

The Prevalence of Thyroid Autoimmunity in Pregnancy and Adverse Neonatal Outcomes at a Secondary Care Hospital in the Middle East

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Abstract

Background and objective

Among the common endocrinological disorders of pregnancy, thyroid disorders rank second after diabetes. Thyroid autoimmunity is linked to sub-fertility, miscarriages, preterm birth, gestational diabetes, and adverse neurodevelopmental sequelae in children. Peroxidase and thyroglobulin autoantibodies may be associated with enhanced global autoimmune state, which may have adverse effects on the fetal or placental development. It is the main cause of hypothyroidism in reproductive-age women and is associated with poor obstetric outcomes. In Gulf countries, a higher prevalence of thyroid antibodies during pregnancy was reported. However, there is paucity of data in the literature in the Gulf countries in this regard. Our study was conducted to assess the effects of thyroid antibodies on adverse maternal and neonatal outcomes in pregnancy in a multiethnic population of Qatar. The study aimed to assess the prevalence of thyroid antibodies in pregnant hypothyroid women and their impact on adverse fetal outcomes in pregnancy.

Design

A Retrospective study of patients' notes (retrospective chart review) was conducted at a secondary hospital in Qatar. Records of the women who delivered from January 2017 to June 2018 were evaluated. A total of 384 women were included after applying exclusion criteria. Neonatal outcomes were compared in hypothyroid women with (group A1) and without thyroid antibodies (group A2) and were compared with euthyroid women (group B). Statistical analysis was performed using SPSS Statistics version 27.0 (Armonk, NY: IBM Corp).

Results

A total of 7978 women delivered during the study period and the prevalence of hypothyroidism in our sample was 3.47%; 33.33% had thyroid antibodies. Women with more than one miscarriage were 30% (odds ratio {OR}: 2.06, 95% confidence interval {CI}: 1.112-3.811, $p < 0.05$), 21.24% (OR: 1.20, 95% CI: 0.676-2.115, $p > 0.05$), and 17% in group A1, A2, and B, respectively. The incidence of preterm births was 10% (OR: 2.22, 95% CI: 0.760-6.495, $p > 0.05$), 4.23% (OR: 0.94, 95% CI: 0.308-2.876, $p > 0.05$), and 4.5% in groups A1, A2, and B, respectively. Small for gestational age infants were 10% (OR: 3.33, 95% CI: 1.036-10.71, $p < 0.05$), 5.93% (OR: 1.97, 95% CI: 0.640-6.023, $p > 0.05$), and 3% in groups A1, A2, and B, respectively. The study revealed an association between thyroid antibodies and adverse maternal and neonatal outcomes in pregnancy.

Conclusion

Thyroid autoimmunity is associated with poor fetal outcomes. In Gulf countries with higher prevalence of endocrinological disorders (obesity and diabetes), thyroid disorders need attention. As fewer studies were reported from these areas with limited results in literature, this study gives an insight into the prevalence of thyroid disorders, thyroid antibodies, and their association with pregnancy outcomes.

Categories: Endocrinology/Diabetes/Metabolism, Obstetrics/Gynecology

Keywords: thyroid autoimmunity, neonatal outcome, pregnancy, thyroid antibodies, euthyroid, hypothyroid

Introduction

Among the endocrinological disorders in pregnancy, thyroid disorders rank second after diabetes. They are common in the general population with a higher preponderance in females. Interaction between estrogen and thyroid hormones is suggested as the cause of higher incidence in females [1,2]. Thyroid antibodies (TA) are reported in five to 15% of people, with a higher prevalence in elderly females [1,2]. Thyroid peroxidase antibodies (TPO-Ab) were noted in more than 80% of cases, thyroglobulin antibodies (TGA) in >50% of cases, and thyroid-stimulating hormone receptor (TSHR) antibodies in 10% of cases with Hashimoto's thyroiditis. TSHR antibodies are found in 90% of cases of Graves' disease. Thyroid peroxidase (TPO), thyroglobulin antibodies (TGA), and TPO antibodies are commonly seen in women with autoimmune

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thyroid disease (AITD) [3]. In pregnancy, the prevalence of thyroid antibodies is 2% to 17% [3,4]. Nearly 20% of women in the first trimester reveal thyroid antibodies [4]. As the pregnancy advances their levels show a decline and in the third trimester, it reaches a nadir. Their levels rise again in the post-natal period [4].

Thyroid disorders are known to be associated with adverse maternal and neonatal outcomes. The presence of thyroid antibodies worsens these outcomes [4,5]. Even euthyroid women with thyroid antibodies in the first trimester develop sub-clinical hypothyroidism in the second and third trimesters [5]. These thyroid antibodies are correlated with poor fetal outcomes [4,5]. Autoimmune hypothyroidism is associated with miscarriage, preterm birth, intrauterine fetal death (IUID), and high birth weight in the offspring [4-6].

