REFERENCES

1. Koss LG. The Papanicolaou test for cervical cancer detection. JAMA 1989;261:737-43.
2. McIndoe WA, McLean MR, Jones R, Mullins PR. The invasive potential of carcinoma in situ of the cervix. Obstet Gynecol 1984;64:451-9.
3. Cartier R. Practical colposcopy. Basel: S Karger, 1977: 106-7.
4. Prendiville W, Davies R, Berry PJ. A low voltage diathermy loop for taking cervical biopsies: a qualitative comparison with punch biopsy forceps. Br J Obstet Gynaecol 1986;93:1054-60.
5. De Haan RW, Kenemans P. Diathermic stripping of cervical lesions. Eur J Gynecol Oncol 1982;3:268-9.
6. Van Nagell JR, Praker JC. Hicks LP, Conrad R, England G. Diagnostic and therapeutic efficacy of cervical conization. AM J OBSTET GYNECOL 1976;124:134-40.
7. Burghardt E, Holzer E. Treatment of carcinoma in situ: evaluation of 1609 cases. Obstet Gynecol 1980;55:539-46.
8. Benedet JL, Anderson GH, Simpson ML, Shaw D. Colposcopy, conization and hysterectomy practices: a current perspective. Obstet Gynecol 1982;60:539-46.
9. Benedet JL, Miller DM, Nickerson KG, Anderson GH. The results of cryosurgical treatment of cervical intraepithelial neoplasia at one, five, and ten years. AM J OBSTET GYNECOL 1987;157:268.
10. Sadoul GD, Beuret TM. Management of 633 cervical intraepithelial neoplasias by CO_2 laser: persistent diseases and recurrences. Lasers Surg Med 1986;6:110.
11. Wright VC. Carbon dioxide laser surgery for cervical intraepithelial neoplasia. Lasers Surg Med 1984;4:145-52.
12. Prendiville W, Cullimore J, Norman S. Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. Br J Obstet Gynaecol 1989;96:1054-60.
13. Whitley PF, Olah KS. Treatment of cervical intraepithelial neoplasia: experience with the low-voltage diathermy loop. AM J OBSTET GYNECOL 1990;162:1272-7.
14. Buxton EJ, Luesley DM, Wade-Evans T. Residual disease after cone biopsy: completeness of excision and follow-up cytology as predictive factors. Obstet Gynecol 1987;70:529-33.
15. Buller RE, Jones HW III. Pregnancy following cervical conization. AM J OBSTET GYNECOL 1982;142:506-13.
16. Kristensen GB. The outcome of pregnancy and preterm delivery after conization of the cervix. Arch Gynecol 1985;236:127-30.

Fetal polycythemia and thrombocytopenia in pregnancies complicated by maternal diabetes mellitus

Douglas R. Salvesen, MD, Michael J. Brudenell, MD, and Kypros H. Nicolaides, MD
London, England

In 40 pregnancies complicated by maternal diabetes mellitus umbilical venous blood was obtained by cordocentesis within 24 hours of elective delivery at 36 to 40 weeks' gestation. The mean fetal hematocrit was significantly higher and the mean platelet count significantly lower than the corresponding values of our reference ranges. Furthermore, blood gas analysis demonstrated these fetuses to be normoxemic but acidemic. The degree of fetal acidemia was significantly associated with both maternal and fetal blood glucose concentrations. The fetal hematologic indices were significantly related to the maternal glycosylated hemoglobin percentage but not to the degree of fetal acidemia or to the maternal or fetal blood glucose concentration at the time of cordocentesis. Fetal acidemia, polycythemia, and thrombocytopenia may contribute to the increased incidence of late unexplained intrauterine deaths in pregnancies complicated by maternal diabetes mellitus. (AM J OBSTET GYNECOL 1992;166:1287-92.)

Key words: Diabetes mellitus, cordocentesis, fetal hematology, blood gases, glycosylated hemoglobin

From the Harris Birthright Research Centre for Fetal Medicine, Department of Obstetrics and Gynaecology, King's College Hospital School of Medicine.
Supported by a grant from John and Carol Wates to D.R.S.
Received for publication May 28, 1991; revised September 23, 1991; accepted September 30, 1991.
Reprint requests: Kypros Nicolaides, MD, Harris Birthright Research Centre for Fetal Medicine, Dept. of Ob/Gyn, Kings College Hospital School of Medicine, Denmark Hill, London, England SE5 8RX.
6/1/34059

