Thieme

Isolated Maternal Hypothyroxinemia May be Associated with Insulin Requirement in Gestational Diabetes Mellitus

Authors
Ömercan Topaloğlu[1], Mehmet Uzun[2], Seda Nur Topaloğlu[3], Ibrahim Sahin[4]

Affiliations
1 Endocrinology, Zonguldak Bülent Ecevit University Faculty of Medicine, Zonguldak, Turkey
2 Oncology, Dokuz Eylül Üniversitesi Tıp Fakültesi, Izmir, Turkey
3 Internal Medicine, Zonguldak Bülent Ecevit University, Zonguldak, Turkey
4 Endocrinology, İnönü Üniversitesi Tıp Fakültesi, Malatya, Turkey

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Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr. Ömercan Topaloğlu
Zonguldak Bülent Ecevit University Medical Faculty
Department of Endocrinology
67600 Derince/Kocaeli
Turkey
Tel.: + 905059681817
drhomercan@hotmail.com

ABSTRACT

An insulin regimen may be necessary for about 30 % of the patients with gestational diabetes mellitus (GDM). We aimed to investigate the association of free T4(fT4) levels with insulin requirement in pregnant women with GDM. We included pregnant women whose TSH levels were within the normal range and who were diagnosed with GDM, and excluded patients with thyroid dysfunction, chronic illnesses, or any previous history of antithyroid medication, levothyroxine, or antidiabetic medication use. The diagnosis and treatment of GDM were based on American Diabetes Association guidelines. Demographic features, previous history of GDM and gestational hypertension were recorded. Baseline (at diagnosis of GDM) fasting blood glucose, HbA1c, TSH, fT4, and fT3 levels were analyzed. We grouped the patients according to their baseline fT4 levels: isolated maternal hypothyroxinemia (IMH) (group A) vs. in the normal range (group B). We grouped those also based on insulin requirement in 3rd trimester. Of the patients (n = 223), insulin requirement was present in 56, and IMH in 11. Insulin requirement was more frequent in group A than in group B (p = 0,003). HbA1c (≥ 47,5 mmol/mol) and fT4 level (lower than normal range) were positive predictors for insulin requirement (OR:35,35, p = 0,001; and OR:6,05, p = 0,008; respectively). We showed that IMH was closely associated with insulin requirement in GDM. Pregnant women with IMH and GDM should be closely observed as regards to glycemic control. If supported by future large studies, levothyroxine treatment might be questioned as an indication for patients with GDM and IMH.

Introduction

Gestational diabetes mellitus (GDM) has been increasingly diagnosed both due to the increasing frequency of the risk factors and more frequently applied screening methods, and also in parallel to an increased rate of obesity worldwide [1]. Although most pregnant women with GDM may be managed by medical nutrition therapy and physical exercise, insulin is required in about 15–30 % of those patients [1, 2].

The results of studies investigating the role of overt or subclinical thyroid dysfunction in the development of GDM are contradictory [3–7]. In some studies, isolated maternal hypothyroxinemia was shown to be associated with the development of GDM [6, 8]. Contrast findings also were reported [4]. In one study, levothyroxine treatment was found to have no effect on the development of GDM in women with isolated maternal hypothyroxinemia [9].

However, the association of isolated maternal hypothyroxinemia with insulin requirement in GDM has not been investigated yet.

We propose that investigation of the factors associated with insulin need in GDM is so important that we could predict insulin need in pregnant women with GDM, and thus prevent the progression of glycemic dysregulation in this population. We aimed to analyze the association of free T4 level measured before the diagnosis of GDM in the 2nd trimester with the insulin requirement in GDM in pregnant women with normal thyroid-stimulating hormone levels.