Multiple mechanisms for adverse outcomes in pregnancy have been described. As the fetal thyroid is functional nearly after 12 weeks of gestation, low maternal thyroxine levels are detrimental to the development of the neurological system of the fetus [6]. In the latter two-thirds of pregnancy, untreated hypothyroidism can lead to cognitive disorders, low intelligence quotient (IQ) levels, activity disorders, and delays in development after birth [6,7]. Thyroid antibodies further potentiate these effects by autoimmune interaction with fetal cells [4,5]. In women with advanced maternal age, the severity increases even more [4,5].

There is a positive correlation between the presence of thyroid antibodies and miscarriage. This effect worsens with increased maternal age [4,5,8]. Women with thyroid antibodies treated with thyroxine have shown lower miscarriage and preterm births in comparison to those not treated [5,6,9,10]. However, some studies have not shown any effect on the miscarriage rate [5]. Better to say there is insufficient data available to make this conclusion. Our study was conducted in a secondary care level hospital in Qatar to assess the effects of thyroid antibodies on pregnancy outcomes.

Materials And Methods

The study is a retrospective chart review, also known as a medical record review. The study was approved by the Institutional Review Board of Medical Research Center, Qatar in 2019 (#MRC-01-18-340). The antenatal patients delivered at a secondary care hospital in Qatar from January 2017 to May 2018 were considered the cohort population. Simple random sampling was used to get the required sample size and to avoid any selection barrier. A total of 7978 women delivered in the study period. Of these, 287 women were diagnosed with hypothyroidism and attended the endocrine clinic. The sample size was 400 patients. Out of these, 200 hypothyroid women were included and 200 women were taken as control by random sampling method. Based on the exclusion criteria 16 hypothyroid pregnant women were excluded. The study population was divided into two main groups; group A which included antenatal patients with hypothyroidism (n=184) and group B (control) which comprised antenatal patients without hypothyroidism (n=200). Group A patients were further divided into those with thyroid antibodies (A1) and those without thyroid antibodies (A2). Post-natal, follow-up was noted at six to eight weeks.

All the pregnant women (18-40 years of age) in the study timeline who had antenatal care in our hospital were included in this study. Patients with recurrent pregnancy loss, overt diabetes, essential hypertension, antenatal care in other hospitals, and incomplete documents/data were excluded. In the control population, euthyroid women with positive thyroid antibodies were excluded. A total of 400 pregnant women were included in the study. After applying exclusion criteria 184 hypothyroid and 200 euthyroid women were part of the study. It was computed based on the effect size (difference in the primary outcome measures between two groups) reported in the literature. Informed consent was not applicable, as the data were retrieved from medical records. Following fetal outcomes; miscarriage, preterm birth (PTB), small for dates infants (SFD), large for date infants (LFD), admissions to neonatal intensive care unit (NICU), and intrauterine fetal death (IUID) were noted in each group and compared with controls (women without hypothyroidism).

Descriptive statistics were used to summarize and determine the sample characteristics and distribution of parameters related to maternal and neonatal parameters. The normally distributed data and results were reported with mean and standard deviation (SD) with a corresponding 95% confidence interval (CI); the remaining results were reported with median and interquartile range (IQR). Categorical data were summarized using frequencies and percentages. The primary outcome measure was to determine and compare the key fetal outcomes among antenatal women with and without autoimmune hypothyroidism. Comparisons of quantitative data between two groups (antenatal women with and without autoimmune hypothyroidism with those without hypothyroidism) were performed by applying the unpaired t-test or Mann-Whitney U test as appropriate. Associations between two or more qualitative variables were assessed using the chi-square (χ^2) test and/or Fisher's exact test as appropriate. The relationship between hypothyroidism and associated factors was estimated by deriving odds ratios (ORs) from the logistic regression model and results were presented and reported with an odds ratio (OR) and associated 95% CI. All p-values presented were two-tailed, and p-values <0.05 were considered statistically significant. All statistical analyses were performed using statistical packages SPSS version 27.0 (Armonk, NY: IBM Corp) and Epi-info (Centers for Disease Control and Prevention: Atlanta, GA) software.

Results

Demographics of women in the study population

Table 1 shows the demographic characteristics of the hypothyroid women in the study population. Both the groups of women were comparable in all these parameters ($p>0.05$). Most of the women were in the age range of 26-35 years. In hypothyroid women with and without thyroid antibodies, 80.95% and 84.3% of women were in this range, respectively ($p>0.05$). Women above 40 years were not included in the study to elude age-related bias. In both groups, nulliparous and multiparous women were in the nearly same proportion. Nulliparous women were 25.4% and 20.66% in each group ($p>0.05$), while multiparous women were 74.6% and 79.34%, respectively ($p>0.05$). Women with thyroid antibodies had a higher likelihood of being overweight (33.33%) and obese (34.93%) in comparison to women without thyroid antibodies (overweight: 24.79% and obese: 29.75%). But the results were not statistically significant ($p>0.05$).

