

# MATERNAL COMPLICATIONS OF PREGNANCY IN DIABETES

**Alin Albai<sup>1</sup>, Bogdan Timar<sup>1</sup>, Romulus Timar<sup>1</sup>, Viorel Serban<sup>1</sup>, Adrian Vlad<sup>1</sup>, Mihaela Rosu<sup>1</sup>, Alexandra Sima<sup>1</sup>, Oana Sdic<sup>2</sup>, Cristina Ilie<sup>2</sup>**

## REZUMAT

La o femeie cu diabet zaharat (DZ), sarcina constituie un important factor de risc atât pentru mamă, cât și pentru făt. Menținerea normoglicemiei pe toată durata organogenezei și, în mod ideal, pe toată durata sarcinii, îmbunătățește prognosticul materno-fetal. Posibilitatea apariției, pe parcursul sarcinii, a complicațiilor acute specifice DZ precum și a agravării sau a inițierii complicațiilor cronice, impune o atentă monitorizare a gravidei pe toată durata acesteia. Rata hipoglicemiilor moderate sau severe este de 3 ori mai crescută în timpul sarcinii, față de perioada de dinaintea acesteia. În timpul sarcinii, CAD apare mai frecvent la gravidele cu DZ tip 1, dar este posibilă și în DZ tip 2 sau în diabetul zaharat gestational. Retinopatia diabetică este o complicație microangiopată a DZ, gravitatea acesteia constând în pericolul cecității. Prezența bolii coronariene la gravida diabetică se caracterizează printr-un risc matern crescut. Neuropatia diabetică poate manifesta, pentru prima oară, în sarcină sau se poate agrava, dacă a fost prezentă, din perioada preconcepției. Prevalența hipertensiunii arteriale este de 15-20% în sarcinile complicate cu DZ, respectiv de 5-7% în sarcinile normale.

**Cuvinte cheie:** diabet zaharat, hipoglicemie, cetoacidoza diabetică, retinopatie, boala coronariană

## ABSTRACT

Pregnancy for a woman with diabetes is an important risk for both mother and fetus. Keeping normoglycemia throughout organogenesis and, ideally, throughout pregnancy, improves the maternal-fetal prognosis. The rate of moderate or severe hypoglycemia, is three times higher during pregnancy compared to the previous period. During pregnancy, diabetic ketoacidosis is more common in women with type 1 diabetes, but it is also possible in type 2 diabetes or gestational diabetes. Diabetic retinopathy is a complication of microangiopathy in diabetes, its severity representing an important danger. The presence of coronary heart disease in diabetic pregnant women is uncommon, this association is characterized by an increased maternal risk. Diabetic neuropathy can occur, for the first time in pregnancy or worsen, if it was present during preconception period. The prevalence of hypertension is between 15 and 20% in diabetic pregnancies, compared to 5-7% in non-diabetic pregnancies.

**Key Words:** diabetes mellitus, hypoglycemia, diabetic ketoacidosis, retinopathy, coronary heart disease

## MATERNAL FETAL RISK STRATIFICATION

Pregnancy for a woman with diabetes is an important risk for both mother and fetus. The first classification of diabetes association was made by Priscilla White (Boston, USA), in 1949, and modified later (in 1956 and 1971), by the same author. The developed criteria are based on estimation of the maternal-fetal risk, on family planning and specific references, including termination of pregnancy, because of the possibility of aggravation of the chronic complications of diabetes, increased risk of occurrence of acute complications (eclampsia) and aggravation of fetal prognosis.<sup>1</sup>

Over time, the initial classification was successively modified by adding another criteria of severity, increasing the risk of maternal-fetal complications. Pregnancy is permitted only in the first 3 classes (A, B, C) and, possible in the 4<sup>th</sup> class.

The presence of RDP, NDC and macrovascular complications contraindicates the pregnancy, due to the possibility of worsening these complications and to the reserved fetal prognosis.

