# STUDY OF SOME COAGULATION DEFECTS IN DIABETIC PREGNANCY

**THESIS**

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By

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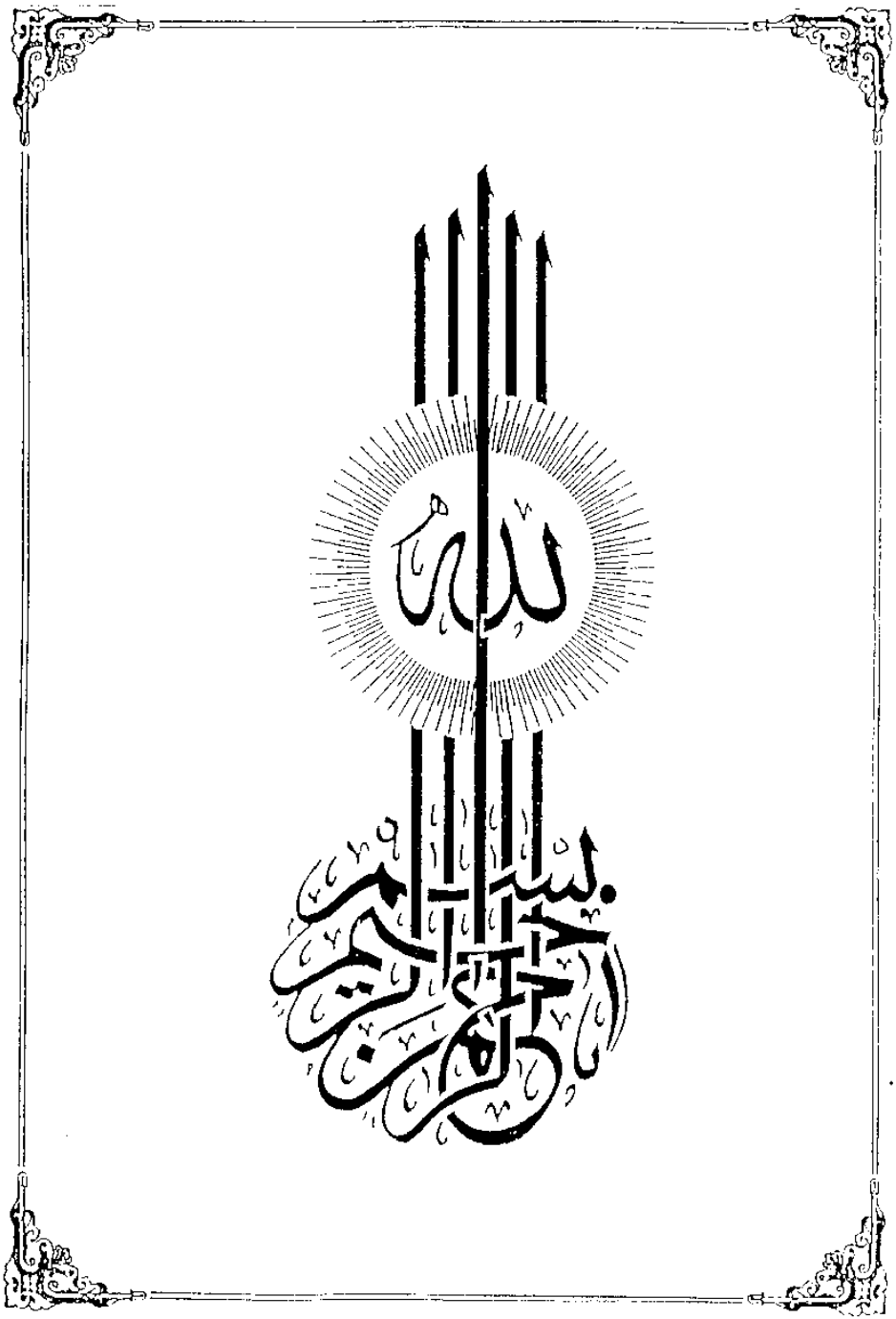

CONTENT



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# Introduction

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Diabetes mellitus is a heterogeneous disorder of carbohydrate metabolism with multiple etiologic factors that generally involve absolute or relative insulin deficiency or insulin resistance or both. All causes of diabetes mellitus ultimately lead to hyperglycemia, which is the hall-mark of this disease syndrom (Olefsky., 1981).

