Prevalence of overt and subclinical hypothyroidism during pregnancy in antenatal care - cross-sectional study, Jeddah, Saudi Arabia

Lubna M. Zahrani (1)
Mada I. Abdulhaq (1)
Taghreed M. Shams (2)
Fayssal M. Farahat (3)

(1) Family Medicine resident – fourth year, King Abdulaziz Medical City, Jeddah, Saudi Arabia
(2) Assistant Professor, Consultant Obstetrics and Gynecology, King Saud bin Abdulaziz University for Health and Sciences, King Abdullah International Medical Research Center, Jeddah, Saudi Arabia
(3) Professor, Public health and community medicine, King Abdulaziz Medical City, Jeddah, Saudi Arabia

Corresponding Author
Lubna Muqnee Zahrani
MBBS, family medicine resident – fourth year,
King Abdulaziz Medical City for National Guard - Jeddah
King Abdulaziz Medical City-Jeddah
Phone:-0560288246
Email: Lubna.qzz@gmail.com

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Abstract

Objective
• To estimate the prevalence of subclinical and overt hypothyroidism in antenatal care clinics
• To evaluate the performance of targeted screening approach based on the risk stratification as recommended by the U.S. Preventive Service Task Force (USPSTF) and adopted by the American Thyroid Association (ATA)

Method: This was a multicenter, cross-sectional study conducted in 386 pregnant women attending routine antenatal visits at 4 antenatal clinics from September 2019 to August 2020. All participants underwent clinical and thyroid function test (TFT) including TSH and T4 levels. Based on risk factor assessment, participants were categorized into low-risk versus high-risk patients. The performance of targeted screening was assessed by comparing the two categories regarding the prevalence of subclinical and overt hypothyroidism and calculating the associated sensitivity, specificity and accuracy.

Result: Overall, the prevalence of dysthyroidism was 11.7% (95% CI=8.6-15.3%) with 10.4% subclinical hypothyroidism and 1.3% overt hypothyroidism cases. No difference in the prevalence of dysthyroidism was found between low-risk and high-risk patients. The performance of the risk stratification-based screening approach in detecting subclinical or overt hypothyroidism showed sensitivity (73.3% and 86.7%), specificity (30.2% and 13.2%), and accuracy (35.2% and 21.8%), using the USPSTF alone and combined with the ATA criteria, respectively.

Conclusion: The application of the targeted screening for subclinical and overt hypothyroidism using the USPSTF and ATA criteria performed poorly in the studied population. Thus, universal screening appears to be a better option.

Key words: Hypothyroidism, Overt, Pregnancy, Screening, Subclinical, Targeted, Universal, U.S. Preventive Service Task Force;

Introduction

Pregnancy involves significant stress on both mother and fetus that may include endocrine disorders such as hypothyroidism, which increases the risk of adverse maternal and fetal outcomes (1).Undiagnosed or inadequately treated hypothyroidism is associated with increased risk for miscarriage, placental abruption, premature rupture of membranes, preeclampsia and stillbirth (2-8). Moreover, thyroid dysfunction in pregnant women may adversely affect the neuropsychological development of their children. Clinical studies showed that children born to hypothyroid mothers are at higher risk for cognitive delay, autism and attention deficit hyperactivity disorder (9–16). On the other hand, the diagnosis of thyroid disorders during pregnancy can be challenging owing to the presence of subclinical forms, in addition to the physiological variations of thyroid function during pregnancy (17).Click or tap here to enter text. Besides, there is consistent evidence that reference ranges should be adapted to the specific population and ethnic group, as well as other clinical and obstetrical parameters (18).

Universal screening of pregnant women with low-risk for thyroid dysfunction is controversial because of insufficient evidence. Therefore, women at high risk are considered the target of systematic screening, which includes the measurement of the thyroid stimulating hormone (TSH) (19). Nevertheless, multiple studies across different countries, such as UK, Czech Republic and China, estimated that targeted screening may result in 30%-88% of overt or subclinical hypothyroidism cases being undiagnosed (20-22).

As a consequence, it is crucial to estimate the probability of developing hypothyroidism during pregnancy among low-risk women with reference to high-risk women, to reflect the most appropriate screening strategy within this specific population. In Saudi Arabia, the prevalence of hypothyroidism during pregnancy is not estimated properly. Two single-center studies in Riyadh region reported a prevalence of subclinical hypothyroidism as high as 10.3 and 13%(23,24). There are no reports for the prevalence of hypothyroidism in pregnant women in Jeddah region so far.

