DUAL ENDOCRINOPATHY - THE NEXUS BETWEEN HYPERGLYCAEMIA (GESTATIONAL DIABETES) AND HYPOTHYROIDISM AMONG PREGNANT WOMEN IN INDIA

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ABSTRACT

BACKGROUND

There have been rising trends in the incidence of hyperglycaemia in pregnancy and hypothyroidism in pregnancy. Both are known to cause adverse maternal and foetal outcomes. An attempt is being made to look at both these problems in conjunction rather than in isolation. The nexus of dual endocrinopathy is being explored in this study.

The aim of the study is to determine the prevalence of hypothyroidism in pregnant women with gestational diabetes mellitus (GDM) in India as well as the association between GDM and hypothyroidism.

MATERIALS AND METHODS

The study subjects were pregnant women attending the Divakars Speciality Hospital Bengaluru, India. They were recruited on their first antenatal visit; excluded were women known to have hypothyroidism as well as those who were taking thyroid medication. GDM testing was carried out according to the Diabetes in Pregnancy Study group India (DIPSI) as per FIGO guidelines and serum TSH estimation was carried with the ADVIA Centaur XL Siemens kit using the CLIA technique. Hypothyroidism was diagnosed if the serum TSH levels were >2.5 µIU/L while GDM was diagnosed if the blood glucose levels were >140 mg/dL.

RESULTS

Thirty-eight of the 315 subjects recruited to take part in the study (12.1%) were diagnosed with GDM, while 277 exhibited a normal glucose tolerance. TSH levels were only available for 251 of the subjects in this study, 87 of whom were diagnosed with hypothyroidism. Of the 251 subjects for whom TSH and blood glucose data were available, only 29 subjects had GDM (12%). Of the 29 subjects who were diagnosed with GDM, 24 (82.7%) were also hypothyroid. A Mantel-Haenszel common odds ratio estimate showed that a weak association existed between TSH levels greater than 2.5 µIU/L and blood plasma glucose levels greater than 140 mg/dL (OR=12.11; 95% CI: 4.42-33.15).

CONCLUSION

There is a considerably high prevalence of hypothyroidism in pregnant women who have been diagnosed with GDM. This study adds to the growing literature regarding the dual endocrinopathy of hypothyroidism and GDM in pregnant women and makes a case for increased observation of pregnant women diagnosed with either endocrinopathy.

KEYWORDS

Gestational Diabetes Mellitus, GDM, Hypothyroidism, India, DIPSI Association.

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BACKGROUND

Gestational Diabetes Mellitus (GDM) is defined as a “carbohydrate intolerance with recognition or onset during pregnancy.”¹ Its clinical significance lies in its adverse short-term and long-term maternal and perinatal outcomes² as well as its role in increasing long-term risk of Type 2 Diabetes Mellitus (T2DM) in both mothers and their offspring.³-⁶

GDM is characterised by defective pancreatic beta-cell function that is caused by a variety of factors including autoimmune disease, insulin resistance and monogenic factors.⁷ It is well-known that obesity and T2DM are contributing factors of GDM.⁸ However, recent studies have also suggested that thyroid dysfunction, particularly hypothyroidism, is associated with increased risk of GDM among pregnant women.⁹,¹⁰ Together with other forms of thyroid dysfunction, hypothyroidism has been shown to have an effect on glucose intolerance.¹¹

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The global prevalence of hypothyroidism in pregnant women has been estimated to be 2-5%. In India, a high prevalence of subclinical hypothyroidism, a form of hypothyroidism characterised by an elevated serum Thyroid-Stimulating Hormone (TSH) concentration, but a normal serum-free thyroxine level has been reported among pregnant women. Subclinical hypothyroidism increases the risk of negative perinatal outcomes and adverse pregnancy outcomes, such as preeclampsia, miscarriages, placental obstruction and preterm delivery. Moreover, overt maternal hypothyroidism is associated with childhood intelligence impairment.

Currently, there is a paucity of data on hypothyroidism and GDM in pregnant women in India. Prasad et al in one of the few studies on GDM and hypothyroidism in India found that GDM was more prevalent in pregnant women with hypothyroidism and that hypothyroidism increased GDM risk. Undiagnosed hypothyroidism during pregnancy could compound the deleterious effects of GDM increasing the incidence of adverse maternal and neonatal outcomes.

