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Polyglandular Autoimmune Syndrome in pregnancy: case report.

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ABSTRACT

Type III Polyglandular Autoimmune Syndrome is a multiple endocrine disorders disease determined by autoimmunity; it can be diagnosed if a patient is affected by Type 1 Diabetes Mellitus and another autoimmune disease, except Addison Disease, for example Autoimmune Hashimoto Thyroiditis or Celiac Disease.

R.D., 34-year-old woman (gravida 2 para 1), was referred to the High Risk Pregnancy Outpatient Clinic at Cannizzaro Hospital in Catania at 8 weeks' gestation. She was affected from type III Polyglandular Autoimmune Disease (Type 1 Diabetes Mellitus, Autoimmune Hashimoto Thyroiditis and Celiac Disease). Pre-conception glycated hemoglobin and thyrotropin levels were normal. This pregnancy was characterized by glycemic instability and the need to increase the insulin units every month. The patient was hospitalized at 32+6 weeks for monitoring fetus and mother health because of inadequate glycemic control and the high insulin dosage required. She was delivered by caesarean section at 36+6 weeks because of uterine contractions, the previous cesarean section, glycemic instability and the gestational age. She delivered a baby boy, birth-weight 3300 g, Apgar 8-9. She was discharged in the fourth day after delivery with good maternal and child prognosis. Literature data and the experience derived by this case report suggest some recommendations to improve obstetrics and neonatologist outcome in the patients affected from type III Polyglandular Autoimmune Syndrome: pre-conception counseling, thyrotropin assay every 4-6 weeks, gluten-free diet, fasting and post-prandial blood glucose level targets.

Keywords: Pregnancy, Diabetes, Hashimoto, Celiac Disease, Polyglandular Autoimmune Syndrome, Management, Outcome, Counseling, Obstetrics, Neonatologist.

SOMMARIO

La Sindrome Polighiandolare Autoimmune di tipo III è un disordine endocrino multi-organo su base autoimmunitaria che può essere diagnosticato in presenza di Diabete Mellito tipo 1 ed un'altra endocrinopatia, ad eccezione della Malattia di Addison, per esempio Tiroidite di Hashimoto o Morbo Celiaco.

RD, 34 anni, G2P1, è stata presa in carico dall'ambulatorio di gravidanza a rischio dell'Ospedale Cannizzaro di Catania nel corso della 8° settimana di amenorrea. La paziente era affetta da Sindrome Polighiandolare Autoimmune di tipo III (Diabete Mellito tipo 1, Tiroidite di Hashimoto e Morbo Celiaco). I valori preconcezionali di emoglobina glicata e tireotropina erano nella norma. La gravidanza è stata caratterizzata da instabilità glicemica con necessità di aumentare il dosaggio insulinico ogni mese. La paziente è stata ricoverata a 32+6 settimane per monitoraggio materno-fetale, a causa dello scarso controllo glicemico e l'elevato dosaggio d'insulina richiesto. A 36+6 settimane è stato eseguito taglio cesareo per l'insorgenza di attività contrattile uterina in paziente già cesarizzata e con scarso controllo glicemico; neonato maschio, peso alla nascita 3300, Apgar 8-9. La paziente è stata dimessa in 4° giornata post-operatoria con buona prognosi, sia materna sia neonatale. I dati della letteratura e l'esperienza derivante da questo caso clinico suggeriscono alcune raccomandazioni per migliorare l'outcome ostetrico e neonatologico nelle pazienti affette da Sindrome Polighiandolare Autoimmune di tipo III: counseling pre-concezionale, dosaggio della tireotropina ogni 4-6 settimane, dieta aglutinata, glicemia a digiuno e post-prandiale entro i valori target.

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INTRODUCTION

Type III Polyglandular Autoimmune Syndrome (PAS III) is a multiple endocrine disorders disease determined by autoimmunity. PAS III can be diagnosed if a patient is affected by Type 1 Diabetes Mellitus (T1DM) and another autoimmune disease, except Addison Disease, for example Autoimmune Hashimoto Thyroiditis (AIT) or Celiac Disease (CD). The prevalence of APS III is 1/20000[1]. T1DM is an insulin-dependent diabetes that occurs when activated T cells attack and destroy most of the beta cells; often there are also humoral autoimmunity events (auto-antibodies). There is a genetic predisposition to T1DM, that is caused by Human Leukocyte Antigen (HLA) gene mutations but it's also necessary the influence of individual and environmental factors to determine physiopathology of diabetes 2.

