# Cord Vaspin Hormone in Large for Gestational Age Neonates

*Thesis*

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**Ayat Alhasafy Abdalhameid Shoaub**

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# List of Abbreviations

| Abb. | Full term |
|---|---|
| **ACOG** | American Congress of Obstetricians and Gynecologists |
| **AGA** | appropriate for gestational age |
| **AGA** | Appropriate for gestational age |
| **BMI** | Body mass index |
| **BPI** | Brachial plexus injury |
| **BWS** | Beckwith- Wiedemann syndrome |
| **CPAP** | Continuous positive airway pressure. |
| **ELISA** | Enzyme linked immune sorbent assay |
| **GDM** | Gestational diabetes mellitus |
| **HAPO** | Hyperglycemia and Adverse Pregnancy Outcomes cooperative research group |
| **HOMA-IR** | The homeostatic model assessment for insulin resistance |
| **IDM** | Infant of diabetic mother |
| **IUGR** | Intrauterine growth restriction |
| **LGA** | Large for gestational age |
| **MCP-1** | Monocyte chemotactic protein-1 |
| **NICU** | A neonatal intensive care unit |
| **NSLCS** | Neonatal small left colon syndrome |
| **OFC** | Occipito frontal circumference |
| **PAI-1** | Plasminogen activator inhibitor-1 |
| **RBP4** | Retinol binding protein 4 |
| **RCP** | Reactive center loop |
| **RDS** | Respiratory distress syndrome |
| **SVF** | Stromal vascular fraction |
| **TNFα** | Tumor necrosis factor-alpha |
| **VEGF** | Vascular endothelial growth factors |
| **WAT** | White adipose tissue |
| **GLUT4** | Glucose transporter 4 |

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# INTRODUCTION

Human pregnancy is characterized by a progressive decrease in insulin sensitivity, which parallels the growth of the feto-placental unit and facilitates the diversion of glucose to the fetus. Gestational insulin resistance is enhanced in pregnancy complications that are associated with disturbed placental function, such as gestational diabetes mellitus (GDM), preeclampsia (PE), and intrauterine growth restriction (IUGR) ***(Zhang et al., 2013).***

A large body of evidence has recently supported the role of adipose tissue in the regulation of insulin resistance through adipocytokines, which are adipocyte-derived hormones. Adipocytokines, include leptin, adiponectin, tumor necrosis factor alpha, interleukin 6, as well as the newly discovered resistin, vaspin and apelin, which are also known to be produced within the intrauterine environment ***(Briana and Malamitsi-Puchner, 2009).***

Large for gestational age (LGA) infants are at increased risk of developing disturbances in glucose metabolism. Maternal hyperglycemia lead to fetal hyperglycemia which in turn stimulates the fetal pancreatic islet cells and causes hyperinsulinaemia. In LGA neonate, hyperinsulinaemia inutero marosomia and may also cause alterations in metabolic programming, which can have long-term effects, such as

impaired glucose homeostasis during child hood ***(Kim et al., 2014).***

Hyperinsulinaemia in large birth weight neonate is usually present before these abnormalities (hypertension, dyslipidaemia, obesity and insulin resistance) become detectable and has been proposed as the common trigger of the constellation. Vaspin was identified as an adipokine with insulin-sensitizing effects, which is predominantly secreted from visceral adipose tissue in a rat model of type 2 diabetes. Studies have recently showed that mRNA of vaspin expression in adipose tissue is related to parameters of obesity and glucose metabolism. There is hypothesizes that circulating vaspin concentration is linked to markers of insulin sensitivity and metabolic disturbance in the LGA infants ***(Fenton, 2003).***

# Aim of the Work

To assess serum vaspin concentration in large for gestational age neonates and to investigate the influence of maternal diabetes on cord blood vaspin.