We conducted a multicenter study to estimate the prevalence of subclinical and overt hypothyroidism among all pregnant women attending antenatal care clinics in primary care centers in Jeddah, Saudi Arabia and to evaluate the performance of targeted screening approach based on the risk stratification as recommended by the U.S. Preventive Service Task Force (USPSTF) and adopted by the American Thyroid Association (ATA) (25,26).

Methods

Design and Setting

A cross-sectional study was carried out at the antenatal clinics of National Guard Hospital (NGH) and the attached primary health centers (PHCCs) in Jeddah, Saudi Arabia from September 2019 to August 2020.

Participants and Sampling

The study involved consecutive pregnant ladies recruited from routine antenatal visits in three PHC centers in NGH and from the antenatal clinic in the main NGH from September 2019 to August 2020. Women aged 18-45 years, presenting at 13 weeks or more gestational age, and without an established thyroid disorder were included. Women previously diagnosed with overt or subclinical hypothyroidism, autoimmune thyroiditis, or hypothyroidism were excluded.

Sample size was calculated by using the single proportion equation in Raosoft software package, based on the assumption that the rate of presence of hypothyroidism is 50%, and a margin error of 5% at the 95% confidence level; the required sample size was 384.

A stratified sampling technique with equal allocation was used to recruit an equal number (N/4) of participants from the three PHCCs and the NGH antenatal clinic. A systematic random sampling was used to recruit all eligible and consenting women from the participating centers.

Tools

A data collection sheet was designed to collect the study data, including: 1) demographic data; 2) obstetrical and medical history such as parity, number of previous abortions, history of infertility, smoking status, etc.; 3) dysthyroidism risk factors using a combination of the checklists recommended by the USPSTF and adopted by the ATA (25,26), including 13 demographic, clinical and biological factors considered for profiling women who are at high risk of thyroid dysfunction during pregnancy (Box 1); 4) clinical parameters including body mass index (BMI), blood pressure, and presence of clinical goiter; and 5) thyroid function test (TFT) including TSH and T4 levels.

Box 1. Factors defining high-risk for thyroid dysfunction among pregnant women

Category	#	Factor
Demographic factors	1	Age above 30 years
	2*	Living in a region with presumed iodine deficiency
Non-specific/ obstetrical factor	3	History of miscarriage or preterm delivery
	4	Type 1 diabetes mellitus or other autoimmune disorders
	5	Infertility
	6	Family history of autoimmune thyroid disease or hypothyroidism
	7	Prior therapeutic head or neck irradiation or thyroid surgery
Thyroid-specific factors	8*	Symptoms or clinical signs suggestive of hypothyroidism
	9	Goiter
	10	Currently receiving levothyroxine replacement
	11	Positive detection of thyroid antibodies, primarily thyroid peroxidase (TPO) antibodies
Additional ATA factors§	12	BMI ≥ 40 kg/m2
	13	Multiple prior pregnancies (≥2)

* Factors not considered in the present study, as Saudi Arabia is not presumed an iodine deficient region (Factor 2), and hypothyroidism symptoms often overlap and are confused with pregnancy symptoms (Factor 8).
§ Additional factors considered by the ATA but not by the USPSTF.

Exposure and Outcome definition

Participants were divided into two groups: low-risk and high-risk category. High-risk category included profiles with targeted screening according to the USPSTF and ATA recommendations, which are defined as the presence of at least one of the identified risk factors (25,26). Consequently, women with none of the listed risk factors were classified as low-risk category. The following two factors (of the 13) were discarded in the study:

- Living in a region with presumed iodine deficiency was discarded as Saudi Arabia is not concerned with such deficiency (27).
- Symptoms or clinical signs suggestive of hypothyroidism were not considered because hypothyroidism symptoms often overlap with pregnancy symptoms (27).