There is a well-recognized association between maternal diabetes mellitus and late unexplained fetal death.[1] Although the cause remains uncertain, there is indirect evidence implicating fetal hypoxia. Thus in diabetic pregnancies the incidence of abnormal fetal heart rate patterns in labor and low Apgar scores at delivery is increased.[2, 3] Furthermore, analysis of cord blood at delivery has demonstrated decreased P_{O_2} and

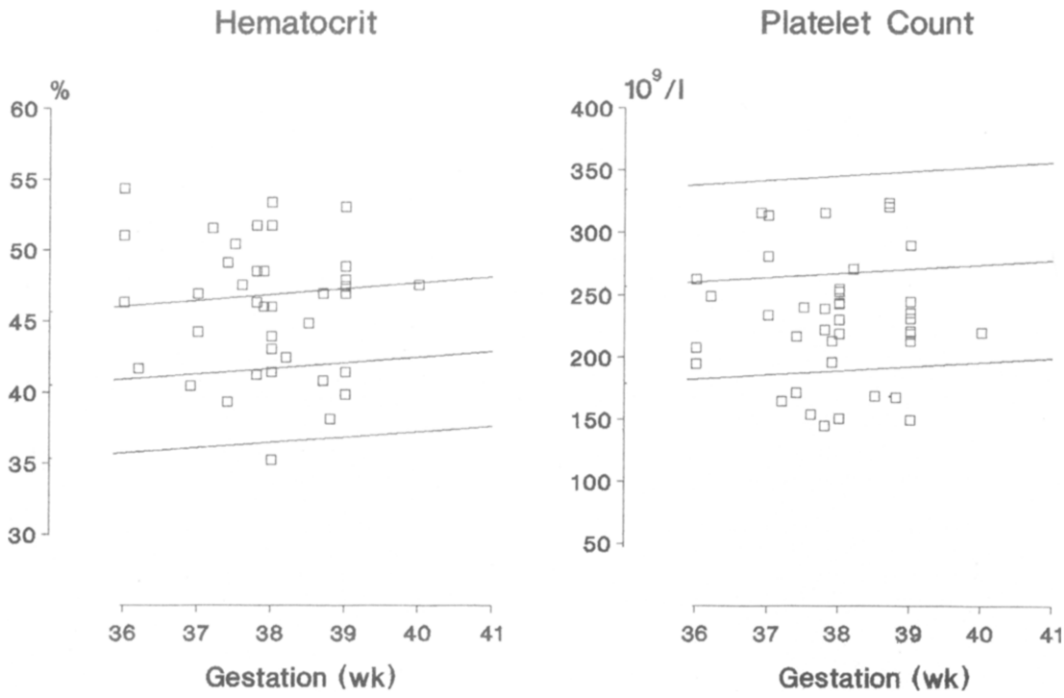

Fig. 1. Hematocrit and platelet count plotted on appropriate reference range (mean with 95th and 5th percentiles) with gestation.

pH and increased erythropoietin concentration in association with neonatal polycythemia.[4-6] More recently Bradley et al.[7] measured fetal blood gases at cordocentesis in pregnancies complicated by maternal diabetes mellitus and reported that the mean pH was significantly lower than in nondiabetic controls.

The aim of the current study was to investigate the relationship between possible hematologic changes in fetuses of diabetic mothers and maternal diabetic control and fetal blood gases. Fetal blood samples were obtained by cordocentesis rather than at delivery because the process of birth itself may influence the measured parameters.

Patients and methods

Umbilical venous blood was obtained by cordocentesis up to 24 hours before delivery at 36 to 40 weeks' gestation in 40 women with established (n = 32) or gestational (n = 8) diabetes. A maternal venous blood sample was also taken from the antecubital fossa before cordocentesis. In each case gestational age was established from the menstrual history (n = 32) or by an early ultrasonographic scan in those with uncertain dates (n = 8). The patients were recruited from our diabetic antenatal clinic. Before giving their written consent, the patients were counseled that the procedure was experimental and that the results would not give any direct benefit to their current pregnancy. The study was approved by our hospital ethics committee.

All patients were insulin treated, and according to the White classification 23 belonged to group B, 15 to group C, and two to group D.[8] None of the patients had chronic hypertension or preeclampsia. The pregnancies were managed expectantly; according to our current policy and in consultation with individual patients, elective delivery was undertaken at 36 to 40 weeks' gestation, depending on fetal growth and well-being and previous obstetric and medical history. In 24 cases the mode of delivery was by elective cesarean section for previous cesarean section (n = 12), suspected macrosomia (n = 5), breech presentation (n = 4), congenital abnormality of the maternal pelvis (n = 1), poor obstetric history (n = 1), and maternal ischemic heart disease (n = 1). Induction of labor was undertaken in 16 patients; 11 had vaginal deliveries and five had emergency cesarean section because of suspected cephalopelvic disproportion (n = 1) or abnormal intrapartum fetal heart rate patterns (n = 4).

