Uteroplacental Unit Disorders and Perinatal Outcomes in Pregnancies Complicated by Diabetes and Obesity

Abstract

Objective. *To assess the uteroplacental alterations and maternofetal outcomes in pregnancies complicated by diabetes (gestational, type 1 or type 2) and / or maternal obesity.* ***Method.*** *The retrospective study on a representative sample of 14,400 births in a period of six years (2003-2008) examined all cases with diabetes - 153 (1.06%) cases and 225 controls. The main outcomes assessed were gestational age, birth weight, Apgar score and maternal and neonatal morbidity. A second analysis on 148 livebirths was done to identify microscopic placental alterations in diabetic and obese patients.* ***Results.*** *There was a particular dispersion of types of diabetes in pregnancy: gestational diabetes 52%, type 1 DM -40% and type 2 diabetes - about 7%. Diabetic women presented an increased age at birth and a significantly higher prepregnancy weight ($p < 0.01$), the blood pressure, it is statistically higher, and caesarean section rate is much higher. Neonate's birthweight is significantly higher, and the Apgar score is lower than control. In obese patients was noted an increased maternal age and value of BP compared to control. Association of obesity increases the risk for hypertension, diabetes, overweight load, lower gestational age at birth, macrosomia, and lower Apgar score. Analysis of placenta showed a variety of macroscopic aspects - edema, congestion, and fibrinoid deposits calcification, characteristic but nonspecific for pregnancy with diabetes.* ***Conclusions.*** *These data confirm the higher incidence of neonatal morbidity by increased risk of metabolic, respiratory, hematological complications as well as fetal trauma, complications of intrauterine growth anomalies. This study confirms the role of uteroplacental histological abnormalities in diabetic pregnancies.*

Keywords: *gestational diabetes, obesity, hypertension, pregnancy*

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Introduction

Gestational diabetes is a metabolic disorder frequently encountered, the prevalence range between 1 and 14% in the U.S., being on average between 2-5%[(1)].

The prevalence of gestational diabetes is directly related to the prevalence of type 2 diabetes in a given population or ethnic group. It reflects the frequency of type 2 diabetes[(2)].

It is difficult to compare the frequency of gestational diabetes among different populations.

The pregnancy complicated by diabetes is a high risk pregnancy, with a higher incidence of obstetrical complications, of the recurrence of gestational diabetes and later development of type 2 diabetes.

In addition, prepregnancy obesity, as an essential component of the metabolic syndrome (MS), is frequently associated with multiple complications during pregnancy, at birth, and also later in life.

Maternal diabetes complicates pregnancy by complex interactions of growth stimulation (through growth factors IGF1 IGF2) but also of intrauterine growth restriction which can alter the normal course of neonatal development.

Diabetes can affect the intrauterine environment by altering the function of uteroplacental unit through vascular oxidative stress and inflammatory mediators.

In an environment in which metabolism is affected, the placenta being the source of oxygen and nutrients, can affect fetal development.

At the onset of pregnancy ovarian steroidogenesis stimulates endometrial responsiveness[3] and the insulin has been demonstrated as being a modulator of ovarian steroidogenesis[4]. Patients with gestational diabetes appear to have abnormalities of both insulin secretion and a marked insulin resistance compared with patients with normal insulin tolerance[5,6,7].

Endothelial dysfunction of decidual capillary network associated with insulin resistance includes a decreased vasodilatation, increased leukocyte-endothelial cell adhesion and vascular permeability[8,9].

In diabetes pregnancy early endothelial cell function injury creates prerequisites of early damage of placental vascular development. As consequence the reactivity to vasoconstrictors or vasodilators stimuli is impaired and in these conditions the placenta can no longer respond properly to altered blood flow conditions[10].

Thus, impaired placental development may contribute to an increased risk of diabetes complications of pregnancy such as pregnancy-induced hypertension, preeclampsia, intrauterine growth restriction, and in a state of relative hypoxia. Variable degrees of syncitio-trophoblast and cyto-trophoblastic alterations have been described, the basement membrane and fetal vessels, which were attributed to hyperglycemic status[11].

