Original Article

Associations and autoimmunity in hypothyroidism among the pregnant ladies attending a tertiary care hospital of Bangladesh

Dutta M[a], Islam MA[b], Afsana F[c], Amin MF[d], Pathan MF[e]

ABSTRACT

Background: *Autoimmune hypothyroidism in pregnancy is a very commonly encountered issue in daily clinical practice. There is an obvious demand for universal screening and treatment with levothyroxine to reduce unwanted events. The aim of the study was to find out the association and autoimmunity among the newly detected hypothyroidism during pregnancy.*

Methods: *This cross-sectional, observational study enrolled 175 pregnant women recruited by convenient sampling from the Department of Obstetrics and Gynecology, BIRDEM General Hospital, with or without diabetes. FT4 and thyroid autoantibodies were advised to those patients who had elevated TSH above the American Thyroid Association 2011-defined trimester-specific reference ranges. TSH, FT4, and anti-thyroid antibodies were tested using the chemiluminescent technique by the ADVIA centaur, Siemens. Data were analysed by SPSS version 25. Non-parametric tests were chosen for statistical analysis.*

Results: *One hundred nineteen (68%) were found in second gravida or more and 56 (32%) were found in primigravida. Among the patients, 54 (30.9%) had a history of past abortion, 34 (19.4%) had a history of subfertility, and 28 (16%) had a family history of thyroid disease. Fifty (28.6%) of the pregnant women had thyromegaly. History of subfertility and a family history of thyroid disease and thyromegaly were significantly ($p = .036$, $p < .001$, $p < .001$) higher in hypothyroid group. TPO antibodies were positive in 69.6% of hypothyroid subjects.*

Conclusions: *It is pertinent to do universal screening of all pregnant ladies including those with high risk factors for hypothyroidism in the first trimester of pregnancy to guide comprehensive management of hypothyroidism and improve the pregnancy outcomes.*

Key words: *Subclinical hypothyroidism, overt hypothyroidism, autoimmunity, pregnancy.*

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Author information

a. Mita Dutta, Medical Officer, Department of Endocrinology, BSMMU, Dhaka, Bangladesh.
b. Mohammad Aminul Islam, Medical officer, Upazilla Health Complex, Rangunia, Chattogram, Bangladesh.
c. Faria Afsana, Associate Professor, Department of Endocrinology, BIRDEM, Dhaka, Bangladesh.
d. Md. Feroz Amin, Professor & Head, Department of Endocrinology, BIRDEM, Dhaka, Bangladesh.
e. Md. Faruque Pathan, Professor of Endocrinology, Director, BIRDEM Academy, Dhaka, Bangladesh.

Address of correspondence: Mita Dutta, Medical officer, Department of Endocrinology, BSMMU, Dhaka, Bangladesh. Email: mitadutta42@gmail.com

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INTRODUCTION

Worldwide, hypothyroidism is commonly observed among the pregnant ladies.[1] The overall prevalence of subclinical hypothyroidism vary from 1.5 to 42. 9%, due to the difference in Thyroid-stimulating hormone (TSH) cut-off selection, ethnicity, iodine intake, gestational age at screening and associated co-morbidities.[2] In Bangladesh, according to Khan et al. Forty one % were suffering from subclinical hypothyroidism in pregnancy using TSH 2.5 mIU/L as the upper limit of normal in pregnancy.[3] Although throughout the globe, the common cause of hypothyroidism in pregnancy is iodine depletion, and in iodine-sufficient areas, the most

common cause is autoimmune thyroiditis.[4] Thyroid autoimmunity is one of the main causes of hypothyroidism among women of childbearing age, suggested by the presence of antibodies to thyroid peroxidase or thyroglobulin.[5] Extensive hormonal adaptations takes place in pregnancy, as a result of interactions between the feto-placental unit and the maternal endocrine system. These adaptations are crucial for successful pregnancy, parturition and lactation. There is marked alteration in every endocrine axis in pregnancy; so that interpretation of biochemical tests used to assess endocrine function require caution.[6] Elevated TSH values in pregnancy have multiple hostile outcomes for both mother and also for fetus.[7-9] However, hypothyroidism is a manageable medical condition in pregnancy that require mass awareness among the population and also to the physician. The aim of the study was to find out the association, and autoimmunity among the newly detected hypothyroidism in pregnancy.