The HLA gene mutations determine high individual predisposition to autoimmune disease like T1DM, AIT and CD. In fact, it's known that a person affected from T1DM has higher risk of AIT and CD, compared to healthy people[1,2].

AIT it is an autoimmune thyroiditis with anti-TPO antibodies (thyroperoxidase), anti-TG antibodies (thyroglobulin) and high serum TSH concentrations in the chronic period of disease. Treatment of AIT is based on levothyroxine sodium to normalize TSH levels[1].

CD is defined as a pertinent intolerance to dietary gluten. In 1888, Samuel Gee first described the clinical features of coeliac sprue 1. It is one of the most common genetic disorders. Its incidence in the European population ranges from 0.03 – 0.04% and the highest incidence rates are found in the countries of northern Europe: Sweden – 2.4/1,000 births, UK – 1.49/1,000. This inflammatory state leads to changes in the small bowel mucosa architecture including increased infiltration of lymphocytes into the epithelial cells, villous atrophy and crypt distortion. These intestinal changes can lead to malabsorption of macro - and micro - nutrients, resulting in symptoms of malabsorption such as weight loss and diarrhea[4]. The only treatment available is the elimination of gluten from the diet, which can lead to mucosal lesions recovery.

In patients with diabetes type 1, celiac disease has been significantly more frequently diagnosed than in the general population[3]. In patients affected by diabetes type 1, celiac disease is usually oligosymptomatic or asymptomatic and the frequency of coexistence of both disorders increases with patient's age and duration of diabetes[3]. A reverse phenomenon is also characteristic, i.e. higher prevalence of diabetes type 1 in celiac disease patients and greater frequency of diabetes-specific antibodies in this group of patients[3].

Women have higher incidence of autoimmune disease than men, with a 3:1 female/male ratio. Furthermore, the most at-risk age is between 30 and 50 years, that is a potentially fertile period of the woman's life. Hence autoimmune diseases have an important role to influence fertility and to determine the outcome of pregnancy. In fact, T1DM and autoimmune diseases increase the risk of abortion, intra-uterine growth restriction (IUGR), placental insufficiency, premature rupture of membranes, cesarean section, pre-eclampsia/eclampsia and preterm birth[4,5]. Fortunately, pregnancy often determines remission of autoimmunity, and the management of these patients is easier. In other cases, especially when pre-conception counseling and planning are inadequate, the management of pregnancy may be difficult[6]. In fact, diabetes decompensation can determine reactivation of the other autoimmune diseases in the patients affected from PAS.

We will show a case of a pregnant woman affected from T1DM, AIT and CD (mixed type III PAS) with the aim to advice a management of the case with good both obstetrics and neonatologist outcome.

CASE REPORT

R.D., 34-year-old woman (gravida 2 para 1) was referred to the High Risk Pregnancy Outpatient Clinic at Cannizzaro Hospital in Catania at 8 week's gestation. Familial medical history was positive for autoimmune disease and T1DM in her brother. She was born by a vaginal delivery and she was a macrosomic baby (birth-weight 4500 g). She had a normal range BMI (22) on admission and she suffered from Celiac disease, Hashimoto's thyroiditis medicated with levothyroxine 50 µg, and type 1 diabetes. On admission she had HbA1c within the normal range (5.9 %). She had menarche at 12 years old, and she has always regular menstrual cycle. Up to the first consultation, her obstetric history was 2G 1P. The first pregnancy was complicated by Gestational Diabetes in the third trimester, and it resulted in cesarean section for glycemic instability. She delivered a female healthy preterm baby in Ancona Hospital (36+6 weeks, birth-weight 3310 g).

Similarly this pregnancy was characterized by glycemic instability and the need to increase the

insulin units every month. Also levothyroxine raised to 75 µg because of a mild elevated TSH level (TSH 3.58 µU/ml).

She suffered from iron deficiency anemia (hemoglobin 10.8 g/dl; iron serum 39 mg/dl) probably resulting from gastrointestinal malabsorption.

Fetal monitoring is considered mandatory in such pregnancies and all the diagnostic tests and surveillance fetal health examination were regular (first trimester screening; second and third trimester ultrasounds; fetal echocardiography, fetal biometry and umbilical artery Doppler velocimetry).

