# End Glycated Proteins In Pregnant Diabetics With Pregnancy Induced Hypertension

*Thesis*
*Submitted For Partial Fulfillment Of*
*The M.D. Degree Of*
*Internal Medicine*

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*2013*

# Acknowledgement

First of all, ultimate thanks are due to God who without his help, this work would not have been accomplished

I would like to express my sincere gratitude to **Professor Aly Al-Ashmawy,** Professor of Internal Medicine, Faculty of Medicine, Cairo University, for his valuable supervision & support.

I would like to express my sincere gratitude to **Professor Hebat-Allah Moustafa**, Professor of Internal Medicine, Faculty of Medicine, Cairo University, for her efforts & for her valuable advices & recommendations.

I would like to express my thanks to **Dr. Ahmed Soliman Nasr**, Assistant Professor of Obstetrics & Gynecology, Faculty of Medicine, Cairo University, who provided me with a lot from his experience & knowledge throughout this work.

I would like to dedicate this work to all my family members who participated in the execution of this work.

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# List of Abbreviations

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|---|---|
| *ACE* | Angiotensin-converting enzyme |
| *ACHOIS* | Australian Carbohydrate Intolerance Study in Pregnant Women |
| *ACOG* | American College of Obstetricians and Gynecologists |
| *ADA* | American Diabetes Association |
| *ADHD* | Attention-deficit/hyperactivity disorder |
| *AEDFV* | Absent end-diastolic flow velocity |
| *ALT* | Alanine Amino-Transferase |
| *ARBs* | Angiotensin II receptor blockers |
| *AST* | Aspartate Amino-transferase |
| *BMI* | Body Mass Index |
| *ChIPs* | Chromatin immunoprecipitations |
| *CRP* | C-reactive protein |
| *DBP* | Diastolic blood pressure |
| *ECG* | Electrocardiogram |
| *FDA* | Food and Drug Administration |
| *GDM* | Gestational Diabetes mellitus |
| *GH* | Gestational hypertension |
| *H3K9* | Histone methylated on K9 |
| *HbA$_{1C}$* | Glycated Hemoglobin |
| *HLA* | Human leucocytic antigen |
| *HUVEC* | Human umbilical vein endothelial cells |
| *IADPSG* | International Association of Diabetes and Pregnancy Study Group |
| *IGF* | Insulin like growth factor |
| *iNOs* | Isoenzyme Nitric oxide synthases |

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| | |
|---|---|
| *IOM* | Institute of Medicine |
| *IRs* | Insulin receptors |
| *IUGR* | Intra uterine growth retardation |
| *LGA* | Large for gestational age |
| *MCP-1* | Monocyte chemotactic protein-1 |
| *NO* | Nitric oxide |
| *NPH* | Neutral protamine hagedorn |
| *NST* | Nonstress test |
| *OGTT* | Oral Glucose tolerance test |
| *PG* | Prostaglandins |
| *PI* | Pulsatility index |
| *PIH* | Pregnancy Induced Hypertension |
| *RDS* | Respiratory distress syndrome |
| *RI* | Resistance index |
| *S/D* | Systolic/ Diastolic |
| *SBP* | Systolic blood pressure |
| *SC* | Subcutaneously |
| *SD* | Standard Deviation |
| *SGA* | Small for gestational age |
| *SMC* | Smooth muscle cells |
| *SOGC* | Society of Obstetricians and Gynecologists of Canada |
| *STZ* | Streptozotocin |
| *USPSTF* | United States Preventive Services Task Force |
| *VCAM-1* | Vascular cell adhesion molecule-1 |
| *VE* | Vascular endothelium |
| *VEGF* | Vascular endothelial growth factor |
| *VEGFR* | Vascular endothelial growth factor receptor |

# INTRODUCTION

# Introduction and Aim of The Work

## Introduction

Diabetes mellitus is described as a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, insulin action or both *(Alberti and Zimmet, 1998)*.

Physiological insulin resistance is noted during late pregnancy and patients with gestational diabetes show more insulin resistance compared with pregnant control subjects with normal glucose tolerance *(Witlin AG and Sibai BM, 1999)*.

Pregnancy induced hypertension (PIH) and /or pre-eclampsia have been associated with hyperinsulinemia in both cross-sectional study designs *(Kaaja R et.al., 1995)* and cohort studies *(Sowers JR et.al., 1995)*.

Glycosylated hemoglobin (HbA$_{1C}$) level reflects the average plasma glucose to which the hemoglobin is exposed during the erythrocyte's life span of about 90 days and may be less influenced by the acute stress of illness *(Laura SG et.al., 2003)*.

Major congenital malformations remain the leading cause of mortality and serious morbidity in infants of mothers with type 1 or type 2 diabetes. Several studies have established an association between elevated maternal glucose or glycated hemoglobin levels during embryogenesis and

high rates of spontaneous abortions and major malformations in newborns *(Kitzmiller JL et.al., 1996).*

Ducey et.al., 1987, stated that a description of uterine systolic/diastolic (S/D) ratio should be part of the clinical evaluation of all pregnant women with hypertension *(Chein et.al., 2000).*

# *Aim of the work*

The aim of this work is to study the levels of end glycated proteins in pregnant diabetics with PIH and the relation of levels of $HbA_{1C}$ to the fetal and placental blood flow in these patients.

