Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i1.4232

ENDEMIC HYPOTHYROID CHALLENGE ON THYROID STATUS OF PREGNANT WOMEN AND ADVERSE OUTCOMES

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Abstract:
Introduction: Pregnancy with thyroid dysfunction is a high risk for developing iodine deficit. All aspects of thyroid hormone economy affected by pregnancy. Thyroid Stimulating Hormone (TSH) level during pregnancy is most reliable test to assess thyroid functional status. **Objectives:** The study objectives were to assess pertinent thyroid functional hormones of pregnant women during last trimester and maternal & neonatal outcomes of pregnancy in this region. **Materials & Methods:** A cross sectional, hospital based study was conducted. Convenient sampling technique was practiced. Sample size was calculated by Classical Sample size Cochran formula. Maternal Goiterous and clinically Non-goiterous maternal groups were recruited for thyroid function status and outcomes of pregnancy. **Results:** Serum TSH levels of maternal Goiterous group were 1.33 ± 0.144 mIU/l, serum free triiodothyronine (FT3) levels were 2.51 ± 0.608 pmol/l, and serum free thyroxin (FT4) were 0.92 ± 0.691 ng/dl. Comparing the maternal Non-goiterous group serum TSH levels were 1.760 ± 0.155 mIU/l, FT3 levels were 1.710 ± 0,381 pmol/l and serum FT4 were 1.310 ± 0.194 ng/dl. Independent t-test was applied to evaluate equality of means and variances, of both maternal groups. Results have shown statistically significant (P <0.05). On percentile analysis serum TSH levels of maternal Goiterous, group 5^{th}, 50^{th} (median), and 95^{th} percentiles were 0.134, 1.090, and 3.508 mIU/l respectively. In Maternal-neonatal outcome high frequency of abortion (29.3%) and low birth weight (LBW) (10.6%) were observed among maternal Goiterous group, Early neonatal deaths occurred (< 7days) 9.33% among neonates of maternal Goiterous group. **Conclusion:** Reduced thyroid function due to endemic goitrous prevalence in the study region demands regular screening for thyroid disorders during pregnancy in order to avoid its adverse consequences on fetal and neonatal differentiating development in general however specifically of brain to avoid wide spread mental retardation.

Keywords: endemic hypothyroidism, pregnancy, thyroid function hormones, neonatal status, adverse outcomes

Introduction:

Hypothyroidism during gestation is a high-risk pregnancy need to evaluate for thyroid dysfunction. Thyroid hormones functions altered during pregnancy. Maternal thyroxin (T4) is transferred to which is necessary for fetal brain development and neonatal growth [1]. TSH level during pregnancy is key test to assess altered thyroid hormones function. Serum TSH level is low in the early phase and detectable during first trimester of pregnancy and moderately increases during last trimesters. As early as 28th weeks of gestation serum TSH level is valuable test in pregnancy to assess thyroid function while comparing with trimester specific ranges [2]. During first trimester, total serum T4 and T3 concentrations rise to 15 times than non-pregnant women, due to high serum Thyroid binding globulin (TBG) concentration [3].

In endemic iodine deficiency, increased TSH level leads to 20%-40% increase in thyroid volume. During 2nd trimester, increased total body mass leads to increase basal metabolic rate, modest tachycardia, and vasodilatation and decrease peripheral resistance along with changes of pregnancy may suggest thyrotoxicosis [4]. FT3 levels may be good indicator of thyroid dysfunction during early pregnancy. Higher FT3 levels and FT3 to FT4 ratio were associated with high BMI, fasting glucose and high LDL in late pregnancy. Maternal FT4 is essential for fetal development during pregnancy. Higher FT3 levels and high FT3 to FT4 ratios are associated increase risk of gestational diabetes and feto-maternal complications [5]. Placental growth and pregnancy development have high influences on the body immune system. The autoimmune response of body is suppressed [6].

A minute amount of iodine needed to prevent deficiency. Different agencies in the world recommends different intake for non-pregnant, pregnant and lactating women, which range from 150-290 ug/ day [7]. Daily recommended intake of 250ug of iodine by the International Council for control iodine Deficiency Disorders (ICIDD), World Health Organization (WHO), and United Nation International Children Emergency Fund (UNICEF) for pregnant and lactating mothers [8]. The European Food Safety Authority (EFSA) recommend 200ug /day intake of iodine for pregnant and lactating mothers [9].

Endemic iodine deficiency is a major cause of hypothyroidism. Goiter becomes endemic in population where the intake of iodine is less than 10ug/day [10]. Iodine deficiency adversely affects growth and mental development in all age groups. Goiter is reflection of chronic iodine deficiency and a good indicator for success of an iodine program [11]. The frequency of thyroid deficiency during pregnancy ranges 0.2% to 3% among developed countries but condition has adversely high frequency among under developed nations. About 2.2 billion people are at risk of Iodine deficiency disorders globally. Out of them, 30-70% have goiter and cretinism reported among 1-10% of population [12].