Complications of the diabetic pregnancy include an increased risk of maternal hypertension and sudden unexplaned fetal death. Each may be associated with an increased tendency for thrombosis ( Weiner et al., 1984).

A hypereoagulable state was demonstrated in diabetes mellitus involving the activation of all mechanisms implicated in coagulation. Abnormalities of both soluble coagulation componants and platelet function are present in diabetic patients with advanced vascular disease. These alterations support the concept of a hypercoagulable state ( Jones and Peterson ., 1981).

Insulin-dependant diabetics demonstrated a significantly elevated and widely varying erythrocyte filterability. Fibrinogen levels in diabetics rose precipitously and were significantly higher than normal throughout gestation. Fibrinogen levels paralleled changes in erythrocyte filterability, with the two parameters positively correlated ( Rodgers

et al., 1988).

Fibrinogen-fibrin degradation products ( F.D.P ) concentration showed a significant elevation in diabetic patients with angiopathy ( Kloczko et al., 1986 ).

Antithrombin III ( AT III ) is the most important inhibitor in blood coagulation ( Rosemberg , 1975 ), and its hereditary deficiency or abnormality increase the tendency of thrombosis ( Mackie et al., 1978). AT III defects can be divided into two groups, namely AT III "true" deficiency and AT III abnormalities, in both cases an increased incidence of thromboembolic disorders was described ( Patrassi et al., 1985 ).

AT III, levels have been reported to be low ( Hughes et al., 1983), normal ( Christe et al., 1984 ) and high ( Borsey et al., 1984 ) in diabetes mellitus.

AT III, is depressed in both diabetes mellitus and pregnancy, with pregnant diabetic subjects displaying the lowest AT III levels (Sower et al., 1980).

# Aim of the Work

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This work is planned to study fibrinogen, fibirnogen-fibrin degradation products ( F.D.P. ) and Antithrombin III ( AT III ) levels in diabetic pregnant patients and will be matched with normal pregnant women and non-pregnant non-diabetic women.

# Review of Literature

# REVIEW OF LITERATURE

## DIABETES MELLITUS

Diabetes mellitus is not a disease in the classical sense but is more probably a syndrome. Thus we have neither a definite and constant aetiopathogenic mechanism nor a well established sequence of events leading to anatomical lesions in the endocrine pancreas ( Domenico and Umberto., 1984 ).

Diabetes mellitus is a disease syndrome best characterized as a state of chronic hyperglycaemia of various aetiologies. It may present with acute symptoms that include thirst, polyuria and unexplained weight loss and these can progress to life threatening ketoacidosis or hyperosmolar coma. Subacute symptoms include the above, together with pruritis vulvae, skin infections, unusual fatigue or visual impairment ( Welborn., 1984).

The occurrence of pregnancy in diabetic woman has always had a fascination for the obestetrician because of the obvious effect which the maternal disease has on both the course of pregnancy and the fetal outcome ( Brudenell., 1982 ).

During the preinsulin era, pregnancy rarely was reported in known diabetic individuals, and the consequences of such pregnancies usually

were disostrous. In one of the earliest collected series of pregnant diabetics, Williams, in 1909, reported a maternal mortality rate of 30% and an overall fetal loss rate of 65%. Since 1921, the avalability of insulin has markedly improved the outlook for both mother and fetus. ( Coustan and Felig., 1988 ).

Perinatal mortality continues at rates of 3 to 5%, considerably above 1 to 2% rate noted in the general population. In addition, major congenital anomalies occure in 6 to 12% of offspring of diabetic mothers, three-to-four fold the rate in the general population ( Simpson et al., 1983 ).

Until very recently, the incidence of congenital anomalies has failed to decline despite on overall decline in perinatal mortality ( Frienkel et al., 1980 ).