Patients and Methods

Study population

Adult pregnant women with GDM who were referred to our clinics between September 2018 and September 2019 were included in this study. This observational, retrospective cohort study was approved by the Clinical Researches Ethics Committee of Balıkesir University Faculty of Medicine with the approval number 2019/120 and was performed in accordance with the ethical standards specified in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

Pregnant adult women diagnosed with GDM by oral glucose tolerance test between the 24th and 28th gestational weeks were included in the study. The patients whose thyroid function tests (free T4, free T3, and thyroid-stimulating hormone) were measured in the 2nd trimester before the 20th week of pregnancy were also included. Only women with singleton pregnancy were included. Those with a history of overt or subclinical hypothyroidism or hyperthyroidism, disorders of glucose metabolism or any other chronic illnesses diagnosed before the pregnancy, or a history of thyroid surgery, or radioactive iodine ablation were excluded from the study. Those who use any medication that affects glucose or thyroid metabolism and those whose data were missing were also excluded.

Data collection

Demographic (age), clinical (gravida, parity, previous history of GDM, gestational hypertension, dietary modification, exercise, insulin requirement, insulin dose, and the number of insulin injections), and laboratory (fasting blood glucose, HbA1c, thyroid-stimulating hormone, free T4, free T3) findings were recorded from the written and electronic files.

Diagnosis of gestational diabetes mellitus

We diagnosed all the patients with GDM, and treated them accordingly, based on the American Diabetes Association (ADA) guideline [10]. We measured 1st and 2nd hour venous plasma glucose levels after an oral 75 gram glucose load. An oral glucose tolerance test (OGTT) was performed between the 24th and 28th weeks of the pregnancy. GDM was confirmed if at least one of the following criteria was met: glucose level at baseline ≥ 92 mg/dl; ≥ 180 mg/dl at 1st hour; ≥ 153 mg/dl at 2nd hour. We measured fasting blood glucose (FBG), and also HbA1c (mmol/mol) at the diagnosis of GDM. We grouped the patients also according to HbA1c level (< 47,5 vs. ≥ 47,5 mmol/mol).

We assessed insulin requirement in the 3rd trimester until the end of the pregnancy. We defined daily insulin dose as the maximum daily total insulin dose in the 3rd trimester of pregnancy.

Thyroid function tests

We measured thyroid stimulating hormone (TSH, mIU/l), free T4 (fT4, ng/dl), and free T3 (fT3, pg/ml) in all patients with the chemiluminescence method using the DxI 800 model device (Beckman Coulter Inc., CA, USA). Thyroid function tests were measured in the 2nd trimester before the 20th week of the pregnancy. TSH levels of all the patients included in the study were within the normal range, which was based on the 2nd trimester-specific reference ranges for TSH defined in the previous American Thyroid Association (ATA) guideline [11]. We defined isolated maternal hypothyroxinemia as a maternal fT4 concentration lower than the reference range with a normal maternal TSH concentration. These tests were evaluated in the 2nd trimester using the method-specific reference range for TSH (0,2–3,0 mIU/l) and fT4 (0,75–1,32 ng/dl). We did not monitor the thyroid test levels throughout the pregnancy. Thyroid autoantibodies were not available in all patients; therefore, we could not analyze the association of clinical and laboratory factors with thyroid autoantibodies.

We grouped the patients mainly based on fT4 level as follows: Group A, isolated maternal hypothyroxinemia vs. Group B, fT4 in a specific reference range. The fT3/fT4 ratio was achieved by division of the fT3 level by the fT4 level. Also, we grouped the patients based on the insulin requirement: absent versus present.

Türkiye is an endemic region for iodine deficiency, therefore all the patients were given iodine supplementation, and LT4 was not prescribed to any patients based on the guideline [11].

Statistical analysis

For all analyses, SPSS software (ver. 22,0; IBM Corporation, NY, USA) was used. The Kolmogorov–Smirnov test was used to assess the normality of the data. When comparing two independent groups in terms of quantitative measures, Mann–Whitney U-tests were used. Pearson's Chi-square tests were used to compare categorical variables. In order to determine the risk groups for parameters affecting the need for insulin requirement, we used multivariate logistic regression analysis with Backward Stepwise (Wald) Method. The Odds Ratio (OR) was used with 95 % confidence intervals (CI) to show that risk groups had how higher risk than the other subjects. Quantitative variables are reported as the median (minimum-maximum) in the tables. Categorical variables are reported as numbers (n) and percentages (%), and p-values < 0,05 were taken to indicate statistical significance.

