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Original Research Paper

RETROSPECTIVE STUDY OF GESTATIONAL DIABETES MELLITUS AND ITS CORRELATION WITH THYROID DISORDERS IN PREGNANCY

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ABSTRACT:

An association between insulin-dependent diabetes mellitus and thyroid autoimmunity has long been recognized. However, studies exploring the association of thyroid dysfunction among GDM mothers and its perinatal complications are sparse in this part of the country. Hence this study was conducted among 88 pregnant women who delivered in a tertiary care centre to determine the prevalence of thyroid disorder among the pregnant women with GDM and the fetal and maternal complications due to the thyroid disorder in GDM. Data was analysed using SPSS V21 for Windows. This hospital based retrospective study was conducted among 88 patients through the case records satisfying the inclusion and exclusion criteria to estimate the prevalence of hypo/hyperthyroidism in patients with gestational diabetes mellitus and to determine the perinatal outcome in gestational diabetes mellitus with hypo/ hyperthyroidism. Our study concludes that the prevalence of hypo/hyperthyroidism among the pregnant women with GDM was 20.5% (95% CI: 12.9%-30.7%). There was no significant association between hypo/hyperthyroidism and caesarean delivery, pre term birth, low birth weight, congenital anomalies and NICU admission. Even in terms of APGAR score and hypoglycaemia there was no significant difference between the groups. There was only one incidence of neonatal death due to extremely low birth weight of the neonate.

Keywords: Gestational diabetes mellitus, thyroid disorders in pregnancy, thyroid dysfunction; pregnancy; perinatal outcome in gestational diabetes mellitus

INTRODUCTION:

The goal of prenatal care is to ensure health of the mother and giving birth to a healthy baby.[1] Complicated hormonal changes occur during pregnancy and the most common of those changes are endocrine conditions, in particular gestational diabetes mellitus and thyroid diseases. Diabetes mellitus (DM) and hypothyroidism disorders are among the most common endocrinopathies during pregnancy. Diabetes during pregnancy is classified as Gestational diabetes (diabetes which was first diagnosed during pregnancy) or pre- gestational diabetes. Incidence of Gestational diabetes mellitus (GDM) varies globally from 2% to 14%.[2] According to the data from the latest edition of the IDF Diabetes Atlas, the global prevalence of hyperglycemia in pregnancy was 15.8%.[3] Data shows that 83.6% of cases were the result of gestational diabetes mellitus.[4-7] Gestational diabetes mellitus (GDM) and especially pre-gestational DM, are known as risk factors for pregnancy complications, effecting both the mother and the fetus, and include amongst them gestational hypertension, cesarean sections, macrosomic fetuses and shoulder dystocia.[8] These patients also have increased morbidity including fetal demise, neonatal hypoglycemia, jaundice, polycythemia and hypocalcemia.[9] About 10%-15% of pregnant women have thyroid dysfunction during the first half of pregnancy which may be hypothyroidism or hyperthyroidism.[10] Hypothyroidism is also a common endocrinopathy during pregnancy, and its incidence range from 2% to 5%.[11] Pregnant women with hypothyroidism, experience a higher rate of first trimester abortions, anemia, post-partum hemorrhage,

gestational hypertension and placental abruption.[12,13] Hence, continuous monitoring and balancing of thyroid functions decreases the prevalence of most of these complications. The prevalence of thyroid dysfunction in pregnant women with type 1 diabetes is about three times more than general population and subclinical hypothyroidism is more prevalent.[14] In some studies 40% of pregnant women with type 1 diabetes have thyroid dysfunction simultaneously.[15] Both thyroid dysfunction and gestational diabetes could be connected with maternal complications like miscarriage, hypertensive disorders (gestational hypertension, preeclampsia), abruptio placentae, preterm delivery, caesarean section deliveries, and birth trauma. [7,8,9,10] Perinatal and neonatal morbidities associated with GDM and thyroid dysfunction include the following: macrosomia, shoulder dystocia, respiratory distress syndrome, neonatal hypoglycemia, polycythemia, hyperbilirubinemia, impaired neurodevelopment of the child, and low birth weight.[16-19] Because of these known complications, screening of pregnant women for these common endocrine disorders (gestational diabetes and thyroid dysfunction) is discussed by endocrinology societies and there are various and up-to-date recommendations in this regard. An association between insulin-dependent diabetes mellitus and thyroid autoimmunity has long been recognized. Management of thyroid diseases in pregnancy is different than in non-pregnant women, due to physiological changes of thyroid hormone economy in the childbearing period. Thyroid dysfunction may affect carbohydrate metabolism and worsen glucose control in diabetic patients. On the other hand, poorly compensated diabetes mellitus may cause alteration in the production and metabolism of thyroid hormones. There is inconsistent evidence regarding the association between thyroid diseases and GDM. Some reports found such an association, while others failed to show this connection. To the best of our knowledge, literature on the prevalence of thyroid disorders among the pregnant women with GDM and their perinatal complications are sparse in this part of the country. Hence this study was conducted to determine the prevalence of hypo/hyperthyroidism among the pregnant women with GDM and also to decipher their association with the maternal and fetal complications in a tertiary care centre.