Cordocentesis was performed without fetal paralysis or maternal fasting or sedation, and all procedures were uncomplicated.[9] Fetal blood was collected into a heparinized syringe (350 μl) for blood gas analysis (Radiometer ABL330, Copenhagen) and for measurement of whole blood glucose (YSI 23A, Yellow Springs Instruments Co., Yellow Springs, Ohio). Fetal blood was also collected in tubes containing ethylenediametetraacetic acid (500 μl) for measurement of hematocrit and platelet and total white blood cell counts (Coulter

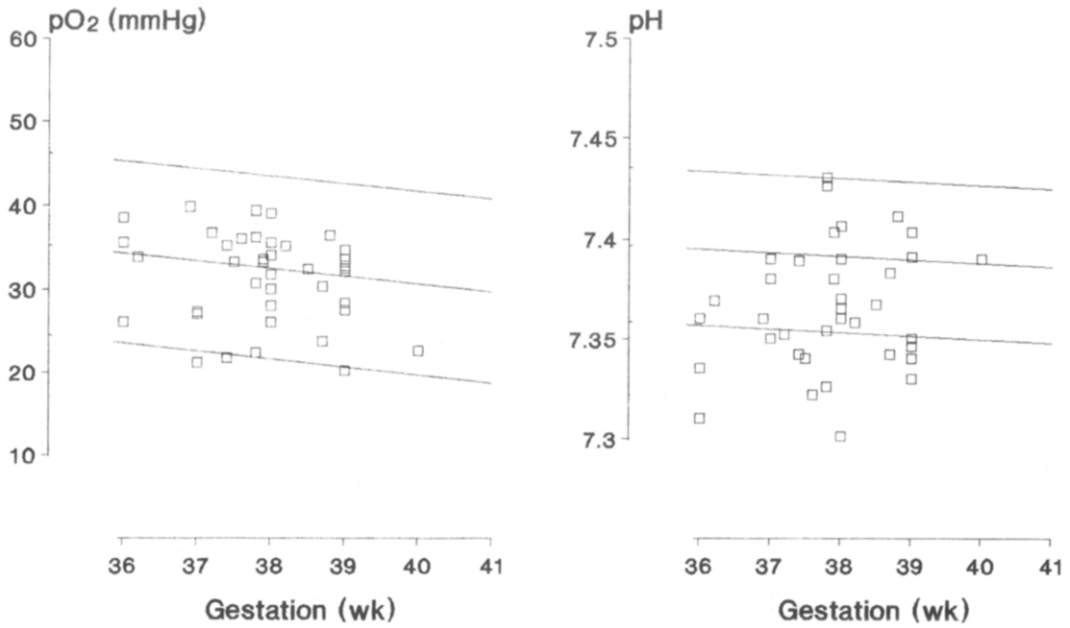

Fig. 2. Umbilical venous blood Po_2 and pH plotted on appropriate reference range (mean with 95th and 5th percentiles) with gestation.

S-Plus, Coulter Electronics, Luton, United Kingdom). Kleihauer testing confirmed that all samples contained only fetal blood. Blood films were stained with Jenner's giemsa on an automatic processing machine, and the corrected white blood cell count and number of erythroblasts per 100 white blood cells were determined. At the time of cordocentesis a maternal blood sample was taken from the antecubital fossa for the measurement of whole blood glucose concentration as described and the glycosylated hemoglobin percentage by electroimmunodiffusion (Corning scanner, Corning, Halstead, United Kingdom).

Umbilical venous blood was also collected at delivery from 26 of the patients; there were 14 elective cesarean sections with patients under epidural ($n = 7$) or general ($n = 7$) anesthesia, five emergency cesarean sections, and seven vaginal deliveries. The cord was double clamped immediately after delivery, and an umbilical venous blood sample was taken in heparinized syringes for measurement of pH.

