# EDITORIAL

# Treatment of Mild Gestational Diabetes Mellitus
## Is It Time For a Controlled Clinical Trial?

Awareness of the clinical and epidemiological significance of gestational diabetes mellitus (GDM) has increased gradually. Whereas the summary reports and recommendations of two International Workshop Conferences on GDM have been helpful in defining common approaches to definitions, diagnostic criteria, and detection of GDM, specific guidelines for the treatment of GDM have been difficult to achieve, particularly a clear definition of the role of insulin therapy (1,2). A well-controlled multicenter trial on the treatment of GDM is needed to document the indications and benefits of treatment and answer the lingering questions about this serious disorder.

### WHAT ARE BENEFITS OF INSULIN THERAPY IN GDM?

O'Sullivan et al. (3–6) first reported reductions in perinatal losses and the frequency of macrosomia (birth weight >4000 g or birth weight >90th percentile value of a reference population of the same gestational age) in the offspring when fixed doses of intermediate-acting insulin were administered to randomly selected women with GDM. The subjects in this large population, studied more than two decades ago, were assigned to insulin treatment or control groups without regard to their degree of glucose intolerance (except for the exclusion of those with symptomatic diabetes or overt hyperglycemia). Limited documentation of metabolic rectification with treatment was available. Moreover, retrospective stratification of the subjects was needed to document that perinatal losses were reduced in obese women >25 yr of age in whom insulin therapy had been initiated by 32 wk of gestation. Roversi et al. (7) reported the virtual absence of macrosomia and perinatal loss among 280 women with GDM treated with maximal tolerated doses (MTD) of short-acting insulin administered 3 times daily in subjects enrolled between 1963 and 1975. The lowest figures were seen in subjects with the least severe glucose intolerance, i.e., those with fasting plasma glucose (FPG) normal for pregnancy (<105 mg/dl; 1,2,8) or class $A_1$ (1,9). The values most commonly used to indicate normal and elevated FPG concentrations during pregnancy have been extrapolated from whole-blood glucose measurements in the original study reported by O'Sullivan and Mahan (8). As described in this study, some investigators use different values to define the normal limits for FPG based on *1*) other formulas to extrapolate from the data cited earlier (8), or 2) determinations of FPG in other groups of pregnant women using different analytical techniques. Outcomes were contrasted with earlier pregnancy experiences of the same women in whom perinatal losses and macrosomia had been high. The fact that a history of such events was used to select subjects for GDM case findings may have introduced some bias in this comparison.

### WHO SHOULD RECEIVE INSULIN THERAPY?

After these promising initial reports, some general principles have been widely accepted for the treatment of GDM. Because rectification of hyperglycemia to within

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normal ranges is the therapeutic goal for women with overt or pregestational diabetes mellitus, there is agreement that the 15–25% of subjects with GDM whose FPG and/or postprandial plasma glucose concentrations are repeatedly elevated while on dietary treatment alone should also receive therapy with insulin. However, even in the implementation of this straightforward principle there are differences. Not all centers have used the same values to define normal fasting and postprandial plasma glucose levels, and some investigators have not initiated therapy with insulin if metabolic deterioration was detected too late (variously defined as 32, 34, or 36 wk).

Most subjects with GDM are in the mild class $A_1$ or FPG <105 mg/dl category (1,9). In the Northwestern University studies, we have found that women with class $A_1$ GDM have disturbances in the metabolism of all insulin-responsive nutrient fuels, i.e., lipids, amino acids, and glucose (10,11). Furthermore, these metabolic alterations are associated with augmented perinatal islet function (10,12,13) and increased birth weight and frequency of macrosomia (10,13); therefore, they fulfill the criteria of the modified Pedersen hypothesis for the mediation of diabetic fetopathy (10,14). The perinatal implications may be different when *1*) subjects with GDM are considered to have elevated FPG at values <105 mg/dl and the population is subdivided into mild and severe categories on that basis, or *2*) the diagnosis of GDM is based on different glucose loads and/or oral glucose tolerance test (OGTT) values other than those recommended by the two workshop conferences (1,2), i.e., the criteria of O'Sullivan and Mahan (8).