METHODS

This cross-sectional, observational study enrolled 175 pregnant women with or without diabetes. Patients were recruited by convenient sampling from March 2018 to March 2023 from the Indoor & Outdoor, Department of Obstetrics and Gynecology, BIRDEM General Hospital. FT4 and thyroid autoantibodies were advised to those patients who had elevated TSH above the American thyroid association 2011-defined trimester-specific reference ranges.[10-12]

ATA defined criteria, euthyroidism considered having TSH 0.1 to 2.5 in first trimester, 0.2 to 3.0 in second trimester, 0.3 to 3 mIU/L in third trimester. Subclinical hypothyroidism defined by TSH above the trimester specific reference range with normal FT4 9.14 to 23.18 pmol/L, overt hypothyroidism TSH above the trimester specific reference range with low FT4 or TSH ≥10 mIU/L.[10-12]

Risk of thyroid disease considered as positive if had any one of the followings**:** Age > 30 years, para ≥2, prior pregnancy loss, history of subfertility, family history of thyroid disease, personal history of any autoimmune disease, thyromegaly, any symptoms of thyroid hypofunction.[13]

Thyroid autoantibodies considered as positive when, TPO- antibody > 60 U/ml and TG-antibody ≥4.5 IU/ml, as per the lab reports. Subfertility is a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse.[14] TSH, FT4, and anti-thyroid antibodies were tested using the chemiluminescent technique by the ADVIA centaur, Siemens. Plasma glucose analyzed by Advia-1800, SIEMENS, USA by glucose oxidase method.

Data were analysed by SPSS version 25. Categorical variables were summarized by using frequency tables, while continuous variables were presented in median and interquartile range (25^{th} and 75^{th} percentiles). Statistical analyses were done by using an appropriate statistical tool like the Pearson Chi-Square Test for categorical variables and the Mann-Whitney U test for continuous variables. The level of significance was fixed at a p value of ≤0.05.

RESULTS

A total of 175 cases were included from the three trimesters of pregnancy in the final analysis. The obstetric and clinical parameters in the studied pregnant women are given in Table I. Among the study subjects, 94 (53.7%) were at 30 years of age or younger. Major portion of the patients were second gravida or more 119 (68%), and 56 (32%) were primigravida; among the patients, 54 (30.9%) had a history of past abortion, 34 (19.4%) had a history of sub ertility, 28 (16%) had a family history of thyroid disease. Fifty (28.6%) of the pregnant women had thyromegaly. By using the ATA 2011 trimester-specific reference limits of TSH (0.1 to 2.5mIU/L in the first trimester, 0.2 to 3mIU/L in the second trimester and 0.3 to 3mIU/L in the third trimester), hypothyroidism was present in 56 (32%) participants; among them, 46 (26.3%) were subclinical hypothyroid, and 10 (5.7%) were overtly hypothyroid. The rest of the participants were euthyroid 119 (68%).

Table I. Obstetric and clinical parameters in the studied pregnant women (N=175)

Variables		Frequency (%)
Maternal age	≤ 30 years	94 (53.7)
	>30 years	81 (46.3)
Pregnancy history	Primi-gravida	56 (32)
	Second-gravida/ more	119 (68)
History of abortion	Yes	54 (30.9)
	No	121 (69.1)
History of subfertility	Yes	34 (19.4)
	No	141 (80.6)
Family history of thyroid disease	Yes	28 (16)
	No	147 (84)
Thyromegaly	Yes	50 (28.6)
	No	125 (71.4)
Thyroid function Status	Euthyroid	119 (68)
	Hypothyroid	56 (32)

History of subfertility and family history of thyroid disease was significantly (p<.05) associated with hypothyroidism (Table II). On the other hand, no significant (p>.05) association was found with age, parity, history of abortion. The risk of thyroid disease is categorized using ATA 2017 described high-risk criteria.

Table II. *Association of clinical characteristics in hypothyroid and euthyroid patients (N=175)*

Variables		Euthyroid (n= 119)	Hypothyroid (n=56)	Odds ratio	CI (95%)	p-value
Age	≤30 years	65 (54.6)	29 (51.8)	1.12	0.593- 2.118	.726
	>30 years	54 (45.4)	27 (48.2)			
Parity	Primigravida	41 (34.5)	15 (26.8)	1.43	0.712- 2.899	.310
	2nd gravida or more	78 (65.5)	41 (73.2)			
H/O abortion	Yes	37 (31.1)	17 (30.4)	0.96	0.485- 1.925	.922
	No	82 (68.9)	39 (69.6)			
H/O subfertility	Yes	18 (15.1)	16 (28.6)	2.24	1.043- 4.831	.036
	No	101(84.9)	40 (71.4)			
Family H/O thyroid disease	Yes	6 (5)	22 (39.3)	12.18	4.570- 32.494	<.001
	No	113 (95)	34 (60.7)			
Thyromegaly	Yes	25 (21)	25 (44.6)	4.04	2.039- 8.012	<.001
	No	94 (79)	31 (55.4)			
Risk of thyroid disease	Yes	98 (82.4)	52 (92.9)	2.78	0.908- 8.545	.069
	No	21 (17.6)	4 (7.1)			

Data presented as frequency (percentage), p-value by Pearson's Chi-Square Test.

Among the hypothyroid patients 39 (69.6%) were positive for TPO-antibody and the remaining 17 (30.4%) were negative for TPO-antibody. But there was no statistically significant (p >.05) difference in the TPO-antibody and TG- antibody status between the two groups of hypothyroidism. Both antibodies (TPO-antibody and TG-antibody) were positive in 18 (39.1%) cases of subclinical hypothyroidism and 5 (50%) cases of overt hypothyroidism, but that was not statistically significant (p =.527) (Table III).