Unpaired Student t tests were applied to investigate if the measured parameters differed from the reference ranges for normal pregnancies. For birth weight and maternal glycosylated hemoglobin percentage, published ranges were used.[9, 10] For the others our reference ranges with gestation were used: hematocrit 2.425 + 0.396 × weeks, SD 0.0211, $n = 311$; platelet count 129.5 + 3.62 × weeks, SD 46.74, $n = 311$; corrected white blood cell count 0.152 + 0.104 × weeks − 0.004 × weeks^2 + 0.0005 × weeks^3, SD 0.0283, $n = 311$; umbilical venous blood pH 7.47 − 0.0023 × weeks, SD 0.0306, $n = 268$; and umbilical venous blood Po_2 62.305 − 0.811 × weeks, SD 7.512, $n = 268$. The patient selection and methods used to establish these ranges were as previously detailed.[11-13] By comparison with the normal ranges, all hematologic parameters, blood gas values and birth weights for the diabetic pregnancies were expressed as the number of standard deviations by which individual values differed from the normal mean for gestation (Δ-value). Regression analysis was then used to define any significant associations between hematologic Δ-values and blood gas Δ-values, birth weight Δ-values, maternal glycosylated hemoglobin percentage, and fetal and maternal blood glucose concentrations. Regression analysis was also used to define the significance of associations in blood gas data at cordocentesis and delivery.

Results

In the 40 diabetic pregnancies the mean fetal hematocrit was significantly higher than the normal mean for gestation (Fig. 1; mean difference 1.014 SD, SE 0.236, $t = 4.29$, $p < 0.0001$). In contrast, mean platelet count was significantly lower (Fig. 1; mean difference −0.802 SD, SE 0.168, $t = -4.77$, $p < 0.0001$). The mean white blood cell count was not significantly different (mean difference −0.273 SD, SE −0.271, $t = -1.01$).

The fetal blood pH was significantly lower (Fig. 2; mean difference −1.087 SD, SE 0.192, $t = -5.67$, $p < 0.0001$), whereas the Po_2 was not significantly different from the appropriate normal mean for gestation

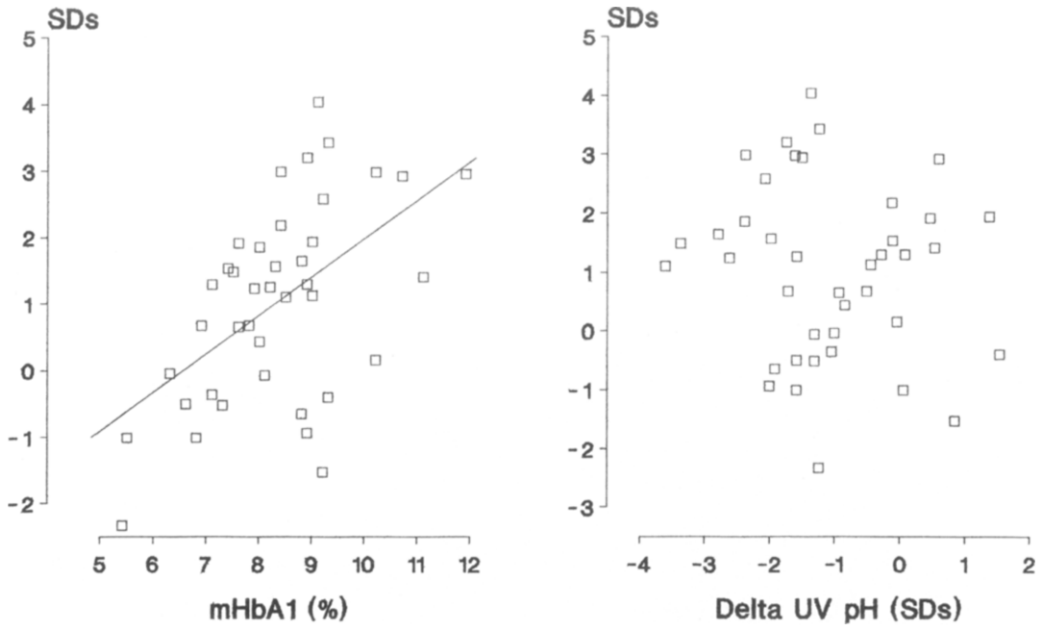

Fig. 3. Relationship between Δ-value of fetal hematocrit and maternal glycosylated hemoglobin percentage *(mHbA$_1$)* and between Δ-value of fetal hematocrit and Δ-value of umbilical venous pH *(Delta UV pH)*.

