

Original Article

A Prospective Controlled Study of Neonatal Morbidities in Infants Born at 36 Weeks or More Gestation to Women with Diet-controlled Gestational Diabetes (GDM-class A1)

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OBJECTIVE:

Infants of gestational diabetes mellitus (GDM)-A1 women are unlikely to experience the marked excursion in maternal glucose levels that may characterize insulin-requiring GDM (class-A2) or insulin-dependent diabetes (IDDM). However, infants born to GDM-A1 women are traditionally managed like infants born to GDM-A2 or IDDM women.

AIMS:

To examine monitoring protocols for infants of GDM-A1 women, and to examine the efficacy of early and frequent feedings to prevent and to treat hypoglycemia.

METHODS:

A total of 92 of 101 infants born to GDM-A1 women (diabetic group) and 68 of 83 infants born to nondiabetic women (control group) at ≥ 36 weeks of gestation were prospectively monitored for the development of hypoglycemia and other morbidities. Blood glucose screening was performed in the diabetic group every 30–60 minutes three times, starting soon after birth and then at 3-hour intervals for 24 hours. Liberal feedings were started shortly after birth and provided every 3 hours for at least 24 hours. All women with GDM-A1 had an HbA1c measured before delivery.

RESULTS:

Both the diabetic and control groups had similar demographics, including LGA incidence. Blood glucose readings before feedings were low (< 40 mg/dl) in 24 of 92 infants (26.1%) from the diabetic group and in 20 of 68 control infants (29%). After the start of oral feedings, all but four

diabetic and three control infants had subsequent glucose readings ≥ 40 mg/dl. No infant had symptoms of hypoglycemia and none from the diabetic group had birth trauma, hypoxic–ischemic encephalopathy, polycythemia, hypocalcemia, or hypomagnesemia. Hypoglycemic episodes in the infants from the diabetic group could be managed with oral feedings alone. Birth weight, gestational age, sex, Apgar scores, and maternal HbA1c levels could not predict low glucose readings on initial screening in infants from the diabetic group.

CONCLUSION:

The incidence of hypoglycemia in infants born to GDM-A1 women at ≥ 36 weeks of gestation is similar to control infants born to nondiabetic women. Low blood glucose levels during the first few hours of life can be prevented or treated with early and frequent oral feeding.

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INTRODUCTION

Perinatal mortality among women with gestational diabetes mellitus (GDM) has declined,^{1,2} but excess neonatal morbidity among this group remains a significant challenge.^{3,4} Infants born to women with GDM are at increased risk of fetal macrosomia, birth trauma, neonatal hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, and hyperbilirubinemia.⁵ Even when dietary therapy alone is effective and maternal glucose levels remain normal, up to 25% of infants of women with gestational diabetes may have hypoglycemia, hypocalcemia, polycythemia, or hyperbilirubinemia.⁶

Comprehensive care of infants of diabetic women is based on studies that include infants, both preterm and term, born to women with different classes of diabetes (classes A through D-R) as a group, and do not take into account the inherent differences between infants born to women with diabetes requiring insulin during pregnancy and infants born to women with diet-controlled class-A1 GDM.^{3,7} The infants born at term gestation to women with diet-controlled GDM (class A1) are less likely to experience the marked excursion in maternal glucose levels that may characterize insulin-requiring GDM (class A2) or insulin-dependent diabetes (IDDM),⁸ but this group of infants is commonly managed like any other infants born to women with insulin-requiring GDM or IDDM.

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We hypothesize that infants born at 36 weeks or more gestation to class A1 GDM women may not have increased morbidity compared to infants born to nondiabetic women and may not require extended routine monitoring of blood glucose or other metabolic problems, if early and frequent feeding practice is followed.

PATIENTS AND METHODS

The study population consisted of infants born at ≥ 36 weeks to women with diet-controlled GDM (class A1) at the Coney Island Hospital in New York over a period of 16 months. Infants born at ≥ 36 weeks to nondiabetic women who had a late entry into clinic prenatal care served as controls. These control women were considered to be high-risk and had a normal glucose challenge test (GCT), normal glucose tolerance test (GTT), or normal HbA1c documented. Classification, diagnosis, treatment, and care of pregnant women with diabetes mellitus were based on the American College of Obstetrics and Gynecology (ACOG) recommendations.⁹ All women with class A1 GDM had an HbA1c measured after admission to the hospital for delivery to determine the adequacy of blood glucose control. Demographic and clinical characteristics of the infants born to women with diet-controlled GDM (class A1) and to nonclinic, nondiabetic women were obtained prospectively from the medical records.

