INTRODUCTION

Diabetes mellitus is a common condition, affecting approximately 7% of pregnant women. Appropriate management has reduced morbidity and mortality ***(Zielinsky et al., 2009).***

Diabetes mellitus in pregnancy can cause many problems for the fetus as significant congenital disorders, risk of premature delivery and increased prenatal morbidity and mortality. In addition, it causes neonatal hypoglycemia, macrosomia and transient hypertrophic cardiomyopathy HCM (observed in up to 35% of fetuses) ***(Cimen et al., 2014).***

Approximately 3-6% of infants of diabetic mothers (IDMs) have congenital cardiac malformations. While 40% of infants of diabetic mothers have hypertrophic cardiomyopathy (HCM) that may or may not be symptomatic. A major finding is hypertrophy of the ventricular and septal walls of the neonatal heart. In all, 5% of neonates born to diabetic mothers suffer from congestive heart failure due to left ventricular outflow obstruction. Fortunately, in most cases, cardiac hypertrophy is transient with spontaneous echocardiographic resolution within the early months after birth, requiring no therapy ***(Leipold et al., 2005).***

Diabetes mellitus affects the fetal heart during early and late gestation. During early gestation, it hinders the proper

expression of genes needed for the correct development of the fetal heart during embryogenesis, causing structural cardiac defects, for example, ventricular septal defects ***(Molin et al., 2004).*** Moreover, during late gestation, fetal hyperinsulinemia due to inadequate maternal glycemic control increases the expression of fetal insulin cardiac receptors. Insulin, an anabolic hormone, causes hyperplasia and hypertrophy of the fetal myocardium specialy the interventricular septum (IVS) due to its abundance of insulin receptors, leading to hypertrophic cardiomyopathy (HCM) ***(Elmekkawi et al., 2015).***

Echocardiography is routinely indicated for fetuses of diabetic women. However, metabolic expression occurs fully from the 24^{th} week onwards ***(Zielinsky et al., 2009).***

In recent decades, with the development of three-dimensional ultrasound (US3D) and the Spatio-Temporal Image Correlation technology (STIC), a new form of prenatal cardiac examination has emerged. This technique allows obtaining cardiac volume and its storage for later reconstruction and analysis of anatomy, presenting the image in the multiplanar and surface mode (rendered), identifying the cardiac chambers, semilunar and atrioventricular valves, and the positioning of vessels and their correlations, and it is also possible to track the cardiac motion by using the cineloop technique ***(Rolo et al., 2011).***

2D ultrasound is basically an axial image, and 3D ultrasound is a volume, and 4D ultrasound is a volume with time and the fifth dimension is how do you bring a level of workflow into ultrasound? And it is basically bordering on the sense of automation.5D technology is a form of automation where you go through and do a scan and you get the results auto populated for you. Five dimensional Ultrasound included features like 5D Heart, 5D CNS (which is aimed at the central nervous system and displays six measurements (BPD, HC, OFD, Cerebellum, Posterior Fossa, Atria lateral ventricle)), 5D Follicle (which identifies and measures multiple ovarian follicles for rapid assessment of follicular size), 5D-LB (fetal long-bone) and 5D-NT (nuchal translucency) ***(Liza, 2015).***

Fetal Intelligent Navigation Echocardiography (FINE) is a novel method for visualization of standard fetal echocardiography views from volume datasets obtained with spatiotemporal image correlation (STIC).This method can simplify examination of the fetal heart and reduce operator dependency ***(Garcia et al., 2016).***

It is a method to: 1) demonstrate nine cardiac diagnostic planes; and 2) spontaneously navigate the anatomy surrounding each of the nine cardiac diagnostic planes (Virtual Intelligent Sonographer Assistance (VIS-Assistance)) ***(Yeo et al., 2013).***

AIM OF THE WORK

The aim of this study is to investigate the utility of 5D fetal echocardiography in the prenatal diagnosis of fetal hypertrophic cardiomyopathy in healthy mothers, controlled diabetic mothers and uncontrolled diabetic mothers.

Study Question:

Does 5D fetal echocardiography have a role in the prenatal diagnosis of fetal hypertrophic cardiomyopathy in healthy mothers, controlled diabetic mothers and uncontrolled diabetic mothers?

