# PREVALENCE OF DIABETES MELLITUS AMONG EGYPTIAN PREGNANT WOMEN WITH ASSESSMENT OF GENETIC COMPONENTS IN THIS CATEGORY OF DIABETICS

THESIS

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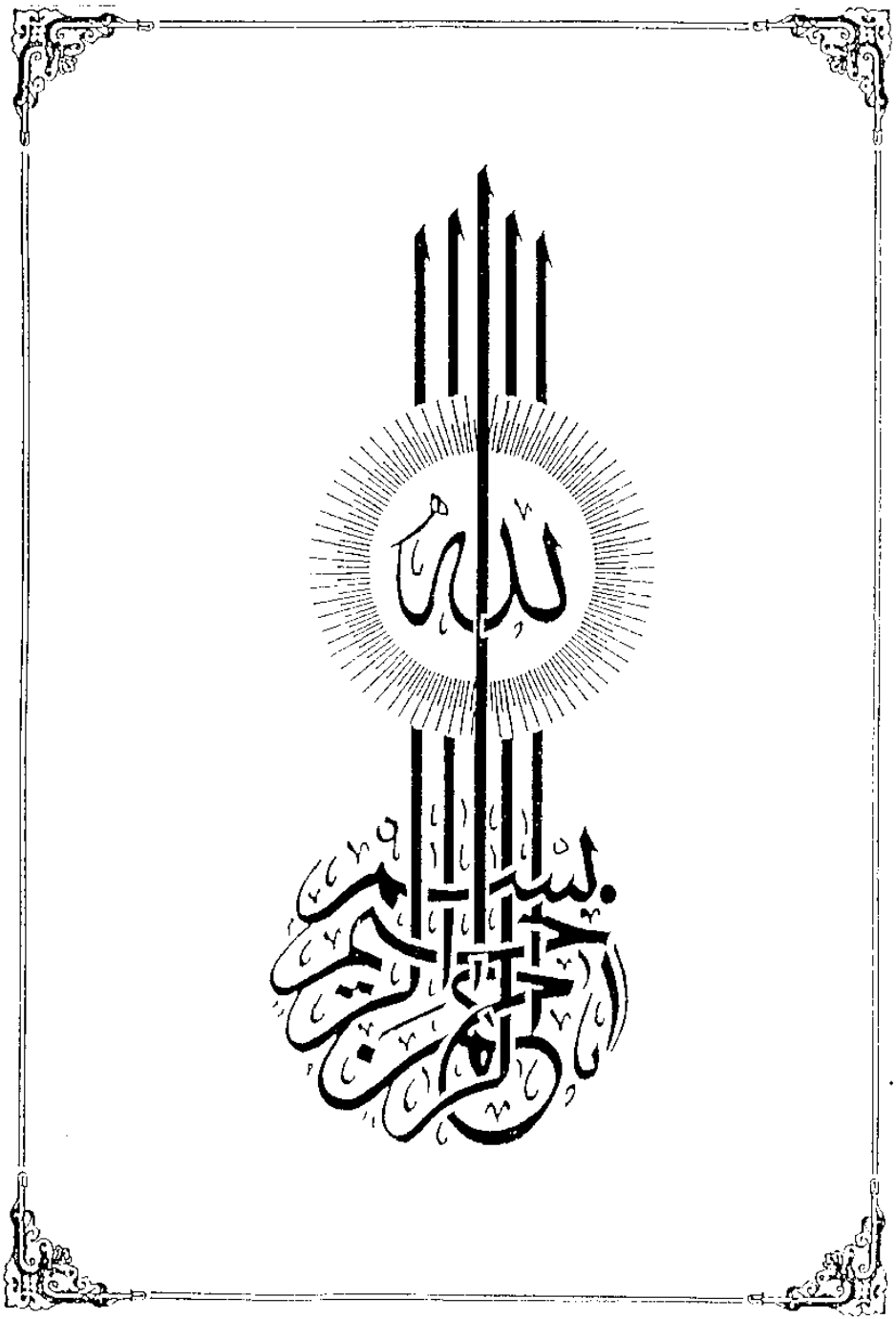
# C O N T E N T S



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# INTRODUCTION

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It is well established that diabetes mellitus in pregnancy is associated with increased risk of fetal and neonatal mortality.

