Soluble Intercellular Adhesion Molecule-1 (sICAM-1) In Macrosomic Infants Of Diabetic Mothers

Thesis

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List of Abbreviations

AGA	Appropriate for gestational age
AMs	Adhesion molecules
BMI	Body mass index
CAMs	Cell Adhesion molecules
cICAMs	Circulating Intracellular adhesion molecules
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DM	Diabetes mellitus
ECM	Extracellular matrix
ELAM-1	Endothelial leucocyte adhesion molecule-1
ELISA	Enzyme linked immunosorbent assay
GDM	Gestational diabetes mellitus
GH	Growth hormone
HbA_1c	Glycosylated haemoglobin
hCS	Human chorionic somatomammotropin
HDL	High density lipoprotein
hPL	Human placental lactogen
ICAMs	Intracellular adhesion molecules
IDDM	Insulin-dependent diabetes mellitus
IDMs	Infants of diabetic mothers
Ig	Immunoglobulin
IGF-1	Insulin like growth factor- 1
IGFBP-3	Insulin like growth factor binding protein- 3
IL-1	Interleukin-1
IL-2	Interleukin -2
IM	Intramuscular
IUGR	Intrauterine growth retardation
LAD	Leucocyte adhesion deficiency
LDL	Low density lipoprotein
MIDM	Macrosomic infant of diabetic mother
NEC	Necrotizing enterocolitis
NMIDM	Non-macrosomic infant of diabetic mother
PG	Phosphatidylglycerol
PTH	Parathyroid hormone
QTc	Corrected QT interval
RDS	Respiratory distress syndrome
SC	Subcutaneous
SGA	Small for gestational age
TG	Triglycerides
VCAM	Vascular cell adhesion mole

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Chapter 1

INFANT OF DIABETIC MOTHER

Background:

Diabetes has long been associated with maternal and perinatal morbidity and mortality. Before the discovery of insulin in 1921 , diabetic women rarely reached reproductive age or survived pregnancy. In fact, pregnancy termination was recommended routinely for pregnant diabetic patients because of high mortality rates ***(Potter and Kicklighter, 2009).***

Pregnancy itself is diabetogenic caused by increased insulin resistance due to the production of hormones like estrogen, progesterone, cortisol, human chorionic somatomammotropin (hCS) and human placental lactogen (hPL). The latter increases lipolysis which provides free fatty acids and ketones as fuels for energy for the pregnant mothers. This spares maternal blood glucose, amino acids and ketones which cross the placenta to the fetus. The influx of nutrients increases fetal insulin production which together with hPL induce somatogenesis ***(Butte, 2000).***

Diabetes mellitus (DM) is a multisystem disease with both biochemical and anatomical consequences. It is a chronic disease of carbohydrate, fat and protein metabolism caused by the lack of insulin in type 1diabetes; beta cells are destroyed, or lack of insulin function in type 2 diabetes due to insulin resistance. Type 1 DM occurs most commonly in juveniles, but can occur in adults ***(Yang et al., 2006).***

DM is the most common medical complication of pregnancy. Gestational diabetes mellitus (GDM); defined as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy, represents approximately 90% of these cases. It affects 2–5% of all pregnancies, while Preexisting diabetes mellitus complicates 0.2% to 0.3%of pregnancies ***(Moshe, 2002).***

GDM develops when a woman is unable to secrete sufficient insulin to compensate for either increase insulin resistance or increase its demand or both during pregnancy. Women who develop GDM are at

increased risk for type 2 diabetes mellitus. The screening and diagnostic methods for GDM remain controversial, especially the threshold values for the diagnosis ***(Ben-Haroush et al., 2004).***

Diabetes in pregnancy carries a significant risk to both the fetus and the mother. Despite major advances in clinical management, we still face a higher incidence of malformations and perinatal morbidity in diabetic compared to non-diabetic population ***(Evers et al., 2004).***

Improved management of diabetes mellitus and advances in obstetrics such as ultrasound and measurement of fetal lung maturity have reduced the incidence of adverse perinatal outcome in infants of diabetic mothers (IDMs). With appropriate management, women with good glycemic control and minimal microvascular disease can expect pregnancy outcomes comparable to the general population ***(Crowther et al., 2005).***

Classification of DM in pregnancy:

Diabetes that antedates pregnancy is grouped by the White's classification, according to the length of disease and presence of vascular complications. White's classification of maternal diabetes will be listed in table (1).

