Review

Therapeutic Results of Insulin Therapy in Gestational Diabetes Mellitus

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SUMMARY

Most studies of gestational diabetes mellitus (GDM) have reported a marked reduction in perinatal mortality with appropriate dietary regimens and good medical and obstetrical surveillance. Nevertheless, fetal morbidity, including macrosomia, has remained high and appears to be linked to factors other than plasma glucose control. In a review of six investigations in which insulin therapy was combined with an appropriate diet, the incidence of fetal macrosomia was reduced in five studies as compared with diet-only treatments. Again, the improvement did not always correlate with altered plasma glucose profiles. Other studies suggest that maternal plasma substrate disturbances other than glucose may contribute to the development of fetal macrosomia. To what extent insulin administration reduces morbidity by containing circulating maternal fuels, such as lipids and amino acids, in a more normal range remains to be determined. Moreover, the role of diet, maternal obesity, and weight gain during pregnancy adds to the complexity of factors influencing obstetrical outcome in gestational diabetes. Until the relative importance of all of these variables is adequately assessed, criteria for selection of women with pregnancy-onset diabetes for insulin therapy are most likely to be based on fasting and postprandial plasma glucose concentrations. DIABETES 1985; 34 (Suppl. 2):97–100.

MATERNAL PLASMA GLUCOSE CONTROL IN GDM: RELATIONSHIP TO PERINATAL MORTALITY AND MORBIDITY

Analyses of large groups of women with all forms of diabetes during pregnancy find a significant correlation between plasma glucose control and perinatal mortality.[1] With respect to gestational diabetes mellitus (GDM), Pettitt et al. reported mortality rates of 1.2% or less if 2-h postchallenge concentrations of glucose were < 160 mg/dl. Above this concentration, mortality rose sharply.[2] In the series reported by Gabbe and co-workers, normal perinatal mortality rates were observed in 196 White's class A pregnant diabetic women who were managed by diet alone and whose fasting serum glucose levels were consistently < 110 mg/dl.[3] Similar results were published by Adashi et al. in their review of 81 cases of GDM who had good control on diet alone.[4] These results contrast to considerably higher rates, often exceeding 20%, when women with GDM, for any reason, elude some form of medical management.

Although the beneficial effects of dietary management on perinatal mortality in GDM are obvious, the relationship between good maternal plasma glucose control and improvement of perinatal morbidity is not. In Gabbe's series, for example, the incidence of fetal macrosomia in his well-controlled subjects was 20% or over twofold greater than in the general hospital population.[3] Other complications, although lower than in White's class B-F, were still significantly increased. In Pettitt's study, late pregnancy 2-h postchallenge glucose levels were predictive of birth weights, prematurity, and certain maternal complications.[2] When these statistics were adjusted for maternal age and degree of obesity, however, the correlations between glucose control and large-for-gestational-age (LGA) neonates were no longer significant. The incidence of LGA was found to be considerably greater in obese versus lean GDM at comparable degrees of glucose control, whether it was good, fair, or poor. These data are noteworthy, since others have shown that prepregnancy obesity level and weight gain during gestation may influence perinatal mortality and birth weight independently of the diabetic state.[5–7]

These observations emphasize the complexity of pregnancy-onset diabetes. The incidence of morbidity, particularly macrosomia, has not fallen in a parallel fashion with perinatal mortality with diet-only regimens. For this reason,

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TABLE 1
Effect of insulin treatment on GDM

