

Prevalence of subclinical hypothyroidism in pregnancy in Saudi Arabia

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ABSTRACT

الأهداف: أثبتت الدراسات مؤخرًا أن قصور الغدة الدرقية دون السريري أثناء فترة الحمل مرتبط بالعديد من المضاعفات السلبية التي تؤثر على الأم والطفل. تهدف هذه الدراسة إلى دراسة مدى انتشار قصور الغدة الدرقية دون السريري لدى النساء الحوامل في المملكة العربية السعودية وجدوى إنشاء برنامج للفحص مبكر.

الطريقة: تم عمل هذه الدراسة في مدينة الملك عبدالعزيز الطبية والعيادات الأولية بالحرس الوطني بخشم العان في مدينة الرياض أثناء شهر أغسطس من عام 2016 كما تم استخدام معلومات جميع النساء الحوامل اللاتي قام أطباؤهن بفحص هرمون الغدة الدرقية لديهن خلال فترة الحمل أثناء الفترة من يناير 2016 و حتى أغسطس 2016. مجموع النساء اللاتي تم إشراكهن في هذه الدراسة هو 384.

النتائج: نسبة النساء اللاتي يعانين من قصور الغدة الدرقية دون السريري في هذه الدراسة هو 50/384 (13%). أثبتت هذه الدراسة أن نسبة حدوث قصور الغدة الدرقية دون السريري أثناء فترة الحمل عند النساء اللاتي تم إجراء الفحص لهن عشوائياً هي ثلاث أضعاف نسبة حدوثه عند النساء اللاتي تم فحصهن بناء على قرار طبيهين المعالج (OR: 3.1; 95% CI: 1.182 to 8.704, $p=0.022$).

الخاتمة: تظهر نتائج هذه الدراسة الحاجة إلى إنشاء برنامج للفحص المبكر لقصور الغدة الدرقية دون السريري أثناء فترة الحمل في المملكة العربية السعودية.

Objectives: To estimate the prevalence of subclinical hypothyroidism (SCH) in Saudi Arabia and assess the need for an SCH screening program.

Methods: This cross-sectional study was conducted at King Abdulaziz Medical City and the Khashmulaan Clinic at the National Guard Health Affairs, Riyadh, Saudi Arabia in August 2016. All women attending the antenatal clinics were

invited to participate in the study. In addition, data were retrieved from the files of pregnant women who had been screened for hypothyroidism from January 2016 to August 2016. A total of 384 pregnant women were included in the study.

Results: The prevalence of SCH in pregnant women in this study was 50/384 (13%) with 95% confidence intervals (CIs): 9.82%-16.80%. Pregnant women who were randomly screened using a survey ($n=127$) were 3 times more likely (OR: 3.1; 95% CI: 1.182 to 8.704, $p=0.022$) to have SCH compared to pregnant women who were screened based on their physician's judgement ($n=257$). Results showed older age (≥ 40 years) was associated with an insignificant decrease in the risk of SCH.

Conclusion: Random screening for SCH in pregnant women showed a higher prevalence in comparison to women who were screened as a result of physician referrals. The results highlight the urgent need for larger studies to investigate the prevalence of SCH as well as the need for an SCH screening program.

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A number of physiological changes occur during pregnancy. Hormonal changes are responsible for the increase in size as well as the function of certain endocrine glands in order to meet both maternal and fetal requirements. The thyroid gland undergoes major changes and alteration in the serum level of thyroid hormone in pregnant women is caused by 2 main hormones: human chorionic gonadotropin (hCG) and estrogen. Thyroid-stimulating hormone (TSH) is secreted by the pituitary gland, and this in turn promotes thyroid hormone secretion. A drop in the levels of circulating TSH is seen in early pregnancy and is caused by the increase in maternal thyroid hormone levels in the first trimester, during which, the fetus is completely dependent on the mother for thyroid hormone production. Maternal thyroid hormone levels return to normal when the fetal thyroid gland begins producing its own hormones.¹ Thyroid hormone plays a significant role in fetal neurocognitive development, and maternal thyroid hormone deficiency may cause severe neurological impairment to the baby. Hypothyroidism may go undetected in many instances as it may not always present overtly. Subclinical hypothyroidism (SCH) is a condition in which circulating thyroid hormone levels are within the normal range, but the serum TSH is elevated.² It has been recognized in recent times that SCH in pregnancy has a significant impact on pregnancy outcomes. It has been reported in several studies to be associated with pregnancy complications such as gestational diabetes (GDM), hypertension, and pre-eclampsia.³⁻⁵ Women with SCH were twice as likely to deliver prematurely compared to subjects whose thyroid function tests were normal. These women also had a 3 times higher chance of developing placental abruption.⁶ It has been reported in other studies that pregnant women with SCH were more likely to suffer miscarriage, especially during the first 20 weeks of gestation.⁷⁻¹⁰ Maraka et al¹¹ showed in their study that SCH affected not only the mother during pregnancy but also neonatal outcomes. Intrauterine growth restriction, small for gestational age, low birth weights, and low Apgar scores were all reported in neonates whose mothers were SCH patients. Several studies report that the prevalence of SCH is on the rise, although there is no consensus on the seriousness of the

