

STUDY OF NEONATAL HYPOGLYCEMIA IN INFANTS OF DIABETIC MOTHERS IN RELATION TO MATERNAL GLYCEMIC CONTROL IN THE LAST TRIMESTER AND DURING LABOR

Thesis

Submitted for partial fulfillment of Master Degree in
Pediatrics

By

Basma Mohamed Shehata

M.B.B.Ch.

Faculty of Medicine – Ain Shams University

Supervised by

PROF. MONA HUSSEIN AL-SAMAHY

Professor of Pediatrics

Faculty of Medicine - Ain Shams University

DR. MOHAMED SAYED ALI

Assistant Professor of Obstetrics and Gynaecology

Faculty of Medicine - Ain Shams University

DR. KHADIGA YEHIA EL-TONBARY

Lecturer of Pediatrics

Faculty of Medicine - Ain Shams University

Faculty of Medicine

Ain Shams University

2011

Acknowledgment

*I am mostly grateful to **Professor Mona EL-Samahy**, professor of Pediatrics, Faculty of Medicine, Ain Shams University for her sincere, constant support, her valuable guidance and encouragement. I was much honored to do this work under her supervision.*

*I am really indebted to **Dr. Mohamed Said Aly**, assistant professor of Obstetrics & Gynecology, Faculty of Medicine, Ain Shams University for his valuable advice that has been of utmost help in performing this work.*

*I would like to express my sincere gratitude to **Dr. Khadiga El-Tonbary** lecturer of Pediatrics, Faculty of Medicine, Ain Shams University for selection of the point of research and her continuous help.*

I wish to thank all the members of the Obstetrics & Gynecology department and NICU Ain Shams University hospital for their great assistance.

I never forget the help and co-operation of the mothers under study. I wish them and their babies good health.

My cordial thanks and appreciation to my family for their continuous encouragement, sympathy and help which were the major factors behind completion of this work.

دراسة مستوى سكر الدم في حديثي الولادة للأمهات المصابات بالسكري و علاقته بمستوى سكر الدم في الأمهات قبل و أثناء الولادة

رسالة
تمهيداً للحصول علي درجة الماجستير في
طب الأطفال

مقدمة من

طبيبة/ بسمة محمد شحاتة
بكالوريوس الطب والجراحة – جامعة عين شمس

تحت إشراف

أ.د/ منى حسين السماحي
أستاذ طب الأطفال
كلية الطب- جامعة عين شمس

أ.م.د./ محمد سيد علي
أستاذ مساعد أمراض النساء و الولادة
كلية الطب- جامعة عين شمس

د./ خديجة يحيى الطنباري
مدرس طب الأطفال
كلية الطب – جامعة عين شمس

كلية الطب
جامعة عين شمس

٢٠١١

CONTENTS

	Page
List of Abbreviations.....	iv
List of Tables.....	vi
List of Figures.....	viii
INTRODUCTION & AIM OF THE WORK	1
REVIEW OF LITERATURE.....	5
Chapter I: Diabetes Mellitus	5
Definition	5
History.....	5
Epidemiology	6
Classification of diabetes	7
<i>Type I diabetes</i>	8
<i>Type II diabetes</i>	8
<i>Gestational diabetes</i>	9
Pathophysiology	12
Diagnosis	13
Complications.....	15
Management	16
Prognosis.....	17
Chapter II: Diabetes and pregnancy.....	18
Introduction.....	18
Classification of diabetes in pregnancy.....	18
Glucose metabolism in normal pregnancy	20
Consequences of the changes in fuel metabolism during diabetic pregnancy	22
Placenta in diabetic pregnancy.....	24
Gestational Diabetes Mellitus	26
Definition and prevalence.....	26
Detection and diagnosis	26
Long term impact of GDM on maternal health	30
Possible complications in diabetic pregnancy.....	31
Management of diabetic pregnancy.....	34

