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Hypertophic cardiomyopathy in infant diabetic mother and glycated albumin in their mothers

Mohamed Ahmed Ali Selim
Resident of pediatrics in Rowd Al-Farag Hospital, Egypt
Corresponding author email: drmohamedselim88@gmail.com

Mohammad El-Sayed Tawfik
Lecture of Pediatric medicine, Faculty of Medicine- Suez Canal University Hospital, Egypt

Mohamed Ossama
Lecture of clinical pathology, Faculty of Medicine- Suez Canal University Hospital, Egypt

Abdelmoneim Khashana
Professor of pediatrics, Faculty of Medicine- Suez Canal University Hospital, Egyp

Engy Khedr
Researcher

***Abstract*---**Background: Hypertrophic cardiomyopathy represents a co-morbidity in infants. It is characterized by thickening of one or both of the ventricular walls including the interventricular septum in addition to systolic and diastolic dysfunction. Gestational diabetes mellitus (GDM) with poorly controlled glycemia is associated with poor pregnancy outcomes. However, adequate markers for glycemic control in GDM have not been fully evaluated. Hypertrophic cardiomyopathy represents a co-morbidity in infants. It is characterized by thickening of one or both of the ventricular walls including the interventricular septum in addition to systolic and diastolic dysfunction. Summary: In summary, we demonstrated the clinical usefulness of GA and GA/HbA1c in monitoring GDM in late pregnancy and predicting infant complications of GDM. Our data suggested that the use of GA and GA/HbA1c in combination with conventional glycemic control indices might be useful for good glycemic control during pregnancy, although our results need validation in larger, better-designed studies.

***Keywords*---**Glycated Albumin, Diabetic, Pregnant, Hypertrophic Cardiomyopathy, Gestational diabetes.

Introduction

Hypertrophic cardiomyopathy represents a co-morbidity in infants. It is characterized by thickening of one or both of the ventricular walls including the interventricular septum in addition to systolic and diastolic dysfunction. It is found in 40% of infants who are born to diabetic mothers, which causes symptoms in 5% (1). This cardiac complication in the infant has also been referred to as pathological ventricular hypertrophy to avoid confusion with the autosomal dominant form of congenital hypertrophic cardiomyopathy (2).

Maternal Diabetes increase the risk of maternal-fetal complications(Melchior et al. 2017) especially in the first trimester, maternal hyperglycemia can cause diabetic embryopathy resulting in major birth defects and spontaneous abortions. During the second and third trimesters, maternal hyperglycemia can cause fetal hyperglycemia, hyperinsulinemia, hypocalcemia, polycythemia, hyperbilirubinemia, myocardial hypertrophy, delayed lung maturation, and large-for-date status (3) many studies shows increased maternal blood glucose level is associated with macrosomia, fetal morbidity and subsequent complications in the neonatal period (4).

Maternal blood glucose passes the placental barrier according to the concentration gradient that can reach up to 234 mg/dl in the fetal circulation causing fetal hyperglycemia which increases insulin secretion from the fetal pancreas and this is called fetal hyperinsuliaemia (5). Fetal hyperinsulinaemia in response to maternal hyperglycaemia is suspected to be the cause of hypertrophic cardiomypathy (HCM) in infants of the diabetic mothers (1).

Glycated hemoglobin (HbA1c) is the current gold standard as glycemic control indicator because it reflects blood glucose levels during the previous one or two months (6) The Scottish Intercollegiate Guideline Network (SIGN) Guideline (Management of Diabetes in pregnancy) recommends maintenance of HbA1c levels as near to the non-diabetic range (81.0–126 mg/dl) (7). Glycated albumin (GA) is used instead of HbA1c recently. It is a ketoamine formed by nonenzymatic glycation of serum albumin (8) and considered as an independent marker that predicts infant complications and monitors glycemic control in pregnant women with diabetes or gestational diabetes (9).

Glycated Albumin reflects changes in plasma glucose within 2-3 weeks (10). HbA1c levels are dependent on hemoglobin so it is normally increased in late pregnancy due to Iron deficiency anemia while glycated albumin (GA) is not correlated with haemoglobin (11). So it is expected to replace HbA1c as the standard glycemic control indicator in the near future (10). However glycated albumin is affected by albumin metabolism so albumin metabolism can affect the result of the test.

This study was conducted to assess the correlation between maternal Diabetes and Hypertrophic cardiomyopathy in neonates using glycated albumin (GA) as an indicator for glycemic control to improve the neonatal outcomes of diabetic mothers and to confirm the utility of glycated albumin as a marker of glycemic control during pregnancy.

Hypertrophic Cardiomyopathy

Definition and Epidemiology of Cardiomyopathy

The official definition of cardiomyopathy by the American Heart Association in 2006 is as follows; "Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic". Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, which may lead to cardiovascular death or progressive heart failure-related disability" (12).

