

# **Study of Metabolic Profile in Infants of Diabetic Mothers**

## **Thesis**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

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## ***List of Abbreviations***

| <b>Abb.</b>           | <b>Meaning</b>                           |
|-----------------------|------------------------------------------|
| <b>ADA</b>            | American Diabetes Association            |
| <b>AGE</b>            | Advanced glycosylation end products      |
| <b>AIB</b>            | Aminoisobutyrate                         |
| <b>AMP</b>            | Adenosinemonophosphate nucleoside        |
| <b>AMPK</b>           | Adenosinemonophosphate nucleoside kinase |
| <b>BALF</b>           | Bronchoalveolar lavage fluid             |
| <b>BMI</b>            | Body mass index                          |
| <b>C0-Carnitine</b>   | Free carnitine                           |
| <b>C10:1</b>          | Decenoylcarnitine                        |
| <b>C10-Carnitine</b>  | Decanoylcarnitine                        |
| <b>C12-Carnitine</b>  | Dedecanoylcarnitine                      |
| <b>C14:1</b>          | Tetradecenoylcarnitine                   |
| <b>C14:2</b>          | Tetradecadienoylcarnitine                |
| <b>C14-Carnitine</b>  | Tetra decanoylcarnitine                  |
| <b>C14-OH</b>         | 3-Hydroxy-tetradecanoylcarnitine         |
| <b>C16:1</b>          | Hexadecanoylcarnitine                    |
| <b>C16-Carnitine</b>  | Hexadecanoylcarnitine                    |
| <b>C16-OH</b>         | 3-Hydroxy-hexadecanoylcarnitine          |
| <b>C18-carnitine</b>  | Octadecanoylcarnitine                    |
| <b>C2-carinitine</b>  | Acetyl carnitine                         |
| <b>C3</b>             | Propionylcarnitine                       |
| <b>C4 – Carnitine</b> | Butyrylcarnitine                         |
| <b>C5- Carnitine</b>  | Isovalerylcarnitine                      |
| <b>C6- carnitine</b>  | Hexanoylcarnitine                        |

## List of Abbreviation

| Abb.                | Meaning                                 |
|---------------------|-----------------------------------------|
| <b>C8-carnitine</b> | Octanoylcarnitine                       |
| <b>CNS</b>          | The central nervous system              |
| <b>CVS</b>          | Cardiovascular system                   |
| <b>DM</b>           | Diabetes mellitus                       |
| <b>EA</b>           | Experimental animals                    |
| <b>ELBW</b>         | Extreme low birth weight                |
| <b>FC</b>           | Fold change                             |
| <b>GA</b>           | Gestational age                         |
| <b>GC-MS</b>        | Gas chromatography-mass spectrometry    |
| <b>GDM</b>          | Gestational diabetes mellitus           |
| <b>GSEA</b>         | Gene Set Enrichment Analysis            |
| <b>HA</b>           | Human adults                            |
| <b>HbA1C</b>        | Glycated hemoglobin                     |
| <b>HN</b>           | Human newborns                          |
| <b>IDM</b>          | Infant of diabetic mother               |
| <b>IGF 1</b>        | Insulin like growth factor 1            |
| <b>IUGR</b>         | Intrauterine growth restriction         |
| <b>LC-MS</b>        | Liquid chromatography-mass spectrometry |
| <b>LGA</b>          | Large for gestational age               |
| <b>LPS</b>          | Lipopolysaccharide                      |
| <b>LSCS</b>         | Lower segment caesarian section         |
| <b>MESA</b>         | Metabolite Set Enrichment Analysis      |
| <b>MMA</b>          | Methylmalonicacidemia                   |
| <b>MVM</b>          | Microvillous membrane                   |
| <b>n</b>            | Number                                  |

## List of Abbreviation

| Abb.                 | Meaning                                                                             |
|----------------------|-------------------------------------------------------------------------------------|
| <b>NADPH</b>         | Nicotinamide adenine dinucleotide phosphate                                         |
| <b>NEC</b>           | Necrotizing enterocolitis                                                           |
| <b>NMR</b>           | Nuclear magnetic resonance                                                          |
| <b>NSCs</b>          | Neural stem cells                                                                   |
| <b>NTDS</b>          | Neural Tube Defect                                                                  |
| <b>NVD</b>           | Normal vaginal delivery                                                             |
| <b>OFC</b>           | Occipitofrontal circumference                                                       |
| <b>OHD</b>           | Oral hypoglycemic drugs                                                             |
| <b>OS</b>            | Oxidative stress                                                                    |
| <b>PCA</b>           | Principal Component Analysis                                                        |
| <b>PGDM</b>          | Pregestational diabetes mellitus                                                    |
| <b>PLS-DA</b>        | Partial Least Squares - Discriminant Analysis                                       |
| <b>PTH</b>           | Parathyroid hormone                                                                 |
| <b>RDS</b>           | Respiratory distress syndrome                                                       |
| <b>ROS</b>           | Reactive oxygen species                                                             |
| <b>SD</b>            | Standard deviation                                                                  |
| <b>SFT</b>           | Skin fold thickness                                                                 |
| <b>SGA</b>           | Gestational age                                                                     |
| <b>SGA</b>           | Small for gestational age                                                           |
| <b>TTN</b>           | Transient tachypnea of the newborn                                                  |
| <b>UPLC/MS</b>       | The urine metabolomics                                                              |
| <b>UPLC-Q-TOF-MS</b> | Ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry |
| <b>VIP</b>           | Variable Importance in Projection                                                   |