A further classification ("Prognostically Bad Signs In Pregnancy") was developed by Pedersen, finding a high fetal mortality for any class of White classification, which was associated with one of the following signs of poor prognosis:<sup>3</sup>

- Acute pyelonephritis: fever  $\geq 39^{\circ}\text{C}$ , pathological urinalysis;

- Pre-coma or ketoacidosis coma: serum bicarbonate 10-15 mEq/liter or  $\leq 10$  mEq/l;

- Toxemia gravidarum, characterized by the presence of 2 criteria: a) blood pressure (BP)  $\geq 150/100$  mm Hg, at least 5 days ahead of schedule, b) edema or weight gain  $> 20$  kg; c) proteinuria  $\geq 300$  mg/24 hours or  $\geq 1$  g/l;

- deficiency in antenatal care of pregnant diabetic women: first gynaecological examination

<sup>1</sup> Department of Diabetology and Metabolic Disease, Victor Babes University of Medicine and Pharmacy, Timisoara, <sup>2</sup>Diabetes Clinic, Clinical Emergency County Hospital, Timisoara

Correspondence to:

Dr. Alin Albai, Diabetes Clinic, Clinical Emergency County Hospital, 10 Iosif Bulbuca Blvd, Timisoara, Tel. +40-749-276215.

Email: alin\_albai@yahoo.com

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**Table 1.** Risk stratification of diabetes pregnancy (according to White).<sup>2</sup>

Type of risk	The onset of diabetes (years)	Duration (years)	Vascular damage	Pharmacotherapy
<b>GD</b>				
<b>A1</b>	Pregnancy	Pregnancy	No	No
<b>A2</b>	Pregnancy	Pregnancy	No	Yes
<b>Preexisting DM</b>				
<b>B</b>	>20	<10	No	Yes
<b>C</b>	10-19	10-19	No	Yes
<b>D</b>	<10	20	RDN or HTA (no preeclampsia)	Yes
<b>F</b>	Any	Any	Nefropathy (proteinuria >500 mg/day)	Yes
<b>R</b>	Any	Any	RDP	Yes
<b>RF</b>	Any	Any	RDP + Nefropathy	Yes
<b>G</b>	Any	Any	Unfavorable obstetrical history	Yes
<b>H</b>	Any	Any	Ischemic heart disease	Yes
<b>T</b>	Any	Any	Kidney transplant	Yes

\*GD-gestational diabetes, DM-diabetes mellitus,HTA-Hypertension, high blood pressure,RDN- non-proliferative retinopathy, RDP –proliferative retinopathy.

examination at birth, pregnant patient with impaired intellectual or poor social status, who came to control in the last trimester of pregnancy.

## **ACUTE METABOLIC COMPLICATIONS**

### **1. Hypoglycemia**

Keeping normoglycemia throughout organogenesis and, ideally, throughout pregnancy, improves the maternal-fetal prognosis. The most important barrier to achieve this objective is the occurrence of hypoglycemia.<sup>4</sup> The rate of moderate or severe hypoglycemia, the latter requiring treatment intervention of another person, are 3 times higher during pregnancy compared to its previous period. The highest incidence is registered in the range of 8 to 16 weeks of gestation, with decreasing frequency of hypoglycemic episodes in the second, respectively, in the third trimester of pregnancy.<sup>4</sup>

Recurrent episodes of hypoglycemia lower the glycemic threshold for the development of counterregulatory hormone responses and the autonomic and neuroglucopenic symptoms. Clinically, at patients with recurrent hypoglycemia, the alarm symptoms appear later (the dwindling blood sugar), or not. Thus, the alteration of alarm symptoms

may explain in part the increased risk of severe hypoglycemia, including hypoglycemic coma during early pregnancy.<sup>5,6</sup>

Factors influencing hypoglycemia in the first trimester of pregnancy are:<sup>7,8</sup>

- Strict metabolic control, achieved most commonly by intensified insulin therapy;
- Increased sensitivity to insulin, found in the first 20 weeks of pregnancy;
- HbA1c treatment targets, more demanding during pregnancy;
- Eclamptic first trimester;
- High frequency of hypoglycemic episodes during preconception period;
- Increased demand for insulin;
- Long duration of diabetes;
- Impaired counterregulatory mechanisms;
- Reduction of insulin clearance.