Classification of cardiomyopathy

There are many classifications of CM based on many characteristics. One of the most used classifications is presented in table 2. Other classification that is also commonly used is division into primary and secondary forms. Other classification that is used by the American Heart Association (AHA) is the division of CM into primary and secondary forms (13).

Primary CMs:

Primary CMs can be further divided into genetic, mixed (genetic and mostly non-genetic) or acquired. Genetic CMs hypertrophic CM (HCM), arrhythmogenic right ventricular CM/dysplasia, left ventricular noncompaction, conduction system disease and ion channelopathies. Mixed CMs encompass dilated CM (DCM) and primary restrictive non-hypertrophied CM. Acquired CMs include inflammatory CM (myocarditis), stress CM (Tako-Tsubo), peripartum CM, tachycardia-induced CM (Tachy-CM) and CM in infants of insulin-dependent diabetic mothers.

Secondary CMs:

Secondary CMs can occur due to a lot of disease including; Infiltrative diseases such as Hurler's disease; endocrine pathologies like diabetes mellitus and; autoimmune disorders (12).

Definition and Epidemiology of Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined as hypertrophied non-dilated ventricle without any other disease that cause hemodynamic disturbance that may produce a pressure on the wall as hypertension. HCM represents 42% of cardiomyopathy cases in childhood with incidence of 0.47/100.000. The incidence of HCM was found to be 69% more common in males, occurred at 10 times the rate in subjects under age 1 (14).

In children, ventricular hypertrophy is considered clinically present when septal wall thickness is above at least two- to three-times the age- and sex-adjusted SDs of the mean of a normative population. While in neonates HCM is considered a rare heart condition in which there is a myocardial injury in the absence of primary sepal, valvular or great vessels anomalies. Fetal presentation of cardiomyopathies is usually uncommon but it has very bad prognosis with high mortality. Moreover, about 40% of infants with symptomatic cardiomyopathy at the time of presentation need heart transplantation or die within 2 years (15).

Table 1: Phenotypically-based classification of hypertrophic cardiomyopathy

Familial Hypertrophic Cardiomyopathy	➢ Sarcomeric Hypertrophic Cardiomyopathy ➢ Maternally-Inherited Hypertrophic Cardiomyopathy Syndromes
Syndromic Hypertrophic Cardiomyopathy	➢ Noonan's Syndrome ➢ Beckwith-Wiedemann Syndrome ➢ Cardio-facial-cutaneous syndrome ➢ Costello syndrome ➢ Lentiginosis (LEOPARD Syndrome)
Neuromuscular disease	➢ Friedreich's Ataxia
Metabolic Disorders	➢ Anabolic steroid therapy and abuse ➢ Carnitine deficiency (Carnitine palmitoyl transferase II deficiency, carnitine-acylcarnitine translocase deficiency) ➢ Fucosidosis type 1 ➢ Glycogenoses type 2, 3 and 9 (Pompe's disease, Forbes' disease, Phosphorylase kinase deficiency) ➢ Glycolipid lipidosis (Fabry Disease) ➢ Glycosylation disorders ➢ I-Cell disease ➢ Infant of diabetic mother ➢ Lipodystrophy, total ➢ Lysosomal disorders (Danon's Disease) ➢ Mannosidosis ➢ Mitochondrial disorders (multiple forms) ➢ Mucopolysaccharidoses type 1, 2 and 5 (Hurler's syndrome, Hunter's syndrome, Scheie's syndrome) ➢ Pre and postnatal Corticosteroid therapy

HCM measurement

Newborns with HCM usually have no symptoms thus; recognition of HCM is usually established during evaluation for a murmur or for who have heart failure or ventricular arrhythmia, which include symptoms like excessive sweating, difficulty feeding, or poor growth. On the other hand, older children are diagnosed during investigations for murmurs, symptom, electrocardiographic abnormalities, or heart murmur, or for family screening following the diagnosis of HCM in a relative (16).

Table 2: Normative M-mode echocardiographic data for neonate according to body weight

