Prevalence of thyroid dysfunction and autoimmunity in pregnant women with gestational diabetes and diabetes type 1

Article *in* Prilozi / Makedonska akademija na naukite i umetnostite, Oddelenie za biološki i medicinski nauki = Contributions / Macedonian Academy of Sciences and Arts, Section of Biological and Medical Sciences · December 2010

Source: PubMed

CITATIONS
48

READS
250

6 authors, including:

Velkoska Nakova Valentina
Goce Delcev University
43 PUBLICATIONS **314** CITATIONS
SEE PROFILE

Brankica Krstevska
Saints Cyril and Methodius University of Skopje
84 PUBLICATIONS **398** CITATIONS
SEE PROFILE

Slagjana Simeonova
29 PUBLICATIONS **224** CITATIONS
SEE PROFILE

Marija Hadzi Lega
University Clinic of Gynecology and Obstetrics
35 PUBLICATIONS **177** CITATIONS
SEE PROFILE

Прилози, Одд. биол. мед. науки, МАНУ, XXXI, 2, с. 51–59 (2010)
Contributions, Sec. Biol. Med. Sci., MASA, XXXI, 2, p. 51–59 (2010)
ISSN 0351–3254
УДК: 616.379-008.64:618.3

PREVALENCE OF THYROID DYSFUNCTION AND AUTOIMMUNITY IN PREGNANT WOMEN WITH GESTATIONAL DIABETES AND DIABETES TYPE 1

Velkoska Nakova V.,[1] Krstevska B.,[2] Dimitrovski Ch.,[2] Simeonova S.,[3] Hadzi-Lega M.,[3] Serafimoski V.[4]

[1] Medical Science Faculty, Goce Delcev University, Stip, R. Macedonia
[2] Endocrinology, Diabetes and Metabolic Disorders Clinic, Medical Faculty, Skopje, R. Macedonia
[3] Gynecology and Obstetrics Clinic, Medical Faculty, Skopje, R. Macedonia
[4] Gastroenterohepatology Clinic, Medical Faculty, Skopje, R. Macedonia

Abstract: *Objective:* The aim of the present study was to determine the prevalence of abnormal thyroid function and antithyroid antibodies during pregnancy in women with diabetes type 1 and gestational diabetes mellitus (GDM).

Methods: The study group included 83 pregnant women who attended the Outpatient Department of the Endocrinology, Diabetes and Metabolic Disorders Clinic in the period from 05.2009 to 11.2009. The one hundred-g. oral glucose tolerance test (OGTT) was conducted on the pregnant women except for women with diabetes type 1. Thyroid functions were evaluated in all the pregnant women. After routine screening for GDM, thirty of the pregnant women were healthy and GDM was diagnosed in forty of them. The rest, thirteen women, had diabetes type 1.

Results: The women who developed GDM showed a mean free thyroxin concentration (fT4) significantly lower than that observed in the healthy pregnant women and women with diabetes type 1. Among the pregnant women with GDM, 10 women or 25% had fT4 concentrations below the lower cut-off with normal thyroid-stimulating hormone concentrations (TSH). A statistically significant difference was found in the prevalence of antithyroid antibodies (anti-TPO) between the (30%) women with diabetes type 1 and (10%) healthy pregnant women ($p < 0.05$). In the women positive for anti-TPO, TSH was significantly higher ($p < 0.05$).

Conclusion: The significantly higher prevalence of hypothyroxinemia in GDM pregnancies and anti-TPO titres in pregnancies with diabetes type 1, than in healthy pregnant women warrants routine screening for thyroid abnormalities in these groups of pregnant women.

Key words: pregnancy**,** gestational diabetes, diabetes type 1, thyroid function, OGTT.

