Gestational Diabetes Mellitus

A Survey of Perinatal Complications in the 1980s

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Neonatal morbidity was assessed in the offspring of 878 mothers with gestational diabetes mellitus (GDM), 132 mothers with pre-GDM, and 380 control subjects. Compared with the control group, the GDM group had a higher incidence of complications, including macrosomia, hypoglycemia, hyperbilirubinemia, hypocalcemia, polycythemia, and major congenital anomalies ($P < 0.05$). Although our GDM patients were stringently managed with diet or diet plus insulin, as indicated, and maintained almost euglycemic values, these neonatal complications could not be eliminated. Our data may be consistent with observations published during the last decade that even subtle degrees of maternal hyperglycemia can have a detrimental effect on perinatal outcome. Most neonatal complications readily respond to therapy if diagnosed and treated early and promptly. Macrosomia can have a detrimental effect on delivery (trauma) and later long-term implications during childhood. Tight metabolic control with diet and, when indicated, insulin treatment may be advantageous in reducing fetal birth weight. Criteria of how tight the metabolic control should be remain to be accurately defined. *Diabetes* 40 (Suppl. 2):74–78, 1991

During the last decade, there has been a dramatic reduction in fetal and neonatal losses in diabetic pregnancy (1,2). Reports at the Second International Workshop-Conference on Gestational Diabetes Mellitus (GDM) provided evidence that the infant of the mother with GDM is at increased risk for several neonatal morbidities, such as macrosomia, hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia (3). Up to 25% of such offspring have been reported to suffer from these complications. Early detection and subsequent strict metabolic control of pregnant women with GDM should decrease the frequency and severity of some of these neonatal complications. The purpose of this study was to *1*) provide information on the incidence of GDM and its perinatal consequences in a large population of pregnant women diagnosed, treated, and followed up during the last decade at a large tertiary teaching hospital in Israel and *2*) summarize the pertinent data from the last decade addressing the magnitude and severity of perinatal (primarily neonatal) complications of GDM and inquire whether specific types of treatment reduce or increase the consequences of GDM.

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RESEARCH DESIGN AND METHODS

Beilinson Medical Center is a large tertiary teaching hospital of the Sackler School of Medicine, Tel Aviv University. The hospital has ~4000 deliveries/yr, and the population consists almost exclusively of Jewish patients, representing the entire ethnic spectrum of the Israeli Jewish population.

At our department, the classification, diagnosis, treatment, and follow-up of GDM patients is based on the specific recommendations proposed by the American Diabetes Association from 1979 to 1985 (3–5). Data for this study were collected from 1 January 1980 to 31 December 1989. All pertinent data were collected prospectively from mothers and neonates during the course of pregnancy and later in the postpartum period. Since 1986, all the data have been computerized and form a data-based system.

All pregnant women identified as having two or more abnormal oral glucose tolerance test (OGTT) values were referred to the high-risk diabetes clinic for further prenatal care. Patients were placed on a diabetic pregnancy diet consisting of ~1200–1600 kcal/day (lower than that usually recommended) and followed up weekly (class A_1; 5a) and daily (classes A_2 and B_1) with blood glucose measurements (fasting and 1 and 2 h after meals). Glycosylated hemoglobin was tested on a monthly basis, and since 1987, glycosylated albumin was tested on a weekly basis. Insulin

treatment was started either when fasting plasma glucose levels were >5.8 mM or when postprandial levels were >7.8 mM. Antepartum surveillance of GDM patients included serial ultrasound examinations every 2–4 wk to assess fetal growth and biophysical profile. Weekly nonstress tests were started at 36 wk, and patients were followed up to 38–40 wk of gestation. At this stage, a decision was made on whether to induce patients with a suspected large for gestational age fetus or continue surveillance until 42 wk, when all patients are electively induced. Induction was performed after ascertaining fetal lung maturity and by application of vaginal prostaglandin E_2 pessaries (3 mg). Elective cesarean section was performed if the estimated fetal weight was ~4500 g.