Participants were classified as normal (normal TSH and T4), subclinical hypothyroidism (TSH above normal range with normal T4), overt hypothyroidism (TSH above normal range and T4 below normal range), or hyperthyroidism (TSH below normal range and elevated T4), according to the results of the TFT. Normal ranges for TSH were defined according to the pregnancy trimester, in accordance with the ATA recommendations: first semester (0.1-2.5 mIU/L), second trimester (0.2-3.0 mIU/L), and third trimester (0.3-3.0 mIU/L) 25. Furthermore, autoimmune thyroiditis was defined as TPO levels >35 IU/mL (28).

Procedure

The study objectives, procedure and terms were explained to the eligible participants, who signed the informed consent. After enrollment, participants were interviewed regarding their demographics, obstetrical and clinical history, in addition to the checklist of risk factors. Afterwards, all the participants underwent a structured physical examination including thyroid palpation to detect a clinical goiter, weight and height measurement with calculation of the BMI, blood pressure measurement using an electronic sphygmomanometer. Finally, blood sample was collected to measure TSH, T4 levels using the standard biological methods in the attached laboratory. Further, TPO was measured for participants who had subclinical hypothyroidism to screen for autoimmune thyroiditis.

Statistical Methods

Data was entered, cleaned and coded in an Excel sheet, then transferred to the Statistical Package for Social Sciences version 21.0 for Windows (SPSS Inc., Chicago, IL, USA) for statistical analysis. Categorical variables are presented as frequency and percentage, while continuous variables are presented as mean ± standard deviation (SD). Accuracy of the risk stratification-based screening approach was explored by analyzing the association of the risk category (high-risk vs. low-risk) with TFT results (normal vs. abnormal) using chi square test, and by calculating the corresponding sensitivity, specificity, negative and positive predictive values and overall accuracy with 95% CI. Furthermore, we tested the performance of the cumulative number of factors in indicating hypothyroidism using the Receiver Operating Characteristics (ROC) curve, where TFT result was analyzed as the dependent variable; results are presented as area under the curve (AUC) with 95% CI, standard error (S.E) and the level of statistical significance. The association of TFT results with the other demographic and clinical data was analyzed using chi square test, Fisher's exact test, or Mann-Whitney U test, as applicable. A p-value of < 0.05 was considered to reject the null hypothesis.

Results

Demographic, clinical and obstetrical characteristics

Three hundred and eighty-six pregnant women were included whose mean (SD) age was 30.11 (6.22) years and 212 participants (54.9%) were in the third trimester. There was high prevalence of overweight (33.4%) and obesity (40.7%). Other obstetrical parameters showed gravidity ≥3 (56.4%) and previous still birth (3.4%) (Table 1).

Table 1: Demographic, obstetrical and clinical data, and thyroid function test findings

Parameter	Category	Frequency	Percentage
Age (years)	Mean, SD	30.11	6.22
Gestational age (weeks)	Mean, SD	26.60	7.78
	Median, range	27	13, 40
Trimester	Second (week 14–27)	174	45.1
	Third (week 28-end)	212	54.9
Gravida	1	95	24.6
	2	73	18.9
	3	63	16.3
	4	51	13.2
	5+	104	26.9
Living children	0	102	26.4
	1	95	24.6
	2	67	17.4
	3	49	12.7
	4	35	9.1
	5+	38	9.8
Previous stillbirth	No	373	96.6
	Yes	13	3.4
Smoking	Yes	5	1.3
	No	381	98.7
BMI (Kg/m2)	Morbid obesity (≥40)	13	3.4
	Obesity 2 (35– 39.9)	49	12.7
	Obesity 1 (30–34.9)	95	24.6
	Overweight (25–29.9)	129	33.4
	Normal (18.5–24.9)	98	25.4
	Underweight (<18.5)	2	0.5
Systolic BP (mmHg)	Mean, SD	110.91	10.91
	Range	84	144
Diastolic BP (mmHg)	Mean, SD	67.94	9.32
	Range	45	98
TSH (IU)	Mean, SD	1.92	1.13
	Range	0.01	7.76
T4 (IU)	Mean, SD	10.67	1.46
	Range	0.89	15.80
TFT result	Normal	341	88.3
	Subclinical hypothyroidism	40	10.4
	Overt hypothyroidism	5	1.3

Abbreviations : BMI : body mass index ; BP : blood pressure ;
TSH : thyroid stimulating hormone ; TFT : thyroid function test ; T4 : thyroxine

Thyroid function test findings

TFTs showed 10.4% cases of subclinical hypothyroidism and 1.3% cases of overt hypothyroidism. Thus, the prevalence of thyroid dysfunction, including both subclinical and overt hypothyroidism, was 11.7% (95% CI=8.6-15.3%) (Table 1).

