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ARTICLE

Relationship between hypothyroidism and gestational diabetes mellitus: a retrospective cohort study

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Background: Approximately 2–10% of pregnant women experience subclinical hypothyroidism during pregnancy. Although some studies have shown that primary hypothyroidism increases the risk of gestational diabetes mellitus (GDM), there are contradictory results. Hence, this study aimed to determine the relationship between hypothyroidism and GDM.
Methods: This is a retrospective cohort study in which the researchers followed up 340 pregnant women (170 with hypothyroidism as exposed group and 170 without hypothyroidism as unexposed group) for GDM. To analyse the data, chi-square, Fisher's exact test and independent t-test were employed.
Results: The incidence of GDM in the hypothyroidism group was higher than that of the group without hypothyroidism (11.8% vs. 10.6%, $p = 0.731$). Moreover, the risk of GDM (95% CI:0.61; 2.02) was 1.11 times higher among women with hypothyroidism. However, the observed association was not statistically significant. The mean two-hour oral glucose tolerance test (OGTT) level in pregnant women with hypothyroidism (108.94 ± 19.89 mg/dl) was significantly higher than in the other group (104.49 ± 18.43 mg/dl) with a *p*-value of 0.033.
Conclusions: This study displayed that the risk of GDM is 11% higher among women with hypothyroidism. Furthermore, the difference in the mean two-hour OGTT level in pregnant women with hypothyroidism was 4.4 mg/dl higher than in the other group.

Keywords: gestational diabetes, pregnancy, subclinical hypothyroidism, thyroid

Background

Gestational diabetes mellitus is defined as a form of glucose intolerance, first detected during pregnancy. It has been the most common complaint during pregnancy, with a prevalence of 9.4–10.6%,[1,2] and is associated with many foetal and maternal adverse outcomes. The short-term complications include macrosomia foetuses, gestational hypertension and preeclampsia, and the long-term complications include postpartum diabetes mellitus, cardiovascular disease, renal disease and disorders of glucose metabolism in the newborn.[3–5]

Thyroid function can be reversibly affected following various hormonal and metabolic changes during pregnancy.[6] Up to 3% of pregnant women experience subclinical hypothyroidism (SCH) due to the elevation of the thyroid stimulating hormone (TSH).[7]

In the study conducted by Prasad *et al.*, the prevalence of gestational diabetes mellitus (GDM) was 8% in pregnant women with a hypothyroidism and 1% in the control group with a *p*-value of 0.034.[8] In contrast, Shahbazian *et al.* revealed that the frequency of thyroid disorders in the case group was lower than in the control group (4.5% vs. 8.6%).[9] Furthermore, in the study conducted by Sharifi *et al.*, the odds ratio of those with GDM was lower than that of the control group in developing clinical hypothyroidism.[10]

All the studies mentioned indicate contradictory results regarding the relationship between GDM and hypothyroidism, confirming the necessity of conducting studies with appropriate methodology. Hence, this study aimed to determine the relationship between hypothyroidism and GDM in pregnant women.

Methods

This is a retrospective cohort study conducted on pregnant women living in rural areas of Amol, a city in the north of Iran, in 2018. The exposed group included pregnant women with hypothyroidism, and the unexposed group comprised pregnant women without hypothyroidism. Initial screening results of routine care for pregnancy were used to categorise the exposed and unexposed group members. Pregnant women with TSH of more than 3 IU/l were allocated to the exposed group. [6] It should be noted that the cases of hypothyroidism in this study include subclinical or overt cases (with previous history or new case).

The researchers used the results of a previous study to determine the minimum number of samples.[8] In that study, the frequency of GDM in pregnant women with hypothyroidism was 8%, while it was 1% among those without hypothyroidism. Given these results, the 95% confidence level, 80% test power, a two-tailed test, the formula for the comparison between the two ratios, and employing STATA version 11 (StataCorp, College Station, TX, USA), the number of samples was estimated to be 328 (164 participants in each group). It was then increased to 340 participants (i.e. 170 samples in each group).