As per institutional guidelines, infants born to diabetic women and nonclinic but nondiabetic women were admitted to the special care nursery (SCN) for monitoring of blood sugar or other morbidities, and for early and frequent breast or formula feedings. Blood glucose screening was performed in all study infants according to the protocol for infants of diabetic women. Blood glucose screening was performed with chromogen reagent strips (Accucheck Advantage, Roche Boehringer Mannheim Diagnostics Systems, Inc., Somerville, NJ.) read by a reflectance meter; true serum glucose was measured by the glucose oxidase method. The blood glucose screening for infants from the diabetic group included chemstrip determinations every 30 to 60 minutes three times, starting soon after birth and then at 3-hour intervals before each feed for the next 24 hours. In control infants, chemstrip monitoring was done twice, once before the start of feedings and then once before the next feeding. Feedings were started shortly after delivery and were preceded by the measurement of blood glucose. Liberal formula or breast feeding every 3 hours was used to prevent hypoglycemia in both the groups and all infants were observed for at least 24 hours.

If a glucose value was borderline or low before the first feeding was given and the infant was asymptomatic, the test was repeated each half hour until the next feeding in both groups. If the glucose level remained abnormally low, or if the infant was symptomatic after the initial oral feeding, the infant was given an intravenous dextrose infusion.³

According to the protocol, hematocrit, serum calcium, magnesium, and phosphorus were measured in infants from the

diabetic group once between 12 and 24 hours of age, and the collection of specimens was timed according to glucose monitoring. Control infants were observed clinically for signs of polycythemia, hypocalcemia, and hypomagnesemia and had a urine toxicology screen sent according to institutional policy. Infants from both groups who required intravenous dextrose infusion soon after birth for indications other than hypoglycemia were excluded from the study.

The infants in the study were classified into large for gestational age (LGA), appropriate for gestational age (AGA), and small for gestational age (SGA).¹⁰ LGA infants with birth weight >4000 g were deemed macrosomic. Chemstrip readings of <40 mg/dl were considered to be hypoglycemic and were confirmed by the true serum glucose concentration. Because it is not unusual to observe a single low blood glucose value, the diagnosis of hypoglycemia was based on two consecutive low glucose values taken no more than 30 minutes apart and confirmed with a laboratory serum glucose determination.³ Hypocalcemia and hypomagnesemia were defined as total serum calcium concentration <6 mg/dl and serum magnesium <1.2 mg/dl, respectively.⁷ Polycythemia was defined as a central hematocrit greater than 65% and hyperbilirubinemia as an indirect bilirubin level >12 mg/dl and/or any jaundice requiring phototherapy.¹¹

Data were expressed as percentage and mean \pm SD, where applicable. The student's *t*-test was used to analyze continuous variables and the χ^2 analysis was used to test differences in all categorical variables. Forward stepwise logistic regression analysis was used to evaluate the contribution of birth weight, gestational age, sex, mode of delivery, Apgar score, macrosomia, and maternal HbA1c in the prediction of low chemstrips before the start of feedings. A *p* value of less than 0.05 was considered to be statistically significant.

This study was approved by the Institutional Review Board of Maimonides Medical Center and Coney Island Hospital.

RESULTS

Between 1 January 1999, and 30 April 2000, 1608 women were admitted to the Coney Island Hospital for delivery. Of these, 99 with a gestational age of 36 weeks or more had diet-controlled gestational diabetes (GDM Class A1) and 83 matched nondiabetic women served as controls. The GDM Class A1 women had 97 singleton births and two sets of twins, while all the nondiabetic women had singleton pregnancies. In all, 16% of all women enrolled were primigravidas and the maternal age ranged from 18 to 44 years (mean $29.9 \pm$ SD 5.6).