Risk factor assessment and risk stratification

The most prevalent risk factors considered by the USPSTF were age > 30 years (45.1%), history of miscarriage or preterm delivery (31.9%), and family history of autoimmune thyroid disease or hypothyroidism (22.8%). None of the participants was reported to be receiving thyroid replacement therapy. By considering the UPSTF criteria, 70.2% of the participants were classified as high-risk; and by combining UPSTF and ATA criteria, 86.8% would be classified as high-risk (Table 2).

Diagnostic value of the risk stratification-based screening approach

There was no difference in the prevalence of abnormal TFT results between low-risk and high-risk categories as per the USPSTF criteria (10.4% vs. 12.2%, p=0.730) and ATA criteria (including the two additional factors) (11.8% vs. 11.7%, p=0.980), respectively. Further, none of the evaluated risk factors was associated with increased percentage of abnormal TFT (Table 2).

Table 2: Assessment of risk factors and their association with the prevalence of abnormal thyroid function test

Parameter / level Risk factors*	Risk factor prevalence (N, %)		Abnormal TFT prevalence (%) (In presence vs absence of factor)	p-value
Demographic factors				
1. Age above 30 years	174	45.1	12.1 vs 11.3	0.874
2. Residence region with presumed iodine deficiency §	0	0.0	-	-
Non-specific/ obstetrical factors				
3. History of miscarriage or preterm delivery	123	31.9	11.4 vs 11.8	1.000
4. Type 1 DM or other autoimmune disorders	23	6.0	8.7 vs 11.8	1.000
5. Infertility	42	10.9	11.9 vs 11.6	1.000F
Thyroid-specific factors				
6. Family history of autoimmune thyroid disease or hypothyroidism	88	22.8	11.4 vs 11.7	0.922
7. Prior therapeutic head or neck irradiation or thyroid surgery	5	1.3	0.0 vs 11.8	1.000 F
8. Symptoms or clinical signs suggestive of hypothyroidism ‡	NA	NA	-	-
9. Goiter	31	8.0	9.7 vs 11.8	1.000 F
10. Currently receiving levothyroxine replacement	0	0.0	-	-
11. Positive detection of thyroid antibodies, primarily TPO antibodies	1	0.3	0.0 vs 11.7	1.000 F
Additional factors by ATA¥				
12. BMI ≥ 40 kg/m2	13	3.4	15.4 vs 11.5	0.655 F
13. Multiple prior pregnancies (≥2)	291	75.4 11.	7 vs 11.6	0.978
USPSTF Risk category (factors 1-11)				
Low	115	29.8	12 (10.4)	
High	271	70.2	22 (12.2)	0.730
USPSTF + ATA Risk category¥ (factors 1-13)				
Low	51	13.2	6 (11.8)	
High	335	86.8	39 (11.7)	0.980

Abbreviations:
ATA: American thyroid association; TPO: thyroid peroxidase; TFT: thyroid stimulating hormone; USPSTF: U.S. Preventive Services Task Force;
* Factors considered for targeted thyroid dysfunction screening in pregnant women according to the USPSTF;
¥ Including 2 extra factors considered by the American Thyroid Association.
§ Factor not considered in the present study as Saudi Arabia is not presumed iodine deficient region.
‡ Factor not considered in the present study as hypothyroidism symptoms often overlap and are confused with pregnancy symptoms.
F Significance level calculated using Fisher's exact test; otherwise, chi square test was used.

The performance of risk stratification-based screening approach in detecting subclinical or overt hypothyroidism showed sensitivity (73.3% vs. 86.7%), specificity (30.2% vs. 13.2%), and accuracy (35.2% vs. 21.8%), using the USPSTF and the USPSTF + ATA criteria, respectively. However, overt hypothyroidism was detected with 100% sensitivity and 30.2% specificity using the USPSTF criteria alone (Table 3).