The research project was first approved by the Ethics Committee of Mazandaran University of Medical Sciences. To undertake the sampling, a list of rural health centres along with information such as the number of pregnant mothers and the number of pregnant mothers with hypothyroidism during 2016 were obtained from the Family Health Unit of Amol Health Network. The researcher then went to the rural health centre and coordinated with the relevant midwife to use the records of pregnant mothers. The initial checklist was completed to apply the inclusion and exclusion criteria and to select the eligible samples. The number of samples in the exposed group was randomly selected based on probability proportional to the size of the total number of exposed individuals in each centre. Thereafter, for each selected exposed sample, one sample was randomly selected from among unexposed individuals. It should be noted that the exposed and unexposed groups were matched according to age group, body mass index and residential area (health centre). If there was more than one unexposed person for each selected exposed one in the centre, a random sampling method was used.

The inclusion criteria included pregnant women aged 21–40 years, with a body mass index of less than 35, and test results in terms of hypothyroidism before pregnancy as well as routine screening for TSH during pregnancy.

On the other hand, pregnant women with chronic and advanced heart, lung and renal diseases, those taking drugs that induce hyperglycaemia (e.g. corticosteroids, cyclosporine, clozapine and olanzapine), those with a history of diabetes, and pregnant women with data incomplete on the records were excluded from the study.

According to the routine care for pregnancy, fasting blood sugar and oral glucose tolerance test (OGTT) with 75 grams of glucose in the first and second hours in the 24th–28th week of pregnancy were done for all pregnant women in both groups. Normal fasting blood sugar is less than 92 mg/dl, first-hour blood sugar is less than 180 mg/dl, and second-hour blood sugar is less than 153 mg/dl.[11] An increase in any of these normal values is considered GDM.

The information was obtained from the records of pregnant mothers in health centres. A checklist was prepared to collect the information, including the age of the pregnant mother, number of pregnancies, height, weight during pregnancy, body mass index, hypothyroidism, gestational age at TSH and OGTT tests, family history of diabetes, hypothyroidism and hypertension, diastolic and systolic blood pressure during pregnancy, TSH and fasting blood sugar test results, and 1-hour and 2-hour OGTT.

Data were fed into SPSS version 25 (IBM Corp, Armonk, NY, USA), and the analysis was performed. Descriptive statistics such as percentage, mean and standard deviation were used to describe the variables. A chi-square test was used for comparing the epidemiological and clinical variables as well as comparing the study outcomes; that is, developing GDM in the two exposed and unexposed groups. Similarly, another chi-square test, as well as Fisher's exact test, was run to compare the outcome of developing GDM in the subgroup of body mass index, age group and the number of pregnancies between the two groups. To compare the mean fasting blood sugar and 1-hour and 2-hour OGTT between the two groups, an independent *t*-test was performed.

Results

Based on the inclusion and exclusion criteria and the definition of exposure, 340 pregnant women were allocated into two groups with 170 participants. Table 1 reveals that the two groups are not statistically different in terms of age group, body mass index, number of pregnancies, and family history of diabetes and blood pressure ($p > 0.05$). However, there is a significant difference between the two groups in terms of family history of thyroid. The frequency of hypothyroidism in the exposed group is higher than in the unexposed group (14.7% vs. 2.4%, $p < 0.001$).

As may be seen in Table 2, no statistically significant differences were observed between the two groups regarding anthropometric data, systolic and diastolic blood pressure, and gestational age at the time of measuring TSH and GTT ($p > 0.05$).

Table 3 indicates that the incidence of GDM was 20 people (11.8%) in the exposed group and 18 people (10.6%) in the unexposed group; the difference is not statistically significant ($p = 0.731$). In other words, the relative risk of GDM was 1.11 times higher in women with hypothyroidism (95% CI 0.61; 2.02).

Table 4 shows that the mean levels of FBS, one-hour OGTT and two-hour OGTT in pregnant women with hypothyroidism (exposed group) were higher than those without hypothyroidism. Significant differences were observed between the two groups in terms of two-hour OGTT ($p = 0.033$).