Introduction

As an autoimmune disease, type 1 diabetes mellitus can be associated with other autoimmune disorders. Autoimmune thyroid disease is the most frequent autoimmune disease associated with type 1 diabetes mellitus. The screening and diagnosis of autoimmune thyroid disease are based on the assessment of anti-TPO [1]. About 10% of women at 16 weeks gestation are positive for anti-TPO, in line with what is found in the general population [2]. Thyroid dysfunction and anti-TPO in pregnancy are associated with multiple clinically relevant events occurring before, during and after pregnancy. The presence of anti-TPO during pregnancy may be associated with recurrent abortions, autoimmune hypo- and hyperthyroidism in pregnancy and an increased risk of postpartum thyroiditis [3]. Several studies have concluded that anti-TPO occur more frequently in pregnant women with diabetes type 1 than in healthy pregnant women [4–6]. Although most type 1 diabetic patients are clinically euthyroid, screening for anti-TPO has been recommended as there is a risk of developing future thyroid dysfunction [7]. However, long-term prospective trials to evaluate the incidence and natural history of thyroid disorders in patients with type 1 diabetes are lacking [8]. Gestational diabetes mellitus (GDM) is associated with many non-organ-specific autoantibodies. High titres of anti-TPO in a GDM pregnancy could potentially further compromise the known foetal and maternal complications associated with GDM [3]. However, few studies have investigated the presence of anti-TPO in women with GDM, and no significant association between diabetes in pregnancy and thyroid function has been reported [2, 9].

The aim of the study was to determine the prevalence of thyroid dysfunction and anti-TPO during pregnancy in women with diabetes type 1 and GDM.

Methods

The pregnant women were outpatients of the Endocrinology, Diabetes and Metabolic Disorders Department of the University Clinical Hospitalin Skopje, R. Macedonia, in the period from 05.2009 to 11.2009. A standard diagnostic 100-g 3-h fasting oral glucose tolerance test (OGTT) was administered.

After an overnight fast and at least 3 days of unrestricted diet (≥ 150g carbohydrate per day) and unlimited physical activity, blood was taken to determinate plasma glucose levels. According to Carpenter and Coustan's criteria [10] the cut-off values were the following: fasting glycaemia: 5.3 mmol/l, 1 h: 10.0 mmol/l, 2 h: 8.6 mmol/ l, 3 h: 7.8 mmol/l. GDM was diagnosed if two or more of the four threshold plasma glucose values were met or were exceeded. In forty women GDM was diagnosed. Thirty healthy pregnant women with a normal glucose tolerance after OGTT were recruited as controls. Thirteen women with previously diagnosed diabetes type 1 who visited the Clinic were also included for analysis. None of the patients and controls had a personal history of thyroid disease and none was receiving any medication that could influence thyroid function. All the pregnant women taking part in the study gave their written consent to be included.

We investigated the following parameters: patient's age, body mass index (BMI), gestational age, fT4, TSH, anti-TPO, and thyroid ultrasound. All parameters were assessed in the groups, at the time of the first visit (for women with diabetes type 1), or at the time of OGTT (for other pregnant women).

Blood samples were drawn at 08:00am after a 14-hour fast. Serum TSH and free T4 concentrations were measured using an Immulite 2000 chemiluminescent analyser (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). The normal range for TSH were 0.2–4.2 mIU/l and for fT4 10.3–24.45 pmol/l. The sensitivity of the assays was 0.004 μIU/ml and 0.3 ng/dl, respectively. Anti-TPO was determined by immunometric assay obtained from Diagnostic Products Corporation (Los Angeles, CA) and for positive test we obtained anti-TPO > 34 iU/ml. Ultrasonographic examination of the thyroid was performed with a CCA–220, 7.5 MHz linear transducer (Toshiba, Japan), effective length 62 mm. Echogenicity was evaluated by a standardized comparison of the echogenicity of the thyroid with the echogenicity of the adjacent muscles: m. sternohyoideus, m. sternothyroideus and m. sternocleidomastoideus, in a longitudinal scan of the thyroid lobes.

Statistical analysis was performed using the Statistics for Windows programme, version 5, 0. Data are given as arithmetic mean ± standard deviation and percents. ANOVA was used to compare mean values between groups. The significance of the differences between anti-TPO positive and negative groups was tested using student t-test. The level of significance was set at $p < 0.05$.

Results

In the total group of 83 subjects, 40 (48.2%) were diagnosed as having GDM, 13 (15.7%) were with diabetes type 1, while 30 (36.1%) were classified

as normal. Mean maternal age was 30.8 ± 5.1 years. Mean gestational age was 22.9 ± 8.3 weeks. Comparisons of clinical characteristics of women are shown in Table 1. The healthy controls and GDM were of a similar age, gestational age and BMI. The women with diabetes type 1 were significantly younger and had a lower BMI than the control and GDM groups. Also they visited the hospital earlier then other two groups.