We classified our GDM patients according to the severity of maternal metabolic derangement reflected by plasma fasting glucose values (A_1 <5.8 mM, A_2 5.8–7.2 mM, and B_1 >7.2 mM; 6).

All newborns were examined in the Neonatology Department by physicians specially trained in this field. The newborns of mothers with GDM were examined immediately postdelivery and followed up very closely during the first 24 h, especially during the first 2 h of life.

The definitions of neonatal complications used in our department were macrosomia, fetal birth weight >4000 g; hypoglycemia, blood glucose <1.7 mM during the first 72 h or <2.2 mM thereafter in full-term newborns and <1.1 mM in preterm newborns; hypocalcemia, serum Ca^{2+} <8 mg/dl in full-term newborns and <7 mg/dl in preterm newborns (total plasma Ca^{2+}; hypomagnesemia, serum Mg^{2+} <1.5 mg/dl; hyperbilirubinemia, bilirubin level >12 mg/dl in absence of hemolysis; polycythemia, venous hematocrit >70% at 2 h of life; hyaline membrane disease (HMD), diagnosis based on clinical findings, blood gases, and chest X ray (excluding all other causes of neonatal respiratory distress).

For statistical analysis, we employed the χ^2 test. $P < 0.05$ was considered significant.

RESULTS

Between 1 January 1980 and 31 December 1989, 39,083 pregnant women were delivered at the Department of Obstetrics and Gynecology, Beilinson Medical Center. One thousand ten of these patients were diagnosed as having diabetes in pregnancy; 878 had GDM (classes A_1, A_2, and B_1), and 132 had pre-GDM (classes B_2–F).

The control group consisted of 380 infants born to healthy mothers who were referred to our service for various reasons and in whom diabetes was excluded by a standard OGTT. These offspring were followed up during the neonatal period exactly as those born to the diabetic mothers.

The 878 GDM patients were subclassified into three groups: 731 A_1, 102 A_2, and 41 B_1 patients. The study population and incidence of diabetes in pregnancy are presented in Table 1. Table 2 compares the outcome of pregnancy in the three groups. There was a significantly higher incidence of macrosomia, hypoglycemia, hyperbilirubinemia, hypocalcemia, polycythemia, and major anomalies in the GDM group compared with the control group ($P < 0.05$). When GDM was subclassified according to the severity of metabolic derangement, each group had a greater incidence of neonatal morbidity, except for hypocalcemia in classes A_2 and B_1 (NS) and major anomalies in class A_1 (NS), compared with the control population.

TABLE 1
Study population and incidence of diabetes in pregnancy, 1980–1989, Beilinson Medical Center

Group	*n*	Incidence (%)
GDM	878 (731 A_1, 106 A_2, 41 B_1)	2.25
Pre-GDM	132	0.34
Control	380	

Total no. of deliveries = 39,083. GDM, gestational diabetes mellitus. See METHODS for GDM classes.

DISCUSSION

In the summary and recommendations of the Second International Workshop-Conference on Gestational Diabetes Mellitus (3), it was stated that even when dietary therapy alone is effective and maternal fasting and postprandial glucose levels are normalized, up to 25% of infants of mothers with GDM may have hypoglycemia, hypocalcemia, polycythemia, hyperbilirubinemia, and macrosomia. We sought to update the observations in light of newer therapeutic approaches to GDM.

In 1954, Pedersen et al. (7) hypothesized that maternal hyperglycemia leads to fetal hyperinsulinemia. This concept was later expanded, and evidence was presented that fetal hyperinsulinemia suppresses the production of surfactant, promotes various growth factors, and induces relative fetal hypoxemia, leading to various neonatal morbidities including HMD, macrosomia, hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, stillbirth, and renal vein thrombosis (8).

Gabbe et al. (9) addressed the issue of incidence and severity of various neonatal complications in 261 GDM patients managed by a uniform protocol. This study reported significant neonatal morbidity arising from hyperbilirubinemia (16%), hypoglycemia (7%), hypocalcemia (1%), traumatic delivery (3%), and other complications. In total, some 85% of offspring of mothers with GDM had some neonatal morbidity. This study together with Lavin et al.'s (10) represented the consensus in the late 1970s and early 1980s on this subject.