METHODOLOGY:

Study design & settings

This hospital based retrospective study was conducted among 88 pregnant women with gestational diabetes mellitus, attending the Department of Obstetrics and Gynecology (Outdoor / Indoor) in a tertiary care hospital from January 20xx to April 20xx. The study was conducted for a period of two years during which retrospective data of patients for 36 months duration was retrieved for the analysis. The study was approved by the ethics committee of the hospital. Informed consent was obtained from all patients before the initiation of study.

Sample size & sampling technique

A total of 88 pregnant mothers meeting the inclusion criteria were included in the study with the diagnosis of gestational diabetes mellitus at the tertiary care hospital during the study period. Sample size was calculated using SAS 9.2 package From review of literature,

Efficacy variable: Prevalence of Raised thyroid hormones in GDM. Null Hypothesis H0: Prevalence of Raised thyroid hormones= 19%[27] H1: Anticipated Prevalence of Raised thyroid hormones = 30.0% Minimum Sample size = 88, Power = 80%, Alpha= 0.05. All the patients were included in the study using consecutive sampling technique. The inclusion and exclusion criteria for the study participants were as follows:

Inclusion criteria

Inclusion criteria included: Pregnant women with (i) Singleton pregnancy; (ii) Gestational diabetes as per WHO laboratory criteria.[22] ; (iii) Complete hospital records and investigations

Exclusion criteria

Exclusion criteria included Patients (with/on) (i) Pre-gestational diabetes mellitus (Type I or Type II DM); (ii) Connective tissue disorder; (iii) Steroidal therapy for any other medical disorder of pregnancy.

