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THE INFLUENCE OF HYPERGLYCEMIA ON THE OUTCOME OF DIABETIC PREGNANCIES

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Abstract

At the beginning of the last century, the association between diabetes mellitus and pregnancy was credited with a high risk of complications and mortality. However, nowadays, such issue no longer bears such a pessimistic approach. Planning the pregnancy during a period of optimal metabolic control and careful monitoring of the pregnant woman significantly reduces maternal and fetal mortality. The most important aspects of fetal pathology are: intrauterine fetal death, congenital malformations, growing disorders (macrosomia or delays in growing), neonatal hypoglycemia, respiratory distress syndrome, hypertrophic cardiomyopathy etc. The fetus's viability is significantly impacted if a quality maternal glycemic control is not obtained at least 3 months prior to birth, as well as throughout the entire pregnancy term (particularly during the first 10 weeks, term during which organogenesis is completed). This systematic review of scientific literature aims to summarize the pathogenic ways in which hyperglycemia may influence the fetus of women with Diabetes Mellitus.

key words: *pregnancy, diabetes mellitus, intrauterine fetal death, congenital malformations, growing disorders.*

Introduction

Before the discovery of insulin, the association between Diabetes Mellitus (DM) and pregnancy was a clinical scarcity as this leaded to a pregnancy with high maternal or fetal mortality and morbidity risk.

Although maternal mortality and morbidity have decreased, they are still quite high in the fetus of the diabetic pregnant woman, which classifies the pregnancy as a high fetal risk. An unsatisfactory glycemic control, particularly within the first 10 weeks of progress of the pregnancy, when organogenesis is completed, will increase the congenital malformations, as well as the miscarriages. Therefore, the presence of hyperglycemia, during the first quarter of the pregnancy, leads to a tripling of fetal

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malformations and a 4 to 8 times multiplication of the risk of miscarriage [1]. The most frequent congenital malformations, associated to the pregnancy of DM women, are those in central nervous system, the heart and the kidney. That is why pregnant women suffering from DM must be notified by the physician, ever since their first appointment, on the possibility of running such major risk involved by an unplanned pregnancy [2].

Maternal hyperglycemia and secondary fetal hyperinsulinism, encountered during the last quarter of the pregnancy, is associated with: fetal macrosomia, delay in pulmonary maturity, fetal hypoxia, respiratory distress syndrome, neonatal hypoglycemia, fetal traumas during birth, hyperbilirubinemia, polycythemia, hypocalcaemia. The risk of congenital malformations in such form of diabetes mellitus is similar to that of pregnant women with normal glucose tolerance. Children with a larger birth weight hold a higher risk of developing further on, during childhood or in their teen years, a metabolic syndrome, obesity or DM [3].

Pathogenesis of fetal complications

Pathogenic mechanisms liable for the negative denouement of complicated pregnancies with DM are not fully known. Studies performed on laboratory animal subjects have led to the assumption that maternal hyperglycemia is the main teratogen agent during pregnancy, along with other maternal teratogen factors often involved, such as ketosis and severe hypoglycemia episodes. The major teratogen processes of the embryo tissue, identified up to this time, include alteration of the metabolism of inositol, arachidonic acid, prostaglandins, folic acid and reactive oxygen species [4,5].

Hyperglycemia leads to a reduction in the expression of glucose carrier genes, GLUT 1, GLUT 2 and GLUT 3, leading to a reduction in the carrying glucose to the embryo and a decrease in the free intra-embryo glucose as these mechanisms act as signals of cellular death. Acceleration of apoptosis, during this stage of the embryogenesis, is responsible for the further development of congenital malformations and miscarriages, encountered in pregnancies of diabetic women [6,7].

Experimental studies suggest that diabetic embryopathy may be caused by cellular destruction, occurred following the overproduction of reactive oxygen species and/or a decrease in the anti-oxidizer defense mechanism in the embryo cells. Alteration of this balance by the hyperglycemia may cause accelerated apoptosis, as well as a faulty embryo development [8].

