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Macrosomia in Newborns of Diabetic Mothers Still a Valid End -Point...or Is It?

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ABSTRACT. Hyperglycaemia is one factor among several other maternal and fetal determinants of neonatal size at birth. The objectives of the present study is to assess the potential role of maternal hyperglycaemia "defined by 3rd trimester mean blood glucose level" together with some other maternal variables as a determinant of fetal weight at birth and the risk of macrosomia "birth weight < 4000 g". Data from 178 diabetic and 219 non-diabetic pregnant women were analyzed using multiple and logistic regression analysis. The results showed that 3rd trimester blood glucose level and duration of gestation, each had a significant positive relation to fetal weight at birth. However, the incidence of delivering < 4000 g baby was primarily related to maternal age in both the diabetic and non-diabetic groups, as well as to maternal body weight and duration of gestation in the non-diabetic group. It is concluded that, macrosomic newborns of diabetic mothers include two varieties of neonatal population: those with true "pathological macrosomia" together with constitutionally large newborns who do not exhibit the stigma of diabetic macrosmia. If macrosomia is to be used as an end-point in evaluating the outcome of management of diabetic pregnancies, a differentiation should be made between these two varieties of neonatal populations.

Keywords: Gestational diabetes, Macrosomia, Hyperglycaemia, Risk factors.

Introduction

With recent developments in antenatal and neonatal care the mortality among infants of diabetic mothers have been reduced to a rate which is almost similar to that of non-mortality is a more appropriate end-point in evaluating the outcome of diabetic pregnancies. In this respect, fetal macrosomia is probably the most commonly reported mor-

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bidity. This is justified by the Pedersen hypothesis, that attributes excessive fetal growth to hyperinsulinaemia which is directly related to maternal hyperglycaemia[1]. Nevertheless, and despite recent development in the management of diabetes in pregnancy, neither fetal macrosomia has been eliminated, nor the extent of its relationship to maternal blood glucose concentration has been well defined[2-5]. This may partly be due to inconsistency, among various authors, in defining macrosomia[6-10]. But more significantly it could be due to the fact that neonatal size at birth is a multifactorial phenomenon that is influenced by several maternal and fetal variables which are seldomly taken in consideration when reporting on fetal outcome of diabetic mothers. Among the maternal variables, demographic, anthropometric, socioeconomic and environmental variables are well recognized factors that affect fetal growth and its eventual weight at birth[11]. Most importantly the fetal genetic growth potential may result in an infant who is larger than a standard cut-off value but totally normal, in the sense that it does not exhibit features of diabetic macrosomia[12]. Unless such variables are taken into consideration the use of neonatal birth weight, as an endpoint, in evaluating outcome of diabetic pregnancies may lead to misleading conclusions. It has been suggested that establishing a standard of birth weight-for-gestational-age may be an oversimplification of a complex relationship between weight, gestational age and other variables that influence size at birth[13].

The objective of the present study is to examine the relative influence of maternal hyperglycaemia, among some other maternal variables, on each of fetal weight at birth and the incidence of large birth weight infants (i.e. macrosomia) in a group of gestational and non-insulin-dependent diabetic mothers and their newborns.

Patients and Methods

This study was conducted at King Abdulaziz University Hospital (KAUH) in Jeddah as part of an on-going research project on gestational diabetes (GDM). The study spun over a period of two years that began on September, 1992. All patients studied had their antenatal care and deliveries at this hospital. According to our protocol, patients - except known diabetic subjects - were screened for gestation GDM using a 100g oral glucose tolerance test (OGTT) between 24 and 30 weeks of gestation. The tests were performed and the results interpreted according to the criteria of the National Diabetes Data Group (NDDG)[14]. Patients with abnormal results were considered as GDM, whether or not insulin treatment was required. The management protocol of diabetic patients in pregnancy have been previously described[15]. Briefly, once the desired level of blood glucose is achieved (fasting and post-prandial blood glucose < 5.8 mmol/l and < 7.0 mmol/l, respectively) whether on diet regimen alone or additional insulin therapy is required, patients were followed-up on an out-patients basis, by at least one set of weekly blood measurements at fasting and two hours post-prandial. More frequent measurements and/or hospital admission were reserved for uncontrolled cases or for those who developed obstetric complications. A minimum of at least one set of measurement of blood glucose per week (fasting and two hours post-prandial) were considered essential criteria for inclusion in the present study.

Patients with known insulin-dependent diabetes (n = 6) were excluded. Also patients were excluded, if they were known chronic hypertensive, developed pre-eclampsia, having multiple gestation or gave birth to malformed infants. Patients in this study have been followed-up by serial ultrasound scans which ensured the reliability of their gestational age.