For over 50 years numerous authorities have advocated that pregnant women with preexisting diabetes be managed by teams of specialized personnel, preferably in centers where high risk obstetric and neonatal service are available. Recently, reports from several diabetes centers have documented that with early, rigorous and coordinated perinatal management, perinatal mortality rates for pregnancies complicated by preexisting diabetes can be reduced to levels in the range of 35 to 46 per 1000 births (Gabbe et al., 1977; Kitzmiller et al., 1978).

These results, however, may not be indicative of the experience of the general pregnant diabetic population particularly of those women delivering outside of major medical centers. First, patients in diabetic centers may be atypical either because they are referred as a result of high risk status or because they live in proximity of teaching hospitals. Second, the outcomes

reported are undoubtedly due in large part to care by providers whose interest and expertise in the care of pregnant women with diabetes surpasses that of physicians who serve the majority of the general pregnant population.

To establish estimates of the incidence of pregnancy complicated by preexisting maternal diabetes and to measure perinatal risks for an unselected population of pregnant diabetic women, a population based study of these pregnancies was undertook.

# REVIEW OF LITERATURE

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## Metabolic and Hormonal Adaptation to Normal Pregnancy

Metabolic adaptations to pregnancy are directed towards:

1) ensuring satisfactory growth and development of the fetus in utero.
2) equipping the fetus with a store of energy to see it through the immediate neonatal period.
3) establishing an adequate maternal bank of energy to secure survival, not only of the fetus and neonate, but also of the infant by means of lactation, in the event of the supply of dietary energy being inadequate at any point during and after the pregnancy.

At any one time, the demand of the first two objectives are competing with that of the third for the available energy. Yet, to ensure successful reproduction, all three must be met (Baird, 1986).

When access to food is unrestricted, pregnancy is above all an anabolic event in which appetite and food

intake are increased, activity is diminished and, in the human, an average of 3.5 kg maternal fat is deposited and 900 g of new protein synthesized in the product of conception and in maternal reproductive tissue (Hytten, 1980).

The overall energy cost of human reproduction is of the order of 75000 k.cal. This is equivalent to an additional daily consumption of 300 k.cal. throughout the pregnancy and the recommended dietary allowances for pregnancy are based on this figure. It is however well documented that many women eat considerably less than the recommended allowances and yet produce perfectly normal, healthy babies and lactate satisfactorily (Whitehead and Paul, 1982).

Moreover, experiments involving pregnant rats have consistently produced data showing that complete fasting for two days in the second half of pregnancy has surprisingly little effect on fetal weight (Girard et al., 1977; Shambaugh et al., 1977).

This indicates that the process whereby the objectives of pregnancy are realized is not dependent on an appropriate increase in energy intake throughout pregnancy. In fact, the metabolic adaptation to pregnancy

appears to be designed primarily to safeguard against variable and restricted energy intake. Current concepts suggest that this is achieved in two main ways:

1) by a reduction in energy expenditure, due to decreased activity combined with increased metabolic efficiency,
2) by phased metabolic activity.

It is generally thought that reduced activity occurs in pregnancy (Baird, 1986).

Whitehead and his colleagues have made serial studies of energy balance in pregnant women living in U.K. (Whitehead et al., 1981) and in Gambia (Prentice et al., 1981). No increase in energy intake was found during pregnancy in either study and neither group of mothers was demonstrably less active when pregnant. Since progress during pregnancy conformed to conventional standards of normality in terms of maternal weight gain and birth weight it was concluded that although subtle changes in activity might have contributed to a reduction in energy expenditure, the increased metabolic requirements of pregnancy must have been met mainly by enhanced metabolic efficiency. This was apparently greater in women in Gambia than in those in the U.K. The

mechanism of this fundamental change in the control of energy balance remains obscure.

