Influence of maternal insulin-dependent diabetes mellitus on neonatal morbidity

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Objective: To compare the neonatal morbidity rates (corrected for gestational age at delivery and method of delivery) among infants of women with insulin-dependent diabetes mellitus and those of women without diabetes.
Design: Historical cohort analysis.
Setting: Tertiary care centre.
Patients: All liveborn infants of women with insulin-dependent diabetes mellitus (IDM group) born between Jan. 1, 1980, and Dec. 31, 1989, each matched for gestational age at delivery, method of delivery and year of birth with two newborns of women without diabetes (control group).
Main outcome measures: Neonatal respiratory distress, jaundice, hypoglycemia, polycythemia, hypocalcemia, intraventricular hemorrhage, seizure and macrosomia.
Results: There were 230 infants in the IDM group and 460 in the control group. Compared with the control group the IDM group had significantly higher incidence rates of glucose infusion (odds ratio [OR] 5.38), birth weight above the 90th percentile (OR 4.15) and neonatal jaundice (OR 1.94). No significant difference was found in the incidence rate of respiratory distress, polycythemia or hypocalcemia. The maternal serum hemoglobin A (HbA) level was not significantly related to birth weight, and neither the serum HbA level nor the presence of macrosomia was predictive of neonatal morbidity. Nearly 25% of the infants in the IDM group were born before 37 weeks' gestation; 48.2% of these were delivered early because of maternal hypertension.
Conclusions: Neonatal morbidity in infants of women with diabetes is determined more by gestational age at delivery than by the maternal diabetes. Within the limits obtained in this study the degree of control of the diabetes does not seem to affect neonatal morbidity.

Objectif : Comparer les taux de morbidité néonatale (rectifiés en fonction de l'âge gestationnel à l'accouchement et de la méthode d'accouchement) des enfants de femmes atteintes de diabète sucré insulinodépendant et des enfants de femmes non diabétiques.
Conception : Analyse des cohortes historiques.
Contexte : Centre de soins tertiaires.
Patients : Tous les enfants nés vivants de femmes atteintes de diabète sucré insulinodépendant (groupe DSI) entre le 1er janvier 1980 et le 31 décembre 1989, chacun étant appareillé suivant l'âge gestationnel à l'accouchement, la méthode d'accouchement et l'année de naissance avec deux nouveau-nés de femmes non diabétiques (groupe témoin).
Principales mesures des résultats : Détresse respiratoire du nouveau-né, ictère, hypo-

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glycémie, polycythémie, hypocalcémie, hémorragie intraventriculaire, attaque et macrosomie.

Résultats : Au total, 230 enfants composaient le groupe DSI et 460 le groupe témoin. Par comparaison avec le groupe témoin, le groupe DSI présentait des taux d'incidence significativement plus élevés de perfusion glucose (risque relatif [RR] de 5,38), de poids de naissance au-dessus du 90e percentile (RR de 4,15) et d'ictère néonatal (RR 1,94). On n'a constaté aucune différence significative du taux d'incidence de détresse respiratoire, de polycythémie et d'hypocalcémie. Le taux sérique maternel d'hémoglobine A (HbA) n'était pas significativement lié au poids de naissance; ni le taux sérique d'HbA ni la présence de macrosomie ne laissait prévoir la morbidité néonatale. Près de 25 % des enfants du groupe DSI étaient nés avant 37 semaines de gestation; la naissance prématurée de 48,2 % de ceux-ci était attribuable à l'hypertension maternelle.

Conclusions : La morbidité néonatale des enfants de femmes diabétiques est davantage déterminée par l'âge gestationnel à l'accouchement que par le diabète maternel. Dans les limites établies dans le cadre de cette étude, le degré de maîtrise du diabète ne semble pas influer sur la morbidité néonatale.

Although various neonatal disorders in infants of women with diabetes mellitus have been widely reported[1-7] their relative risk is difficult to assess either because of lack of control groups or because comparison is made with morbidity rates in the general newborn population. Since prematurity is also strongly associated with neonatal morbidity, comparisons that fail to account for the fact that 25% of infants of women with diabetes are born before 37 weeks' gestation[8] overrepresent the degree of neonatal morbidity directly attributable to maternal diabetes.

