

PREDICTIVE FACTORS AND INCIDENCE OF COMPLICATIONS IN APPARENTLY HEALTHY FULL TERM INFANTS OF DIABETIC MOTHERS

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هدف الدراسة: لتحديد المضاعفات التي تصيب أطفال الأم المصابة بالسكري المعافين ظاهرياً من الأمراض لدى ولادتهم وتحديد إمكانية توقع تلك المضاعفات .
طريقة الدراسة: أجريت الدراسة في وحدة الحضانة بمستشفى الملك فهد الجامعي واستمرت لمدة 18 شهراً. الأطفال المدرجين في الدراسة هم أطفال الأم السكرية الخاليين من الأعراض عند ولادتهم ووزن ولادتهم يساوي أو يزيد عن 2000 غ. أمهات الأطفال مصبن بمرض السكري الحاملي أو السريري. كل هؤلاء الأطفال لوحظوا في وحدة الحضانة لمدة لا تقل عن 48 ساعة. خلال تلك المدة، أجريت فحوص دموية لهؤلاء الأطفال تضمنت تعداد الدم ونسبة كل من الجلوكوز والبروتين والكالسيوم. مجموعة الأطفال المرضى تتضمن كل طفل من هؤلاء احتاج إلى مراقبة أو علاج بالمستشفى لمدة تزيد عن 48 ساعة من وقت ولادته.

نتائج الدراسة: مجموع الأطفال المدرجين في الدراسة كان 188 طفلاً بمعدل أوزان 3411 ± 616 غ وكان معدل عمرهم الحاملي $38 \pm 2, 1$ أسبوع. نسبة المضاعفات لديهم كانت كالتالي : نقص السكر (31%) ، نقص الكالسيوم (4%) ، احمرار الدم (13%) ، اليرقان (18%) نقص الوزن (2%) أما زيادة وزن الولادة فقد كان (30%) إن استخدم طريقة التراجع الاحصائي ساعدت في إمكانية توقع زيادة نسبة حدوث هذه المضاعفات فقد ظهر بأن معالجة الأم بالأنسولين ، نقص التحكم بمرض السكر ، اختناق الوليد ، نقص السكر المبكر واحمرار الدم كانت شائعة في مجموعة الأطفال المرضى مع نسبة أود: 2.41 ، 2.91 ، 9.65 ، 3.88 ، 3.74 بالترتيب .

الخلاصة : تم تحديد نسبة المضاعفات المشاهدة عند أطفال الأم السكرية الخاليين من الأعراض ظاهرياً عند ولادتهم ، وقد تم تحديد بعض العوامل المرضية التي قد تزيد من إمكانية حدوث تلك المضاعفات.

الكلمات المرجعية: أطفال الأم السكرية، المعافين، المضاعفات.

Aim: To determine the incidence of different complications of the apparently healthy full-term infants of diabetic mothers (IDMs) and whether these complications could be predicted early.

Methods: A prospective study was performed in the Nursery Unit of King Fahd Hospital of the University in Al-Khobar over an 18-month period. Eligible neonates were those full-term IDMs who were asymptomatic at birth, with birth weight ≥ 2000 g and whose mothers had gestational or pregestational diabetes. AUDMs were routinely observed for at least 2 days. A complete blood count, glucose, bilirubin and

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calcium serum levels were monitored. The morbidity study group included all IDMs who experienced complications requiring treatment or observation for > 48 hours.

Results: One hundred and eighty eight infants with a birth-weight of 3411 ± 616 g and with gestational age of 38.5 ± 1.2 weeks were enrolled in the study. Asymptomatic hypoglycemia (31%) was mostly mild and transient. The rate of other complications such as hypocalcemia (4%), polycythemia (13%), hyperbilirubinemia (18%), intrauterine growth retardation (2%) with 30% rate for large gestational age. Using a logistic regression model; maternal insulin therapy, poor diabetic control, birth asphyxia, early neonatal hypoglycemia and polycythemia were found to be highly predictive of morbidity with an odd ratio of 2.41, 2.91, 9.65, 3.88 and 3.74 respectively.

Conclusion: Complications of apparently healthy IDMs appear to be very mild and transient. These were found to be strongly associated with specific perinatal events.

Key Words: Infant of diabetic mother, full-term, complications.