Placenta of patients with uncomplicated diabetes is generally larger, immature choryoangiotic, highly vascularised. There are no specific histological placental abnormalities in diabetes and hypertension tasks compared to cases with hypertension only. Instead, pregnancies with diabetes have an increased risk of villous inflammation - villitis, corioamniotitis and funisitis[12,13,14,15,16,17].

Perhaps genetic factors and environmental interaction may explain this increased risk, recent data from the literature support the role of oxidative stress, the inflammatory response mediators, and of the cytokines in the pathogenesis of mechanisms of glucose intolerance in diabetes mellitus[10].

The objective of this study was to analyze the main maternal fetal results in pregnancies complicated by diabetes and obesity as key elements of the metabolic syndrome.

Utero-placental compartment was also studied and the role of placental abnormalities in relation to birth outcomes in the context of metabolic syndrome.

Method

The retrospective study assessed a representative sample of 14,400 births in the Department of Obstetrics and Gynecology, Hospital "Dr. I. Cantacuzino", Bucharest during a period of six years (2003-2008). The investigational was divided into three groups: 1 - only with obesity BMI> 30kg/m (n = 10), 2 - diabetes only (n = 132) and 3 - the combination of diabetes, obesity (n = 21). In total there were 153 cases with diabetes during pregnancy. Control group included 215 cases with no associated pathology.

The main factors were evaluated: maternal age, parity, pregestational weight, weight gain and blood pressure. The main outcomes assessed gestational age, birth weight, Apgar score and maternal and neonatal morbidity. Placental abnormalities were also evaluated.

Inclusion criteria: single pregnancy, gestational or overt diabetes - type 1 or type 2, pregestational obesity (BMI> 30 kg/m^2).

Exclusion criteria: inflammatory diseases, systemic lupus and other immunological diseases, benign tumoral pathology, malignancy, alcohol abuse, smoking, drug use and other inflammatory diseases that may contribute to fetal growth restriction: asthma, rheumatoid arthritis.

Statistical analysis included Student t-test for ordinal variables and Chi-square test for categorical ones.

Results

Data analysis showed a predominance of gestational diabetes, followed by type 1 diabetes, and then by the type 2 (Table 3). Diabetes prevalence of about 1.06% of total births, which is situated at the lower compared with literature data from the U.S. This is probably a particular distribution for our country and maybe of underreported gestational diabetes (Table 2 and Table 3).

Statistical analysis of demographic data (Table 6) showed that gestational age at birth of cases with diabetes is significantly lower compared to control.

Also, there is a strong association between obesity and diabetes as an essential component of the metabolic syndrome and significantly higher values of blood pressure in cases associated with obesity alone or with diabetes.

Rank parity and age at birth was significantly higher in group involving diabetes and obesity, suggesting more frequent association of comorbidities and the influence of nutritional and metabolic imbalance expressed by obesity or metabolic syndrome, which occur or overlap in a woman's life, especially during pregnancy.

Newborn weight and caesarean section index was significantly higher in the group with diabetes alone or diabetes associated with obesity versus control.

Neonatal morbidity in relation to fetal trauma is considerably higher in the group with obesity or diabetes and obesity, probably due to fetal macrosomia and labor abnormalities (Table 7) .

Neonatal hypocalcaemia is one of common features of diabetic pregnancies and is seen with increased frequency in the group with both diabetes and diabetes associated with obesity.

Respiratory distress syndrome is a group with increased frequency in diabetes associated with obesity, suggesting the role of associated pathology in this group that can influence birth outcomes.

Fractures in the clavicle, the neurological syndrome and congenital anomalies did not differ significantly, and the relatively small number of cases cannot give valid results.