Table (1): Modified White's classification of diabetes in pregnancy ***(Hare and White, 1980).***

Class	Description
A	Abnormal GTT at any age or of any duration treated only by diet therapy
B	Onset at age 20 years or older and duration of less than 10 years
C	Onset at age 10-19 years or duration of 10-19 years
D	Onset before 10 years of age, duration over 20 years, benign retinopathy, or hypertension (not preeclampsia)
D1	Onset before age 10 years
D2	Duration over 20 years
D3	Calcification of vessels of the leg (macrovascular disease), formerly called Class E
D4	Benign retinopathy (microvascular disease)
D4	Hypertension (not preeclampsia)
R	Proliferative retinopathy or vitreous hemorrhage
F	Nephropathy with over 500 mg/day proteinuria
RF	Criteria for both classes R and F
G	Many pregnancy failures
H	Evidence of arteriosclerotic heart disease
T	Prior renal transplantation
Gestational diabetics	
A1	Diet-controlled gestational diabetes
A2	Insulin-treated gestational diabetes

Classes B through T require insulin treatment.

Incidence:

Insulin-dependent diabetes mellitus (IDDM) occurs in 0.5% of all pregnancies. In addition, 1-3 % of women exhibit biochemical abnormalities during pregnancy consistent with gestational diabetes ***(Gomella et al., 2004).***

Etiology of diabetes mellitus:

The etiological classification of DM will be listed in table (2).

Table (2): Etiologic classification of diabetes mellitus ***(The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).***

I. Type 1 diabetes (ß-cell destruction, usually leading to absolute insulin deficiency)
A. Immune mediated
B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III. Other specific types
A. Genetic defects of ß-cell function
Maturity onset diabetes of the youth (MODY) type 1,2,3,4,5 and 6
B. Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
C. Diseases of the exocrine pancreas
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
D. Endocrinopathies
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
E. Infections
1. Congenital rubella
2. Cytomegalovirus
F. Uncommon forms of immune-mediated diabetes
1. "Stiff-man" syndrome
2. Anti–insulin receptor antibodies
G. Other genetic syndromes sometimes associated with diabetes
1. Chromosomal abrasion such as: Down's syndrome ,
Klinefelter's syndrome and Turner's syndrome
2. Hereditary neurological disorders as: Friedreich's ataxia ,
Huntington's chorea and Myotonic dystrophy.
3. Paternal and maternal imprinting as in Laurence-Moon-Biedl Syndrome and Prader-Willi syndrome, respectively.
4. Porphyria
5. Wolfram's syndrome
H. Drug- or chemical-induced
1. Vacor , Pentamidine , Nicotinic acid , Glucocorticoids ,Thyroid
Hormone, Diazoxide, ß-adrenergic agonists, Thiazides,
Dilantin and α-Interferon.
IV. Gestational diabetes mellitus (GDM)

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

Maternal complications in diabetic pregnancy:

Maternal complications increased twofold or more with high glucose concentrations and included cesarean section and clinical chorioamnionitis. Chorioamnionitis in combination with high maternal glucose concentration increased the risk of very preterm delivery almost 12-fold. Complications included delivery by cesarean, pregnancy-induced hypertension (diastolic blood pressure of >90 mmHg). ***(Scholl et al., 2001).***

• Diabetic keto-acidosis:

Ketoacidosis is potentially lethal to the fetus at any stage of pregnancy. Women should be instructed to test their urine for ketones if their blood glucose readings are high or if they feel unwell ***(Abourawi, 2006).***

• Chorioamnionitis:

Clinical chorioamnionitis (two or more of the following: uterine contractions, fever, maternal or fetal tachycardia, uterine tenderness, foul-smelling discharge or amniotic fluid, leukocytosis) ***(Scholl et al., 2001).***

• Deterioration of nephropathy:

Baseline assessment of renal function by serum creatinine and urinary protein excretion (urine albumin/creatinine ratio, or 24-hour albumin excretion) should be undertaken before conception. Angiotensin converting enzyme-inhibitors, beta blockers and diuretics should be avoided in pregnant women if they are being used for hypertension. Methyl-Dopa or Labetalol may be substituted ***(Abourawi, 2006).***

• Visual deterioration/retinopathy

• Vomiting (gastric neuropathy)

• Miscarriages

• Pre-eclampsia

• Polyhydramnios

• Premature delivery (Sibai et al., 2000).