In the study by Robert and associates[9] the relative risk of respiratory distress was 23.7 in infants of women with diabetes when compared with the general newborn population; it fell to 5.6 when corrected for gestational age. More recently Hanson, Persson and Stangenberg[10] and Mimouni and collaborators[11] found that the risk of respiratory distress is related to gestational age and mode of delivery, not the presence of maternal diabetes.

Since a stage appears to have been reached at which maternal diabetes has little influence on disorders commonly described in infants of such women, we conducted a study to establish the relative risk of various disorders in infants of women with diabetes mellitus (IDM group) when gestational age and mode of delivery are controlled for.

Methods

We included all women with insulin-dependent diabetes that preceded pregnancy (White's class B through R/F[12]) who gave birth in our perinatal centre between Jan. 1, 1980, and Dec. 31, 1989. (White's classification measures the duration of maternal diabetes and renal or retinal involvement.[12]) Stillbirths were recorded but not included in the analysis.

During the study period all patients were cared for by a team consisting of an obstetrician, endocrinologist, dietitian and nurse coordinator. Patients measured their blood glucose level at home after fasting and 2 hours postprandial at least 4 days per week. Target values for blood glucose levels were 5.6 and 6.8 mmol/L respectively. The serum hemoglobin A (HbA) level was measured monthly; the level obtained within a month before delivery was related to neonatal outcome. Admission to hospital was reserved for medical or obstetric indications; in the absence of these, delivery was postponed to at least 38 weeks' gestation. Amniocentesis was rarely performed before elective delivery after 37 weeks' gestation. Counting of fetal movements and nonstress testing when indicated were the usual methods of assessing fetal well-being.

The blood glucose level was monitored hourly during labour and maintained at between 5.0 and 7.0 mmol/L through glucose insulin infusion.

The control group, assembled from the hospital delivery database, consisted of two newborns of women without diabetes matched with each study newborn for gestational age, mode of delivery and calendar year of delivery. One set of twins in the IDM group was matched with two sets in the control group. The birth-weight percentile, corrected for sex and gestational age, was determined with the Aberdeen birth-weight percentile curves.[13]

Respiratory distress was recorded as mild (any respiratory abnormality treated with supplementary oxygen with headbox, transient tachypnea, grunting, apnea) or moderate to severe (any respiratory problem necessitating assisted ventilation). Intraventricular hemorrhage was diagnosed on the basis of ultrasound findings with the use of standard criteria.[14] Birth injury was considered to be a bony fracture or peripheral nerve injury.

Hyperbilirubinemia was recorded if the total serum bilirubin level within 5 days after delivery was more than 250 μmol/L in babies born at or beyond 37 weeks' gestation or more than 200 μmol/L in those born before 37 weeks' gestation. The rate of neonatal jaundice was defined as the combined incidence of

hyperbilirubinemia in the two gestational age categories. Hypocalcemia was considered to have occurred if the serum calcium level was less than 2.0 mmol/L within 24 hours after birth. Polycythemia was considered to be present if the cord hemoglobin level was more than 200 g/L.

Because of routine early feeding of infants of women with diabetes, hypoglycemia in the untreated state could not be truly assessed. Instead, we recorded the use of intravenous 5% dextrose within the first 12 hours of life. Seizures in the first 7 days of life were recorded in both groups.

Chi-squared analysis was used to compare proportions and the paired Student *t*-test to compare means. Because multiple comparisons were made in the same database, significance was set at a p value of less than 0.01.

Results

Of 230 liveborn infants in the IDM group delivered during the study period 56 (24.3%) were born before 37 weeks' gestation. Of these, 38 (67.9%) were delivered electively, 27 (71.1%) because of maternal hypertension. In the IDM group, as the severity of the diabetes increased from less than 10 years' duration with no retinopathy or nephropathy (White's class B) to diabetes complicated with retinopathy or nephropathy or both (class R/F) the mean gestational age at delivery decreased (Table 1). The mean age at delivery, a matched variable, was 37.6 (standard deviation [SD] 2.1) weeks in the IDM and control groups.

