Comparison of universal and targeted screening for thyroid dysfunction in pregnant Egyptian women

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Abstract

Objective: To compare universal vs targeted screening for thyroid dysfunction and to estimate the prevalence of hypothyroidism in pregnant Egyptian women.

Subjects and methods: A total of 168 of pregnant women who attended the outpatient obstetric clinic at Ain Shams University Hospital (Cairo, Egypt) for antenatal care between September 2011 and December 2011 were enrolled. Based on the detailed data collection and results of laboratory testing, they were subdivided into the high- and low-risk group for thyroid disease according to the most recent Endocrine Society clinical practice guidelines, as well as into groups by trimester for application of American Thyroid Association guidelines. The group values were subjected to statistical analysis for estimating the prevalence of clinical and subclinical hypothyroidism and for identifying significant differences.

Results: Of the 168 patients, 104 were classified into the low-risk group and 64 into the high-risk group. Using the trimesteric and normal population cutoff values for thyroid functions, the prevalence of hypothyroidism was found to be 56% \((n=94)\) and 44.6% \((n=75)\) respectively. No statistically significant differences were found between the high- and low-risk group regarding prevalence of either clinical or subclinical hypothyroidism, and no significant differences were found regarding the prevalence of hypothyroidism in the first, second, or third trimester.

Conclusion: Use of the most recent Endocrine Society clinical practice guidelines led to missed detection of clinical or subclinical hypothyroidism in 34.5% of pregnant women. Universal screening of pregnant women for thyroid dysfunction should thus be adopted throughout Egypt.

Introduction

Thyroid dysfunction and thyroid autoimmunity are among the most common endocrine disorders that influence fetal and maternal outcomes in both the short- and long-term (1). Approximately one-third of cases of hypothyroidism and subclinical hypothyroidism in pregnant women are not detected when using a strategy of targeted screening of high-risk patients based on review of thyroid profile (2). Despite this problem and the accumulating evidence supporting the use of universal screening, the controversy regarding whether to use targeted or universal screening has continued over the past decade (1, 2). Resolving this controversy is important, as maternal thyroid dysfunction has been associated with a number of adverse outcomes, including preterm birth, placental abruption, fetal death, and long-term impaired neuropsychological development (3). Even the presence of thyroid autoantibodies in the absence of thyroid dysfunction can increase the risk of miscarriage and preterm delivery (2).

Over the past several decades, better understanding of thyroid physiology and immunology in addition to
advancement in thyroid function testing has led to recognition of the importance of early detection and appropriate treatment of gestational thyroid dysfunction (4). Despite this recognition, to our knowledge, few studies have investigated the screening of thyroid dysfunction in pregnant women in the Middle East, and none has examined women in Egypt. Among the few studies conducted in the Middle East, one study in Jordan reported that the prevalence of subclinical hypothyroidism in pregnant Jordanian women was 20.8% (5). To further examine this finding and fill the study gap regarding the best means of detecting the prevalence of hypothyroidism in pregnant women, we compared the virtue of universal and targeted high-risk screening for thyroid dysfunction and estimated the prevalence of thyroid dysfunction in pregnant Egyptian women.

Subjects and methods
Between September 2011 and December 2011, 200 consecutive pregnant women attending the outpatient obstetric clinic at Ain Shams University Hospital (Cairo, Egypt) for antenatal care and examination were invited to enrol in this study. The study inclusion criteria were healthy pregnant women aged over 18 years with singleton pregnancy. The study exclusion criterion was the use of medications that could interfere with the results of thyroid function tests (e.g. amiodarone, contrast media, or corticosteroids) for at least 6 months before enrolment. After obtaining approval for this study from the Ethical Committee of Faculty of Medicine, Ain Shams University, and a signed informed consent from each participant, all participants were instructed to undergo an interview to obtain a detailed history, and then undergo a clinical examination and laboratory testing of a blood sample for thyroid function and thyroid antibodies. Demographic and clinical data; data concerning personal and family history (in first- and second-degree relatives) of thyroid disorders and/or other autoimmune diseases such as type 1 diabetes; data concerning residence necessary to determine whether the participant lived in an iodine-depleted area; data concerning current and/or past use of antithyroid medication, levothyroxine replacement therapy, and/or radiiodine therapy; data regarding history of thyroid surgery and/or therapeutic head or neck irradiation; and data regarding history of miscarriage, preterm delivery, and/or infertility were recorded. Based on analysis of the data, the participants were categorized into the low- and high-risk group according to the most recent Endocrine Society clinical practice guidelines for the assessment of high-risk thyroid dysfunction in pregnant women (6) as well as into the first-, second-, and third-trimester groups according to gestational age (first trimester <13 weeks, second trimester 13–27 weeks, and third trimester 28 weeks to birth).

