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Study of biochemical changes in gestational diabetes mellitus

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Background: Pregnancy induces progressive changes in maternal carbohydrate metabolism. As pregnancy advances insulin resistance and diabetogenic stress due to placental hormone necessitate compensatory increase in insulin secretion. When this compensation is inadequate gestational diabetes develops. According to ADA, approximately 7% of all pregnancies are complicated by Gestational Diabetes Mellitus.
Aim: The aim of this study to estimate Glycated hemoglobin, Microlbumin and Lipid profile in Gestational Diabetes mellitus.
Materials and methods: 50 GDM cases were compared with age and sex matched 50 normal control groups for estimation of HbA1c, microalbumin along with lipid profile, and data obtained was statistically analysed.
Results: Fasting plasma glucose levels, plasma glucose levels 1 hour, and plasma glucose levels 2 hours after 75 gm oral glucose administration (oral glucose tolerance test) were significantly higher in patients with gestational diabetes as compared to controls. Glycated hemoglobin was observed to be statistically increased (p<0.0001) and cholesterol, triglycerides, increased significantly. Micro-albumin levels lies within normal ranges in GDM cases.
Conclusion: Our study shows abnormal glucose levels, an HbA1c, cholesterol and triglycerides level which plays a role in GDM. Early diagnosis of gestational diabetes provides safe baby and motherhood and in particular it will reduce the severity of complications, mainly foetal and maternal morbidity and mortality.

Keywords: Lipid profile, Glycosylated haemoglobin (HbA1c), Oral glucose tolerance test, Micro-albumin (MA), End Stage Renal Disease (ESRD) and Gestational diabetes mellitus (GDM)

Introduction

Gestational Diabetes Mellitus is "Carbohydrate intolerance of variable severity with the onset and first recognition during the present pregnancy" 1. It is a controversial clinical entity believed to be unmaking of a compensated metabolic abnormality characterized by relative insulin deficiency and increased insulin resistance.Moderate increase in blood glucose level particularly following ingestion of meal and changes in the levels of circulating free fatty acids, triglycerides, cholesterol and phospholipids.Diabetes is estimated to complicate 2-5% of all pregnancies of which 90% of those are detected during pregnancy2 i.e., Gestational Diabetes Mellitus and the rest are overt or pre-gestational i.e., Type 1 or Type 2.

As HbA1C levels closely correlates to blood sugar level in GDM, it is therefore a reliable indicator of overall glycemic control among the patients of diabetes in pregnancy. Also, elevated glucose levels have adverse effects on the foetus throughout pregnancy. As a result, meticulous glycemic controls required for optimal maternal and foetal outcomes. Similarly, Microalbuminuria is defined as urinary excretion of albumin that is persistently above the normal range of <30 mg although below the detectable range of conventional dipstick method. The development of Microalbuminuriais accepted as a poor prognostic sign during uncomplicated pregnancy and is associated with increasing maternal and perinatal morbidity and mortality. The hypertriglyceridemia described in GDM is directly related with the foetal macrosomia characteristic of this pathology and a positive correlation between maternal Triglycerides levels and neonatal body weight or fat mass has been found in GDM

GDM is a heterogeneous disorder in which age, obesity and genetically determined insulin resistance all contribute to the severity of disease.

The hyperglycemia in these patients appears to be a consequence of an increase in hepatic glucose production and peripheral insulin resistance.In Indian context our women have 11 fold increased rate of developing intolerance during pregnancy when compared to Caucasian women. Among the ethnic groups in south Asian countries, Indians have the highest rate of GDM. The recent data shows 6.5% prevalence of GDM in our country.India falls under moderately high risk group, with the advent of western life style, incidence of type II DM is raising precipitously. So number of women with GDM is also raising, hence it needs this study.