The study area consists of mountainous, sub- mountainous & Indus riverine belt with significant prevalence of thyroid disorders among mothers resulting in mentally retorted children in district Dera Ghazi Khan of Southern Punjab, Pakistan. Hypothyroidism is common among women of reproductive age, residing in the endemic areas. The study objectives were estimation of thyroid functional hormones of Goiterous and Non-Goiterous during last trimester of pregnancy and report maternal–neonatal outcomes of pregnancy.

Material &Methods:

Pakistan has many iodine deficient regions declared by WHO, with high prevalence of thyroid disorders and one of them selected for current study. Main burden of thyroid disease listed from mountainous and sub-mountainous regions. Study was conducted by department of Physiology, IMBB University of Lahore in collaboration with departments of Gynecology & Obstetric of Teaching DHQ Hospital Dera Ghazi Khan during January-September 2022. This was a cross sectional, hospital based study. Convenient sampling technique was utilized.

Pregnant mothers with singleton pregnancy attending antenatal clinic during last term of gestation recruited. Subjects were evaluated for symptoms and signs of hypothyroidism and hyperthyroidism.

The total three thousands and fifty-six (N=3056) were clinically examined for detection of study participants. Seventy-five were engaged as Maternal Goiterous Group (n=75) suffering from maternal hypothyroidism and Non-Goiterous Maternal Group (n=30). The study sample size calculated by Classical Sample size formula of Cochran; Subjects having goiter were evaluated on clinical examination for thyroid enlargement, and cases of hyperthyroidism were excluded from the study. Subjects selected during last trimester of pregnancy. Subjects having twin pregnancy, Pre-eclampsia, eclampsia, diabetes, hypertension antepartum hemorrhage and hydromnios excluded. Subjects having history of anti-thyroid medication and thyroid operation excluded. Data collected by using pretested structured questionnaire by interview and Clinical examination method by two-member research team of medical specialist working in the institution. Team members were well aware about social norms and local languages. Family history of goiter and thyroid surgery and anti-thyroid medication entered in evaluation proforma. Age, educational status, socioeconomic status, area of residence, duration of stay and gestational age transcribed.

All subjects' blood samples collected aseptically, prepared to harvest sera, and stored at-20 ^{o}C. Serum TSH levels, FT3 and FT4 Levels were estimated by Chemi-illumination Microparticle Immunoassay (CMIA), ARCHITECT fully automated ELISA, ABBOT.

The research protocol was approved by Ethical Review committee of D G Khan Medical College Dera Ghazi Khan (ERC/GKMC, 27/22 dated 10-9-2022) and Board of Advanced Studies & Research University of Lahore (76/BASR/UOL,07/2023 Dated 04-05-2023. The subjects signed the written, informed consent. Subjects' data coded to ensure confidentiality of data and to avoid subject's identification. The total study participants were seventy-five Maternal Goiterous Group (n=75) and Maternal Non-Goiterous Group (n=30). Data analyzed by using SPSS version 18.0 for basic statistics.

Results:

A total seventy-five hypothyroid pregnant mothers were selected by simple convenient sampling which was labeled as Maternal Goiterous Group (n=75). Subjects selected were from pregnant mothers admitted in Gynecology & Obstetric department of Allama Iqbal Teaching hospital Dera Ghazi Khan for delivery purpose throughout last trimester of gestation. Study participants were suffering from maternal endemic hypothyroid Goiter and first time diagnosed as case of maternal hypothyroidism, labeled as Maternal Goiterous group (n=75). A group of Non-Goiterous mothers during third trimester recruited for comparison of study results. Age (Mean ± SD) of pregnant women of both maternal groups was 28.36 ± 4.62 years.

TSH levels of maternal Goiterous group were 1.33 ± 0.144 mIU/l, serum FT3 levels were 2.511 ± 0,608 pmol/l, and serum FT4 were 0.92 ± 0.691 ng/dl. Maternal Non-Goiterous group results shown of TSH levels were 1.760 ± 0.155 mIU/l, FT3 levels 1.710 ± 0,381 pmol/l, and serum FT4 were 1.310 ± 0.194 ng/dl. On comparison of serum TSH and FT4 levels of Maternal goiterous Group with Non-goiterous Group, results were statistically significant ($P<0.05$). On comparison of serum FT3 levels of both Maternal Groups, results were highly significant statistically ($P<0.00$) (Table 01).