impact of SCH on pregnancy outcomes. In the general population, the prevalence of SCH among pregnant women is estimated to be 2% to 3%.¹² In a study done on Caucasian women by Knight et al,¹³ the prevalence was found to be 13.9%. Prevalence of SCH in the United States ranged from 2% to 2.5%.¹¹ On the other hand, the prevalence of SCH in Belgium has been reported to be 6.8%, and as high as 13.7% in Spain.¹⁴ A cross-sectional, multicenter study undertaken in India showed that 13.1% of pregnant women had hypothyroidism. The majority of these cases were subclinical and in the first trimester of pregnancy.¹⁵ Another study conducted in a tertiary hospital in India on a total of 461 women showed an increase in the number of cases of SCH. In the Democratic Republic of Congo the prevalence of SCH was found to be 8% and the prevalence of isolated hypothyroxinemia was 12%.¹⁶ In a study done on pregnant women in Teheran, Iran, the prevalence of hypothyroidism was found to be 4.2%, of which 89.1% of cases were subclinical.¹⁷ Although the outcomes associated with SCH in pregnancy pose a huge risk for both the mother and her offspring, screening for SCH is not universally carried out in antenatal settings in Saudi Arabia. Furthermore, there is a lack of data on the prevalence of SCH in pregnancy in Saudi Arabia.

The aim of the present study is to estimate the prevalence of SCH among pregnant women in Saudi Arabia and to question the importance of establishing a national SCH screening program in the country.

Methods. This multicenter, cross-sectional study was conducted at King Abdulaziz Medical City, a tertiary hospital, and the Khashmulaan Clinic at the National Guard Health Affairs (NGHA), a primary care center in Riyadh, Saudi Arabia, during the month of August 2016. Ethical approval was obtained from the King Abdullah International Medical Research Center IRB office, memo reference number: IRBC/700/16.

A literature search of PubMed was carried out in order to find related articles and previously published data. Pregnant women attending the antenatal clinic at the tertiary hospital as well as those admitted for OB/GYN care and women attending the antenatal clinic at the primary care center were all invited to participate in this study. In addition, data were retrieved from the files of high-risk patients who were screened for hypothyroidism by their physicians from January to August 2016. A total of 384 pregnant women were included in this observational study.

All patients who had any history of thyroid dysfunction or disease, patients using drugs that may interfere with thyroid function such as levothyroxine,

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methimazole, iodide, lithium, amiodarone, and corticosteroids, and patients diagnosed with autoimmune diseases, such as connective tissue diseases, were excluded from the study.¹⁸

All the ethical principles for medical research involving human subjects outlined in the WMA Declaration of Helsinki, as revised in October 2013 were followed.¹⁹ The procedure was explained to all patients included in the study, and informed consent was obtained. A copy of the consent form signed by the patient was given to the participants of the study as well. Pregnant women who refused to participate at any point in the study were excluded.

The medical histories of all study participants were recorded on a predesigned proforma. Note was made of patients who were diagnosed with type 2 diabetes mellitus (T2DM) or gestational diabetes mellitus (GDM). Weights and heights were measured and body mass indexes (weight in kg/height in meters²) were calculated; a BMI of 30 or more was considered abnormal. Blood samples were collected from those patients who fulfilled the inclusion criteria. Free T4 (FT4) and TSH were measured using electrochemiluminescence immunoassay (ECLIA). Subjects with TSH levels between 2.5 mIU/L and 10 mIU/L and FT4 within trimester-specific ranges were considered to have SCH according to the American Thyroid Association Guidelines.² A hexokinase-mediated reaction was utilized to measure fasting blood glucose, and levels higher than 95 mg/dL were considered abnormal according to the American Academy of Family Physicians' Guidelines.²⁰

Prior assumptions of test significance level $\alpha=0.05$ were made at the 95% confidence interval (CI) for a single proportion of SCH with a precision or margin of error = 5%. In a study conducted by Yassaee et al, 4.2% of pregnant woman had SCH.¹⁷ The minimum required sample size was $n=383$, and nQuery Advisor (Statistical Solutions Ltd., Cork, Ireland) was used to estimate and report the sample size. When the sample size is 383 patients, a 2-sided 95% CI for a single proportion using the large sample normal approximation will extend 5% from the observed 4.2% of SCH in pregnant women.

