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Antenatal assessment of fetal outcome in pregnant diabetics

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1 Introduction

One of the major risks in the pregnancy of a diabetic women is the higher prevalence of neonatal problems. In the newborn period hypoglycemia, visceromegaly, polycythemia,hyperbilirubinemia and a characteristic aspect can be typical features of children of diabetic mothers, and their perinatal morbidity and mortality is significantly increased [4, 6]. Modern management of pregnant diabetic women tries to reach normoglycemia which ideally should be achieved before conception but at least immediately after the diagnosis of pregnancy [5, 10]. It has been shown that normoglycemia for the full length of pregnancy can be achieved [1] under optimal circumstances with continuous modifications of the insulin dose based on daily measurements of the blood glucose levels by the trained patient and biweekly controls by the physician.

Glycosylated hemoglobin (HbA1) serves as a parameter for long-term assessment of the mean blood glucose, but its value is limited by the fact that during pregnancy an increased number of young erythrocytes are released resulting in false low measurements [2].

WEISS [12] was the first to emphasize the importance of an insulin determination in amniotic fluid for the management of diabetes in pregnancy. Because of the long half-life of insulin in amniotic fluid a measurement of this parameter can be considered another index for the long-term diabetic control, and the same applies for C-peptide which is formed in equimolar amounts with insulin during the proteolytic cleavage of proinsulin [3].

Our study was designed to determine which of the three parameters (HbA1, amniotic fluid insulin or C-peptide) has the best prognostic power with regard to neonatal problems due to maternal diabetes.

Curriculum vitae

WOLFGANG BURKART, *M. D., was born in 1950 in Winterlingen, West Germany. From 1968 to 1980 he studied Chemistry at the Universities of Karlsruhe und Freiburg from which he was graduated in 1980. From 1973 to 1981 he studied medicine at the University of Freiburg and received his M.D. degree in 1981. Since 1981 he has been working at the Department of Obstetrics and Gynecology, University of Münster. His main fields of interest are endocrinology, diabetes and obstetrics.*

2 Patients and methods

HbA1-concentrations were measured biweekly in 57 pregnant diabetic women, 2 of which belonged to White's class A, 24 were class B, 12 class C and in 19 patients the severity of diabetes was class D (n = 15) or more (n = 4). We used the microcolumn method (PanChem, Kleinwallstadt, FRG) because its handling is simple and the results obtained correlate well with the $HbA1_c$-determination according to the method of TRIVELLI [11]. Mean values were calculated from the measurements between the 30th and 40th week of pregnancy, and in those patients in whom only a few values could be obtained because of late registration.

For normal control values we used the measurements in 72 non-diabetic patients after the 30th week of pregnancy. In those patients a routine oral glucose tolerance test was performed and venous blood was obtained at the same time for HbA1-determination. Only HbA1 values in those patients were used whose 100 g glucose tolerance test was not pathologic according to the criteria of O'SULLIVAN [9]. The HbA1 measurements were performed between the 30th and 40th week of pregnancy and up to three days after delivery.

The present study includes pregnancies in which an amniocentesis between the 34th and 37th week was consented to by the patient. This constitutes about 52% of the total number of diabetic pregnancies in our center during the observation period from 1981–1984. Using commercially available test kits we measured amniotic fluid insulin (Serono, Freiburg, FRG) and C-peptide (Byk Malinckrodt). The values were assessed following the curves described before [3]. There were no complications from the amniocenteses. For counselling purposes we used a risk figure of 0.3% [7].

The newborns were evaluated routinely by the pediatricians according to their clinical presentation and glucose requirements post partum. The minimum requirements for classifying a child as having "major symptoms" were hypoglycemia of less than 30 mg% for more than 7 days and body weight above the 90th percentile. Most of these children had visceromegaly and/or hyperbilirubinemia, some exhibited increased hematocrit values, cardiomyopathy or hypocalcemia. One child suffered from respiratory distress syndrome. Minor alterations in blood glucose levels which could be controlled by frequent meals were not considered.