Table 5 illustrates the comparison between the frequency of GDM by the subgroups of body mass index, age group and number of pregnancies. Although there is a difference in the incidence of GDM between the two groups, it is not statistically significant. However, GDM occurred more in the subgroups with a body mass index of 30.0–34.9 (25% vs. 11.4%, $p = 0.097$), age group 31–40 years (15.8% vs. 7%, $p = 0.141$) and among women with more than one pregnancy (13.7% vs. 10.9%, $p = 0.539$) in the exposed group.

Discussion

This cohort study was designed to assess the relationship between hypothyroidism and the incidence of GDM. It revealed that the risk of GDM is 11% higher among women with hypothyroidism compared with those without hypothyroidism, although the difference was not statistically significant ($p = 0.731$). Furthermore, the mean difference of the two-hour OGTT level was significantly 4.4 mg/dl higher in pregnant women with hypothyroidism ($p = 0.033$).

A meta-analysis conducted by Gong *et al*.[12] aimed to determine the association between hypothyroidism and the risk of GDM in 2016. In this meta-analysis, three initial studies[13–15] investigated the association between overt hypothyroidism and an increased risk of developing GDM. In two studies,[13,14] overt hypothyroidism was significantly associated with an increased odds ratio of developing GDM. One of these studies was conducted in Finland in 2010. Of 54 people in the case group, 4 (7.41%) and of 4 708 people in the control group, 61 (1.29) participants suffered from GDM.[13] Another study conducted in the USA in 2013 showed that 298 (9.36%) of 3 183 participants in the case group, and 10 805 (4.98%) of 216 901 participants in the control group had GDM.[14] Another study that did not find a significant relationship, as mentioned in the meta-analysis, was conducted by Sahu *et al*. in India in 2010. In this study, one of the 29 participants (3.45%) in the case group, and 18

Table 1: Comparison of the frequency of age groups, body mass index and family history based on exposed and non-exposed groups*

Variables	Non-exposed *n* (%)		Exposed *n* (%)	Total *n* (%)	*p*-value
Age group (years)	21–30	113 (66.5)	113 (66.5)	226 (66.5)	1.000
	31–40	57 (33.5)	57 (33.5)	114 (33.5)	
BMI** (kg/m^2)	< 25	62 (36.5)	63 (37.1)	125 (36.8)	0.992
	25–30	64 (37.6)	63 (37.1)	127 (37.4)	
	30–35	44 (25.9)	44 (25.9)	88 (25.9)	
Gravidity (number)	1	69 (40.6)	68 (40.0)	137 (40.3)	0.912
	>1	101 (59.4)	102 (60.0)	203 (59.7)	
Family history (yes)	Thyroid disorder	4 (2.4)	25 (14.7)	29 (8.5)	< 0.001
	DM	13 (7.6)	14 (8.2)	27 (7.9)	0.841
	HTN	2 (1.2)	8 (4.7)	10 (2.9)	0.054

*The exposed group included pregnant women with hypothyroidism, and the unexposed group embraced pregnant women without hypothyroidism, **BMI: body mass index.

of 552 participants (3.26%) in the control group had diabetes.[15] Combining the results of these three studies, Gong *et al.* revealed that pregnant women with overt hypothyroidism were 1.89 times more at risk of developing GDM in comparison with pregnant women without overt hypothyroidism.[12] Combining the results of the first six studies that had worked on SCH, Gong *et al.* concluded that the odds ratio of GDM in pregnant women with SCH was significantly 1.56 times higher than that of those without SCH.[12] In the study by Prasad *et al.*, the prevalence of GDM was 8% in pregnant women with hypothyroidism and 1% in the control group, with $p = 0.034$.[8]

The evidence presented in the above studies is consistent with the results of the present study, although the increase in GDM rate in the exposed group compared with the unexposed group was not statistically significant in the present study. However, this increased risk can be clinically important. Moreover, the mean two-hour OGTT value in pregnant women with hypothyroidism was significantly higher than in those without hypothyroidism.