Demographic		Hypothyroid with thyroid-antibody, n (%)	Hypothyroid without thyroid-antibody, n (%)	OR	95% CI	P-Value
Age (years)	Overall					0.372
	20-25	8 (12.70%)	17 (14.05%)	0.94	0.381-2.324	0.895
	26-30	26 (41.27%)	53 (43.80%)	0.87	0.466-1.614	0.653
	31-35	25 (39.68%)	49 (40.50%)	1.02	0.546-1.909	0.950
	36-40	1 (1.59%)	2 (1.65%)	0.96	0.085-10.793	0.973
Parity	Nulliparous	16 (25.40%)	25 (20.66%)	1.31	0.637-2.680	0.465
	Multiparous	47 (74.60%)	96 (78.51%)	0.77	0.373-1.568	0.465
	Overall					0.267
Body mass index (BMI)	Normal weight (BMI <25 kg/m ²)	20 (31.75%)	55 (45.45%)	0.56	0.294-1.058	0.074
	Overweight (BMI = 25-29.9 kg/m ²)	21 (33.33%)	30 (24.79%)	1.52	0.779-2.955	0.221
	Obese (BMI >30 kg/m ²)	22 (34.92%)	36 (29.75%)	1.27	0.663-2.423	0.474

TABLE 1: The demographic characteristics of the hypothyroid women with and without thyroid antibodies in the study population.

OR: odds ratio, CI: confidence interval

Prevalence of hypothyroidism and thyroid antibodies

The overall prevalence of hypothyroidism in the study population was 3.60% (287 {hypothyroid pregnant women delivered} / 7978 {total women delivered in the study period}). A total of 35% of women had hypothyroidism before pregnancy. And 25.56% of women had the first diagnosis in the first trimester while 22.78% and 16.67% of women were diagnosed in the second and third trimester, respectively. A total of 33.33% of all hypothyroid women had thyroid antibodies. Thyroid peroxidase antibodies (TPO-Ab) were noted in all these cases and thyroglobulin antibodies (TGA) in 4.44% of women. All the women with thyroglobulin antibodies also had TPO-Ab.

Level of thyroid antibodies hormones in the study population

In women with hypothyroidism with thyroid antibodies, the value of TSH ranged from 3.2 to 40.47 mIU/L at the time of diagnosis. The average value of TSH in this group was 8.11 mIU/L. The level of free T4 was in the

range of 0.01-15.24 pmol/L, with an average of 11.4 pmol/L. In hypothyroid women without thyroid antibodies, the average level of TSH and free thyroxine (FT4) were 5.55 mIU/L and 11.08 pmol/L, respectively (TSH ranged from 2.62 to 29.56 mIU/L and FT4 ranged from 5.6 to 15.91 pmol/L). In women with thyroid antibodies, higher levels of TSH were noted in comparison to those without thyroid antibodies; levels of FT4 were similar (Table 2).

Variables	Number of women	Range of FT3	Average FT3 (pg/mL)	Range of FT4	Average FT4 (pmol/L)	Range of TSH	Average TSH mIU/L
Euthyroid women	201	2.87-10.9	4.59	6.11-14.31	10.83	1.11-2.7	1.81
Hypothyroid women without antibody	120	2.48-10.9	4.1	5.6-15.91	11.08	2.62-29.56	5.55
Hypothyroid women with antibody	63	3.08-11.2	4.25	0.01-15.24	11.4	3.2-40.47	8.11

TABLE 2: Range and average of FT3, FT4, and TSH in the study population.

FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid-stimulating hormone

Neonatal outcomes

A comparative analysis was carried out between hypothyroid women with (n=63) or without (n=120) thyroid antibodies and euthyroid women (n=201) were taken as control. Intrauterine fetal deaths (IUFD) were excluded in calculating statistics for preterm birth (PTB), small for dates (SFD) infants, large for dates (LFD) infants, and neonatal intensive care unit (NICU) admissions. Neonatal outcomes were noted in each group and then compared with the control. Statistical analysis was performed.

Neonatal outcomes were compared in hypothyroid women with and without thyroid antibodies and a comparative analysis was done with euthyroid women in the study population. Number of women with previous miscarriages were more frequent in the group with thyroid antibodies (34.04%) as compared to hypothyroid women without thyroid antibodies (25.26%). Hypothyroid women had a higher prevalence of miscarriage as compared to euthyroid women and the results were statistically significant ($p < 0.05$).

Incidence of preterm births was 10%, 4.2%, and 4.5% in hypothyroid women with and without thyroid antibodies and euthyroid women, respectively. A positive correlation was noted between preterm birth and thyroid antibodies, however, the results were not statistically significant ($p > 0.05$). Incidence of small for dates infants were 10%, 5.88%, and 3% in hypothyroid women with and without thyroid antibodies and euthyroid women, respectively. A positive correlation between small for date babies and the presence of thyroid antibodies was noted and the results were statistically significant (OR: 3.592, 95% CI: 1.114-11.588, $p < 0.05$).