Body weight (kg)	RVAWd (mm)	RVDd (mm)	IVSd (mm)	IVSs (mm)	LVDd (mm)	LVDs (mm)	LVPWd (mm)	LVPWs (mm)	AoD (mm)	LAD (mm)
2.0–2.5	1.3	3.3	1.7	2.4	11.7	6.6	1.6	1.8	5.6	6.6
	2.5	7.6	3.0	4.0	15.8	9.6	2.7	2.7	7.4	10.6
	3.6	11.8	4.3	5.5	19.9	12.6	3.8	3.7	9.1	13.0
2.5–3.0	2.0	5.4	2.2	2.4	12.9	7.1	2.2	2.7	6.2	8.0
	2.9	8.6	3.7	4.2	16.0	9.9	3.3	3.9	8.0	10.8
	3.7	11.8	4.5	6.0	19.1	12.6	4.3	5.2	9.8	13.6
3.0–3.5	2.2	7.0	2.7	2.6	12.0	7.8	2.5	2.8	6.6	8.6
	2.9	8.9	3.7	4.4	16.1	11.0	3.5	3.9	8.3	10.8
	3.7	10.8	4.7	6.0	20.3	14.2	4.4	5.1	10.0	13.8
3.5–4.0	2.3	6.2	2.6	3.3	13.0	8.5	2.4	2.9	7.1	8.3
	3.0	9.0	3.6	4.6	16.9	11.7	3.5	4.1	8.6	11.5
	3.6	11.7	4.6	5.2	20.8	14.9	4.7	5.3	10.0	14.7
4.0–4.5	2.4	6.5	2.7	3.7	14.2	8.6	2.5	3.7	6.8	9.9
	3.0	9.4	3.8	5.0	18.2	12.1	3.6	4.7	9.3	13.2
	4.0	12.2	5.2	6.3	22.1	15.7	5.2	5.7	11.7	16.4

AoD = aortic root dimension; IVSd = interventricular septum end-diastolic thickness; IVSs = Interventricular septum end-systolic thickness; LAD = left atrium dimension; LVDd = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameters; LVPWd = left ventricular posterior wall end-diastolic thickness; LVPWs = left ventricular posterior wall end-systolic thickness; RVAWd = right ventricular anterior wall end-diastolic thickness; RVDd = right ventricular end-diastolic diameter
The mean value is the middle number, the value above −2SD and the value below +2SD

First of all, family history should be an important feature for making the diagnosis of HCM, attention mainly on previous cardiomyopathy, rhythm problems, sudden cardiac or unexplained death, cardiac surgery or presence of other cardiac disease in relatives. The diagnosed is based on the clinical evaluation, identification of characteristic physical findings, a complete patient and family history, and a variety of specialized tests (17).

The most important tests may include x-ray studies (e.g., computed tomography), electrocardiography (ECG), or echocardiography. The EKG, which records the electrical activities of heart muscle, may reveal abnormal electrical patterns (arrhythmias).The echocardiogram is the test of choice in the condition. The echocardiogram is a definitive noninvasive assessment tool which provides information about ventricular size, wall thickness, systolic and diastolic function, outflow obstruction, and valvar insufficiency in nearly all children (18).

In case of HCM, the echocardiogram shows characteristic thickening of the heart. Furthermore, it defines the muscle abnormality and determines if there is scar in the heart a cardiac magnetic resonance imaging (MRI) may be ordered. Three additional tests that may be performed for evaluation of heart disease are cardiac catheterization, cardiac magnetic resonance imaging (MRI) and radionuclide ventriculogram (19).

Cardiac catheterization provide the ability to evaluate the oxygen content, measure blood pressure in the heart, evaluate heart function, obtain small samples of myocardial tissue for microscopic evaluation, or thoroughly identify certain anatomical abnormalities. Cardiac MRI is similar to echocardiography but it uses magnetic waves instead of sound waves. Small amounts of low-dose radioactive materials (tracers) are injected during radionuclide ventriculogram into a vein and then into the heart. Then special cameras produce pictures of the heart by an energy released from the Tracers. The children with cardiomyopathy should have specific investigation to recognize any possible associated disorders such as metabolic disorders, as the cardiomyopathy may be a part of a larger genetic disorder (20).

In the newborns of diabetic mothers, HCM presents as a complication of gestational or previously existing maternal diabetes. In the classic assessment, the fetus's iastolic function uses Doppler analysis of both the mitral and tricuspid valves inflow signals. The pulsed Doppler waveforms are biphasic and obtained at the tip of atrioventricular valves, with E-wave that presents the early ventricular filling volicity; and the A-wave that indicates the flow volicity during atrial contraction in the pre-systole. Normally, when the E/A ratio during pregnancy is under 1, this indicates that the fetus's myocardium is relatively stiff in compare to normal newborns. On the other hand, the increase in the inversion of the E/A is related to ventricular diastolic dysfunction.

