RESEARCH ARTICLE

Effect of gestational diabetes mellitus on maternal thyroid function and body mass index [version 1; referees: 1 approved, 1 approved with reservations]

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Abstract

Background: The exact influences of thyroid functions on body mass index (BMI) are ill-defined in euthyroid pregnant women with gestational diabetes mellitus (GDM).

Objectives: To investigate the effect of GDM on maternal thyroid functions and BMI.

Methods: A case- control study was conducted in Saad Abualila Hospital, Khartoum, Sudan June to August 2015. Cases included women with GDM and healthy pregnant women as controls. Thyroid hormones [thyroid-stimulating hormone (TSH), free tri-iodothyronine (FT3), and free thyroxine (FT4)] and anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies were measured.

Results: BMI was significantly increased in GDM patients (26.3 (2.7) Kg/m^2) compared with the control group (24.3(1.8) Kg/m^2, P = 0.001). Levels of FT3 and FT4 were significantly decreased in GDM patients (0.632 (0.408 – 1.074) pg/ml; 0.672 (0.614 – 0.960) ng/dl) compared with the healthy pregnant women (0.820 (0.510–1.385) pg/ml, P = 0.021; 0.840 (0.767–1.200) ng/dl, P < 0.001). In contrast, anti-TPO and anti-TG were significantly higher in GDM patients (11.13 (7.969 –13.090) IU/ml; 14.40 (10.91–20.69) IU/ml) compared with the control group (8.90 (6.375–10.48 IU/ml, P = 0.022; 10.50 (8.2–13.95) IU/ml, P = 0.010). BMI correlated negatively with FT3 (r = – 0. 375, P = 0.002) and FT4 (r = – 0. 316, P = 0.009) and positively with anti-TPO (r = 0.361, P = 0.002) and anti-TG (r = 0.393, P = 0.010).

Conclusion: The present results add further evidence for decreased free thyroid hormones, increased anti-thyroid autoantibodies and higher BMI in patients with GDM compared to healthy pregnant women. BMI correlated directly with FT3 and FT4, but failed to demonstrate significant association with TSH.

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Introduction

Abnormal thyroid function and glucose tolerance have been both reported during pregnancy[1–3]. It was hypothesized that thyroid hormones gradually increase during the first trimester, but decrease gradually over the rest of pregnancy[4–6]. The steady rise of human chorionic gonadotropin (hCG) hormone during the first trimester was claimed to induce follicular thyroid cells to release of tri-iodothyronine (T3) and thyroxine (T4)[7], which negatively feedback on thyroid-stimulating hormone (TSH)[8]. During the second and third trimesters, TSH increases while T3 and T4 decrease following hCG withdrawal. Lower levels of free T3 (FT3) and T4 (FT4) over the last two thirds of pregnancy can also be explained by high thyroid hormones transport proteins concentrations induced by placental estrogens[9]. Alternatively, higher levels of diabetogenic hormones, reduced physical activity, decreased energy expenditure, increased carbohydrate consumption, lack of adequate sleep and other stresses during gestation increase insulin requirements of pregnant women[3]. Increased insulin requirement enhances development of gestational diabetes mellitus (GDM) in susceptible pregnant women *e.g.* obese women[10], and those with dysfunctional pancreatic β-cells[11] or insulin resistance[12].

Weight gain is common among subjects with insulin resistance[13] as well as those with hypothyroidism[14]. During pregnancy, the degree of insulin resistance seems to influence levels of thyroid hormones[15] and pattern of change in maternal body mass index (BMI)[16]. In contrast to overt cases of thyroid disorders, the exact influences of T3 and T4 on BMI are ill-defined in euthyroid pregnant women[17–20]. According to Ashoor *et al.,*[18], FT4 decreased while FT3 increased with higher BMI scores. Although paradoxical effects of FT3 and FT4 on maternal weight were also demonstrated in other reports[17,19], some studies failed to reproduce these findings[20]. The euthyroid subjects studied by Milionis *et al.,* did not show association between BMI and FT3 or FT4. However, the same study showed significant positive correlations between BMI and total T3 (TT3) as well as between BMI and total T4 (TT4) in females, but not males[20]. The present study aimed to investigate the effects of GDM on the maternal thyroid function and BMI. In addition, correlations between BMI, FT3 and FT4 were assessed to clarify how thyroid hormones affect maternal weight during pregnancy.