Table 1 – Табела 1

Comparisons of clinical characteristics of pregnant women
Споредба на клиничките карактеристики на бремените жени

Variables	Healthy controls (30)	Diabetes type 1 (13)	GDM (40)	p
age (years)	30,5 ± 5,2	27,4 ± 3,8	32,1 ± 5,1	0,012
gestational age (weeks)	25,4 ± 6,3	12,5 ± 7,2	24,7 ± 7,5	< 0,001
BMI (kg/m^2)	28,5 ± 5,8	24,7 ± 5,1	28,9 ± 6,1	0,011
fT4	13,8 ± 2,3	13,8 ± 2,1	11,7 ± 2,4	**0,0006**
TSH	1,8 ± 1,0	2,2 ± 1,6	1,9 ± 1,3	0,6
anti-TPO	3 (10%)	4 (30,8%)	6 (15%)	–

BMI – body mass index, fT4 – free thyroxin, TSH – thyroid-stimulating hormone, anti-TPO – antithyroid peroxides antibody.
BMI – индекс на телесна маса, fT4 – слободен тироксин, TSH – тиреостимулирачки хормон, anti-TPO – антитела против тироидната пероксидаза.

The women who developed GDM showed a mean fT4 concentration significantly lower than that observed in the healthy pregnant women and women with diabetes type 1. Among the pregnant women with GDM, 10 women or 25% had fT4 concentrations bellow the lower cut-off of 10.2 pmol/l (vs. 3.3% in control group and 7.7% with diabetes type 1).

Hypothyroidism was present in only 1 woman (1.2%) who had either low fT4 or high TSH and she had GDM. Subclinical hypothyroidism was present in 4 women (4.8%) who had normal fT4 and high TSH. Two of them had GDM, one had diabetes type 1, and one was from the control group. Summary 3.3% from the control group, 7.7% with diabetes type 1, and 7.5% with GDM had thyroid dysfunction. None had subclinical or clinical hyperthyroidism.

Healthy controls who were anti-TPO positive (3/30) had thyroid ultrasonografic changes. Two of them had decreased echogenicity, but normal fT4

and TSH concentrations. The third had a larger thyroid gland (goitre) and subclinical hypothyroidism. There were differences in the prevalence of anti-TPO among the three groups. But only the differences between healthy controls and diabetes type 1 were statistically significant (p = 0.04). Anti-TPO were found in 30.8% (vs. 10%, 15% in healthy controls and GDM, respectively) of pregnant women with diabetes type 1.

Mean values of fT4 and TSH in the women with and without anti-TPO are shown in Table 2. In the women positive for anti-TPO, fT4 were higher (wit hout reaching statistical significance) while TSH was significantly higher (p = 0002).

Table 2 – Табела 2

Thyroid function in women by thyroid antibody status
Тироидна функција според присуството на антитироидните антитела

Variables	anti-TPO positive	anti-TPO negative	p
fT4	13,3 ± 2,1	12,7 ± 2,6	0,46
TSH	3,1 ± 1,8	1,7 ± 1,0	**0,002**

Discussion

In the present study we found that women with GDM had mean fT4 concentrations significantly lower than healthy pregnant women and women with diabetes type 1. In humans before 20 weeks gestation, when the foetal thyroid gland becomes active, the mother is the unique source of thyroid hormones [11]. This highlights the importance of adequate maternal thyroid secretion. Recently, an increased risk of impaired cognitive development has been reported, not only in children of women with undetected or inadequately treated thyroid deficiency during pregnancy [12], but also in children of pregnant women with increased titres of anti-TPO and normal thyroid function [13]. Our results showed that pregnant women with GDM and diabetes type 1 have a prevalence of anti-TPO (15% and 30% respectively) that is greater than that observed in the healthy pregnant women (10%). Only the prevalence of anti-TPO between controls and women with diabetes type 1 was statistically significant. This corresponds with other findings. Ortega-Gonzalez *et al*. [14] also found no differences in the prevalence of anti-TPO among pregnant healthy Mexican women and women with GDM.

Multiple studies have shown that anti-TPO is present in 10% of women at 16 weeks' gestation [2]. The prevalence in our study was also 10% for heal-

thy pregnant women, but 15.7% in all 83 pregnant women. This suggests that screening for thyroid dysfunction is indicated, especially in women with diabetes type 1. Also, women with anti-TPO positively had statistically higher TSH, although their fT4 was lower, the differences did not reach statistical significance. No postnatal follow-up was done in women positive for anti-TPO.