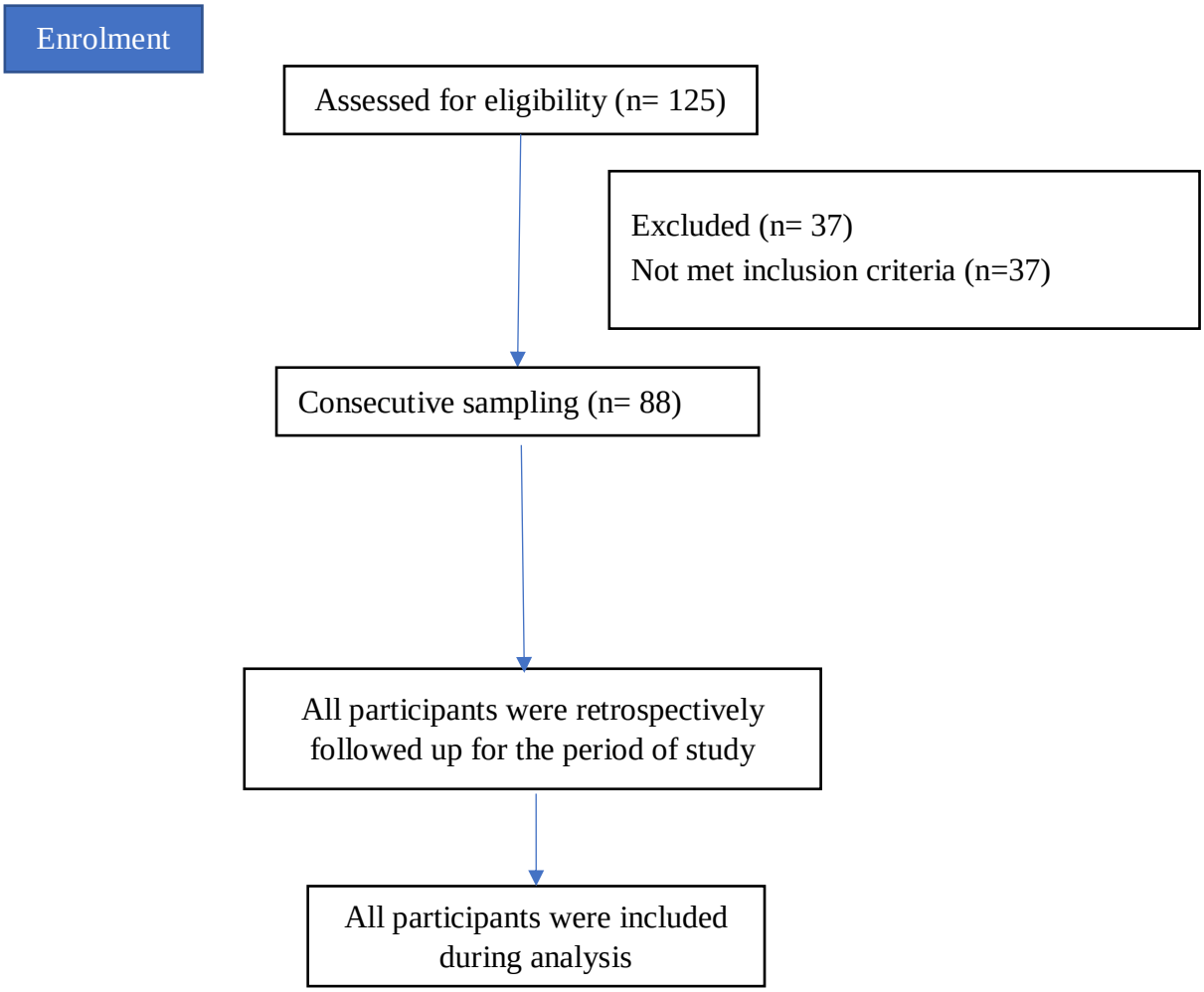

Fig 1: Consort flow diagram for selection of study participants

Treatment methods

After obtaining permission from the institutional ethics committee and data on demographic characteristics, medical and obstetric history, pregnancy outcomes, including maternal and neonatal morbidity and mortality, were retrieved from computerized database. The diagnosis of the different types of diabetes mellitus as per WHO criteria and hyper/hypothyroidism status were used as recorded in our computerized database.

Diagnosis of Gestational Diabetes Mellitus

Diagnosis of Gestational Diabetes Mellitus was done on the basis of the following procedure

Before the procedure

Patient was informed not to eat or drink anything for about eight hours before the test but not more than fourteen hours.

During the procedure

The first venous sample was taken after the requisite time of fasting (8-14hrs). The sample was collected in a fluoride bulb under all aseptic precautions. The study subject was asked to drink a Dextrose monohydrate solution containing 75gms of anhydrous dextrose powder in 250-400ml of water over a period of 20-30 min. The timing of completion of drinking of the solution was noted. Second venous test sample was collected an hour after the solution was drunk. The third venous sample were taken two hours after the solution was drunk. Care was taken to take samples in an aseptic manner and in a fluoride bulb. The test subjects were instructed not to eat or drink anything in the intervening test period nor to exert in any manner.

Timings: Between 20-24 weeks of pregnancy.

Diagnosis of Hyper/Hypothyroidism

Patient's venous blood sample was taken early in the morning in a plain bulb. Using chemiluminescent assay, serum concentrations of free thyroxine(T4), triiodothyronine(T3), and Thyroid stimulating hormone were recorded.

Operational definitions

Criteria for Diagnosis of GDM (WHO).[22]

Plasma Threshold Glucose	mmol/L	mg/dl	Above cumulative
Fasting	5.1	92	8.3
1-hr OGTT	10.0	180	14.0
2-hr OGTT	8.5	153	16.1

If two or more plasma levels using the above-mentioned criteria were found to be abnormal, then the patients were diagnosed as the gestational diabetes.