Methods

A case- control study was conducted in Saad Abualila Hospital, Khartoum, Sudan from June to August 2015. Pregnant women with singleton pregnancies who attended the hospital antenatal screening for diabetes mellitus were approached to participate in the study. After signing an informed consent, each pregnant woman was asked about her age, obstetric and medical profile. The weight and height were measured and BMI was calculated and expressed as weight (kg)/height (m^2). Women were excluded from the study if they were smokers, had history of hypertension and personal history of cardiovascular disease, had previous medical history of diabetes, were taking any medication (apart from iron supplementation), and had prior significant medical illnesses.

Coustan and Carpenter[12] criteria were adopted for the diagnosis of gestational diabetes, by which after a 100-g oral glucose load, two or more of the following plasma values were met or exceeded: fasting 95 mg/dl, 1 h 180 mg/dl, 2 h 155 mg/dl, and 3 h 140 mg/dl. Women with normal values were included as controls.

Venous blood specimens (5 ml) were drawn from the median cubital vein and collected in vacutainer blood-collecting tubes. The tube specimens were allowed to clot and then were centrifuged for 10 min at 3,000×g to separate the serum which was stored at −20°C until analysis for thyroid hormones (TSH, free T3, and free T4) using immunoassay analyzer (AIA 360, Tosoh, Japan), following the manufacturer's instructions. Specific anti-thyroperoxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibody profiles were analyzed using enzyme-linked immunosorbent assay (ELISA, Euroimmun, Lübeck, Germanykits).

Statistics

SPSS for Windows (version 16.0) was used for data analyses. Continue variables were checked for normality and their difference was compared between cases and controls using T-test and Mann-Whitney U, when the data were normally and not normally distributed, respectively. Spearman correlations were performed between the different variables. $P < 0.05$ was considered statistically significant.

Ethics

The study received ethical clearance from the Research Board at the Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Khartoum, Sudan.

Results

Table 1 shows the means (standard deviation, SD) of basic characteristics of the studied GDM patients and control group (34 women in each arm) including the age and gestational age. BMI was significantly higher in GDM patients (26.3 (2.7) Kg/m^2) compared with the control group (24.3 (1.8) Kg/m^2, $P = 0.001$).

Levels of FT3 and FT4 were significantly decreased in GDM patients (0.632 (0.408–1.074) pg/ml; 0.672 (0.614–0.960) ng/dl respectively) compared with the healthy pregnant women (0.82 (0.510–1.385) pg/ml, $P = 0.021$; 0.840 (0.767–1.200) ng/dl, $P < 0.001$ respectively, Table 2). In contrast, anti-TPO and anti-TG were significantly higher in GDM patients (11.13 (7.969–13.090) IU/ml; 14.40 (10.91–20.69) IU/ml respectively) compared with the control group (8.90 (6.375–10.48 IU/ml, $P = 0.022$; 10.50 (8.2–13.95) IU/ml, $P = 0.010$ respectively), Table 2, Figure 1–Figure 5.

Table 1. Comparing the mean (SD) of the basic characteristics of women with GDM and controls.

Variable	Cases (n=34)	Controls (n=34)	P
Age, years	31.8(5.5)	30.3(3.6)	0.178
Parity	2.4(2.0)	2.5(1.7)	0.789
Gestational age, weeks	27.7(1.3)	28.1(1.6)	0.262
Body mass index, Kg/cm^2	26.3(2.7)	24.3(1.8)	0.001
Hemoglobin, g/dl	11.1(1.1)	11.2(1.3)	0.638

Table 2. The median (interquartile) of thyroid function and antibodies in women with gestational diabetes mellitus and healthy controls.