## WHAT IS MOST APPROPRIATE THERAPY FOR CLASS $A_1$ GDM AND WHAT END POINTS SHOULD BE USED TO JUDGE EFFECTIVENESS OF SUCH THERAPY?

With the general advances in obstetric and neonatal care made in the last two decades, elimination of perinatal loss is no longer a sufficient end point. Instead, success must be achieved by reducing the frequency and severity of macrosomia and the other effects of fetal hyperinsulinism (e.g., neonatal hypoglycemia, hyperbilirubinemia, and respiratory system complications) and minimizing the consequences of macrosomia (e.g., operative deliveries and birth trauma in short-term diabetes and obesity diabetes or other developmental disturbances in the long term).

## HAVE OUR OBJECTIVES BEEN MET IN TREATMENT OF MILD GDM?

Reduction in the frequency of infants with macrosomia has been reported frequently in women with mild GDM treated with insulin despite differences related to variations in *1*) GDM case finding, *2*) methods of screening for potential GDM, *3*) diagnostic tests and criteria for the diagnosis of GDM, *4*) selection of cases for therapy with insulin, *5*) type of insulin and dose administered, and *6*) numbers of subjects studied and kinds and numbers of control subjects used for comparisons. This trend is consistent with the expected effects of insulin therapy if meaningful rectification of material metabolic disturbances and the attendant distortions of the fetal tissue culture milieu have been achieved (10). However, insulin therapy has not always been more successful than dietary treatment, and corresponding improvements in obstetrical outcomes and reductions in neonatal morbidities have not been found to be consistent.

An analysis of the key findings of several studies is instructive. Coustan et al. (15,16) have reported reductions in the frequency of macrosomia in offspring of mothers with GDM treated with insulin during pregnancy. In the first study, 72 women with GDM were randomly assigned to a routine prenatal diet, therapeutic diet, or therapeutic diet plus insulin. In the second study, insulin therapy was given prophylactically in addition to a therapeutic diet to 115 women with plasma glucose values within physiological ranges. Perinatal outcomes were compared with those in a group treated with therapeutic diet alone (184 subjects) and a group who received only routine prenatal dietary advice (146 subjects) after the diagnosis of GDM. Lower frequencies of operative delivery, traumatic delivery, and neonatal hypoglycemia were seen in the insulin-treated group of subjects in the second but not the initial study. However, the patient groups did not all receive their obstetrical care from the same providers. Maternal age (>25 yr) was not related to the outcomes. Persson et al. (17) assigned 202 women with GDM randomly to treatment with diet alone or diet plus insulin. A subgroup of the diet-treated group (14%) had insulin treatment added when prescribed limits for hyperglycemia were exceeded on diet alone. Frequencies of macrosomia and neonatal hypoglycemia were relatively low and did not differ in the two groups but were not specifically compared with such events in controls with normal carbohydrate metabolism. Bellman (18) followed a group of 92 women including 25 with normal carbohydrate metabolism and 68 with GDM. Therapy with insulin was initiated when subjects with GDM displayed mild or moderate deviations from the limits of normoglycemia established in the controls. Frequencies of macrosomia were 14 and 15% in the diet- and diet-plus insulin-treated groups, respectively; however, operative deliveries and neonatal hypoglycemia were higher in the insulin treated subjects. Leiken et al. (19) treated 107 subjects with mild GDM [defined as FPG <95 mg/dl (class A)] with diet alone and 74 subjects with elevated FPG [>95 mg/dl (class A/B)] with fixed doses of NPH insulin (15 U). The frequency of macrosomia in diet-treated (class A) or normal-weight insulin-treated (class A/B) subjects did not differ from that in controls (normal glucose screening tests); whereas macrosomia was present in more of the obese insulin-treated class A/B subjects (29%). Goldberg et al. (20) compared outcomes in two groups with GDM (58 in each group), matched for

