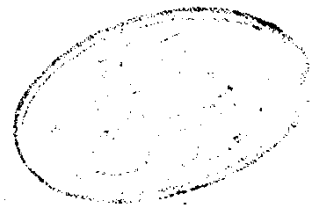
OUTCOME OF PREGNANCIES IN DIABETIC MOTHERS.



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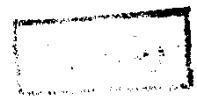

Submitted for the partial fulfilment for the Requirement for the Master Degree Gynaecology and Obstetrics

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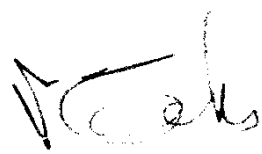

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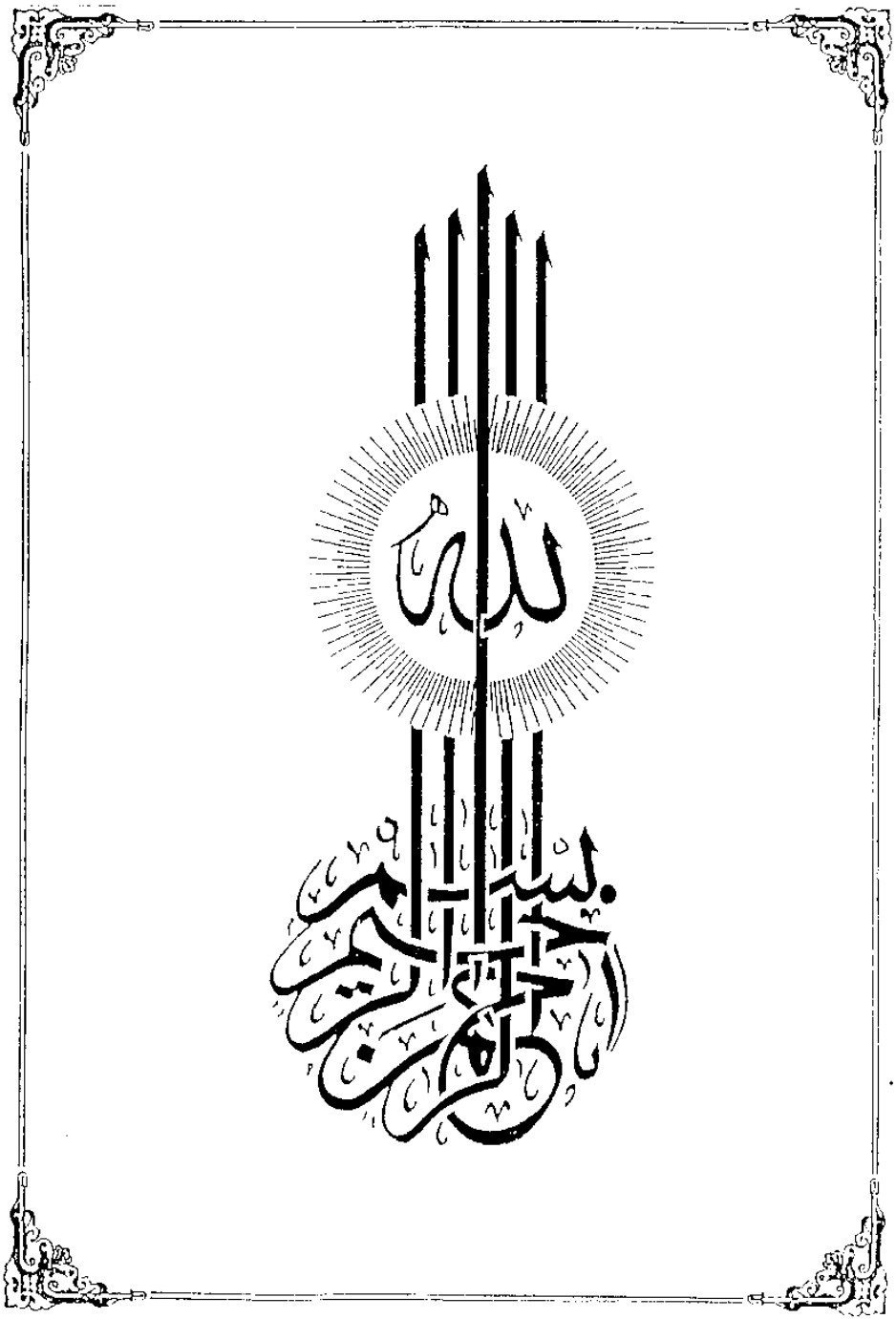
C O N T E N T S



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INTRODUCTION

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Infants of diabetic mothers have greater morbidity than infants of non diabetic women. Many infants of insulin dependent diabetic women may experience an uneventful clinical course, and even more infants of gestationally (chemically) diabetic women do well (Cornblath, M. et al., 1976), (Schwartz, R., et al., 1982). The more closely metabolically controlled the diabetic pregnant patient, the greater the potential for a normal infant. In recent series, perinatal mortality, except for congenital anomalies, approaches that for infants of non diabetic mothers. (Jovanovic, L. et al. 1980), (Kitzmiller, J. L. et al. 1978).