The prevalence of large for dates babies in all the three groups was nearly similar (11.73%, 10.92%, and 9%, respectively). A higher incidence of neonatal ICU admissions (with respiratory morbidity) was noted in women with thyroid antibodies (21.67%) and hypothyroid women (15.97%) as compared to euthyroid women (8.5%). Results were statistically significant in both groups of hypothyroid women with (OR: 2.98, 95% CI: 1.351-6.561, $p < 0.05$) and without thyroid antibodies (OR: 2.05, 95% CI: 1.017-4.112, $p < 0.05$). Intrauterine fetal deaths were higher in women with thyroid antibodies (5%, OR: 10, 95% CI: 1.021-97.916, $p < 0.05$) as compared to hypothyroid women without thyroid antibodies and euthyroid women and the results were statistically significant (Table 3).

Variables		Hypothyroid women, n (%)	Euthyroid women, n (%)	OR	95% CI	p-Value
Previous miscarriage	With Ab	16 (34.04%)	27 (15.43%)	2.83	1.364-5.868	0.005
	Without Ab	24 (25.26%)	27 (15.43%)	1.85	0.998-3.439	0.050
Preterm birth	With Ab	6 (10%)	9 (4.5%)	2.36	0.804-6.918	0.118
	Without Ab	5 (4.20%)	9 (4.5%)	0.93	0.304-2.846	0.899
Small for dates	With Ab	6 (10%)	6 (3.00%)	3.59	1.114-11.588	0.032
	Without Ab	7 (5.88%)	6 (3.00%)	2.02	0.663-6.163	0.216
Large for dates	With Ab	7 (11.67%)	18 (9%)	1.34	0.530-3.368	0.540
	Without Ab	13 (10.92%)	18 (9%)	1.24	0.584-2.632	0.575
NICU admission	With Ab	13 (21.67%)	17 (8.5%)	2.98	1.351-6.56	0.007
	Without Ab	19 (15.97%)	17 (8.5%)	2.05	1.017-4.112	0.045
Intrauterine fetal death	With Ab	3 (5%)	1 (0.5%)	10.00	1.021-97.916	0.048
	Without Ab	2 (1.65%)	1 (0.5%)	3.33	0.299-37.156	0.328

TABLE 3: Neonatal outcomes in hypothyroid women with and without thyroid antibody in comparison with euthyroid women.

Ab: antibody, NICU: neonatal intensive care unit, OR: odds ratio, CI: confidence interval

Neonatal outcomes were also compared between hypothyroid women with and without thyroid antibodies. Prevalence of preterm labor (10% versus 4.2%), small for dates babies (10% versus 5.88%), NICU admissions (21.67% versus 15.97%), and intrauterine fetal death (5% versus 1.65%) was higher in women with thyroid antibodies as compared to hypothyroid women without thyroid antibodies. However, the results were not statistically significant ($p < 0.05$). No difference was noted in the prevalence of large for date babies in both groups. A higher prevalence of women with previous miscarriages was noted in women with thyroid antibodies as compared to those without thyroid antibodies (34.04% versus 25.26%) (Table 4).

Variables	Hypothyroid women with antibody, n (%)	Hypothyroid women without antibody, n (%)	Odds Ratio	95% CI	p-Value
Previous miscarriage	16 (34.04%)	24 (25.26%)	1.53	0.714-3.266	0.275
Preterm birth	6 (10%)	5 (4.20%)	2.51	0.734-8.594	0.142
SFD	6 (10%)	7 (5.88%)	1.78	0.570-5.546	0.322
LFD	7 (11.67%)	13 (10.92%)	0.32	0.406-2.859	0.882
NICU admission	13 (21.67%)	19 (15.97%)	1.46	0.663-3.195	0.349
IUFD	3 (5%)	2 (1.65%)	2.98	0.484-18.287	0.239

TABLE 4: Neonatal outcomes in hypothyroid women with and without thyroid antibodies.

SFD: small for dates, LFD: large for dates, NICU: neonatal intensive care unit, IUFD: intrauterine fetal death

Discussion

Thyroid antibodies are noted in 2-17% of women during pregnancy [10]. But they are also noted in euthyroid women. Euthyroid women with thyroid antibodies autoimmunity are commonly noted to have high TSH levels >4 mU/L during pregnancy. It is also correlated with iodine intake and ethnicity [10]. Levels of TSH in

women with thyroid antibodies autoimmunity are also higher than in those without thyroid antibodies [9]. Thyroid antibodies attain peak serum levels in the first trimester and reduce to nearly 60% in the later pregnancy [11,12]. TSH levels in women with thyroid antibodies autoimmunity are accelerated with advancements in the period of gestation. An increase in TSH level from 1.7 mIU/L at 12 weeks to 5.5 mIU/L at term is reported. Hence a four-weekly assessment is recommended during pregnancy [10]. As the placenta is permeable to thyroid antibodies, there is a possibility of its effect on the fetus [13]. Many fetal complications like miscarriages, preterm birth, IUGR, and birth weight disorders are associated with thyroid autoimmunity [5,14].