Echocardiographic findings seen in HCM

The cause of the cardiac enlargement reported in infants of diabetic was considered a problem until the emergence of improved echocardiologic techniques in the 1970s. Since then, many reports have described the echocardiologic findings of the newborns of diabetic mother who have cardiomyopathy. These findings include the following:

1. When compared with control groups of newborn infants, infants have significant thickening of interventricular septum (IVS), the right ventricular and the left ventricular free walls(1).
2. Among the most severely affected infants, the septum is disproportionately thickened, and the IVS to LV free wall ratio usually exceeds 1.5 (21) .
3. The internal dimensions of both the RV and LV chambers usually are not enlarged and do not differ from those of normal infants(22).
4. The subgroup of the infants with clinical findings of congestive heart failure (CHF) tends to have the most marked findings of myocardial and septal hypertrophy. So, the most severely affected infants who suffered from significant hypertrophic myocardial changes were significantly more likely to develop symptoms of CHF(23) .
5. As stated, the symptomatic infants with clinical findings of CHF are more likely to have echocardiographic evidence of LV outflow tract obstruction. The echocardiographic findings suggestive of outflow tract obstruction include systolic anterior motion of the mitral valve so that it comes into apposition with the septum, midsystolic closure or fluttering of the aortic valve leaflets, and a measurable LV outflow diameter of less than 5 mm(24).
6. Echocardiographic indices of systolic LV function (percent of shortening fraction) in the infants usually are reported to fall in the normal to above

normal range. Moreover, the subgroup of them with symptoms of CHF has LVs that appear to be unusually hypercontractile. Although some IDMs with congestive heart failure do have truly diminished LV function, this finding appears to be atypical (25).

7. Using pulsed Doppler ultrasound, the estimation of cardiac output and LV stroke volume have been reported to be reduced significantly in hose infants with septal hypertrophy. The relationship is inversely related as follows; infants of diabetic mothers with the greatest degree of septal hypertrophy showed tendency to have the lowest estimates of LV stroke(26).

In summary, the echocardiographic findings in the IDM demonstrate generalized myocardial hypertrophy with a disproportionate thickening of the septum. Symptomatic IDMs in general have the most significant hypertrophic changes and are more likely to have evidence of LV outflow tract obstruction and enhanced contractility and to have evidence of reduced cardiac output. Based on these echocardiographic findings, the characteristic chest radiographic finding of cardiac enlargement likely represents myocardial hypertrophy rather than dilation of the cardiac chambers significantly.

Myocardial hypertrophy in newborns of diabetic mothers

The most frequent cause of myocardial hypertrophy that presents prenatally is observed among the fetuses of diabetic mothers. In about 25% of the cases, it presents as a complication of gestational or previously existing maternal diabetes. Emerged evidence showed that the left ventricular diastolic function is impaired in fetuses with myocardial hypertrophy (27).

Also the ventricular septum is preferentially affected, both the left and right ventricular walls may be involved (Figure 7). In-utero, the manifestations are not often clear, however, the hypertrophy can be easily detected by standardized fetal echocardiograph by comparing septal thinking with an established nomograms. A septal thickening more than two standard deviations for a given gestational age is considered abnormal (28).

Histological features include both increased nuclear and sarcolemmal mass, as well as the vacuolization of hyperplastic myocardiocytes. The exact cause of myocardial hypertrophy in fetuses for diabetic mothers remains unclear. However, fetal hyperinsulinemia is considered as a suggestive cause. Moreover, the association between high insulin level in the amniotic fluid and HCM has also been demonstrated recently. Giving that information, post-natal regression of this cardiomyopathy is dependent on normalizing the insulin levels. Moreover, the increased thickness of the septum during pregnancy is thought to have association with the increased levels of IGF-1 (29).

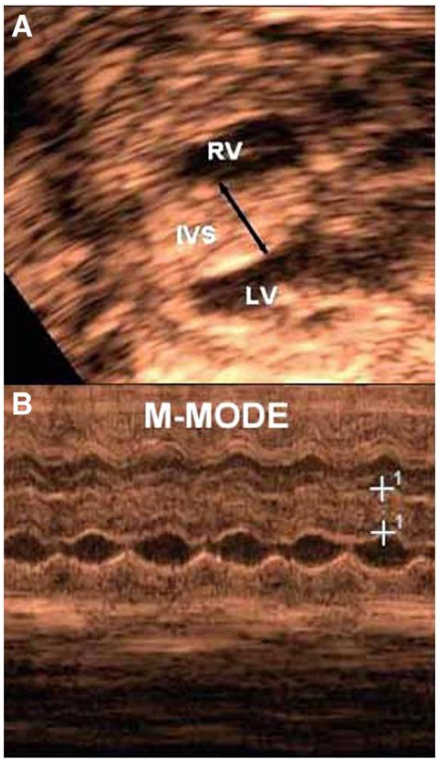

Figure 1: A: Cross-sectional four-chamber view from a 33-week fetus of a diabetic mother with severe septal hypertrophy. B: M-mode tracing obtained from the same case showing increased thickness of the interventricular septum (distance between markers = 6.3 mm). RV = right ventricle; LV = left ventricle; IVS = interventricularseptum.

