

Joanna Taybert

PROCREATION IN FAMILIES WITH INBORN ERROR OF METABOLISM – NEW CHALLENGES FOR MEDICAL CARE

PROBLEMY PROKREACJI W RODZINACH OBCIĄŻONYCH WRODZONĄ WADĄ METABOLIZMU – NOWE ZADANIA DLA SYSTEMU OPIEKI ZDROWIA

Consultation Unit in Screening Department
Institute of Mother and Child, Warsaw, Poland

Abstract

Several years ago genetic counseling with the estimation of the risk of the disease in the next pregnancies of the same parents was the only offer for the family with a child with an inborn error of metabolism (IEM). Nowadays diagnostics and treatment of IEM improve. So there are more and more adult patients thinking about having their own offspring. Each woman with IEM who wants to have own child needs special medical care from preconception time up to postpartum period. Depending on the type of disease, such elements as the mother's diet and medicines used for her treatment may influence the foetus and child health and development. In the opposite the growing foetus may have an influence on mother's metabolic status and on her health complications. Therefore interdisciplinary team of specialists should be involved in the health care of women with inborn errors of metabolism.

Key words: pregnancy, inborn errors of metabolism

Streszczenie

Do niedawna dla rodziców dziecka z wrodzoną wadą metabolizmu (IEM) udzielenie porady genetycznej wraz z oceną ryzyka powtórzenia się choroby u następnego dziecka tych samych rodziców było jedyną ofertą. Obecnie zwiększyła się możliwość zarówno diagnostyki, jak i możliwości leczenia, mimo, że wyleczenie jest w dalszym ciągu niemożliwe. Stąd zwiększa się liczba dorosłych pacjentów z IEM chcących mieć własne dzieci. W tych przypadkach każda kobieta z IEM od okresu przedkonceptyjnego po okres połogu wymaga specjalnej, wielospecjalistycznej opieki medycznej. Należy bowiem pamiętać, że zarówno dieta oraz leki stosowane u matki mogą mieć wpływ na zdrowie i rozwój płodu i dziecka, jak również płód może wpływać na stan metaboliczny matki i wywołanie powikłań podstawowej choroby u matki.

Dlatego też interdyscyplinarny zespół specjalistów powinien być zaangażowany w opiekę nad chcącą mieć dziecko kobietą z rodziny obciążonej występowaniem IEM.

Słowa kluczowe: ciąża, wrodzone wady metabolizmu

INTRODUCTION

Several years ago the most important question for a family with a child with an inborn error of metabolism (IEM) was to get a genetic counseling about the estimation of the risk of the disease in the next pregnancies of the same parents. Nowadays the processes of the diagnostic and treatment of patients with some IEM improved so evidently that there are more and more adult patients with IEM thinking about having their own offspring. This fact creates the need of new oriented public health organization.

Genetic counseling

Genetic counseling for the parents should be the implication of establishment of diagnosis of IEM. The risk of the disease occurrence for the next pregnancies in this couple may be different according to the mode of inheritance. The most frequent is autosomal recessive mode with the risk of 25% irrespective of sex of the baby. The risk increases up to 50% in the case of autosomal dominant disorders (e.g. some of persistent hyperinsulinemic hypoglycaemias) or X-linked disorders for male fetuses (e.g. ornithine transcarbamylase deficiency, X-linked adrenoleukodystrophy). Individual genetic counseling is needed for the mothers of the children with mitochondrial disorders with mtDNA mutations. The risk seems to be proportional to the degree of heteroplazmy particularly in ovarian cells.

Availability of mutation analysis for confirmation of diagnosis done on biochemical or enzymatic basis is important especially for X-linked disorders (especially recessive). In some of these patients the disease is caused by *de novo* mutation and the risk of repetition of the disease in this family will be equal to the one in whole population.

The genetic consultation should be offered also for adolescents/young adult patients of both sexes before planning family. Depending of mode of inheritance the risk of occurrence of the disease in children can be different in comparison with their parents.

Is the early diagnosis in foetus important?

“Should I do a prenatal diagnostics in the case of next pregnancy? Will it be helpful?” This is the often question of the mothers of the children with IEM. The talk with the geneticist should also help to answer.

From “metabolic” point of view in the particular case (disease) the question is: how early diagnosis is needed for implementing treatment. In the great number of diseases the pregnancy is the safe period for the child because of metabolic detoxification done by organism of the mother. Only in a few diseases treatment is (can be) recommended already *in utero* (e.g. methylmalonic aciduria with cobalamin C deficiency). In some of IEM diagnostic procedures and treatment should be available immediately after delivery (e.g. ammonia analysis, hemodiafiltration, accordingly) therefore the child should be born in a hospital with high grade reference. In some, metabolic analysis should be done in first days of life (e.g. aminoacidopathies) before the first symptoms

of disease occur. In others (e.g. some storage diseases, X-linked adrenoleukodystrophy) examination can be done in the next weeks or months. For these children some “prophylactic” recommendations for the time of diagnostics can be ordered.