Rates of miscarriages are higher in women with hypothyroidism [14]. Studies have demonstrated a nearly two-fold increase in thyroid antibodies as compared to women without them [15,16]. The exact mechanism for the increase in miscarriages is not known. However, several theories have been suggested which include high levels of endometrial cytokines, Ab-mediated mild thyroid antibodies hypofunction, non-organ specific autoimmunity, and human chorionic gonadotropin (hCG) receptors cross-immunity by thyroid antibodies in these women [17,18]. Imaizumi et al. have suggested the possibility of fetal resorption which was noted in active immunization in murine [19]. In our study, higher miscarriage rates were noted in women with thyroid antibodies autoimmunity (OR: 2.059, 95% CI: 1.112-3.811, $p=0.0215$) and the results were statistically significant.

Preterm birth (PTB) is associated with neonatal morbidity, mortality, and long-term effects. It also lays economic impacts on the hospitals and the parents. Despite advancements in obstetrics, preterm birth is still unpredictable. Many studies in the past have correlated PTB with hypothyroidism. The effects of thyroid antibodies on PTB have been evaluated by many authors with variable results. Many authors have reported a higher incidence of PTB in women with thyroid antibodies. Glinoe et al., Ghafoor et al., and Kumru et al. in their studies have demonstrated that women with thyroid antibodies have a higher likelihood of preterm delivery. Their results were statistically significant [20-22].

In a meta-analysis by Negro, Thangaratnam et al., and He et al., an association of preterm births (PTB) with thyroid antibodies was observed. All these studies revealed a positive correlation between PTB with TPO antibodies [23-25]. In our study also a higher incidence of PTB was observed in women with thyroid antibodies. The incidence of PTB was 10% (OR: 2.22, 95% CI: 0.760-6.495, $p=0.145$) in women with thyroid antibodies, 4.23% (OR: 0.9416, 95% CI: 0.308-2.876, $p=0.9159$) in women with hypothyroidism without thyroid antibodies, and 4.5% in the control group. The results were not statistically significant. Negro et al. also noted that women with thyroid antibodies who were treated with levothyroxine had a lower incidence of PTB as compared to those who were not treated (7% versus 22.4%, $p<0.05$) and the result was statistically significant [12]. In this regard, very few studies are available and further studies are required to establish the correlation with PTB.

The effects of hypothyroidism on neonatal birth weight have been studied by many authors. In a few studies, hypothyroidism is correlated with low birth weight (LBW) [26-29], in some with high birth weight (HBW) [30,31], and some have not reported any effect [32]. Karakosta et al. in their study reported that hypothyroid women with thyroid antibodies have three times higher risk for LBW (OR: 3.1, 95% CI: 1.2-8.0) as compared to controls. However, women with normal TSH levels with thyroid antibodies did not affect birth weight [27,28]. Till now, no causal relationship with birth weight has been established. The mechanism behind LFD infants with autoimmunity is suggested to be linked to a high prevalence of obesity and diabetes in women with thyroid antibodies [30,31].

In this study, a higher prevalence of small for dates (SFD) infants was noted in women with thyroid antibodies (10%, OR: 3.33, 95% CI: 1.0368-10.71, $p=0.0433$) as compared to women without thyroid antibodies (5.93%) and controls (3%). Few studies have noted a correlation between hypothyroidism and large for dates infants. Negro et al. in 2011 noted an insignificant difference in high birth weight neonates in hypothyroid women with and without thyroid antibodies [23]. In our study higher neonatal intensive care (NICU) admissions were noted in women with thyroid antibodies. In some studies, no association was noted [33] and some authors have reported prolonged NICU stay in neonates of hypothyroid women with thyroid antibodies [29,34]. Kiran et al. have noted lower NICU admissions in women with thyroid antibodies [35]. Meena et al. in 2016 have noted poor neonatal outcomes even in euthyroid women [33].

In a study by Janna et al. in 2016, 1025 women with stillbirth were evaluated to assess the utility of thyroid antibody function in this group. Only 2% of women were known to have thyroid antibody disease. But in the rest of the women, nearly 18% of them were diagnosed to have thyroid antibodies abnormality. Out of these, 16.23% had clinical or sub-clinical hypothyroidism [36]. Chen et al. reported a higher incidence of fetal loss in women with overt thyroid antibody dysfunction. With a doubling of TSH levels, a 60% increase in the incidence of child loss was noted in their study [37]. In another study, IUGR was noted in 2.4% of women with thyroid peroxidase antibodies and 3.1% of women with thyroglobulin antibodies. In women without thyroid antibodies, none of them had any fetal loss [35]. In a study by Meena et al., no difference was noted in IUGR in both groups. Most of these studies had a small sample size of women with IUGR [23,33,35,37]. Studies with a larger sample size are recommended in this regard.

Treatment with L-thyroxine has been associated with better neonatal outcomes [38]. Reduced incidence of PTB and miscarriage were observed by Negro et al. after treatment with L-thyroxine [12]. Gartner et al. have reported reduced levels of thyroid antibodies after Selenium supplementation [39]. These women should be monitored every four to six weeks till reference TSH levels are attained and then in every trimester. The dose of therapy should be adjusted with TSH levels. Neonates of these women have a higher incidence of low TSH at birth and thyroid antibodies. Zhang et al. in their study reported that 28% of neonates had a TSH value more than the reference range for age [40]. These neonates need full evaluation and follow-up. Thus, pre-pregnancy control is required to reduce neonatal complications [41].