Prognosis

In infants of diabetic mothers, HCM is usually reversible and frequently mild or asymptomatic. However, it can be severe leading to fetal or neonatal death. Most often, the symptomatic infants require only supportive care with supplemental oxygen, but β-adrenergic blockers (like propranolol) may be needed to improve the ventricular output. Hyperinsulinaemia in infant's resultant from maternal hyperglycaemia has been implicated as the cause of HCM in infants of the diabetic mothers (2).

In non-resolved HCM, the survival percentage for pediatric HCM is about 97% at five years and then 94% at 10 years from presentation. The age at death in children with HCM peaks before one year of age. The main cause of in death Cardiomyopathy is the Heart failure, although SCD also can occur. In children with HCM who survive infancy, sudden cardiac death is a very common complication. The incidence of sudden cardiac death in children and adolescents is 6.2 /100,000. Generally, 36% of cases of pediatric sudden cardiac death cases are related to HCM compared with 3% DCM (18).

The worst prognosis was for children less than one year of age, which had heart failure, low weight, lower left ventricular fractional shortening or end-diastolic ventricular septal thickness or higher left ventricular end-diastolic posterior wall thickness at the time of diagnosis. In a PCMR analysis, the risk of death or heart transplantation was significantly increased when two or more risk factors were present. However, most affected infants are clinically asymptomatic and have resolution of the hypertrophy within months (27).

Diabetes Mellitus

Diabetes mellitus overview

Diabetes mellitus (DM) is a common problem in eastern society and is becoming common in the rest of the world. It is not a disease but a syndrome made up of several diseases with similar symptoms, signs, and complications but with different etiologies. It was classified by etiology and pathology as type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), "other", and gestational diabetes mellitus (GDM). The class "other" consists of many problems but makes up less than 1% of the people with diabetes and will not be further discussed here. GDM affects about 5% to 6% of pregnant women and in most instances is an early form of T2DM. T1DM accounts for 5% to 10% of people with diabetes and T2DM affects the remainder, ie, about 90% of those with the disease (30).

Classification of DM

I. Type I Diabetes Mellitus:
This type accounts for only 5–10% of those with diabetes and is also known as insulin-dependent type of diabetes (IDDM) or juvenile-onset diabetes. It arises as a result of cellular-mediated autoimmune which targets and destructs the β-cells of the pancreas. The presence of autoantibodies against the pancreatic islet cells is the hallmark of type 1 diabetes (31). Markers of the immune destruction of the β-cell include autoantibodies to islet cells, autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD, GAD65), zinc transporter protein (ZnT8A) and autoantibodies to the tyrosine phosphatases (IA2 and IA2β) are found in those with Type1 DM (32).

II. Type II Diabetes Mellitus:
Type2 diabetes develops typically after the middle age and accounts for more than 90% of adults with DM, most patients with type2 diabetes are adults, but it can also occur in children and adolescents, there is a stronger genetic component to type2 diabetes than to type1 diabetes (33). It is well-known by its relative deficiency in the level of insulin caused by pancreatic β-cell dysfunction as well as insulin resistance in the target organs. Recently, the global rise in obesity, sedentary lifestyles, and an ageing population has quadrupled the incidence and prevalence of type 2 diabetes making it the sixth leading cause of disability in 2019. Moreover, It is a pressing issue that leads to more socioeconomic pressures on the individual and overwhelming costs to global health economies (30).

III. Gestational Diabetes Mellitus (GDM):

Gestational diabetes mellitus (GMD) is defined as any degree of glucose intolerance that first started, or recognized during pregnancy. However, this definition ignores the possibility that glucose intolerance may have not been recognized before pregnancy, and so, the term hyperglycemia in pregnancy seems to be more accepted by the Endocrine Society. The American Diabetes Association (ADA) has classified GDB as diabetes diagnosed in the final two trimesters in women with no history of Diabetes type1 or 2 (34).

Consequences of Gestational Diabetes

The importance of understanding and preventing GDB lies on the wide consequences of GDM for both the mother and her fetus as follows:

1. The Mother

GDM increases the risk of bad outcomes on both short and long terms. It is associated with antenatal depression, preeclampsia, preterm birth, and cesarean section. Moreover, 60% of pregnant women with GDM develop type2 diabetes later on (35). On the other hand, other studies had shown that the vasculature of women who experienced GDM had is altered predisposing them to cardio vascular diseases (CVDs) (36).

