GESTATIONAL DIABETES MELLITUS AND THE DEVELOPMENT OF CLEFT LIP / PALATE IN NEWBORNS

A. Kozma¹, V. Radoi^{2,*}, R. Ursu², C.L. Bohaltea², H. Lazarescu³, S. Carniciu⁴

¹“Alessandrescu – Russescu” National Institute for Mother and Child Health - Research Department in Social Pediatrics and Obstetrics, ²“Carol Davila” University of Medicine and Pharmacy Faculty of Medicine - Medical Genetics, ³National Institute of Rehabilitation, Physical Medicine and Balneology, ⁴Center for Research, Diagnosis and Treatment in Diabetes and Metabolic Diseases Corposana, Bucharest, Romania

Abstract

Background. Several studies observed metabolic disorders in pregnancy as risk factors for birth defects, including orofacial clefts. Diabetes is associated with approx. 10% of the pregnancies, but in Romania, less than 5%. An obese and diabetic woman has 3 times more risk for an offspring with a craniofacial defect than healthy women suggesting that diabetes mellitus contributes to their pathogenesis with complex mechanisms.

Case report. We present the case of a newborn 4 days old, male with neonatal hypoglycemia, cleft lip and proportionate (symmetric) macrosomia. His mother is a 35 years old Caucasian woman with no important personal risk factors and no known history of diabetes mellitus. The glucose tolerance test performed to the mother at about 10 weeks during pregnancy led to the diagnosis of gestational diabetes.

Discussion. The gestational diabetes mellitus diagnosed since the 10th week of pregnancy, the hyperglycemia status during pregnancy and the fetal overgrowth (macrosomia at birth) indicate the possible factors that lead to the Orofacial cleft (OFC).

Conclusion. With the increased prevalence of obesity, diabetes, and the evidence of association of these syndromes with OFCs, it is recommended that mothers planning to become pregnant to follow healthy habits, maintain healthy weight, and be screened for possible diabetes prior to conception and early in pregnancy.

Key words: orofacial cleft, gestational diabetes mellitus, GDM, birth defect, diabetes, teratogenesis.

INTRODUCTION

In the opinion of World Health Organization (WHO), there is an increase in prevalence of metabolic diseases, including obesity, metabolic syndrome and diabetes (1). Several studies observed these metabolic

disorders as risk factors for birth defects in women if diagnosed before or during pregnancy (2-4).

Several risk factors have been reported to be involved in the development of birth defects, amongst these being genetic anomalies. Genetic mistakes during gamete-genesis are known to be the cause of numerous birth defects and congenital malformations (5). While genetic alterations produced before fertilization account for more than 40% of all birth defects, most defects produced post-fertilization are generated by teratogenic factors and have mostly proven not to be of a genetic cause (5, 6).

Etiology of orofacial clefts

Orofacial clefts (OFCs) have a multifactorial etiology due to a combination between genetic and environmental factors. Some of the most common birth defects are orofacial clefts, with an estimated incidence of 10.5 / 10000 livebirths for cleft lip with or without cleft palate and 6.4 / 10 000 for cleft palate alone (7, 8).

Orofacial clefts are defined as structural anomalies due to the abnormal maxillary development during embryogenesis. They represent a lack of continuity of the upper lips, upper alveolar ridge and palate, with a partial or complete effect upon these structures (3, 9).

The environmental factors that are involved in the risk of orofacial clefts include some behaviors during pregnancy and before pregnancy like: alcohol consumption, certain medications and smoking. Supplement intake, eating behavior and their environmental factors including maternal nutritional status (4, 10, 11), diabetes mellitus (3, 8, 12) and others have also been associated with the incidence of OFCs (Table 1) (6-8).

Abnormalities can occur at any level of the genetic material (Table 1). Up to 6% of all birth defects

*Correspondence to: Viorica Radoi - “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania, E-mail: viorica.radoi@yahoo.com

Table 1. Orofacial cleft risk factors (5-7,9,13). Causes for orofacial cleft

Genetic factors	Environmental and teratogenic factors	Maternal risk factors
Single gene mutations (IRF6, VAX1, FGFR2, BMP4)	Occupational	Alcoholism
Genomic locations (8q24)	Pesticides	Smoking
Chromosomal abnormalities (numerical / structural)	Chemical substances (e.g. solvents)	Drug addiction (amphetamines, steroids, illegal substances, benzodiazepines, a.o.)
Polygenic factors	Phenytoin	Folate deficiency
	Valproic Acid	Zinc deficiency
	Retinoic acid	Gestational or pregestational diabetes
		Maternal age over 40 y.o.

Figure 1. Cleft lip with or without unilateral/bilateral cleft palate (adapted from (16)).

are due to an abnormal number or structural conformation of the various chromosomes, single gene mutations occurring in approx. 7.5% and polygenic factors in up to 30% of all cases (9, 13).