*Chapter 1*

# INFANTS OF DIABETIC MOTHERS

## Definition

Infant of diabetic mother (IDM) is an infant born to woman who is suffering from diabetes mellitus, but this term refers specifically to the neonate born to a woman who had persistently hyperglycemia during pregnancy ***(Mimoun et al., 2013).***

## Pathophysiology:

The probable pathogenic sequence is that maternal hyperglycemia causes fetal hyperglycemia, and the fetal pancreatic response leads to fetal hyperinsulinemia. Hyperinsulinemia and hyperglycemia then cause increased hepatic glucose uptake and glycogen synthesis, accelerated lipogenesis and augmented protein synthesis. Related pathologic findings are hypertrophy and hyperplasia of the pancreatic islet P-cells, increased weight of the placenta and infant organs except for the brain, myocardial hypertrophy increased amounts of cytoplasm in liver cells and extramedullary hematopoiesis hypertrophy, increased amounts of cytoplasm in liver cells; and extramedullary hematopoiesis ***(Maayan-Metzger et al., 2015).***

## Maternal Fetal Metabolism in Normal Pregnancy

In the pregnant woman, each meal sets in motion a complex series of hormonal actions, including a rise in blood glucose and the secondary secretion of pancreatic insulin, glucagon, somatomedins, and adrenal catecholamines ***(Logan et al., 2017).***

These adjustments ensure that an ample, but not excessive, supply of glucose is available to the mother and fetus. Compared with nonpregnant subjects, pregnant women tend to develop hypoglycemia (plasma glucose mean = 65-75 mg/dL) between meals and during sleep.

This occurs because the fetus continues to draw glucose across the placenta from the maternal bloodstream, even during periods of fasting. Interprandial hypoglycemia becomes increasingly marked as pregnancy progresses and the glucose demand of the fetus increases ***(Elmekkawi et al., 2015)***.

Levels of placental steroid and peptide hormones (eg, estrogens, progesterone, and chorionic somatomammotropin) rise linearly throughout the second and third trimesters. Because these hormones confer increasing tissue insulin resistance as their levels rise, the demand for increased insulin secretion with feeding escalates progressively during pregnancy. By the third trimester, 24hour mean insulin levels are 50% higher than in the non-pregnant state ***(Vela-Huerta et al., 2012)***.

## Maternal Fetal Metabolism in Diabetes

If the maternal pancreatic insulin response is inadequate, maternal and fetal hyperglycemia will result as an expected sequele. This typically manifests as recurrent postprandial hyperglycemic episodes. These postprandial episodes are the most significant source of the accelerated growth exhibited by the fetus suffering from this unhealthy condition. 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 ***(Elmekkawi et al., 2015)***.

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 51.0% 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 ± 2.7 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 2hour 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% ***(Stenninger et al., 2010).***

## Clinical manifestations:

Infants of diabetic mothers often bear a surprising resemblance to each other. They tend to be large and plump as a result of increased body fat and enlarged viscera, with puffy plethoric facies resembling that of patients who have been receiving corticosteroids **(Fig. 1).**

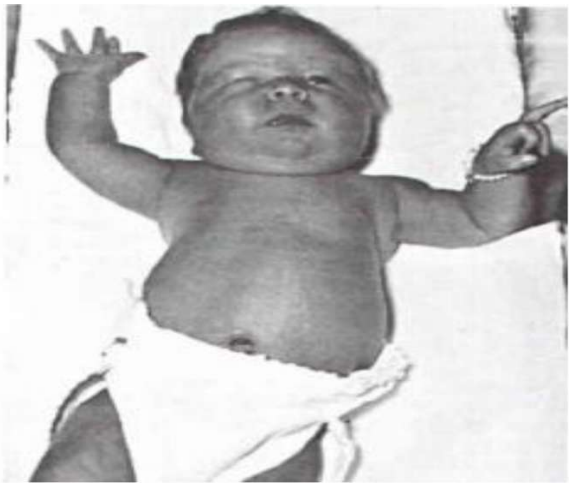

**Figure (1):** Infant of diabetic mother. Large, plump, plethoric infant of a gestational diabetic mother. The baby was born at 38 wk of gestation but weighed 4408 g ***(Stoll, 2016).***