The goals of this study were two fold- 1) To determine the prevalence of hypothyroidism in pregnant women diagnosed with GDM, and 2) To investigate whether an association exists between GDM and hypothyroidism. It is hoped that this study will add to the existing literature regarding GDM and hypothyroidism and inform clinical practices and guidelines in India.

**MATERIALS AND METHODS**

**Study Participants** - Pregnant women who received antenatal care at Divakars Specialty Hospital, Bengaluru, India, from October 2015 to November 2016 were recruited on their first antenatal visit irrespective of their gravida status and whether their pregnancies were single- or multifetalus. Women who were known to have hypothyroidism or who were on thyroid medication were excluded from the study; however, a separate assessment of the prevalence of GDM in this group was noted. The details of the study were explained to each subject in English and the native language and informed consent was obtained thereafter through a signature. The study protocol was approved by the Institutional Ethics Committee of Divakars Specialty Hospital.

**GDM Testing and Serum TSH Estimation** - GDM testing was carried out according to the Diabetes in Pregnancy Study Group India (DIPSI) as per FIGO guidelines. Participants ingested 75 g glucose that had been dissolved in 300 mL water. After 2 hrs., the participant’s venous blood samples were collected and glucose levels were measured with an auto-analyser. GDM was diagnosed if the blood glucose levels were >7.8 mmol/L or >140 mg/dL. Serum TSH estimation was carried out at the clinical laboratory of Divakars Speciality Hospital using the ADVIA Centaur XL Siemens kit using the CLIA technique. In this study, hypothyroidism was diagnosed if the serum TSH levels were greater than 2.5 µIU/L. The subjects’ obstetricians were aware of the studies and had access to the GDM and hypothyroidism diagnoses. Those subjects who tested positive for GDM or hypothyroidism were placed on a treatment regimen.

**Statistics** - For descriptive statistics, the number of subjects, mean, Standard Deviation (SD), minimum and maximum values were calculated for continuous variables and the case number and percentage were computed for categorical values. For correlation analysis, logistic regression was performed and the odds ratio was estimated. Analyses were conducted with IBM SPSS Statistics version 23.

**RESULTS**

Data from a total of 315 subjects were analysed in this study. As shown in Table 1, the mean (SD) blood glucose concentrations and TSH values of subjects were 117.75 (18.05) mg/dL and 2.18 (1.52) µIU/L, respectively. Thirty-eight subjects (12.1%) were diagnosed with GDM, while 277 exhibited a normal glucose tolerance (Table 1). TSH levels were only available for 251 of the subjects in this study; eighty-seven subjects (34.7%) were diagnosed with hypothyroidism, while 164 (65.3%) were euthyroid (Table 1).

Of the 251 subjects for whom both TSH and blood glucose data were available, only 29 had GDM (12%). Of the 29 subjects who were diagnosed with GDM, 24 (82.7%) were also hypothyroid. A Mantel-Haenszel common odds ratio estimate was conducted to estimate the association between hypothyroidism and GDM. As shown in Table 2, a weak association was found between TSH levels greater than 2.5 µIU/L and blood plasma glucose levels greater than 140 mg/dL (OR=12.11; 95%, CI: 4.42-33.15). The prevalence of hypothyroidism in the subjects with normal glucose tolerance was found to be 28.4% (63/222).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma blood glucose, mg/dL</td>
<td>117.75 ± 18.05</td>
</tr>
<tr>
<td>&gt;140 (GDM)</td>
<td>38 (12.1)</td>
</tr>
<tr>
<td>≤140 (normal glucose tolerance)</td>
<td>277 (87.9)</td>
</tr>
<tr>
<td>TSH, µIU/L</td>
<td>2.18 ± 1.52</td>
</tr>
<tr>
<td>&gt;2.5 (hypothyroid)</td>
<td>87 (34.7)</td>
</tr>
<tr>
<td>≤2.5 (euthyroid)</td>
<td>164 (65.3)</td>
</tr>
</tbody>
</table>

*Unless stated otherwise, values are presented as n (%).