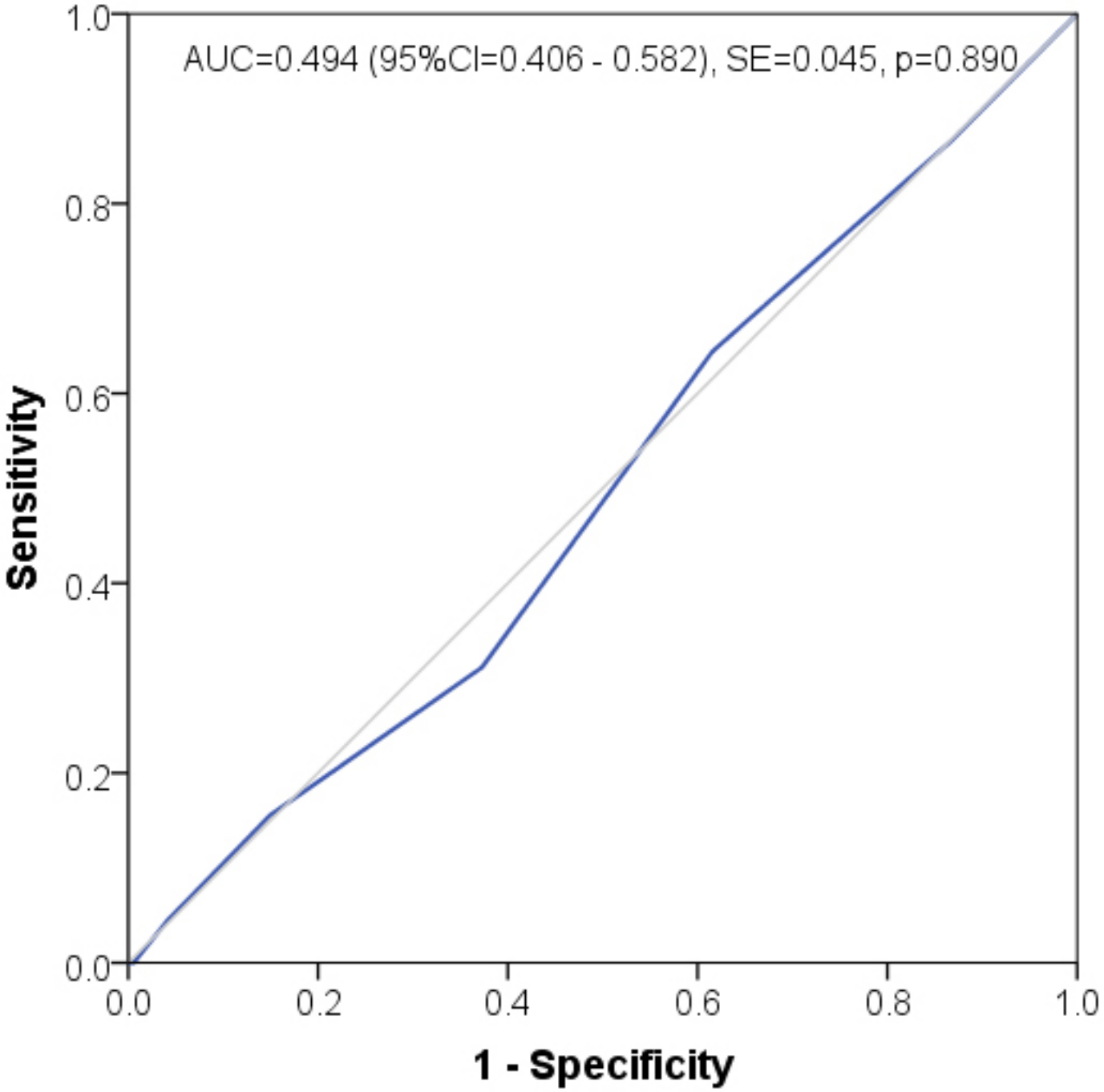
Table 3: Performance of risk stratification approach in the screening for hypothyroidism and over hypothyroidism in pregnant women

Condition	**Subclinical or overt hypothyroidism**				**Overt hypothyroidism**	
Criteria	**USPSTF**		**USPSTF + ATA**		**USPSTF**	
Parameter	**Value**	**95%CI**	**Value**	**95%CI**	**Value**	**95%CI**
Sensitivity (%)	73.3	58.1 – 85.4	86.7	73.2 – 95.0	100.0	47.8 – 100.0
Specificity (%)	30.2	25.4 – 35.4	13.2	9.8 – 17.3	30.2	25.6 – 35.1
PPV (%)	12.2	10.3 – 14.4	11.6	10.5 – 13.0	1.9	1.7 – 2.0
NPV (%)	89.6	83.7 – 93.5	88.2	77.2 – 94.3	100.0	-
Accuracy (%)	35.2	30.5 – 40.2	21.8	17.8 – 26.2	31.1	26.5 – 36.0