Aims and Objectives

According to ADA, approximately 7% of all pregnancies are complicated by Gestational Diabetes Mellitus. It is one of the major endocrine abnormality which represent the largest unique young women at high risk for adverse effects of abnormal glucose tolerance towards maternal and foetal outcome. Pregnancy is the special situation, as far as the pregnancy is concerned in which potential adverse effects on the foetus and mother is of paramount importance and should be clearly identified. With this background, a case control study was undertaken in GDM women. Abnormal lipid and lipoprotein concentrations in patients with GDM may lead to atherosclerosis. Lipoprotein (a) and or apolipoprotein(s) could be an index of atherogenic status. Dyslipidemia may contribute to accelerate the development of glucose imbalance and increase incidence of cardiovascular morbidity and mortality. For the management of patients with GDM and to prevent cardiovascular disease (CVD), it is important to characterize and quantify the types of lipids and lipoproteins. So in view of above facts, present study is planned with the following objectives:

Objectives To analyze and estimate the serum lipid profile alterations i.e. Total cholesterol, Triglyceride, VLDL cholesterol, LDL cholesterol in patients of GDM and compare with the age matched controls. To determine co-relation of ratio of Total cholesterol and HDL cholesterol and LDLC/HDLC as atherogenic biomarkers in GDM patients. To analyze and estimate HbA1C in GDM cases and compare with controls.To evaluate Micro-albumin levels in GDM cases and compare with controls. This study is aimed to observe the relationship between HbA1c, Micro-albumin levels and lipid profile with GDM cases.

Materials and Methods

The present study was conducted in the Department of Biochemistry, Rangaraya Medical College, Kakinada, and Andhra Pradesh, India. The present study was undertaken to determine biochemical changes in Gestational Diabetes mellitus patients. Venous blood was collected to analyse the parameters HbA1c, OGTT values, lipid profile and urine for micro-albuminafter the consent was obtained both from cases and controls. The study includes 50 pregnant cases between the age group of 18-40 years compared with 50 pregnant control groups having same age group

Inclusion Criteria: 1 No known diabetes in first-degree relative 2 No history of abnormal glucose tolerance 3. No history of poor obstetric outcome.

Exclusion Criteria: Pre-existing diabetes, corticosteroid therapy, History of Hypertension, known foetal anomaly, history of previous stillbirth, preterm delivery, history or clinical features suggesting chronic liver disease, Polycystic ovarian syndrome, pregnancy with anaemia, pregnancy with renal diseases, OGTT incomplete cases. Blood samples were obtained from the subjects after proper consent and explanation. Blood samples were centrifuged at 2000 g for 10 min.

Statistical analysis: The observed values were compared with control group for statistical analysis. All data were expressed as mean SD. Statistical analysis was done by student T test. Differences with 'p' value less than 0.05 were considered to be statistically significant. Analysis of Total Cholesterol by CHOD-POD method Triglycerides by GPO method Direct HDL-Cholesterol by POLYMER-DETERGENT METHOD LDL cholesterol by Friedewald's Formula VLDL cholesterol by Friedewald's Formula, HbA1C and Microalbumin by Nephelometry method.

Results

In the present study 50 Gestational Diabetes cases and 50 normal healthy pregnant of age 18 – 40 years were enrolled in case and control study.

Table 1: Levels of different biochemical parameters in Gestational Diabetes Mellitus cases and control group.

S. No	Parameters	Controls(n=50)	Cases(n=50)	p Value
1	FBS	77.96± 3.89	106.76 ± 5.47	<0.0001*
2	1st hr OGTT	115.96 ± 4.38	183.4 ± 4.19	<0.0001*
3	2nd hr OGTT	94.42 ± 2.46	156.36 ± 2.31	<0.0001*
4	T. Cholesterol	150.7 ± 9.11	199.38 ± 19.04	<0.0001*
5	T.G.L	160.86 ± 8.20	215.42 ± 20.04	<0.0001*
6	HDL	35.36 ± 2.06	30.32 ± 2.69	<0.0001*
7	LDL	82.64 ± 9.09	126.34 ± 18.37	<0.0001*
8	VLDL	32.3 ± 1.67	42.94 ± 4.06	<0.0001*
9	HbA1C	4.948 ± 0.309	6.144 ± 0.125	<0.0001*
10	Micro albumin	11.806 ± 3.439	12.32 ± 2.416	0.3893

Table 1 shows a significantly higher fasting blood sugar, HbA1C, Total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol levels in GDM Patients than the control group (p<0.0001). GDM patients had significantly lower HDLC levels when compared to the controls (p value < 0.0001). Micro albumin level shows no statistically significance in GDM Patients than the control group (p=0.389)