On percentile analysis serum TSH levels of Maternal Goiterous Group 5^{th}, 50^{th} (Median), and 95^{th} percentiles were 0.134, 1.090, and 3.508 uIU/l respectively and, serum FT3 levels of Maternal Goiterous Group 5th, 50^{th} (Median) and 95^{th} percentile was 1.624, 2.560 and, 3.140 Pmol/l respectively. On Percentile analysis of serum FT4 levels of Maternal Goiterous Group 5th, 50^{th} (Median) and 95^{th} percentile was 0.650, 0.850 and, 1.260 ng/dl respectively (Table 02).

Maternal Goiterous Group showed history of abortion 29.3% (n=22) vs 18.5% from Maternal Non-Goiterous Group (n=30). Results showed 1.3% case of oligohydramnios and 1.3% case of Cord around neck were among Maternal Goitrous Group. Neonatal Study Group showed 10.66% (n=08) cases of low birth weight and 9.33% (n=07) cases of early neonatal death. P value > 0.05 was considered as non-significant, < 0.05 was significant and 0.001 was considered highly significant statistically (Table 03).

Table 01 comparison of thyroid assay between maternal goiterous and non-Goiterous Groups

Parameter	Maternal Group	Number	Mean ± SEM*	Range	P-Value
TSH (Maternal)	Non-Goiterous (Clinical)	n=30	1.760 ± 0.155	0.630 – 3.480	0.03
	Goiterous Group	n=75	1.332 ± 0.144	0.001 – 7.160	
FT3 (Maternal	Non-Goiterous	N=30	1.710 ± 0.381	0.770 -12.090	0.00
	Goiterous Group	N=75	2.511 ± 0.608	1.001 – 3.611	
FT4 (Maternal)	Non-Goiterous	N=30	1.310 ± 0.194	0.780 -5.200	0.02
	Goiterous Group	N=75	0.92 ± 0.691	0.58 – 5.00	

Table 02 Percentile analysis (5 to 95) of serum FT3, TSH and FT4 of Maternal goiterous Group (n=75) in last trimester of pregnancy

Name of Group	Variables	Numbers	5^{th}	10^{th}	25^{th}	50^{th}	75^{th}	90^{th}	95^{th}
Goiterous Group	Serum FT3	n=75	1.624	1.700	2.170	2.560	2.880	3.118	3.140
	Serum FT4	n=75	0.650	0.686	0.790	0.850	0.950	1.040	1.260
	Serum TSH	n=75	0.134	0.276	0.610	1.090	1.760	2.678	3.508

Table 03 Outcomes complications reported among Maternal goiterous group and their Neonates

Name of Group	**Maternal Goiterous Group** n=75			**Neonatal Group** N=62		
Parameters Of Groups	Complications	Number	Prevalence	Parameters	Number	Prevalence
	H/O Abortion	n=22	29.3%	LBW	08	10.6%
	Still Birth	n=01	1.33%	Early Neonatal Death	07	9.3%
	Oligo-hydromnios	n=01	1.33%			------
	Cord around Neck	n=01	1.33%			------
	Anemia	05	6.7%	Anemia	03	4.8%

Discussion:

This is a pioneer study to establish levels of maternal Non-goiterous group (Euthyroid) TSH, FT3 and FT4 during third trimester of gestation. Many countries of the world have not yet established reference ranges of thyroid hormones during gestation. South Asian Region countries (SARC) has not documented unique data of thyroid hormones reference ranges of pregnant females, which is need of time for diagnosis and management of thyroid dysfunction. Maternal reference levels recommended by the Royal College of Obstetrician and Gynecologist were serum TSH 1.79± 0.85mIU/l, FT3 1.711

± 2.089 pmol/l and FT4 1.31 ± 1.07 ng/dl, and current study results were contrary to RCOG recommendations [13].

No trimester specific reference ranges of serum T3, TSH, FT3 and FT4 among healthy pregnant women, a standard for diagnosis and treatment of thyroid disorders during pregnancy are not settled yet in Pakistan. Internationally advocated that every tertiary care hospital should establish its own trimester specific reference ranges of thyroid hormones levels based on population of that area. Reference ranges were also not available on national level. So the present study reports of Maternal goiterous group levels of serum thyroid assay have been contrary to recommended levels by American Thyroid Association [14].

Alexander et al (2017) reported serum thyroid hormone levels evaluation of thyroid dysfunction during gestation. FT3 estimation was a precise test. The upper TSH level reference limit of 2.5mIU/l, 4.0mIU/l during first and subsequent trimesters, when population based reference ranges (fifth – 98 percentile) not documented. FT4 were between 2.5 - 97.5 and serum FT3 levels were 4.1-4.4pg/ml, 4.0-4.2 p/ml during last two trimester. Results of Maternal Goiterous Group of thyroid assay of present work are contrary to this study [15]. Variations reported may due to differences in population, its geographical diversity and food customs.