Criteria for diagnosis of Hyper/Hypothyroidism.[22]

S.TSH (mIU/L)	Free T4	Free T3	Diagnosis
<0.3	Normal	Normal	Subclinical hyperthyroidism
>4	Normal	Normal	Subclinical hypothyroidism
<0.3	High	Normal	Hyperthyroidism
>4	<4.8	Normal	Hypothyroidism

Statistical analysis

Data was analysed using SPSS V21 for IBM for windows. Continuous variables like age, birth weight is presented as mean (SD). Categorical variables like parity status, mode of delivery, BMI category are presented as frequency and percentages. The prevalence of hypo/hyperthyroidism is presented as percentages with 95% confidence interval (95% CI). Chi square test was used to determine the association between perinatal complications and thyroid status of the pregnant women. A p value of <0.05 was considered statistically significant.

Approval of research review Board

Timings: As soon as the subject registers for antenatal care.

Outcome measures

Proportion of pregnant women with GDM diagnosed with hypo/hyperthyroidism Association of thyroid disorders with maternal and fetal complications.

The ethical approval was sought from the Institutional Ethics Committee (IEC). Confidentiality was maintained by limiting the identifying variables to the minimum. Data was analysed in aggregate and access to the collected data was limited only to me and my guide.

RESULTS:

The mean age of the study participants was 30.6 (4.8) years. The median age was 30.0 (28.0-34.0) years with a minimum of 21 years and a maximum of 44 years. The median time of diagnosis of GDM among the pregnant mothers was 24.0 (22.0-28.0) weeks with a minimum of 16 weeks and a maximum of 35 weeks.

Table 1. Age distribution of the study participants (N=88)

Age category in years	Frequency (n)	Percentage
20-30	47	53.4
>30	41	46.6
Total	**88**	**100.0**

Table 1 shows that nearly half (46.6%) of the pregnant women were >30 years old. None of the pregnant women were of teenage pregnancy.

Table 2. Distribution of the study participants by their parity (N=88)

Parity	Frequency (n)	Percentage
Primi	77	87.5
Multi	11	12.5
Total	**88**	**100.0**

Table 2 shows that majority (87.5%) pregnant women were primiparous

Table 3. Distribution of the study participants by BMI (N=88)

Weight determination was at the time of booking/Registration visit.

BMI category (kg/m^2)*	Frequency (n)	Percentage
Normal (18.5-22.9)	4	4.5
Overweight (23.0-24.9)	22	25.0
Obese (≥25.0)	62	70.5
Total	**88**	**100.0**

***WHO Asia Pacific Classification**

The mean pre-pregnancy BMI of the pregnant women was 26.8 (3.2) kg/m^2 with a minimum of 22.0 kg/m^{2}and a maximum of 40.2 kg/m^2. Table 3 shows that obesity was observed in 70.5% of the study participants.

Table 4. Distribution of participants by period of gestation (N=88)

Period of gestation (weeks)	Frequency (n)	Percentage
<37	8	9.1
37-38	26	29.5
38-39	39	44.3
39-40	5	5.7
≥40	10	11.4
Total	**88**	**100.0**

Table 4 shows that period of gestation were 38-39 weeks in 44.3% of the participants followed by 37-38weeks which was observed in 29.5% of the participants. Preterm delivery occurred in 8 (9.1%) pregnant women

Table 5. Incidence of Hypo/Hyperthyroidism among the study participants (N=88)

Hypo/Hyperthyroidism	Frequency (n)	Percentage (95% CI)
Yes	18	20.5 (12.9-30.7)
No	70	79.5 (69.3-87.1)

Table 5 shows that the prevalence of Hypo/Hyperthyroidism was 20.5% (95% CI: 12.9%-30.7%) among the pregnant women with gestational diabetes mellitus. All the patients were Hypothyroid, on Thyroxine replacement therapy.