The mean 3rd trimester blood glucose level was calculated for each patient from the arithmetic mean of all measurements of blood glucose performed between 30 weeks of gestation and until the time of delivery. According to the results, patients were classified into three groups: well-, moderate-, and poorly-controlled groups (mean blood glucose < 4.7, < 5.8 and ≥ 5.8 mmol/l, respectively)[16]. Large birth weight fetus (fetal macrosomia) was defined as a fetal weight > 4000g at birth[8].

Data were analyzed using SPSS-PC statistical package version 0.3 for windows (SPSS Inc., Microsoft Corp., Chicago IL, USA) on IBM compatible PC. Student-t test was used to test the difference between characteristics of non-diabetic and diabetic mothers. Multiple linear regression was used to allow for simultaneous evaluation of the effect of some independent "risk" variables namely: maternal age, weight (at time of OGTT testing), gravidity, type of diabetes, mode of treatment (diet or insulin), gestation week at delivery, fetal sex and 3rd trimester mean blood glucose on the dependent outcome variable namely, fetal birth weight. Multiple logistic regression analysis was performed to estimate the relative risk of having a baby weighing more than 4000 g against each of the independent "risk" variables - that turn-up to have significant relation to birth weight - using a stepwise backward elimination process[17]. A P-value of < 0.05 was considered statistically significant.

Results

Over a period of 24 months, 1412 patients had undergone OGTTs. In 219 (15.5%) patients the results of the tests were considered abnormal. However, only 178 patients satisfied the study inclusion criteria. Of the 41 excluded patients, 35 had few than one measurements of blood glucose per-week, 3 patients were found to have insulin dependent diabetes, 2 patients developed pregnancy-induced hypertension, and one patient gave birth to a twin. For each diabetic case, the subsequent patient with normal OGTT results was recruited as a control case provided that the same inclusion criteria, as in the diabetic group, were satisfied. Thus, a total of 219 women were included as non-diabetic controls.

In the diabetic group, 119 (66.9%) patients were identified as GDM, and 59 patients (33.1%) as having non-insulin dependent diabetes mellitus (NIDDM). The latter diagnosis was made if a patient gave a history suggestive of diabetes either during or outside a previous pregnancy. During pregnancy, insulin was required in 104 (58.4%) patients while the rest were controlled by diet therapy alone. Table 1 shows the studied maternal characteristics, pregnancy outcome, type and mode of treatment in each of the "well", "moderately" and "poorly" controlled diabetic patients. Only 5.1% (9 patients) achieved tight "well" degree of metabolic control and thus were excluded

from further statistical analysis. Among the "moderately" and "poorly" controlled groups, there was no significant difference in maternal characteristics, fetal birth weight and the incidence of macrosomia. However, in the poorly-controlled group, significantly higher incidence of babies were delivered by cesarean section whether primary of secondary.

TABLE 1. Comparison between some maternal criteria, pregnancy outcome, type and treatment of diabetes in well, moderately and poorly-controlled diabetic patients. Data are expressed as mean ± SD and percentage as appropriate. (Blood glucose in mmol/dl x 18 = mg/dl).

	Well-controlled n 9 = (5.1%)	Moderately-controlled n = 50 (28.1%)	Poorly-controlled n = 119 (66.9%)
Age	28.4 ± 5.3	30.44 ± 4.22	31.43 ± 5.7
Gravida	36 ± 1.7	5.42 ± 3.2	5.75 ± 3.1
Weight	69.38 ± 17.2	76.74 ± 15.5	77.5 (± 15.7)
% Caesarean section Primary Secondary	(22%) 1 1	(22%) 1 10	(36.1%)*** 6 37
Birth weight (g)	2832 (± 483)	3387 (± 680)	3529 (± 579)
Babies > 4000 g (%)	-	7 (14.0%)	22 (18.5%)
Mean blood glucose Maximum Minimum	4.43 (± 0.2) 4.65 3.95	5.4 (± 0.3) 5.75 4.75	7.15 (± 1.3) 12.7 5.8
Type of diabetes Gestational (%) NIDD (%)	 7 (77.8%) 2 (22.2%)	 42 (84%) 8 (6%)	 69 (57.9%) 50 (42.0%)
Treatment of DM Diet (%) Insulin (%)	 4 (44%) 5 (55%)	 29 (58%) 21 (40%)	 85 (71.4%) 34 (28.6%)

**** P Value < 0.001.

TABLE 2. Criteria of diabetics and non-diabetic patients. Date are expressed as means + SD and percentage as appropriate.** and * denote P value of < 0.001 and < 0.05 respectively.