Study Hypothesis:

We assume that 5D fetal echocardiography has a role in the prenatal diagnosis of fetal hypertrophic cardiomyopathy in healthy mothers, controlled diabetic mothers and uncontrolled diabetic mothers.

Study Outcomes:

1. Primary outcome: measuring of interventricular septum thickness (IVS)of the fetal heart by 5D ultrasound
2. Secondary outcome:
    a. Measuring of right myocardial wall thickness (RMWT) of the fetal heart by 5D ultrasound.
    b. Measuring of left myocardial wall thickness (LMWT) of the fetal heart by 5D ultrasound.
    c. Finding of any other structural abnormalities of the fetal heart by 5D ultrasound.

Chapter 1

DIABETES MELLITUS AND PREGNANCY

Incidence of diabetes mellitus:

Diabetes mellitus is the most common medical complication of pregnancy. Pregestational diabetes and gestational diabetes mellitus (GDM) complicate approximately 10% of all pregnancies. Gestational diabetes mellitus (GDM) is defined as a glucose intolerance which is first diagnosed in pregnancy and remains below the cutoff value for manifest diabetes ***(Kleinwechter et al., 2014)***. Gestational diabetes mellitus (GDM) represents approximately 90% of diabetic pregnancies ***(Stuebe et al., 2011).***While all types of diabetes are on the rise, there has been a disproportionate growth of preexisting diabetes in young women of reproductive age ***(Lawrence et al., 2008).***

Diabetes is one of the most common pre-existing maternal disorders and complicated approximately 1.3% of all pregnancies ***(Shand et al., 2008***). Most women with pregestational diabetes (PGD) characterized by disturbance in glucose metabolism may be due to variable degrees of insulin resistance (type 2), or a consequence of autoimmune destruction of the pancreatic β-cells (type 1). With increasing numbers type 1 diabetes diagnosed among youth and high

prevalence of obesity among women of child-bearing age, the demographic pattern of PGD is changing ***(Lapolla et al., 2008)***.

Risk factors of diabetes mellitus:

Obesity is a well-known risk factor for diabetes. Approximately 80% of diabetics within the general population are overweight or obese. Obesity has been cited as a poor prognostic indicator in pregnant women with diabetes, but this relationship remains incompletely elucidated ***(Hruby et al., 2016).***

The known risk factors for Gestational Diabetes Mellitus (GDM) are advanced age (≥35 yrs.), overweight or obesity, excessive gestational weight gain, excessive central body fat deposition, family history of diabetes, short stature (<1.50 m), excessive fetal growth, polyhydramnios, hypertension or preeclampsia in the current pregnancy, history of recurrent miscarriage, offspring malformation, fetal or neonatal death, macrosomia, GDM during prior pregnancies and polycystic ovary syndrome. In addition to the most common factors the sedentary lifestyle may also be a risk factor for GDM ***(Pons et al., 2015).***

Table (1): Diabetes Screening and Diagnosis (According to American Diabetes Association (ADA) 2016 Guideline):

Screening for Gestational Diabetes (GDM)	
Pregnant women with risk factors	Test for undiagnosed type 2 at first prenatal visit using standard diagnostic criteria
Pregnant women without known prior diabetes	Test for GDM at 24-28 weeks
Women with GDM	Screen for persistent diabetes 6-12 wks postpartum using OGTT and standard diagnostic criteria
Women with a history of GDM	Lifelong screening for diabetes or prediabetes every ≥3 yrs
Women with a history of GDM and prediabetes	Lifestyle interventions or metformin for diabetes prevention
One-step diagnosis strategy	**Two-step diagnosis strategy**
Perform 75-g OGTT with plasma glucose measurement Test in the morning after the patient has fasted for ≥8 hours Repeat test at 1 and 2 hours after initial measurement	Step 1: Perform a 50-g nonfasting GLT with plasma measurement at 1 hour If PG measured 1 hour after the load is ≥140 mg/dL (7.8 mmol/L), proceed to 100-g OGTT
Diagnosis is confirmed when PG levels meet or exceed: Fasting 92 mg/dL (5.1 mmol/L) 1 hr: 180 mg/dL (10.0 mmol/L) 2 hr: 153 mg/dL (8.5 mmol/L)	Step 2: Perform 100-g OGTT while patient is fasting Diagnosis is confirmed when two or more PG levels meet or exceed: Fasting: 95 mg/dL or 105 mg/dL (5.3/5.8) 1 hr: 180 mg/dL or 190 mg/dL (10.0/10.6) 2 hr: 155 mg/dL or 165 mg/dL (8.6/9.2) 3 hr: 140 mg/dL or 145 mg/dL (7.8/8.0)