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## Introduction

Women with diabetes mellitus or who develop diabetes mellitus during pregnancy can present some particular challenges for mothers and her infants. Gestational diabetes mellitus is a condition in which women without previous diagnosis as a case of diabetes exhibit high blood glucose levels during pregnancy especially during 3<sup>rd</sup> trimester (*Donovan, 2010*).

Pregestational diabetes mellitus, gestational diabetes mellitus may be associated with a variety of fetal effects (diabetic fetopathy) including increased rate of spontaneous abortion, intra uterine fetal death, congenital anomalies, neurodevelopmental problems, and increase risk of perinatal complications. Additional problems include fetal growth disturbance causing increase or decrease birth weight, hyperglycemia and hyperinsulinemia. Optimal control of maternal blood glucose is known to reduce these changes (*Epub, 2011*).

Fetal hypoxia and acidemia have been reported in pregestational diabetic pregnancies in relation to poor glycemic control, but it is still uncertain whether this is the cause in apparently well controlled gestational diabetes (*Bjog, 2009*).

The infants of gestational diabetic mothers sometimes have increased umbilical blood glucose levels, reduction in oxygen saturation and oxygen content together with increased lactate concentration despite normal maternal glucose level reflecting altered fetal metabolism. These data suggest that good maternal metabolic control achieved by currently used methods of monitoring glucose control is not sufficient to ensure a normal oxygenation status and metabolic milieu for the fetus in gestational diabetes mellitus pregnancies (**Sacco, 2009**).

The goal of infants of diabetic mothers' screening is to detect disorders that are threatening to life or long-term health problems before they become symptomatic. Early treatment of these disorders may significantly reduce mortality and morbidity in affected infants. An infant may present with a positive infant screen for one of the complication of infants of diabetic mothers before clinical manifestations are present or recognized (**Pasquali and Longo, 2011**).

Extended metabolic screening of infants of diabetic mothers might disclose hidden metabolic disorders that can be related to early or late complications in those neonates. Metabolic profile of infants of diabetic mothers include different markers include amino acid profile and acylcarintine profile. Most amino acids (except argininosuccinic acid and alloisoleucine) are present in the plasma within a normal range

in healthy individuals. Mild elevations of 5 to 10 percent above normal usually are not significant elevations are reported only in groups of amino acids and specific disorders (**Weiner, 2006**).

Analysis of acylcarnitine conjugates is performed by tandem mass spectrometry (MS/MS) as amino acids. It may show abnormal increase or decrease in their levels in specific disorders (**Cleary and Green, 2005**).

## **Aim of the Study**

The aim of this work is to study the metabolic profile (amino acid, and acylcarnitine profile) among infants of diabetic mothers to determine the infants outcome by correlation of this profile with profiles of other diseases.

## Diabetes and Pregnancy

Diabetes is the most common metabolic disorder affecting pregnancy. Its prevalence seems to be growing in parallel with the epidemics of overweight and obesity. Recognizing and treating diabetes or any degree of glucose intolerance in pregnancy results in lowering maternal and fetal complications (*Negrato and Gomes, 2013*).

Pre-gestational diabetes (ie, diabetes diagnosed before pregnancy, type 1 or type 2 diabetes mellitus) comprises approximately 13 percent of all diabetes in pregnancy, while gestational diabetes mellitus (GDM) (ie., diabetes with onset or first recognition in pregnancy) comprises the remaining 87 percent (*Wier et al., 2010*).

The prevalence of pre-gestational diabetes has been increasing [due to the increasing prevalence of type 2 diabetes in women of reproductive age. The prevalence of GDM is also increasing, paralleling the increasing prevalence of obesity and undiagnosed type 2 diabetes in these women (*Shaw et al., 2010*).

The mainstay of the medical management of pre-gestational diabetes involves frequent monitoring of blood glucose levels with adjustment of diet and insulin therapy to achieve normoglycemia. Normoglycemia is important because