A total of 92 of 101 infants born to GDM Class A1 women and 68 of 83 infants born to control women at ≥ 36 weeks of gestation were prospectively enrolled. Nine infants from the diabetic group and 15 infants from the control group were excluded. Seven of the

| Characteristics | Diabetic group (n=92) | Control group (n=68) | Significance |
|--------------------------------------|-----------------------------------|-----------------------------------|--------------|
| Birth weight (g) | 3207.3±492.6 (range 2250–4950) | 3081.8±573.8 (range 1870–4425) | NS |
| Gestational age (weeks) | 38.4±1.3 (range 36–41) | 38.3±1.4 (range 36–41) | NS |
| Race (Asian/Hispanic/Black/White) | 52(56.5%)/24/9/7 | 16/11/27(39.7%)/14 | |
| Mode of delivery (C-section/NVD) | 22(24%)/70 | 15(22%)/53 | NS |
| Sex (M/F) | 48(52.2%)/44 | 33(48.5%)/35 | NS |
| Apgar score >7 at 5 minutes | 100% | 100% | NS |
| LGA/SGA | 15(16.3%)/1 | 9(13.2%)/2 | NS |
| Macrosomia (birth wt ≥ 4 kg) | 3 | 4 | |
| Hyperbilirubinemia | 7(7.6%) | 5(7.3%) | NS |

*Data are expressed as mean±SD and percentage, where applicable.
NS=not significant.

| Parameters | Diabetic group (n=92) | Control group (n=68) | Significance |
|---|--------------------------|-------------------------|--------------|
| Chemstrip values (mg/dl) | | | |
| Before start of feedings | 55.1±20.9 | 50.9±19.2 | NS |
| 3 hours after first feeding | 58±10.2 | 61.8±16.4 | NS |
| Low chemstrip readings (<40 mg/dl) before start of feedings | 24 (26.1%) | 20 (29%) | NS |
| Hypoglycemia (true serum glucose <40 mg/dl) | 4 (4.3%) | 3 (4.4%) | NS |

*Data are expressed as mean±SD and percentage, where applicable.
NS=not significant.

nine infants from the diabetic group and three of the 15 control infants excluded from the study had transient tachypnea of the newborn, one infant from each group had meconium aspiration syndrome, and one infant from each group was septic at birth. All these infants were excluded as intravenous dextrose infusions were started soon after birth because of respiratory problems. The other 10 control infants excluded had a positive urine toxicology screen.

Demographic and clinical characteristics of the study population are shown in Table 1. Both the diabetic and control groups were similar in birth weight, gestational age, sex distribution, Apgar score, mode of delivery, and number of LGA infants. In sum, 56.5% of infants in the diabetic group were born to women of Asian origin while 39.7% infants from the control group were black.

All infants from both groups had an Apgar score of 7 or more at 5 minutes and none had any clinical evidence of hypoxic–ischemic encephalopathy. Hyperbilirubinemia requiring

phototherapy was seen in seven (7.6%) of 92 infants from the diabetic group and five (7.3%) of 68 control infants; one of the infants from the diabetic group also had ABO incompatibility. The incidence of hyperbilirubinemia was similar in both the groups ($p = NS$).

Chemstrip readings obtained before the start of feedings at 30–60 minutes of age were low (<40 mg/dl) in 24 (26.1%) of 92 infants from the diabetic group and in 20 of 68 infants (29%) from the control group (Table 2) ($p = NS$). After the start of oral feedings, in all but four infants from the diabetic group, subsequent chemstrip readings obtained over a 24-hour period were ≥ 40 mg/dl (Figure 1). None of the 92 infants from the diabetic group had symptoms of hypoglycemia. In the four (4.3%) infants of the diabetic group with initial low chemstrip values, the glucose readings obtained half an hour after the first feeding were higher than before but were still in the hypoglycemic range (<40 mg/dl). In these four infants, chemstrip readings were >40 mg/dl at the next measurement, 1 hour after the start of