Chapter III: Infant of Diabetic Mother.....	42
Introduction.....	42
Pathophysiology	42
Diabetic embryopathy.....	45
Clinical manifestations	46
Mortality/Morbidity.....	47
Fetal macrosomia	48
Structural congenital anomalies	52
Intrauterine growth restriction.....	54
Birth trauma	55
Fetal hypoxia	58
Hypoglycemia	59
Hypocalcemia and hypomagnesemia	60
Respiratory distress syndrome	61
Polycythemia.....	62
Hyperbilirubinemia	63
Neurologic development and ossification centers	63
Associated surgical anomalies.....	64
.....	
Management	66
Prognosis	67
Chapter IV: Neonatal hypoglycemia.....	68
Introduction	68
The risk category of newborns with neonatal hypoglycemia ..	69
Incidence	70
The mechanisms of neonatal hypoglycemia.....	70
Clinical presentation	72
.....	
Management	73
<i>Persistent or refractory hypoglycemia</i>	<i>76</i>
<i>Management of persistent hypoglycemia</i>	<i>77</i>
<i>Management of refractory hypoglycemia.....</i>	<i>78</i>
<i>Drug doses</i>	<i>79</i>
PATIENTS AND METHODS	80

RESULTS.....	90
DISCUSSION	10
	7
CONCLUSION AND RECOMMENDATIONS.....	12
	4
SUMMARY	12
	6
REFERENCES.....	13
	0
APPENDIX.....	-
ARABIC SUMMARY	-

LIST OF ABBREVIATIONS

β-cells	: Beta cells
ACA	: Anterior Cerebral Artery
ADA	: American Diabetes Association
BMI	: Body Mass Index
CAH	: Congenital Adrenal Hyperplasia
CS	: Cesarean Section
CTG	: Cardiotopography
DKA	: Diabetic ketoacidosis
DM	: Diabetes Mellitus
eGFR	: estimated Glomerular Filtration Rate
EBM	: Expressed Breast Milk
EPO	: Erythropoietin
FGF-2	: Fibroblast growth-2
FPG	: Fasting Plasma Glucose
GCT	: Glucose Challenge Test
GDM	: Gestational Diabetes Mellitus
GR	: Glucose Requirement
HbA1c	: Hemoglobin A _{1C} (glycated hemoglobin)
HONK	: Hyperosmolar non-ketotic state
IDM	: Infant of diabetic mother
IGF-1	: Insulin-like growth factor-1
IGT	: Impaired Glucose Tolerance
IUGR	: Intrauterine growth restriction
LGA	: Large for gestational age
NCG	: NICE clinical guidelines
NDDG	: National Diabetes Data Group
NICU	: Neonatal Intensive Care Unit
NIDDM	: Non-insulin dependant diabetes mellitus

NIH	⋮	National Institutes of Health
NSLCS	⋮	Neonatal small left colon syndrome
OFC	⋮	Occipito-Frontal Circumference
OGTT	⋮	Oral Glucose Tolerance Test
PG	⋮	Post-Load Glucose
PGDM	⋮	Pre-Gestational Diabetes Mellitus
PVH	⋮	Pathologic ventricular hypertrophy
RBS	⋮	Random Blood Sugar
RDS	⋮	Respiratory Distress Syndrome
RVT	⋮	Renal Vein Thrombosis
SD	⋮	Standard Deviation
SGA	⋮	Small for gestational age
TBG	⋮	Total Blood Glucose
TCUS	⋮	Trans-Cranial Ultrasound
TTN	⋮	Transient Tachypnea of the Newborn
WHO	⋮	World Health Organization
VD	⋮	Vaginal Delivery

LIST OF TABLES

Table No.	Title	Page
REVIEW OF LITERATURE		
I	Etiological classification of disorders of glycemia.....	11
II	Criteria for the diagnosis of diabetes	13
III	White's classification of diabetes during pregnancy	19
IV	Fetal problems associated with maternal hyperglycemia according to trimesters of gestation	23
V	Diagnosis of GDM with a 100-g or 75-g glucose load.....	30
VI	Malformations associated with pre-existing diabetes.....	53
VII	Hypoglycemia risk categories and their management	75
VIII	Staged investigation or persistent/refractory hypoglycemia.....	77
RESULTS		
1	Distribution of the studied group of diabetic mothers as regard general data.....	90
2	Distribution of the studied group of diabetic mothers as regard history of abortion	90
3	Distribution of the studied group as regard maternal DM.....	91
4	Results of maternal blood glucose measurements	92
5	Distribution of the studied mothers as regard HBA1C measurement results.....	92
6	Distribution of the studied group as regard mode and duration of delivery.....	93
7	Clinical data of the studied newborns.....	94

8	Distribution of the studied newborns as regard antenatal investigations	96
9	Distribution of the studied group as regard infant's congenital anomalies	97
10	Relation between congenital anomalies and clinical data of the newborns.....	98
11	Relation between maternal DM data and congenital anomalies in the newborn infants	99
12	Relation between maternal blood glucose levels and infants' congenital anomalies	99
13	Changes of mean infant blood glucose levels after birth. (immediately until 1 hour after birth)	101
14	Mean infant blood glucose levels in relation to congenital anomalies	102
15	Correlations between maternal RBS during labor and data of newborn infants	103
16	Correlation between maternal HBA _{1C} and infant birth weight	105