Antenatal diabetes care:

The National Institute for Health and Care Excellence (NICE) have developed diabetes pregnancy guidelines with a clear emphasis on improving provision of prepregnancy and antenatal diabetes care ***(NICE guideline 63, 2008).*** The NICE guideline recommendations for prepregnancy preparation include taking 5 mg preconception folic acid, presenting for antenatal care before 8 weeks' gestation and avoiding potentially harmful medications. The 2015 update lowered the maternal glycaemic control target from HbA1c < 7.0% (53 mmol/mol) to HbA1c < 6.5% (48 mmol/mol) and recommended elective delivery between 37+0 and 38+6 weeks' gestation ***(NICE guideline 63, 2015).***

Responding to the NICE guidelines, a National Pregnancy in Diabetes (NPID) audit was established to document the pregnancy preparation, antenatal care and fetal health outcomes for pregnant women with (type 1) and (type 2) diabetes ***(Murphy et al., 2013).***

Table (2): Glycemic Targets in Pregnancy (according to American Diabetes Association (ADA) 2016 Guideline):

	Pregestational diabetes	**Gestational diabetes mellitus (GDM)**
Fasting	≤90 mg/dL (5.0 mmol/L)	≤95 mg/dL (5.3 mmol/L)
1-hr postprandial	≤130-140 mg/dL (7.2-7.8 mmol/L)	≤140 mg/dL (7.8 mmol/L)
2-hr postprandial	≤120 mg/dL (6.7 mmol/L)	≤120 mg/dL (6.7 mmol/L)
A1C	6.0-6.5% (42-48 mmol/L) recommended <6.0% may be optimal as pregnancy progresses Achieve without hypoglycemia	

Complications of diabetes with pregnancy:

The importance of diabetes in pregnancy stems from the fact that it carries a significant risk to both the fetus and the mother. Despite major advances in clinical management, we are still facing a higher incidence of malformations and perinatal morbidity compared to the non-diabetic population ***(Lawrence et al., 2008).***

Compared with healthy women, those with GDM have increased risk of primary cesarean delivery, preeclampsia, birth weight > 90%, shoulder dystocia, traumatic delivery, skeletal (sacral agenesis), genito-urinary abnormalities and neonatal intensive care unit admission ***(Klemetti et al., 2012).*** Similarly, those with preexisting diabetes (type 1), (type 2) have an

increased risk of spontaneous abortion, congenital anomalies, perinatal mortality, stillbirth, neonatal hypoglycemia and hyperbilirubinemia over nondiabetics, making pre-pregnancy care particularly glycaemic control and obstetrical interventions of great importance ***(Catalano et al., 2012).***

Although asymptomatic in its clinical course, GDM is associated with an increased risk of complications related to pregnancy and childbirth. In the long term, the risk of developing manifest type 2 diabetes is significantly increased in women with GDM in the years following initial diagnosis. GDM during pregnancy is associated with an up to 7-fold increase in the risk of manifest T2D compared with normoglycemic pregnancies ***(Rayanagoudar et al., 2016).***

Management of diabetes mellitus with pregnancy (according to American Diabetes Association (ADA) 2016 Guideline):

Management of pregestational diabetes

Insulin is the preferred medication for pregestational type 1 and type 2 diabetes not adequately controlled with diet, exercise, and metformin. Most insulins are category B; glargine, glulisine, and degludec are category C.

Insulin management during pregnancy is complex as it requires frequent titration to match changing requirements plus referral to specialized center recommended.

Hypoglycemia education important before and during pregnancy to prevent hypoglycemia which is more common with type 1 diabetes.

Women with type 1 diabetes are at risk for ketoacidosis at lower blood glucose levels than in the nonpregnant state so provide education on prevention and treatment of diabetic ketoacidosis.