Table 3 summarizes most of the studies published during the last decade on the management of GDM, reporting the incidence of the various perinatal and neonatal complications. In our study, conducted between 1980 and 1989, the incidence of GDM was 2.3%, which we believe accurately reflects the true incidence among Jewish Israeli women.

The goals of management were maternal euglycemia and fetal maturity. Although most of our patients were normoglycemic, reflected by daily blood glucose profiles, glycosylated hemoglobin, and fructosamine, we could not eliminate entirely the neonatal complications. We had 18% macrosomia, 5.1% hypoglycemia, 16.5% hyperbilirubinemia, 13.3% polycythemia, 5.5% hypocalcemia, and 3% major anomalies, all of them significantly higher than in the control group. In the GDM group itself, there was no significant difference between the three subgroups in the incidence of various neonatal complications.

TABLE 2
Neonatal complications in offspring of diabetic mothers and control infants, 1980–1989, Beilinson Medical Center

Complication	GDM				Pre-GDM	
	A_1 (n = 731)	A_2 (n = 106)	B_1 (n = 41)	Total (n = 878)	B_2-F (n = 132)	Control (n = 380)
Macrosomia	18.2*	17.9*	14.6*	17.9*	25.0*	5.6
Hypoglycemia	5.2*	5.7*	2.4*	5.1*	7.8*	0.9
Hyperbilirubinemia	16.4*	16.9*	17.1*	16.5*	16.7*	8.2
Hypocalcemia	6.0*	2.8	2.4	5.5*	4.5*	2.7
Polycythemia	13.9*	9.4*	12.2*	13.3*	3.8	4.9
Thrombocytopenia	0.5	0.7		0.6	0.8	0.9
Hyaline membrane disease	1.2	1.9		1.3	1.6	1.4
Minor anomalies	19.8	20.7	19.5	19.9	20.5	21.0
Major anomalies	2.7	3.8*	4.9*	3.0*	6.1*	1.8

Values are percentages. GDM, gestational diabetes mellitus.
*P < 0.05 vs. control.

Thus, despite "tight" metabolic control achieved in all these studies, the incidence of neonatal morbidity and especially macrosomia in offspring of mothers with GDM remains not very different from that reported in the previous decade.

Significantly, during recent years, more and more evidence has been presented documenting the influence of even subtle degrees of maternal hyperglycemia (levels below those that would classify the patient as having GDM) on perinatal outcome.

Jovanovic and Peterson (17), Frisoli et al. (18), and Leikin et al. (19) reported that women with a positive glucose challenge test (GCT) and normal OGTT had a higher incidence (12–28%) of macrosomic offspring (Table 3). However, Weiner (20) could not show any significant difference between the positive-GCT–negative-OGTT group (12.6%) and the general population (13.3%).

Tallarigo et al. (23) noted a surprising correlation between macrosomia rate and the 2-h glucose value during a 100-g OGTT (all 4 values were normal). Levels of <5.6 mM were associated with a 9.9% incidence of macrosomia, whereas 5.6–6.6 mM produced 15.5% and 6.7–9.1 mM produced 27.5% macrosomic babies. Weiner (20) showed similar results in the correlation between the 2-h value of an OGTT and the incidence of macrosomia, which ranged from 4.4 to 22.2%.

TABLE 3
Incidence of neonatal complications in GDM (positive OGTT) and incidence of macrosomia when OGTT was normal