Variable	Gestational diabetes mellitus (n=34)	Healthy controls (n=34)	P
TSH, mIU/ml	2.037(1.053–3.323)	2.401(1.888–2.811)	0.283
Free T3, pg/ml	0.632(0.408–1.074)	0.820(0.510–1.385)	0.021
Free T4, ng/dl	0.672(0.614–0.960)	0.840(0.767–1.200)	< 0.001
Anti-TPO, IU/ml	11.13(7.969–13.090)	8.900(6.375–10.48)	0.022
Anti-TG, IU/ml	14.40(10.91–20.69)	10.50(8.2–13.95)	0.010

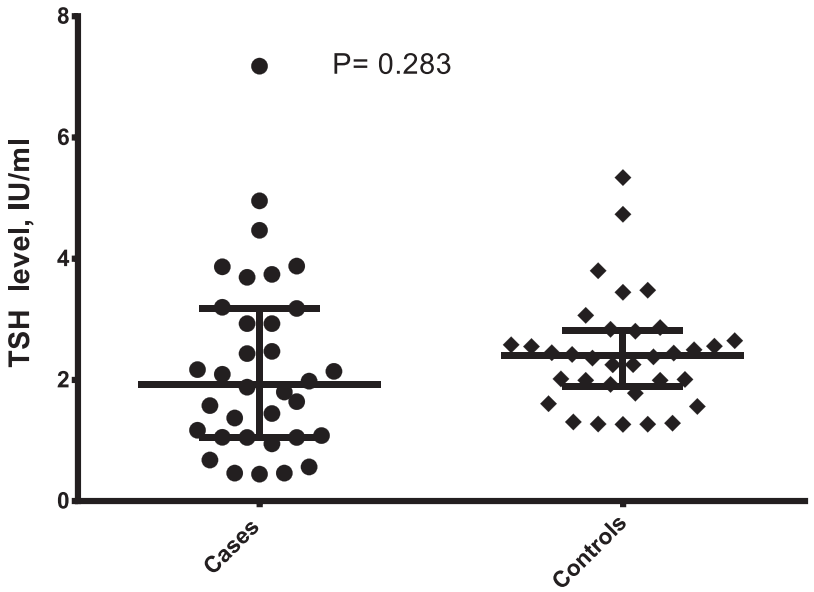

Figure 1. Thyroid-stimulating hormone in patients and controls.

BMI correlated negatively with FT3 (r = – 0.375, P = 0.002) and FT4 (r = – 0.316, P = 0.009) and positively with anti-TPO (r = 0.361, P = 0.002) and anti-TG (r = 0.393, P = 0.010).

There was no significant difference in TSH levels between GDM patients (2.037 (1.053–3.323) mIU//ml) and healthy pregnant women (2.401 (1.888–2.811) mIU//ml, P = 0.283) and no significant correlation with BMI (r = – 0.094, P = 0.446), Table 3.

Dataset 1. Raw data for effect of gestational diabetes mellitus on maternal thyroid function and body mass index

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Basic characteristics of participants.

Discussion

In accordance with the present results, previous reports demonstrated an associations between GDM and decreased thyroid hormones, increased anti-thyroid autoantibodies and higher BMI[1,15,22–24]. The associations between FT4, maternal weight, and GDM were recently investigated by Haddow and his group in more than 9000 singleton, euthyroid women in the FaSTER (First and Second Trimester Evaluation of Risk) trial[2]. An earlier report documented an inverse association between maternal weight and FT4 in the second trimester[2]. In a subsequent separate report on the same cohort, FT4 odds ratio for GDM was significant in the second (1.89), but not in the first (1.11) trimester[1]. Comparable findings were shown by Cleary-Goldman *et al.*, when they demonstrated 1.7 odds ratio of hypothyroxinemia in GDM patients during the second trimester[24]. Oguz *et al.*, confirmed decreased