A slight reduction in the serum level of free $T_3$ and $T_4$ (Finucane et al., 1976) and a rise in reverse $T_3$ (Burman et al., 1976) have been reported but seem insufficient to account for the phenomenon of reduced energy expenditure during pregnancy.

Hervey (1969) has suggested that in intact female rats, the hypothalamic centre controlling total body fat is reset by progesterone.

Since it has been postulated that brown adipose tissue (BAT) plays an important role in the regulation of energy balance in nonpregnant animals, this was studied by Argin and Williamson (1980) in pregnant rats. It was found that the fat free weight of intercapsular BAT increased by 65% during pregnancy, declined by 24% at parturition, and showed little change from birth to mid-lactation when the weight was not significantly different from the pre-mating value. One can only speculate on the physiological significance of these changes. The rate of BAT lipogenesis paralleled that of tissue weight but the fate of the newly synthesized lipid is unknown. If the function of lipogenesis in BAT

was the same as in the liver, i.e. to produce lipid for storage or oxidation in other tissues, then it would be expected to follow the same trends as for hepatic lipogenesis, which was not the case. If, on the other hand, the newly synthesized fatty acids were oxidized in situ then energy would be dissipated rather than conserved.

Cooney and Newsholme (1982) have drawn attention to the fact that since BAT has a high capacity for glucose utilization and this glucose could be either oxidized or converted to lipid, and since these pathways are sensitive to insulin, BAT could play a quantitatively important role in blood glucose homeostasis. The relevance of this to the metabolic adaptation in pregnancy is unknown.

It used to be thought that energy needs specific to pregnancy would be greatest during the final weeks of pregnancy when the fetus grows most rapidly. This concept was not disturbed by early studies of human pregnancy which were invariably cross sectional and in which the deposition of fat was estimated indirectly by measuring total body water. However, one of the first studies which attempted to measure fat deposition more directly (by serial measurements of skin fold thickness)

indicated clearly that normal pregnancy is characterized by two distinct phases of metabolic activity and that deposition of maternal stores occurs predominantly in the first half of pregnancy (Taggart et al., 1967). It was also noted that the increase in fat was not uniform in the different sites of the body being greatest in the thighs, abdomen and back and this pattern of distribution is unlike that in non-pregnant obese women who decrease or increase their skin fold thickness proportionally all over the body when their weight alters.

This suggested that deposition of fat was under endocrine control. The concept of biphasic metabolism of carbohydrate, fat and protein, which serves to spread the energy cost and protein requirement of pregnancy over the whole of gestation is now well documented. It is thought that this is probably programmed by the placental steroid hormone balance, which is not affected by environmental factors such as diet but determined rather by growth of the placenta, and that this is responsible for:

1) Conserving energy in early pregnancy (the state designated by Freinkel et al. (1979) as "facilitated anabolism".

2) Redirecting available energy to the fetus in late pregnancy ("accelerated starvation")
3) Promoting economical use of protein (vital for development of the fetal brain) through pregnancy (Baird, 1986)

Change in carbohydrate metabolism in pregnancy:

The actual plasma glucose concentration pertaining during pregnancy in the course of a day is the important thing as far as the fetus is concerned, yet studies involving serial measurements of the true (ie estimated by an enzymatic method) plasma glucose concentration throughout pregnancy are few. In a longitudinal study (Lind et al., 1973) involving 19 healthy women during and after pregnancy, the mean fasting blood glucose level at 10 weeks gestation was found to be slightly, but significantly, lower than the mean non pregnant (10-12 weeks postpartum) value but no significant change occurred thereafter.

Nairn, Baird and Scrimgeour (submitted for publication) have measured the true plasma glucose concentration in post absorptive (3h post-prandial), venous blood samples obtained serially at <12, 16 and 32 week gestation, at term and at 6 weeks post partum, from 86 ran-