Although the role of hypoglycemia in the development of embriopathy can not be excluded because of lack of clinical studies, theoretically, the most vulnerable period of organogenesis, in relation to maternal hypoglycemia, is between 4 and 6 weeks of gestation.<sup>9</sup>

### **2. Diabetic ketoacidosis**

Diabetic ketoacidosis (DKA) is an acute metabolic complication, serious for both mother and baby. It

occurs with a prevalence of 1-3% of all pregnancies associated with diabetes. During pregnancy, DKA is more common in women with type 1 diabetes, but it is also possible in type 2 diabetes or gestational diabetes (GD). It is seen more frequently in the second and third trimester of pregnancy, quarters characterized by progressive insulin resistance state. A proportion of 78-90% of episodes of DKA are recorded in this period.<sup>10</sup>

Although, maternal mortality rate in the association DKA + pregnancy is not exactly determined, because of relatively low prevalence of this complication, there are studies that range it between 5 and 15%.<sup>11</sup>

In pregnant diabetic women, DKA can develop at less elevated blood glucose values, than in non-pregnant women.

Risk of fetal death in the presence of DKA is still high, mortality can reach 50%.<sup>12</sup>

The main causes of development of DKA in diabetic pregnancy are:<sup>13</sup>

- Early eclamptic;
- Adaptative hormonal changes;
- Infections, especially of the urinary tract;
- Lack of adherence to the insulin treatment of the pregnant woman;
- Damage to the insulin pump;
- Corticosteroids and beta-sympaticomimetics used in lung maturation and to stop preterm labor;
- Diabetic gastroparesis.

A percentage of 57% of cases of DKA have as precipitating factor vomiting and beta-sympathetic medications.<sup>14</sup>

Fetal mortality depends on metabolic decompensation and the severity of maternal complications. Although, in many cases, the causes for losing the pregnancy during the mother's DKA remain unclear in present, there have been incriminated:<sup>15,16</sup>

- Fetal hypoxia occurring due to reducing blood flow to the placenta sector;
- Reduction of fetal myocardial contractility and/or cardiac arrhythmias, hypokalemia consequences of maternal and/or fetal hyperinsulinism;
- Moving to the left of the oxyhemoglobin dissociation curve, due to reduced diphosphoglycerate, resulting in decreased release oxygen to fetal tissues.<sup>2,3</sup>

## **CHRONIC DEGENERATIVE COMPLICATIONS**

### **1. Diabetic retinopathy**

Diabetic retinopathy (DR) is a complication of microangiopathia in diabetes, its severity representing an important danger. Pregnancy is a major risk factor

in its development and progression. Thus, pregnancy in a diabetic patient may worsen preexisting DR or even favor the de novo microvascular abnormalities. Most proliferative DR progresses result in impaired vision. In such situations, it is necessary to apply laser photocoagulation treatment, even during pregnancy, which may allow further course of pregnancy, until the fetus is compatible with viability. Postpartum and in most situations, DR is reversible, partially or to the initial state.<sup>17</sup>

Regarding the DR evolution during pregnancy, the literature data are contradictory. According to numerous studies, 16-85% of retinopathy progress during pregnancy. In the progression of DR are involved the following factors:<sup>18,19</sup>

- Non-modifiable risk factors: diabetes duration, severity of retinopathy at the onset of pregnancy and poor metabolic control before pregnancy;
- Modifiable risk factors: preexisting or induced hypertension, a strict glycemic control with repeated episodes of hypoglycemia, anemia.