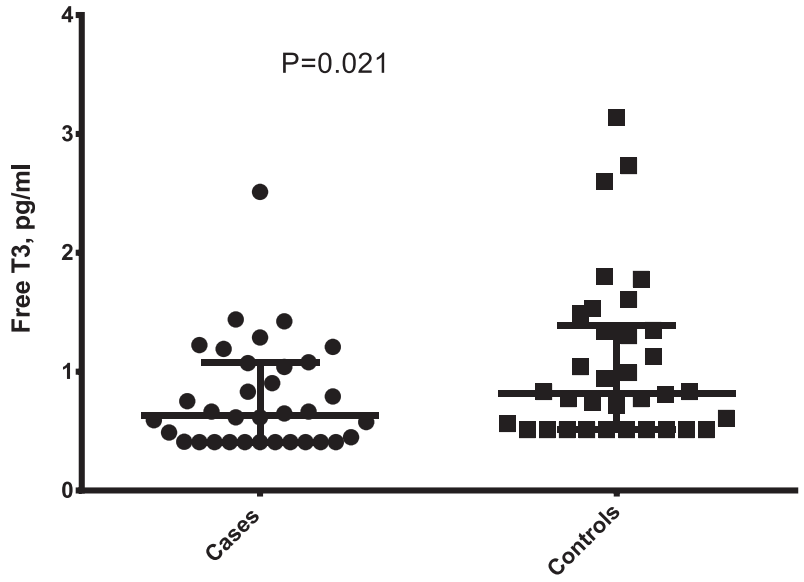

Figure 2. **Free tri-iodothyronine (FT3) in patients and controls.**

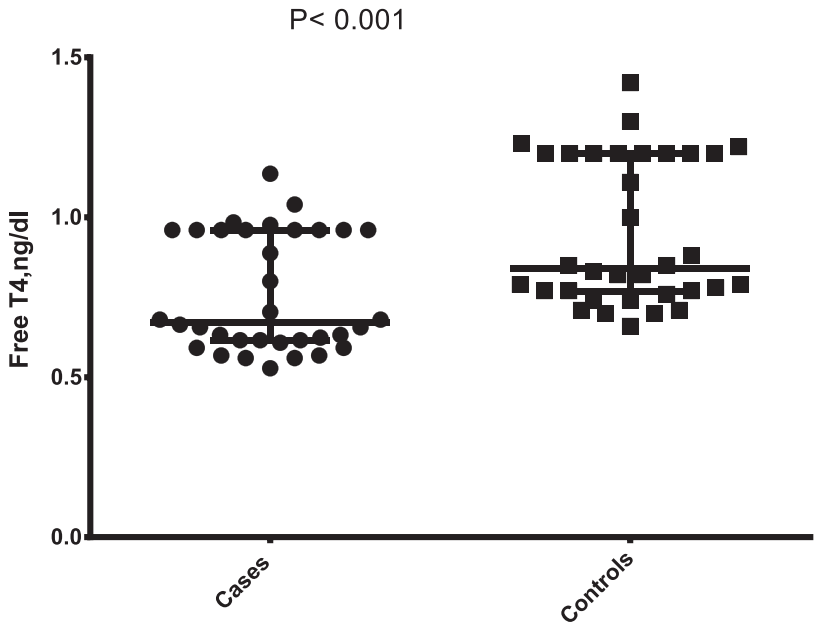

Figure 3. **Free thyroxine (FT4) in patients and controls.**

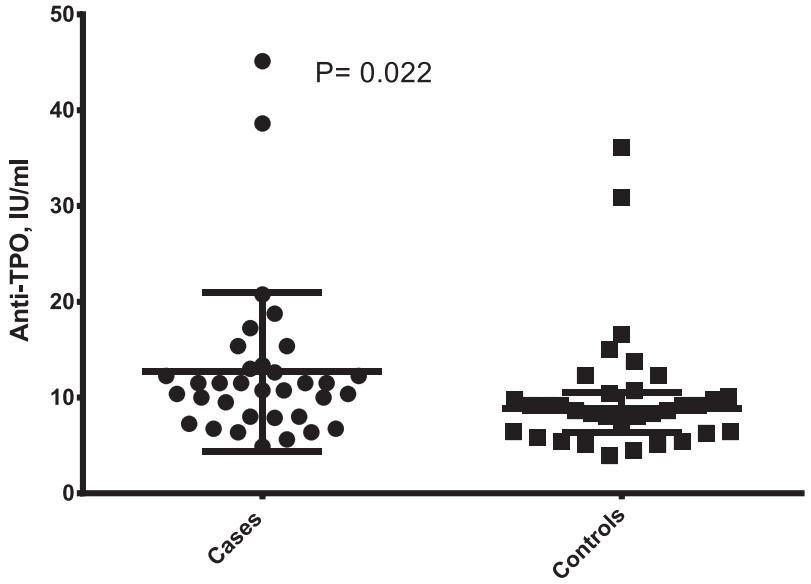

Figure 4. Anti-thyroid peroxidase (anti-TPO) in patients and controls.

