# Cardiac Abnormalities in Fetuses of Diabetic Mothers

Thesis
Submitted for partial fulfillment of Master Degree in Pediatrics

## By Ramy Mohamed El-Sayed

M.B.,B.CH. of Medicine and Surgery Faculty of Medicine – Ain Shams University

#### **Under Supervision of**

#### **Prof. Dr. Nevin Mohamed Mamdouh**

Professor of Pediatrics Faculty of Medicine – Ain Shams University

#### Prof. Dr. Sherif Fekry Hendawy

Professor of Obstetrics and Gynecology Faculty of Medicine – Ain Shams University

#### Dr. Omneya Ibrahim Youssef

Assistant Professorof Pediatrics Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2015

## بِسْم اللَّهِ الرّحمَنِ الرّحيمِ

(...رَبِّ أُوزِعنِي أَن أَشكُرَ نِعمَتَكَ الَّتِي أَن أَشكُرَ نِعمَتَكَ الَّتِي أَنْ عَلْيَ وعَلى والدَيَّ وَأَنْ عَلَيَ وعلى والدَيَّ وَأَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ وأَدْخِلْنِي وَأَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ وأَدْخِلْنِي بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ)

بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ)

## صدق الله العظيم

النمل. اية رقم 19



**P**raise be to **ALLAH**, The Merciful, The Compassionate for all the gifts **I** have been offered; One of the gifts is accomplishing this research work.

Words cannot adequately assure my deepest thanks and gratitude to *Prof. Dr. Nevin Mohamed Mamdouh,* Professor of Pediatrics, Faculty of Medicine – Ain Shams University, for her continuous encouragement, constructive criticism and continuous assistance. I really have the honor to complete this work under her supervision.

I would like to express my deepest thanks and gratitude to **Prof. Dr. Sherif Fekry Hendawy**, Professor of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University, for his unlimited help, valuable guidance, continuous encouragement and forwarding his experience to help me complete this work.

I can't forget to thank with all appreciation and gratitude **Dr. Omneya Ibrahim Youssef**, Assistant Professor of Pediatrics, Faculty of Medicine – Ain Shams University for her valuable assistance, kind supervision, her great efforts and time she has devoted to this work.

I can never forget to thank all patients who willingly participated in this study, as well as the physician and nurses, who were totally supportive during all steps of data collection.

Last but not least all thank and gratitude go to my Family, especially my Parents, my wife and my childrens, for pushing me forward in every step in my life.

Ramy Mohamed El-Sayed

#### **List of Contents**

| Subject Page                                     | No. |
|--|-----|
| List of Abbreviations                            | i   |
| List of Tables                                   | ii  |
| List of Figures                                  | v   |
| Introduction                                     | 1   |
| Aim of the Work                                  | 3   |
| Review of Literature                             |     |
| Pregnancy & Diabetes                             | 4   |
| Impact of Maternal Diabetes on Fetal Development | 11  |
| Fetal Cardiac Abnormalities of Diabetic Mother   | 21  |
| Fetal Echocardiography                           | 40  |
| Fructosamine.                                    | 64  |
| Patients and Methods                             | 72  |
| Results  | 78  |
| Discussion                                       | 93  |
| Summary  | 102 |
| Conclusion                                       | 106 |
| Recommendations                                  | 108 |
| References                                       | 108 |
| Arabic Summary                                   |     |

#### **List of Abbreviations**

| 2D         | Two-dimensional                              |
|------------|--|
| 3D         | Three-dimensional                            |
| 4D         | Four-dimensional                             |
| ADA        | American Diabetes Association                |
| AO         | Aorta  |
| AVSD       | Atrioventricular septal defect               |
| BSA        | Body surface area                            |
| <b>CAT</b> | Common arterial trunk                        |
| CM         | Cardiomyopathy                               |
| DM         | Diabetes mellitus                            |
| DORV       | Double outlet right ventricle;               |
| EM         | Epithelio-mesenchymal                        |
| GCT        | Glucose challenge test                       |
| GDM        | Gestational diabetes mellitus                |
| HAPO       | Hyperglycemia and Adverse Pregnancy Outcomes |
| HhAlc      | Glycosylated hemoglobin                      |

#### List of Abbreviations

**HCM**.....Hypertrophic cardiomyopathy **HDL**.....High-density-lipoprotein **HLHS**.....Hypoplastic left heart syndrome **IAA**.....Interrupted aortic arch IADPSG .....The International Association of the Diabetes and Pregnancy Study Groups **IDM**...... Infant of a diabetic mother **IUGR**.....Intrauterine growth restriction **IVST**.....Interventricular septal thickness LA....Left atrium LDL....Low-density-lipoprotein LGA....Large for gestational age LV....Left ventricle NAFLD......Non alcoholic fatty liver disease **NASH**.....Inflammatory steatohepatitis **NBT**.....Nitroblue tetrazolium colorimetric NTB.....Nitrotetrazolium-blue **OGTT**.....Oral glucose tolerance test