Thus, a first possible mechanism is the quality of glycemic control. Placental hormones, insulin-like growth hormone 1 (IGF-1) and angiogenic factors isolated from the vitreous of patients with proliferative DR, appear to play an important role in exacerbating the retinopathy.<sup>20,21</sup>

HLP activity that mimics the action of growth hormone could, theoretically, be involved in the progression or occurrence of retinal vascular lesions. Vascular changes caused by high concentrations of estrogen and progesterone during pregnancy may also contribute to worsening the retinopathy.<sup>22,23</sup>

Both progesterone and IGF-1 are involved in the release of VEGF (vascular endothelial growth factor), in the retinal vascular endothelium, its role in promoting angiogenesis being well established. High concentrations of VEGF lead to the occurrence of neoformation vessels and increased vacular permeability.<sup>24,25</sup>

Cardiovascular and hemodynamic changes seen in pregnancy are also implicated in the retinal vascular damage. Thus, increased cardiac output and total blood volume, and reduce peripheral vascular resistance, play important roles in the exacerbation of DR.<sup>26</sup>

Hypertension, preexisting or pregnancy-induced, is associated with worsening retinopathy.

Also, the high blood pressure during labor may cause retinal bleeding in women with pre-existing retinal lesions.

### **2. Diabetic nephropathy**

Medical advances made in various areas (diabetes, obstetrics, gynaecology, neonatology) and widespread

use of different classes of antihypertensive drugs, have helped improve the final results of complicated tasks with diabetic nephropathy (DN). It may be present before or it may manifest, for the first time in pregnancy, complicating currently 5-10% of all pregnancies.<sup>27</sup>

Normal pregnancy is characterized by an increased glomerular filtration rate (GFR), decreased serum creatinine values and mildly increased values of albuminuria. GFR can double in the first 18 weeks of gestation, and creatinine values ( $< 71 \text{ mmol/l}$  [ $0.8 \text{ mg/dL}$ ]) tend to be lower than in the absence of pregnancy. Pregnant women with diabetes who haven't had DN during the preconception period may develop an increase in albuminuria. In the presence of microalbuminuria (30-300 mg/24 hours) or proteinuria of 190-499 mg/24 hours at the onset of pregnancy, they may worsen transiently, spontaneously returning to baseline values postpartum. Macroalbuminuria ( $> 300 \text{ mg/24 hours}$ ) or proteinuria  $> 500 \text{ mg/24 hours}$  after the onset of pregnancy, can result in impaired renal function in 20% of cases when it is initially preserved. Pregnancy in a patient with already impaired renal function can cause a further deterioration in 30-40% of cases.<sup>28,29</sup>

In the presence of DN, fetal mortality and morbidity are affected because of:<sup>30</sup>

- Increased risk of the mother to develop hypertensive complications;
- Increased risk of premature birth, due to the development of preeclampsia;
- Placental dysfunction, causing delay in fetal intrauterine growth.

Pregnancy outcome is influenced by the degree of renal impairment, the presence or absence of hypertension and the severity of proteinuria. Thus, the obstetric outcome of the fetus, and of the renal function in long-term, is favorable, in the absence of hypertension, and if proteinuria is less than 1g/24 hours and creatinine below 120 micromol/L, from preconception and during the first 20 weeks of pregnancy.

### 3. Coronary heart disease

The presence of coronary heart disease (CHD) in diabetic pregnant women is uncommon, this association is characterized by an increased maternal risk. Before conception, all patients with long-term diabetes or symptoms suggestive of CHD, require cardiological consultation.

In women with CHD, the cardiovascular changes during pregnancy and the birth itself cause an increase in myocardial oxygen requirements. Factors such as increased cardiac output (30-50%  $\uparrow$ ), increased total blood volume ( $\uparrow$  40-50%) and heart rate ( $\uparrow$  10 b/

min), reduced BP ( $\downarrow$  10 mm Hg) and systemic vascular resistance, increased venous return during uterine contractions and bleeding during birth, may favor myocardial infarction and heart failure, because the myocardial oxygen intake does not meet its needs.<sup>32</sup>