Table 6. Time of diagnosis of Hypo/Hyperthyroidism (N=18)

Time of diagnosis	Frequency (n)	Percentage
Pre-gestational	12	66.7
Gestational	6	33.7

Among 18 pregnant women with Hypo/Hyperthyroidism, 12 women had their diagnosis during their pre-gestational age and the remaining six women were diagnosed during their pregnancy. **(Table 6)**

Table 7. Distribution of participants by mode of delivery (N=88)

Mode of delivery	Frequency (n)	Percentage
Normal vaginal	41	46.6
Caesarean	47	53.4
Total	**88**	**100.0**

Table 7 shows that more than half (53.4%) of the delivery was caesarean delivery among which 30 (34.1%) was elective caesarean section and the remaining 17 (19.3%) was emergency caesarean section.

Table 8. Gender distribution of the child (N=88)

Gender of the child	Frequency (n)	Percentage
Male	54	61.4
Female	34	38.6
Total	**88**	**100.0**

Table 8 shows that the majority (61.4%) of the newborns were males with a M: F of 3:2

Table 9. Distribution of the neonates by their birth weight (N=88)

Birth weight category (kg)	Frequency (n)	Percentage
Low birth weight (<2.5)	12	13.6
Normal (2.5 and above)	76	86.4
Total	**88**	**100.0**

Table 9 shows that 13.6% of the newborns were low birth weight infants and the remaining 86.4% were of normal weight

Table 10. Early neonatal complications among the babies (N=88)

Early neonatal complications	Frequency (n)	Percentage
Hypoglycaemia		
Yes	5	5.7
No	83	94.3
NICU admission		
Yes	13	14.8
No	75	85.2

Table 10 shows that neonatal complications with NICU admission were present in 14.8% neonates. Among the complications, hypoglycemia was present in five neonates. The other complications were undescended testes, small PFO shunting, etc. There was one neonatal death among the newborns. APGAR score at 1 minute and 5 minute was 7 or above among all the newborns. Maternal complications were observed in none of the mothers.

Table 11. Association of Hypo/Hyperthyroidism with low birth weight of the neonate (N=88)

Hypo/Hyperthyroidism	Low birth weight (kg)		p value
	Yes n (%)	No n (%)	
Yes	2 (11.1)	16 (88.9)	0.726
No	10 (14.3)	60 (85.7	

Table 11 shows that there was no significant association between the prevalence of Hypo/Hyperthyroidism and low birth weight of the neonates (p=0.726).

Table 12. Association of Hypo/Hyperthyroidism with NICU admission (N=88)

Hypo/Hyperthyroidism	NICU admission		p value
	Yes n (%)	No n (%)	
Yes	2 (11.1)	16 (88.9)	0.624
No	11 (15.7)	59 (84.3)	

Table 12 shows that there was no significant association between the prevalence of Hypo/Hyperthyroidism and NICU admission of the neonates (p=0.624).

Table 13. Association of Hypo/Hyperthyroidism with congenital anomalies (N=88)

Hypo/Hyperthyroidism	Congenital anomalies		p value
	Yes n (%)	No n (%)	
Yes	2 (11.1)	16 (88.9)	0.738
No	6 (8.6)	64 (91.4)	

Table 13 shows that there was no significant association between the prevalence of Hypo/Hyperthyroidism and congenital anomalies (p=0.738).

Table 14. Association of Hypo/Hyperthyroidism with preterm delivery (N=88)

Hypo/Hyperthyroidism	Preterm delivery		p value
	Yes n (%)	No n (%)	
Yes	3 (16.7)	15 (83.3)	0.210
No	5 (7.1)	65 (92.9)	

Table 14 shows that the patients with hypo/hyperthyroidism had higher chance of preterm delivery (16.7%) when compared to the pregnant women without thyroid disorder but it was not found to be statistically significant (p=0.210).

Table 15. Association of Hypo/Hyperthyroidism with mode of delivery (N=88)

Hypo/Hyperthyroidism	Mode of delivery		p value
	Normal vaginal n (%)	Caesarean n (%)	
Yes	8 (44.4)	10 (55.6)	0.838
No	33 (47.1)	37 (52.9)	

Table 15 shows that there was no significant association between the presence of hypo/hyperthyroidism and mode of delivery among the pregnant women with GDM (p=0.838).