Table 1: Mean gestational age of 230 infants of women with insulin-dependent diabetes mellitus (IDM group), by White's classification[12]

White's class	No. (and %) of infants	Mean gestational age (and SD),* wk
B	105 (45.7)	38.0 (1.8)
C	61 (26.5)	37.4 (2.2)
D	31 (13.5)	37.5 (1.9)
R/F	31 (13.5)	36.3 (2.6)

*SD = standard deviation.

During the study period there were four neonatal deaths in the IDM group (all due to lethal anomalies) and none in the control group. In addition, there were four stillbirths in the IDM group: one infant had lethal anomalies, was delivered at 24 weeks' gestation and weighed 250 g; one was born at 33 weeks to a noncompliant woman with class R/F diabetes and weighed 2035 g; one was born at 34 weeks to a woman with class B diabetes under good control and weighed 2240 g; and one was born at 37 weeks to a woman with poorly controlled class C diabetes and weighed 5310 g. Of the eight perinatal deaths five were directly due to lethal anomalies.

The mean serum HbA level 1 month before delivery was 7.5% (SD 1.3%) (extremes 4.0% and 10.8%).

Certain variables differed significantly ($p < 0.01$) between the two groups (Table 2). The mean blood glucose level in the 94 control infants in whom it was measured was 2.6 (SD 0.9) mmol/L, as compared with 2.2 (SD 0.9) mmol/L in the 169 IDM infants in whom it was measured ($p < 0.001$). In the IDM group 48.5% of the infants had blood glucose values of 2.1 mmol/L or less, as compared with 31.9% of the control infants ($p = 0.009$). However, glucose infusion was used almost four times more frequently in the IDM group than in the control group.

Of the 22 anomalies in the IDM group 11 were severe and included tracheoesophageal fistula, cleft palate, caudal regression, obstructive uropathy from posterior urethral valve defect and cardiac defect. Minor anomalies included hypospadias, hernia of the umbilical cord, deformity of an ear, extra digit and hydrocele. In the control group there were seven severe anomalies, including Down's syndrome, Klippel–Feil syndrome, spina bifida, hydrocephalus and tracheoesophageal fistula. The minor anomalies in-

Table 2: Variables that differed significantly* between the IDM group and the control group

Variable	Group; no. (and %) of infants: IDM (n = 230)	Control (n = 460)	Odds ratio (and 95% confidence interval)
Use of glucose infusion	86 (37.4)	46 (10.0)	5.38 (3.51–8.27)
Birth weight			
> 90th percentile	75 (32.6)	48 (10.4)	4.15 (2.71–6.37)
> 4000 g	53 (23.0)	33 (7.2)	3.87 (2.36–6.36)
Anomalies	22 (9.6)	12 (2.6)	3.95 (1.83–8.65)
Neonatal jaundice	44 (19.1)	50 (10.9)	1.94 (1.21–3.08)

*$p < 0.01$.

cluded hydronephrosis, inguinal hernia and hydrocele. Since the serum HbA level was unavailable for nearly a quarter of the women with diabetes during the first trimester we could not correlate the fetal anomalies with control of maternal diabetes in the first trimester.

Table 3 lists the variables that did not differ significantly between the IDM and control groups. No significant difference was found in the prevalence rates of respiratory distress (19.1% and 12.6% respectively; $p = 0.023$) or of respiratory distress necessitating assisted ventilation (4.4% and 3.0%; $p = 0.691$). Only two infants in each group born after 36 weeks' gestation required assisted ventilation. Also, the prevalence rate of respiratory distress was higher among the infants in the IDM group delivered by means of cesarean section than among the control infants delivered by the same means (23.5% v. 14.0%; $p = 0.02$); it was also higher among all the infants born by means of cesarean section than among those delivered vaginally (17.2% v. 11.3%; $p = 0.045$).

Being a matched variable the cesarean section rate in the two groups was identical. Although the groups were not initially matched for sex and cesarean section without a trial of labour, the rate of these two variables was almost the same in the two groups.