Another issue is that differences in the overall incidence of GDM in different geographical areas may be one reason for the discrepancy in the intensity of the relationship. In the present study, the incidence of GDM was about 11%, but it was less in the first three[13–15] studies mentioned in the meta-analysis.[12]

The results of some studies are inconsistent with the results of the present study. For instance, Shahbazian *et al.* reported that the frequency of thyroid disorders in the case group was lower than in the control group (4.5% vs. 8.6%) in Ahvaz, southwestern Iran.[9] Similarly, Tudela *et al.* investigated the association of subclinical thyroid disease with the incidence of GDM in 24 883 pregnant women.[16] They indicated that women with hyperthyroidism had a significantly lower chance of developing GDM, while it has been shown that thyroid disorders (both hypothyroidism and hyperthyroidism) are associated with insulin resistance.[17,18] A study by Cleary-Goldman *et al.* on hypothyroidism and pregnancy outcomes was undertaken on 10 990 women in the first and second trimesters of pregnancy with tests of TSH, FreeT4, and anti-thyroglobulin and anti-thyroid peroxidase antibodies.[19] They observed no relationship between hypothyroidism and GDM in the first trimester of pregnancy. Another study was conducted by Sharifi *et al.* on thyroid function and its relationship with insulin resistance in women with GDM compared with

Table 2: Comparison of age, BMI, height, weight, systolic and diastolic blood pressure mean based on exposed and non-exposed group*

Variables	Non-exposed group mean ± SD	Exposed group mean ± SD	*p*-value
Age (years)	28.2 ± 5.1	28.2 ± 5.1	0.933
BMI** (kg/m^2)	26.8 ± 4.0	26.6 ± 4.1	0.635
Height on first visit (cm)	160.3 ± 5.6	160.5 ± 6.2	0.653
Weight on first visit (kg)	68.4 ± 10.5	68.9 ± 12.5	0.687
Weight on second visit (kg)	74.1 ± 10.9	75.5 ± 12.6	0.272
Weight on third visit (kg)	78.9 ± 11.0	79.1 ± 12.9	0.910
Systolic blood pressure on first visit (mmHg)	99.1 ± 10.3	100.9 ± 12.3	0.163
Diastolic blood pressure on first visit (mmHg)	61.9 ± 7.7	63.5 ± 8.1	0.062
Systolic blood pressure on second visit (mmHg)	100.3 ± 9.8	101.5 ± 11.2	0.331
Diastolic blood pressure on second visit (mmHg)	62.7 ± 8.1	62.7 ± 8.1	0.974
Systolic blood pressure on third visit (mmHg)	101.7 ± 8.9	102.2 ± 10.9	0.606
Diastolic blood pressure on third visit (mmHg)	62.8 ± 8.3	63.2 ± 8.0	0.716
Gestational age at the time of TSH test (week)	8.8 ± 3.0	8.3 ± 2.1	0.054
Gestational age at the time of OGTT (week)	26.9 ± 3.2	26.9 ± 3.2	0.987

*The exposed group included pregnant women with hypothyroidism, and the unexposed group comprised pregnant women without hypothyroidism, **BMI: body mass index.

Table 3: Comparison of the incidence of gestational diabetes among the exposed and non-exposed groups*

Variable		Non-exposed group *n* (%)	Exposed group *n* (%)	Total *n* (%)	*p*-value	Risk ratio (95% CI)
GDM**	No	152 (89.4)	150 (88.2)	302 (88.8)	0.731	1.11 (0.61–2.02)
	Yes	18 (10.6)	20 (11.8)	38 (11.2)		

*The exposed group included pregnant women with hypothyroidism, and the unexposed group comprised pregnant women without hypothyroidism, **GDM: gestational diabetes mellitus.