Moreover, some studies have demonstrated the significant role played by free radicals in the functioning of the placenta. Oxidative destructions of trophoblastic cells, occurred during the early stages, at pregnancy or at the level of the placenta, during the time of maternal circulation stabilization, may lead to miscarriage [9]. The first proof, quite undisputable, of the involvement of oxidative stress in the diabetic embryopathy pathogenesis was the demonstration of the fact that treatment by anti-oxidizing agents normalized, on a large scale, the rate of *in vitro* and *in vivo* malformations.

High glucose *in vitro* concentrations lead to a decrease in the embryo inositol production, due to inadequate take-over, thereby leading to an embryonic inositol deficiency, simultaneous with an increased rate of embryonic dysmorphogenesis [10,11].

Alteration of the metabolism of arachidonic acid and prostaglandins is also involved in the pathogenesis of congenital malformations. Intraperitoneal arachidonic acid injections, in pregnant diabetic rats, have diminished the rate

of neural tube destruction. Similar results were obtained by supplementing the diet of rats with arachidonic acid and its addition into the growth environment blocked the embryonic dysmorphogenesis, induced by hyperglycemia [12].

The risk of congenital malformations, including the flaws of the neural tube in the case of diabetic pregnancies, has increased by 2 to 5 times, compared to normal, non-diabetic pregnancies. In the United States, diet improvement by using folic acid, at the end of the '90s, coincided with the reduction in the occurrence of neural tube flaws, from 37.8 to 30.5 every 100,000 births, i.e. a reduction of around 20%. The acid folic treatment increased its concentration, at embryo level, and reduced, almost completely, the dysmorphogenesis induced by hyperglycemia [13].

Fetal mortality and morbidity

The most important complications of the conception product are: miscarriage, congenital malformations, perinatal mortality, growth disorders, respiratory distress syndrome, diabetic cardiomyopathy, neonatal hypoglycemia, hyperbilirubinemia, calcium and magnesium disorders, polycythemia, the potential for diabetes transmission etc.

During the last decades, a better understanding of the importance of glycemic control and pre-conception planning has led to a reduction in perinatal mortality rates and diabetic pregnancies. *Miscarriage* complicates between 15% and 30% of diabetic pregnancies and it is defined by the spontaneous loss of the pregnancy before the 20th week of gestation [14]. In the event of an optimal glycemic control, its rate is no different to that of the general population, but it is however correlated with the long term of DM, with unsatisfactory glycemic control and with the presence of microangiopathic complications. The rate of miscarriages is more reduced in pregnant women having pursued an adequate pre-conception program, within specialized centers [15].

Perinatal mortality contains unexplained intrauterine fetal death and death at birth. *Unexplained intrauterine fetal death* most frequently occurs after week 36 of gestation and is favored by: diabetic micro-angiopathy, unsatisfactory glycemic control, fetal macrosomia and pre-eclampsia. *Death at birth* is defined as intrauterine fetal death installed after 20 weeks of gestation, in the United States, after 22 weeks in France, after 24 weeks in the UK and Denmark, and after 28 weeks in Sweden. In contrast, the World Health Organization (WHO) recommended that such definition be based more likely on fetal weight (≥ 500 g) than on gestational age [16].

The real reasons of fetal death remain however unclear. The most frequent causes incriminated are: hypoxia and fetal acidosis, decrease in the placenta blood flow and hypokalemia, liable for the occurrence of tachyarrhythmia.

The rate of perinatal death in complicated pre-gestational DM pregnancies has dramatically decreased during the last 3 decades, from 250 every 1000 births to 20 every 1000 births. However, recent pre-population studies performed by the UK, Denmark, France, the Netherlands and the USA have discovered that it stays at 2.5 – 9 times higher than that in the general population.

Fetal malformations are liable of up to 50% of perinatal deaths. The prevalence of malformations within complicated diabetic pregnancies is strictly related to the precarious quality of glycemic control (HbA1c), to the duration of DM and the increased maternal risk. The total prevalence of anomalies within

diabetic pregnancies is of 6.7%, compared to 2% within the general population.

Although congenital malformations contain a wide spectrum, some tend to be more frequently encountered within the complicated pregnancies with DM. The highest prevalence is held by the caudal dysplasia syndrome, whose risk is 200-400 times higher, compared to the general population. Other malformations frequently found are those of the central nervous system, the cardiovascular, urogenital and gastrointestinal system (Table 1).