Ref.	Macrosomia	Hypoglycemia	Hyperbilirubinemia	Hypocalcemia	Polycythemia	RDS	Malformation
GDM							
9	20.0	7.0	16.0	1.0	1.0	1.0	5.0
10	29.0	11.0	9.0		2.0	2.0	
11	16–17	17–19	7–17		0–3	0–10	1.5
12	25.0	2.5	50.0			0.7	4.0
13	13.0	12.5	38.4		11.1	6.4	6.4
14	26.0		8.0			3.0	2.0
15	32.0	11.3	10.3			1.0	5.0
16	10.1	6.0	6.0	3.3	4.0	2.7	
This study	17.9	5.1	16.5	5.5	13.3	1.5	3.0
Positive GCT							
17	27.7						
18	27.0						
19	11.9						
20	12.6						
Abnormal OGTT value							
21	24.0						
22	18.0						
2-h OGTT value							
23							
<5.6 mM	9.9						
5.6–6.6 mM	15.5						
6.7–9.1 mM	27.5						
20							
<5.6 mM	4.4						
5.6–6.6 mM	12.3						
6.7–8.8 mM	15.3						
8.9–9.9 mM	22.2						

Values are percentages. GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; GCT, glucose challenge test; RDS, respiratory distress syndrome.

TABLE 4
Tight metabolic control achieved with prophylactic insulin treatment and incidence of macrosomia

Ref.	Diet only	Diet + insulin
24	14.8	5.9 (10 N)*
25		1.9
26	39.0	4.0
27	36.4	7.0 (20 N + 10 R)
28	18.5	7.0*
29	13.3	15.0
30	6.4	16.2 (15 N)
Lean		5.7
Obese		29.0
31		5.8 (10 N + 70 R)
32	16.0	5.8*
33	26.5	5.9 (20 N + 10 R)*

Values are percentages. Insulin dose (in U) is given in parentheses. N, intermediate-acting insulin; R, rapid-acting insulin.
*$P < 0.05$ vs. diet only.

Two additional studies by Langer et al. (21) and Lindsay et al. (22) analyzed women with only one abnormal OGTT value and reported an incidence of macrosomia of 18–24% (control 6.6–12%).

Thus, not only is classic GDM (2 abnormal 100-g OGTT values) associated with abnormal fetal outcome, even milder degrees of glucose tolerance can cause fetal and neonatal morbidity. These facts emphasize that we have yet to define normal maternal glucose tolerance.

Several investigators suggested a standard prophylactic dose of insulin in the management of GDM to achieve tight metabolic control, hopefully preventing fetal macrosomia. Table 4 summarizes studies published from 1975 to 1990 dealing with the prophylactic insulin treatment of GDM. Although most of these studies achieve a reduction in the incidence of macrosomia, we still lack precise information about the optimal glycemic level.

In 1989, Langer et al. (16) attempted to empirically assess the optimal level of long-term maternal control in GDM. They sought to determine the level of maternal glycemia at which perinatal morbidity could be reduced. By dividing the GDM population into three groups according to their mean blood glucose level throughout pregnancy, this study demonstrated a relationship between the level of glycemic control and neonatal outcome. The low–mean blood glucose group had a high incidence of intrauterine growth retardation (20%) compared with the middle (9%) and high (9%) groups ($P < 0.001$). In the high–mean blood glucose group, an approximate twofold increase was found in the incidence of large for gestational age infants compared with control infants ($P < 0.03$). Thus, although even minimal elevations in maternal glycemia may be detrimental, overly vigorous blood glucose control is also associated with excessive morbidity.

In conclusion, despite years of meticulous study, a paucity of information exists regarding the optimal level of glycemia that should be targeted to reduce perinatal morbidity and yet not cause any harm to intrauterine development. From a neonatal perspective, GDM can have short- and long-term complications. Hypocalcemia, hypomagnesemia, and hyperbilirubinemia are easily recognized and readily treated. Hypoglycemia (neurological damage) and polycythemia (neurological damage and renal vein thrombosis) present the greatest danger, but even these can be promptly diagnosed and corrected. Macrosomia, on the other hand, once established, cannot be reversed. It can cause immediate consequences, i.e., birth trauma to mother and neonate. It can also cause delayed chronic morbidity to the offspring by inducing obesity and diabetes in later life.

Therefore, our efforts should be directed toward determining the precise etiology of and devising strategies for the prevention of macrosomia. To do so, we will first have to study the fetus (the real patient) to define normal and abnormal fetal intrauterine metabolic environment.

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