Table 2: Total cholesterol / HDL and LDL/HDL ratio in GDM patients and controls

Serum lipid	GDM patients n= 50	Controls n=50	P value	Inference
TC/HDL-C	6.56±0.06	4.26±0.01	<0.0001	Highly significant
LDL-C/ HDL-C	4.15±0.32	2.32±0.17	<0.0001	Highly significant

Table 3: Pearson correlation coefficient (r value) HbA1C in cases correlation with

S. No	Parameter	r Value
1	FBS	+0.918
2	1st hr OGTT	+0.277
3	2nd hr OGTT	+0.163
4	T. Cholesterol	+0.077
5	T.G.L	+0.1535
6	HDL	-0.249
7	LDL	+0.133
8	VLDL	-0.135
9	Microalbumin	0.018

In this table HbA1C is positively correlated with FBS, Totalcholesterol, TGL, LDL, VLDL and negatively correlated with HDL values

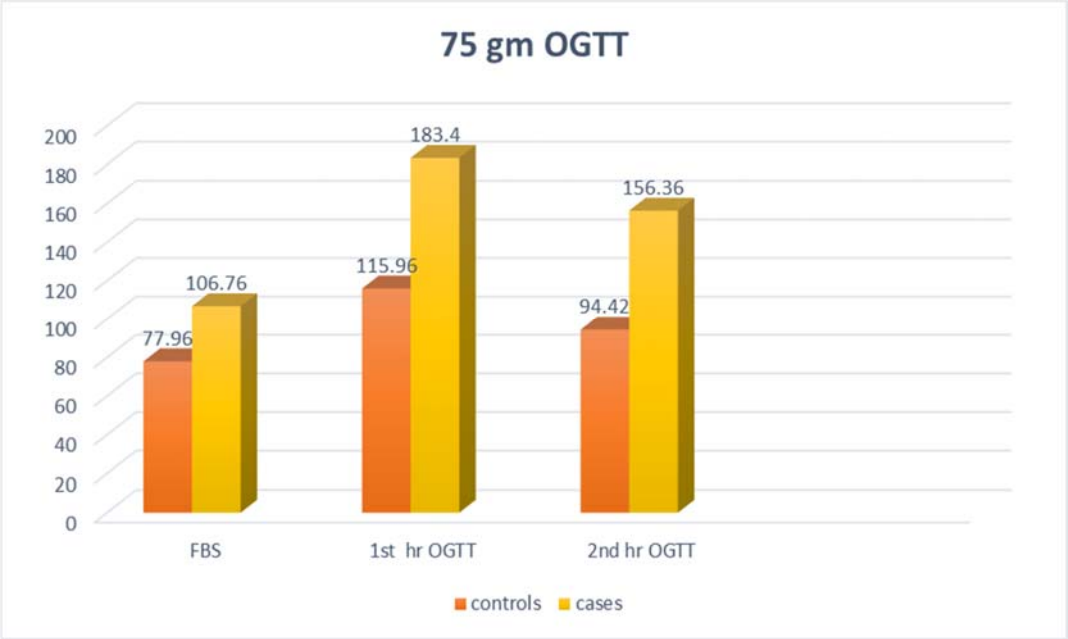

Fig 1. Comparison of 75 gm OGTT values between GDM patients & control groups

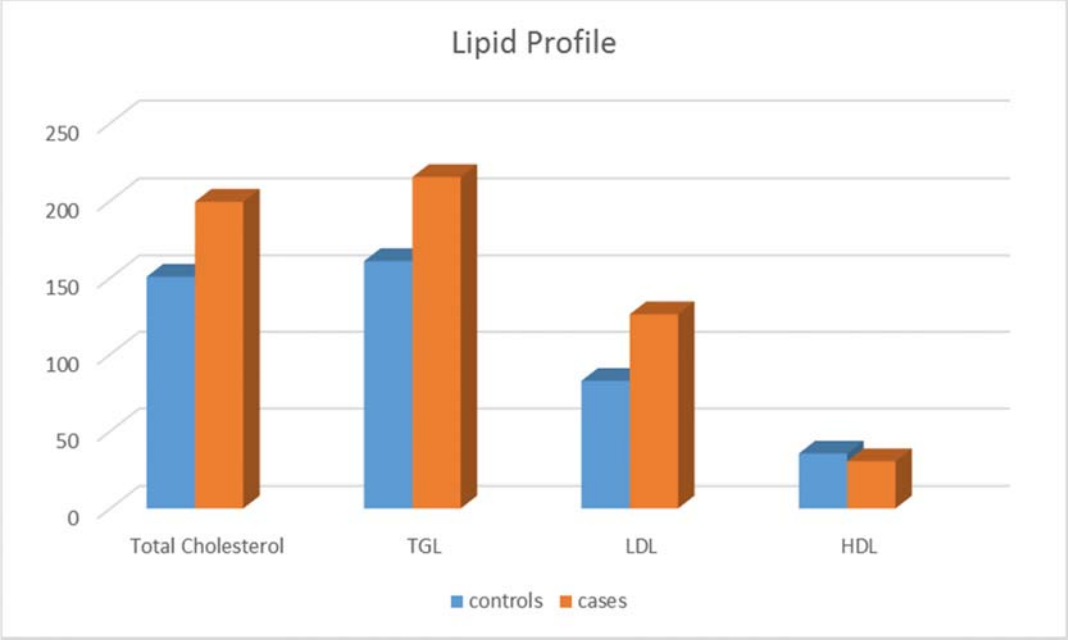

Fig 2. Comparison of serum lipid profile between GDM patients &control groups

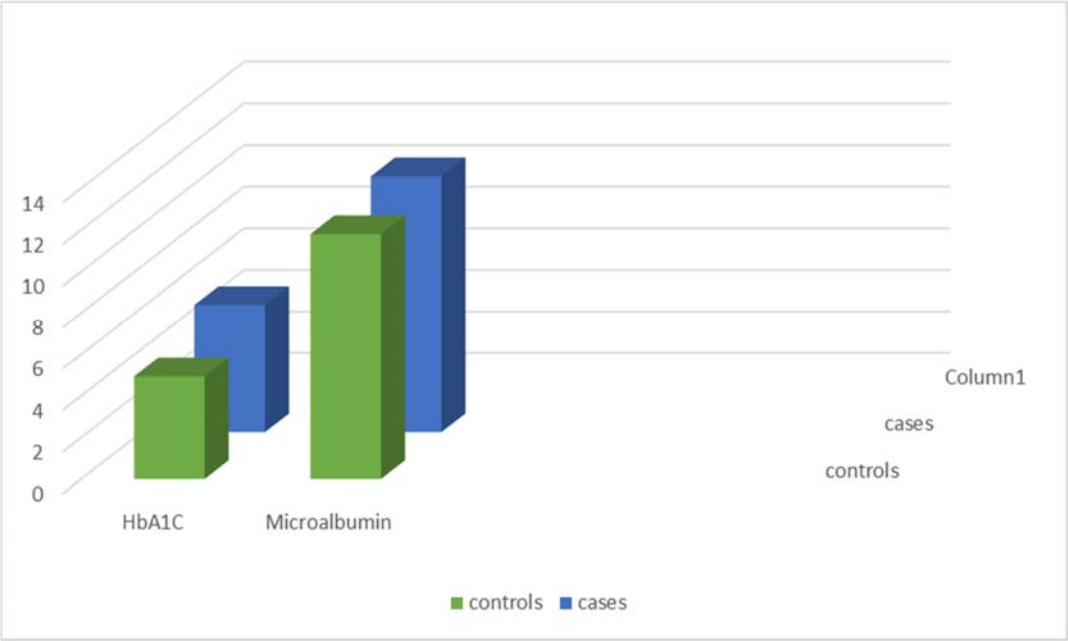

Fig 3. Comparison of HbA1C & Microalbumin between GDM patients and control groups