USPSTF: US Preventive Services Task Forces criteria, considering the presence of any of the following risk factors: age>30 years, residence in region with iodine deficiency (not applicable in the present study), history of miscarriage, preterm delivery or infertility, type 1 DM or other autoimmune disorders; Family history of autoimmune thyroid disease or hypothyroidism; Prior therapeutic head or neck irradiation or thyroid surgery; symptoms or clinical signs suggestive of hypothyroidism (not used in the present study); clinical goiter; currently receiving levothyroxine replacement; previous positive thyroid antibodies.
USPSTF + ATA (American Thyroid Association): include morbid obesity and multiple prior pregnancy (≥2), in addition to the previous risk factors.
95% CI: 95% confidence interval; PPV: positive predictive value; NPV: negative predictive value.

The ROC curve analysis showed AUC=0.494 (p=0.890), indicating poor performance of the number of cumulative risk factors in predicting thyroid dysfunction in pregnant women (Figure 1).

Figure 1. ROC curve analysis of hypothyroidism during pregnancy as a function of the number of cumulative risk factors



AUC. Area under the curve; S.E: standard error; CI: confidence interval

Table 4: Other demographic and clinical factors associated with abnormal thyroid function test

Parameter	Category	Normal TFT		Abnormal TFT		p-value
		N	%	N	%	
Age (years)	Mean, SD	30.12	6.20	30.02	6.49	0.919t
Smoking	Yes	5	100.0	0	0.0	
	No	336	88.2	45	11.8	1.000F
Gravida	1	84	88.4	11	11.6	
	2	67	91.8	6	8.2	
	3	56	88.9	7	11.1	
	4	46	90.2	5	9.8	
	5+	88	84.6	16	15.4	0.657
Living children	0	90	88.2	12	11.8	
	1	88	92.6	7	7.4	
	2	59	88.1	8	11.9	
	3	40	81.6	9	18.4	
	4	34	97.1	1	2.9	
	5+	30	78.9	8	21.1	0.083
Previous stillbirth	Never	331	88.7	42	11.3	
	1+	10	76.9	3	23.1	0.184F
Gestational age (weeks)	Median, P75	26	34	28	35	0.324M
Trimester	Second	158	90.8	16	9.2	
	Third	183	86.3	29	13.7	0.172
BMI (Kg/m2)	Morbid obesity	11	84.6	2	15.4	
	Obesity 2	41	83.7	8	16.3	
	Obesity 1	82	86.3	13	13.7	
	Overweight	117	90.7	12	9.3	
	Normal	88	89.8	10	10.2	
	Underweight	2	100.0	0	0.0	0.738
Systolic BP (mmHg)	Mean, SD	110.67	10.98	110.67	10.98	0.234
Diastolic BP (mmHg)	Mean, SD	67.65	9.29	70.11	9.43	0.096

BMI: Body mass index; BP: blood pressure; TFT: thyroid function test
Test used: M Mann-Whitney U test; F Fisher's exact test; otherwise, chi square test.; P75: 75th centile.

Discussion

Summary of findings

The accuracy of screening for thyroid dysfunction among pregnant women is crucial to prevent the associated morbidity and anticipate the cost-effectiveness of a nationwide screening program in balance with the economic burden of the disease. Findings from the present cross-sectional study showed a prevalence of thyroid dysfunction of 11.7%, of which 10.4% was subclinical and 1.3% was overt hypothyroidism. Although anti-TPO test results were missing for two-thirds of hypothyroid women, positive detection was found in 5 out of 11 (45.5%) tested women. The application of the risk stratification-based screening approach in the study population enabled detecting thyroid dysfunction among pregnant women with 73.3-86.7% sensitivity and 13.2-30.2% specificity, depending on the criteria used, resulting in an overall accuracy of 21.8-35.2%. On the other side, the use of USPSTF criteria alone enabled detecting overt hypothyroidism with 100% sensitivity and 30.2% specificity. Further, the number of cumulated risk factors was not significantly indicative for hypothyroidism.