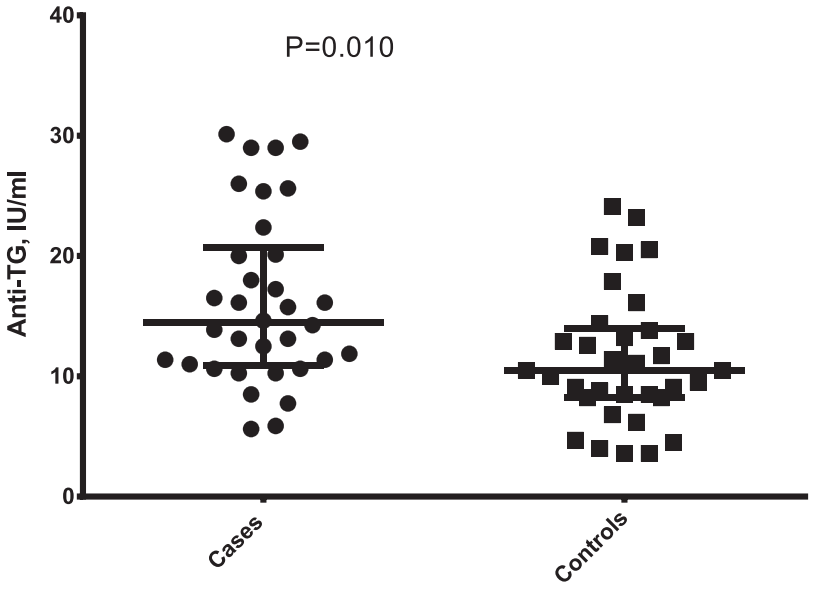

Figure 5. Anti-thyroglobulin (anti-TG) in patients and controls.

Table 3. Correlation between BMI, thyroid hormones and thyroid antibodies.

Variables	BMI		TSH		FT3		FT4		Anti-TPO	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
BMI	–	–	–0. 094	0.446	–0.375	0.002	–0. 316	0.009	0.361	0.002
TSH	–0.094	0.446	–	–	0.008	0.949	0.029	0.815	0.063	0.607
FT3	–0.375	0.002	0.008	0.949	–	–	0.399	0.001	– 0.749	0.001
FT4	–0.316	0.009	0.029	0.815	0.399	0.001	–	–	–0.752	0.001
Anti-TPO	0.361	0.002	0.063	0.607	–0.749	0.001	–0.752	0.001	–	–
Anti-TG	0.393	0.010	0.144	0.240	–0.724	0.001	–0.763	0.001	0.834	0.001

FT4 in 50 GDM patients compared with 60 non-GDM pregnant women; however, the mean of FT4 levels remained within the normal reference range in both groups[15]. Cases with isolated maternal hypothyroxinemia constituted 8% and 14% of GDM patients during the second and third trimesters respectively; however, similar cases were absent in the control group[15]. In another study, GDM patients showed lower FT4 compared to healthy pregnant women as well as those with type 1 diabetes mellitus. According to the same study, type 1 diabetic women had higher prevalence of anti-TPO compared with healthy pregnant women[22].

