folia medica

Folia Medica 62(2): 408-11
DOI: 10.3897/folmed.62.e48580

Case Report

Autoimmune Polyglandular Syndrome Type 2 and Pregnancy

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Received: 18 Nov 2019 ♦ **Accepted:** 24 Nov 2019 ♦ **Published:** 30 June 2020

Citation: Yanachkova V, Chaveeva P, Staynova R, Milcheva R. Autoimmune polyglandular syndrome type 2 and pregnancy. Folia Med (Plovdiv) 2020;62(2):408-11. doi: 10.3897/folmed.62.e48580.

Abstract

Autoimmune polyglandular syndromes are combinations of various endocrine and nonendocrine autoimmune diseases, as well as the presence of elevated organ-specific antibody titers. We present a clinical case of a 41-year-old pregnant patient with type 2 autoimmune polyglandular syndrome, combining Addison's disease, Hashimoto's thyroiditis and hypogonadism. The pregnancy was achieved after the use of assisted reproductive technology. During the pregnancy the patient was strictly monitored. Glucocorticoid and mineralocorticoid replacement therapy was adjusted according to the electrolyte profile and general condition of the patient. Management during pregnancy was difficult due to fluctuations in electrolyte levels, thyroid hormones and orthostatic manifestations. Prior to delivery adrenal crisis occurred, but the condition was successfully managed. No complications were reported for the mother and the newborn.

Keywords

Addison's disease, autoimmune polyglandular syndrome, Hashimoto's thyroiditis, pregnancy

INTRODUCTION

Autoimmune polyglandular syndromes (APS) are combinations of various endocrine and nonendocrine autoimmune diseases, as well as the presence of elevated organ-specific antibody titers. Often the term 'polyglandular' could be misleading due to the fact that some patients have many endocrine disorders and others have nonendocrine disorders.[1] Patients with one autoimmune disorder are at high risk for an expression of APS. The chance of unlocking a second autoimmune disease in these patients is between 30 and 50 times more common than in the rest of the population.[2] A quarter of the patients with an autoimmune disease will develop a second one during their lifetime.[1]

APS could occur at any age, although different types have age predilection for manifestation. There are four types of APS, but in compliance with the clinical case, a major focus will be put on the APS type 2, which is the most common syndrome.[3,4]

APS type 2 is characterized by: Addison's disease (100%) that may be associated with either autoimmune thyroid disease (Schmidt syndrome) or type 1 diabetes mellitus (Carpenter syndrome), or with both. Addison's disease and autoimmune thyroiditis are more common (70-82% of cases), whereas the combination of Addison's disease and type 1 diabetes mellitus occurs in 30-52% of cases. Non-endocrine disorders such as vitiligo, autoimmune hepatitis, gastritis, pernicious anemia and myasthenia gravis can also present. APS type 2, which is the most common syndrome (1-2:10000/year), may occur at any age in both sexes, but there is a prevalence in middle-aged women, mostly in fourth or fifth decade. The female-to-male ratio is 3:1. APS type 2 includes a heterogeneous group of moderately inherited diseases. Approximately half of the patients with APS type 2 have relatives with autoimmune diseases.[2-6]

CASE REPORT

A 41-year-old female patient diagnosed with Addison's disease, Hashimoto's thyroiditis and primary ovarian insufficiency presented in the endocrinology consulting room in February, 2018. The woman became pregnant after a sixth consecutive in vitro fertilization (IVF) procedure with a donor egg. The first endocrine pathology was established in 2002 – Hashimoto's thyroiditis, a hypothyroid phase.

*At the time of examination, the patient was on thyroid hormone replacement therapy with levothyroxine 50 μg daily. Since 2008, Addison's disease started with classical symptomatology and skin pigmentation, with established autoimmune genesis. Diagnostic tests (magnetic resonance imaging) of the pituitary and adrenal glands were performed and no pathological changes were detected. At the time of the primary examination, the patient was well compensated with prednisolone therapy (7.5 mg/daily) (***Table 1***).*

Table 1. Results of laboratory tests before IVF procedure

Test	Result	Normal range
TSH[±]	1.19 mIU/L	0.27 – 4.20 mIU/L
FT4[§]	11.8 pmol/L	9.0 – 17.0 pmol/L
Prolactin	198 mIU/L	135 – 635 mIU/L
Potassium	4.6 mmol/L	3.5 – 5.6 mmol/L
Sodium	134 mmol/L	136 – 151mmol/L
Blood glucose (fasting)	4.35 mmol/L	3.9 – 6.1 mmol/L
Creatinine	81 μmol/L	50 – 115 μmol/L
ASAT	20 U/L	0 – 40 U/L
ALAT	15 U/L	0 – 40 U/L
Protein	74 g/L	60 – 80 g/L
Albumin	46 g/L	35 – 55 g/L

[±]TSH, Thyroid-stimulating hormone; [§]FT4, Free thyroxine

Since her adolescence, the woman had an irregular menstrual cycle. Polycystic ovary syndrome is not established. Over the years, she had been treated with various hormonal medications to induce pseudomenstruation. A hyperprolactinemia was established in 2002 and was considered idiopathic. The woman was taking bromocriptine tablets for a short period of time. From the family history, the patient has a sister with Addison's disease, Hashimoto's thyroiditis – a hypothyroid phase and primary ovarian insufficiency.