The patient was hospitalized at 32+6 weeks for monitoring fetus and mother health because of inadequate glycemic control and the high insulin dosage required (Humalog 26+25+24; Lantus Solostar 36 units).

Blood pressure and routine blood examination were normal: stable hemoglobin (10.8 g/dl), low iron serum level (28 mg/dl); electrolytes and function kidneys tests within normal limits (serum sodium 137 mmol/L, potassium 3.7 mmol/L, clorum 108 mmol/L; creatinine 0.60 mg/dl and no proteinuria).

She followed a gluten-free 2000 calories diet, she had daily diabetes visits and appropriate insulin therapy modification. Strict glycemic control continued throughout the entire pregnancy and she self-monitored plasma glucose 7 times daily: fasting glucose at 8 on the morning; pre-meals and 1 H post-meals. Furthermore, there were some episodes of severe hypoglycemia in the evening and in the middle of the night.

She was delivered by Caesarean section at 36+6 weeks because of uterine contractions, the previous cesarean section, glycemic instability and the gestational age. She delivered a baby boy, birth-weight 3300 g, Apgar 8-9.

Post-operative course was regular and all laboratory examinations were in the normal range (hemoglobin 10.1 g/dl). After delivery, there was a significant increase in insulin sensitivity; so, it was necessary a reduction of the dose of insulin to approximately 50 % of the pregnancy dose: Humalog 8 UI+14 UI +10UI, Lantus 16 UI in the night; and self-monitoring of plasma glucose every two hours.

She was discharged in the fourth day after delivery and she had a moderate glycemic control.

DISCUSSION

An autoimmune disease (AID) is characterized by tissue damage, caused by self-reactivity of different effectors mechanisms of the immune system, namely antibodies and T-cells and/or environmental predisposition. There is an activation of the adaptive immune response with tissue damage and inflammation in the absence of any infection, exposure to toxins or tumor growth[1].

Type 1 diabetes is one of the most frequent endocrine disorders. Although T1DM onset was once thought to be restricted to children and adolescents, it can occur at any age, with the highest rate of incidence below the age of 30 years[3]. Approximately 50 T1DM susceptibility genes have been identified to date. These genes also carry a potential risk for various autoimmune diseases occurring simultaneously or within a narrow time interval and might explain to some extent why additional endocrine autoimmune diseases are comorbid in one third of all T1DM patients[8-12]. These associated autoimmune disorders are either glandular diseases [e.g., Addison's disease or autoimmune thyroid disease (AITD)] that lead to polyglandular autoimmune syndrome (PAS) or non-glandular autoimmune diseases (e.g., rheumatoid arthritis or celiac disease)[7].

Several linkage studies showed the importance of genetic predisposition and the association of T1D with polymorphisms in the specific HLA loci on chromosome 6p21.3 8. HLA class II loci are assumed to be responsible for 40%-50% genetic risk 8 and graded 1 as follows: the highest risk was found in DR3/4 heterozygotes, followed by DR4 homozygotes, DR3 homozygotes and DR4 heterozygotes combined with another DR allele [1].

Furthermore, many non-HLA polymorphisms that appear to make a smaller contribution to the manifestation of T1DM have been identified [1]. Nevertheless, a concordance rate lower than 50% in monozygotic twins, a manifestation of T1DM in 10% of the carriers of high-risk genes and a 15-fold difference in the disease incidence among European Caucasians indicates that genetics alone cannot explain disease onset [9]. In contrast, an increase in patients with low-risk or protective HLA genotypes emphasizes the importance of environmental factors such as viral infections, nutrition and chemicals or epigenetics, respectively[1].

PAS, characterized by a combination of at least two autoimmune endocrinopathies, can be classified into a juvenile form (PAS type I) and an adult form, which is then subdivided according to the specific constellation of autoimmune glandular diseases (PAS types II-III).

1) Type I PAS (APECED-autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy): a monogenic autoimmune syndrome caused by defects in the AIRE gene located on chromosome 21. Its major components include candidiasis of the skin and mucous membranes, hypoparathyroidism, and Addison's disease. Its inheritance exhibits an autosomal recessive pattern. PAS type 1 affects children around the age of 10-12-10.