Thirty minutes after collection of a venous sample from each participant using a vacutainer, the sample was centrifuged at 112 g for 10 min and the serum was frozen at −20 °C until analysis. Thyroid-stimulating hormone (TSH; normal population range 0.4–4.2 mIU/l), free thyroxine (FT4, normal population range 0.8–2 ng/dl), free triiodothyronine (FT3, normal population range 1.4–4.2 pmol/l), and anti-thyroid peroxidase (anti-TPO; values >35 IU/ml considered positive for the presence of anti-TPO antibodies) were measured using the Accubind ELISA Kit (Monobind, Inc., Lake Forest, CA, USA). The intra-assay coefficients of variation (CV) for TSH, FT4, FT3, and anti-TPO were 8.1–6.6, 3.25–10.98, 2.4–11.9, and 4.2–5.7% respectively; the inter-assay CV were 5.9–9.3, 6.01–10.81, 10.2–13.1, and 4.5–6.8% respectively.

As no trimester-specific reference ranges for the assessment of thyroid function in pregnancy had been established for the Egyptian population at the time of the study, the Guidelines of the American Thyroid Association (ATA) for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum recommendations were applied (Table 1) (7). After diagnosis, the patients with hypothyroidism were divided into the clinical and subclinical hypothyroidism groups according to the ATA guidelines. Clinical hypothyroidism was defined as a serum TSH level >2.5 mIU/l in the first trimester or >3 mIU/l in the second and third trimesters in conjunction with a decreased FT4 concentration, or as a TSH level ≥10.0 mIU/l irrespective of the FT4 level. Subclinical hypothyroidism was defined as a serum TSH level between 2.5 and 10 mIU/l and a normal FT4 level (7).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Trimester-specific reference ranges according to the guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy (7).</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mIU/l)</td>
<td>FT4 (pmol/l)</td>
</tr>
<tr>
<td>First trimester</td>
<td>Second trimester</td>
</tr>
<tr>
<td>0.1–2.5</td>
<td>0.2–3.0</td>
</tr>
<tr>
<td>3–5.7</td>
<td>2.8–4.2</td>
</tr>
<tr>
<td>0.83–1.27</td>
<td>0.71–1.05</td>
</tr>
</tbody>
</table>

TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine.
Table 2  Demographic characteristics of the study participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± s.d.</td>
<td>26.03 ± 4.93</td>
</tr>
<tr>
<td>Gestational age, n (%)</td>
<td>1–13 weeks (first trimester)</td>
</tr>
<tr>
<td></td>
<td>85 (50.6)</td>
</tr>
<tr>
<td></td>
<td>14–27 weeks (second trimester)</td>
</tr>
<tr>
<td></td>
<td>53 (31.5)</td>
</tr>
<tr>
<td></td>
<td>28 weeks to term (third trimester)</td>
</tr>
<tr>
<td></td>
<td>30 (17.9)</td>
</tr>
<tr>
<td>Risk factors for thyroid dysfunction, n (%)</td>
<td></td>
</tr>
<tr>
<td>Age over 30 years, n (%)</td>
<td>25 (14.9)</td>
</tr>
<tr>
<td>History of thyroid dysfunction or prior thyroid surgery</td>
<td>0 (0)</td>
</tr>
<tr>
<td>History of post partum thyroiditis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Family history of thyroid disease</td>
<td>7 (4.2)</td>
</tr>
<tr>
<td>Symptoms of thyroid dysfunction</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Positive for thyroid antibodies (anti-TPO antibodies)</td>
<td>15 (8.9)</td>
</tr>
<tr>
<td>History of type 1 diabetes</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>History of other autoimmune disorders</td>
<td>0 (0)</td>
</tr>
<tr>
<td>History of miscarriage or preterm delivery</td>
<td>31 (18.5)</td>
</tr>
<tr>
<td>History of therapeutic head or neck irradiation</td>
<td>0 (0)</td>
</tr>
<tr>
<td>History of infertility</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Residing in an area of known moderate to severe iodine deficiency</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Statistical analysis