The pregnancy was achieved after the use of assisted reproductive technology. During the pregnancy, the following levels were regularly tested: electrolytes, thyroid-stimulating hormone (TSH), free thyroxin (FT4), blood glucose, blood pressure and electrical activity of the heart. Up to 20 weeks' gestation, the dose of levothyroxine was adjusted smoothly. There was no need for dose adjustment of prednisolone. At 20-21 weeks gestation due to fatigue, weakness and orthostatism, some laboratory tests were performed. Sodium concentration was 133 mmol/L (136-151 mmol/L), potassium – 5.7 mmol/L (3.5-5.6 mmol/L), and blood glucose (fasting) was 3.7 mmol/L (3.9-6.1 mmol/L). Prednisolone was uptitrated to 20 mg/daily which led to normalization of electrolyte levels. At 24 weeks' gestation the levels of electrolytes were as follows: potassium 5.78 mmol/L and sodium 134 mmol/L. Fludrocortisone 0.1 mg tablets, with an excellent effect on the electrolyte levels and the arterial blood pressure, were added to the prednisolone therapy. Until the end of pregnancy, the patient continued with the treatment and electrolyte levels were monitored every 2 weeks. The fetal growth, amniotic fluid and placental function were normal for the gestational age. No structural defects or markers for chromosomal abnormalities were detected during the first trimester screening test and fetal anatomy assessment.

There was a planned cesarean section at 38 weeks' gestation. Two days before the surgery, there were sudden complaints of severe fatigue, vomiting, abdominal pain, diarrhea, fever (38.3°C) and orthositis. It was assumed that it was a case of an acute adrenal crisis. The patient was admitted for an emergency cesarean section. The results from the laboratory tests were as follows: complete blood count (CBC) – normal, potassium 5.8 mmol/L, sodium 136 mmol/L, and blood glucose – 3.7 mmol/L. Prior to the surgery, the patient was adequately hydrated with saline solution. A parenteral corticosteroid was administered, following a scheme. Once the treatment with intravenous administration of corticosteroid and fluid support started, the patient's complaints decreased. A healthy female baby was born: weight 2900 g, height 49 cm, Apgar score at birth – 8. After the delivery, the dose of prednisolone was gradually reduced to the dose, administered before the pregnancy. The treatment with fludrocortisone was discontinued.

DISCUSSION

Combined autoimmune diseases, in this case, Addison's disease, hypothyroidism, premature ovarian failure or combined hormonal deficits lead to infertility. In the rare cases of pregnancy, there is a high risk of complications. During pregnancy, maternal endocrine disorders may have an adverse effect on the developing fetus. On the other hand, the pregnancy itself may affect maternal chronic conditions.[7]

The fetoplacental unit controls the hormonal effect on the fetus and it is also responsible for the changes occurring in the maternal hypothalamic-pituitary-adrenal axis, as well as the hypothalamic-pituitary-thyroid axis.[7]

Pregnancy itself, alters the synthesis of adrenal steroids, which leads to physiological hypercortisolism. There is an increase in total and free cortisol, adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH) and corticotropin-binding globulin (CBG) levels. The placenta produces biologically active CRH and ACTH, and stimulates the maternal pituitary and adrenal glands. CBG increases 3 to 4 fold, following the increase in estrogens,

and leading to an increase in total cortisol. Elevation of free cortisol starts at 11 weeks' gestation, with preserved circadian rhythm. The activity of the renin-angiotensin-aldosterone system begins to increase after 8 weeks' gestation. Progesterone exerts an anti-mineralocorticoid effect leading to a reduction in vascular resistance. Up to 33 weeks, 90-95% of fetal cortisol is delivered from maternal adrenal production. After that period there is a progressive increase in fetal cortisol production. This is also a reason for women with Addison's disease to experience improvement in the condition in the last trimester. On the other hand, the fetus is relatively protected by the excess of the administered glucocorticoids due to the activity of the placental 11-beta-hydroxysteroid dehydrogenase.[7,8]

Similarly, under the influence of estrogens and placental hormones, there occurs a demand on the maternal thyroid to compensate the needs of both the mother and the fetus throughout the pregnancy. Hence, any endocrine disorder disturbs the fine balance of regulation, which very often leads to disturbances during pregnancy.