The problems of hypothyroidism in pregnancy include pregnancy-induced hypertension, placenta abruption, postpartum haemorrhage, impaired infant neurodevelopment and low birth weight. The incidence of hypothyroidism in pregnant women is estimated to be 2.5% [15]. Five (6.0%) women in this study had hypothyroidism or subclinical hypothyroidism, and 12 (35%) women had low fT4, but normal TSH. In the first trimester, hypothyroxinaemia was associated with preterm laboir (OR 1.62; 95% CI 1.00–2.62) and macrosomia (OR 1.97; 95% CI 1.37–2.83) [16]. Although debated, the overall evidence seems to suggest that isolated gestational hypothyroxinaemia should be supplemented with thyroxin [17]. Glinoer advocates screening of all pregnant women for fT4, TSH and anti-TPO. In women with positive anti-TPO but TSH between 2 and 4 mIU/l, although normal, treatment with thyroxin should be considered [18]. Both the American Association of Clinical Endocrinologists and the Endocrine Society support thyroid function test screening for all pregnant women. For now, there is agreement that further research is much needed in order to provide more objective evidence [15]. For the moment there is no consensus for screening for all pregnant women, but it should be done in high risk groups: chronic autoimmune thyroiditis, diabetes mellitus, iodine deficiency, familial history of thyroid disease, goitre, previous spontaneous abortion, infertility, and clinical signs of hypothyroidism.

Conclusion

Thyroid abnormalities are frequent during pregnancies, especially pregnancies complicated with diabetes. The significantly higher prevalence of hypothyroxinaemia in GDM pregnancies and anti-TPO titres in pregnancies with diabetes type 1, than in healthy pregnant women warrants routine screening for thyroid abnormalities in these groups of pregnant women.

REFERENCES

1. Prazny M., Skrha J., Limanova Z. *et al*. (2005): Screening for associated autoimmunity in type 1 diabetes mellitus with respect to diabetes control. *Physiol. Res;* 54: 41–48.

2. Olivieri A., Valensise H., Magnani F. *et al*. (2000): High frequency of antithyroid autoantibodies in pregnant women at increased risk of gestational diabetes mellitus. *European Journal of Endocrinology;* 143: 741–747.

3. Agarwal M.M., Dhatt G.S., Punnose J., Bishawi B., Zayed R. (2006): Thyroid function abnormalities and antithyroid antibody prevalence in pregnant women at high risk for gestational diabetes mellitus. *Gynecological Endocrinology;* 22(5): 261–266.

4. Bech K., Hoier-Madsen M., Feldt-Rasmussen U., Jensen B.M., Molsted-Pedersen L., Kuhl C. (1991): Thyroid function and autoimmune manifestations in insulin-dependent diabetes mellitus during and after pregnancy. *Acta Endocrinologica;* 124: 534–539.

5. Alvarez-Marfany M., Roman S.H., Drexler A.J., Robertson C., Stagnaro-Green A. (1994): Long-term prospective study of postpartum thyroid dysfunction in women with insulin dependent diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism;* 79: 10–16.

6. Weetman A.P. (1994): Insulin-dependent diabetes mellitus and post partum thyroiditis: an important association (Editorial). *Journal of Clinical Endocrinology and Metabolism;* 79: 7–9.

7. Chang C-C., Huang C-N., Chuang L-M. (1998): Autoantibodies to thyroid peroxidase in patients with type 1 diabetes in Taiwan. *European Journal of Endocrinology;* 139: 44–48.

8. Umpierrez G.E., Latif K.A., Murphy M.B. *et al*. (2003): Thyroid dysfunction in patients with type 1 diabetes a longitudinal study. *Diabetes Care;* 26: 1181–1185.

9. Lapolla A., Betterle C., Sanzari M. *et al*. (1996): An immunological and genetic study of patients with gestational diabetes mellitus. *Acta Diabetologica;* 33: 139–144.

10. Roggenbruck L., Kleinwechter H.J., Demandt N., Dörner K.M. (2004): Diagnostics of gestational diabetes: which cutoff-values are valid for capillary whole blood. *Clin Lab;* 50: 403–408.

11. Utiger R.D. (1999): Maternal hypothyroidism and fetal development. *New England Journal of Medicine;* 341: 601–602.

12. Haddow J.E., Palomaki G.E., Allan W.C. *et al.* (1999): Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *New England Journal of Medicine;* 341: 549–555.