3 Results

The mean value of all HbA1-measurements of those patients who had normal 100 g oGTT was 6.4 ± 1.1% in our series. For the evaluation of the insulin and C-peptide levels in the 34th–37th pregnancy weeks those values were considered normal which corresponded to the 99th percentile of a distribution derived from the concentration of these peptides in 275 non-diabetic pregnancies. These limits were found to be 23 µU/ml insulin and 3 ng/ml C-peptide (table I). The cut-off points of 18 µU/ml insulin and 2.6 ng/ml C-peptide used in tables II and IIIa, b are derived from the mean values of

Table I. Predictability of neonatal morbidity in infants of diabetic mothers.

parameter	limits	children without major symptoms		children with major symptoms		specificity	sensitivity
		correctly low	false elevated	correctly elevated	false low		
insulin	23 µU/ml	96% (n = 46)	4% (n = 2)	56% (n = 5)	44% (n = 4)	96%	56%
	18 µU/ml	83% (n = 40)	17% (n = 8)	78% (n = 7)	22% (n = 2)	83%	78%
C-peptide	3 ng/ml	88% (n = 42)	12% (n = 6)	50% (n = 4)	50% (n = 4)	88%	50%
	2,6 ng/ml	75% (n = 36)	25% (n = 12)	50% (n = 4)	50% (n = 4)	75%	50%
HbA1	7,5%	77% (n = 37)	23% (n = 11)	44% (n = 4)	56% (n = 5)	77%	44%

Table II. Prediction of a healthy child and of major symptoms.

	Prediction of a healthy child			Prediction of major symptoms		
parameter	limit	proportion of normal values*	predictive value	limit	proportion of elevated values**	predictive value
insulin	23 μU/ml	46/50	92%	18 μU/ml	7/15	47%
	18 μU/ml	40/42	95%	23 μU/ml	5/ 7	72%
C-peptide	3 ng/ml	42/46	91%	3 ng/ml	4/10	40%
	2,6 ng/ml	36/40	90%	2,6 ng/ml	4/16	25%
HbA1	7,5%	37/42	88%	7,5%	4/15	27%
				9%	4/ 9	44%

* ratio of correctly diagnosed normal values over total of normal values
** ratio of correctly diagnosed elevated values over total of elevated values

Table IIIa. Prediction of a healthy child based on more than one parameter.

condition	correct prediction*	predictive value
insulin below 18 μU/ml and HbA1 below 7,5%	29/30	97%
insulin below 18 μU/ml, HbA1 below 7,5% and C-peptide below 3 ng/ml	28/28	100%
insulin below 18 μU/ml and C-peptide below 3 ng/ml	35/37	95%

Table IIIb. Prediction of major symptoms based on more than one parameter.

condition	correct prediction*	predictive value
insulin above 18 μU/ml and HbA1 above 7.5%	3/ 5	60%
insulin above 18 μU/ml and C-peptide above 3 ng/ml	4/ 7	57%
insulin above 18 μU/ml, C-peptide above 3 ng/ml and HbA1 above 7.5%	2/ 3	66%
insulin above 23 μU/ml, C-peptide above 3 ng/ml and HbA1 above 7.5%	2/ 3	66%
2 of 3 parameters above limit (18 μU/ml, 3 ng/ml, 7.5%)	6/11	54%

* number of correctly predicted cases over total of cases fulfilling conditions

those concentrations found in healthy children of diabetic mothers. The rate of correct predictions is given in the tables.

Nine of the 57 children whose mothers had a determination of glycosylated hemoglobin and an amniocentesis, had major neonatal complications. The mean glucose application in those children during the first 24 hours was 7.8 mg/kg body weight/minute as opposed to 4.2 mg in healthy children of diabetic mothers.

4 Discussion

Table I indicates that 75–96% of the children without neonatal symptomatology had normal values of one of the three parameters, depending on the cut-off points chosen. The narrower the normal range is defined, the lower is the number of children with normal values. If the insulin cut-off point is lowered from 23 to 18 μU/ml, the percentage of children with normal values of amniotic fluid insulin decreases from 96 to 83%. C-peptide shows a similar decrease of normal values in non-symptomatic patients from 88 to 75%. The rate of values measured correctly as elevated increases from 56 to 78% in the case of insulin.

In the case of C-peptide the introduction of a lower limit increases the rate of false low values, the rate of correctly or falsely increased values remains unchanged. We conclude from our data

that the upper limits of the three parameters should be 7.5% for HbA1, 18 μU/ml for amniotic fluid insulin and 3.0 ng/ml for C-peptide.

When trying to derive a prognosis from these elevated values and to test the predictive value of all three parameters, the results in table II have to be considered. It is obvious that the prediction of a healthy baby is easy. Depending on the parameter chosen a correct prediction can be expected in 83 to 95% of all cases. The determination of amniotic fluid insulin is associated with a predictive value based on an upper limit of 18 μU/ml. The prediction of newborn morbidity can also be achieved using the same criteria. For this purpose the determination of amniotic fluid insulin is most useful with values higher than 23 μU/ml being clearly pathologic. The determination of C-peptide and HbA1 is less useful but values higher than 9% HbA1 can be considered pathologic in 44% of the cases.

