mother and infant's well-being, it is vital to evaluate the exact burden of the disease. Amulti-center study assessed the prevalence of Subclinical Hypothyroidism during Early Pregnancy in Pakistan (PRECIOUS). The results of this study showed that 34.5% of women (high-risk pregnancy) had thyroid dysfunction. Tariq et al. highlighted the lack of awareness of Pakistani pregnant women towards hypothyroidism, which requires extensive awareness and screening programs. 17 Several studies are showing an association between mild maternal thyroid hormone insufficiency in pregnancy and impaired neuropsychological development of the offspring. A recent study found that lower free thyroxine (FT4) levels and higher free triiodothyronine (FT3) to FT4 ratios in pregnant women are associated with several adverse metabolic parameters relating to obesity, glycemia, insulin resistance, and lipid profile. These adverse metabolic parameters are responsible for the poor obstetric outcomes observed in pregnant women with mild maternal thyroid insufficiency18Multiple physiological functional changes seen during pregnancyinclude:1. An increase in the production of total triiodothyronine (T3) and thyroxin (T4) due to the stimulatory effects of beta-human chorionic gonadotrophins (β-hCG) and human chorionic thyrotrophic (hCT)2. A decrease in the production of thyroid-stimulating hormone (TSH) from the anterior pituitary gland due to the high concentration of β-hCG levels during the first trimester 3. A two-to-three-fold increase in concentrations of thyroid hormone-binding globulin (TBG). In-utero exposure to maternal hypothyroidism is associated with unfavorable outcomes as it increases the chances of intrauterine death, low fetal birth weight, fetal distress, and irreversible fetal brain damage which manifests as mental retardation, cerebral palsy, and poor cognitive development. Even sub-clinical hypothyroidism is associated with a higher miscarriage rate, preterm delivery, and a lower IQ of the child. This situation is particularly relevant to the local population since Pakistan has one of the highest reported rates of childhood mental retardation in the world. A study conducted in this regard on pregnant women visiting a hospital in Lahore reported that 14.6% of the women had higher than normal TSH levels.[19]

Subclinical hypothyroidism with increased TSH levels and normal fT4 values is found to be more common than overt hypothyroidism. Considering the high occurrence rate as well as the detrimental effects of thyroid diseases for both mother and baby, the need for thyroid screening during pregnancy is under discussion in recent times. Although the literature shows that screening for subclinical hypothyroidism is cost-effective, the number of studies showing the results and benefits of screening has not yet reached an appropriate level. The exact prevalence of thyroid dysfunction in pregnancy should be identified to perform community-based screenings healthily. Our study aimed to investigate the frequency of thyroid dysfunction amongst a specific population of pregnant women.[20]

Conclusion:

It is concluded from our study that SCH is prevalent in our local population. This high prevalence of undiagnosed subclinical hypothyroidism in our local population is alarming. Well-timed TSH screening during antenatal visits is crucial, as multiple adverse obstetrical and fetal outcomes are associated with this condition. Antenatal screening will help us to avoid maternal and fetal poor outcomes associated with SCH.

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