Adverse pregnancy outcome in Saudi women diagnosed with overt hypothyroidism during pregnancy , with and without thyroid peroxidase antibodies.

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Abstract: **Background**: there has been increased evidence of unfavorable pregnancy outcome in hypothyroid women especially in those with thyroid peroxidase antibodies (anti-TPO). **Objective**: To detect the pregnancy outcome of overt hypothyroid patients with and without anti-TPO. **Methods:** This cohort study was conducted on 125 pregnant Saudi women recently diagnosed with overt hypothyroidism selected from antenatal care at Madina Maternity and Children hospital and Ohud hospital between July 2009 and June 2012. TPO antibodies were measured by chemiluminescent immunoassay in all patients .Patients received treatment and were followed up till delivery .All maternal complications, perinatal and neonatal outcomes were recorded. **RESULTS**: overt hypothyroidism women with anti-TPO (31.2%) were older (34.5±7.73 vs. 29±6.55 years, p=0.005), had more disturbed thyroid function (higher TSH (44.2 ±10.0 VS. 29.5±6.47, p=0.001), lower FT4 (8.0±1.13 vs. 9.1 ± 1.09,p=0.001) and FT3 (3.0± 0.73 vs. 3.4±0.71 ,p=0.021). They had more complications with pregnancy (OR4.4,95 %CI1.96-9.8,p=0.001) including GDM (p=0.001) and IUFD (p=0.002). Also they had more loss of their pregnancies (OR3,95 %CI1.09-7.99) ,lower gestational age at delivery (35.2±5.33vs.37.7±1.19,p=0.001) and more CS (OR2.4,95%CI1.03-5.46, p=0.09) . Newborn babies of seropositive patients had significantly lower Apgar score (7.5±2.13vs.8.5±0.93, p=0.001). And birth weight (2.6±0.45vs.2.7±0.45, p=0.048) than sero-negative women .Significant correlation with anti-TPO was detected with age, thyroid function and most pregnancy outcomes .**Conclusion**: TPO sero-positivity greatly increases the pregnancy risk associated with overt hypothyroidism among Saudis and hence those patients should be screened early in pregnancy and monitored aggressively.
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Key words: Thyroid Peroxidase Antibody (TPO), Thyroid, Pregnancy

1. Introduction

Over the last decade, there has been enhanced awareness of the morbidity of hypothyroidism during pregnancy. Maternal hypothyroidism could adversely affect maternal and fetal outcomes with greater risk in overt, rather than subclinical hypothyroidism (1-3). The prevalence of overt hypothyroidism during pregnancy is estimated to be 0.3–0.5% .Autoimmune thyroiditis represents the commonest cause of maternal hypothyroidism (4) followed by post radio-iodine therapy , thyroidectomy ,iodine deficiency and transient thyroiditis .Decreased fertility is well known in untreated maternal hypothyroidism (5). If conception happened , the risk of pregnancy complications is high including abortion ,gestational hypertension ,abruption placenta and postpartum hemorrhage (1-3) .Also ,the neonatal complications are increased with possible preterm birth ,low birth weight ,and respiratory distress .Even later on children born to uncontrolled hypothyroid mothers have the risk of low IQ scores ,neuropsychological developmental indices and learning abilities (5-9). Many researchers have found adverse pregnancy out comes in women with autoimmune thyroiditis even in the absence of thyroid dysfunction (10,11). At animal model, autoimmune thyroiditis is found to be associated with reduced fertility and higher incidence of fetal loss. It is thought that anti-TPO antibody may affect post-implantation embryo development , leading to fetal loss (12) .During pregnancy ,the titres of antibodies decrease to protect fetus from abortion ;but just after delivery they rise back to their pre-pregnancy levels(13).It has been suggested that anti-thyroid antibodies may serve as peripheral markers for abnormal T cell function that is thought to be responsible for pregnancy loss (14) .It seems that the combination of overt hypothyroidism and autoimmune thyroiditis , as the underlying cause , represents composite risk for adverse pregnancy outcomes .Moreover, this combination was found in one study to predict later on set of thyroid dysfunction as well as diabetes (15) .There are no enough studies were performed among pregnant Saudi despite the presumed high rates thyroid dysfunction (17). This study aimed at detecting the pregnancy outcome of overt hypothyroid patients with and without anti-TPO.