Yang et al (2019) reported thyroid hormones ranges during pregnancy in large Chinese population. Their study was hospital based, long duration and sample size was forty-six thousands two hundred and sixty-two (n=46,262) with no history of goiter, no thyroid diseases and anti-thyroid medication. Current study was also hospital based with lesser duration. Current study results of Maternal Goiterous Group serum thyroid assay were contrary to Yang et al. (2019) study [16]. because of different study population, iodine status, and dietary habits.

Almomin et al (2016) reported maternal trimester specific thyroid hormone levels from Basra (Iraq). Their study participants were normal healthy pregnant women selected from different medical centers both public and private hospitals, from Basra city of Southern Iraq. Out of 893 selectively referred mothers, 643 evaluated. In the present study Maternal goiterous Group results of serum TSH, FT3 and FT4 dissimilar to Almomin et al., 2016 [17], work, may be due to different subjects' characteristics of both studies.

Alawad et al (2015) reported thyroid function tests among pregnant women with pre-eclampsia of Khartoum-Sudan. Study was case control with sample size of one hundred pregnant women (n=100) during 2nd and 3rd trimester of pregnancy, hospital based and of three-month duration. Study participants were divided in to two groups i.e. Study group (n=50) of pregnant women with pre-eclampsia, and Control group (n=50) of normal pregnant women. Current study results of both groups Maternal Non-Goiterous Group and Maternal Goiterous Group serum thyroid assay were contrary to Alawad et al. (2015) this article study, may be due to different study populations [18].

Mahadil et al (2020) reported thyroid functions and feto-maternal outcomes during pregnancy. High frequency of hypothyroidism reported among pregnant women and anemia and LBW were common among neonates of mother suffering hypothyroidism whom are in accordance with current study findings [19]. Feigl et al (2022) reported effects of thyroid dysfunctions during pregnancy and outcomes among mothers with polycystic ovary syndrome (PCOS). Serum thyroid assay were lower among pregnant women having thyroid disorders with PCOS and significant association of Maternal-neonatal complications reported among FT4 levels. Current study findings of low thyroid hormones levels and maternal- neonatal complication were in accordance with Feigl et al. (2022) [20].

Yasmin et al (2022) reported prevalence (8%) of thyroid disorders during pregnancy from a tertiary care hospital of Bahawalpur region, Punjab Pakistan. Thyroid disorders during pregnancy and feto-maternal outcomes complication were low from Bahawalpur. Current study findings of high prevalence of thyroid disorders and maternal- neonatal complications were contrary to Yasmin et al. (2022) study [21]. Kumar et al (2023) reported high prevalence of thyroid disorders during pregnancy (31.6%) hypothyroidism and highly significant association between thyroid disorders and maternal-neonatal complications. High frequency of feto-maternal complications reported among hypothyroid patients' vs hyperthyroidism. Current study findings are in accordance with Kumar et al. research work [22].

Study Limitations:
The study limitations are, i) limited sample size ii) Single center study iii) unavailability of thyroid data iv) community cultural issues v) financial constrains vi) lack of previous study vii) multi-center study with large sample size are need to be conducted.

Conclusion:
Thyroid function hormones level during last trimester were lower among Goiterous Maternal Group than Non-Goiterous Group and lower than international recommendation. High prevalence of maternal and neonatal adverse effects of endemic hypothyroidism reported. Screening for thyroid disorders is need of time during preconception period and during early pregnancy period to reduce subsequent maternal morbidity as well as mortality and neonatal brain development.

Abbreviations:
TSH-----Thyroid Stimulating hormone
LBW---- Low birth weight
FT3 ----- Free Tri-iodothyronine
FT4------ Free Thyroxin
PCOS---- Polycystic Ovarian Syndrome
SARC---- South Asian Region countries
ICIDD---- International council for IDD
UNICEF--- United Nation International Children Emergency Fund
EFSA------European Food Safety Authority

Declaration:
1. Ethical Approval & Consent to participate
The Research project approved by Ethical Review committee of GKMC, Dera Ghazi Khan and Board of Advanced Studies & Research, University of Lahore.
Written, informed consent form dully signed by each participant
2. Consent for Publication: Not Applicable
3. Availability of Data and Materials:
Data sheets used /analyzed during current research are available from Corresponding author, on reasonable request.
4. Disclaimer: This manuscript is part of Ph.D. thesis of 1st author
5. Conflict of interest: None
6. Funding Source: Nothing to declare
7. Authors Contributions:
ARK Principal Investigator, Conceived, Study Design, Data collection, Data Analysis, Writing of manuscript
MRD Research methodology, Research design, Manuscript approval
AMC Research design, Supervision and approval of manuscript
All Authors have critically reviewed and approved the final draft and are responsible for contents and similarity index of the manuscript.
8. Acknowledgements: Not Applicable

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