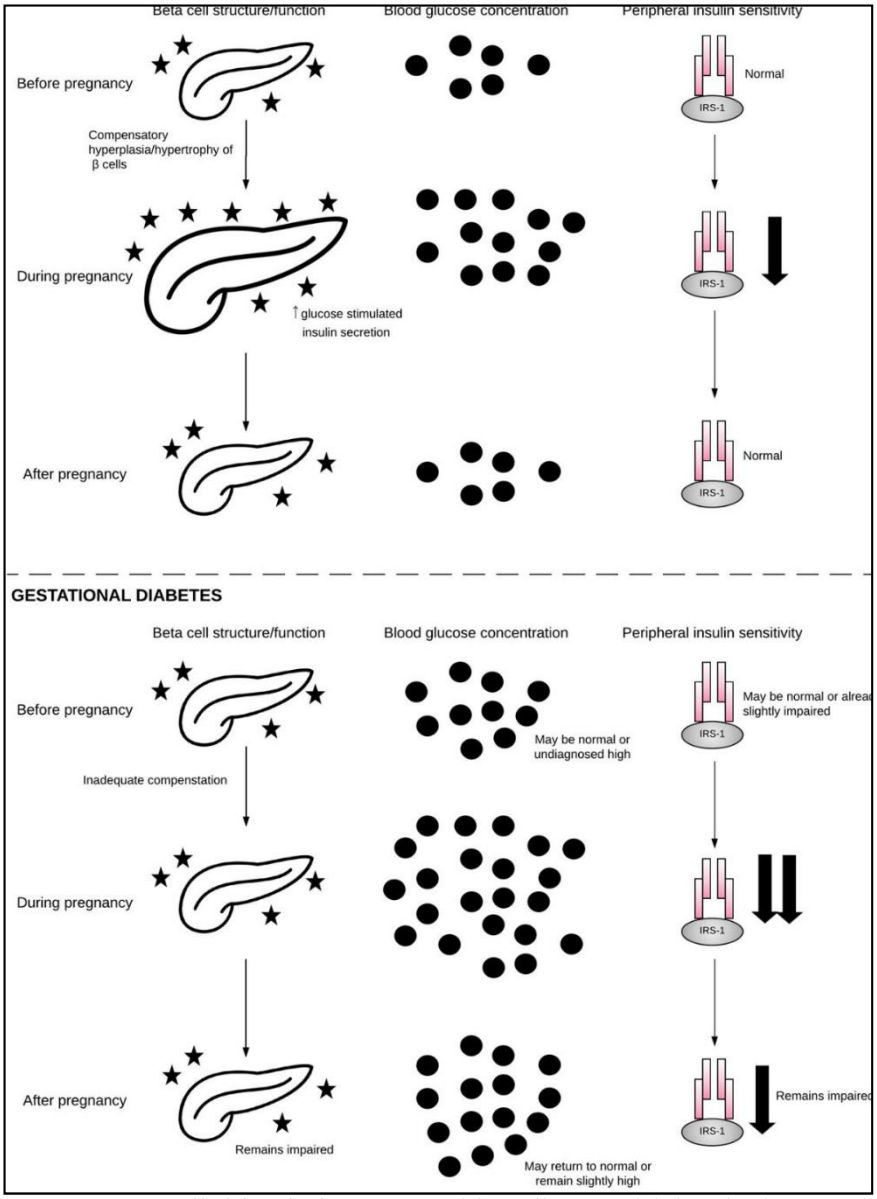

Figure 1: Beta cell, blood glucose, and insulin sensitivity during normal pregnancy and GDM

2. The Child

GDM also lead to both short and long term consequences for the fetus as the increased transport of glucose, amino acids and fatty acids stimulates the fetus to produce more insulin and insulin like growth factor 1(IGF-1). This may lead to fetus overgrowth represented as macrosomia, which in turn predispose to shoulder dystocia. Moreover, this excess in insulin production may lead to beta cell dysfunction and insulin resistance (37). When delivered, those babies have an increased risk of hypoglycemia as a result of their bodies' homeostasis on the mothers' hyperglycemia; all of this may predispose them to prolonged brain

injury. Moreover, emerged evidence has shown that GDM increases the risk of still birth. On the long term, those babies have an increased risk of developing T2DM and CVDs especially, hypertrophic cardiomyopathy (38).

Indicators of Glycemic Control

Plasma glucose measurement is considered as an important part of glycemic control during pregnancy; however, it is actually difficult to measure blood glucose in all patients. So, it is very important to use indicators of glycemic control such as HbA1c, glycated albumin (GA), fructosamine, and 1,5-AG to assess the glycemic control condition.

3. HbA1c

HbA1c is a ketoamine formed by binding between the aldehyde group of glucose and valine at the N-terminus of the hemoglobin β-chain. The life span of red blood cells is 120 d, therefore the HbA1c levels reflect the glycemic control status during the past 1 to 2 months. Those findings have been reported: 50% reflect plasma glucose level during the past 1 mo.; while 25% reflect plasma glucose level during the past 1 to 2 mo.; and 25% reflect plasma glucose level during the past 2 to 4 months (39). Clear evidence on the development and progress of complications has been reported during the Diabetes Control and Complications Trial (DCCT) study, and HbA1c evidently become a gold standard indicator of glycemic control (40) so, it is nesseary to maintainn glycemic control in pregnant women with DM or patients with GDM using HbA1c and SMBG as indicators (41).