2. Methods

This cohort study was conducted on pregnant Saudi women attending the antenatal clinic at Madinah Maternity and Children Hospital and Ohud hospital ,Madinah from June 2011 to July 201 2 . The 2 hospitals are the main referral hospitals for AlMadinah Area that has more than 1.6 million populations . The sample size depends on the number of patients fulfilling the inclusion and exclusion criteria during the time period of the study .Inclusion criteria included Saudi women of any parity of any age and of any associated diseases and at any trimester who were first diagnosed to have overt hypothyroidism during pregnancy. Women with subclinical hypothyroidism, poorly controlled hypothyroidism on treatment were excluded. Also women who were receiving any drug that can alter thyroid function tests or had past history of Grave disease, or other thyroid disease, or received radioiodine therapy were also excluded. All included women underwent a complete thyroid valuation including physical examination ,thyroid ultrasound and the measurement of serum free T4 (FT4) , freeT3 (FT3), thyroid-stimulating hormone (TSH) and anti-thyroid peroxidase autoantibodies (anti-TPO). The thyroid function tests (FreeT4 ,FreeT3, and TSH)and anti- TPO were assessed initially for all using adjusted laboratory values for each trimester of pregnancy .Radio- immunoassay was used for thyroid function tests (Kits for Free T3 and Free T4 : Monobind ; TSH : Immuno-tech). Anti-TPO was assessed using enzyme linked immune-sorbant assay (ELISA) (Normal range: up to 40 IU/ml). Patients received treatment and were followed up in a combined antenatal–medical clinic till delivery. All maternal complications, perinatal and neonatal outcomes were recorded.

Statistics:

The data were analyzed using SPSS software version11. Data were expressed as mean ± SD for quantitative parametric measures and both number and percentage for categorized data. Patients were divided into two groups according to presence or absence of TPO anti body. Independent Student T test and Chi-square were used for comparison between the 2 groups. Excel was used to generate figures. All tests were 2-tailed and considered significant when $p<0.05$.

3. Results

In table one, 125 Saudi women were first diagnosed during pregnancy with overt hypothyroidism with high rate of adverse pregnancy outcome (37.6%). Anti-TPO was detected in 39ofthem with prevalence rate of 31.2%.Table 2 shows comparison between anti-TPO negative and positive women. Hypothyroid women with positive TPO antibodies were older (34.5 ±7.73 vs .29 ±6.55 years ,p=0.005) ,had more disturbed thyroid function (higher TSH (44.2±10.0VS.29.5±6.47,p=0.001) ,lower FT4 (8.0±1.13vs.9.1±1.09,p=0.001), and lower FT3 (3.0±0.73vs.3.4±0.71,p=0.021). Also they had lower gestational age at delivery (35.2 ±5.33 vs. 37.7±1.19, p=0.001) and higher complications including IUFD (p=0.002) and GDM (p=0.001).Table 3 shows the odd ratio of the risk of positive TPO-AB among hypothyroid women. They had more complication with pregnancy (OR4.4,95%CI1.96-9.8,p=0.001. Also they had more loss of their pregnancies (OR3,95%CI1.09-7.99) , (Figure1) and more CS (OR2.4,95% CI1.03-5.46 ,p=0.09) (Table2, Figure2) . In Table 4 and Figure 3,18 out of 31 cases of GDM (58.1%) were in the sero-positive group (p=0.001). All cases of IUFD belonged to the sero-positive group (p=0.001). In Table 4 , sero-positive patients had significantly lower APGAR score (7.5±2.13 vs. 8.5±0.93) and birth weight (2.6±0.45 vs .2.7±0.45,p=0.048). Significant correlation with anti-TPO was detected with age ,thyroid dysfunction and most pregnancy outcome (Table5) including pregnancy complications (r=.333, p=0.000) ,GDM (r=.333,p=0.000),endresultofpregnancy(r=0.196,p=0.029),IUFD(r=0.297,p=0.002),GA at delivery (r =-.354 , p = 0.000) , mode of delivery (r=0.197,p=0.40) , Apgar score (-.308,p=0.001) ,and birth weight (r=-.189,p=0.048).