In the IDM group logistic regression analysis showed that there was no significant relation between the maternal serum HbA levels and either the neonatal birth weight or the neonatal morbidity rate ($p = 0.051$). Furthermore, a birth weight of more than 4000 g was not predictive of neonatal morbidity in the IDM group.

Discussion

The infants in the IDM group had a significantly higher incidence of glucose infusion, macrosomia and jaundice than the control infants; however, they were not at significantly increased risk of respiratory distress, polycythemia, hypocalcemia or a low Apgar score. Shoulder dystocia, intraventricular hemorrhage and seizures occurred rarely in the two groups, and no infant suffered an injury during birth.

Although the mean blood glucose level was lower in the IDM group than in the control group, the true risk of neonatal hypoglycemia in infants of women with diabetes was underrepresented, since early feeding was routine and glucose infusion was used when a trend of falling blood glucose levels was noted.

In keeping with others[11,15–17] we found a trend toward an increased incidence of respiratory distress in the IDM group that was more pronounced in those delivered by cesarean section. Although this trend was not significant, perhaps diabetes, even at the level of control achieved in this study, continues to exert a small adverse effect on neonatal respiratory function.

The high incidence rate of macrosomia in the IDM group despite good control of maternal diabetes as well as the lack of association between birth weight and maternal serum HbA levels is well recognized.[18–21] The fluctuations in the maternal blood glucose levels that were present even in the women with

Table 3: Variables that did not differ significantly between the two groups

Variable	Group; no. (and %) of infants	
	IDM	Control
Cesarean section		
All	136 (59.1)	272 (59.1)
With no trial of labour	85 (62.5)	175 (64.3)
Male sex	113 (49.1)	231 (50.2)
Respiratory distress (all grades)	44 (19.1)	58 (12.6)
Serum bilirubin level		
> 200 μmol/L if born before 37 weeks' gestation	26 (46.4) (n = 56)	35 (31.3) (n = 112)
> 250 μmol/L if born at or beyond 37 weeks' gestation	18 (10.3) (n = 174)	15 (4.3) (n = 348)
Cord hemoglobin level > 200 g/L	32 (15.7)*	47 (12.1)*
Serum calcium level < 2.0 mmol/L	21 (17.8)*	25 (24.5)*
Apgar score		
< 4 at 1 min	18 (7.8)	18 (3.9)
< 7 at 5 min	11 (4.8)	12 (2.6)
Seizure	3 (1.3)	1 (0.2)
Intraventricular hemorrhage (all grades)	2 (0.9)	3 (0.7)
Injury during birth	0	0

*Percentage of newborns in whom this was measured.

well-controlled diabetes may have been large enough to stimulate fetal insulin production and excess fetal growth without increasing maternal levels of glycosylated hemoglobin. Because there is little evidence from our study that macrosomia is associated with neonatal morbidity, efforts to reduce the incidence of macrosomia in women with diabetes would be without tangible benefit to the fetus and not without increased risk of hypoglycemia for the mother.[22]

Reports of rates of injury during birth in excess of 10% among macrosomic infants of diabetic women[17,23,24] have led to the recommendation that such infants be delivered by cesarean section.[23,24] Because none of the infants in our study were injured during birth our experience would not support this recommendation, which would have increased the cesarean section rate in the IDM group, from 59% to more than 70%.

We could not confirm that the infants in the IDM group were at increased risk of polycythemia, possibly because of adequate control of the maternal diabetes.[25] A reduced prevalence rate after cesarean section has been reported by others[26] and may be due to differences in timing of cord clamping.

Our findings confirm the high risk of premature delivery of infants of women with diabetes primarily because of maternal hypertension,[7,27] a complication that does not appear to be moderated by good control of the diabetes.[27] Whether current trials of prophylaxis with acetylsalicylic acid in patients at risk of pre-eclampsia will offer hope in this area remains to be seen.

The prevalence rate and relative risk of congenital anomalies in the IDM group were similar to those in other series.[28] Possibly because of reduced frequency of other severe disorders and improved neonatal care, anomalies were the main cause of all neonatal deaths in our study. The limitations of avoiding anomalies through the control of maternal glucose levels in the first trimester have recently been highlighted.[29] Although avoidance would be ideal, high-resolution ultrasonography at 18 weeks' gestation can identify many of the main life-threatening anomalies before viability and provide the opportunity to offer termination of pregnancy.