Above mentioned pregnancies are usually safe for the mothers. An exception is the pregnancy with long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficient foetus. This pregnancy increases risk of HELLP (Hemolytic anemia; Elevated Liver enzymes; Low Platelet count) syndrome in a mother and need additional, careful observation of her liver function and blood cell count. This information about the disease should be given to the obstetrician at the early stage of the pregnancy.

Procreation of IEM patients

National screening programmes for some IEM allows to establish greater number of patients the early diagnosis and early treatment. It is very important since nowadays more and more adult patients with IEM thinking about having their own children.

The aspects of procreation are much more complicated in woman with IEM then in man, for whom the inheritance and genetic counseling are the most concerning.

The most known is the course of pregnancy in PKU woman, that led to compilation of recommendations for the woman in the procreation period taking in consideration the fact that only extremely careful dietary regimen (with regular control) in the time before and during pregnancy can support health of the child [1]. Now the European experts have elaborated the new common recommendations for diagnostics and treatment patients with phenylketonuria (unpublished yet).

In the literature there is still a limited number of data about the course of pregnancies in woman with IEM other than phenylketonuria.

There does not exist a one universal pattern of pregnancy for every IEM.

Some diseases in their course present some gynecological disturbances that seem to lead to decreased fertility. The best known is hypergonadotropic hypogonadism in classical galactosaemia [2]. In glycogen storage disease type I delayed menarche, irregular cycles and polycystic ovaries were reported, but fertility was not assessed as impaired [3].

Good metabolic control before and during pregnancy is recommended. Only increased number of clinical control and laboratory assessments in pregnancy can help to avoid deficiencies of nutritional agents or substances restricted in basal treatment. E.g. in patients with maple syrup urine disease or isovaleric aciduria during pregnancy increasing of protein requirement was showed [4, 5]. Also increasing of glucose requirement in patients with glycogen storage diseases type III or I was observed [6, own experience]. Maternal hypoglycaemia may be unfavourable for both mother and child [6].

There is still lack of sufficient experience with the influence of mother's treatment on the foetus. Some “orphan drugs” have no recommendation for use during pregnancy. But we can not expect any clinical trials in this field. Our knowledge is often based on case reports. E.g.

Laet et al in „Recommendations for the management of tyrosinaemia type 1” not excluded nitisinone therapy of the mothers during pregnancy basing on reports of three successful pregnancies course on this drug [7]. In some diseases treatment with drugs typically not recommended during pregnancy (FDA pregnancy class C) is predicted to be of less risk of complications for mother and child then treatment interruption, e.g. granulocyte colony stimulating factor in glycogen storage disease type IB patients [8].

There is only a small amount of multicentre collaborative studies on particular IEM. They are required and useful. E.g. the data collected by such study about the patients with Gaucher disease on enzymatic replacement therapy and their children showed no adverse effects of used enzyme (alglucerase or imiglucerase) on fetuses or breast-fed infants [9]. Nowadays the use of imiglucerase in pregnancy in symptomatic patients (including patients treated before conception) is approved by the European Medicines Agency and the Food and Drug Administration.

In some diseases complications may manifest not only during pregnancy but also during the peri- and postpartum period. Tanner et al observed in patients with lysinuric protein intolerance the increased risk of anemia, toxemia during pregnancy, bleeding complications during delivery and intrauterine growth retardation in their children [10]. Especially this group of patients seems to be in high risk of complications during pregnancy [10, 11]. In several others IEM the peripartum and postpartum period is the most dangerous for the mother. For some amino acids disorders (e.g. glutaric aciduria type 1, ornithine transcarbamylase deficiency) the increasing energy requirement during involution of uterus is the most hazardous time for the mother and need especially careful treatment [10, 12, 13, 14, 15, 16, 17]. Management of this period includes first of all monitoring of the mother's life functions, biochemical parameters according to disease, energy (glucose) infusions and supplementation of disease specific drugs.

We should also remember about influence of pregnancy for the mother, especially for already existing complications of her disease (e.g. adenoma in glycogen storage diseases, cardiomyopathy in glycogen storage disease type III). There is a need of individual special monitoring [3, 6].

CONCLUSIONS

Each pregnancy and delivery in a woman with IEM needs special medical attention. The prior communication among specialists about special needs for the peri- and postpartum period is very important for the success. Therefore the gynecologist should be also involved in the interdisciplinary team working together in the problem of procreation in mother with IEM.

It is to stress, that often only a careful multidisciplinary team can make the course of pregnancy safe for mother and child.

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Address for correspondence:

Taybert Joanna

Consultation Unit in Screening Department

Institute of Mother and Child, Warsaw

ul. Kasprzaka 17A, 01-211 Warszawa

tel. (+48 22) 32-77-321

e-mail: joanna.taybert@imid.med.pl