Table 1: Description of the studied hypothyroid pregnant women.

Age in years: Mean ± Sd	30.82 ±7.34
TSH (IU/L): Mean ± Sd	34.11±10.29
FT4 (IU/L): Mean ± Sd	8.77±1.23
FT3 (IU/L): Mean ± Sd	3.26±.73
Anti-TPO: n(%)	***39 (31.2%)***
Pregnancy complications: n(%)	47 (37.6%)

Table 2: Comparison between Anti-TPO negative and hypothyroid women

	TPO-Ab–ve (n=86)	**TPO-Ab+ve (n=39)**	**p-value**
Age in years ***Mean ± Sd***	29±6.55	34.5±7.73	**0.000***
Gestational age in weeks ***Mean ±Sd***	19.2±5.16	20.1±5.35	0.404
TSH (IU/L) ***Mean ±Sd***	29.5±6.47	44.2±10.0	**0.001***
T4 (IU/L) ***Mean ±Sd***	9.1±1.09	8.0±1.13	**0.001***
T3 (IU/L) ***Mean ±Sd***	3.4±0.71	3.0±0.73	**0.021***
Gestational age at delivery ***Mean ±Sd***	37.7±1.19	35.2±5.33	**0.000***
Abnormal end result ***Abortion*** ***IUFD***	9 (60.0/100.0) 0 (0.0/0.0)	6 (40.0/60.0) 4(100.0/40.0)	0.433 **0.002***
Complications** ***GDM*** ***PIH***	13 (41.9/56.5) 10 (55.6/43.5)	18 (58.1/69.2) 8 (44.4/30.8)	**0.001*** 0.190

IUFD: intrauterine fetal death GDM: gestational diabetes mellitus PIH: pregnancy induced hypertension.
N.B. *p-value is significant at <0.05 level ** Some cases has more than one complication

Table3: Odd ratio of the risk of TPO-AB among hypothyroid women.

	TPO-Ab–ve (n=86)	**TPO-Ab+ve (n=39)**	**χ^2–test (p-value)**	**Odd's Ratio (OR)**	**95%Confidenceinterval(CI)**
Pregnancy outcome ***-Ends in delivery*** ***-Others***	77(72.6/89.5) 9(47.4/10.5)	29(27.4/74.4) 10(52.6/25.6)	4.794 **(0.029*)**	**3.0**	1.09-7.99
Mode of delivery** ***-Vaginal*** ***-CS***	49(77.8/63.6) 28(59.6/36.4)	14(22.2/42.4) 19(40.4/57.6)	4.247 **(0.039*)**	**2.4**	1.03-5.46
Associated complications with pregnancy ***-Absent*** ***-Present***	63(80.8/73.3) 23(48.9/26.7)	15(19.2/38.5) 24(51.1/61.5)	13.845 **(0.001*)**	**4.4**	1.96-9.80

CScesareansectionN.B.*p-valueissignificantat<0.05levelFourcasesendsinIUFD**

Table4: adverse complications of neonates born to overt hypothyroid mothers.

