PROSTACYCLIN DEFICIENCY AS A POSSIBLE ETIOLOGICAL FACTOR OF SUPERIMPOSED PREECLAMPSIA IN DIABETIC PREGNANCIES

Thesis
Submitted for Partial Fulfilment of the Requirement of the Master Degree in Obstetrics and Gynecology

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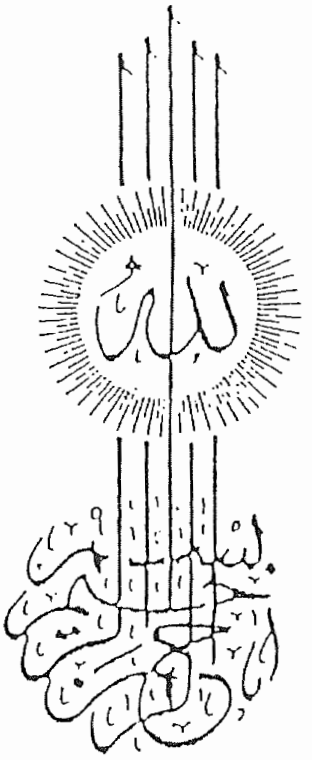

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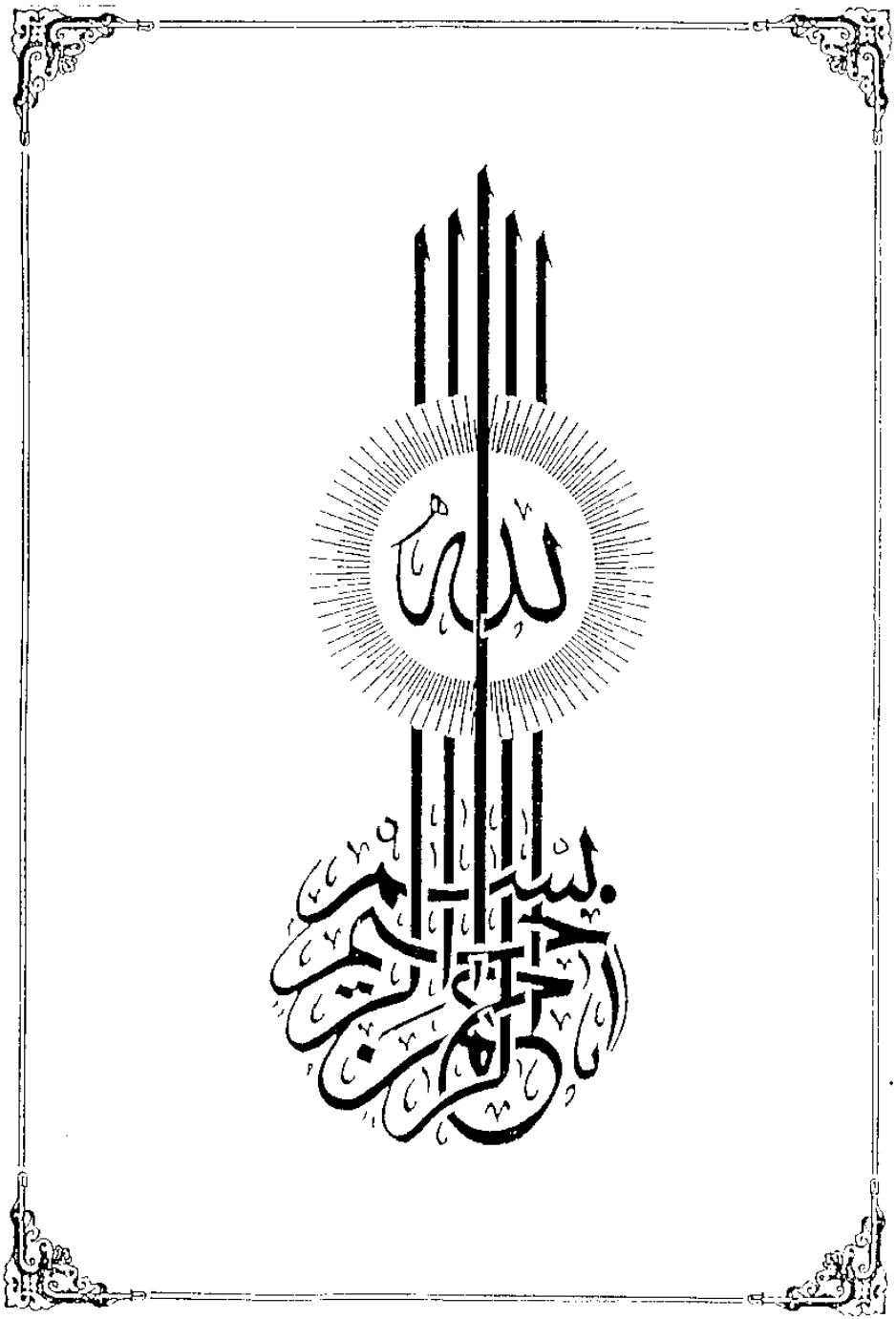

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The Candidate

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Insulin dependent diabetic patients are at increased risk for hypertensive disorders of pregnancy (Siddiqi et al., 1991). Recently preeclampsia was found in 9.9% of diabetic pregnancies compared with 4.3% in controls (Van Assche et al., 1993) and the incidence increased with severity of diabetes.