Table 4: Comparison of fasting blood sugar, one-hour and two-hour oral glucose tolerance test mean between exposed and non-exposed groups*

Variables	Non-exposed SD ± mean	Exposed SD ± mean	*p*-value (independent *t*-test)
FBS** (mg/dl)	81.73 ± 7.06	82.49 ± 8.43	0.374
One-hour OGTT*** (mg/dl)	134.31 ± 25.78	134.52 ± 27.06	0.941
2-hour OGTT (mg/dl)	104.49 ± 18.43	108.94 ± 19.89	0.033

*The exposed group included pregnant women with hypothyroidism, and the unexposed group comprised pregnant women without hypothyroidism, **FBS: fasting blood sugar, ***OGTT: oral glucose tolerance test.

Table 5: Comparison of the frequency of gestational diabetes based on body mass index, age group and gravidity by expose and non-expose groups*

Variable		GDM	Non-exposed *n* (%)	Exposed *n* (%)	*p*-value
BMI** (kg/m^2)	<25	No Yes	59 (95.2) 3 (4.8)	61 (96.8) 2 (3.2)	0.680
	25–29.9	No Yes	54 (84.4) 10 (15.6)	56 (88.9) 7 (11.1)	0.455
	30–34.9	No Yes	39 (88.6) 5 (11.4)	33 (75.0) 11 (25.0)	0.097
Age group (years)	21–30	No Yes	99 (87.6) 14 (12.4)	102 (90.3) 11 (9.7)	0.525
	31–40	No Yes	53 (93.0) 4 (7.0)	48 (84.2) 9 (15.8)	0.141
Gravidity (number)	1	No Yes	62 (89.9) 7 (10.1)	62 (91.2) 6 (8.8)	0.792
	<1	No Yes	90 (89.1) 11 (10.9)	88 (86.3) 14 (13.7)	0.539

*The exposed group included pregnant women with hypothyroidism, and the unexposed group comprised pregnant women without hypothyroidism, **BMI: body mass index.

healthy pregnant women in Zanjan, Iran. They studied 142 pregnant women and revealed that there was no significant relationship between serum TSH levels of the pregnant women and blood sugar, insulin and insulin resistance.[10] Likewise, in a case-control study conducted by Hassani *et al*. in Qazvin, Iran, the mean level of TSH in the case group (2.9 ± 1.1 IU/l) was higher than that of the control group (1.8 ± 0.8 IU/l) with $p = 0.012$.[11]

According to the results of the above studies, it can be concluded that one cannot decisively claim a correlation between hypothyroidism and the incidence of GDM. Therefore, it cannot be stated that there is a causal relationship between hypothyroidism and GDM. Part of the discrepancies in the results is probably related to the methodology, design and implementation of the studies. Another reason may be the different distribution of the disease in different geographical areas. Unlike other studies, most studies conducted in Iran have found either a weak or a reverse association between hypothyroidism and GDM. Moreover, one of the possible challenges of the studies is the disproportionate number of samples in the case and control groups; in cases where the disease is rare, the number of participants in the control group can be up to four times higher than that of the case group. Based on the results of the present study, considering the 11.8% incidence of GDM in the hypothyroidism group and 10.6% incidence in the other group, the required sample size to prove the hypothesis with a confidence level of 95% and test power of 80%, for a one-tailed test, is estimated to be 17 410 participants (8 705 in the exposed group and 8 705 in the unexposed group). Undoubtedly, this number of samples is only possible with multi-centre studies so that the existing birth cohorts can be a suitable platform for this study.

One of the limitations of the present study is the potential information deficiency in the records of the studied samples; however, this situation was the same in both groups.

Conclusions

This study showed that the prevalence of GDM in pregnant women with hypothyroidism is higher than those without hypothyroidism, though this relationship was not significant and the study could not confirm the hypothesis. Also, the two-hour OGTT level in pregnant women with hypothyroidism was significantly higher than in those without hypothyroidism. Given the findings of the present study and the results of comparative studies, especially the conflicting results of studies conducted in Iran compared with other countries, it is necessary to design studies with appropriate methodology.

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