Women with type 2 diabetes are at risk for obesity so recommended weight gain during pregnancy: 15-25 lb for overweight and 10-20 lb obese.Glycemic control easier to achieve in type 2 than in type 1 but can require higher insulin doses.

Recommendations for Gestational Diabetes Mellitus (GDM)

Lifestyle management as Medical nutrition, physical activity, weight management.While in pharmacologic therapy, Insulin is first line. Sulfonylureas may be inferior to insulin and metformin due to increased risk of neonatal hypoglycemia and macrosomia and no long-term safety data. Metformin may be preferable to insulin for maternal health if can control hyperglycemia but may increase risk of prematurity, lower hypoglycemia and weight gain. Also long-term outcomes in offspring not known.

Recommendations for Postpartum Follow-Up in Women with GDM

An oral glucose tolerance test (OGTT) is recommended at the 6- to 12-week postpartum visit as GDM is associated with increased maternal risk for type 2 diabetes. Also test women with GDM every 1-3 years if her 6- to 12-wk OGTT is normal.

The frequency of screening is based on the presence of risk factors: family history, pre-pregnancy BMI, or need for insulin or OAD medications during pregnancy.Ongoing screening may be done with any glycemic test (A1C, fasting plasma glucose, OGTT) using nonpregnancy cut points.

Metformin and intensive lifestyle changes prevent or delay progression to type 2 diabetes.

Chapter 2

ANATOMY AND EMBERYOLOGY OF FETAL HEART

The heart begins to beat at about 22-23 days after conception (about 6 weeks after the last menstrual period). Therefore, the heart is one of the earliest differentiating and functioning organs ***(Sylva et al., 2014).***

The heart is totally mesodermal in origin. It forms initially from two tubes located bilaterally (on either side) of the trilaminar embryo in the cranial (head) region. The image below shows these primitive tubes developing in an embryo approximately 18 days after conception. At this early embryo, these are multiple blood islands dispersed throughout the embryo. These will form the early blood vessels. At the most cranial end of the embryonic disc these blood islands are actually the primitive heart tube ***(Person et al., 2005).***

The disc-like embryo then undergoes a process of folding, in which both the cranial and lateral parts of the embryo fold ventrally (forwards). This brings the heart-forming region to a ventral (frontal) position. Heart tubes fuse together to form a single primordial heart tube situated in the midline of the embryo, ventral to the pharynx ***(Kelly et al., 2002).***

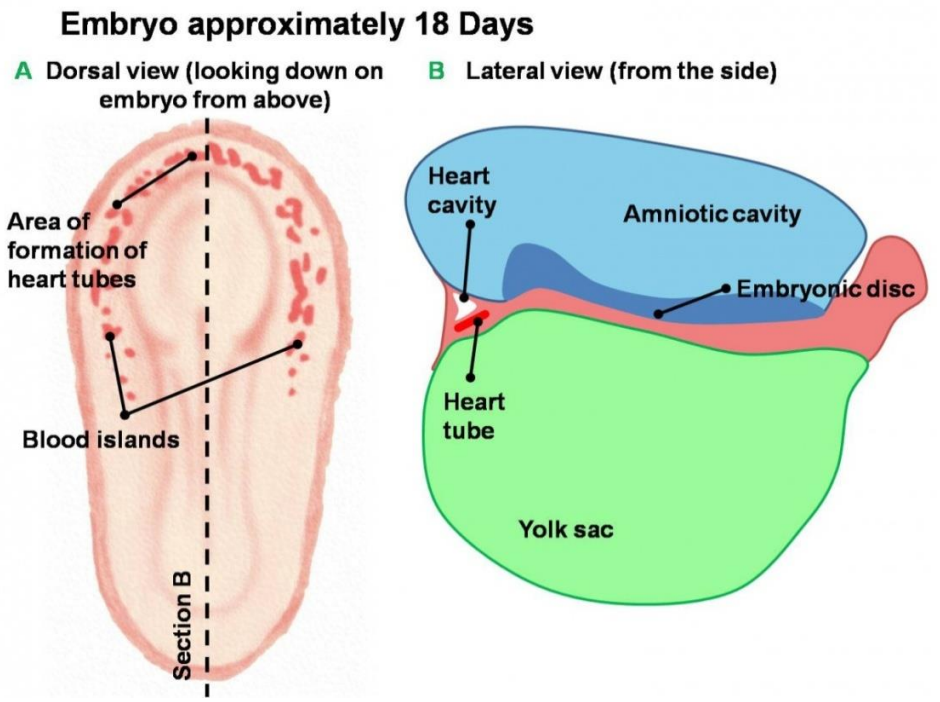

Figure (1): Embryo approximately 18 days.