Table 1. Prevalence of GDM and Hypothyroidism

<table>
<thead>
<tr>
<th>Variable</th>
<th>GDM (n=29)</th>
<th>OR (95%, CI)</th>
<th>P</th>
<th>Non-GDM (n=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2.5 (hypothyroid)</td>
<td>24 (87.2)</td>
<td>12.11 (4.42-33.15)</td>
<td>&lt;0.0001</td>
<td>63 (28.4)</td>
</tr>
<tr>
<td>≤2.5 (euthyroid)</td>
<td>5 (18.2)</td>
<td>139 (71.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Association between TSH Values Greater than 2.5 µIU/L and Glucose Tolerance Test Plasma Glucose Concentration above 140 mg/dL.
DISCUSSION

Several studies have reported prevalence rates ranging from 2.7-30% of hypothyroidism in patients with diabetes.\textsuperscript{21,22} In this study, the prevalence of hypothyroidism among subjects with GDM was 87.2% considerably higher than the values reported in the literature. This high prevalence maybe subject specific, a manifestation of the longstanding iron deficiency in India,\textsuperscript{23} although iodised salt has been recommended since the 1980s, environmental and social factors have reduced its accessibility by parts of the population.\textsuperscript{23} In fact, Vermiglio et al\textsuperscript{24} found that prevailing iron deficiency during pregnancy resulted in significantly high levels of TSH towards the end of the first trimester that progressively increased until term; thus it is plausible that the high prevalence of hypothyroidism in this study population can be attributed to wide-spread maternal iron-deficiency in India.

Although, we did not investigate whether a causal relationship exists between GDM and hypothyroidism, it is well known that maternal thyroxine (T\textsubscript{4}) and triiodothyronine (T\textsubscript{3}) have an effect on glucose metabolism\textsuperscript{25,26} and some, but not all studies have shown that hypothyroidism affects insulin resistance.\textsuperscript{11} However, an increased incidence and increased risk of subclinical hypothyroidism has also been reported in pregnant women with GDM.\textsuperscript{9,10} Thus, it is equally plausible that the presence of one endocrinopathy in this study population increased susceptibility to the other; however, detailed studies would be required to validate this claim.

Hypothyroidism and GDM are common complications of pregnancy. Individually, they have been shown to contribute to adverse obstetric outcomes.\textsuperscript{2,3,17,18} In combination, they have been shown to increases rates of first trimester abortions, preeclampsia, polyhydramnios, placental abruption, preterm deliveries, caesarean sections, postpartum haemorrhage and intrauterine foetal deaths.\textsuperscript{27} Although, universal GDM screening is advised by the current Diabetes in Pregnancy Study group India (DIPSI) as per FIGO guidelines,\textsuperscript{20} because the benefits of addressing maternal thyroid deficiency are still unclear, universal screening of all pregnant women for hypothyroidism is not recommended by most professional groups.\textsuperscript{28,31} However, case finding among pregnant women at high risk of thyroid disease has been recommended,\textsuperscript{28,31} whereby high-risk women are described as those with a family history for autoimmune thyroid disease, presence of goiter, signs and symptoms suggestive of thyroid dysfunction, personal history of type 1 diabetes or other autoimmune disease, history of neck irradiation, previous miscarriages or preterm deliveries.\textsuperscript{28} This study suggests that women with GDM should be categorised as high risk for hypothyroidism and thus should have their TSH levels monitored closely during pregnancy.

The findings of this study should be interpreted in light of the following limitations. Our study was aimed primarily at identifying the prevalence of hypothyroidism in pregnant women with GDM as well as the association between hypothyroidism and GDM, so a longer follow-up to identify the significance of these thyroid abnormalities is unknown. Furthermore, the sample size in this study was quite small, and we believe this might explain, in part, the weak association we found between hypothyroidism and GDM.

CONCLUSION

The prevalence of hypothyroidism in pregnant women who have been diagnosed with GDM is considerably high in India. As a combined endocrinopathy of hypothyroidism and GDM during pregnancy has the potential to result in deleterious obstetric outcomes, women diagnosed with GDM should be screened for hypothyroidism and vice versa.

REFERENCES