INTRODUCTION

It has been recognized for many years that infants of diabetic mother (IDMs) are at increased risk of perinatal morbidity. It has been estimated that IDMs account for 5% of all admissions to neonatal intensive care units.¹ Disorders of fetal growth (40%), hypoglycemia (25-50%), hypocalcemia (10-20%), polycythemia (10-40%) prematurity (15%), hyperbilirubinemia (20-25%), respiratory distress (15%), and intrapartum asphyxia (15%) are some of the clinical problems still affecting the IDMs.¹⁻³ All these values mentioned above were calculated from a general population of IDMs including term, preterm, symptomatic, and asymptomatic neonates. Complications and postnatal care should certainly not be the same for all neonates of diabetic mothers. Some modern series suggest that neonatal complication rates are now so low in full term IDMs that routine admission would not be justified.⁴ To our knowledge, no precise data of the incidence of complications of apparently healthy full-term IDMs has been reported in the literature. A prospective study was therefore, conducted in an attempt to answer the follow-

ing questions: What is the incidence of the different complications of the apparently healthy full-term IDMs? Could these complications be predicted early during the first day of life? Answers to these questions will help pediatricians to make decisions as to whether or not to routinely admit apparently healthy full-term IDMs to the special care baby unit.

METHODS

This prospective study was performed in the Nursery Unit at King Fahd Hospital of the University, Al-Khobar over an 18-month period from January 1996 to June 1997. The study protocol was approved by the local human ethics committee. Informed parental consent was obtained prior to study entry. Eligible neonates of diabetic mothers were those full-term infants weighing ≥ 2000 g admitted to Nursery Unit at birth. Gestational age was calculated from the last menstrual period, consistent within two weeks with the gestational age as measured by clinical assessment. All studied infants were asymptomatic at birth. Transiently and mildly hypotonic infants born with mild birth asphyxia (as defined below) were also included in this study. All the mothers of studies neonates had gestational or pregestational diabetes and were

managed with both diet and insulin or with diet only. The criteria for exclusion from the study included all IDMs born with severe or moderate asphyxia, respiratory distress, sepsis or suspected sepsis, hemolytic jaundice and congenital anomalies or metabolic diseases that required admission to the Neonatal Intensive Care Unit.

Maternal Care

Perinatal data were obtained by maternal interviews and charts. Antenatal control and management of maternal diabetes had been performed in the Obstetric Department. The 100 g, 3-hour oral glucose tolerance test on venous plasma was adopted by our obstetricians as a diagnostic test for gestational diabetes.⁵ Once gestational diabetes was diagnosed, diet therapy was initiated as the primary way to control glucose. A fasting glucose level of more than 100 mg/dL (5.8 mmol/L) and a postprandial glucose level exceeding 120 mg/dL (6.7 mmol/L) indicated the need for insulin treatment.⁵

According to the weekly sugar profile (the mean of fasting, three postprandial and midnight glucose measurements) maternal diabetic control was classified into three types: tight, fair and poor control if maternal sugar profile were <120 mg/dL (6.7 mmol/L), 120-140 mg/dL (6.7-7.7 mmol/L), and >140 mg/dL (7.7 mmol/L) respectively.⁶

Neonatal Care

All infants of diabetic mothers were routinely observed in the Neonatal Care Unit for at least 2 days. At birth, serum glucose, complete blood count, calcium level, and blood gases were performed from blood from the umbilical cord. Requirement for resuscitation or sodium bicarbonate was noted. In the unit, early feeding was practiced. Neonatal glucose level

was monitored by a glucometer (ONE TOUCH II™, California, USA) at 1, 2, 4, 8, 16, 24, 36 and 48 hours of life. Serum glucose was monitored more frequently if hypoglycemia was detected. If the glucometer value of glucose level was less than 40 mg/dL (2.2 mmol/L), serum glucose level was requested. A serum glucose concentration of less than 40 mg/dL (2.2 mmol/L) was considered as hypoglycemia.² All infants were observed for clinical signs of hypoglycemia including: apnea, cyanosis, seizures, temperature instability, hypotonia and sweating. After the initial oral feeding, if glucose level remained abnormally low, a peripheral intravenous infusion of 2 ml/kg D10W was administered.³ A continuous infusion of D10W, 8 mg/kg/minute of glucose was usually ordered. Persistent hypoglycemia was defined as the presence of at least 2 plasma glucose values < 40 mg/dL. Serum calcium level was performed at 48 hours of life. Hypocalcemia was defined as a central hematocrit level greater than 65%. Neonatal hyperbilirubinemia was defined as a total serum bilirubin greater than 8 mg/dL (136 mmol/L) and 13 mg/dL (221 mmol/L) at 24 hours and 48 hours of life, respectively.⁸ Phototherapy was started whenever the indirect bilirubin level reached > 13 mg/dL (221 mmol/L) during the first 48 hours of life.⁸ Perinatal asphyxia was defined by the presence of fetal distress before delivery (fetal heart rate, late decelerations or prolonged fetal bradycardia), and neonatal asphyxia (1-minute Apgar score ≤ 6 associated with umbilical cord blood gas showing metabolic acidosis).⁹ Infants were considered large for gestational age (LGA) if their birth weight was ≥ 90th percentile and small for gestational age (SGA) when their birth weight was ≤ 10th percentile.¹⁰