Table 1 General and demographic characteristics

	Media	Minimum	Maxim um	Std. dev.
Age	28.39	17	43	5.040
Rang gesta	2.93	1	14	2.141
Parity	1.48	1	8	0.812
Abortions	1.45	0	11	1.742
Gestational age	37.93	28	42	2.408
Prepregnancy weight	63.58	42	110	12.672
Weight gain	16.26	2	37	6.31
Prepregnancy BMI	23.03	14.7	43.0	4.84
Term BMI	28.25	17	51.7	5.47
Systolic AP	121.84	90	200	15.630
Dyastolic AP	70.93	50	120	10.025
Mean AP	87.97	63	147	10.955
Apgar	8.07	0	10	1.923
Newborn weight	3315.42	1200	5250	679.936

Table 2 Analysis of study group according to diabetes type, neonate sex and presentation

		Cases	Percent %
Diabet es		153	40.5
Diabetes	Type 1	62	16.4
	Type 2	11	2.9
	GDM	80	21.2
Sex	Male	216	57.1
	Female	162	42.9
Presentation	cranial	367	97.1
	pelvic	11	2.9

Table 3 Diabetes distribution

	GDM	Type 1 DM	Type 2 DM	Total
No. cases	80	62	11	153
Percent %	52.28	40.52	7.18	100

Table 4 Neonatal patology

	Cases	Percent %
Cranial hematoma	30	7.9
Hypocalcemia	212	56.1
Neonatal Icter	69	18.3
Clavicule fracture	3	0.8
Shoulder distocy	3	0.8
SDRA	36	9.5
Neurologic syndrome	20	5.3
Urogenital malformations	10	2.6

Table 5 Maternal morbidity

	Cases	Percent %
Vaginal/cervical lacerations	49	13
Cesarean section	126	33.3
Placental findings		
Calcifications	118	31.2
Focal infarctisations	35	9.3
Meconial stain	21	5.6
Others	64	16.9

Table 6 Statistical analysis of investigational group according to general characteristics and main perinatal outcomes

	Control N = 225	Obesity alone N = 10	Diabetes alone N = 153	Diabetes & obesity N = 21
Age	27.66 ± 4.5	31.10 ± 3.9 **p=0.01**	28.4 ± 5.2 NS	34.57 ± 4.8 **p<0.001**
Gesta	2.87 ± 1.86	3.2 ± 1.8 NS	2.86 ± 2.46 NS	3.81 ± 2.63 NS
Para	1.42 ± 0.62	1.6 ± 0.69 NS	1.42 ± 0.76 NS	2.29 ± 1.87 **p=0.049**
Abortions	1.44 ± 1.56	1.6 ± 1.7 NS	1.44 ± 2 NS	1.52 ± 1.88 NS
Gestational age	38.55 ± 2	38.9 ± 1.6 NS	36.97 ± 2.6 **p<0.001**	37.19 ± 2.87 **p=0.005**
Prepregnancy weight	58.94 ± 8.17	94.5 ± 11 **p<0.001**	64.55 ± 10.4 **p<0.001**	90.29 ± 9.12 **p<0.001**
Prepregnancy BMI	21.39 ± 3.56	33.29 ± 3.73 **p<0.001**	23.21 ± 3.64 **p<0.001**	33.77 ± 3.20 **p<0.001**
Weight gain	17.52 ± 6.43	16.5 ± 6.65 NS	14.98 ± 5.24 **p<0.001**	11.33 ± 7.48 **p<0.001**
Systolic AP	118.6 ± 11.13	130.5 ± 15 **p=0.001**	123.56 ± 18 **p=0.005**	140 ± 22 **p<0.001**
Dyastolic AP	70.52 ± 7.58	75.5 ± 10 **p=0.047**	69.51 ± 11 NS	81.9 ± 13.6 **p<0.001**
Mean AP	86.61 ± 7.36	93.9 ± 10.56 **p=0.003**	87.6 ± 13 NS	101.33 ± 15 **p<0.001**
Apgar	8.35 ± 1.54	8.6 ± 0.51 NS	7.79 ± 2.1 p=0.008	6.67 ± 3.41 **p=0.036**
Birthweight	3224 ± 572.7	3224 ± 572.7 NS	3433 ± 793 p=0.023	**3606.19** ± 827 **p=0.05**
Cesarean	19%	10% NS	57% p<0,05	48% **p<0.05**

Table 7 Neonatal morbitity

%	Control N = 225	Obesity alone N = 10	Diabetes N = 153	Diabetes & obesity N = 21
Cranian hematoma	15	30*	10	19
Hipocalcaemia	47	40	71*	62*
Neonatal jaundisse	20	30	16	14
Clavicle fracture	7	0	6	5
ARDS	9	10	9	14*
Neurologic Sd	6	0	6	0
Congenital abnormalities urogenital	3	0	2	0