Table I. Association between fetal hematocrit, platelet count, blood gas values (pH and Po_2), fetal umbilical venous glucose concentration, fetal birth weight, and maternal glycosylated hemoglobin percentage

	Δ-Value of hematocrit (r)	*Δ-Value of platelet count (r)*
Δ-Value of platelet count	−0.358*	
Δ-Value of pH	−0.133	−0.132
Δ-Value of Po_2	−0.032	−0.285
Δ-Value of birth weight	0.171	0.015
Umbilical venous glucose concentration	0.091	−0.002
Maternal glycosylated hemoglobin	0.537†	−0.348*

All values except maternal glycosylated hemoglobin and umbilical venous glucose concentration were expressed as difference from normal mean for gestation in standard deviations (Δ-values).

*$p < 0.05$.

†$p < 0.001$.

(Fig. 2; mean difference −0.201 SD, SE 0.128, $t = -1.57$). The maternal glycosylated hemoglobin percentage and birth weight were significantly higher than the appropriate normal means for gestation (mean difference 1.882 SD, SE 0.309, $t = 6.10$, $p < 0.0001$ and mean difference 1.007 SD, SE 0.206, $t = 4.89$, $p < 0.0001$, respectively).

The associations between Δ-values for fetal hematologic findings and those for fetal blood gases, fetal blood glucose concentration, fetal size, and maternal glycosylated hemoglobin are shown in Table I. There were significant associations between Δ-values for fetal hematocrit and platelet count. In addition, Δ-values for both fetal hematocrit (Fig. 3) and platelet count (Fig. 4) were significantly associated with maternal glycosylated hemoglobin but not with fetal blood gas values, fetal glucose concentration, or Δ-value for fetal weight. There was a significant association between both the maternal and the fetal blood glucose concentration and Δ-value for fetal pH ($r = -0.449$, $p < 0.01$ and $r = -0.397$, $p = 0<0.05$, respectively).

In the 26 patients in whom umbilical venous blood pH was measured both at cordocentesis and at delivery there was no significant association between the predelivery and postdelivery data ($r = 0.15$). In all but one case the pH after delivery was lower than the pH at cordocentesis, and the greatest decrease was in those patients with vaginal deliveries (Fig. 5).

All infants were healthy at birth and normal anatomy was confirmed. There was no clinical evidence of any thromboses in the neonatal period.

Comment

This study has demonstrated that in pregnancies complicated by maternal diabetes mellitus some fetuses are acidemic, polycythemic, thrombocytopenic, and macrosomic. Furthermore, there are significant asso-

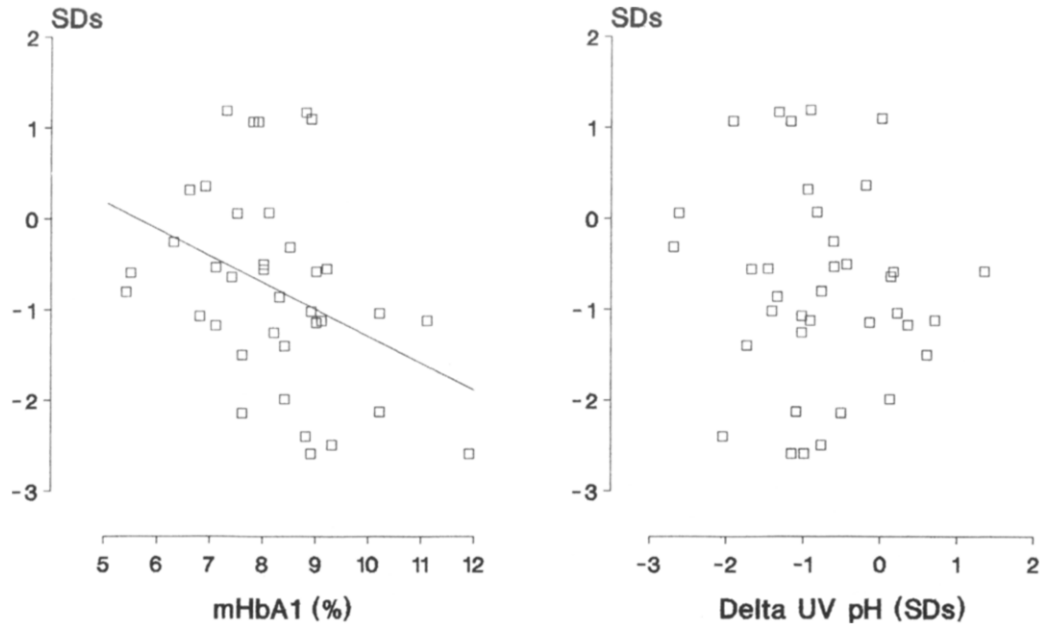

Fig. 4. Relationship between Δ-value of fetal platelet count and maternal glycosylated hemoglobin percentage *($mHbA_1$)*, and between Δ-value of fetal platelet count and Δ-value of umbilical venous pH *(Delta UV pH)*.