Myocardial lesions and the risk of pulmonary edema in diabetic pregnancies complicated by CHD, are most common during the first 12 weeks postpartum. During this period, cardiovascular hemodynamic changes return to baseline. Immediately after natural birth, there is a 60-80% increase in cardiac output due to removing the obstacle of vena-cava system.<sup>33</sup>

### 4. Diabetic neuropathy

Diabetic neuropathy (DNE) is characterized by a broad spectrum of clinical manifestations. Their development in the cardiovascular, digestive and urogenital tract, impairing sweating and early warning symptoms of hypoglycemia, may complicate the pregnancy's therapeutic attitude. Many of these symptoms are changes characteristic of pregnancy, and so DNE can be unnoticed by the physician. It can occur, for the first time in pregnancy or worsen, if it was present during preconception period. Thus, these complications must be identified, evaluated and treated, even from this period.<sup>34</sup>

## HYPERTENSION IN PREGNANCY

High blood pressure (hypertension) complicates, in general, one of 10 pregnancies, being more common in the group of pregnant women with DM. The prevalence of hypertension is 15-20% in diabetic pregnancies, respectively 5-7% in normal pregnancies. The prevalence of preeclampsia in type 1 diabetic pregnancies, but with normal values of albuminuria, is 6-10%, increasing to 42% in cases of pregnant women with microalbuminuria, respectively, to 64% for macroalbuminuria.<sup>35</sup>

Pregnancy outcome is influenced by the presence of preeclampsia or chronic hypertension. Thus, preeclampsia predisposes the mother to develop the following complications: abruptio placentae, cerebral hemorrhage, disseminated intravascular coagulation, maternal death. Pregnancies associated with diabetic chronic hypertension have an increased risk of preeclampsia, miscarriage, intrauterine death and premature birth.

The following factors were associated with an adverse prognosis in pregnancies complicated by diabetes and preeclampsia:<sup>37</sup>

- SBP  $\geq 160 \text{ mm Hg}$  or DBP  $\geq 110 \text{ mmHg}$ ;
- Proteinuria  $> 500 \text{ mg/24 hours}$ ;
- Acute pulmonary edema;

**Table 2.** Classification of hypertension in pregnancy.<sup>35,36</sup>

<b>BP Type</b>	<b>Diagnosis criteria</b>
<b>Chronic BP</b>	SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg, before pregnancy or in the first 20 weeks of pregnancy <b>or</b> HBP discovered for the first time in pregnancy, with remaining high values after birth.
<b>BP induced by pregnancy (transient)</b>	SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg, discovered for first time after 20 weeks of pregnancy <b>and</b> Normalization of BP after 12 weeks postpartum <b>and</b> Absence of proteinuria or other signs of preeclampsia. <i>*Persistent hypertension after 12 weeks - chronic BP (diagnosis was established retrospectively)</i>
<b>Preeclampsia</b>	SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg + proteinuria ( $>$ 300 mg/24 hours) + edema, after the 20th week of pregnancy.
<b>Chronic BP with superimposed preeclampsia</b>	Chronic BP + proteinuria ( $>$ 300 mg/24 hours) after the 20th week of pregnancy + edema <b>or</b> Increase over 15% of BP in women with ND. in the first 20 weeks of pregnancy <b>or</b> Worsening proteinuria and/or thrombocytopenia ( $<$ 100000/mm <sup>3</sup> ) and/or hepatocytolitic syndrome.

\*According to some authors. BP values  $\geq$ 135/85 mmHg in diabetic pregnant women are employed in the diagnosis of hypertension; \*\*BP-blood pressure, SBP-systolic blood pressure, DBP-diastolic blood pressure.

- Eclampsia;
- Disseminated intravascular coagulation thrombocytopenia ( $<$ 100000/mm<sup>3</sup>);
- Hepatocytolysis syndrome;
- Oligohydroamnios;
- Intrauterine fetal growth retardation.

## CONCLUSION

During pregnancy of diabetic women there is a significant possibility that acute, specific diabetes complications appear and also that chronic complications progress or develop. Thus, careful monitoring of diabetic pregnancy is mandatory for its entire duration.

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