In the post-natal period, these thyroid antibodies rise again and a study by Chen et al. in 2016 has noted a higher incidence of postpartum thyroiditis in women with thyroid antibodies (42.31% versus 7.14%) in comparison to control [29]. Hence post-natal follow-up at six weeks should be considered mandatory in these women for adjustment of the dose of the therapy. Gulf countries are known to have a high prevalence of population with high body mass index and a high prevalence of endocrinological disorders. Very few studies are published on neonatal outcomes in women with thyroid autoimmunity in this region [42-44]. More studies in this regard in Gulf countries will aid in to conclude.

Strengths and limitation

Our study included a thorough analysis of association between maternal thyroid antibodies and neonatal outcomes. This study has excluded age-related bias as study participants were less than 35 years of age. In advanced maternal age, neonatal outcomes may be poor and the prevalence of thyroid antibodies may be high. As the study was performed on a multi-ethnic population, ethnicity-related bias was excluded. In Gulf countries with higher prevalence of endocrinological disorders e.g., obesity and diabetes, thyroid disorders need attention and fewer studies were reported with limited results. This study gives an insight into the prevalence of thyroid disorders, thyroid antibodies, and its association with pregnancy outcomes. The limitation of this study is that it was retrospective and of a reasonable sample size. Future studies with a larger sample size will aid in clearer recommendations.

Conclusions

It is well established that hypothyroidism in pregnancy is associated with maternal and neonatal complications. These complications may be worsened in women with thyroid antibodies. Attaining normal TSH levels during pregnancy through adequate and timely management could possibly reduce these complications. Hence a combined strategy of maternal and fetal surveillance should be implemented on these women. A multidisciplinary approach involving an obstetrician, physician endocrinologist, and neonatologist should be planned for this cohort of women. This should also include a post-natal follow-up. Close monitoring of TSH levels in each trimester and appropriate adjustments in the therapy is the key to preventing neonatal complications. We provide further evidence that thyroid autoimmunity in our heterogeneous population in the Middle East, is associated with adverse outcomes in both early and late pregnancy, and suggest that further research into both the prevalence of these complications and the effect of thyroxine treatment is undertaken. In euthyroid women with thyroid antibodies in pregnancy, the initiation of the therapy is not yet recommended because of insufficient evidence to reduce miscarriage and PTB. Future studies in this regard may draw some clear consensus.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Review Board of Medical Research Center, Qatar issued approval #MRC-01-18-340. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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References

1. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE: Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab.* 2002, 87:489-99. [10.1210/jcem.87.2.8182](https://doi.org/10.1210/jcem.87.2.8182)
2. Amouzegar A, Gharibzadeh S, Kazemian E, Mehran L, Tohidi M, Azizi F: The prevalence, incidence and natural course of positive antithyroperoxidase antibodies in a population-based study: Tehran thyroid