After data collection, revision, verification, and standardization, data analysis was performed using SPSS, version 16 (SPSS, Inc.). The value of a continuous variable was presented as the mean ± s.d. and the value of a categorical variable as the number (percentage). The Student’s t-test was used to compare quantitative variables in two independent groups, the χ² test to compare qualitative variables in different groups, the Mann–Whitney U test to compare nonparametric variables, and Pearson’s correlation analysis to determine the correlation between quantitative data. P value < 0.05 was considered significant.

Results

Of the 200 pregnant women invited to participate in the study, 168 who underwent both the detailed history taking and laboratory testing were enrolled. Among the 168 women, 104 (61.9%) and 64 (38.1%) were found to be at low and high risk of developing thyroid dysfunction respectively. As can be observed in Table 2, which shows their demographic characteristics, the most prevalent risk factor for developing thyroid dysfunction was history of miscarriage or preterm delivery (18.5%; n = 31). Among the 104 participants at low risk, 53 (51%) were in the first trimester, 34 (32.7%) in the second trimester, and 17 (16.3%) in the third trimester. Among the 64 at high risk, 32 (50%) were in the first trimester, 19 (29.7%) in the second trimester, and 13 (20.3%) in the third trimester. Regarding number of risk factors, 47 of the 64 (73.4%) in the high-risk group had one risk factor and 17 (26.6%) had two or more risk factors. However, only one of the 64 patients in the high-risk group (1.6%) and nine of 104 in the low-risk group (8.7%) had isolated hypothyroxinaemia. Moreover, 15 (23.4%) of the 64 in the high-risk group were positive for thyroid antibodies, of whom six of the 15 (40%) were euthyroid and thyroid antibody-positive.

The prevalence of TSH > 2.5 mIU/l during the first trimester and TSH > 3 mIU/l during the second and third trimesters among all 168 patients was found to be 56% (n = 94). No statistically significant differences were found between the high- and low-risk group regarding the prevalence of either clinical or subclinical hypothyroidism, TSH level, or FT₃ level (Table 3, Figs 1 and 2).

However, levels of anti-TPO antibodies and FT₄ were found to be significantly higher in the high-risk group (P = 0.0001 and 0.015 respectively; Figs 3 and 4). Among all 168 patients, no significant differences were found regarding the prevalence of hypothyroidism in the first, second, or third trimester (Table 4). The prevalence of hypothyroidism in the first, second, and third trimesters among the low-risk group was 50.9, 58.8, and 64.7% respectively (χ² = 1.18, P = 0.55), while among the high-risk group it was 50, 63.2, and 61.5% respectively (χ² = 1.02, P = 0.59). Although the high-risk group was found to be significantly older than the low-risk group (29.06 ± 24.16 years respectively; t = 7.62, P = 0.0001), no statistically significant correlation was found between age and TSH, FT₄, FT₃, and anti-TPO antibody levels (r = 0.031, ns).

Table 3  Comparison of prevalence of hypothyroidism in the high- and low-risk groups. Comparison between the high- and low-risk group to assess the prevalence of euthyroidism, subclinical hypothyroidism, and clinical hypothyroidism; the total prevalence of hypothyroidism was subsequently compared between the two groups.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>High-risk group (n = 64)</th>
<th>Low-risk group (n = 104)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hypothyroidism</td>
<td>28 (43.8)</td>
<td>46 (44.2)</td>
<td>0.049</td>
<td>0.97</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>28 (43.8)</td>
<td>44 (42.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical hypothyroidism</td>
<td>8 (12.5)</td>
<td>14 (13.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of hypothyroidism</td>
<td>36 (56.3)</td>
<td>58 (55.8)</td>
<td>0.004</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*χ² test was applied.*
When assessed according to the normal population reference ranges for thyroid values, 75 of the 168 patients (44.6%) were found to have hypothyroidism, and no statistically significant difference was found regarding the prevalence in the low-risk group (45.2% or 47/104) and the high-risk group (43.8% or 28/64 patients; \( \chi^2 = 0.033, P = 0.85 \)). The remaining 93 pregnant women (55.4%) showed normal thyroid function; of these 93 women, 36 (38.7%) were in the high-risk group and 57 (61.3%) were in the low-risk group. When the normal population cutoff values for thyroid function were applied, 28 of the 85 patients (32.9%) in the first trimester, 29 of the 53 (54.7%) in the second trimester, and 18 of the 30 (60%) in the third trimester were found to have hypothyroidism.