Summary

Our findings show that with careful management of diabetes during pregnancy gestational age, not maternal diabetes, is the prime determinant of neonatal morbidity. Although inadequate control of maternal diabetes will undoubtedly compromise neonatal outcome, our results suggest that further tightening of control is unlikely to improve the outcome unless it can safely prolong pregnancy; an association has so far not been established.

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Conferences

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Du 9 au 13 sept. 1993 : Les soins spécialisés en crise? — 62e Assemblée annuelle du Collège royal des médecins et chirurgiens du Canada
Vancouver
Anna Lee Chabot, chef, section des réunions et assemblées, Bureau des affaires des Associés, Collège royal des médecins et chirurgiens du Canada, 774, prom. Echo, Ottawa, ON K1S 5N8; tél (613) 730-6233 ou (613) 730-8177; fax (613)730-8830

Sept. 9–13, 1993: Specialty Care in Crisis? — 62nd Annual Meeting of the Royal College of Physicians and Surgeons of Canada
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Anna Lee Chabot, head, meetings and assemblies section, Office of Fellowship Affairs, Royal College of Physicians and Surgeons of Canada, 774 Echo Dr., Ottawa, ON K1S 5N8; tel (613) 730-6233 or (613) 730-8177; fax (613) 730-8830

Sept. 10, 1993: Health Care Aide Clinic Day
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Sybil Gilinsky, Continuing Education Department, Baycrest Centre for Geriatric Care, 3560 Bathurst St., North York, ON M6A 2E1; tel (416) 789-5131, ext. 2365

Sept. 10–12, 1993: International Symposium on Neurocritical Care
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International Symposium on Neurocritical Care, c/o Venue West Conference Services, Vancouver, BC V6B 5C6; tel (604) 681-5226, fax (604) 681-2503

Sept. 16–19, 1993: Comprehensive Review in Toxicology
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Sept. 20–22, 1993: Alzheimer's Disease International 9th Annual Conference — Global Challenge, Local Action
Toronto
Alzheimer Society of Canada, 201–1320 Yonge St., Toronto, ON M4T 1X2; tel (416) 925-3552, fax (416) 925-1649

Sept. 27, 1993: Multicultural Health Care — Meeting the Challenge
Toronto
Gina Borenstein, manager, Public Relations, Scarborough Grace Hospital, 3030 Birchmount Rd., Scarborough, ON M1W 3W3; tel (416) 495-2404

Sept. 27–29, 1993: 1st International Conference on Community Health Nursing Research
Edmonton
Shirley Stinson or Karen Mills, c/o Edmonton Board of Health, 500–10216–124 St., Edmonton, AB T5N 4A3; tel (403) 482-1965, fax (403) 482-4194

Oct. 6–8, 1993: Canadian Waste Management Conference — Innovative Waste Management Solutions: an Outlook for the Future
Saint John, NB
Susan Clarke, technical seminar coordinator, Technology Development Branch, Environment Canada, Unit 100, Asticou Centre, 241 Cité des Jeunes Blvd., Hull, PQ K1A 0H3; tel (819) 953-5227, fax (819) 953-9029

Du 6 au 8 oct. 1993 : Conférence canadienne sur la gestion des déchets — Solutions innovatrices en matière de gestion des déchets : Perspectives d'avenir
Saint-Jean, N-B
Susan Clarke, coordonnatrice des séminaires techniques, Direction du Développement Technologique, Environnement Canada, Unité 100, Centre Asticou, 241, Cité des Jeunes, Hull, QC K1A 0H3; tél (819) 953-5227, fax (819) 953-9029

Oct. 7–10, 1993: 3rd Congress of the Asian Pacific Society of Respirology (organized by the Singapore Thoracic Society)
Singapore
Secretariat, 3rd Congress of the Asian Pacific Society of Respirology, 336 Smith St. 06-302, New Bridge Centre, Singapore 0105; tel 011-65-227-9811, fax 011-65-227-0257

Oct. 15, 1993: Nursing Clinic Day
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