Table 1. Major congenital malformations detected in children of women with diabetes mellitus (adapted from the National Collaborating Centre for Women's and Children's Health) [17]

Type of malformations	Specific malformations	Prevalence (every 100 births)	Relative risk compared to that of pregnant women without diabetes
Cardiovascular system	Transposition of large vessels Ventricular septal flaw Coarctation of the aorta Asymmetric septal hypertrophy	3 – 10	3 – 5
Caudal regression syndrome		0.2 – 0.5	200 – 400
Central nervous system	Neural tube flaws (including anencephaly) Microcephaly Isolated hydrocephaly	2.1	2 – 10
Digestive tube	Duodenal atresia Anorectal atresia Esophagus atresia Hypoplastic colon	1	3
Muscular-skeletal system	Varus equin Arthrogryposis	0.8 – 2.4	2 – 20
Orofacial clefts		1.8	1.5
Urinary tract	Ureteral duplication Poly-cystic kidney Renal dysgenesis Hydronephrosis	1.7 - 3	2 - 5

Fetal growth disorders encountered in pregnancies of women suffering from diabetes mellitus are *fetal macrosomia* and *delays in the growth of the fetus.*

Fetal macrosomia is defined as weight at birth in excess of 4000 g, without considering the gestational age or, more specifically, when reference is made to same, with a weight ranging beyond the percentile 90.

Macrosomia increases the risk of *fetus traumas* during birth (shoulder dystocia with brachial paralysis, broken collarbone), delays in pulmonary maturity with a risk of fetal asphyxiation, neonatal hypoglycemia, hyperbilirubinemia, hypocalcaemia, polycythemia, obesity and metabolic syndrome during childhood or later on.

Such complications may be prevented by: obtaining and maintaining throughout the entire pregnancy of an optimal glycemic control, the timely tracing of macrosomic fetuses by ultrasound, caesarian birth of macrosomic fetuses, in order to reduce obstetrical risks and asphyxia.

Fetal macrosomia is the most frequent diabetic fetopathy and its prevalence stands at 15-45% within complicated diabetes mellitus pregnancies [17].

Maternal hyperglycemia holds the main part in the fetal macrosomia pathogenesis. Therefore, it leads to consecutive fetal hyperglycemia, whose consequence is the exaggeration of insulin secretion, with fetal hyperinsulinism. Along with glucose, ramified amino-acids,

triglycerides and free fatty acids stimulate the fetal insulin secretion. The anabolic effect of insulin determines stimulation of lipogenesis and protein synthesis, as well as the increase in peripheral takeover of glucose and gluconeogenesis. The fetal hyperinsulinic status is accompanied by splenomegaly. The most interested organs being the following: heart, pancreatic tissue, liver, fatty tissue, spleen [16,17].

Fetal hyperinsulinemia may alter the surfactant synthesis, the protein synthesized by the type 2 pneumocytes, therefore being involved in delaying the development of the fetal respiratory system. Clinical manifestation is that of acute respiratory failure. Chronic hypoxia, encountered during the gestation term, shall stimulate the enhancement of extra-medullary fetal erythropoiesis, thereby favoring the occurrence of polycythemia. A precarious metabolic control shall determine a rise in the share of glycolysis hemoglobin, of the total hemoglobin, with the left travel of the dissociation curve of oxyhemoglobin, thereby favoring the occurrence of chronic hypoxia [18].

Other factors involved in fetal macrosomia are: age of the mother, ethnicity, number of previous pregnancies, body mass index in the pre-conception period, the male gender of the fetus and the gestational age at birth.

The respiratory syndrome distress, by the hyaline membrane disease, is a severe complication with lethal potential, much more frequently encountered in the newborns of diabetic mothers. Its frequency is 6 times higher among diabetic pregnant women, compared to that among mothers with normal glucose tolerance, its progress being severe and thereby, death arises during the first 48 hours of life.

The causes for neonatal respiratory distress are: the precarious glycemic control throughout the entire pregnancy, the inbreathing of meconium, transitory tachypnea, hypertrophic cardiomyopathy, polycythemia and blood hyper-viscosity. They usually have a benign progress and the prognosis for the newborn is favorable.