Table 16. Correlation between the fasting blood glucose and TSH levels (N=88)

	Correlation coefficient (r)	p value*
Fasting blood glucose (mg/dl) * TSH levels (µIU / ml)	0.091	0.401

***Pearson correlation**

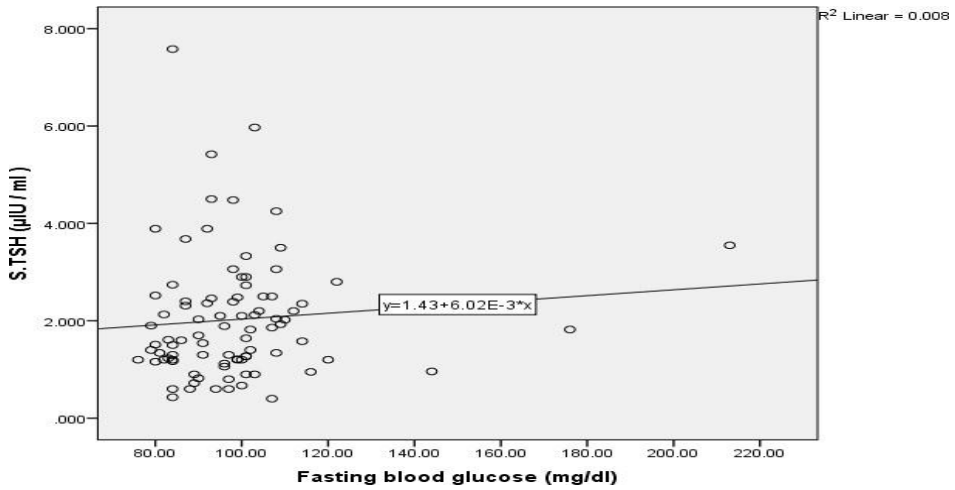

Figure 1. Scatter plot showing the Correlation between the fasting blood glucose and TSH levels (N=88)

Table 16 and Figure 1 show that there was no significant correlation between the fasting blood sugar and TSH levels among the pregnant women with GDM (r=0.091; p=0.401).

DISCUSSION:

Patterns of ontogeny of fetal cerebral cortex deiodinases and thyroid hormone receptors that begin by 7-8 weeks' gestation, can be an evidence that thyroid hormone is important in fetal neurodevelopment.[50] Thyroid dysfunction specially mild or subclinical hypothyroidism is associated with impaired neurodevelopment in the offspring and there is a link between this problem and mental retardation in the newborn.[51-53] Above and over this, an association between insulin-dependent diabetes mellitus and thyroid autoimmunity has long been recognized. Hence determining the prevalence of thyroid disorder among the pregnant women with GDM and the fetal and maternal complications due to the thyroid disorder in GDM was of utmost importance, as the perinatal complications due to thyroid disorder and GDM is considered to provide synergistic effect. The relationship between hypothyroidism and GDM is depicted in the image below.

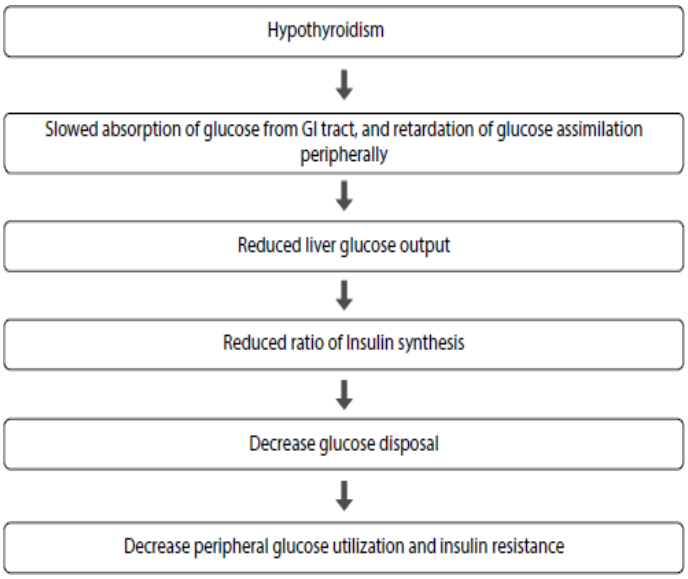

Figure 2 -Image showing the relationship between hypothyroidism and insulin resistance