#### **□**List of Abbreviations

**OR**.....Odds ratio

**PA**.....Pulmonary artery

**PVH**.....Pathologic ventricular hypertrophy

**PVH**.....Pathologic ventricular hypertrophy

**PVPI**.....Pulmonary vein pulsatility index

**RA**.....Right atrium

**RBCs**.....Red blood cells

**RV**.....Right ventricle

**SGA**.....Small for gestational age

SSA.....Anti-Ro

SSB.....Anti-La

**T1DM** ......Type 1 diabetes mellitus

**T2DM** ......Type 2 diabetes mellitus

**TBA**.....Thiobarbituric acid colorimetric

**TDI**.....Tissue Doppler imaging

**TGA**.....Transposition of the great arteries

TGA.....Transposition of great arteries

| MI iet  | of Ahh | reviations |
|---------|--------|------------|
| BEILI5L | OI ADD | reviamons  |

TOF&PA....Tetralogy of Fallot with pulmonary atresia

**TOF**.....Tetralogy of Fallot

**TTTS**.....Twin-twin transfusion syndrome

VSD.....Ventricular septal defect

## **List of Tables**

| Table No           | . Title   | Page No. |
|--------------------|---|----------|
| <b>Table (1):</b>  | Perinatal mortality and neonatal infants of diabetic mothers  | <u> </u> |
| <b>Table (2):</b>  | Congenital anomalies associated of diabetic mothers           |          |
| <b>Table (3):</b>  | Common indications echocardiography                           |          |
| <b>Table (4):</b>  | General recommendations echocardiography                      |          |
| <b>Table (5):</b>  | Essential components of echocardiogram                        |          |
| <b>Table (6):</b>  | Comparison between group I ar regards demographic data        |          |
| <b>Table (7):</b>  | Comparison between group I ar regards laboratory data         |          |
| <b>Table (8):</b>  | Comparison between group I ar regards echocardiographic data. |          |
| <b>Table (9):</b>  | Comparison between group Ia as regards demographic data       | •        |
| <b>Table (10):</b> | Comparison between group Ia as regards laboratory data        |          |
| <b>Table (11):</b> | Comparison between group Ia as regards echocardiographic da   |          |
| <b>Table (12):</b> | Comparison between group Ic as regards demographic data       |          |
| <b>Table (13):</b> | Comparison between group Ic as regards Hb A1c levels          | • •      |
|                    |   |          |

### **List of Tables** (Cont.)

| Table No           | . Title  | Page No.        |
|--------------------|--|-----------------|
| <b>Table (14):</b> | Comparison between group I as regards echocardiographic                            | • •             |
| <b>Table (15):</b> | Correlation between maternal age, number of birth ar laboratory and echocardiograp | nd descriptive, |
| <b>Table (16):</b> | Correlation between HbA1c levels and descriptive, leechocardiographic data         | aboratory and   |

## **List of Figures**

| Figure No           | Title   | Page No.                 |
|---------------------|---|--------------------------|
| Figure (1):         | Cells from the epiblast detach a through the primitive groove to endoderm and mesoderm layers                                 | o form the               |
| <b>Figure (2):</b>  | The single heart tube shows c outlining future structures   |                          |
| Figure (3):         | Looping of the single endocardia transforms it into a complex for structure   | ourchamber               |
| Figure (4):         | One heart disease—several med several genes (Bajolle et al., 2009)  |                          |
| <b>Figure (5):</b>  | Tetralogy of Fallot. Outflow shows a orta (AO) overriding septal defect.  | ventricular              |
| Figure (6):         | Trunucus arteiosus  | 31                       |
| <b>Figure (7):</b>  | Fetal cardiomyopathy  | 33                       |
| Figure (8):         | Double Outlet RV  | 34                       |
| Figure (9):         | Hypoplastic left heart syndrome   | 35                       |
| <b>Figure (10):</b> | Ventricular Septal Defect (Rajia e  | t al., 2011)36           |
| <b>Figure (11):</b> | AV Septal Defect (Barboza et al.,   | 2002)36                  |
| <b>Figure (12):</b> | Illustration of the tomographic pla<br>image the fetal cardiovascular sys   |                          |
| <b>Figure (13):</b> | Illustrations of the anatomical co<br>each of the designated tomograph<br>planes used for imaging of<br>cardiovascular system | nic imaging<br>the fetal |