4. Fructosamine

HbA1c is a glycation product of hemoglobin and GA is a glycation product of albumin on the other hand, fructosamine is the Universal name of all glycated proteins without specificity. As a result of wide spread of albumin (composing 60-70% of all the plasma proteins), the characteristics of fructosamine are pretty much similar to those of GA. Nevertheless, this method measures other glycated proteins as well; thereby, there is a problem that in case of myeloma as the fructosamine measured by this method is high (42). Moreover, it has been showed that fructosamine is associated with a larger intra-individual variability compared to HbA1c, with many disadvantageous for detecting a significant change (43). HbA1c is expressed as the ratio of hemoglobin and GA is expressed as the ratio of albumin; thereby, HbA1c and GA are not influenced by dilution of serum. Furthermore, fructosamine is influenced in dilutional anemia and by serum protein concentration; fructosamine measured by this method is apparently low.

5. Glycated albumin (GA)

GA is a ketoamine that is formed from binding between four lysine residues of albumin and glucose by non-enzymatic reaction. In other words, GA is similar to HbA1c as a compound, but the binding rate between albumin and glucose is 4.5 times higher than that between hemoglobin and glucose. Also Ga is the indicator of choice to evaluate the glycemic control in short period as the half-life of the albumin is about 14 day. Besides, the postprandial plasma glucose is reflected by GA more accurately than HbA1c (44). Evaluation of mean plasma glucose level at a time point closer to the time of consultation with a doctor and evaluation of postprandial plasma glucose level are important, and GA is useful in this respect. Moreover, we reported that GA is not affected by iron deficiency state or iron

deficiency anemia. Also It should be noted that evaluation of measured GA levels requires attention in some conditions such as nephrotic syndrome and abnormal thyroid function becouse of GA is influenced by albumin metabolism. Unlike fructosamine. Dilutional anemia during pregnancy does not affect GA (44).

The association between outcomes (neonatal complications and birth weight) and indicators of glycemic control (GA and HbA1c) is been analyzed by the Japanese Society of Diabetes and Pregnancy. This analysis was considered the upper limits in normal pregnant women (HbA1c: 5.7%; GA: 15.7%); for neonatal complications, the incidences of neonatal hypoglycemia, polycythemia, and respiratory disorder were found to be significantly higher in the group of women with GA of more than 15.7%. Moreover, reports shows that the group of women with GA of more than 15.7% have higher incidence of large-for gestational age compared with the group of women with GA of 15.7% or less. Furthermore, there was no significant increase in the incidence in the group of women with HbA1c of more than 5.7% compared with the group of women with HbA1c of 5.7% or less. Although a more accurate analysis should be made, GA is superior to HbA1c for prediction of perinatal complications (11).

Although a more accurate judgment should be made by ROC analysis for different cut-offs, GA is superior to HbA1c for prediction of perinatal complications. Furthermore, appropriate regression analysis is necessary to see if the indicator remains significant after eliminating the iron factors. As they demonstrated in their patients, if HbA1c is apparently high during the end stage of pregnancy, it may be misinterpreted that glycemic control has worsened and excessive insulin therapy may be performed, leading to hypoglycemia and increased incidence of perinatal complications of mothers and infants. Hence, management based on GA is essential during pregnancy also from the viewpoint of perinatal complications(45).

HbA1c in comparison to GA as indicator of glycemic control

The Japanese Society of Diabetes and Pregnancy reports that, HbA1c tends to decrease during the middle stage of pregnancy and increase during the end stage of pregnancy according to an analysis of 574 normal pregnant women; while GA decrease gradually toward the end stage of pregnancy (46). Japanese normal pregnant women had reported the range for HbA1c and GA which is 4.4% to 5.7% for HbA1c and 11.5% to 15.7% for GA. In general, there is a dramatic difference between the time course of HbA1c and GA during pregnancy, so which indicator of glycemic control is reliable? We investigated the effect of iron deficiency on HbA1c in 17 normal pregnant women. There are significant increase in HbA1c start from the middle stage of pregnancy from the middle stage of pregnancy (week: 20-23) to the end stage of pregnancy (week: 32-33) (4.7% ± 0.2% vs 5.1% ± 0.2%; $P < 0.0001$) (46).