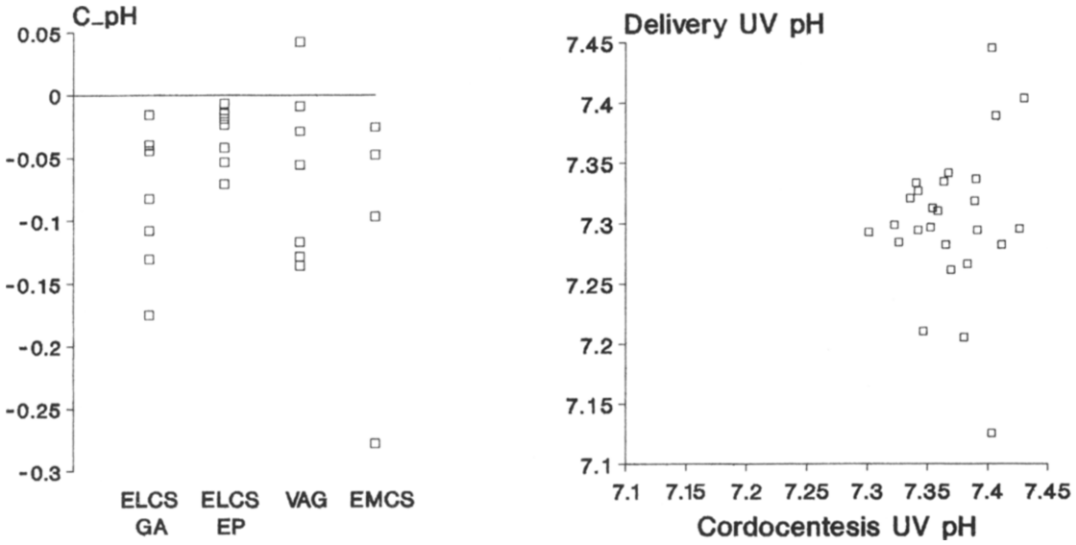

Fig. 5. Change in umbilical venous blood pH *(C pH)* between cordocentesis and delivery in 26 patients *(left)*, according to mode of delivery; elective cesarean section with patients under general anesthetic *(ELCS GA)*, elective cesarean section with patients under epidural anesthetic *(ELCS EP)*, vaginal delivery *(VAG)*, and emergency cesarean section *(EMCS)*. Relationship between umbilical venous blood pH *(UV pH)* at cordocentesis and delivery *(right)*.

ciations between the degree of polycythemia and thrombocytopenia and maternal glycemic control, as reflected in increased maternal glycosylated hemoglobin percentage. The lack of a significant association in the umbilical venous blood pH between results at cordocentesis and those at delivery demonstrates that fetal biochemistry may be altered by the process of birth.

The finding of acidemia in a substantial proportion of the fetuses provides support for the concept that altered acid-base status may contribute to the increased

incidence of late unexplained stillbirths in pregnancies complicated by maternal diabetes. The significant association between both maternal and fetal glucose concentrations and the degree of fetal acidemia suggests that the latter may be the consequence of increased metabolic rate, which is a result of fetal hyperglycemia. The data provide an extension to the previous observations of Bradley et al.,[7] who reported that fetal acidemia was not associated with hypoxemia. Chronic hyperglycemia in pregnant sheep results in increased fetal glycolysis, accumulation of lactate, and fall in pH.[14, 15] Fetal anaerobic glycolysis may occur in the presence of hyperglycemia, because animal studies have shown there is reduced capacity for oxidative metabolism and gluconeogenesis and low pyruvate dehydrogenase activity in intrauterine life.[16] Furthermore, minor elevations in fetal blood glucose are associated with acidemia in the absence of hypoxemia.[15]

In the neonatal period polycythemia is most commonly defined as a hematocrit >65%, and the reported incidence in infants of diabetic mothers is 16% to 34%.[6, 17] This wide range may be partly a consequence of the different methods used in these studies, including gestational age, mode of delivery, time of cord clamping, and the site and time of sampling. In our study polycythemia is defined as a hematocrit >95th percentile for gestational age, and the incidence was 40%. The significant association of fetal hematocrit with maternal glycosylated hemoglobin percentage, but not with fetal or maternal glucose concentration at cordocentesis, implies that long-term rather than short-term glycemic control is important in the development of polycythemia. Pedersen's theory[18] suggests that maternal hyperglycemia causes fetal hyperglycemia and hyperinsulinemia. Insulin may stimulate erythropoiesis either through a direct effect on the marrow[19] or indirectly through increased metabolic rate, tissue hypoxia, and consequent erythropoietin release.