Criterion	Diabetic	Non-diabetic
Maternal age	31 ± 5.3	27.4 ± 5.2**
Gravida	5.5 ± 3.1	4.5 ± 2.6**
Maternal weight	76.9 ± 15	69.4 ± 15**
Gestational week	38.7 ± 1.6	39.5 ± 1.7**
Fetal birth weight	3454 ± 627	3350 ± 517
Macrosomia	29 (16.3%)	18 (8.0%)*

When all the diabetic patients were pooled together and compared to the corresponding non-diabetic control group, the former group was significantly more older, higher in gravidity, heavier in body weight and had shorter period of gestation (Table 2). But there was no significant difference in the mean fetal birth weight between the two groups. However, the incidence of macrosomic babies was significantly higher in the diabetic compared to the non-diabetic group (29 babies "16.3% vs 18 babies "8.0%", respectively).

Fetal Birth Weight and the Risk of Fetal Macrosomia in Non-Diabetic Group: Linear regression analysis showed a significant association between fetal birth weight and each of the maternal body weight and gestational age at delivery. None of the other variables tested namely: maternal age, gravidity and fetal sex showed such association with fetal birth weight. When logistic regression analysis was used to test for the risk factors of having a macrosomic baby, each of maternal age, maternal body weight and gestational age at delivery was significantly related to fetal macrosomia (Table 3).

TABLE 3. Logistic regression models for having macrosomic baby (> 4000 g) in diabetic and non-diabetic groups in relation to the studied independent risk variables. * = P < 0.05.

Variable	Diabetic		Non-diabetic	
	B	Odd ratio (95% CO)	B	Odd ratio (95% CO)
Mothers age	0.146*	1.12 (1.03, 1.23)	0.139*	1.15 (1.04, 1.27)
Mothers weight	0.003	1.003 (0.98, 1.03)	0.04*	1.04 (1.07, 1.38)
Gestational age	0.152	1.64 (0.89,1.52)	0.6303*	1.88 (1.12,3.16)
Gravida	- 0.147	0.864 (9.79,1.05)	- 0.042	0.96 (0.75, 1.34)

Fetal Birth Weight and Risk of Fetal Macrosomia in the Diabetic Group: Linear regression analysis showed a significant relationship between fetal birth weight and each of: mean blood glucose during the 3rd trimester (P< 0.005) and gestational age at birth (P< 0.0017), respectively. Furthermore, the interaction between these two variables (i.e. Mean blood glucose and gestational age at birth) had significantly improved their relationship to birth weight (P< 0.001). There was however, no statistically significant relationship between birth weight and any of the other variables namely: maternal age, maternal body weight, gravidity or fetal sex and the type or mode of treatment of diabetes.

On logistic regression analysis, the risk of having a large baby (> 4000 g) increases *significantly (P< 0.008) with increasing* maternal age, even after controlling for the other studied variables (Table 3).

Discussion

Fetal macrosomia has traditionally been considered as the whole mark of uncontrolled GDM. According to Pedreson's hypothesis, a tight control of maternal blood glucose, should decrease the incidence of macrosomic infants, among pregnant women with diabetes, to a rate which is almost similar to that of a NIDDM population[1]. In the present study, only 5% of patients had a well "i.e. tight" control of their diabetes. Such degree of metabolic control would ideally require the use of home glucose monitoring machines preferably with memory back-up. These facilities are presently unavailable in our set-up. This situation - though unsatisfactory - offers us an opportunity to further explore the relative influence of hyperglycaemia on fetal weight at birth and the incidence of macrosomia.

Our results show that the mean blood glucose during the 3rd trimester is the primary factor, together with gestational age, that influence fetal weight at birth. This however, was not the case when macrosomia - as defined by birth weight > 4000g - was considered. Instead, increasing maternal age turned-up to be the most significant risk factor for macrosomia. This may explain the finding that the incidence of macrosomia among the two subgroups of diabetic mothers, i.e the moderately-, and poorly-controlled groups, were not significantly different, despite different levels of metabolic control. Since there was no difference in neither the mother's age nor in any of the other studied maternal variables between the two sub-groups. The results of the present study agree with other reports in respect to the relationship between the degree of maternal glycaemia and birth weigh[18]. It is possible that, in our population, the increased maternal age is simply a marker for other risk factors that may not have been tested in the present study such as maternal height, new weight gain...etc,[18].