13. Pop V.J., de Vries E., van Baar A.L. *et al.* (1995): Maternal thyroid peroxidase antibodies during pregnancy: a marker of impaired child development? *Journal of Clinical Endocrinology and Metabolism;* 80: 3561–3566.

14. Ortega-Gonzalez C., Liao-Lo A., Ramirez-Peredo J., Carino N., Lira J., Parra A. (2000): Thyroid peroxidase antibodies in Mexican born healthy pregnant women, in women with type 2 or gestational diabetes mellitus, and in their offspring. *Endocr Pract;* 6: 244–248.

15. Lazarus J.H., Kokandi A. (2000): Thyroid disease in relation to pregnancy: a decade of change. *Clin Endocrinol (Oxf);* 53: 265–278.

16. Cleary-Goldman J., Malone FD., Lambert-Messerlian G. *et al*. (2008): Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol;* 112(1): 85–92.

17. Pop V.J., Vulsma T. (2005): Maternal hypothyroxinaemia during (early) gestation. *Lancet;* 365: 1604–1606.

18. Glinoer D. (2003): Management of hypo- and hyperthyroidism during pregnancy. *Growth Horm IGF Res;* 13: S45–S54.

Резиме

ПРЕВАЛЕНЦА НА ТИРОИДНА ДИСФУНКЦИЈА И АВТОИМУНОСТ КАЈ БРЕМЕНИ ЖЕНИ СО ГЕСТАЦИСКИ И ТИП 1 ДИЈАБЕТЕС

Велкоска Накова В.,[1] Крстевска Б.,[2] Димитровски Ч.,[2] Симеонова С.,[3] Хаџи-Лега М.,[3] Серафимоски В.[4]

[1] Факултет за медицински науки, Универзитет „Гоце Делчев“, Штип, Р. Македонија
[2] Клиника за ендокринологија, дијабетес и метаболни нарушувања, Медицински факултет, Скопје, Р. Македонија
[3] Клиника за гинекологија и акушерство, Медицински факултет, Скопје, Р. Македонија
[4] Клиника за гастроентерохепатологија, Медицински факултет, Скопје, Р. Македонија

Апстракт: *Цел:* Да ја одредиме преваленцата на тироидната дисфункција и антитироидните антитела за време на бременост кај жени со гестациски и тип 1 дијабетес.

Материјали и методи: Во студијата беа вклучени 83 бремени жени кои се јавија на Клиниката за ендокринологија, дијабетес и метаболни нарушувања во Скопје, во периодот од мај до ноември 2009. На сите бремени жени, освен оние со претходно дијагностициран дијабетес тип 1, им беше направен 100 гр орален глукозен толерантен тест (ОГТТ). Тироидната функција им беше испитана на сите бремени жени. На рутинскиот скрининг за гестациски дијабетес (ГДМ), триесет бремени жени беа здрави, а четириесет имаа ГДМ. Останатите 13 бремени жени вклучени во студијата имаа дијабетес тип 1.

Резултати: Пациентките со ГДМ имаа статистички значајно пониски вредности на серумскиот слободен тироксин во споредба со здравите и жените со дијабетес тип 1. Помеѓу бремените жени со ГДМ, 10 или 25% имаа концентрации на слободен тироксин под долната референтна граница со нормални вредности на

тиреостимулирачкиот хормон. Статистички значајна разлика пронајдовме во преваленцата на антитироидни пероксидазни антитела (анти-ТПО) помеѓу жените со дијабетес тип 1 (30%) и здравите бремени жени (10%), ($p < 0,05$). Жените кои беа позитивни за анти-ТПО, имаа статистички значајно повисока концентрација на тиреостимулирачкиот хормон ($p < 0,05$).

Заклучок: Статистички значајно повисоката преваленца на хипотироксинемија кај ГДМ и анти-ТПО титарот кај бремени жени со дијабетес тип 1 наспроти здравите бремени жени, го оправдува рутинскиот скрининг за тироидна дисфункција кај бремени жени со дијабетес или присутен ризик фактор за ГДМ.

Клучни зборови: бременост, гестациски дијабетес, дијабетес тип 1, тироидна функција, ОГТТ.

Corresponding Author:

Velkoska Nakova V.
Faculty of Medical Science,
Goce Delcev University,
2000 Stip, R. Macedonia

E-mail: valentina.velkoska@yahoo.com