According to the present findings, BMI correlates negatively with FT3 and FT4, but positively with anti-TPO and anti-TG antibodies. In contrast, our results failed to demonstrate significant correlation between BMI and TSH. Increased odds of hypothyroxinemia and anti-TPO positivity among pregnant women with BMI ≥ 30 kg/m^2 during the first 8 weeks of gestation was reported before[25]. Although several previous studies failed to establish an association between BMI and TSH after 8 weeks of gestation[26–28], at least one study was able to do so when these two parameters were assessed during early pregnancy[25]. It was hypothesized that the peak of hCG hormone towards the end of the first trimester simulates simultaneous increase of thyroid hormones and reciprocal inhibition of TSH release[7,8,18]. Except for a temporal fall of TSH levels by the end of first trimester, both TSH and BMI steadily increase throughout pregnancy[26,27]. This explains why previous studies were able to prove significant positive correlation between BMI and TSH during the early 8 weeks of gestation[25], but failed to reproduce same results during hCG surge[26–28]. However, failure of our results as well as other studies[28] to document significant correlation between TSH and BMI during later stages of pregnancy is difficult to explain on the same basis and should motivate researchers in the field to investigate for possible explanation(s).

Although the effects of thyroid hormones on body weight are easy predictable in cases with hypo- and hyperthyroidism, the influences of T3 and T4 on BMI are ill-defined in cases of euthyroidism[26–28]. The inverse relationship between FT4 and BMI demonstrated with the present results agreed with several previous reports[17–19], but not others[20]. Likewise, the association between FT3 and BMI is a more contentious issue[18,20]. In a prospective cohort aimed to establish reference intervals of thyroid hormone concentrations among Finnish pregnant women, FT4 decreased while FT3 increased with higher BMI scores[17]. Same finding were reproduced by Ashoor *et al.,* while assessing thyroid function before the start of the second trimester[18]. The paradoxical effects of FT3 and FT4 on maternal weight were further supported by Bassols *et al.*, when they demonstrated significant direct association between FT3/FT4 ratio and BMI[19]. In contrast, a Greek study in euthyroid subjects failed to demonstrate the association between BMI and FT3 or FT4. The same study showed significant positive correlations between BMI and TT3 as well as between BMI and TT4 in females, but not males[20]. A possible explanation for different patterns of association between T3, T4 and BMI in previous reports is likely because of failure to adjust for confounders like caloric intake[29,30]. For example, conversion of T4 to T3 peripheral deiodinases is depressed in cases with caloric deprivation[29] and enhanced with overfeeding[30]. This may explain the reciprocal effects of FT3 and FT4 and consequently the direct association between the FT3/FT4 ratio and BMI in cases with reduced caloric intake[31]. In well-fed states, peripheral deiodinase activity will not be augmented and consequently BMI is expected to correlate positively with thyroid hormones levels[20]. In conditions where FT3 and FT4 are below expected, increased TSH enhances leptin release and consequently BMI[32]. This may explain why FT3 and FT4 may negatively correlate BMI irrespective of caloric intake.

Of note, deiodinase activity and insulin resistance were not assessed in the present study. Direct measures of deiodinase activity (*e.g.* hepatic deiodinase-1 mRNA) are difficult to evaluate because obtaining the required tissue samples is inconvenient. However, the T3/T4 ratio was proved to correlate well with deiodinase activity and can act as a surrogate for hepatic deiodinase-1 mRNA[31]. Evaluation of insulin resistance using parameters like Homeostasis Model Assessment (HOMA) in future studies will enable more clarification about the potential influence of insulin resistance on the relationship between BMI, FT3 and FT4. Another limitation of this study is that dietary composition and caloric intake were not evaluated among the studied women.

Conclusion

The present results add further evidence for decreased free thyroid hormones, increased anti-thyroid autoantibodies and higher BMI in patients with GDM compared to healthy pregnant women. BMI correlates positively with FT3 and FT4, negatively with anti-TPO and anti-TG antibodies, but failed to demonstrate significant association with TSH. Further studies that also evaluate deiodinase activity, caloric intake and indictors of insulin resistance are desirable for better understanding for the relationship between BMI, FT3 and FT4 in patients with GDM.

Consent

Written informed consent to participate in the study and publish clinical details was obtained by the participants.