The group of IDMs which experienced complications that required treatment or observation for > 48 hours was defined as the "morbidity group", the rest was defined as the "no morbidity group".

Statistical analysis

The Chi-square test with the Fisher exact test, when appropriate, was used for nominal data. A two-tailed T-test was used for the comparison of means of continuous variables. To predict factors that increase the risk of delaying discharge for more than 48 hours, logistic regression with the forward method was used. The dependent variable was either 'yes' (morbidity group) or no (no-morbidity group). Data with odds ratios (OR) were used to express the magnitude of the association between the morbidity group and the independent variables such as: pregestational diabetes, insulin treatment, poor diabetic control, mode of delivery, mild perinatal asphyxia, early hypoglycemia, polycythemia, LGA and SGA. Data were analyzed using SPSS 6.0 for windows. A p-value of <0.05 or a 2-tailed test was taken as statistically significant.

RESULTS

During the study period, 188 apparently healthy full-term infants of diabetic mothers including one set of twins were enrolled in the study. The mean birth weight was 3411 ± 616 g and the mean gestational age of 38.5 ± 1.2 weeks. The maternal characteristics and outcome of all the patients are shown in Table 1. Past history of LGA, SGA or congenital malformations were found in 42 cases (22%). Parent obstetric history relating to the maternal diabetes such as polyhydramnios, preeclampsia or maternal hypertension was found in 39 cases (20%). Incidence of different types of complications in apparently healthy full-term IDMs is listed in Table 2. Hypoglycemia appeared during the first 4 hours in all hypoglycemic infants. There were 8 cases of persistent hypoglycemia and only 4 infants required intravenous infusion for more than 24 hours (Table 3). In all cases, serum glucose

Table 1: Maternal characteristics and outcome

Characteristics	No.	%
Pregestational diabetes	26	14
Insulin treatment	63	33.5
Cesarean delivery	37	20
Poor diabetic control	21	11

Table 2: Morbidity of apparently healthy full-term IDM

Complications	No.	%
Any hypoglycemia	59	31
Persistent hypoglycemia	8	4
Hypocalcemia	8	4
Mild birth asphyxia	9	5
Polycythemia	25	13
Hyperbilirubinemia	34	18
LGA	58	30
SGA	4	2

Table 3: Causes of delay of discharge of IDM for > 48 hours (Morbidity group)

Causes	No.	%
Jaundice requiring phototherapy*	28	15
Persistent hypoglycemia†	4	2
Hypocalcemia‡	7	4
Poor sucking§	4	2
Total	43	23

*Indirect hyperbilirubinemia >13 mg/dL during the first 48 hrs of age

†Requiring D10W intravenous (IV) infusion for >48 hrs.

‡Calcium level <7.5 mg/dL requiring IV calcium

§Feeding with gastric tube for >48 hrs.

was normalized in the second day of life. Eight cases of hypocalcemia were discovered at 48 hours of life. Three of these cases had calcium level of 6 to 7 mg/dL and 5 cases, calcium level of >7 mg/dL and <8 mg/dL. Hypocalcemia was treated with intravenous calcium. All cases of hypocalcemia were persistent. Twenty-five patients (13%) had polycythemia; 19 of these required partial exchange transfusion because their hemotocrit exceeded 67%. From 34 patients (18%) with hyperbilirubinemia, 28 patients had been treated with phototherapy (Table 3). Delayed discharge for more than 48 hours of birth was found in a total of 43 infants (23%) (Table 3).