Fetal complications in diabetic pregnancy:

- ***Congenital anomalies****: cardio-vascular, central nervous system, skeletal (sacral agenesis), and genito-urinary*
- ***Excessive fetal growth*** *(macrosomia)*
- ***Fetal growth retardation*** (in diabetic pregnancy complicated by nephropathy and macrovascular disease causing placental insufficiency) **(*Farrell et al., 2002).***

Neonatal complications in diabetic pregnancy:

- ***Traumatic delivery, especially shoulder dystocia***
- ***Pulmonary surfactant deficiency causing respiratory distress syndrome (RDS)***
- ***Hypoglycaemia***
- ***Hypocalcaemia***
- ***Hypomagnesaemia***
- ***Polycythaemia***
- ***Hyperbilirubinaemia***

(Farrell et al., 2002)

Pathophysiology:

When insulin is insufficient to meet the considerable demands placed on the insulin secretory reserves in pregnancy, significant derangements occur in the maternal metabolism. These changes are reflected in the metabolic environment of the conceptus ***(Hod, 2002).***

It is generally accepted that metabolic disturbances in the mother mediate virtually all the adverse effects of DM on the offspring ***(Manderson et al., 2003).***

The fetus is subjected to high levels of glucose during times of maternal hyperglycemia as glucose traverses the placental membranes. Using a carrier-mediated facilitated diffusion mechanism, fetal glucose levels are maintained at a level that is 20-30 mg/dl lower than those of the

mother. On the other hand, insulin is unable to cross from maternal to fetal circulation ***(Hod et al., 1999).***

A number of key hypotheses have helped to define the relationships between maternal metabolism and adverse outcomes. The Pederson hypothesis (Pederson, 1965) holds that maternal hyperglycemia leads to fetal hyperglycemia, which in turn causes fetal β-cell hyperplasia and increased insulin secretion. Freinkel (1985) later extended this hypothesis to include, other maternal substrates reaching the fetus especially amino acids, which also stimulate fetal insulin secretion. This surfeit of mixed nutrients in the presence of elevated fetal insulin concentrations is responsible for macrosomia. The carryover of fetal hyperinsulinemia after birth and the hyperresponsivness of the β-cell in the newborn cause hypoglycemia ***(Kitzmiller and Davidson, 1998).***

Maternal hyperglycemia and fetal hypoxemia are shown to be responsible for structural congenital anomalies of the rapidly developing organs of the fetus during the early weeks of gestation while continuing hyperglycemia and hypoxemia in the second and third trimesters are factors related to the production of cardiomyopathy, delay in lung maturation and polycythemia ***(Manderson et al., 2003).***

Metabolic problems such as hypoglycemia, hypocalcemia, hypomagnesemia and hyperbilirubinemia are common neonatal morbidities ***(Coetzee and Levitt, 2000).***

The fetal neonatal events attributable to fetal hyperglycemia and hyperinsulinemia are illustrated in figure(1).