Study	Group	N	Birth weight (g) or % large babies	Perinatal mortality (%)
1 O'Sullivan et al.[9]	Diet + insulin	101	5.9%*	1%*
	Diet only	108	14.8%	6%
2 Roversi et al.[10]	Diet + insulin			
	FPG < 105 mg/dl	110	1.9%	1.8%
	FPG ≥ 105 mg/dl	47	10.7%*	2.1%
	Untreated previous pregnancies	267	—	29.2%*
3 Metzger et al.[11]	Diet only, FPG < 105 mg/dl	30	3537 ± 109 g	—
	Diet + insulin, FPG ≥ 105 mg/dl	16	3657 ± 105 g	—
	Diet only, FPG ≥ 105 mg/dl	11	4109 ± 198 g*	—
4 Oppermann et al.[12]	Diet + insulin			
	FPG < 95 mg/dl	23	4%*	1.3%†
	FPG ≥ 95 mg/dl	67	33%	2.2%‡
	Diet only			
	FPG < 95 mg/dl	128	39%	1.3%†
	FPG ≥ 95 mg/dl	25	44%	2.2%‡
5 Gyves et al.[13]	Diet only	156	32%	1.1%*
	Diet + insulin	27		
	Untreated previous pregnancies	288	30%	9.7%
6 Coustan et al.[14]	No treatment	146	17.8%	0.7%
	Diet only	184	18.5%	1.0%
	Diet + insulin	115	7%*	0.8%

Large babies are those with birth weights exceeding the 90th percentile for gestational age. Asterisks indicate a significant difference between this value and other corresponding values in the same study. The superscripts † and ‡ denote combining of perinatal mortality rates from a given FPG group who did or did not receive insulin therapy.

the effect of insulin therapy on the outcome of GDM pregnancies is examined in this light.

INSULIN THERAPY IN GDM: A REVIEW OF SIX INVESTIGATIONS

Table 1 summarizes six studies in which the effects of insulin administration on perinatal outcome are compared with some type of control group.

Study 1. The reports of O'Sullivan and co-workers have several unique aspects.[8,9] Throughout this work, GDM was confined to women whose onset was truly in the last trimester. Medical and obstetrical management, including diet, were uniform and assignment to a single daily injection of 10 U of NPH insulin was randomized. Degree of impairment of OGTT in the groups was relatively mild and comparable before treatment was begun. Of some importance was the additional finding that insulin therapy also had no major effect on postprandial blood glucose concentrations as compared with the diet-only group. The women reported in this study were selected out of his original investigations, since they were shown to develop overt diabetes during a 15-yr follow-up. All were over the age of 25 yr. From these standpoints we have a very homogeneous group of mild GDM who had the same risk for developing permanent diabetes in later life. A low, fixed dose of NPH insulin significantly reduced both perinatal mortality and the incidence of large babies without altering plasma glucose control. In some unknown manner, insulin provided a protective effect that could not be achieved with diet alone.

Study 2. Roversi's series was carried out in a different manner.[10] Over 200 White's class A patients, including early, mid, and late pregnancy-onset types, were treated with maximal doses of regular insulin three times daily regardless of pretreatment blood glucose profiles. The majority (two-thirds) had fasting plasma glucose (FPG) of < 105 mg/dl; the remainder were between 105 and 129 mg/dl. After treatment, mean glucose concentrations, based on six determinations/24 h, were < 100 mg/dl. His regimen substantially reduced perinatal mortality of previous pregnancies (29.2%) over 10-fold. The incidence of macrosomia and large-for-gestational-age babies was close to the normal range. Although there were no control subjects on diet alone in this study, and although obesity level and dietary regimens were not defined, the results suggest that insulin therapy does have a beneficial effect on perinatal outcome including fetal macrosomia.

Study 3. The abstract report of Metzger et al.[11] supports the conclusions of the Roversi investigation. Three groups of GDM women were subdivided into (1) FPG < 105 mg/dl on diet only, (2) FPG ≥ 105 mg/dl on diet and insulin, and (3) FPG ≥ 105 mg/dl on diet alone. Mean birth weights of group 3 exceeded 4000 g (macrosomia), whereas birth weights of groups 1 and 2 were comparable and significantly lower than in group 3. The authors concluded that fasting plasma glucose is predictive of fetal macrosomia and that insulin therapy reduces birth weight to some extent.