Fetal thrombocytopenia, like polycythemia, was associated with maternal glycosylated hemoglobin percentage but not with maternal or fetal blood glucose concentration at the time of cordocentesis. The most likely cause of the mild fetal thrombocytopenia is increased platelet consumption, because previous studies have demonstrated that in infants of diabetic mothers there is increased platelet aggregation.[20] The abnormalities in infants of diabetic mothers include increased platelet endoperoxide formation and decreased vascular prostacyclin production.[20, 21]

The combination of fetal polycythemia (with consequent hyperviscocity) and increased platelet aggregation could offer an explanation for the increased incidence of intravascular thromboses in infants of diabetic mothers.[22, 23] Indeed, it could lead to intrauterine thrombotic episodes, offering an alternative to acidemia as the underlying cause for late unexplained intrauterine deaths. In a postmortem study of 4000 neonatal deaths the incidence of venous thromboses in infants of diabetic mothers was 15.8% compared with an incidence of <1% in the remaining cases.[23] Furthermore in the infants of diabetic mothers the thrombi showed more frequent organization and calcification, suggesting intrauterine formation.

In pregnancies complicated by maternal diabetes the incidence of unexplained stillbirths has been reduced with intense multidisciplinary antenatal care; however, it remains a well-recognized complication of diabetic pregnancy.[24] Fetal acidemia and increased tendency for intravascular thromboses, either individually or in combination, could be the underlying cause.

REFERENCES

1. Beard RW, Lowy C. The British survey of diabetic pregnancies. Br J Obstet Gynaecol 1982;89:783-6.
2. Brudenell JM. Delivering the infant of a diabetic mother. J R Soc Med 1978;71:211-21.
3. Mimouni F, Miodovnik M, Tariq A, Siddiqi TA, Khoury J, Tsang RC. Perinatal asphyxia in infants of insulin-dependent diabetic mothers. J Pediatr 1988;113:345-53.
4. Madsen H, Ditzel J. Changes in red blood cell oxygen transport in diabetic pregnancy. Am J Obstet Gynecol 1982;143:421-4.
5. Kaiser IH, Goodlin RC. Alterations in pH, gases and hemoglobin in blood and electrolytes in plasma of fetuses of diabetic mothers. Pediatrics 1958;22:1097-109.
6. Shannon K, Davis J, Kitzmiller JL, Fulcher SA, Koenig HM. Erythropoiesis in infants of diabetic mothers. Pediatr Res 1986;20:161-5.
7. Bradley RJ, Brudenell JM, Nicolaides KH. Fetal acidosis and hyperlacticaemia diagnosed by cordocentesis in pregnancies complicated by maternal diabetes mellitus. Diabet Med 1991;8:464-8.
8. White P. Diabetes mellitus in pregnancy. Clin Perinatol 1974;1:331-47.
9. Yudkin PL, Aboualfa M, Eyre JA, Redman CWG, Wilkinson AR. New birth weight and head circumference centiles for gestational ages 24-42 weeks. Early Hum Dev 1987;15:45-52.
10. Worth R, Potter JM, Drury J, Fraser RB, Cullen DR. Glycosylated haemoglobin in normal pregnancy: a longitudinal study with two independent methods. Diabetologia 1985;28:76-9.
11. Nicolaides KH, Economides DL, Soothill PW. Blood gases, pH and lactate in appropriate and small for gestational age fetuses. Am J Obstet Gynecol 1989;161:996-1001.
12. Nicolaides KH, Snijders RJM, Thorpe-Beeston JG, Van den Hof MC, Gosden CM, Bellingham AJ. Mean red cell volume in normal, anemic, small, trisomic and triploidy fetuses. Fetal Ther 1989;4:1-13.
13. Van den Hof MC, Nicolaides KH. Platelet count in normal, small and anemic fetuses. Am J Obstet Gynecol 1990;162:735-9.
14. Phillips AF, Rosenkrantz TS, Porte PJ, Raye JR. The effect of chronic fetal hyperglycemia on substrate uptake by the ovine fetus and conceptus. Pediatr Res 1985;19:659-66.
15. Robillard JE, Sessions C, Kennedy RL, Smith FG. Metabolic effects of constant hypertonic glucose infusion in well-oxygenated fetuses. Am J Obstet Gynecol 1978;130:199-203.
16. Hommes FA, Kraan GPB, Berger R. The regulation of ATP synthesis in fetal rat liver. Enzyme 1973;15:351-60.
17. Gamsu HR. Neonatal morbidity in infants of diabetic mothers. J R Soc Med 1978;71:211.