## List of Figures (Cont.)

| Figure No           | . Title Page No  | <b>)</b> . |
|---------------------|--|------------|
| <b>Figure (14):</b> | Tetralogy of Fallot.   | 54         |
| <b>Figure (15):</b> | D-transposition of great arteries  | 56         |
| <b>Figure (16):</b> | Hypoplastic left heart syndrome  | 57         |
| <b>Figure (17):</b> | Hypoplastic aorta  | 58         |
| <b>Figure (18):</b> | Truncus arteriosus   | 59         |
| <b>Figure (19):</b> | Atrioventricular canal defect  | 60         |
| <b>Figure (20):</b> | Double outlet right ventricle  | 61         |
| <b>Figure (21):</b> | Dilated cardiomyopathy   | 62         |
| <b>Figure (22):</b> | Hypertrophic cardiomyopathy  | 62         |
| <b>Figure (23):</b> | Ventricular septal defect  | 63         |
| <b>Figure (24):</b> | The reaction of glucose and protein to form fructosamine   | 65         |
| <b>Figure (25):</b> | Pulmonary vein flow assessment   | 75         |
| <b>Figure (26):</b> | Septal tissue Doppler (TDI)  | 76         |
| <b>Figure (27):</b> | Distribution of maternal illness during pregnancy in group I   |            |
| <b>Figure (28):</b> | Distribution of Hb A1c values in studied groups  | 80         |
| <b>Figure (29):</b> | Distribution of serum fructosamine values in studied groups  | 83         |
| <b>Figure (30):</b> | Correlation between pulmonary vein pulsatility index(PVPI) and interventricular thickness (IVST) in group I. | 88         |

## List of Figures (Cont.)

| Figure No           | . Title   | Page No.       |
|---------------------|---|----------------|
| Figure (31):        | Correlation between intervent thickness (IVST) (cm) and geographic (GA)(weeks) in group I | estational age |
| <b>Figure (32):</b> | Correlation between HBA1c le pulmonary vein pulsatility incogroup I.                      | lex (PVPI) in  |
| <b>Figure (33):</b> | Correlation between HBA1c le interventricular septal thickness in group I                 | ss (IVST)(cm)  |
| <b>Figure (34):</b> | Correlation between HBA1c leserum fructosamine levels (µm I.                              | ol/L) in group |
| <b>Figure (35):</b> | Correlation between HBA1cle gestational age (GA) (weeks) in                               |                |
| <b>Figure (36):</b> | Correlation between serum levels (µmol/L) and pulr pulsatility index (PVPI) in grou       | nonary vein    |
| <b>Figure (37):</b> | Correlation between serum levels (µmol/L) and gestation (weeks) in group I.               | nal age (GA)   |
| <b>Figure (38):</b> | Correlation between serur levels and interventricular sep (IVST) in group I               | otal thickness |

#### Introduction

The consequences of uncontrolled diabetes mellitus (DM) during pregnancy are severe to both mother and fetus. The risk of congenital malformations among infants of diabetic mothers is related to the diabetic control these mothers receive (Alien et al., 2007).

Maternal DM affects the fetal heart both structurally and functionally. In early gestation, it has a teratogenic effect causing primary cardiogenesis defects. In late gestation, it causes a unique form of hypertrophic cardiomyopathy (*Chaudhari et al.*, 2008).

Cardiomegaly is a common finding in stillborn infants of mothers with DM and may contribute to the risk of fetal death in these pregnancies (*Russell et al.*, 2008).

Given the increased risk of congenital abnormalities among infants of diabetic mothers, an appropriate biochemical and ultrasonographic screening process and a detailed evaluation of fetal cardiac structure should be offered to all pregnant women with diabetes (*Wilson et al.*, 2007).

The timing of development of the myocardial changes in the fetus of the diabetic mother has been well demonstrated by fetal echocardiography. Fetal echocardiographic investigations suggest the onset of hypertrophy occurs even before 20 weeks of gestation with documentation of increased ventricular septal thickening relative to fetuses in non diabetic pregnancies (Macklon et al., 1998).

Fructosamines are keto-amines formed by a non-enzymatic reaction between glucose and a protein (60-70% of which is glycosylated with albumin in serum), depending upon the severity and the duration of the hyperglycemia. Therefore, serum fructosamine directly reflects the dynamics of blood glucose concentration and correlates significantly with the mean plasma glucose levels from the preceding 1 to 3 weeks (*Weerasekera et al, 2000*).

Fructosamine testing has been available since the 1980s. Both fructosamine and HbAlc are used primarily as monitoring tools to help diabetics control their blood sugar, but the A1C test is much more popular and more widely accepted. However, the American Diabetes Association (ADA) recognizes both tests and says that fructosamine may be useful in situations where the A1C cannot be reliably measured (*Goldstein et al*, 2004).