Knowledge of the character of the maternal diabetes, prior pregnancy history, and complications occuring during pregnancy allows the physician caring for the infant to anticipate many of the potential fetal and neonatal complications and to be present at delivery.

Studies of perinatal morbidity and mortality from diverse centers attest to the success of the above principles. In 1974, Pedersen et al. published a review of their experience over a 26-year period with an analysis of 1332 diabetic pregnancies (Pedersen, J., et al. 1974). Perinatal mortality varied directly with maternal severity of diabetes as judged by two commonly used maternal

classification schema: Whites original classification of diabetes in pregnancy and Pedersen's Prognostically Bad Signs in Pregnancy (PBSP) classification. White's revised classification is based on duration of diabetes and the presence of late vascular complications, (Hare, J. W. et al. 1980), while the PBSP classification includes abnormalities of the current pregnancy. The risk to the fetus was increased when the PBSP classification was "added" to the white classification. While these investigators noted an improvement in non diabetic pregnancy outcome during this same period, they emphasized that the improved classification schema combined with increased experience were the major reasons for the improved results in the diabetic pregnancies. This improved perinatal mortality has been confirmed at many centers in the United States and in Europe. While the frequency of macrosomia has decreased, the rate is still higher than that in infants born to non diabetic women. In a recent survey of macrosomic infants (large for gestational age > 95 percent weight for gestational age), most of these infants have been born to obese mothers, not all of whom have glucose intolerence as judged by post partum glycohemoglobin studies (Pollak, A. et al. 1981), (Widness, J. A., et al. 1981).

Neverthless, the gestational diabetic with glucose intolerence during late pregnancy remains often undiagnosed

and may have an infant at greater risk for perinatal complications.

An evaluation of perinatal mortality has been published by Teramo et al. from Helsinky, Finland (Teramo, K., et al. 1979). Their study focused on two time periods: 1970-1971 and 1975-1977. In 1974 the principles of obstetric monitoring and the treatment of pregnant diabetics and their infants were updated. The review focused on the differences resulting from those changes in management, which involved increased monitoring and more frequent hospitalization for metabolic control, especially in the third trimester. In 1975-1977 all diabetic patients were hospitalized from the 32nd week of pregnancy until delivery. Strict maintenance of normoglycemia (blood glucose $<$ 120 mg/dl) was the goal of management and, in the latter years, a permanent interdisciplinary team was in charge of the treatment of the patient. Gestational age of the infant was increased significantly; however, mean birth weights were unchanged. The perinatal mortality rate fell markedly as did neonatal morbidity. The authors concluded that while advances were obvious, the final answers were far from apparent because of the significant percentage of neonatal morbidities still present. Since the long-term effects of many of the neonatal morbidities remain to be defined, further efforts must be directed to minimize their incidence.

Similar conclusions about strict metabolic control were mentioned by Jerwell et al. who recently evaluated their experience in Norway between 1967-1976 (Jervell, J. et al. 1980). A total of 1035 births to diabetic mothers were registered during the 10-year period. Not only did perinatal mortality fall by 30 percent, but the duration of gestation increased from 35.5 to 37 weeks over the same period. The number of infants who were appropriate for gestational age (AGA) increased from 53.3 percent to 70.7 percent. The care of these pregnant diabetics also occured more commonly in university clinics and regional hospitals (from 38.7 percent in 1967-1968 to 77.1 percent in 1975-1976). The impact of these interventions did not affect malformation rates, which were still more common by a factor of 50 percent in infants born to those women compared with the general population.

Thus, the maintenance of a good metabolic state, including euglycemia, should diminish, but not completely eradicate, the increased perinatal and neonatal mortalities and morbidities noted in the diabetic pregnancy.

Aim of Work

The aim of this work is to prove that good control of diabetes mellitus during pregnancy will improve the perinatal outcome of pregnant diabetic women.