Statistical analyses. Data analyses were performed using SAS 9.4. Categorical data were summarized using count and percent. The prevalence of SCH in pregnant women was reported in terms of percent and 95% CIs. Hosmer-Lemeshow and Cox and Snell tests were used to evaluate the goodness-of-fit for the 2 models. All tests were 2-sided, and a $p \leq 0.05$ was considered significant.

Results. The demographic characteristics of the sample were presented by counts and percentages and tested by Chi-square to determine their associations with SCH status (Table 1). This study included ($n=384$) pregnant women in which 127 (33.1%) women were screened for TSH and T4 levels and 257 (66.9%) women their data were retrieved from the medical records. The majority (89.3%) of women were aged less than 40 years and obesity was found to be 53.9% (Table 1). The mean age of the study participants was 31.6 with age ranged from 16 to 51 years old. The prevalence of SCH in the study participants was 50/384 (13%) with 95% CIs: 9.82%-16.80% (Figure 1), the majority of them were in their third trimester (Figure 2).

The Chi-square analysis (Table 1) indicated that age, FBS, SBP, obesity, diabetes, and GDM were not significantly associated with subclinical hypothyroidism ($p > 0.05$). However, Chi-square analysis revealed that higher prevalence of subclinical hypothyroidism was found in pregnant women who were randomly screened

Table 1 - Prevalence of subclinical hypothyroidism and participants' characteristics.

Levels	Overall N=384	No 334 (87%)	Yes 50 (13%)	P-value
<i>Age</i>				
<40	343 (89.3)	297 (86.6)	46 (13.4)	0.580
≥40	39 (10.2)	35 (89.7)	4 (10.3)	
<i>Fasting blood sugar</i>				
Normal	194 (80.2)	168 (86.6)	26 (13.4)	0.195
Abnormal	48 (19.8)	38 (79.2)	10 (20.8)	
<i>Systolic blood pressure</i>				
Normal	207 (96.3)	178 (86.0)	29 (14.0)	0.324
Abnormal	8 (3.7)	6 (75.0)	2 (25.0)	
<i>Diastolic blood pressure</i>				
Normal	208 (96.3)	178 (85.6)	30 (14.4)	1.000
Abnormal	8 (3.7)	7 (87.5)	1 (12.5)	
<i>Obese</i>				
Yes	202 (53.9)	179 (88.6)	23 (11.4)	0.376
No	173 (46.1)	148 (85.5)	25 (14.5)	
<i>Diabetes</i>				
Yes	44 (11.5)	36 (81.8)	8 (18.2)	0.280
No	340 (88.5)	298 (87.6)	42 (12.4)	
<i>Gestational diabetes</i>				
Yes	35 (9.1)	31 (88.6)	4 (11.4)	1.000
No	349 (90.9)	303 (86.8)	46 (13.2)	
<i>Screening for subclinical hypothyroidism</i>				
Records	257 (66.9)	230 (89.5)	27 (10.5)	0.037*
Survey	127 (33.1)	104 (81.9)	23 (18.1)	

Values are presented as number and percentage (%).

*Significant at $\alpha = 0.05$.

Table 2 - Factors associated with subclinical hypothyroidism.