It is now recognized that normalization of maternal fuel metabolism, which previously had been emphasized in late pregnancy to prevent perinatal mortality and morbidity, must be attempted at conception and during early pregnancy in order to lower congenital malformation ( Fuhrmann et al., 1984 ).

## Fuel and Hormone Metabolism in Pregnancy :

In normal nondiabetic woman, pregnancy is associated with profound change in fuel metabolism circulating levels of glucose and aminoacids

are reduced and levels of free fatty acids, ketones and triglycerides are increased, while secretion of insulin in response to glucose is augmented. The overall metabolic state has been characterized as one of "accelerated starvaion" ( Freinkel et al., 1980 ).

Pregnancy also has a diabetogenic effect on the mother, as is indicated by (1) the development of diabetes is genetically predisposed women during pregnancy and the reversion to completely normal carbohydrate metabolism post partum, (2) an increase in the upper limits of normal in the 2-hour circulating glucose level during glucose tolerance testing, (3) higher post prandial glucose levels after ingestion of a standard meal, (4) diminished responsiveness to injected insulin ( Coustan and Felig., 1988 ).

As early as the 5th week of gestation, maternal glucose levels after an overnight 12- to 14- hour fast are 15 to 20 mg/100 ml lower than in the nongravid state. Plasma glucose levels are significantly lower during sleep ( 11.0 P.M. to 8.0 A.M.) in the second and third trimesters compared with the nongravid state ( Cousins et al., 1980).

Falling maternal glucose levels result in a decline in fasting insulin concentrations, which in turn lead to an exaggrtation of starvation ketosis ( Coustan and Felig., 1988 ).

Blood levels of betahydroxybutyric acid and acetoacetic acid are two

to four times higher in pregnancy after no more than an overnight fast ( Metzger et al., 1982 ).

During late normal pregnancy, fasting levels of cholesterol and triglycerides are markedly elevated compared with the nonpregnant state ( Hollingswoth et al., 1982 ).

## Fetal-Maternal Fuel Hormones Relationships :

Fuel requirement of the developing fetus are not primarily, although not exclusively, by glucose. Glucose not only provides the energy necessary for protein synthesis but also is the precursor for the synthesis of fat and the formation of glycogen ( Battaglia and Meschia., 1978 ).

The overall level of glucose uptake required to meet these synthetic and oxidative needs has been estimated at 20 mg/min at term, representing a glucose utilization rate of 6 mg/kg/min ( Page., 1969 ). Similar results have been demonstrated in human fetuses in the second and third trimesters ( Cowett et al., 1983 ).

Glucose turnover in the human neonate has been reported to average 3.2 to 4.2 mg/kg/min ( Kalhan et al., 1977 ). This rate of glucose utilization is in excess that observed in the normal adult, in whom glucose turnover occurs at a rate of 2.0 to 2.5 mg/kg/min ( Felig., 1973).

With respect to the transfer of glucose to the fetus, the level of

glucose in fetal blood is generally 10 to 20 mg/100 ml below that in the maternal circulation, indicating that diffusion per se favors the net movement of glucose from mother to fetus ( Coustan and Felig., 1988 ) . However, the rate of glucose delivery is more rapid than can be accounted for on this basis, and consequently the process of glucose transfer is described as one of "facilitated diffusion". This process has been shown to be carrier mediated but is not energy dependent ( Rice et al., 1979 ).

In contrast to the rapid movement of glucose to the fetus, maternal free insulin and glucagon fail to traverse the placenta, although antibody-bound insulin may do so ( Battaglia., 1984 ).

Insulin is present in the fetus at 9 to 11 weeks of gestation and its secretion is stimulated in response to increased glucose avaliability and even more effectively in response to aminogenic stimulation ( Obenshain et al., 1970 ).

The importance of fetal insulin to growth is underscored by the occurence of macrosomia and hyperinsulinemia in the infants of diabetic mothers ( Ogata et al., 1980 ). Continuous infusion of insulin so as to achieve euglycemic hyperinsulinemia in the rhesus monkey fetus results in macrosomia and organomegaly, including hyperplasia of the liver, heart, spleen and placenta ( Susa et al., 1979 ).