REVIEW

# *Chapter 1*

## *Pregnancy and Diabetes Mellitus*

Normal pregnancy has been characterized as a "diabetogenic state". Abnormal maternal glucose regulation occurs in 3-10% of pregnancies. Pregnancy is characterized by insulin resistance with a compensatory increase in β-cell response and hyperinsulinemia, thus it may predispose some women to develop diabetes.

Insulin resistance usually begins in the second trimester and progresses throughout the remainder of the pregnancy. Insulin sensitivity is reduced by as much as 80%. Placental secretion of hormones, such as progesterone, cortisol, placental lactogen, prolactin, and growth hormone, is a major contributor to the insulin-resistant state seen in pregnancy. The insulin resistance likely plays a role in ensuring that the fetus has an adequate supply of glucose by changing the maternal energy metabolism from carbohydrates to lipids. There is increased maternal adipose deposition, decreased exercise, and increased caloric intake. These and other endocrinologic and metabolic changes ensure that the fetus has adequate supply of fuel and nutrients at all times. Gestational diabetes occurs when pancreatic function is not sufficient to overcome the insulin resistance created by changes in diabetogenic hormones during pregnancy *(Cianni et al., 2003)*.

On the other hand, the adipose tissue is now considered an active organ, capable of secreting substances such as adipokines, which may play a role in the pathogenesis of insulin resistance. Resistin, leptin serum and placental levels increase as pregnancy progresses, which is in contrast to

levels of adiponectin. These levels correlate with the state of reduced insulin sensitivity often developed in the latter stages of pregnancy *(Gomez et al, 2008)*

## *Maternal-Fetal Metabolism in Diabetes mellitus:*

If the maternal pancreatic insulin response is inadequate, maternal and, then, fetal hyperglycemia results. This typically manifests as recurrent postprandial hyperglycemic episodes. These postprandial episodes are the most significant source of the accelerated growth exhibited by the fetus.

Surging maternal and fetal glucose levels are accompanied by episodic fetal hyperinsulinemia. Fetal hyperinsulinemia promotes excess nutrient storage, resulting in macrosomia. The energy expenditure associated with the conversion of excess glucose into fat causes depletion in fetal oxygen levels.

These episodes of fetal hypoxia are accompanied by surges in adrenal catecholamines, which, in turn, cause hypertension, cardiac remodeling and hypertrophy, stimulation of erythropoietin, red cell hyperplasia, and increased hematocrit. Polycythemia (hematocrit >65%) occurs in 5-10% of newborns of diabetic mothers. This finding appears to be related to the level of glycemic control and is mediated by decreased fetal oxygen tension. High hematocrit values in the neonate lead to vascular sludging, poor circulation, and postnatal hyperbilirubinemia.

During a healthy pregnancy, mean fasting blood sugar levels decline progressively to a remarkably low value of $74 \pm 2.7$ (standard deviations [SD]) mg/dL. However, peak postprandial blood sugar values rarely exceed 120 mg/dL. Meticulous replication of the normal glycemic profile

during pregnancy has been demonstrated to reduce the macrosomia rate. Specifically, when 2-hour postprandial glucose levels are maintained below 120 mg/dL, approximately 20% of fetuses demonstrate macrosomia. If postprandial levels range up to 160 mg/dL, macrosomia rates rise to 35%.

## New terminology and diagnostic criteria:

The term "gestational diabetes" has been used to define women with onset or first recognition of abnormal glucose tolerance during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) continues to use this terminology *(Committee opinion no. 504, 2011)*.

However, in 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG), an international consensus group with representatives from multiple obstetrical and diabetes organizations, recommended a change to this terminology *(International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger et al., 2010)*. In this system, diabetes diagnosed during pregnancy is classified as overt or gestational. In January 2011, the American Diabetes Association (ADA) endorsed this recommendation. *(American Diabetes Association, 2011)*

### Overt diabetes:

A diagnosis of overt diabetes can be made in women who meet any of the following criteria at their initial prenatal visit:
- Fasting plasma glucose $\geq$126 mg/dL, or
- $HbA_{1C}$ $\geq$6.5 percent using a standardized assay, or
- Random plasma glucose $\geq$200 mg/dL that is subsequently confirmed by elevated fasting plasma glucose or $HbA_{1C}$.

These thresholds were chosen because they correlate with development of adverse vascular events, such as retinopathy and coronary artery disease.

The rationale for this change is that an increasing proportion of young women have overt but as yet unrecognized type 2 diabetes due to the increasing prevalence of obesity and lack of routine glucose screening/testing in this age group.

In addition, about 10 percent of women formerly classified as having gestational diabetes have circulating islet-cell antibodies; these women may have a "latent" form of type 1 diabetes *(Järvelä et al., 2006)*. Their risk of developing type 1 diabetes is not known, but specific Human leucocytic antigen (HLA) alleles (DR3 or DR4) appear to predispose to the development of type 1 diabetes after delivery, as does the presence of islet-cell antibodies *(Ferber et al., 1999)*. Gestational diabetes in lean pregnant women, need for insulin treatment of gestational diabetes, diabetic ketoacidosis during pregnancy, and postpartum hyperglycemia also suggest preexisting unrecognized type 1 diabetes.

Identifying overt diabetes early in pregnancy may be important because these women are at increased risk of having a child with a congenital anomaly and may be at increased risk of complications from diabetes (nephropathy, retinopathy) *(Omori and Jovanovic, 2005)*. Early identification and treatment of hyperglycemia may reduce these risks.