2) Type II PAS: defined as a combination of autoimmune adrenal insufficiency with autoimmune thyroid disease and/or type 1 diabetes mellitus. It is characterized by obligatory occurrence of autoimmune Addison's disease in combination with thyroid autoimmune diseases and/or type 1 diabetes mellitus. Women are three times more likely to develop it than men[2, 3]. The prevalence of PAS II increases gradually in the first decade of life and reaches the highest values between 25-40 years of age 10.

3) Type III PAS: composed of autoimmune thyroid diseases associated with endocrinopathy other than adrenal insufficiency. It mainly affects women in their 30s. Thyroiditis usually occurs first. PAS III can be further classified into the following three subcategories:

A – Autoimmune thyroiditis with immune-mediated diabetes (T1DM) mellitus (also known as polyglandular autoimmune syndrome type 3 variant);

B – Autoimmune thyroiditis with pernicious anemia;

C – Autoimmune thyroiditis with vitiligo and/or alopecia and/or other organ-specific autoimmune disease (celiac disease, hypogonadism, and myasthenia gravis), organ-nonspecific or systemic autoimmune diseases (sarcoidosis, Sjögren syndrome, rheumatoid arthritis)[11].

PAS type III is the most frequent subtype of polyglandular autoimmune diseases 3. The co-occurrence of autoimmune-induced hypothyroidism (generally caused by chronic lymphocytic Hashimoto's thyroiditis) and T1DM is often accompanied by hypoglycemia due to increased insulin sensitivity. Hypothyroidism leads to a reduction in glucose reabsorption in the duodenum and glucose release from the liver.

Overt hyperthyroidism is accompanied in 50% of the cases by glucose intolerance and in 3% of the cases by overt diabetes. The impaired glucose tolerance is due to decreased insulin sensitivity and decreased hepatic storage of glycogen, whereas both secretion of glucagon and intestinal glucose absorption are enhanced leading to hyperglycemia 3. Onset of T1DM in patients autoimmune thyroid disease (Grave's disease and Hashimoto's thyroiditis) occurred at a mean age of 34 years in 0.78% and 1.17% of cases, respectively 3.

PAS III syndromes exhibit polygenic inheritance and are connected with the HLA system. Several gene variations present in both autoimmune thyroiditis and T1DM have been identified. The most important susceptibility genes are polymorphisms in protein tyrosine phosphatase non-receptor type 22, cytotoxic T lymphocyte antigen 4 (CTLA-4), MHC class I polypeptide-related sequence A, and HLA. Thus, the association of endocrine autoimmune diseases is primarily due to a common genetic predisposition. The HLA class II haplotypes DRB1*03-DQA1*0501-DQB1*0201 and DRB1*04-DQA1-0301-DQB1*0302 have been reported to be associated with isolated T1DM as well as with T1DM within the scope of adult PAS 3.

While a role for HLA class I-recognizing CD8 T cells has been known to affect T1DM and celiac disease, recent studies also showed a joint susceptibility for these diseases in HLA class II 3. HLA-DQ2 can be found in 90% of patients with celiac disease and in 55% of patients with T1DM, while HLA-DQ8 is present in approximately 10% and 70%, respectively [1]. In patients with HLA-DQ2-DQ8 heterozygosity, a transdimer (DQ2α/8β) binds a gliadin peptide and T1D-specific antigens, which implicates both gluten and the gut microbiome as additional factors or triggers for autoimmune [1].

We report this case of type 3 PAS since it illustrates a number of interesting points.

- Firstly, the varied clinical disease meeting the criteria for PAS IIIa and IIIc;
- Type 1 diabetes onset at adult age, after two autoimmune diseases and after the first pregnancy. So this one is the trigger point of the pancreas autoimmunity;
- Thirdly, despite significant glycemic instability with frequent episodes of hypoglycemia, anemia due to iron deficiency; there were no obstetric complications and no adverse outcomes of the fetus.

There is very little published information addressing the problem of polyglandular autoimmune syndromes but there are data on the single disorders. For example it is recognized that AIT is associated with higher rates of infertility due to anovulatory cycle, early miscarriages due to the associated hormonal changes and to the presence of anti-thyroid antibodies that may react

against the structures of the placenta or fertilized egg and cause problems in embryo implantation[7], gestational hypertension, preterm birth, small for gestational age[8].