Table III. Antibody status in subclinical and overt hypothyroidism patients (n=56)

Variables		Subclinical hypothyroidism (n=46)	Overt hypothyroidism (n=10)	p-value
TPO-Ab	U/ml	99 (57.25-725)	110 (51-1000)	.764
TPO-Ab	Positive	32 (69.6)	7 (70)	1.00
	Negative	14 (30.4)	3 (30)	
TG-Ab	Positive	20 (43.5)	5 (50)	.707
	Negative	26 (56.5)	5 (50)	
Both	Positive	18 (39.1)	5 (50)	.527
(TPO-Ab & TG-Ab)	Negative	28 (60.9)	5 (50)	

Data were expressed as median followed by interquartile range in parentheses or frequency (percentage). Subclinical hypothyroidism and overt hypothyroidism were categorized by ATA 2011 criteria. TPO-Ab >60 U/ml and TG-Ab ≥4.5 IU/ml considered as positive. p-value obtained by Mann-whitney U test, Pearson's Chi-Square Test or Fisher's Exact Test as applicable. TPO-Ab Thyroid peroxidase antibody, TG-Ab Thyroglobulin antibody.

DISCUSSION

In this study, 56 (32%) patients had hypothyroidism, and remaining 119 (68 %) were euthyroid when TSH cut value was used by ATA 2011. Similarly, study findings of another tertiary care hospital in Bangladesh found the overall prevalence of hypothyroidism at 29.7% based on the trimester-specific reference ranges of serum TSH of pregnancy in their study.[15] Another recent study in India found the prevalence of SCH at 25.3% by ATA 2011 defined trimester-specific reference ranges of TSH.[16]

In this study, history of subfertility (p =.036) and family history of thyroid disease (p value <.001) were significantly higher among the hypothyroid patients. Another study on Iraqi pregnant women assembled robust evidence of subfertility and a family history of thyroid disease in pregnancy (hypothyroidism). They found subfertility in 66.3% of subclinical hypothyroidism and 16.7% of overt hypothyroidism. A family history of thyroid disease was found in 58.3% of SCH and 66.7% of OH. Both parameters were statistically significant (p =.001 and p =.002) for hypothyroidism.[17]

Studies show that abortions and parity are associated with future autoimmune diseases in females.[18] Some others found no association.[19] In this study, no significant association was found with parity (p =.310), past history of abortion (p =.922) among the hypothyroid patients.

According to the ATA, the thyroid gland can increase in size during pregnancy (enlarged thyroid = goiter). There is usually a 10-15% increase in size. Pregnancy-associated goiters occur more frequently in iodine-deficient areas of the world. In our study, thyromegaly was present in 50 (28.6%) out of the 175 pregnant ladies, and among them, 25 (44.6%) had hypothyroidism, showing a significant association (p .001) of goitre with hypothyroidism. Similarly, another study in Bangladesh also found a significant association between goitre (21.1%) in pregnancy and thyroid dysfunction (p = 0.001).[15]

Study participants were further classified into two categories (having any risk factor for developing thyroid disease or not) as per the recommendation of the ATA-

2017 guideline. The risk factors were age > 30 years, para 2 or more, prior pregnancy loss, history of subfertility, family history of thyroid disease, type 1 diabetes or other autoimmune diseases, and presence of thyromegaly. In this study, out of 56 hypothyroid patients, 52 (92.9%) had one or more of the risk factors for developing thyroid disease, and 4 (7.1%) had no risk for developing thyroid disease. Total 25 (14.28%) of the study participants had no risk factors of developing thyroid disease. On a different note, a study by Islam et al. found that nearly half (48.4%) of the participants had no risk factor and 27.2% had a single risk factor.[15]

In this study, 39 (69.6%) were positive for TPO-antibody among them, 69.6% were subclinically hypothyroid, and 70% were overtly hypothyroid. Although no statistically significant discordance (p >.05) was observed in antibody status between the two groups, it still indicates autoimmunity is the prime cause of hypothyroidism in pregnancy. Similarly, study conducted by Kiran et al. found a prevalence of 74.7% positive thyroid antibodies in hypothyroid pregnant women.[20] According to the ATA 2017, thyroid autoantibodies can be detected in 30 to 60% of pregnant women with an elevated TSH. So it is apparent that autoimmunity in hypothyroidism, even in pregnancy, is quite high.

Limitations

It was a single hospital-based study that lacks generalization of findings to the overall population and may contain institution-based bias. An ultrasound of the thyroid was not performed in cases of thyromegaly.

Recommendation

Routine screening of thyroid function status should be considered in the first trimester of pregnancy with or without risk factors of hypothyroidism.

Conclusions

In pregnancy autoimmune hypothyroidism is quite common in our community. Family history of thyroid disorder, subfertility, and thyromegaly were significantly higher in hypothyroid group. If universal screening is not applied, there is a 7.1% chance of missing the hypothyroidism cases that are mainly subclinical.

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Conflicts of interest: Nothing to declare

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