Addison's disease, or primary adrenal insufficiency, is a rare chronic disease characterized by glucocorticoid or mineralocorticoid deficiency. In developed countries, the most common reason for this (about 70% of all cases) is autoimmune adrenalitis.[3,8,9] Women with Addison's disease have markedly reduced fertility with multifocal genesis, especially when combined with another autoimmune disorder such as Hashimoto's disease and/or type 1 diabetes mellitus. On the other hand, adrenal insufficiency leads to the loss of androgens, which affects the fertility, libido and sexual activity. Considering this fact, pregnancies in patients with Addison's disease are rare.[3,8,9]

The course of pregnancy in patients with Addison's disease is associated with a number of complications and the risk of an adrenal crisis. Quite often, the main symptoms that mark the onset of an Addison's crisis may be linked to pregnancy-related complaints, such as severe fatigue, nausea and vomiting. This in turn leads to an adverse outcome for the mother and the fetus. It is very important to maintain adequate glucocorticoid replacement therapy to avoid the adverse effects of over-treatment (gestational diabetes mellitus, weight gain, arterial hypertension) and of under-treatment (low birth weight, adrenal crisis in the mother, electrolyte imbalance).[8,9]

There is no ideal replacement dose of glucocorticoid therapy for pregnant women with Addison's disease. Most of them require a 20-40% increase in the baseline dose after 24th week. This process simulates the physiological elevation in the cortisol levels during that period of a normal pregnancy. With regard to the mineralocorticoids, renin is not an adequate indicator of the need of replacement treatment during pregnancy, since there is a physiological elevation in its levels. Progesterone is known to have an anti-mineralocorticoid action and its levels increase during pregnancy. This may lead to augmenting therapy with mineralocorticoid in some pregnant patients with Addison's disease.[9,8] Fludrocortisone is administrated according to the electrolyte profile and the general condition. The patient should be informed about potential benefits and risks of using the medication during pregnancy. Fludrocortisone is classified as pregnancy category C by the Food and Drug Administration. Nevertheless, when necessary, it is applied under the strict control of the patient's condition and fetal monitoring.[8-11]

Hashimoto's autoimmune thyroiditis is one of the most common conditions observed in women in reproductive age who have fertility problems. The immune response, which is 5-10 times more common in women, stimulates organ-specific and organ-non-specific autoimmunity. The abnormal immune response leads to the release of cytokines, then the endometrial (T-cell) profile is altered, resulting in impaired implantation. On the other hand, the hypothyroid phase of this condition leads to a disorder in the production of sex steroids by a discontinuation of the hypothalamic-pituitary axis function, reduction in sex hormone binding globulin (SHBG) levels, elevated free testosterone. The metabolic clearance of androstenedione and estrone is reduced, which increases the aromatization of peripheral estrogens. The results are: menstrual abnormalities, infertility, increased incidence of spontaneous abortions and complications, related to a future pregnancy.[12,13] During pregnancy thyroid dysfunction leads to several complications including preeclampsia, prematurity and intellectual impairment in the offspring.[14]

It is crucial that patients with proven hypothyroidism (as is the case with our patient) have frequent thyroid hormone control and adequate dose titration of levothyroxine in order to maintain the recommended targets for pregnant women.

In case of insufficient secretion of both glucocorticoids and thyroid hormones, we should remember that thyroid hormones stimulate cortisol metabolism. Therefore, it is very important to provide an adequate replacement dose of glucocorticoid and only then to add or increase the dose of levothyroxine.

In our case, the woman got pregnant with adequate metabolic, electrolytic and hormonal balance after pre-conception counseling. This pre-conception planning played a significant role in order to obtain a good outcome for both mother and baby. Management during pregnancy was difficult due to fluctuations in electrolyte levels, thyroid hormones and orthostatic manifestations. Overall, we can expect good maternal and fetal outcomes in properly treated patients.

CONCLUSION

In conclusion, multiple autoimmune syndromes may be associated with a number of complications in the course of pregnancy and pose a major clinical challenge. Accurate and timely diagnosis as well as proper treatment (especially the good pre-conception compensation), allow a normal pregnancy outcome.

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Аутоиммунный полигландулярный синдром 2-го типа и беременность

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Дата получения: 18 ноября 2019 ♦ **Дата приемки:** 24 ноября 2019 ♦ **Дата публикации:** 30 июня 2020

Образец цитирования: Yanachkova V, Chaveeva P, Staynova R, Milcheva R. Autoimmune polyglandular syndrome type 2 and pregnancy. Folia Med (Plovdiv) 2020;62(2):408-11. doi: 10.3897/folmed.62.e48580.

Резюме

Аутоиммунные полигландулярные синдромы представляют собой комбинации различных эндокринных и неэндокринных иммунных заболеваний, а также наличие повышенных титров органоспецифических антител. Мы представляем клинический случай 41-летней беременной пациентки с синдромом аутоиммунного полигландулярного синдрома 2-го и сочетанием болезни Аддисона, тиреоидита Хашимото и гипогонадизма. Беременность была достигнута с помощью вспомогательных репродуктивных технологий. Больная находилась под пристальным наблюдением во время беременности. Заместительная терапия глюкокортикоидами и минералокортикоидами была назначена в соответствии с элекролитным профилем и общим состоянием больной. Контролировать заболевание во время беременности сложно из-за колебаний уровня электролитов, гормонов щитовидной железы и ортостатических проявлений. Кризис надпочечников произошёл до родов, но состояние было успешно преодолено. Никаких осложнений не произошло с матерью или новорожденным.

Ключевые слова

болезнь Аддисона, аутоиммунный полигландулярный синдром, тиреоидит Хашимото, беременность

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