Segments of the Heart Tube

At this stage the tube already has minor constrictions within it, indicating sections of the heart tube that will form parts of the adult heart. The most caudal (tail end) segment of the heart tube is the sinus venosus which will later become the ends of the major veins carrying blood to the heart as well as parts of the atria. The next segments are the primitive atrium and primitive ventricle which will become the atria and ventricles of the adult heart. Cranial to these segments are the bulbus cordis, most of which will become the right ventricle, and the truncus arteriosus which forms the pulmonary and aortic trunks carrying blood away from the heart ***(Moorman et al., 2003).***

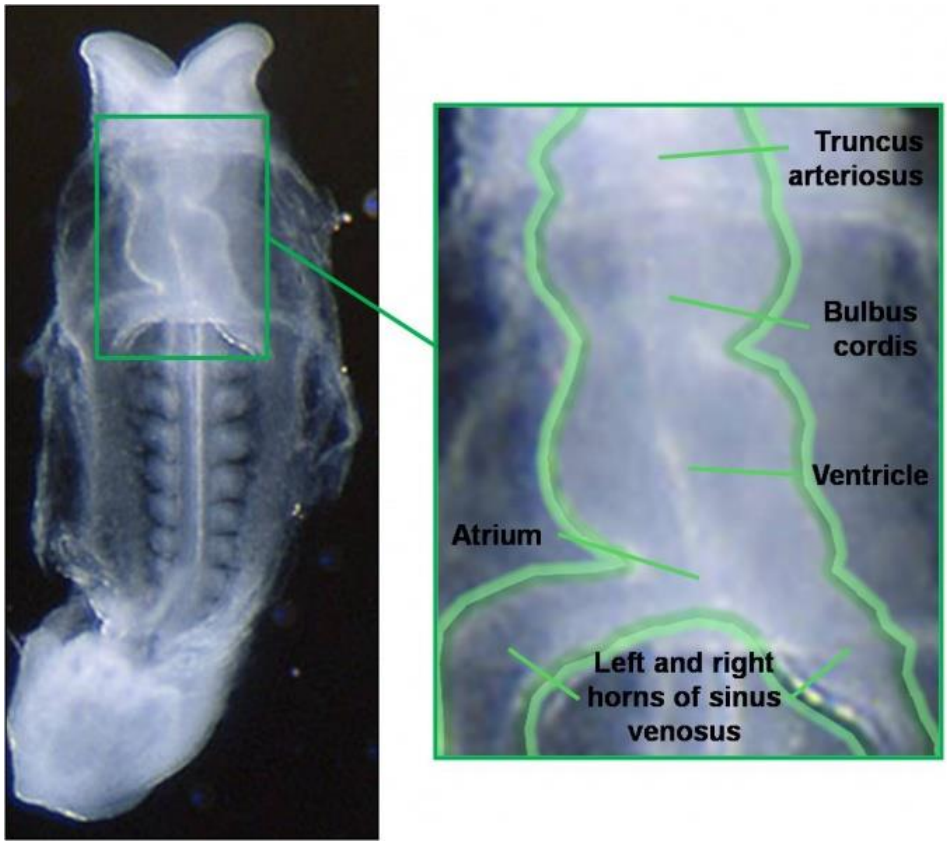

Figure (2): 22 day embryo showing segments of heart tube

Heart Tube Looping

This tubular heart undergoes a process of looping during week four of development to form a shape that resembles that of the adult heart. It initially forms a C-shape (with the convex portion of the C situated on the right side of the embryo) and then an S-shape. Eventually the atria are brought backwards and upwards so that they lie cranially and behind the ventricles ***(Moorman et al., 2003).***