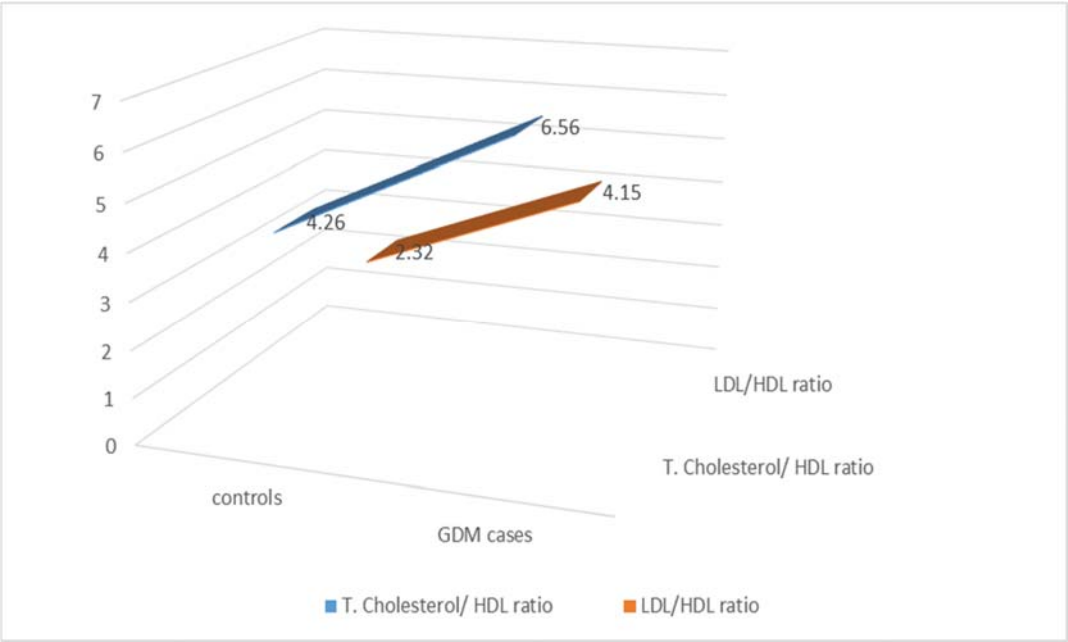

Fig 4: Mean variation of TC/HDL and LDL/HDL between GDM patients and controls

Discussion

Gestational diabetes mellitus (GDM) is a pregnancy complication that is becoming more prevalent with recent population trends in obesity and advancing maternal age. A diagnosis of GDM not only increases risk for maternal and foetal complications during pregnancy, but also significantly increases a women's risk of both type 2 DM and cardio vascular disease (CVD) [3]. in the postpartum. Even women with milder forms of abnormal glucose homeostasis during pregnancy, specifically gestational impaired glucose tolerance, are at increased risk, justifying the recent recommendations to tighten the diagnostic criteria for GDM. In the present study 100 subjects were included, of which 50 were GDM cases and 50 were normal healthy age and gender matched controls. In the study group, GDM cases were in the age group of 18 to 35 years. Controls were also of similar age group.In the present study it is shown that GDM patients had higher levels of HbA1C than the age matched controls and are highly significant ($p < 0.001$).The present study is in agreement with other similar studies are Farhena Ahmed. et.al (2013), Vijayam Balaji [4] et.al.(2007)

Glycemic control in normal pregnancy is characterized by 'accelerated starvation'. Accelerated starvation leads to lower fasting glucose levels. The normal decrease in maternal insulin sensitivity during pregnancy is beneficial for the growth of the fetus, since postprandial hyperglycemia enhances glucose transfer to the fetus. Enhanced glucose transfer to the fetus is referred to as 'facilitated anabolism' and is a result of enhanced maternal lipolysis, which occurs because of the inability of insulin to

suppress lipolysis in adipose tissue. However, these alterations in the metabolism of carbohydrates and lipids may lead to hyperglycemia and ketosis. Some hormones produced by the placenta (estrogen, cortisol, and human placental lactogen) can have a blocking effect on insulin, which usually begins about 20 to 24 weeks into the pregnancy. As the placenta grows, more of these hormones are produced, and insulin resistance becomes greater. Normally, the pancreas is able to make additional insulin to overcome insulin resistance, but when the production of insulin is not enough to overcome the effect of the placental hormones, GDM results. Most of the women reverting to normal after delivery, will suggest that the placenta is the major contributing organ in the development of GDM.The main cause of insulin resistance during GDM is post-cellular defect manifested by a decreased phosphorylation of tyrosine residues in insulin receptors and insulin receptor substrate-1, while serine phosphorylation is increased which inhibit insulin signalling from activating GLUT4 translocation[5]. Finally, GDM is probably produced by a complex and variable interaction of all the factors - pregnancy-induced factors, genetic, diet and environmental.