Table 4: Factors associated with delayed discharge of IDM (Morbidity group)

Variable	B	Odds ratio	p-value
Poor diabetic control	1.069	2.91	0.030
Maternal insulin therapy	0.883	2.41	0.025
Birth asphyxia	2.267	9.65	0.003
Hypoglycemia within the first 4 hours of birth	1.357	3.88	0.010
Polycythemia	1.32	3.74	0.012

From Logistic Regression Model

Table 4 shows the logistic beta slopes, the odds ratio, and the p-values of the five factors found by logistic regression analysis to be predictive of morbidity group of IDMs early after birth. There was no significant difference between the two groups (morbidity and no-morbidity groups) in maternal age, maternal weight gain during pregnancy, maternal glucose profile and neonatal birth weight. Bilirubin level at 24 hours of age was significantly more in the morbidity group 7.5 ± 2.2 mg/dL versus 5.6 ± 2 mg/dL in the no-morbidity group ($p=0.002$). Hypocalcemia was associated with at least one of the factors listed on Table 4.

DISCUSSION

A previous study has shown that prematurity is the most important factor predisposing to severe neonatal complications among the general population of IDMs.¹¹ In our study, it was found that apparently healthy full-term IDMs experienced relatively lower incidence of complications such as: hypocalcemia, polycythemia, hyperbilirubinemia, and intrauterine growth retardation than in the general population of IDMs.^{2,3} Although, the incidence of hypoglycemia was not significantly decreased in this group of infants, it seemed to be very benign and transient. Only 4% of infants had more than one

reading of hypoglycemia with a total normalization of serum glucose at 24 hours after birth. This rapid improvement of hypoglycemia could be explained by the significant increase in plasmatic glucagon of IDMs during the first 24 hours of life.¹² The incidence of hypocalcemia was significantly low in our patients (4%) compared with 10% to 20% in the general population of IDMs.² It would be even much lower (1.5%) if hypocalcemia was defined as a calcium level ≤ 7 mg/dL (1.7 mmol/L).³ Hypocalcemia in IDMs was found to be potentiated by prematurity and asphyxia.¹³ The selection of our patients as a full-term IDMs could explain the low incidence of hypocalcemia. The incidence of LGA infants is approximately 8% in infants of non-diabetic women and about 26% in the general population of infants of diabetic mothers.³

In our study, the incidence of LGA infants was higher reaching 30%. This increased LGA incidence might be related to the exclusion of preterm infants from our study. Macrosomia is increasingly common after 37 weeks gestation, with the highest rate at 41 weeks gestation and over.¹⁴

The most important factor responsible for delaying discharge from the nursery was hyperbilirubinemia. A recent study found that none of 1140 newborns who had bilirubin level lower than 5 mg/dL on the first day of life subsequently developed serum bilirubin concentration of 17 mg/dL or more.¹⁵ In our patients, the mean bilirubin level at 24 hours of birth was greater in the morbidity group (7.5 mg/dL) compared with 5.6 mg/dL in the no-morbidity group, so these results are similar to those reported in a previous study.¹⁵ Using Logistic Regression model, maternal insulin therapy, poor diabetic control, birth asphyxia, early neonatal hypoglycemia within the first 4 hours of birth and polycythemia were found to be highly predictive of morbidity in IDMs. All these factors are easy to obtain on admission or during the first hours of life. Gabbe et al¹⁶ observed a 65% inci-

dence of neonatal morbidity among 260 women treated with insulin. It is now widely accepted that the degree of glyce-mic control achieved in the diabetic preg-nant women significantly affected perina-tal outcome.⁶ Hanson et al¹¹ found that an elevated maternal glycosylated hemoglo-bin as an index of a poor diabetic control was associated with increased neonatal morbidity. What is important is whether it is necessary for pediatricians to routinely admit all IDMs to the special care baby unit.

In our opinion, the above predictors of morbidity are helpful in making decisions for the management of apparently healthy full-term IDMs. The following guidelines are therefore, suggested: At 4 hours of birth, the absence of any of the predictors shown in Table 4 would allow for a rou-tine postnatal care and discharge from the nursery within the normal time period. Admission to the nursery might be consid-ered, if the presence of at least one of these predictors was associated with bilirubin level of ≥ 5 mg/dL at 24 hours of birth. Admission policy in this group of infants should, therefore, be based on the presence or absence of predictors of mor-bidity, condition at birth and subsequent development of hypoglycemia and/or hyperbilirubinemia. Such a policy has obvious advantages in terms of improving cost-effectiveness and perhaps would con-tribute to better continuation rates of breast-feeding.

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