Embryological development

Development of the facial structures and form occurs between the 4th and 8th weeks of gestation. During the embryological development intermaxillary segment includes the labial component, the upper jaw and a palatal component. The palatal part will be the basis for the development of the triangular primary palate and the labial component will form the philtrum of the upper lip. The intermaxillary segment and especially the maxillary prominences both play a part in the development of the definitive palate, formed by the two palatine shelves, which, by fusing together after changing their position from oblique to horizontal above the tongue, will result in the secondary palate. The triangular primary palate will fuse anteriorly with the palatine shelves, the nasal septum joining the palate by growing down towards it (6, 8, 14).

The maxillary and mandibular prominences derive from the first branchial arch, they being the origin of maxilla and mandible, amongst other structures. Apart

from the brachial arches, the frontonasal prominence, a structure that will fuse with the maxillary prominences, represents the embryological origin of the philtrum and nostrils. The development of a cleft lip is the effect of failures during this process (Fig. 1) (6, 8, 14-16).

Epidemiological data

The chance of clefting in a newborn appears more frequently if a parent, a sibling or a relative has had the defect. Orofacial clefts may cause dental problems and this can determinate complications in feeding, speech, hearing, and very possible social integration. This abnormality can be corrected by dental care, surgery, speech psychotherapy and also with psychosocial intervention (9, 16).

The prevalence of dental anomalies in children with congenital clefts is becoming more frequent and it is treated as an additional clinical marker for determining the risk of clefts. The timely and sequenced treatment of clefts in the maxillofacial area is of vital importance. Oral health is a major condition precedent for surgical and orthodontic treatment of patients with clefts. Healthy milk and permanent teeth allow for effective orthodontic and surgical treatment with maximum long-term effect (4, 17).

Figure 2. Cleft lip in the presented case - newborn of 4 days old.

Gestational diabetes mellitus and OCFs

Diabetes is associated with approx. 10% of the pregnancies, but in Romania, only under 5% (18). Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance, which starts or is recognized for the first time during pregnancy. The possibility that the intolerance could be prior to birth is not excluded. It is usually diagnosed at 24 to 28 weeks of gestation by elevated fasting plasma glucose levels on glucose tolerance testing (18). Obese women are at higher risk of developing GDM than non-obese counterparts (19, 20).

Considering that pregnancy in obese and diabetic women is 3 times more risky for an offspring with a craniofacial defect than in nonobese, nondiabetic women suggests that obesity and diabetes mellitus contribute to the pathogenesis of this type of congenital anomalies (17). In these cases the risk for birth defects associated with gestational diabetes opposite to established diabetes mellitus is less clear (15, 17, 21, 22).

Some authors consider possible diabetes affecting pregnant women even before the period of developing gestational diabetes and it is also probable that there exists a glucose intolerance before pregnancy. (17, 22).

Although it has been reported that hyperglycemia early during pregnancy has negative effects on the fetal development, the degree and severity of hyperglycemia are not necessarily correlated with the malformation per se. Factors responsible for these abnormalities have not been delineated, although evidence suggests that altered glucose levels play a role and that insulin is not teratogenic. In this respect, a significant correlation exists between the severity and duration of the mother's disease and the incidence of malformations (4-6, 21).

Preconceptional diabetes is a known risk factor for fetal congenital malformations, including oro-facial clefts (23-29). It is assumed that in the early stages of pregnancy, the harmful effect of hyperglycemia causes the more frequent occurrence of syndromes and malformations in gestational diabetes, as a direct effect

of low control or lack of control during pregnancy. Some studies show uncertainty about the association of hyperglycemia with the increased risk of malformations and syndromes occurring during pregnancy (30, 31).

The risk of congenital anomalies in children born of mothers with T1DM and T2DM (type 1 and type 2 diabetes mellitus), diagnosed before pregnancy, is 3 to 4 times higher than in offspring's of nondiabetic mothers and has been reported to be as high as 80% in the offspring of diabetics with long-standing disease (2, 32, 33). Maternal diabetes mellitus seems to be more frequently a cause for congenital malformations than gestational diabetes mellitus. Neural tube defects, cardiovascular defects and orofacial clefts are amongst the most frequent of these congenital malformations. (6, 8, 22). Orofacial clefts seem to be highly correlated with pre-pregnancy diabetes mellitus (15, 34).

In gestational diabetes mellitus, it is known that the insulin resistance that develops during pregnancy is similar to that observed in T2DM, with impaired insulin action. This is a result of postreceptor alterations involving glucose transport and intracellular metabolism in insulin-sensitive tissues (19, 35). Obesity and heredity influence the degree of insulin resistance (20).