Factor	Reference	B	SE	Wald	P-value	Odds ratio	Lower	Upper
Age ≥ 40 (years)	<40	0.262	0.783	0.112	0.738	1.299	0.280	6.029
Fasting blood sugar	Normal	0.003	0.698	0.000	0.997	1.003	0.255	3.939
Systolic blood pressure	Normal	0.478	0.974	0.241	0.623	1.613	0.239	10.875
Diastolic blood pressure	Normal	0.205	1.189	0.030	0.863	1.227	0.119	12.611
Obese	No	-0.700	0.544	1.658	0.198	0.497	0.171	1.441
Diabetes	No	1.199	0.697	2.957	0.085	3.315	0.846	12.996
Gestational diabetes	No	0.688	0.930	0.546	0.460	1.989	0.321	12.312
Survey screening	Records	1.165	0.509	5.232	0.022*	3.207	1.182	8.704
Constant		-2.369	0.444	28.467	0.000	0.094		

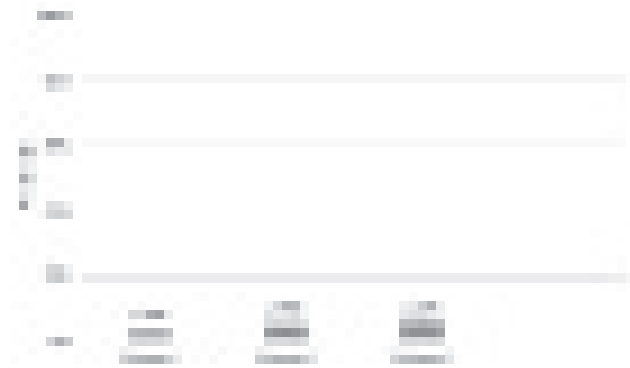
*Significant at $\alpha = 0.05$

compared to pregnant women who were screened based on their physician's judgement (18.1% versus 10.5%, $p=0.037$).

A multiple logistic regression model was used to determine the independent factors associated with SCH (Table 2). Adjusting for the other confounding factors, pregnant women who were randomly screened were 3 times more likely (OR 3.1, 95% CI, 1.182 to 8.704; $p=0.022$) to have SCH compared to pregnant women who were screened based on their physician's judgement (Table 2).

Discussion. The results of this study were found to be comparable to those reported in neighboring countries; for example, a study conducted in India found a prevalence rate of 13.13%.¹⁵ The prevalence of SCH among pregnant women appears to be higher in eastern countries than in western countries, such as the United States, where the prevalence is only 3%.²¹ The results obtained highlight the need for large epidemiological studies that would better estimate the prevalence of SCH in pregnant women in Saudi Arabia. In addition, ethnicity and environmental factors may play a role in the varying prevalence of SCH across regions. Further research is required to evaluate the environmental risk factors that play a role in the development of SCH and result in a higher prevalence of SCH in a specific region. In a study carried out on pregnant Egyptian women, targeted screening for thyroid dysfunction was compared to universal screening. The results showed that targeted screening of only high-risk pregnant women resulted in missing 34.5% of women with thyroid dysfunction.²²

Subclinical hypothyroidism in pregnancy has been found to have a significant impact on pregnancy outcomes. Several studies have reported that it is associated with pregnancy complications such as gestational diabetes (GDM), hypertension, and pre-

**Figure 1** - Prevalence of subclinical hypothyroidism in pregnancy.**Figure 2** - Prevalence of subclinical hypothyroidism according to trimester.

eclampsia.³⁻⁵ In a study conducted on 508 pregnant women in Pakistan, SCH was shown to be strongly associated with GDM. High TSH levels were reported in 61.5% of women with GDM compared to 6% in healthy controls.²³ Women with SCH were found to be twice as likely to deliver prematurely compared to

subjects whose thyroid function tests were normal. These women also had a 3 times higher chance of developing placental abruption.⁶ Other studies have reported that pregnant women with SCH are more likely to suffer miscarriage, especially during the first 20 weeks of gestation.⁷⁻¹⁰

Maraka et al¹¹ found that SCH affected both the mother during pregnancy and also neonatal outcomes. Intrauterine growth restriction, small for gestational age, low birth weights, and low Apgar scores were all reported in neonates whose mothers were SCH patients. In a study conducted on urban Japanese subjects, TSH levels were measured twice: the first measurement was carried out during the first trimester, while the second was carried out during the third trimester. These measurements were compared to the neonates' birth weight. The results showed that a decrease in TSH levels is an independent determinant of neonatal birth weight.²⁴