Prevalence of subclinical and overt hypothyroidism

Findings from the present study are concordant with epidemiological figures reported in other studies. Locally, a study from Riyadh, in 2018, estimated the prevalence of subclinical hypothyroidism as 13% among women attending the antenatal clinics (29). Internationally, an Indian study,(30) which included 400 pregnant patients, showed 12% prevalence of hypothyroidism, including 9% subclinical and 3% overt hypothyroidism, which is similar to our findings. Additionally, the same study reported 52% cases of positive anti-TPO antibody detection among hypothyroid women, which could be assumedly comparable to our findings that showed positive detection among 5 out of 11 hypothyroid women who were tested.

Lower rates were found in an Iranian study that evaluated 3,158 pregnant women. It showed, approximately 4.7% prevalence of hypothyroidism including 4.2% subclinical and 0.5% overt hypothyroidism, and the majority of cases were diagnosed in the first trimester (31). A Turkish study screened 1,416 consecutive pregnant women in their first semester and found 22.3% cases of subclinical and 1.6% of overt hypothyroidism, for an overall 23.9% prevalence of thyroid dysfunction by using the cutoff value proposed in the 2017 ATA recommendation (32). This variability between the different studies may result from regional discrepancies in the risk factors, notably the odd risk in endemic versus non-endemic regions.

Cost-effectiveness implication of targeted screening

The application of the USPSTF criteria in the study population classified 70.2% of the pregnant women as being at high-risk for thyroid dysfunction, thereby enabling the detection of overt hypothyroidism with 100% sensitivity and 30.2% specificity, for an overall prevalence of 1.3%. By assuming the generalizability of these findings in the target population, the implementation of a targeted screening strategy based on the USPSTF criteria would result in 70.2% of all pregnant women undergoing blood TFT to rule out overt hypothyroidism and no undiagnosed cases. In other terms, such an approach would enable ~30% cost-effectiveness by comparison to a systematic blood test screening. This supports superior cost-effectiveness of the risk-based targeted screening by reference to systematic screening in overt hypothyroidism, as the screening approach is quasi costless in that it relies only on the patient's medical history. In absence of screening, data from the literature estimated between 0.2% and 1% prevalence of undiagnosed overt hypothyroidism in pregnant women living in an iodine deficient region(33-36). In Saudi Arabia, further local studies are warranted to provide an accurate estimate of the performance and cost-effectiveness of targeted screening versus universal screening.

On the other hand, by considering both overt and subclinical hypothyroidism, the application of the USPSTF criteria failed to detect approximately 27% of the cases of thyroid dysfunction (sensitivity = 73.3%), out of an overall prevalence of 13.7%; whereas only 12.2% of those who were classified as high-risk tested positive in TFT (PPV=12.2%). This suggests that in every 1,000 pregnant women, 733 would have to undergo blood TFT to confirm or rule out thyroid dysfunction, while 37 would be misclassified as low-risk among the remaining 267 others and would go undiagnosed. By combining the USPSTF and ATA criteria, the performance of the approach was not improved significantly, as its application would result in 16 cases misclassified as low-risk in every 1,000 evaluated women, whereas 868 would undergo blood TFT.

This is supported by observations from another local study, which found 10.5% prevalence of subclinical hypothyroidism in pregnant women who were screened based on a risk stratification method versus 18.5% who were randomly enrolled in the study (29). Similar observations were reported in international studies, where targeted screening was associated with up to one-third hypothyroid women being undiagnosed(33,34). Such inference questions both the effectiveness and cost-effectiveness of the targeted screening strategy based on the USPSTF approach and suggests considering universal blood TFT screening to prevent morbidity and health expenditures resulting from undiagnosed thyroid dysfunction.

This leads to examine the relevance of universal screening from a cost-effectiveness perspective. A cost-effectiveness analysis showed that universal screening of hypothyroidism during the first pregnancy trimester was more cost-effective than risk-based screening approach, with an incremental cost-effectiveness ratio of $7,258 per quality-adjusted life-year (QALY). However, compared to no screening, either approach was cost-effective (37). Another study that focused on subclinical hypothyroidism found that universal screening would enable approximately $83,564 cost-saving and 5.9 QALYs for every 1,000 women who are screened; and according to the analysis model, universal screening remains cost-effective even for a prevalence of the condition as low as 0.25%. However, the latter cost-effectiveness model was based on the cost-savings resulting from a hypothetical reduction of the incidence of low intellectual quotient in offspring as an effect of thyroid hormone replacement therapy prescribed in diagnosed women(38).