**= statistical signifficant p<0.05*

Table 8 Morphological placental disorders

	Control (n = 43)	Obesity alone (n = 82)	Diabetes alone (n = 7)	Diabetes & obesity (n = 16)
Abnormal findings %	37	63	14	50

To assess the disturbances occurring in uteroplacental unit, a second analysis included 148 births in the same period. Investigational group (105 cases) was divided into three groups: obesity - pregestational BMI> 30kg/m^2 (n = 82), only diabetes (Type 1, Type 2 or gestational) (n = 7), diabetes and obesity (n = 16). Control group (43 cases) included pregnant women without associated pathology at birth.

In all these cases histopathological aspects of the placenta were recorded. Were described a variety of macroscopic aspects - edema, congestion, calcification or fibrinoid deposits.

Optical microscopy showed in most cases a combination of alterations such as: hialin areas, fibrinoid deposits, vascular congestion and intravillous hemorrhage, areas of necrosis, microcalcifications sometimes vascular microtromboses and vascular ectasies. Percentage of each of these alterations varies. Presence of at least two histopathological alterations was recorded as positive.

Placenta of patients with diabetes has been the subject of numerous histopathological studies in the last five decades[18,19,20,21].

There is a growing trend in the percentage of placental histological abnormalities in pregnancies associated with obesity or diabetes and obesity compared to control.

In the present study, approximately 40% of the placentas of patients with diabetes had villosities with normal aspect of morphological maturity in relation to gestational age. Remaining 60% presents deterioration as a result of gestational age, without a characteristic appearance, however, in half of cases was noted villous immaturity, and in half the cases accelerated villous maturity. Villous edema is common, particularly with a lower degree of swelling.

There is a tendency, but not in all cases to find a villous stroma with fibrosis, having an increased number of syncytial deposits. Cytotrophoblastic cells are numerous and prominent, while the basal membrane shows a moderate degree of diffuse thickening.

Villous vascularisation vary much - in many placentas there is normally vascularized villous, in other cases there is a hypovascularisation and hypoperfusion, while in others villous vessels are numerous and very congestive.

An important feature is the presence of large number villosities undergoing a process of fibrinoid necrosis. One aspect of "proliferative endarteritis" fetal stem arteries, often with a pronounced aspect of lesions is found in approximately one quarter of cases, but no alterations were found in placental vessels to be considered as a manifestation of classic diabetic angiopathy.

Discussions

Data analysis confirms the results of other studies in which pregnancies associated with diabetes are at increased risk of maternal and fetal morbidity, a high index of macrosomia, fetal trauma, of dystocia, but biological and neonatal disorders - hypocalcemia, hyperbilirubinemia, hypoglycemia, syndrome respiratory distress syndrome, neurological or congenital anomalies.

Relatively small number of cases does not allow drawing valid results on congenital anomalies. Ano-

ther feature is the relatively low index of diabetes in the study population compared with literature data.

Histopathological analysis of the placental alterations confirmed literature data, as described a complex of anomalies.

Diabetic placenta typically presents an increased villous area, as well as an increased capillary surface and the vilos capillary basement membrane thickness significantly decreased - morphological changes that were considered to facilitate the transfer of oxygen through the placenta[22,23]. Increase in diabetic placental capillary bed is delivered as a result of marked longitudinal capillary growth[24].

Ultrastructural alterations

There are contradictory results with electron microscopy studies conducted so far from those recorded in optical microscopy[25,26,27].

Aspects of electron-microscopy showed mainly an increase of number of cytotrophoblastic cells, particularly of intermediate type with frequent mitoses, small diffuse foci of syncytial necrosis, an increased number of secretory vesicles, mitochondria and Golgi corpuscles in syncitiotrophoblast and a thickening of the trophoblastic basal membrane. Picnotic vesicles were observed with increased frequency and the rough endoplasmic reticulum is dilated. Syncitial surface microvilli have a normal aspect and density. According to other studies microvilli presented an increased density in the free surface of syncitiotrophoblast[28,29].