On the other hand, there is no significant change s in GA. Mean corpuscular hemoglobin (MCH), transferrin saturation, and serum ferritin, which are indicators of iron deficiency, showed a decrease toward the end stage of pregnancy; there was a significant negative correlation between HbA1c and MCH, transferrin saturation, and serum ferritin. Furthermore, there was no significant

correlation between GA and MCH, transferrin saturation, and serum ferritin. Based on these findings, the iron deficiency progresses during the end stage of pregnancy in normal pregnancy, and therefore HbA1c level increases **(46)**. So, HbA1c may not be a trustful indicator of the glycemic control during pregnancy, especially at the end stage. Nevertheless, the increase of HbA1c may not occur if the pregnant women take in a sufficient amount of iron during pregnancy **(46)**.

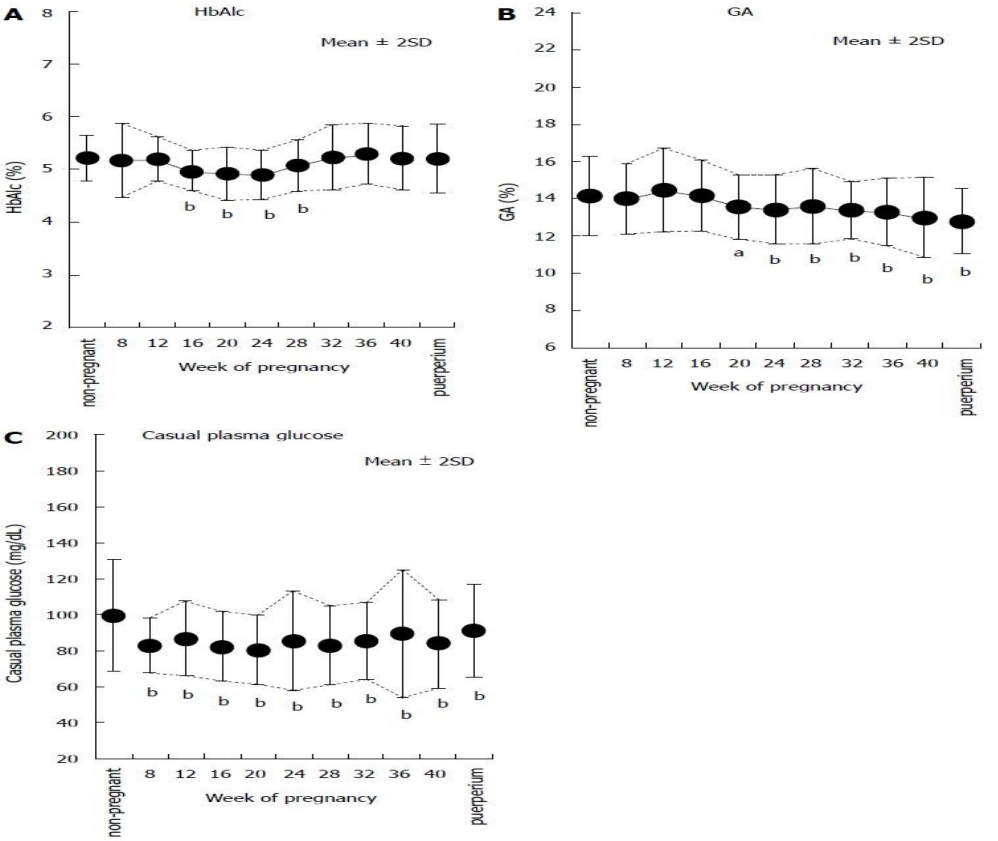

Figure 2: Time courses of indicators of glycemic control in normal pregnant women. The time courses of HbA1c (A), GA (B), and casual plasma glucose (C) in normal pregnant women are shown (modified from Ref.[73]). $^{a}P < 0.05$, $^{b}P < 0.01$ vs non-pregnant women. HbA1c: Hemoglobin A1c; GA: Glycated albumin.

Summary

Maternal hyperglycemia can cause diabetic embryopathy resulting in major birth defects and spontaneous abortions. Hypertrophic cardiomyopathy represents a co-morbidity in infants. It is characterized by thickening of one or both of the ventricular walls including the interventricular septum in addition to systolic and diastolic dysfunction. It is found in 40% of infants who are born to diabetic mothers, which causes symptoms in 5%. This cardiac complication in the infant has also been referred to as pathological ventricular hypertrophy to avoid confusion with the autosomal dominant form of congenital hypertrophic cardiomyopathy. Glycated Albumin reflects changes in plasma glucose within 2-3

weeks. HbA1c levels are dependent on hemoglobin so it is normally increased in late pregnancy due to Iron deficiency anemia while glycated albumin (GA) is not correlated with hemoglobin. So it is expected to replace HbA1c as the standard glycemic control indicator in the near future. However glycated albumin is affected by albumin metabolism so albumin metabolism can affect the result of the test.

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