Results

A total of 223 pregnant women with the diagnosis of GDM were analyzed. Median age was 32 (21–43). Isolated maternal hypothyroxinemia (Group A) was detected in 4,93 % (n = 11) of the patients. Age, gravida, parity, daily insulin dose, FBG, HbA1c, and TSH levels were similar both in Group A and B. fT4 level was higher in Group B, fT3/fT4 ratio in Group A (p < 0,001 and p = 0,009, respectively). Insulin requirement was present in 25,11 % (n = 56) of the patients.

The ratio of insulin requirement was 23,11 % in Group B and 63,63 % in Group A (p = 0,003). FBG and HbA1c levels were higher in the patients whose insulin requirement was present (p = 0,029 and p = 0,005, respectively). The number of insulin injections per day was > 2 in 50 % (n = 28) of the patients whose insulin requirement was present. Gestational hypertension (present), dietary modification (absent), HbA1c (≥ 47,5 mmol/mol), and fT4 level (lower than normal range) were associated with insulin requirement (▶ **Table 1**). The number of patients with HbA1c of < 38,8 versus ≥ 38,8 mmol/mol was similar in Groups A and B, or in those for whom insulin was required or not (not shown in the tables).

In multivariate logistic regression analysis, HbA1c (≥ 47,5 mmol/mol) and fT4 level (lower than normal range) were positive predictors for insulin requirement [OR: 35,35 (4,28–291,63), p = 0,001; and OR: 6,05 (1,61–22,63), p = 0,008; respectively] (▶ **Table 2**).

Discussion

We showed that isolated maternal hypothyroxinemia (IMH) was detected in a minority of the patients, and insulin was required in about one-fourth of those. Higher HbA1c and IMH predicted insulin requirement in GDM, but fT3/fT4 ratio was not associated with it.

▶ **Table. 1** Comparison of the clinical and laboratory parameters according to the presence of isolated maternal hypothyroxinemia or insulin requirement.

	fT4 Groups			**Insulin requirement**			
Parameters	**Group A Isolated maternal hypothyroxinemia (n = 11)**	**Group B Normal fT4 level (n = 212)**	**p– Value**	**Absent (n = 167)**	**Present (n = 56)**	**p-Value**	**Total (n = 223)**
	Median (min–max)			**Median (min–max)**			**Median (min–max)**
Age (years)	28 (23–39)	32 (21–43)	0,539	32 (21–43)	33 (22–42)	0,732	32 (21–43)
Gravida	2 (1–4)	2 (1–6)	0,691	2 (1–6)	2 (1–6)	0,506	2 (1–6)
Parity	1 (0–3)	1 (0–4)	0,709	1 (0–4)	1 (0–3)	0,469	1 (0–4)
Daily insulin dose (U/day)	18 (4–33)	15 (4–62)	0,825	NA	15,5 (4–62)	NA	15,5 (4–62)
FBG (mg/dl)	79 (74–92)	83 (70–121)	0,259	82 (70–99)	86 (74–121)	**0,029**	83 (70–121)
HbA1c (mmol/mol)	33,3 (27,9–41,0)	34,4 (21,6–51,9)	0,810	34,4 (21,6–47,5)	35,5 (25,7–51,9)	**0,005**	34,4 (21,6–51,9)
TSH (mIU/l)	1,34 (0,77–3)	1,40 (0,20–3)	0,812	1,31 (0,20–3)	1,54 (0,41–3)	0,138	1,40 (0,20–3)
fT4 (ng/dl)	0,82 (0,54–0,92)	0,94 (0,67–1,32)	**< 0,001**	0,94 (0,65–1,32)	0,92 (0,54–1,27)	0,658	0,92 (0,54–1,32)
fT3 (pg/ml)	2,74 (2–3,47)	2,63 (1,70–3,83)	0,640	2,61 (1,70–3,83)	2,70 (2–3,69)	0,100	2,65 (1,70–3,83)
fT3/fT4 ratio	3,11 (2,51–5,34)	2,71 (1,70–4,57)	**0,009**	2,70 (1,70–5,34)	2,84 (1,98–3,48)	0,095	2,75 (1,70–5,34)
	n			**n**			**n**
Gestational hypertension (absent/present)	10/1	209/3	0,061	166/1	53/3	**0,020**	219/4
Previous GDM (absent/present)	11/0	191/21	0,273	153/14	49/7	0,361	202/21
Dietary modification (absent/present)	1/10	6/206	0,246	3/164	4/52	**0,047**	7/216
Exercise adherence (absent/present)	4/7	147/65	**0,023**	118/49	33/23	0,104	151/72
Insulin requirement (absent/present)	4/7	163/49	**0,003**	NA	NA	NA	167/56
Number of insulin injections (≤ 2/> 2 per day)	3/4	25/24	0,686	NA	28/28	NA	NA
HbA1c (< 47,5 vs. ≥ 47,5 mmol/mol)	11/0	203/9	0,485	166/1	48/8	**< 0,001**	214/9
fT4 (lower than normal range/in normal range)	NA	NA	NA	4/163	7/49	**0,003**	11/212