- study. *PLoS One*. 2017, 12: [10.1371/journal.pone.0169283](https://doi.org/10.1371/journal.pone.0169283)
3. Nakamura H, Usa T, Motomura M, et al.: Prevalence of interrelated autoantibodies in thyroid diseases and autoimmune disorders. *J Endocrinol Invest*. 2008, 31:861-5. [10.1007/BF03346432](https://doi.org/10.1007/BF03346432)
 4. Balucan FS, Morshed SA, Davies TF: Thyroid autoantibodies in pregnancy: their role, regulation and clinical relevance. *J Thyroid Res*. 2013, 2013: [10.1155/2013/182472](https://doi.org/10.1155/2013/182472)
 5. Ross DS: Overview of thyroid antibodies disease and pregnancy . UpToDate. 2020,
 6. Delitala AP, Capobianco G, Cherchi PL, Dessole S, Delitala G: Thyroid function and thyroid disorders during pregnancy: a review and care pathway. *Arch Gynecol Obstet*. 2019, 299:327-38. [10.1007/s00404-018-5018-8](https://doi.org/10.1007/s00404-018-5018-8)
 7. Pääkkilä F, Männistö T, Hartikainen AL, et al.: Maternal and child's thyroid function and child's intellect and scholastic performance. *Thyroid*. 2015, 25:1363-74. [10.1089/thy.2015.0197](https://doi.org/10.1089/thy.2015.0197)
 8. Prummel MF, Wiersinga WM: Thyroid autoimmunity and miscarriage. *Eur J Endocrinol*. 2004, 150:751-5. [10.1550/eje.0.1500751](https://doi.org/10.1550/eje.0.1500751)
 9. Glinoe D: Miscarriage in women with positive anti-TPO antibodies: is thyroxine the answer? . *J Clin Endocrinol Metab*. 2006, 91:2500-2. [10.1210/jc.2006-0834](https://doi.org/10.1210/jc.2006-0834)
 10. Alexander EK, Pearce EN, Brent GA, et al.: 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017, 27:315-89. [10.1089/thy.2016.0457](https://doi.org/10.1089/thy.2016.0457)
 11. Glinoe D, Riahi M, Grün JP, Kinthaert J: Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid antibodies disorders. *J Clin Endocrinol Metab*. 1994, 79:197-204. [10.1210/jcem.79.1.8027226](https://doi.org/10.1210/jcem.79.1.8027226)
 12. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H: Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab*. 2006, 91:2587-91. [10.1210/jc.2005-1603](https://doi.org/10.1210/jc.2005-1603)
 13. Seror J, Amand G, Guibourdenche J, Ceccaldi PF, Luton D: Anti-TPO antibodies diffusion through the placental barrier during pregnancy. *PLoS One*. 2014, 9: [10.1371/journal.pone.0084647](https://doi.org/10.1371/journal.pone.0084647)
 14. De Vivo A, Mancuso A, Giacobbe A, et al.: Thyroid function in women found to have early pregnancy loss . *Thyroid*. 2010, 20:633-7. [10.1089/thy.2009.0323](https://doi.org/10.1089/thy.2009.0323)
 15. Stagnaro-Green A, Roman SH, Cobin RH, el-Harazy E, Alvarez-Marfany M, Davies TF: Detection of at-risk pregnancy by means of highly sensitive assays for thyroid autoantibodies. *JAMA*. 1990, 264:1422-25. [10.1001/jama.1990.03450110068029](https://doi.org/10.1001/jama.1990.03450110068029)
 16. Chen L, Hu R: Thyroid autoimmunity and miscarriage: a meta-analysis. *Clin Endocrinol (Oxf)*. 2011, 74:513-9. [10.1111/j.1365-2265.2010.03974.x](https://doi.org/10.1111/j.1365-2265.2010.03974.x)
 17. Twig G, Shina A, Amital H, Shoenfeld Y: Pathogenesis of infertility and recurrent pregnancy loss in thyroid autoimmunity. *J Autoimmun*. 2012, 38:275-81. [10.1016/j.jaut.2011.11.014](https://doi.org/10.1016/j.jaut.2011.11.014)
 18. Lee YL, Ng HP, Lau KS, Liu WM, O WS, Yeung WS, Kung AW: Increased fetal abortion rate in autoimmune thyroid disease is related to circulating TPO autoantibodies in an autoimmune thyroiditis animal model. *Fertil Steril*. 2009, 91:2104-9. [10.1016/j.fertnstert.2008.07.1704](https://doi.org/10.1016/j.fertnstert.2008.07.1704)
 19. Imaizumi M, Pritsker A, Kita M, Ahmad L, Unger P, Davies T: Pregnancy, and murine thyroiditis: thyroglobulin immunization leads to fetal loss in specific allogeneic pregnancies. *Endocrinology*. 2001, 142:823-9. [10.1210/endo.142.2.7966](https://doi.org/10.1210/endo.142.2.7966)
 20. Glinoe D, Soto MF, Bourdoux P, et al.: Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *J Clin Endocrinol Metab*. 1991, 75:421-7. [10.1210/jcem-75-2-421](https://doi.org/10.1210/jcem-75-2-421)
 21. Ghafoor F, Mansoor M, Malik T, Malik MS, Khan AU, Edwards R, Akhtar W: Role of thyroid peroxidase antibodies in the outcome of pregnancy. *J Coll Physicians Surg Pak*. 2006, 16:468-71.
 22. Kumru P, Erdogdu E, Arisoy R, et al.: Effect of thyroid dysfunction and autoimmunity on pregnancy outcomes in low risk population. *Arch Gynecol Obstet*. 2015, 291:1047-54. [10.1007/s00404-014-3533-9](https://doi.org/10.1007/s00404-014-3533-9)
 23. Negro R: Thyroid autoimmunity and pre-term delivery: brief review and meta-analysis. *J Endocrinol Invest*. 2011, 34:155-8. [10.1007/BF03347047](https://doi.org/10.1007/BF03347047)
 24. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A: Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ*. 2011, 342: [10.1136/bmj.d2616](https://doi.org/10.1136/bmj.d2616)
 25. He X, Wang P, Wang Z, He X, Xu D, Wang B: Thyroid antibodies and risk of preterm delivery: a meta-analysis of prospective cohort studies. *Eur J Endocrinol*. 2012, 167:455-64. [10.1530/EJE-12-0379](https://doi.org/10.1530/EJE-12-0379)
 26. Wikner BN, Sparre LS, Stiller CO, Källén B, Asker C: Maternal use of thyroid hormones in pregnancy and neonatal outcome. *Acta Obstet Gynecol Scand*. 2008, 87:617-27. [10.1080/00016340802075103](https://doi.org/10.1080/00016340802075103)
 27. Karakosta P, Alegakis D, Georgiou V, et al.: Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. *J Clin Endocrinol Metab*. 2012, 97:4464-72. [10.1210/jc.2012-2540](https://doi.org/10.1210/jc.2012-2540)
 28. Su PY, Huang K, Hao JH, et al.: Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. *J Clin Endocrinol Metab*. 2011, 96:3234-41. [10.1210/jc.2011-0274](https://doi.org/10.1210/jc.2011-0274)
 29. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG: Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol*. 2005, 105:239-45. [10.1097/01.AOG.0000152345.99421.22](https://doi.org/10.1097/01.AOG.0000152345.99421.22)
 30. Brix TH, Kyvik KO, Hegedüs L: Low birth weight is not associated with clinically overt thyroid disease: a population based twin case-control study. *Clin Endocrinol (Oxf)*. 2000, 53:171-6. [10.1046/j.1365-2265.2000.01025.x](https://doi.org/10.1046/j.1365-2265.2000.01025.x)
 31. Andersen SL, Olsen J, Wu CS, Laurberg P: Low birth weight in children born to mothers with hyperthyroidism and high birth weight in hypothyroidism, whereas preterm birth is common in both conditions: a Danish National Hospital Register study. *Eur Thyroid J*. 2013, 2:135-44. [10.1159/000350513](https://doi.org/10.1159/000350513)
 32. Männistö T, Väärasmäki M, Pouta A, et al.: Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. *J Clin Endocrinol Metab*. 2009, 94:772-9. [10.1210/jc.2008-1520](https://doi.org/10.1210/jc.2008-1520)
 33. Meena A, Nagar P: Pregnancy outcome in euthyroid women with anti-thyroid peroxidase antibodies . *J*