Our study reported that the prevalence of hypo/hyperthyroidism among the pregnant women with GDM was 20.5% (95% CI: 12.9%-30.7%). Parveen H et al[22] in their study had found that the hypothyroidism was diagnosed in 33.3% of the study participants. There was a significant positive correlation between the TSH levels and blood glucose levels in their study. However, our study did not report any correlation between the fasting blood glucose levels and TSH levels. The reason could be due to smaller sample size in our study. On the contrary a study by Shahbazian H et al[20], the results showed that 25.6% of pregnant women with pre-gestational diabetes and 4.5% of women with GDM and 8.6% of control group had thyroid dysfunction. Similarly, a study by Ruas L et al[32] also reported a lower prevalence of thyroid dysfunction among the patients with GDM. However, in a study by Lal L et al[27], it was found that 42% had thyroid disorders (19% hyperthyroid and 23% hypothyroid) among those with GDM. The prevalence was much higher compared to our study findings. However, our study reports are supported by various other studies, which showed similar prevalence of thyroid dysfunction.[23,24] The difference could be due to the fact that type-1 diabetes mothers were included in some studies and in a way, mainly due to the smaller sample size across various studies. Several case control studies conducted elsewhere, had shown that the prevalence of thyroid disorders was significantly higher among the pregnant women with GDM when compared to the normal pregnant mothers.[23,24,29,31,33,42-44] However, a study by Shahbazian H et al[20] had shown that there was no statistically significant difference between thyroid dysfunction in GDM group and control group. Hence a wider section or a longer duration study group of pregnant women of Indian ethnicity would be more representative of the actual prevalence. With regards to perinatal complications, our study showed that there was no significant association between hypo/hyperthyroidism and caesarean delivery, pre term birth, low birth weight, congenital anomalies and NICU admission. Even in terms of APGAR score and hypoglycemia there was no significant difference between the groups. There was only one incidence of neonatal death on day 3 of life in view of septic shock on NICU admission in an extremely low birth weight of the neonate. Some of the studies have proved an association between the thyroid disorder and the perinatal complications. For instance, a study by Stohl HE et al[25], had reported that caesarean delivery was significantly higher in women with hypothyroidism versus women with hyperthyroidism ($p = 0.002$). However, the same study has reported that there were no differences between groups with respect to preterm delivery, postpartum hemorrhage or hypertensive disorders of pregnancy. Casey BM et al[36], in their study observed that the pre-term delivery was two-fold higher among the mothers with subclinical hypothyroidism. Neonatal complications and gestational diabetes were significantly more in overt hyperthyroidism group in a study conducted by Sahu

MT et al[38]. Some other studies have supported our study findings. A study by Karakosta P et al[21]had found that there was no association for pre-term deliveries between the groups. Similarly, a study by Hasani F et al[33], has found that no differences were found regarding the APGAR scores and anthropometric variables between the groups ($p>0.05$). The absence of significant statistical significance could have been due to the lesser sample size. Hence it is warranted that the clinicians must look at more diverse studies of thyroid dysfunction with GDM, to look for the clinical significance to arrive at a conclusion on the feto-maternal complications. One of the major limitations of the study is the lesser sample size and hence the issue of generalizability, which questions our external validity. Hence it would be safe to extrapolate our study results to the similar setting provided clinical significance exists. Moreover, the temporal association could not be made possible, owing to the nature of the study design and always there is a possibility of reverse causal association with thyroid disorders and GDM. Hence longitudinal studies with a larger sample size on a multicentric level would help to establish our study results on a robust level.

CONCLUSION

Our study concludes that the prevalence of hypo/hyperthyroidism among the pregnant women with GDM was 20.5% (95% CI: 12.9%-30.7%).There was no significant association between hypo/hyperthyroidism and caesarean delivery, pre term birth, low birth weight, congenital anomalies and NICU admission. Even in terms of APGAR score and hypoglycaemia there was no significant difference between the groups. There was only one incidence of neonatal death due to extremely low birth weight of the neonate. Longitudinal studies with a larger sample size on a multicentric level would help in better understanding of the association of thyroid dysfunction among GDM mothers and its perinatal complications.

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