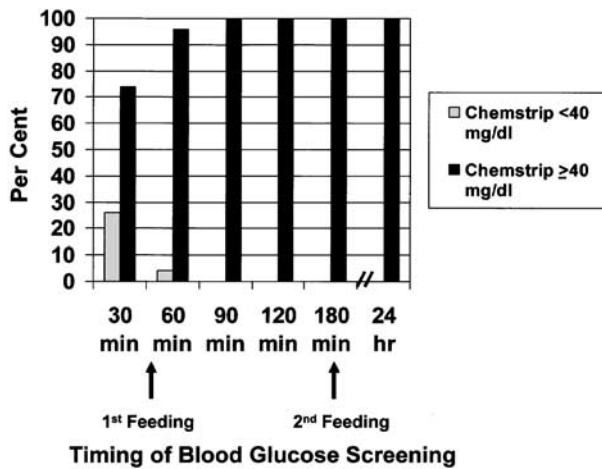


Figure 1. Percentage of infants in the diabetic group with chemstrips >40 mg/dl or <40 mg/dl at time intervals between 30 minutes and 24 hours of life.

feedings, and continued to be >40 mg/dl for all subsequent feedings during a subsequent period of 24 hours. None of the infants from the diabetic group required intravenous dextrose infusion.

In 17 of 20 infants from the control group who had low chemstrips before the start of feedings, the chemstrip values rose to ≥ 40 mg/dl when measurements were repeated one-half hour after the first feeding. In the other three (4.4%) control infants, low glucose levels persisted one-half hour after feedings were started, qualifying for a diagnosis of hypoglycemia. In one of the three infants, subsequent chemstrips at 1 hour after the first feedings were still low and required intravenous dextrose infusion for treatment; in the other two, low chemstrips rose to >40 mg/dl by 1 hour after the first feedings were given and continued to be >40 mg/dl. None of the infants from the control group became symptomatic for hypoglycemia.

Table 3 shows the trend in the chemstrip readings in infants from the diabetic group over a 24-hour period and in control infants before the first and second feedings. The chemstrip readings (mean±SD) before the start of feedings at 30–60 minutes of age were similar in both the groups, and so were the chemstrip readings (mean±SD) before the next feedings which were due at around 3 to 4 hours of age (Table 2).

None of the 92 infants from the diabetic group were polycythemic and none had hypocalcemia or hypomagnesemia. Hematocrit values in all infants from the diabetic group ranged between 37.5% and 64.9% (mean 52.6%±SD 6.0); only 10 of the 92 infants had hematocrit values of 60% or greater. Serum calcium and magnesium values in all infants from the diabetic group ranged between 8 and 10.7 mg/dl (mean 9.1 mg±SD 0.6) and from 1.2 to 4.8 mg/dl (mean 1.9 mg/dl±SD 0.6), respectively. None of the control infants had clinical signs of polycythemia, hypocalcemia, or hypomagnesemia. None of the infants in the diabetic group, including 15 who were large for gestational age

Table 3 Trends in Chemstrip Readings in Diabetic and Control Groups*

| Timings of blood glucose screening | Chemstrip values (mg/dl) in control group | Chemstrip values (mg/dl) in diabetic group |
|------------------------------------|---|--|
| 30 minutes | 50.9±19.2 | 55.1±20.9 |
| 60 minutes | | 59.9±15.7 |
| 90 minutes | | 59.8±14.6 |
| 3 hours | 61.8±16.4 | 58±10.2 |
| 6 hours | | 60.7±10.1 |
| 9 hours | | 58.9±11.3 |
| 12 hours | | 61.5±10.5 |
| 15 hours | | 65.5±11.3 |
| 18 hours | | 65±10.7 |
| 24 hours | | 67±13.9 |

*All values are expressed as mean±SD.

(LGA), had clinical evidence of birth trauma. None had any obvious congenital malformation. In the control group, three infants had birth trauma: one with a clavicular fracture, one with an Erb’s palsy, and one with a large cephalhematoma.

HbA1c values in Class A1 GDM women whose infants were enrolled for the study ranged from 3.9% to 6.7% (mean 5.4%±SD 0.6). Birth weight, gestational age, sex, Apgar scores, and maternal HbA1c levels could not predict low chemstrip readings on initial screening for blood glucose before the start of feedings in infants from the diabetic group.