min: Minimum; max: Maximum. NA: Not available.

▶ **Table 2** Multivariate binary logistic regression analysis demonstrating clinical predictors for insulin requirement in gestational diabetes mellitus.

Variables	Insulin requirement (present)	
	OR (95 % CI)	p-Value
fT4 (lower than normal range)	6,05 (1,61–22,63)	**0,008**
HbA1c (≥ 47,5 mmol/mol)	35,35 (4,28–291,63)	**0,001**
Dietary modification (absent)	4,83 (0,99–23,25)	0,051
Gestational hypertension (present)	9,82 (0,93–103,85)	0,058

GDM can easily be diagnosed with universal screening by glucose load in the 24–28th weeks of pregnancy [10]. Also, since thyroid function has been frequently screened in pregnant women, mild thyroid dysfunctions, such as subclinical hypothyroidism and IMH, have been increasingly encountered in those [11]. The IMH prevalence has been shown to range between 1 % and 18,8 % in various studies [8, 12]. Hypothyroxinemia might be developed as a result of relative iodine deficiency, which leads the thyroid gland to produce T3 rather than T4 to preserve iodine, but also may be observed in the iodine sufficiency state [13]. IMH may be associated with preterm birth, macrosomia, neonatal intraventricular hemorrhage, and poorer neuropsychological development in the offspring [14, 15]. IMH was found to be associated also with an increased risk of GDM in some studies [8, 16, 17]. The association was shown in the patients with IMH either in the 1st or the 2nd trimester of pregnancy. In other studies, no associations were reported between IMH and GDM [8, 18–21]. In one study analyzing IMH both in the 1st and 2nd trimester of pregnancy, IMH was found not to be associated with GDM [12]. In another large study, IMH in early pregnancy (< 20 weeks) was found to increase the risk of preeclampsia, placenta abruption or previa, and preterm delivery but not GDM [19].

The effects of thyroid hormones on glucose metabolism have been shown to be complicated [22]. Triiodothyronine (T3) was known to stimulate pancreatic beta-cell proliferation in rats [23]. T3 was also shown to increase insulin secretion and act as an anti-apoptotic factor for pancreatic beta cells [24]. Thyroid hormones increase intestinal glucose absorption and hepatic glucose output via stimulating glycogenolysis and gluconeogenesis and increase glucose intolerance [25, 26]. Given these mechanisms, thyrotoxicosis may obviously be expected to be related to glycemic dysregulation [22, 27]. However, hypothyroidism, subclinical hypothyroidism, and IMH were shown to increase the risk of GDM [16, 17, 22, 28]. Urinary iodine excretion was shown to be negatively correlated with glucose levels in type 2 diabetes [29]. In one study, lower placental iodine was found to increase the risk of GDM and be negatively associated with neonatal insulin concentration in cord blood and HOMA-IR index [30]. Although the exact mechanism was not known, the association of IMH with insulin requirement in GDM in our study might be due to higher insulin resistance due to lower maternal iodine status. However, in another study, higher maternal urinary iodine excretion was associated with GDM compared to lower urinary iodine excretion [31].