	TPO-Ab–ve (n=86)	**TPO-Ab+ve (n=39)**	**p-value**
APGAR score ***Mean ±SD***	8.5±0.93	7.5±2.13	**0.001***
Birth weight ***Mean ±SD***	2.7±0.45	2.6±0.45	**0.048***
Need for NICU ***No*** ***Yes***	68(70.8/81.9) 15(60.0/18.1)	28(29.2/73.7) 10(40.0/26.3)	0.299

NICU: neonatal intensive care unit .N.B.*p-value is significant at<0.05level

Table5: Significant correlation with anti-TPO

	Correlation coefficient(r)	Significance
Age	.336**	0.000
TSH	.663**	0.000
T4	-.442**	0.000
T3	-.206*	0.021
Complications	.333**	0.000
GDM	.333**	0.000
End result of pregnancy	.196*	0.029
IUFD	.297**	0.002
GA at delivery	-.354**	0.000
Mode of delivery	.197*	0.40
Apgar score	-.308**	0.001
Birth weight	-.189*	0.048

*Correlation is significant at the 0.05level**Correlation is significant at the 0.01 level

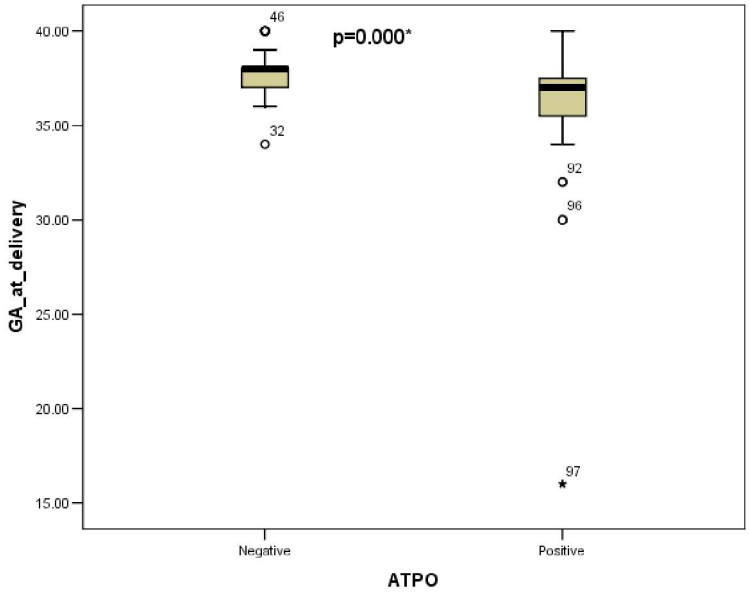

Figure1:GA in weeks at delivery and TPO state

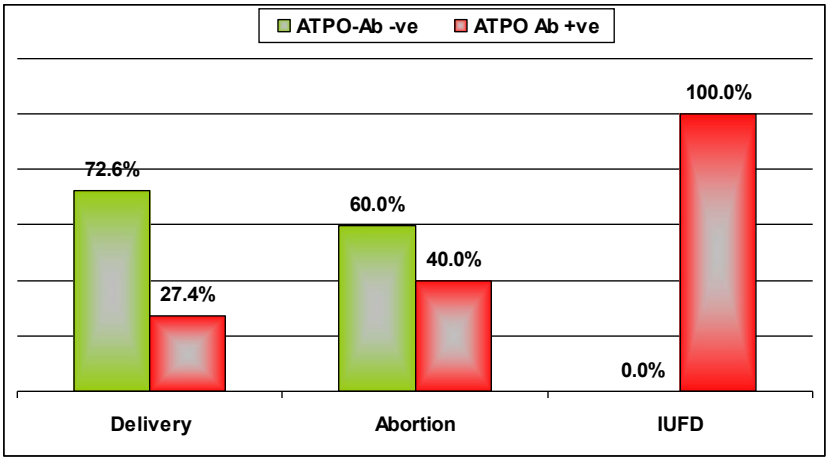

Figure2: TPO- Ab state by pregnancy out come

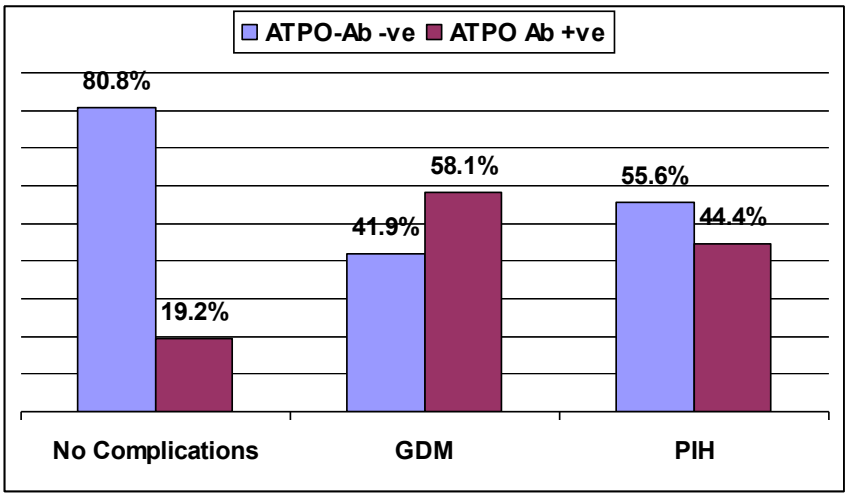

Figure3: Complications with pregnancy by ATPO-Ab.

4. Discussion

Inthisstudy,125 Saudi women were first diagnosed during pregnancy with overt hypothyroidism over1year with high rate of adverse pregnancy outcome (37.6%) especially among anti-TPO positive women .This finding agrees with our previous report of high prevalence of overt hypothyroidism among the same population (9.3%)(17). Anti-TPO was present in 31.2% of the hypothyroid pregnant women compared to 40% in a recent Indian study (18) . This finding acknowledges that autoimmune thyroiditis is the most common cause of hypothyroidism during pregnancy (4). Other workers found that anti-TPO is present in about 10% of pregnant women in early gestation irrespective to their thyroid function tests .Anti-TPO could be considered as a predictor of an increased incidence of subclinical hypothyroidism during pregnancy and also of postpartum thyroid dysfunction (19) . Paradoxically ,pregnancy often is associated with lower levels of thyroid autoantibodies with postpartum rebound elevation (20).