CHAPTER I

METABOLIC ADJUSTMENTS IN NORMAL AND DIABETIC PREGNANCY

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Though not definitely proved, it is generally accepted that firm metabolic control, in terms of normal or near-normal blood glucose concentration, plays a central role for the outcome of diabetic pregnancy (Coustan D. R., et al. 1980), (Fuhrmann, K. et al. 1983), (Gabbe , S. G. et al. 1977), (Jovanovic, L. et al. 1982), (Karlsson, J. et al. 1972), (Kitzmiller, J. L., et al. 1978). As glucose easily crosses the placental barrier, the fetus will be exposed to either sustained or intermittent hyperglycemia if the maternal diabetes is poorly controlled (Rice, P. A., et al. 1979), (Stenger, V., et al. 1966). Glucose crosses the placenta by facilitated diffusion and the fetus is thus protected from minor fluctuations in maternal glucose concentration (Rice, P. A., et al. 1979).

FUEL AND HORMONE METABOLISM IN NORMAL PREGNANCY:

In the normal non diabetic woman, pregnancy is associated with profound changes in fuel metabolism. The circulating levels of glucose and amino acids are reduced and levels of free fatty acids, ketones, and triglycerides are increased, while the secretion of insulin in response to glucose is augmented. The overall metabolic state has

been characterized as one of "accelerated starvation" (Freinkel, N. 1980). Pregnancy also have a diabetogenic effect on the mother as is indicated by (a) the development of diabetes in genetically predisposed women during pregnancy and the reversion to completely normal carbohydrate metabolism post partum, (b) an increase in the upper limits of normal in the 2-hour blood glucose level during glucose tolerence testing, (c) higher post prandial glucose levels after ingestion of a standard meal (Cousins, L., et al. 1980), (Freinkel, N. 1980), and (d) diminished responsiveness to injected insulin. This seeming paradox of coexistence of diabetes with a tendency toward fasting hypoglycemia can best be explained in the context of fetal-maternal placental fuel hormone interactions that exist in the fasting, as well as in the fed state.

Fetal-Maternal Fuel-Hormone Relationship:

The fuel requirements of the developing fetus are met primarily, although not exclusively, by glucose (Adam,P.A.J. 1971), (Battaglia, F. C., et al. 1978). 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. The level of glycogen stores in liver and muscle in the fetus, per gram of tissue, is substantially greater than that in the adult. The overall level of glucose uptake required to meet these synthetic and oxidation needs has been estimated at 20 mg per minute at term, (Page, E. W.

1969) representing a glucose utilization rate of 6 mg per kg of body weight per minute. Glucose turn over in the human neonate has been reported to average 4.2 mg per kg per minute (Kalhan, S. C. et al. 1977). This rate of glucose utilization is in excess of that observed in the normal adult, in whom glucose turnover occur at a rate of 2 to 2.5 mg per kgm per minute (Felig, P. 1973).

With respect to the transfer of glucose to the fetus, the level of glucose in fetus blood is generally 10 to 20 mg per 100 ml below that in the maternal circulation, indicating that diffusion per se favors the net movement of glucose from mother to fetus. 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, P., et al. 1979). The importance of maternal glucose levels in regulating glucose delivery to the fetus may relate not only to the provision of adequate substrate but also to the avoidance of excess substrate delivery. Teratogenic effects of high concentrations of glucose (500 to 1500 mg per 100 ml) have been observed in rat and mouse embryos maintained in tissue culture (Cockroft, D.L. et al. 1977), (Sadler, T. S. 1980). Thus, while glucose delivery is necessary for the growth and development of the fetus, excessive glucose transfer (the expected consequence of

maternal hyperglycemia) may alter embryogenesis.

In contrast to the rapid movement of glucose to the fetus, maternal insulin and glucagon fail to traverse the placenta. Fetal glucose utilization is thus not directly dependent on maternal insulin availability, On the other hand, fetal insulin is believed to play a central role in the growth of the conceptus. (Susa, J. B., et al. 1979). Insulin is present in the fetus at 9 to 11 weeks of gestation, (Like, A., et al. 1972), and its secretion is stimulated, albeit sluggishly, in response to increased glucose availability and even more effectively in response to amino genic stimulation (Grasso, S., et al. 1968), (Obenshain, S. S., et al. 1970). The importance of fetal insulin to growth is under scored by the concurrence of macrosomia and hyperinsulinemia in the infants of diabetic mothers. (Ogata, E. S., et al. 1980), (Pedersen,J., 1977). Furthermore, 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, J. B., et al. 1979).

In addition to the transfer of glucose, amino acids are actively transported by the placenta from the maternal to the fetal circulation (Holzman, I. R., et al. 1979).