Clinical implication of subclinical hypothyroidism in pregnant women

The previous observations lead us to a crossroad: whether subclinical hypothyroidism could be considered as a pathological entity with significant clinical implication. Review and meta-analyses of longitudinal studies show that subclinical hypothyroidism develops in 3-15% of pregnant women, and is associated with several maternal and fetal adverse outcomes. Maternal adverse outcomes include pre-eclampsia, premature rupture of membranes, placenta abruption, gestational hypertension, and gestational diabetes. Fetal adverse outcomes include abortions, preterm delivery, cognitive delay, intrauterine growth retardation, and neonatal death (2,30,39). However, the benefits of a therapeutic intervention including levothyroxine therapy are highly controversial. While some trials reported reduction in the incidence of preterm births, abortions and low birth weight offspring, the core evidence from the majority of studies and meta-analyses does not conclude significant benefit of levothyroxine therapy in subclinical hypothyroidism to prevent the adverse maternal or fetal outcomes (2,39-43). Recommendations 28 and 29 from the 2017 Guidelines of the ATA specify the indications of levothyroxine therapy in subclinical hypothyroidism during pregnancy depending on anti-TPO antibody status, and emit strong recommendation to treat TPO-Ab positive women with TSH greater than the pregnancy-specific reference range based on moderate-quality evidence, as well as TPO-Ab negative ones with TSH >10.0 mU/L based on low-quality evidence. On the other hand, the Guidelines strongly do not recommend treating TPO-Ab negative women with TSH within the pregnancy-specific reference range, based on high-quality evidence (25).

Clinical implication of overt hypothyroidism in pregnant women

On the other hand, the efficacy of treating overt hypothyroidism and autoimmune thyroid disease during pregnancy is supported by growing evidence. Overt hypothyroidism diagnosed during pregnancy is managed by levothyroxine therapy using doses that should be titrated against TSH level, and aims to obtain and maintain maternal euthyroidism throughout the pregnancy and lactation period. Ideally, the treatment should be started in the pre-conception period, which requires education and awareness raising among the population (44). Recommendation 27 in the 2017 Guidelines of the ATA, based on moderate-quality evidence (strongly recommends) highlights the relevance of treating overt hypothyroidism during pregnancy (25). An efficacy study based on prospective data showed that perinatal outcomes among overt hypothyroidism women who were treated were similar to euthyroid ones(36). Regarding autoimmune thyroid disease, a randomized trial showed significant reduction (70%) in the risk of preterm delivery among women with autoimmune thyroid disease who were treated with levothyroxine with reference to those who were untreated (45).

Altogether, high sensitivity of the risk-based targeted screening and the possibility of implementing significant intervention in overt hypothyroidism are in favor of the implementation of such a screening program in Saudi Arabia. However, further local studies are warranted to confirm the high performance found in the present study and to analyze the cost-effectiveness of such screening strategy at the national level.

Conclusion

Findings from the present cross-sectional study showed the prevalence of thyroid dysfunction of 11.7% among pregnant women (10.4% were subclinical and 1.3% were overt hypothyroidism). The application of the targeted screening for subclinical and overt hypothyroidism using the USPSTF and ATA criteria performed poorly in the studied population and its implementation would result in 16 to 37 undiagnosed cases per 1,000 evaluated women. Thus, universal screening appears to be a better option; however, the cost-effectiveness of such an approach may be impacted by the absence of therapeutic implication in subclinical forms, to date, which represent a high proportion of cases. On the other hand, the risk-based screening approach was highly sensitive in case detection of overt hypothyroidism. However, further local studies are warranted to confirm the performance of targeted screening in overt hypothyroidism and to analyze the cost-effectiveness of such screening strategy at the national level.

Authors contribution:

Both authors Lubna Zahrani and Mada Abdullhaq contributed equally in literature search, study design, data collection, data analysis and manuscripts writing, TS data collection, manuscripts writing and supervision FF study design, all authors reviewed the manuscript .

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