Data availability

F1000Research: Dataset 1. Raw data for effect of gestational diabetes mellitus on maternal thyroid function and body mass index, 10.5256/f1000research.9084.d127599[33]

Author contributions

EAA and IA designed the study; HA and DAR carried out experimental protocols; IA, MFL analyzed and interpreted the data; MFL, IA wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no supporting grants were involved in this work.

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Data Source

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Current Referee Status: ✔ ?

Version 1

Referee Report 31 October 2016

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? **Tuija Männistö**
Northern Finland Laboratory Centre, Nordlab, Oulu, Finland

I read with interest the paper by Dr. Ali et al., describing a case-control study on thyroid function and autoimmunity during pregnancy among women with GDM. The study was small, but adequately powered to answer the study question - if women with GDM have poorer thyroid function or more thyroid antibodies than women without GDM. The statistical methods were adequately used in the study.

My concern with the methods was with the description of the control group, who are referred as healthy pregnant women. I would prefer that the controls would be described as women without GDM as the reader is not aware if these women have other pregnancy complications such as preeclampsia or fetal growth restriction.
Another concern was the definition of euthyroidism - the Figure 1 clearly shows that some women had high TSH concentrations during pregnancy, some of which exceeded that of recommended euthyroid range specified by the American Thyroid Association, for instance. How did the authors define euthyroidism? The definition needs to be added to the Methods. Also, the authors should consider using a pregnancy-specific definition of euthyroidism, which may affect their results. At least they should do a sensitivity analysis after excluding women with TSH higher than pregnancy-specific reference ranges to see if their results hold. The observed results could be due to underlying hypothyroidism among women with GDM - this should also be discussed in more detail.

Also, it would be interesting to see a comparison between women with GDM with normal BMI and controls with normal BMI to see if GDM has an independent effect on thyroid function and autoimmunity irrespective of BMI. However, I wonder if the study population is big enough for this type of analysis.

Specific comments:

Abstract
In the Objectives please correct 'thyroid dysfunctions' to thyroid dysfunction.
In the Methods please note that thyrotropin is a pituitary hormone, not a thyroid hormone.
Please also add information on the statistical methods used in the Methods-section of the abstract.
In the Results please add explanation as to what the figures are in the parentheses. Please also pay special note on the spacing between words, it seem some spaces are lacking.

Introduction
The physiological changes in thyroid function during pregnancy are well described and accepted by the medical community. Therefore it was weird that the authors referred these as hypothesized and claimed

(the first few sentences in the first paragraph). Could the authors reword these sentences?

Methods
Please add the conversion factor for plasma glucose levels to mmol/l.
Please also add the laboratory method used to measure glucose, if available. If not available, please indicate if glucose was measured by a laboratory that participates in an external quality control program.
In the Statistics section, please change 'Continue variables' to 'Continuous variables'.

Results
I presume that the gestational age in Table 1 is the timepoint when women entered the study? If so, please indicate this more clearly.
Throughout the manuscript, please spell Kg as kg.
Instead of decreased, I would use the word lower when describing differences between GDM cases and controls.
Please round all results to two decimals as they are more meaningful clinically (also applies to Table 2).

Table 1
Please add a space between the mean and SD.
Please correct Kg/cm^2 to kg/m^2

Discussion
Second line: please correct to 'an association'
I think the study by Cleary-Goldman et al. studied the association between thyroid dysfunction and GDM, not the other way around (a subtle but important difference).
I would love to see some discussion on the iodine status of the studied population.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

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This article studies the effect of gestational diabetes on maternal thyroid function and BMI. A case control study was done in Sudan and thyroid hormone levels and thyroid autoantibody testing was done.

With the increasing abnormalities in thyroid function such as subclinical disease seen in pregnancy, this study further consolidates existing literature with decreased thyroid hormone levels and increased thyroid autoantibodies in gestational diabetes.

This study also looked at the association between BMI and thyroid parameters. However, the conclusion

states that BMI correlates positively with free thyroid hormones but the discussion says a negative correlation was present. Also the conclusion says BMI was negatively associated with thyroid autoantibodies but the discussion says the opposite. I assume this may be a typographical error in the conclusion section. Please address this issue.

Otherwise this study, with its limitations adds interesting data to the preexisting literature on the subject.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.