Adverse pregnancy outcome in our study was high (37.6%) and could first be explained by untreated overt hypothyroidism during pregnancy as our patients received treatment after their first trimester (1-3). In utero ; early exposure to maternal hypothyroidism is very crucial before the gestational age of 16 weeks after which the infantile thyroid starts to function (2,9).

The second explanation of the adverse pregnancy outcome in this study is the high prevalence of anti-TPO (31.2%) among our pregnant women. Compared to sero-negative hypothyroid women, sero-positive women showed more disturbed thyroid function, more complications with pregnancy, more pregnancy losses , lower gestational age at delivery, more cesarean sections, lower APGAR score and lower infants birth weight. Moreover, significant anti-TPO correlations were detected with most pregnancy adverse outcomes. These findings agree with previous work performed in other populations (13,15,18).

The main strength of this study is the finding of over rather than subclinical hypothyroid cases diagnosed late in their antenatal care. Failure to distinguish the pure effect of thyroid autoimmunity on pregnancy outcome in this study could be a limitation. However still in the presence of overt and late diagnosis of hypothyroidism, the presence of thyroid autoimmunity augments its adverse effects.

Conclusion:

Undiagnosed over hypothyroidism and autoimmunity are prevalent among Saudi women .Maternal overt hypothyroidism is a disorder with great potential to adversely affect maternal and fetal health. This hazard is greatly increased in the presence of thyroid autoimmunity. Hence, this condition needs early detection and easily treated, we suggest that early screening for maternal hypothyroidism and autoimmunity among Saudi women especially elderly one should be considered. We recommend aggressive management of hypothyroid sero-positive women with prompt initiation of treatment and strict follow-up. Heath education to the public regarding early diagnosis and management of thyroid diseases during pregnancy are also recommended

Disclosure:

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