Prostacyclin is the most potent vasodilator and inhibitor of platelet aggregation known what so ever (Mocanda et al., 1979); Several studies have attempted to assess prostacyclin production in preeclampsia and other pregnancy complications. Several maternal groups have demonstrated a deficiency of its production by measuring plasma level of stable prostacyclin metabolites (Ylikorkala et al., 1981) and urinary prostacyclin metabolites (Goodman et al., 1982). There is decrease in prostacyclin production with an increase in thromboxane production.

The aim of this study is to find out the role of prostacyclin deficiency as an etiological factor in the causation of superimposed preeclampsia in diabetic pregnancy.

DIABETES WITH PREGNANCY

DIABETES WITH PREGNANCY

Variety of endocrine disorders can complicate pregnancy but the most common of these, Diabetes mellitus, is made more difficult to manage by pregnancy and increases appreciably the risk of a number of pregnancy complications (Cunningham et al., 1993). The diabetic pregnant women have a greater incidence of preeclampsia, infection, post partum bleeding and caesarean deliveries (Cousins, 1987).

Incidence :

By diagnostic criteria acceptable to most, it is estimated that 1 percent of the general population of child bearing age women now has overt diabetes and about one fourth of these have type I insulin dependent diabetes mellitus (Foster, 1991). The incidence of preeclampsia associated with diabetes is approximately 15% and it is associated with poor glycemic control and end organ damage (Siddiqi et al., 1991).

Classification:

Diabetic patients should be classified to indicate the severity of their condition and the prognosis of the pregnancy. The National Diabetes Data Group (1979) classified diabetes into primary, secondary and gestational diabetes.

National Diabetes Data Group classification of diabetes.

New Name	Old Name
Type I IDDM: insulin dependent diabetes mellitus.	juvenile diabetes juvenile onset diabetes Ketosis prone diabetes Brittle diabetes
Type II NIDDM: Non insulin dependent diabetes mellitus	Adult onset diabetes Maturity onset diabetes Ketosis resistant diabetes Stable diabetes
Type III GCI : Gestational carbohydrate intolerance	Gestational diabetes

Foster (1991) gave sòme characteristic for type I and type II diabetes mellitus, shown in the next table.

Characteristic	Type I (Insulin dependent)	Type II (Non-insulin dependent)
Genetic locus	Chromosome 6	Chromosome 11 (?)
Age of onset	Younger < 40 y	Older > 40 y
Habitus	Normal to wasted	Obese
Plasma insulin	Low to absent	Normal to high
Plasma glucagon	High, suppressible	High, resistant
Acute complications	Ketoacidosis	Hyper osmolar coma
Insulin therapy	Responsive	Responsive to resistent
Sulfonylurea therapy	Unresponsive	Responsive

(Foster, 1991).

The classification system most commonly used is that of Priscilla White (White classification). This system separates patients into groups according to the age of onset and the duration of the disease and the presence or absence of micro or macro vascular changes (Hare and White, 1980).

White's classification of diabetes during pregnancy	
* Gestational diabetes	Discovered during pregnancy; glycemia may or may not be maintained by diet alone and insulin may be required.
* Class A	Discovered before pregnancy, controlled with diet alone; any duration or age of onset.
* Class B	Onset 20 years or older or duration less than 10 years.
* Class C	Onset age 10-19 years or duration 10-19 years.
* Class D	Onset age under 10 years; duration over 20 years; background retinopathy.
* Class R	Proliferative retinopathy or vitreous Hge.
* Class F	Nephropathy with over 500 mg/day proteinuria
* Class RF	Criteria of both classes R & F coexist.
* Class H	Arterio Sclerotic heart disease clinically evident.
* Class T	Prior renal transplantation

The next table shows the classification suggested by the American College of Obstetricians and Gynerologists (1986).

Pregestational Diabetes					Gestational Diabetes		
Class	Age of onset	Duration (years)	Vascular Disease	Therapy	Class	Fasting plasma Glucose	Post prandial plasma Glucose
A	Any	Any	None	A.1,diet only	A-1	<105 mg/dL and	< 10 mg/dl
B	over 20 y	< 10 y	None	insulin	A-2	> 105 mg/dL and	/ or > 120 mg/dl
C	10 to 19	10 - 19	None	insulin			
D	Before 10	> 20	Benign retinopathy	insulin			
F	Any	Any	Nephropathy	insulin			
R	Any	Any	proliferative retinopathy	insulin			
H	Any	Any	heart disease	insulin			

From American College of Obstetricians and Gynecologists (1986).

Pathogenesis:

Type I diabetes mellitus is immune mediated and develops in genetically susceptible persons. The genetics of type I diabetes is complex but there is general agreement that there is an association with the HLA-D histocompatibility complex located on chromosome 6. This genetic background is triggered by viral infection. There is inflammatory insulinitis and lymphocytic infilteration of the islets. Subsequently, there is B-cell surface modification and immune stimulation of antibodies against the abnormal B-cell. This leads to eventual destruction of the cell and resultant diabetes (Foster, 1991).

There has been no HLA association discovered with type II Non insulin dependent diabetes mellitus. The disease has a familial occurrence and nearly 40% of siblings and a third of offspring develop abnormal glucose tolerance or obvious diabetes (Foster, 1991). Its pathophysiology is abnormal insulin secretion and insulin resistance in target tissues. Most patients are obese and it was found that peripheral resistance induced by obesity leads to B-cell exhaustion.

Role of hormones in pathogenesis:

In early pregnancy, increase placental production of estrogen and progesterone leads to B-cell hyperplasia and increase insulin secretion in response to a glucose load, also glucagon deposition is increased in peripheral tissues and