DISCUSSION

Gestational diabetes mellitus occurs in as many as 3–12% of pregnancies in the US. In the 1988 National Maternal & Infant Health Survey (NMIHS), diabetes was reported to occur in 4% of pregnancies with live births and, of these pregnancies, 88% were complicated by gestational diabetes.¹² Although there has been continuing improvement in outcome for infants born to diabetic mothers, these infants remain a high-risk population.

Our findings suggest that neonatal morbidity in infants born to GDM Class A1 women is similar to that seen in infants of nondiabetic women. Unlike infants of insulin-dependent diabetic and insulin-requiring GDM women, infants born to GDM Class A1 women at 36 weeks of gestation or more, and who are otherwise healthy, are not at increased risk of developing hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, hyperbilirubinemia, birth trauma, or birth asphyxia.

Data from the medical literature have shown that, at birth, umbilical cord plasma glucose levels correlate with maternal values.¹³ In most cases, blood glucose levels decrease during the first 2 hours of life and then start to rise and stabilize.³ In our

study, both the control and the diabetic groups had a similar incidence of low chemstrips and repeat low chemstrips. All these hypoglycemic episodes in the diabetic group could be successfully treated with oral feedings. None of the infants from the diabetic group were symptomatic or required intravenous dextrose infusion.

The definition of clinically significant hypoglycemia remains one of the most contentious issues in contemporary neonatology.¹⁴ It is not possible to define a blood glucose level that requires intervention in every newborn infant because there is uncertainty over the level and duration of hypoglycemia that can cause damage, and little is known of the vulnerability, or lack of it, in the brain of infants at different gestational ages. The standard of care in most neonatology units involves close surveillance if the plasma glucose concentration is less than 40 mg/dl.⁷ Intervention is recommended if plasma glucose remains below this level, if the level does not increase after a feed, or if abnormal clinical signs develop.

We believe that the reduced excursion of blood glucose levels during pregnancy in women with diet-controlled gestational diabetes has led to a low incidence of transient hypoglycemia in infants from the diabetic group. This low incidence of hypoglycemia in infants from the diabetic group is not different from the control group in our study, nor from the reported incidence of transient hypoglycemia that affects up to ~3% of apparently healthy full-term infants born to nondiabetic women.³ Given a ~27% incidence of hypoglycemia reported in infants born to women with diabetes (classes A through D-R),¹¹ a post hoc calculation using the GB-STAT statistical software package confirmed that with an alpha of 0.05 and a beta of 0.20, we would have needed 63 infants in the diabetic group to detect a reduction in risk of hypoglycemia to ~3%, which is similar to the reported incidence of transient hypoglycemia in apparently healthy full-term infants born to nondiabetic women.

Approximately half of the infants of pre-existing diabetic and gestational diabetic women develop early transient hypocalcemia.^{15,16} Often, hypocalcemic infants display low serum magnesium values.³ Although the cause for the high incidence of this complication is unclear, it is well recognized that it relates to the severity of maternal diabetes, and perinatal distress.¹⁷ Polycythemia, hyperbilirubinemia, and macrosomia have been reported in a greater proportion of infants of diabetic women than infants in the general population.¹⁸ Although some of the variation in incidence may be related to definition, most authors agree that excess macrosomia is in part related to maternal glucose control.¹⁹ The infants of women with diet-controlled GDM (class A1) are less likely to experience the marked excursion in maternal glucose levels, thereby explaining the small number of macrosomic infants and the low frequency of other morbidities which approached that of infants of nondiabetic women in the present study.

As the infants born to GDM Class A1 women at 36 weeks of gestation or more do not have an increased incidence of

morbidities, routine monitoring of such infants for blood glucose for an extended period adds unjustified laboratory and personnel expense, is traumatic to the newborn infants, and prolongs their length of stay in the SCN. Unlike infants born to insulin-requiring GDM (class A2) or insulin-dependent diabetic women, infants born at 36 weeks or more gestation to class A1 GDM women can be managed like any other normal full-term infant born to a nondiabetic woman. They do not require routine glucose monitoring after the first 2–3 hours of life, and low chemstrip readings or hypoglycemic episodes in them during the first few hours of life can be prevented and managed with early and frequent oral feeding.

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