**Discussion**

Despite continuous discussion regarding the best means of screening for thyroid dysfunction in pregnant women over the past 2 decades, universal screening for this population has not been adopted due to lack of evidence of its efficacy. Although several studies have provided evidence that universal screening for thyroid dysfunction, including subclinical hypothyroidism, in pregnant women is cost-effective (8), professional associations of endocrinologists and obstetricians do not have sufficient evidence upon which to base the recommendations for universal screening (9, 10). Such evidence is especially lacking in the Middle East, particularly in Egypt, in which no previous studies have examined thyroid dysfunction among pregnant women. To further examine this finding and fill the study gap regarding the best means of detecting the prevalence of hypothyroidism in pregnant women in the Middle East, the present study compared the virtue of universal screening and targeted screening of high-risk patients for thyroid dysfunction and the prevalence of thyroid dysfunction in pregnant Egyptian women.

A substantial and comparable prevalence of thyroid dysfunction (clinical and subclinical hypothyroidism) was found in the low- and high-risk group, regardless of trimesteric or normal population cutoff values applied. Specifically, 12.5 and 13.5% of the high- and low-risk group, respectively, were found to have clinical hypothyroidism and 43.8 and 42.3%, respectively, to have subclinical hypothyroidism. In previous comparisons of women at low and high risk, one study concluded that high-risk women have a more than sixfold higher risk of hypothyroidism during the first trimester, while another reported that they have a 1.5-fold higher risk of hypothyroidism during early pregnancy compared with low-risk women (1, 11). In line with the current study, which found that targeted screening failed to detect hypothyroidism in 55.8% of the low-risk group, Horacek et al. (12) found that it failed to detect hypothyroidism in 55% of pregnant women, while Chang et al. (13) reported that it failed to detect hypothyroidism in 80.4% of their studied population.

A high prevalence of thyroid dysfunction in all patients, and no significant difference in prevalence between the high- and low-risk group, was found in the current study. In contrast, in a study of screening for thyroid dysfunction during the first trimester, Wang et al. (14) found a higher prevalence of elevated TSH level in only the high-risk group than that in the non-high-risk group (10.9 vs 7%). However, in agreement with the
present study, Wang et al. found that targeted screening failed to detect thyroid dysfunction in 81.6% of their sample. Similarly, after finding that 46.4% of the pregnant women in whom they had detected hypothyroidism had no risk factors, Matuszek et al. (15) concluded that conducting targeted screening would have resulted in failure to identify these apparently not-at-risk women.

Controversy continues regarding the links between subclinical hypothyroidism and isolated hypothyroxinemia and poor fertility and maternal and fetal outcomes. Subclinical hypothyroidism has been found to be the most prevalent thyroid dysfunction in pregnant women, with a reported prevalence of 4.6–11.8% (16). In accordance, a high prevalence of subclinical hypothyroidism was found in both the high-risk group (43.8%) and low-risk group (42.3%) in this study; we also noted isolated hypothyroxinemia in 1.6 and 8.7% of the high- and low-risk group patients respectively. This finding is significant, as subclinical hypothyroidism has been linked to poor maternal and fetal outcomes (17), and women with subclinical hypothyroidism and thyroid antibodies have recently been found to be at increased risk for miscarriage, preeclampsia, and perinatal mortality (18). Despite these findings, there is no sufficient evidence for the efficacy of levothyroxine therapy on fetal and maternal outcomes in pregnant women with subclinical hypothyroidism (19).