The clinical manifestations of the respiratory distress syndrome are those of the acute respiratory failure: dyspnea, tachypnea, cyanosis, intercostal and subcostal recession. The review of blood gases is essential as they demonstrate the presence of acidosis and hypoxia [19].

Hypertrophic cardiomyopathy features the hypertrophy of the inter-ventricular septum, which may lead to a massive obstruction of the blood ejected from the left ventricle, during the systole. Its occurrence is strictly connected to the severity of the mother's metabolic imbalance and with fetal hyperinsulinism [20].

Hypoglycemia is the most frequently encountered acute metabolic complication in the newborns of women with diabetes mellitus. It is defined by a glycemia below 40 mg/dL (2.2 mmol/l), occurred during the first 12 hours of life, in the presence or absence of clinical manifestations. The prevalence of this phenomenon is around 25-40%, the glycemic control of the mother, in the second period of the pregnancy and during labor, being the main decisive factors of their occurrence [21].

The responsible mechanism was not yet clarified. The classical model, proposed by Pedersen and Freinkel, argues that maternal hyperglycemia determines fetal hyperglycemia with postpartum hyperinsulinism. Therefore, at birth, the glucose input cutoff from the mother to the newborn suffering from hyperinsulinism favors the occurrence of hypoglycemia. Other authors have suggested that it is more likely that the acute maternal hyperglycemia, at the time of birth, than chronic hyperglycemia may act as the main etiological factor determining the occurrence of neonatal hypoglycemia [22].

Neonatal *hypocalcaemia and hypomagnesemia* are correlated with the mother's glycemic control, severity of the disease and prematurity.

Hypocalcaemia, defined by a value of Ca < 7 mg%, occurs during the first 72 hours postpartum and is associated with an insufficient growth of parathyroid hormone synthesis. Its prevalence stands at 50% in complicated DM pregnancies, and that of hypomagnesemia (Mg < 1.5 mg/dL), at 38% [23].

The cause of hypomagnesemia and hypocalcaemia is not yet fully understood. It was assumed that hypomagnesemia may be due to the mother's magnesium deficits, during the pregnancy, due to the polyuria occurred in the case of a precarious glycemic control. The fetal calcium deficiency may lead to functional hypoparathyroidism, thereby leading to a neonatal hypocalcaemia, whenever the maternal calcium input, occurred by means of the feto-placenta barrier, is cut off [24].

Hyperbilirubinemia (total serum bilirubin > 12 mg/dl) is more frequently detected in newborns of diabetic mothers. It occurs early, ever since the first hours postpartum, with a prevalence of 20-25% in complicated diabetic pregnancies.

The pathogenic mechanism remains however uncertain, although numerous assumptions were set forth. Initially, prematurity was deemed to be the main cause of hyperbilirubinemia, but its intervention was dismissed. Therefore, the factors currently incriminated are: polycythemia, hemolysis, alteration of the hepatocyte function and the newborn's traumas at birth, poor maternal metabolic control [25].

Neonatal *polycythemia*, defined as a value of the venous hematocrit in excess of 65%, is usually associated with hyperbilirubinemia. The potential favoring factors for its occurrence are: uterine hypoxemia stimulating the increase in the production of erythropoietin, the alteration of the uterus-placenta blood flow [26].

Conclusions

Even though maternal mortality has been reduced, prenatal fetus morbidity and mortality continue to remain at a high level in the pregnancy of diabetic women, which makes it further a pregnancy with high fetal risk, in the case of an unsatisfactory glycemic control, leading to a compromised fetal vitality and a high risk of congenital malformations.

The necessary measures for improving the prognosis of the pregnancy associated with diabetes mellitus are: education of all female patients with potential to procreate, starting from puberty, in relation to the implications of a pregnancy, the need for an optimal glycemic control, ever since the pre-conception period, as well as the possibilities of using contraceptive methods, the planning and monitoring of pregnancy installation in a period of excellent metabolic balance, the performance, at earliest of times, of a first post-conception examination with the diabetologist, maintaining a normal glycemic level throughout the entire term of the organogenesis and, ideally, throughout the entire term of the pregnancy and adherence of the pregnant women to the treatment.

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