18. Pedersen J. The pregnant diabetic and her newborn. ed 2. Baltimore: Williams & Wilkins, 1977:211-20.
19. Golde DW, Bersche N, Cline MJ. Hormonal effects on erythroid stem cells. In: Stamatoyannapoulos G, Niehuis AW, eds. Cellular and molecular regulation of haemoglobin switching. New York: Grune & Stratton, 1979:305-21.
20. Stuart MJ, Elrad H, Graeber JE, et al. Increased synthesis of prostaglandin endoperoxides and platelet hyperfunction in infants of mothers with diabetes mellitus. J Lab Clin Med 1979;94:12-7.
21. Stuart MJ, Sunderji SG, Walenga RW, Setty BNY. Abnormalities in vascular arachidonic acid metabolism in the infant of the diabetic mother. BMJ 1985;290:1700-2.
22. Foley ME, Collins R, Stronge JM, Drury MI, MacDonald O. Blood viscosity in umbilical cord blood from babies of diabetic mothers. J Obstet Gynecol 1981;2:93-6.
23. Oppenheimer EH, Esterly JR. Thrombosis in the newborn: comparison between diabetic and nondiabetic mothers. J Pediatr 1965;67:549.
24. Brudenell M, Doddridge MC. Diabetic pregnancy. Edinburgh: Churchill Livingstone, 1989:90-2.

Actocardiotocographic monitoring of triplets during vaginal delivery

Jim van Eyck, PhD,[a] and Birgit Arabin, PhD[b]
Zwolle, The Netherlands, and Berlin, Germany

A case is reported in which fetal monitoring during vaginal delivery of triplets was performed with the MT 430 actocardiotocograph. This method provides optimal monitoring of multiple pregnancies because the fetal heart rate tracings of three fetuses, together with recordings of fetal movements and uterine contractions, can be visualized on one display. (Am J Obstet Gynecol 1992;166:1293-4.)

Key words: Actocardiotocograph, triplets, fetal monitoring, delivery

The numbers of multiple births have increased dramatically in many countries as a result of the widespread use of ovulation-inducing agents and assisted reproductive technologies. For example, in the United States the number of twins and triplets—higher-order births increased by 33% and 101%, respectively, during the decade between 1978 and 1988. Similar increases have been observed in the United Kingdom and Germany.

At present, the mode of delivery of triplets is controversial. If the vaginal route is chosen, along with other requirements it is mandatory to obtain optimal monitoring of all three fetuses. In 1984 Maeda[1] described the actocardiotocograph, which permits registration of the fetal heart rate (FHR) tracing in combination with fetal movements and uterine contractions.[1] Recently an advanced model, the MT430 actocardiotocograph (Toitu Co., Ltd., Tokyo, Japan), was developed for use with multiple pregnancies, and first attempts were made to define fetal behavior in twins.[2]

From the Department of Perinatal Medicine, Sophia Hospital Zwolle, and the Department of Obstetrics and Gynecology, University Hospital Steglitz/Free University Berlin.
Received for publication August 20, 1991; revised November 11, 1991; accepted November 26, 1991.
Reprint requests: Jim van Eyck, MD, PhD, Department of Perinatal Medicine, Sophia Hospital Zwolle, Dr. Van Heesweg 2, 8025 AB Zwolle, The Netherlands.
6/1/35279

Case report

A 30-year-old woman, para 1, became pregnant with triplets after in vitro fertilization. At 14 weeks' gestation elective cerclage was performed. At 26 weeks the patient was admitted for bed rest because of increasing mechanical discomfort. Periodic ultrasonographic examinations revealed three fetuses, in vertex position, having normal growth. External FHR tracings, and Doppler flow measurements of the umbilical artery were normal in all three fetuses. At 35 weeks the cerclage suture was removed, after which labor began. After artificial rupture of the membranes of the first amniotic sac, a scalp electrode was placed on the fetal head, followed by insertion of a catheter for measurement of intrauterine pressure. The second and third fetuses were externally monitored with respect to FHR and fetal movement. Five hours after amniorrhexis full dilatation was present. Shortly thereafter the three infants were born in vertex position during a 15-minute period. Throughout labor and delivery, FHR tracings of all three fetuses, together with recordings of uterine contractions and fetal movement of the two externally