LIST OF FIGURES

Fig. No.	Title	Page
REVIEW OF LITERATURE		
I	Main symptoms of diabetes	15
II	Result of maternal hyperglycemia (modified Pedersen's hypothesis)	24
III	The fetal and neonatal events attributable to fetal hyperglycemia and fetal hyperinsulinemia.....	44
IV	Infant of diabetic mother	48
V	Babygram.....	51
VI	Erb's palsy	57
VII	Gastrograffin enema	66
VIII	Effect of Hypoglycemia at the cellular level	72
IX	Flow Chart for the management of accucheck < 3 mmol/l in an asymptomatic infant	73
X	Algorithm for prevention and management of hypoglycemia in babies at risk	75
RESULTS		
1	Distribution of the newborn infants according to mode of delivery	93
2	Distribution of the newborn infants according to Apgar score at 5 min.....	95
3	Distribution of the newborn infants according to birth weight	95
4	Types of congenital anomalies	97
5	Distribution of the newborn infants according to blood glucose level	100
6	Changes of mean infant blood glucose levels after birth (immediately until 2 hours after birth).....	101

7	Mean infant blood glucose levels in relation to congenital anomalies	102
8	Correlation between maternal RBS and Apgar score at 5 minutes.....	104
9	Correlation between RBS of mothers during labor and blood sugar level of the newborn at birth	104
10	Correlation between maternal HBA _{1C} and birth weight of the newborn	105

INTRODUCTION

Diabetes Mellitus has long been associated with maternal and perinatal morbidity and mortality. Fetal and neonatal mortality rates were as high as 65% before the development of specialized maternal, fetal and neonatal care. Since then, infants of diabetic mothers (IDMs) have experienced a nearly 30-fold decrease in morbidity and mortality rates.

Infants born to mothers with glucose intolerance are at an increased risk of morbidity and mortality related to the following:

- Respiratory distress
- Growth abnormalities (large for gestational age [LGA], small for gestational age [SGA])
- Congenital malformations
- Hypoglycemia
- Polycythemia
- Hypocalcemia, hypomagnesemia and iron abnormalities (**Nold & Georgieff, 2007**).

About 3-10% of pregnancies are affected by abnormal glucose regulation and control. Of these cases, 80-88% are related to abnormal glucose control of pregnancy or gestational diabetes mellitus (**Nold & Georgieff, 2004**).

The quantitative definition of hypoglycemia in the newborns remains elusive because it is a surrogate marker for central nervous system energy deficiency (**Straussman et al., 2010**).

Infants born to diabetic mothers tend to have a high rate of hypoglycemia on the first day of life when a relatively high cut-off point ($> \text{ or } = 47 \text{ mg/dl} = 2.6 \text{ mmol/l}$) is used. Infants born large for gestational age as well as those born to mothers with juvenile diabetes mellitus are at higher risk and should be closely monitored (**Maayan-Metzger et al., 2009**).

Hypoglycemia is caused by hyperinsulinemia due to hyperplasia of fetal pancreatic beta cells consequent to maternal-fetal hyperglycemia. Because the continuous supply of glucose is stopped after birth, the neonate develops hypoglycemia because of insufficient substrate. Stimulation of fetal insulin release by maternal hyperglycemia during labor significantly increases the risk of early hypoglycemia in these infants (**Barnes-Powell, 2007**).

Hypoglycemia may present within the first few hours of life. Although the infant is generally asymptomatic, symptoms may include jitteriness, irritability, apathy, poor feeding, high pitched or weak cry, hypotonia, or frank seizure activity. Hypoglycemia that requires intervention may persist for as long as one week (**Cornblath et al., 2000**).

Hypoglycemia in the newborn may be associated with both acute decompensation and long term neuronal loss (**Straussman et al., 2010**).

Third trimester glycemic parameters are more powerful predictors of fetal growth than glycemic parameters earlier in pregnancy or during preconception (**Herranz, 2007**).

It has been shown that in a diabetic mother, maternal hyperglycemia during the last four hours and during labor significantly increases the risk of early neonatal hypoglycemia (*Murthy, 2002 & Barnes-Powell, 2007*).