Study 4. Oppermann and Camerini-Davalos[12] classified 243 GDM according to FPG < 95 mg/dl or ≥ 95 mg/dl. These two groups, in turn, were subdivided further according to diet alone or to diet and insulin.

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The results demonstrate a substantial reduction in the incidence of large babies with insulin regimens administered to the FPG < 95 mg/dl group. This was not evident in GDM with FPG ≥ 95 mg/dl. Not shown in the table are additional statistics revealing that 60% of LGA births were associated with maternal obesity and the majority were over 25 yr of age. Moreover, of the 33% of GDM with FPG > 95 mg/dl who were treated with insulin, 27% were considered to be in less-than-excellent control (FPG > 80 and 2-h postchallenge glucose > 120 mg/dl).

The authors concluded that the large-birth-weight syndrome is of multifactorial origin that is influenced by metabolic control, maternal obesity, age, and probably other factors.

Study 5. In the investigation of 183 GDM by Gyves et al., insulin therapy was reserved for those women whose 2-h pc plasma glucose exceeded 120 mg/dl.[13] Like results of other studies, the combination of diet alone or with insulin administration substantially reduced perinatal mortality to a normal range as compared with previous pregnancies. However, there was no discernible effect of diet or diet and insulin on LGA statistics. The authors also suggested that factors other than plasma glucose control influence fetal morbidity. In their series, maternal age had no bearing on these parameters. They speculated that the use of liberal diets with relatively higher caloric content than those prescribed in other series may have had some influence on large birth weights.

Study 6. The report of Coustan and co-workers[14] represents a much larger population of GDM than studied earlier by this group.[15] In this study, there were 445 GDM: 184 received diabetic diets alone, 115 received diet and insulin (starting dose of 10 U regular and 20 U NPH each morning), and 146 had neither diets nor insulin prescribed. Mean age (all > 25 yr) and mean midpregnancy weight were similar. Patients were included who had diagnoses made between the 20th and 36th wk. From Table 1, one can see uniformly normal (≤ 1%) perinatal mortality rates in each group. Fetal macrosomia, however, was profoundly influenced by management and was lowest in the insulin-treated group (7%), which is within the expected range of 10% for a normal population. The diet-treated and untreated mothers had an incidence of macrosomic babies of 18.5% and 17.8%, respectively.

The incidence of macrosomia also anticipated the mode of operative delivery and birth trauma. The degree of glucose intolerance at time of delivery, as well as glucose control during management, had no relationship to the incidence of macrosomia. The authors suggested that insulin does reduce the frequency of large babies and traumatic delivery in a manner that does not necessarily relate to plasma glucose control.

RELATIONSHIPS BETWEEN DIFFERENT MATERNAL PLASMA SUBSTRATE DISTURBANCES AND FETAL MACROSOMIA AND MORBIDITY IN GDM

A brief review of metabolic profiles observed in women with pregnancy-onset diabetes is relevant to our discussion, because the majority of substrate abnormalities are regulated by insulin. If uncorrected, they also could impact on fetal well-being and perinatal outcome and may explain why glucose control in GDM does not always relate statistically to conditions such as fetal macrosomia.

In the report of Persson and Lunell,[16] diurnal fluctuations of plasma glucose, free fatty acids, glycerol, and beta-hydroxybutyrate in moderately obese, gestational diabetic women on diet alone (1600 kcal/day) were higher than in normal pregnant subjects, but results were not significantly different. Similar data were obtained by Gillmer et al. in their investigations of glucose and free fatty acid profiles in GDM women.[17] Metzger and co-workers, however, subdivided their pregnancy-onset diabetic subjects into two subgroups based on fasting plasma glucose concentrations < 105 or ≥ 105 mg/dl. Under well-controlled dietary conditions, a continuum emerged that revealed significantly higher concentrations of several plasma substrates including glucose, free fatty acids, triglyceride, and selected plasma amino acids, particularly in individuals with higher basal glucose concentrations.[18] In obese, gestational diabetic women, plasma lipoprotein disturbances also have been defined that are distinct from levels in lean GDM.[19,20] Thus, it appears that a broad spectrum of plasma substrate abnormalities may emerge in pregnancy-onset diabetes that bears some relationship to the severity of GDM and that is modified further by the presence of obesity.