Maternal age, previous history of GDM, family history of type 2 diabetes mellitus, pre-conceptional body mass index, FBG, 1st-hour or 2nd-hour glucose level on OGTT, and HbA1c were found as predictors for insulin use in GDM [32–34]. In the other studies, the gestational week at the time of the diagnosis of GDM, abdominal subcutaneous fat thickness, and HOMA-IR were associated with insulin treatment in GDM [34–36]. IMH was not analyzed as a predictor for insulin use in GDM in any previous study. We showed that IMH or HbA1c (≥ 47,5 mmol/mol), but not FBG, was a predictor for insulin requirement in GDM. We could not analyze pre-conceptional BMI or serum insulin levels during OGTT. We found that higher HbA1c levels at the diagnosis predicted insulin requirement in GDM, similarly in the previous studies [33, 36]. Actually, an increased HbA1c level may already be expected to be an important determinant of insulin use in a pregnant woman with GDM. Of the patients, 10 % with HbA1c ≥ 47,5 mmol/mol did not require insulin treatment since insulin treatment was based on both biochemical measurements and follow-up by self-monitoring of blood glucose levels. Also, we found that the HbA1c cut-off value of 38,8 mmol/mol was not associated with insulin requirement. In a previous study, HOMA-IR was shown to be associated with insulin requirement in GDM [36]. We did not measure plasma insulin levels, and hence, could not calculate HOMA-IR scores.

Isolated AntiTPO positivity in early pregnancy was shown to be associated with an increased risk of GDM [37]. The frequency of AntiTPO positivity was found to be higher in the patients with GDM [21]. In one study, the effect of AntiTPO on GDM was shown to be independent of thyroid function tests [21]. However, other studies showed no relationship between GDM and thyroid autoimmunity [38, 39]. In one study, low maternal fT4 levels were found to be associated with increased levels of BMI, HbA1c, and fasting plasma glucose, but it was also found that AntiTPO positivity did not affect the adverse pregnancy outcomes [16]. In that study, the frequency of AntiTPO positivity was similar in those with or without IMH. As far as we know, the association of AntiTPO positivity with insulin requirement in GDM has not been studied in previous studies. In a previous ATA guideline, AntiTPO positivity was not defined as a prerequisite for IMH [11]. However, in some studies including the patients with negative AntiTPO, IMH rates were found to be relatively lower, but insulin requirement was not analyzed [12, 19]. We could not analyze AntiTPO positivity in our study.

fT3/fT4 ratio was also shown to be associated with adverse metabolic outcomes such as obesity, GDM, insulin resistance and obesity in pregnant women [16, 40]. fT3/fT4 ratio has not been studied before as regards to the insulin requirement in GDM. We found that fT3/fT4 ratio was higher in the patients with IMH than in those with normal fT4, but it was not associated with insulin requirement.

In an interventional study on pregnant women with hypothyroxinemia, the effect of levothyroxine treatment on adverse pregnancy outcomes and perinatal complications was investigated [9]. Levothyroxine treatment was shown to decrease the rate of miscarriage and neonatal intensive care unit admission, but it did not affect the development of GDM. The impact of LT4 on insulin requirement in GDM was not investigated in that study. In our study, we did not treat the patients with IMH with LT4 but showed that

IMH increased about 6 times the risk of insulin requirement in patients with GDM. We prescribed iodine supplementation in all the patients but did not make a routine follow-up for TSH or fT4 measurement.

Strength and limitations

As far as we know, our study is one of the original studies investigating the association of insulin requirement in GDM with fT4 level. Our study sample was relatively small compared the previous studies reported in the literature. Since only a minority of the patients did have available results for thyroid autoantibodies, we could not analyze the association of thyroid autoantibodies with insulin requirement or IMH. We did not include an interventional arm, which may indicate the effect of LT4 treatment or iodine supplementation in IMH on the clinical course of GDM.

Conclusion

We showed that IMH and increased HbA1c levels predicted the insulin requirement in GDM. Our study is the first study showing the association of IMH with insulin requirement in GDM. Pregnant women with GDM should be under close follow-up especially if IMH is detected. Future interventional studies will reveal the effect of LT4 treatment or iodine supplementation on the course of GDM in pregnant women with IMH. Our findings, if supported by large studies, may bring up that IMH may be questioned for LT4 treatment in pregnant women with GDM.

Conflict of Interest

The authors declare that they have no conflict of interest.

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