Two main hypotheses can be made to explain the higher risk of obstetric complications in women with celiac disease. The malabsorption that characterizes celiac disease may lead to nutrient deficiencies (iron, vitamin B2), which can be associated with adverse pregnancy outcomes, specifically, IUGR, SGA, and LBW. Furthermore, women with celiac disease often show increased levels of serum auto anti-bodies, including anti-transglutaminase and anti-thyroid antibodies that have been linked to several pregnancy complications such as pre-term birth and stillbirth[12].

It's recommended a TSH assay every 4-6 weeks during pregnancy in the patients affected from AIT; goal TSH concentrations in pregnancy are 0,1-2,5 μU/ml in the first trimester, 0,2-3 μU/ml in the second trimester and 0,3-3 μU/ml in the third trimester[6].

Instead, management of T1DM in pregnancy it's already known. Particularly, it's fundamental the carbohydrate metabolism compensation in the pre-conception phase to obtain glycosylated hemoglobin (HbA1C) less than 7% or as close as possible to 6%[6]. Furthermore, diet and body mass index (BMI) are important because reduction of the weight body determines improvement of carbohydrate compensation.

In our case report, the patient get pregnant with adequate metabolic and endocrine balances after pre-conception counseling: BMI=22, HbA1C=5,9%, TSH=1,72 μU/ml and gluten-free diet. In our opinion, according to literature data, this pre-conception planning was very important in order to obtain a good outcome for both mother and child.

Hypoglycemia occurs in up to 50% of pregnancies in women with T1DM; it may occur in patient with bad insulin correction of an elevated post-prandial glucose[6]. Also hyperglycemia is a serious complication of T1DM in pregnancy because it may induce diabetic ketoacidosis (DKA). Factors that may predispose to DKA include infection, insulin omission or use of medication such as glucocorticoids (to induce fetal lung maturity)[6].

Management was difficult because of instability glucose level without recommended target (fasting 80-110 mg/dl, 1-hour post-meals 100-155 mg/dl 6) and consequent necessity to repeatedly increase insulin dose. This issue could be determined by T1DM and the other endocrine disease with altered glucose absorption and release; furthermore, insulin requirements change according to gestational age, increasing in the first 9 weeks, decreasing between 9 and 16 weeks, increasing until the 37th week and decreasing in the last weeks of pregnancy[6]. In the reported case, the patient was admitted to hospital stay during the 33th week of pregnancy because of glucose blood level instability despite the high insulin doses, to prevent eventual hypoglycemia episodes or to control them in hospital.

CONCLUSION

Type 1 diabetic patients exhibit an increased risk of other autoimmune disorders such as autoimmune thyroid and coeliac disease. So it justifies an extensive serologic and functional screening for additional autoimmune glandular and gastrointestinal diseases, because early detection of antibodies and latent organ-specific dysfunction is advocated to take appropriate action in order to prevent full-blown disease and to identify both patients at risk for developing PAS, as well as subclinical PAS that may already be present.

In clinical practice regular screening of autoantibodies is warranted because the test may later become positive.

In families with clustering of T1DM patients or in families of patients with PAS, the risk for associated autoimmune diseases and endocrine or autoimmune involvement of the first-degree relatives is significantly high. Within a few years, approximately one third of T1D patients will develop thyroid autoantibodies and thyroid dysfunction leading to PAS type III.

We should also examine gastrin, iron, and vitamin B12 levels and perform a complete blood count at yearly intervals.

This screening should also be done in patient with recurrent obstetric complications (infertility, miscarriages, preterm birth, low birth weight, gestational hypertension, preeclampsia), because an appropriate diet or therapy could prevent these complications.

The combination of insulin treatment, diet and self-monitoring of glucose levels is the cornerstone of treatment optimization in TIDM pregnant.

Pregnant patients with T1DM and/or other autoimmune disease are complex and require a multi-specialist approach before and during pregnancy which should include a diabetologist, obstetrician (perinatal specialist), neonatologist

and dietitian. This team approach can all improve pregnancy outcomes for mothers and their infants.

Literature data and the experience derived by this case report suggest some recommendations to improve obstetrics and neonatologist outcome in the patients affected from type III PAS:

- Pre-conception counseling, in order to improve body weight and to obtain pre-conception BMI, HbA1C and TSH target levels;
- TSH assay every 4-6 weeks and eventual change of levothyroxine sodium dosage;
- Gluten-free diet;
- Fasting and post-prandial blood glucose level targets.

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