Similarly, among non-diabetic patients advanced maternal age, weight and duration of gestation significantly increased the risk of delivering babies > 4000 g. In clinical practice such mothers (i.e. the older and heavier ones) are the more likely to develop GDM and NIDDM, hence, their basic risk for having babies weighing > 4000 g is expected to be high, regardless of their diabetes. Thus macrosomic newborn of diabetic mothers include variable proportions of newborn with true "pathological macrosomia", that actually reflect their mother's degree of glyaemic control, together with those who are constitutionally large but do not exhibit the stigma of macrosomia. The proportion of the latter group of fetuses, are likely to be higher than average, among older and heavier mothers. regardless of their diabetes.

However, the role of hyperglycaemia in enhancing fetal growth as a whole, hence increasing the risk of fetal macrosomia, can not be ignored, provided that a differentiation is made between true "pathological hyperglycaemia" and constitutionally large newborns. The former condition is due to accelerated growth of the fetal "soma" or body, particularly the insulin-sensitive tissues namely adipose tissue[19,20]. Hence, in an ideal set-up the diagnosis of "pathological macrosomia" should not be based on a given cut-off point of fetal weight. Other neonatal morphometric measures such as neonatal pondral index or skin fold thickness, that avoid the problem associated with birth-weight for gestational age, may be a more accurate method for the diagnosis of altered fetal growth[19-22].

Of clinical significance, is the strong positive interaction between 3rd trimester blood glucose level and the duration of gestation on fetal weight at birth. Such relationship may be attributed to increased duration of exposure of the growing fetus to the deleterious anabolic effect to fetal hyperinsulinaemeia. Thus, it highlights the importance of adequate glycaemic control particularly during the 3rd trimester.

Taken together, the results of the present study suggest that the use of birth weight as an end-point in assessing pregnancy outcome among diabetic mothers is an oversimplification and may be misleading. Even the often utilized birth weight standards, are likely to differ from one another because of the difference in variables such as patients population, time and location[23,24]. Instead, when assessing the outcome of diabetic pregnancies a differentiation should be made between the constitutionally large fetuses and those who display features of true pathological macrosomia. Such a differentiation is important in order to avoid misleading conclusion particularly from studies on population, such as the local one, where advanced maternal age, parity and maternal obesity, which are well recognized risk factors for both increased fetal weight as well as decreased glucose tolerance, are relatively common.

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زيادة حجم مواليد الأمهات المصابين بمرض البوال السكري - هل تعتبر ذو أهمية؟

حسن نصرت

قسم أمراض النساء والتوليد ، كلية الطب والعلوم الطبية ، جامعة الملك عبد العزيز

جـــــدة - المملكة العربية السعودية

المستخلص . يعتبر ارتفاع نسبة السكر في الدم مجرد أحد العوامل المسؤولة عن ازدياد حجم ا لجنين . الهدف من هذه الدراسة هو تقييم مدى تأثير زيادة نسبة السكر في دم الأم على وزن الجنين فوق ٤٠٠٠ جم . تم تجميع معلومات عن ١٧٨ مريضة حامل ومصابة بالبوال السكري ومقارنتها بعدد ٢١٩ حامل لا تعاني من البوال السكري . وبمقارنة المجموعتين تبين أن كل من مستوى سكر الدم لدى الأم الحامل في الجزء الأخير من الحمل ومدة الحمل نفسها لهما تأثير إيجابي على وزن الجنين ، ولكن احتمالات أن يكون وزن الجنين أكثر من ٤٠٠٠ جم كان متعلق مباشرة بعمر الأم وذلك في كل مرضى البوال السكري والحوامل اللاتي يعانين من نفس المرض . كما أن وزن الأم ومدة الحمل كان لهما تأثير إيجابي على احتمال أن يكون الجنين أكبر من ٤٠٠٠ جم في السيدات اللاتي لا يعانين من البوال السكري . ونتيجة هذه الدراسة تدل على أن المواليد الذين يصل وزنهم إلى أكثر ٤٠٠٠ جم يتضمنوا نوعين من الحالات . أولاً مواليد يعانون من تأثير مرض البوال السكري وارتفاع نسبة السكر في دم الأم وهنا تعتبر زيادة وزن المولود غير صحية ، وآخرون أصحاء ولكن زائدين في الوزن . لذا فإذا كان وزن الجنين سيستخدم كدليل على مدى كثافة العلاج أو شدة المرض في حالات البوال السكري فلا بد أن يؤخذ في الاعتبار أن هناك عوامل أخرى تؤثر في زيادة وزن الجنين وإن ارتفاع وزن الجنين قد يكون طبيعيًا وعلامة صحية .