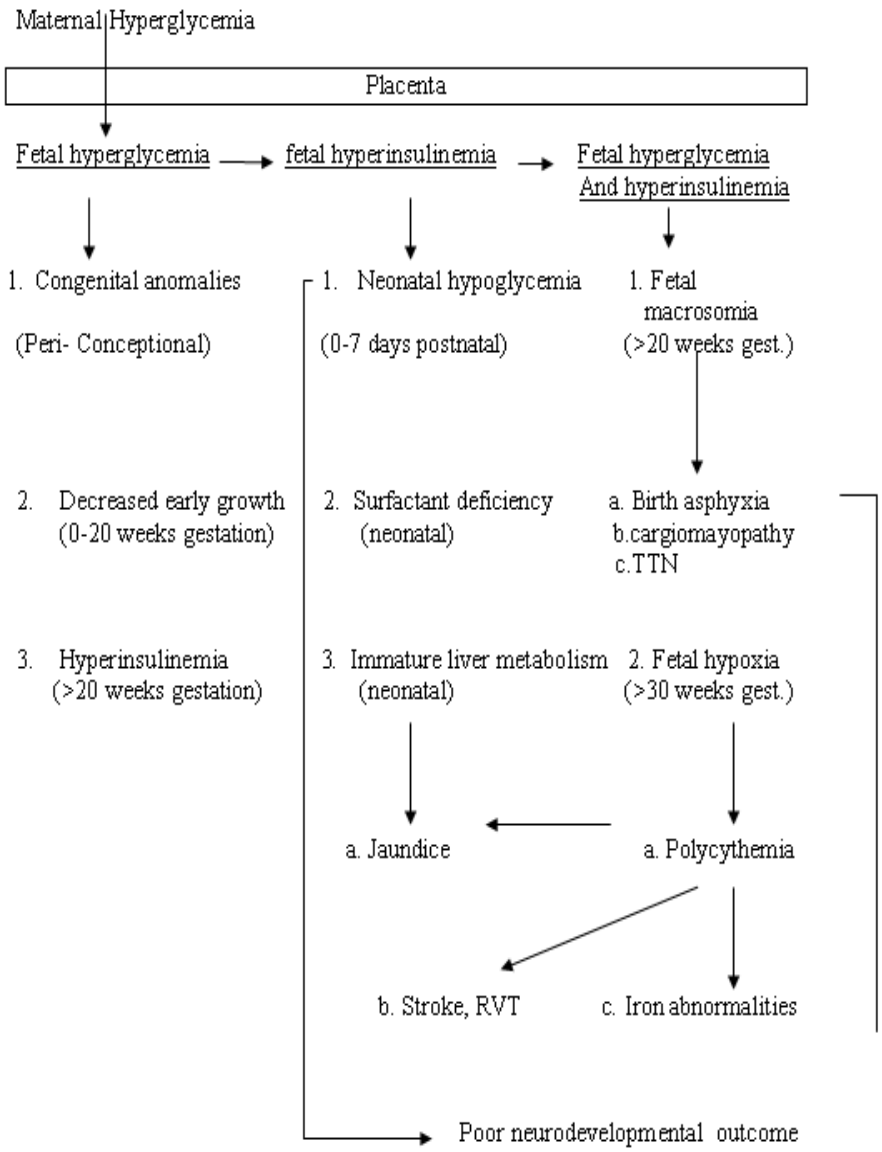

Figure (1): The fetal neonatal events attributable to fetal hyperglycemia (column 1), fetal hyperinsulinemia (column 2), or both in synergy (column 3). Time of risk is denoted in parentheses ***(Nold and Georgieff, 2004).***
TTN: Transient tachypnea of newborn, **RVT:** Renal vein thrombosis.

Complications frequently encountered in IDMs:

[I] Metabolic complications

1) Hypoglycemia

Definition:

Hypoglycemia is defined as a blood glucose level < 35 mg/dl in a preterm or term infant. It is present in up to 40% of IDMs, most commonly in macrosomic infants. It usually presents within 1-2 hours after delivery ***(Gomella et al., 2004).***

Others, define hypoglycemia as mild if serum glucose concentration was 30-39 mg/dl, moderate if serum glucose concentration 20-29 mg/dl, and severe if <20mg/dl ***(Schwartz and Teramo, 2000).***

Although definitions are controversial, most authors agree that neonatal hypoglycemia is a plasma glucose concentration of <45 mg/dl (2.5 mmol/liter) within the first 24 hours of life, or <50 mg/dl (2.8 mmol/liter) thereafter; levels lower than this place the neonate at risk for hypoglycemic-induced neurologic dysfunction ***(Newborn Nursery QI Committee, 2006).***

Therefore, on the basis of recent developmental, neuroanatomic, metabolic and clinical studies, the goal is to maintain the glucose value above 45 mg/dl in the first day, and more than 50mg/dl thereafter ***(Crowther et al., 2005).***