Taking into account more than one single parameter, the accuracy of the prediction "healthy child" reaches 100% (table IIIa, b). The accuracy of the prediction of major neonatal problems cannot be further increased, it ranges between 54 and 66% if all three parameters are assessed simultaneously. It should be taken into account that the significance of the results is limited due to the sample size.

According to our results the concentration of insulin in amniotic fluid is the most reliable parameter for the evaluation of developing fetal impairment. This is in contrast to Lin et al [8], who found C-peptide to be more reliable. It is obvious that a statement can be made with much higher certainty when the other parameters are also taken into account. For the exclusion of severe neonatal disease HbA1, amniotic fluid insulin and C-peptide have to be lower than 7.5%, 18 μU/ml and 3.0 ng/ml respectively. If two of these three parameters are below these limits, a fetal impairment can be excluded with more than 90% certainty.

An amniotic fluid insulin level of more than 23 μU/ml can be considered as a strong indicator of neonatal disease. The accuracy of this prediction is more than 70%. An increase of the insulin level to more than 18 μU/ml has to be evaluated by taking the other parameters into account: A fetal compromise has to be assumed in more than 60% of the cases if all three values are increased. If only two values are elevated, the accuracy of the prediction is lowered to about 50%.

Summary

The predictive value of three parameters (amniotic fluid insulin and C-peptide, and HbA1) in prognosticating major neonatal symptomatology was investigated in 57 pregnancies of diabetic women. The prediction of a healthy neonate can be achieved with a 90% accuracy by measurement of the amniotic fluid insulin alone. The correct prognosis for a child with major neonatal problems due to maternal diabetes can be made with 70% certainty using the same method. All other parameters can be judged less valuable based on our results. By using more than one of those parameters mentioned, the prediction of a healthy child can be made more correctly with a certainty of almost 100%. The accuracy in predicting a child with major symptoms cannot be increased any further.

Keywords: Amniotic fluid C-peptide, amniotic fluid insulin, HbA1, infants of diabetic mothers.

Zusammenfassung

Antenatale Vorhersage des Neugeborenenzustandes bei schwangeren Diabetikerinnen

In 57 Schwangerschaften von Diabetikerinnen wurde der prädiktive Wert dreier Parameter: Fruchtwasser-Insulin, Fruchtwasser-C-Peptid und HbA1 untersucht. Die Vorhersage eines gesunden Neugeborenen ist durch die Bestimmung des Fruchtwasserinsulingehaltes mit einer Sicherheit von über 90% möglich, die eines Kindes mit

ausgeprägter diabetischer Fetopathie jedoch nur mit 70%iger Sicherheit. Bei den anderen Parametern ist der prädiktive Wert geringer.
Durch die gleichzeitige Wertung mehrerer der obengenannten Parameter kann die Zuverlässigkeit der Vorhersage eines gesunden Kindes auf nahezu 100% gesteigert werden, die Vorhersage eines kranken Kindes wird nicht sicherer als durch die Bestimmung von Fruchtwasserinsulin allein.

Schlüsselwörter: Diabetische Fetopathie, Fruchtwasser-C-Peptid, Fruchtwasserinsulin, HbA1.

Résumé

Estimation antenatale du devenir fœtal chez les diabétiques enceintes
On a exploré la valeur prédictive de trois paramètres (insuline dans le liquide amniotique, peptide C et Hb A1) face à la symptomatologie néonatale majeure au cours de 57 grossesses chez des femmes diabétiques. On peut prévoir un nouveau-né en bonne santé avec une fiabilité de 90% en déterminant uniquement l'insuline dans le liquide amniotique. La prévision correcte d'un enfant qui présentera des problèmes néonataux majeurs secondaires au diabète maternel est possible avec une fiabilité de 70% en utilisant la même méthode. En se fondant sur nos résultats, on peut juger tous les autres paramètres comme moins valables.
En utilisant plus d'un des paramètres mentionnés, on peut prédire correctement un enfant en bonne santé avec une fiabilité proche de 100%. Toutefois, la fiabilité de la prévision d'un enfant qui présentera des symptomes majeurs, ne peut pas être augmenté de la sorte.

Mots-clés: Enfants de mères diabétiques, HbA1, insuline dans le liquide amniotique, peptides C du liquide amniotique.

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