phenotypic characteristics and severity of glucose intolerance at the time of the diagnosis and monitored with 2-h postprandial glucose measurements at clinic visits. One group also performed self-monitoring of blood glucose (SMBG) frequently. Insulin therapy was initiated if fasting and/or postprandial values exceeded 95 or 120 mg/dl, respectively. The SMBG group was treated with insulin more often (50 vs. 21%) and had significantly less macrosomia (9 vs. 24%). On the other hand, the SMBG group (who had a lower frequency of macrosomia, presumably because of more frequent and intensive treatment with insulin) also underwent operative delivery more often (53 vs. 35%). Weiss et al. (21) have used an unorthodox and more invasive approach to identify the need for treatment of GDM with insulin (all having similar OGTT values). Amniotic fluid insulin concentrations were measured at 28–32 wk gestation in 88 subjects with GDM. The 19 with high amniotic fluid insulin (designated class A/B) received therapy with multiple doses of short-acting exogenous insulin. The 69 with normal amniotic fluid insulin values (designated class A) were treated with diet alone. Macrosomia was found in 4 of 51 (7.8%) control, in 11 of 69 (20.4%) class A, and in 1 of 19 (5.3%) class A/B insulin-treated subjects.

In this issue of *Diabetes Care*, Drexel et al. (p. 761) report their efforts to prevent perinatal morbidity in GDM by tight metabolic control. Insulin therapy was initiated without a trial of diet alone if one or more values during the OGTT were ≥200 mg/dl. The therapeutic goals were capillary blood glucose concentration <130 mg/dl 1 h after breakfast, absence of ketonuria, and weight gain ≤1 kg/mo. When blood glucose concentration exceeded the acceptable range in diet-treated subjects, insulin treatment was added (lente, ≥12 U/day).

Whereas insulin was used in most subjects, the frequency of macrosomia was not different in the intensively treated subjects with GDM (group 2) and the normal control group, whereas the frequency of macrosomia in the group of GDM with limited treatment (group 3) was significantly higher than in group 2. However, the frequency of unphysiological modes of delivery and of neonatal morbidity did not differ among the three groups of subjects. In addition, obesity, an important confounding variable in several of the studies cited, was not a common feature of these subjects. The protocol used in this study led to earlier diagnosis and treatment of GDM than what currently exists in most centers. Was the early intervention per se or treatment with insulin most important in the outcomes? Thus, the article by Drexel et al., like many of the studies mentioned, is encouraging, particularly with respect to the potential reduction in the frequency of macrosomia in GDM.

## WHERE DO WE GO FROM HERE?

O'Sullivan et al. (6) called for a definitive prospective study in one of the promising early studies from this group. Freinkel (22) illustrated the public health implications of the problem in the opening session of the first International Workshop Conference on GDM when he pointed out that, in the United States alone, as many as 90,000 pregnancies/yr are complicated by GDM. The need for answers is becoming urgent as efforts to identify women with GDM are more universally applied in populations of pregnant women throughout the world. Thus, the economic and manpower costs of aggressive therapeutic efforts are potentially enormous. It is therefore vital that a clear consensus be reached regarding the treatment of mild GDM.

How can the impact of several specific therapeutic modalities that are directed at reducing the frequency and severity of perinatal morbidities in GDM be evaluated most effectively? First, many subjects (women with normal carbohydrate metabolism and those with mild GDM) will be needed to document treatment-related decreases in birth weight, neonatal morbidities, and operative interventions (taking all confounding variables into consideration). Second, rigidly defined and imposed protocols (preferably suitable for later application in routine clinical practice) must be used for screening, detection, diagnosis, medical treatment, method and timing of delivery, and neonatal evaluation. It is apparent that it may require a large-scale controlled clinical trial, probably multicenter in nature, to fulfill these conditions. The study by Drexel et al. and previous publications strongly suggest that definitive answers can be obtained. In view of the magnitude of the clinical problem, the time for such a clinical trial in the treatment of mild GDM may be at hand.

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