In our study urine micro albumin levels were measured in both GDM cases and controls which lies within normal ranges in GDM cases verses controls and statistically not significant. It might be due to our GDM patients had normal blood pressure so protected from microalbuminuria. It explains measurement of microalbuminuria in GDM cases seems to be a useful additional parameter for risk evaluation of hypertensive disorders.

In this study, it was observed that lipid profile parameters like (T.C, TGL, LDL and VLDL cholesterols) respectively were significantly elevated ($p<0.0001$) in GDM cases when compared with controls. But serum HDL-C was significantly ($p<0.0001$) decreased in GDM patients when compared with controls. Due to decrease lipolytic clearance of TGs and due to elevation of hepatic lipase activity which is thought to result in increased HDL catabolism.[6]This agreed with a study by Kalpana Rani and H.Asare- Anane *et al*. VLDL level increases when triglyceride level increases. The results of this study are in agreement with reports by Amraei and Azemati [7]. Aziz and Mahboob *et al.* [8]. The increased levels of triglycerides, total cholesterol and LDL cholesterols observed in GDMs is as a result of increase fat storage[9] and progesterone[10] in the second trimester of pregnancy, that act in a way to reset the lipostat in the hypothalamus leading to increase in the lipids concentration. Triglycerides appear to affect cardiovascular risk in several ways. They are the metabolic disarray of elevated triglycerides, low HDL-C, and small dense LDL (sd LDL) that characterizes atherogenic dyslipidemia which play a major role in overall cardiovascular risk. The triglyceride rich lipoproteins chylomicrons, VLDL and their remnants appear to be present in atherosclerotic plaque, indicating that the cholesterol in TG-enriched lipoproteins may directly contribute to atherosclerosis.

HDL cholesterol levels for the GDM case were significantly lower than the controls. The results of this study, is however consistent with a report by Aziz and Mahboob, who reported significantly lower HDL levels in GDM compared with normal pregnant control women. Amraei and Azemati and Koivunen *et al.* [11]. also reported significantly lower HDL levels in pregnant women with impaired glucose tolerance than the controls. HbA1c shows positive correlation with Total cholesterol, LDL and triglyceride in GDM cases and negative correlation with HDL because lipoproteins are known to undergo glycosylation which are harmful in two ways 1) Halflife of glycosylated HDL is decreased and glycosylated LDL stays longer in circulation 2) glycosylated lipoproteins are immunogenic and could damage the arterial endothelium. Atherogenic index of plasma (AIP) is statistically significant in GDM pts ($p<0.0001$) when compared to controls as shown. This significant rise suggests atherogenic effects of oxidized LDL. And is a significant indicator contributing to the risk of heart disease. The increased significance is directly proportional to increased risk of developing ischemic heart disease and vice versa.

Conclusion

GDM is a prevalent and potentially serious condition that may lead to adverse effects in both mothers and neonates. It is associated with pre-eclampsia, increased caesarean rates, and macrosomia. The detection and treatment of this condition reduces the risks for the mothers as well as for babies.

The present study was conducted in GDM cases to estimate the various biochemical parameters like FBG, HbA1C, microalbumin and lipid profile.

Our study shows normal micro albuminuria. As GDM subjects had normal blood pressure or adequately treated for their HTN. MA is considered an early marker of proteinuria, a risk factor for ESRD. The primary determinants of ESRD in these people are HTN and DM. Increased FBG in GDM cases verses controls is due to gestational impaired glucose tolerance Increased triglycerides is due to decrease activity of endothelial insulin dependent lipoprotein lipase activity resulting diminished triglyceride clearance and excess (on hepatic VLDL secretion) insulin action may underline raised serum triglycerides. That insulin resistance and compensatory hyperinsulinemia are associated with atherogenic plasma lipid profile – increased triglyceride and decreased HDL. High triglycerides may contribute to additional pathological process including increased coagulability, impaired fibrinolysis, impaired endothelial function[12], and increased inflammation.

Increased LDL levels in GDM cases are due to greater glycation of LDL and are more prone for oxidation. Decreased HDL is due to increased glycation of Apo AII, which accelerates HDL catabolism[13] Atherogenic index of plasma is calculated as ratio of Total cholesterol/HDLC it has been used as an indicator to predict the risk of atherosclerotic episodes[14] in GDM cases and then predisposed to accelerated development of cardio vascular diseases (CVD) in later life.

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