Pedersen originally postulated that hyperglycemia of the diabetic mother results in transplacental passage of excessive amounts of glucose to the fetus, exaggerated stimulation of the fetal endocrine pancreas, and fetal hyperinsulinemia.[21] The increased insulin secretion, in turn, promotes excessive tissue growth (macrosomia) and has been implicated in neonatal hypoglycemia[21] and the respiratory distress syndrome.[22] Over the years, this hypothesis has been broadened to include other maternal fuels as conceptualized by Freinkel[23] and as depicted in Figure 1.

It is of interest that concentrations of triglyceride and/or FFA have been correlated with neonatal birth weight by some investigators.[24,25] In view of the placental disposition of lipid fuels that allows for passage of FFA to the fetus, this could represent additional substrate for tissue storage and growth. In addition, maternal plasma amino acid concentrations very likely play a role in the genesis of fetal hyperinsulinemia, since

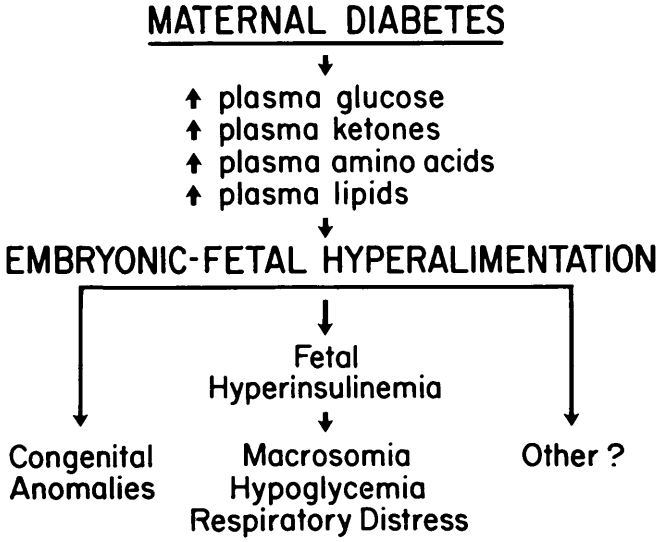

FIGURE 1. Relationship of maternal plasma fuel disturbances in diabetic pregnancies to fetal hyperinsulinemia and perinatal complications. Reprinted with permission.[28]

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the fetal islet is more responsive to this substrate than to glucose in earlier stages of pregnancy.[26] The islet-priming effect of amino acids in early to midgestation, together with their synergistic action with glucose in late pregnancy, may amplify fetal hyperinsulinemia over and above that achieved with glucose alone. In this regard, Freinkel and co-workers, in their studies of GDM, have found a significant correlation between neonatal birth weight and maternal plasma levels of alanine, serine, and isoleucine.[23] Our own studies of diabetes in pregnancy also suggest that maternal average total plasma amino acid concentrations as well as certain specific amino acids correlate more closely with neonatal birth weight than do levels of plasma glucose control and HbA_{1c}.[27]

CONCLUSIONS

From the observations available to us to date, it appears that gauging insulin therapy according to glucose control in GDM may be excluding perturbations of other important maternal plasma substrates that influence macrosomia and morbidity and that are controlled by insulin.

While the general consensus of this conference supports the use of insulin administration in GDM women who have FPG $\geq$ 105 mg/dl and/or 2-h plasma glucose concentrations $>$ 120 mg/dl, it has not been determined whether there is a need to prescribe insulin in a prophylactic manner even in GDM who have excellent glucose control. Until substrate parameters other than plasma glucose are examined more comprehensively, this question cannot be answered. In addition, the role of diet, maternal age, obesity, and weight gain during pregnancy should come under closer scrutiny during future assessments of various insulin regimens.

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