The relationship of placental abnormalities and the metabolic control

Placental changes apparently are not related to the severity of maternal diabetes, but it seems linked to the metabolic control[20].

There has been demonstrated so far no influence of metabolic control on placental alterations[19]. The literature data has not found until now significant differences between groups of placental histological alterations with a good periconceptional control of diabetes than those without control. Similar changes were found, the same alterations both in insulin tightly controlled pregnancies to alterations observed in previous pregnancies with poor metabolic control.

Pathogenesis of placental deterioration

Although the spectrum of abnormalities together show a characteristic pattern, however none of the anomalies found in the placenta of diabetic patients is not specific in any way to diabetes.

Placental alterations are not different in macrosomic fetuses than those with normal weight in patients with diabetes[30].

It was suggested that the placenta undergoes hypoxic alterations in maternal diabetes either as a result of a reduced uteroplacental blood flow, either due to a decrease of intervillous space due to large hypertrophic villi[31].

Syncytial necrosis seems not to be the result of uteroplacental ischemia because decidual maternal arteries are morphologically normal in diabetic pregnancies, except hypertensive disorders.

There is a normal conversion of spiral arteries into uteroplacental vessels[32,33]. Doppler studies have confirmed this.

Another explanation for the placental focal necrosis is the oxidative stress[30,31], knowing the role on the pathogenesis of diabetic complications in both in adults and during pregnancy.

Excessive prominence of cytotrophoblastic cells in diabetic placenta seems to be mainly the result of lack of cytotrophoblastic regression, which is one of the features of villous immaturity.

The cytotrophoblastic hyperplasia aspects observed in electron microscopy, especially in intermediate type with higher mitotic activity, occurs in reaction to syncytial necrosis, being a phenomenon of repair of damaged syncitiotrophoblast where cytotrophoblastic cells plays the role of stem cells for syncitiotrophoblast.

Functional significance of placental deterioration

Until now was not demonstrated an alteration of placental transfer function, morphological markers of trophoblast function were found at a normal level. Dilated rough endoplasmic reticulum and increased secretory intracytoplasmatic vesicles show increased secretory activity and synthesis. Normal appearance of syncytial microvili, with increased density, increasing pinocitose vesicles and increased area for maternal fetal exchange shows a placental transfer function at least maintained or often increased.

That children of mothers with diabetes generally have significantly greater weight is due mainly to stimulating influences of fetal hyperinsulinaemia and of other endocrine factors involved in regulating of fetal growth and development. Therefore it is unlikely that adverse effects on the fetus should be assigned only to placental dysfunction.

Long-term effects of diabetes

The importance of systematic screening for diabetes is that mothers who had gestational diabetes are at increased risk of developing diabetes later in life (20-80%) (Wein P, et al 1992 GM Egeland, 2001), and increased risk for development of the metabolic syndrome. This syndrome is commonly associated with type 2 diabetes and cardiovascular complications later in life. And the baby of diabetic mothers as epidemiological studies of Baker (1989) is an inverse relationship between birth weight and adult CVD mortality.

Is demonstrated in children of mothers with diabetes an increased risk for several diseases: IGT, diabetes,

obesity and a decreased in neurobehavioral capacity and adiposity in childhood is strongly correlated with juvenile hypertension.

Conclusions

Diabetes and obesity during pregnancy are strongly correlated with important maternofetal complications.

The short term complications there is a high risk for perinatal mortality, metabolic, respiratory and hematological complications, fetal trauma at birth, as well as intrauterine growth disorders, an increased cesarean index, and a lower Apgar score.

Although uteroplacental unit disorder plays a key role in diabetic pregnancies, and taken together, the spectrum of abnormalities suggest a characteristic pattern, however none of placental alterations alone is not specific to diabetes.

Therefore, further investigation is needed (the study of oxidative stress, endothelial disorders, vascular endothelial factors VEGF and their receptor expression, molecular disorders etc.) to highlight the role of other factors involved in placental complex disorders in diabetic pregnancies.

An early diagnosis and active screening strategy may allow identification of pregnancies with diabetes, the metabolic control during pregnancy and a closer surveillance later in life for the risk of developing diabetes or hypertension, major cardiovascular risk factors. ■

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