The mechanisms underlying the effects of maternal hyperglycemia on the developing fetus may involve increased oxidative stress, epigenetic changes, hypoxia, and apoptosis. The environment influence is sustainable due to the fact that not all progeny is affected and not to the same extent. Maternal diet may influence pregnancy outcomes. Maternal diabetes through hyperglycemia or hyperinsulinaemia and possible hypoxia, that lead to high levels of advanced glycation products (7), results in DNA damage (alters embryonic transcriptional profiles and increases the variation between transcriptomic profiles as a result of altered gene regulation) (12, 14, 20).

In women with gestational diabetes, the risks for recurrence of gestational diabetes in future pregnancies and also for the progression to T2DM are elevated. Maternal postnatal testing for diabetes mellitus should be undertaken at least 6 weeks following delivery (4, 14).

CASE PRESENTATIONS

We present the case of a newborn of 4 days old, male with neonatal hypoglycemia and cleft lip (Figure 2). All the procedures were done in agreement with Helsinki Declaration, as well as the institutional ethics regulations. Written informed consent was obtained from the mother for publishing the data as well as the

photo. The patient's weight and length were 4100 g and 53 cm, respectively. These parameters diagnose the patient with proportionate (symmetric) macrosomia.

Fetal macrosomia, one of most important fetal growth disorders, is defined as "a weight at birth higher than the 90th percentile from the normal average for the gestational age, gender and race" (36, 37). This is more frequent in mothers with diabetes mellitus (pre-existing or gestational). Maternal hyperglycaemia leads to fetal hyperglycaemia, that stimulates the pancreatic β -cells and increases fetal insulin synthesis, mechanism responsible for fetal growth and the neonatal hypoglycemia mentioned before (18, 38, 39).

He is the only child of the family, his mother being a 35 years old Caucasian woman with no important personal risk factors (non-smoker, no alcohol consumption, no drug usage, overweight (BMI =28.8 kg/m²), no known history of diabetes mellitus. The heredocollateral history of the mother was with a grandmother with T2DM (20 years of syndrome, 9 treated with insulin therapy, deceased by myocardial infarction at age of 74), and 2 aunts with T2DM controlled with oral antidiabetic agents. From the personal history of the mother, there is to mention the age of menarche at 11 years old.

Two consecutive routine blood tests revealed high glucose levels and the glucose tolerance test was performed to the mother at about 10 weeks during pregnancy, and according to the criteria of gestational diabetes diagnosis, detected high glucose levels lead to a suspecting pre-existing degree of glucose intolerance, despite the overweight (not obese, that increases the risk of both diabetes and birth defects). The mother, was diagnosed with gestational diabetes, as any degree of glucose intolerance first recognized during pregnancy asks for. The values were: fasting plasma glucose à jeun – 132 mg/dL, 1-hour postprandial plasma glucose – 205 mg/dL, 2-hours postprandial plasma glucose – 178 mg/dL and HbA1c 6.53%. Other relevant blood tests were in normal ranges of values.

Cleft lip was identified through the 1st trimester ultrasound, with the indication for prenatal diagnosis. The chorionic villi cytogenetic analysis revealed a normal 46XY male karyotype.

Further genetic testing was performed, at mother's request, by using a multigene NGS (Next Generation Sequencing) panel including 17 genes associated with the development of orofacial clefts. The result of the analysis was negative for pathogenic or unknown/uncertain significance (VUS) variants.

DISCUSSION

Considering the fact that no causes were determined for the patient's cleft lip and also taking into consideration the association with hyperglycemia and the absence of any other signs or symptoms, the most probable conclusion was that the cause for the observed pathology was the undiagnosed pre-existing maternal diabetes mellitus. The gestational diabetes mellitus diagnosed since the 10th week of pregnancy, the hyperglycemia status during pregnancy and the fetal overgrowth (macrosomia at birth) indicate the possible factors that lead to the diagnosis of cleft lip.

In reproductive age women, the risk of OFC can be reduced by promoting healthy habits such as maintaining a body weight appropriate to age and height and also maintaining a balanced metabolic status. It was found that during preconception and in the first month of pregnancy, it is recommended to screen in time to detect the existence of Gestational Diabetes Mellitus. Prevention of OFC and other congenital malformations involves early control of hyperglycemia, hyperinsulinemia and other associated metabolic abnormalities.

In conclusion, it is recommended that when women start planning to become pregnant, prior to conception and early in pregnancy, to maintain healthy weight and to follow healthy habits. The screening for possible diabetes is also indicated.

The findings in all the studies mentioned before indicates needfulness of rigorous control of Diabetes Mellitus during pregnancy, including early diagnosis, management, and assessment of capillary glucose levels to decrease adverse maternal and neonatal outcomes in these women.

Children with orofacial clefts require complex and expensive surgical and medical treatments. While much research has been carried out on potential genetic and environmental causes, for the vast majority of cases the etiology remains uncertain.

Conflict of interest

The authors declare that they have no conflict of interest.

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