However, the optimal glucose value and risk for neurological sequelae probably varies from infant to infant depending on their brain maturity, glycogen stores, presence of hypoxia or ischemia, activity of gluconeogenic pathways, glucose transport status and brain glucose demand ***(Cornblath and Ichord, 2000).***

Wilker (2008), mentioned that the clinical definition of hypoglycemia is Whipple's triad:

a) Reliable measurement of a low glucose level.

b) Signs and symptoms consistent with hypoglycemia (development of clinical signs or symptoms may be a late sign of hypoglycemia).

c) Resolution of signs and symptoms after blood glucose level is restored to normal range.

Incidence:

The incidence of hypoglycemia in IDMs has been reported as high as 50% in some studies. The incidence of hypoglycemia is highest at 1-4 hours of age, after the fall in plasma glucose following the cessation of maternal glucose infusion. The hypoglycemia in IDMs is usually transient and easily treated. With good prenatal diabetic control, the incidence of hypoglycemia has decreased ***(Potter and Kicklighter, 2009).***

Hypoglycemia is the most common metabolic derangement in IDMs with polycythemia and is observed in 12-40 % of them ***(Taylor et al., 2002).***

The strongest predictor for neonatal hypoglycemia is the mean maternal glucose level during labor. The higher the cord plasma glucose value, the greater the likelihood the infant will develop hypoglycemia within the first hours of life ***(Moore and Warshak, 2005).***

Pathophysiology:

Maternal DM is characterized by glucose intolerance and insulin absence or resistance. Mothers with glucose intolerance are frequently treated with exogenous insulin to maintain normoglycemia. Whereas maternal glucose traverses the human placenta relatively easily, maternally derived or exogenous insulin does not ***(Kicklighter, 2001).***

The fetus becomes hyperglycemic and stimulates islet cell proliferation and insulin production. As long as maternal glycemic status is controlled and transplacental glucose delivery remains steady, fetal glucose metabolism remains stable. This could be compromised by wide swings in maternal serum glucose concentrations caused by inconsistent maternal glycemic control. Periods of chronic maternal (and fetal) hyperglycemia result in accelerated fetal growth, whereas sudden

reductions in maternal glucose concentrations place fetuses with islet cell hyperplasia at an increased risk for hypoglycemic episodes. Both events have been implicated in the increased fetal mortality rate seen in diabetic pregnancies ***(Lucas, 2001).***

Before delivery, the increase in cellular glucose uptake in response to the increased insulin secretion is matched by the increased availability of glucose from the mother. After delivery, sudden separation of placenta causes withdrawal of the transplacental supply of glucose without a proportional effect on the hyperinsulinism, resulting in hypoglycemia and attenuated lipolysis during the first hours after birth. However, this hyperinsulinism is transient and typically resolves within 1-2 days following birth ***(Ferry et al., 2005).***

The neonatal shift to gluconeogensis with fatty acid use may provide an insufficient supply of substrate, thus the infant may experience hypoglycemia. Also, with hypoglycemia, the body responds with increased counter regulatory hormones and production of ketones for use as an energy source. With continued hyperinsulinemia, this production of ketones is inhibited, thus lowering the source of energy for these infants even further ***(Potter and Kicklighter, 2009).***

Although hyperinsulinism is probably the main cause of hypoglycemia, the blunted glucagon response aggravated by decreased hepatic responsiveness to glucose that occurs in IDMs may be contributing factor for hypoglycemia ***(Corbett et al., 2003).***

The levels of epinephrine and norepinephrine are also elevated in IDMs, suggesting that hypoglycemia in these infants may also be related to adrenal medullary exhaustion ***(Coetzee and Levitt, 2000).***

Hypoglycemia in small for gestational age(SGA) infants born to mothers with vascular disease may be due to inadequate glycogen stores, it may be also present later at 12 to 24 hours of age ***(Rehan et al., 2002).***

Large for gestational age and preterm infants are at highest risk to develop hypoglycemia. Perinatal asphyxia, hypothermia and maternal glucose infusion during labor increase the risk for hypoglycemia ***(Potter and Kicklighter, 2009).***