- Obstet Gynaecol India. 2016, 66:160-5. [10.1007/s13224-014-0657-6](https://doi.org/10.1007/s13224-014-0657-6)
34. Moleti M, Sturniolo G, Di Mauro M, Russo M, Vermigli F: Autoimmune Thyroid antibodies diseases and pregnancy. *Ann Thyroid*. 2018, 3: [10.21037/aot.2018.07.03](https://doi.org/10.21037/aot.2018.07.03)
 35. Kiran Z, Sheikh A, Islam N: Association of thyroid antibodies status on the outcomes of pregnant women with hypothyroidism (maternal hypothyroidism on pregnancy outcomes, MHPO-4). *BMC Pregnancy Childbirth*. 2021, 21: [10.1186/s12884-021-03594-y](https://doi.org/10.1186/s12884-021-03594-y)
 36. Männistö T, Mendola P, Reddy U, Laughon SK: Neonatal outcomes and birth weight in pregnancies complicated by maternal thyroid disease. *Am J Epidemiol*. 2013, 178:731-40. [10.1093/aje/kwt031](https://doi.org/10.1093/aje/kwt031)
 37. Chen X, Jin B, Xia J, Tao X, Huang X, Sun L, Yuan Q: Effects of thyroid peroxidase antibody on maternal and neonatal outcomes in pregnant women in an iodine-sufficient area in China. *Int J Endocrinol*. 2016, 2016: [10.1155/2016/6461380](https://doi.org/10.1155/2016/6461380)
 38. Rovelli R, Vigone MC, Giovanettoni C, et al.: Newborn of mothers affected by autoimmune thyroiditis: the importance of thyroid function monitoring in the first months of life. *Ital J Pediatr*. 2010, 36: [10.1186/1824-7288-36-24](https://doi.org/10.1186/1824-7288-36-24)
 39. Gartner R, Gasnier BC, Dietrich JW, Krebs B, Angstwurm MW: Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. *J Clin Endocrinol Metab*. 2002, 87:1687-91. [10.1210/jcem.87.4.8421](https://doi.org/10.1210/jcem.87.4.8421)
 40. Zhang D, Cai K, Wang G, et al.: Trimester-specific reference ranges for thyroid hormones in pregnant women. *Medicine (Baltimore)*. 2019, 98: [10.1097/MD.00000000000014245](https://doi.org/10.1097/MD.00000000000014245)
 41. Spencer L, Bubner T, Bain E, Middleton P: Screening and subsequent management for thyroid dysfunction pre-pregnancy and during pregnancy for improving maternal and infant health. *Cochrane Database Syst Rev*. 2015, [10.1002/14651858.CD011263.pub2](https://doi.org/10.1002/14651858.CD011263.pub2)
 42. Fallatah AM, Hasanain A, Babatin H, Nassibi KM, Thigah S, Abduljabbar HS: Pregnancy outcomes among obese pregnant women with hypothyroidism: medical record review of a single tertiary center in Saudi Arabia. *Cureus*. 2020, 12: [10.7759/cureus.6938](https://doi.org/10.7759/cureus.6938)
 43. Saki F, Dabbaghmanesh MH, Ghaemi SZ, Forouhari S, Omrani GR, Bakshayeshkaram M: Thyroid autoimmunity in pregnancy and its influences on maternal and fetal outcome in Iran (a prospective study). *Endocr Res*. 2015, 40:139-45. [10.3109/07435800.2014.966384](https://doi.org/10.3109/07435800.2014.966384)
 44. Iravani AT, Saeedi MM, Pakraveshteh J, Hamidi S, Abbasi M: Thyroid autoimmunity and recurrent spontaneous abortion in Iran: a case-control study. *Endocr Pract*. 2008, 14:458-64. [10.4158/EP.14.4.458](https://doi.org/10.4158/EP.14.4.458)