Thyroid hormone levels and requirements vary greatly during the hormonal and physiological changes accompanying pregnancy (20). In the current study, the prevalence of hypothyroidism was found to be similar in the first-, second-, and third trimesters, which supports Brent (21) who recommended performing universal screening for thyroid dysfunction early in pregnancy as well as during the second- and third trimesters. While another study concluded that screening should be performed during the second trimester (22), Moleti et al. (23) found that >40% of screened women were diagnosed with hypothyroidism in the early and late second trimester compared with 57% in the first trimester. Several researchers have also expressed great concern regarding hypothyroidism during the first trimester, as the fetus at that period is entirely dependent on maternal thyroid hormone levels, having not yet become able to make its own endogenous supply (24, 25).

Our findings indicate that the use of trimesteric cutoff values in all trimesters, which yield detection rates of 50.6, 60.4, and 63.3% in the first, second, and third trimesters respectively, allows for more accurate detection of thyroid dysfunction compared with the use of normal population cutoff values, which yield detection rates of 32.9, 54.7, and 60% respectively. As review of these figures indicates, use of normal population cutoff values would lead to missed detection in ~17% of women in the first trimester. In accordance with the accumulating evidence that TSH values are lower throughout pregnancy than previously believed, the most recent ATA guidelines recommend using trimesteric reference ranges in screening for thyroid dysfunction. However, several studies have found variation in prevalence among national populations and ethnicities (7). A study of the Australian population found that using ATA cutoff values for non-pregnant women compared with population-derived cutoff values during the first trimester resulted in misclassification in 20.5% of women (26). Likewise, a study of the Iranian population identified cutoff values that are higher than ATA values. Despite recognizing the potential for missed detection or misclassification when using ATA cutoff values, they were used in the present study, as the small
sample size did not allow for derivation of study population cutoff values. Nevertheless, we acknowledge that differences in cutoff values among populations warrant further research.

Our study showed that 15 of 64 (23.4%) women in the high-risk group were positive for thyroid antibodies, and of these 15 women, six (40%) were euthyroid and positive for antibodies. A recent review concluded that three meta-analyses documented a positive relationship between thyroid autoimmunity and miscarriage, with two meta-analyses estimating the prevalence of thyroid autoimmunity in pregnancy at 10% (16). Although this rate is higher than that found in the current study, the difference could be attributed to the relatively small sample size examined here.

### Limitations

The study did not test for iodine deficiency, which could have partially contributed to the results. A 1992 survey by the Egyptian Nutrition Institute in collaboration with the World Health Organization (WHO) reported the prevalence of iodine deficiency in Egypt as indicated by the total goiter rate among mothers and their preschool children to be 6–7% and to be lowest in metropolitan Cairo (http://ftp.fao.org/ag/agn/nutrition/ncp/egy.pdf; accessed 8th March 2014). To prevent iodine deficiency, the Egyptian Government has been fortifying table salt with iodine since 1996 (http://www.unicef.org/egypt/Landscape_Analysis_Report_January_2013.pdf; accessed 8th March 2014). The latest (2008) Demographic Health Statistics study reported that 79% of all Egyptian households and 88% of households in a lower urban Egyptian region were using iodized salt (27). Nevertheless, several studies have found evidence of the increasing prevalence of iodine deficiency. Among them, a study of 113 pregnant women in West Cairo reported an iodine-deficiency prevalence of 29.2%, although 15% were found to have hypothyroidism (28). Another recent study has identified low iodine status in 80 non-pregnant Egyptian women with thyroid nodules despite their use of iodized salt (29). Unfortunately, no recent large survey for iodine status in Egypt has been conducted since 1992.

### Conclusion

Our results indicate that use of the most recent Endocrine Society clinical practice guidelines for assessing high-risk thyroid dysfunction in pregnant women supplemented by ATA guidelines leads to missed detection of clinical or subclinical hypothyroidism in 34.5% of pregnant women. This finding is significant, as maternal clinical hypothyroidism cases can have deleterious effects on both the mother and fetus. We, therefore, recommend that universal screening of pregnant women for thyroid dysfunction can be adopted as a standard practice in antenatal care throughout Egypt.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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### Author contribution statement

All authors have participated sufficiently in the conception and design of this work or the analysis and interpretation of the data, as well as the writing and reviewing of the final version of the manuscript.

### References


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