Many other studies; however, claim that SCH has little or no effect on the mother or infant. An observational cohort study carried out by Bernardi et al²⁵ reported that although there was a high prevalence of SCH in their study cohort (19%), a statistically significant difference was not found in the subsequent live birth rate when comparing women with SCH and euthyroid women. A prospective study conducted to determine the effect of gestational SCH on neurodevelopment in early infancy also concluded that there was no evidence of neurodevelopmental deficit.²⁶ Despite this, some studies have demonstrated that SCH may continue to affect children throughout their lives. Many suggest a relationship between maternal thyroid function during pregnancy and the offspring's neuropsychological development. In the United States, an observational cohort study found that maternal thyroid dysfunction during early pregnancy was associated with poor scholastic performance in adolescents.²⁷ In addition, a systematic literature search of Pubmed and Embase and a Web of Science meta-analysis by Fan et al,²⁸ which included 6 studies, showed that thyroid abnormalities in pregnant women may have an impact on the neuropsychological development of their children. There is also increasing evidence linking SCH to attention deficit hyperactivity disorder (ADHD) and autistic symptoms in offspring.^{29,30}

Currently, there is increasing evidence emphasizing the effect of SCH on mothers and their offspring. Thyroid screening in pregnant women and early treatment of SCH during pregnancy has been reported to improve, reverse, or decrease the impact of various maternal and neonatal outcomes associated with SCH.

In 2010, a clinical trial in Italy concluded that in thyroid dysfunction detected by screening of patients with a low risk for thyroid disease during pregnancy, treatment was associated with better pregnancy outcomes.³¹ Another study found that early treatment of maternal hypothyroidism and SCH with levothyroxine reversed the effects on progeny.³² Experiments performed on rats showed that early maternal SCH treatment resulted in improvements in offspring's brain development, learning, and memory functions.³³ In another study carried out on mice, early treatment of maternal SCH with levothyroxine was found to reverse the adverse effects on the offspring's spatial learning caused by the condition.³² A review article published in 2016 suggests the correction of maternal hypothyroxinemia with levothyroxine in order to prevent abnormal neural development in the offspring.³⁴

In a meta-analysis of randomized controlled trials published in PubMed, Embase, Web of Science, Chinese BioMedical Literature Service System, and China National Knowledge Infrastructure databases, Levothyroxine therapy was found to significantly reduce pregnancy complications and was found to be associated with better pregnancy outcomes.³⁵ In China, a study found that treatment of maternal SCH decreased the number of spontaneous abortions among females with SCH, but this was not statistically significant when compared with women who did not receive any treatment.³⁶ A clinical trial was conducted to test the effect of levothyroxine on pregnant women diagnosed with SCH. Drug therapy was associated with a decreased risk of low birth weight and low Apgar scores among women with SCH.³⁷ In Spain, screening patients at both high and low risk for thyroid disease proved to be more cost effective compared to no screening and screening only high-risk patients.³⁸ Data on the subject in Saudi Arabia is lacking, and longitudinal studies on the cost-effectiveness of implementing universal screening for SCH in pregnancy in Saudi Arabia are needed to further evaluate whether universal screening in Saudi Arabia is justified.

Study limitations. This study excluded women who were known to have thyroid or autoimmune diseases, however, it did not test for other causes of hypothyroidism in these women, such as iodine deficiency and autoimmune disease. Furthermore, as this study is a cross-sectional study, the results may be subjected to non-response bias as many women who were invited to participate in the study refused participation or opted to withdraw after initial participation.

In addition, the prevalence of SCH in non-pregnant women in Saudi Arabia is not known, the high

prevalence in pregnancy may be attributed to the high prevalence of thyroid disease in women in Saudi Arabia. Comparative studies may be needed to further assess the relationship between pregnancy and thyroid gland dysfunction in Saudi Arabia.

In conclusion, random screening for SCH in pregnant women showed a higher prevalence in comparison to women that were screened as a result of physician referral. The results highlight the urgent need for larger studies to investigate SCH prevalence as well as the need for an SCH screening program.

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Student Corner

We invite students from a variety of medical disciplines to submit original contributions based on their supervised research.

The Student Corner of Saudi Med J aims to help students explore research opportunities and network with other peers and mentors in the same field.

Submission Guidelines

Submitted Abstracts should include the following:

- Title should be descriptive
- Author's names and affiliation (specify college level/year, academic degree of Senior Author)
 - Abstract must be structured and not more than 300 words
 - The following are the typical headings:

Objectives (background, why the study was done, specific aims)

Methods (setting, date of study, design, subjects, intervention and analysis)

Results (findings, data and statistical tests) and

Conclusion (general interpretation of results)

General Information on Abstract Submission

Submitted Abstracts should be co-authored by a Senior Supervisor

Abstracts will be reviewed by Student's Corner Section Editor

There is no fee to submit an Abstract

Ethical Approval should be provided

Non-indexed materials