CLINICAL CASE

AUTOIMMUNE THYROID DISEASE AND PREGNANCY, WHAT COULD BE A COMMON FACTOR?

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ABSTRACT

Autoimmune thyroid disease is more common in women than men, which is known to all physicians regardless of specialty. Currently is not uncommon for the diagnosis of a thyroid disease to be established following investigations performed as a preconception assessment or during the first weeks of pregnancy. It is important to note that pregnancy is accompanied by several adjustments both in terms of thyroid physiology and immune system, which may influence the evolution of an autoimmune thyroid disease in a pregnant woman. We want to emphasize their importance by presenting the case of a 26-year-old patient whose medical history, in terms of thyroid function, shifts from euthyroid to thyrotoxicosis and then to autoimmune myxedema over the course of two and a half years.

KEYWORDS: *pregnancy, Graves' disease, TRAb, autoimmune myxedema*

INTRODUCTION

Thyroid disorders are 4 to 5 times more common in women versus men, and especially in women of reproductive age [1], [2]. During normal pregnancy, a series of maternal physiological changes occur that induce complex endocrine and immune responses [2]. Pregnancy has a major influence on maternal thyroid gland as her thyroid hormones play a vital role in the development of the fetus and the functioning of the placenta [1]. For this reason, it is not uncommon to detect several thyroid abnormalities in the "routine" assessment performed on pregnant women.

The most common thyroid disorders during pregnancy are hypo- and hyperthyroidism. Of these, autoimmune thyroid disease (AITD) is the leading cause of hypothyroidism during pregnancy, with a prevalence between 5 - 20% of cases. Regarding hyperthyroidism, the most common etiology is transient gestational thyrotoxicosis, representing 1 - 3% of cases, while the prevalence of Basedow disease diagnosed in pregnant women varies between 0.1% - 0.4% [1]–[5]. Other less common causes of thyroid disease in pregnancy are nodular thyroid disease or thyroid cancer [1], [6].

CASE PRESENTATION

The patient M.G., 26-year-old from non-endemic area, smoker ~ 2.4PA, with no family history of endocrine pathology, is hospitalized in our clinic for thyroid evaluation on December 20, 2021.

From her medical history we found the following information:

- In the fall of 2019, the patient was diagnosed with small goiter with normal thyroid function.

- Nine months later, in July 2020, being in the second trimester of pregnancy, the second pregnancy, the patient is diagnosed with thyrotoxicosis: TSH: <0.0025 (0.35-4.94 μU / mL), fT4: 1.65 (0.7-1.48 ng/dL) associated with elevated levels of antithyroid peroxidase antibodies (ATPO> 100). At the same time, the ophthalmological evaluation performed establishes the presence of active Graves ophthalmopathy, with asymmetric involvement, predominantly left eye. In this context, the patient receives the recommendation to initiate antithyroid therapy with Propylthiouracil of 200 mg / day, given in three doses. Subsequently without other documents regarding the evolution or medical monitoring under antithyroid treatment during pregnancy.

- In December 2020, the patient gives birth prematurely at 34 weeks of gestation, with the cessation of antithyroid therapy and without further investigation in the postpartum period.

- Four months after birth, in April 2021, functional thyroid tests were repeated showing the presence of autoimmune myxedema, the patient being in this period without specific thyroid treatment. She started thyroid replacement therapy with Levothyroxine. During 2021 she was assessed in terms of thyroid function (Table 1), the tests showing persistent myxedema despite significant increase in Levothyroxine dose.

In December 2021, one year after birth, the patient presented in our clinic. Her main symptoms were dry eye, sandy sensation in the eyes, accentuation of exophthalmos in recent months and also, she has asthenia and bilateral forefoot edema.

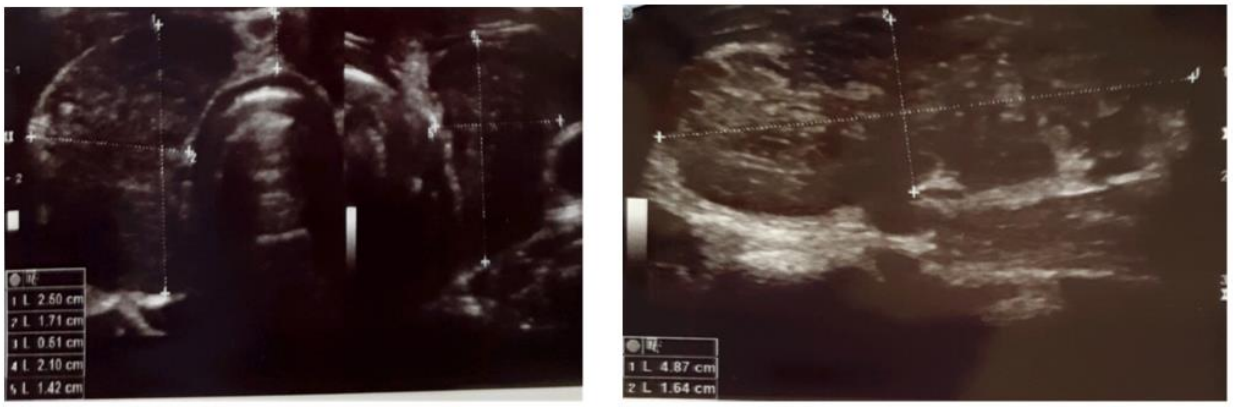
Clinical examination indicated a normal-weight patient: G=53 kg, H=156 cm, IMC= 21.78 kg/m2, normotensive: TA=103/79 mmHg, with a heart rate of 66 beats / minute, with clinical signs of myxedema: infiltrated facies, dry and dehydrated skin, with associated exophthalmos, mainly right eye involvement and bilateral palpebral edema. In terms of thyroid changes, we find a small goitre of hard consistency, but mobile with swallowing.

Parameter	**04.2021**	**05.2021**	**08.2021**	**11.2021**
TSH (0.35-4.94 μUI/mL)	98.12	56.6	90.64	146
fT4 (0.7-1.48 ng/dL)	< 0.42	0.46	0.61	< 0.3
ATPO (0-35 UI/mL)	>1.000	-	-	>1.000
Therapy	Starts LT4 50 ug/day	Increase LT4 to 100 ug/day	Increase LT4 to 150 ug/day	LT4 150 ug/zi

Table 1 - Evolution of thyroid functional tests during 2021

Biological evaluation revealed the presence of a discrete normochromic normocytic anemia (Hgb: 11.7 g/dL (12-15.5)), hypercholesterolemia (214.7mg/dL (0-200)) and hepatic cytolysis syndrome (AST: 39. (0-32 U/L), ALT: 35.9 (0-31U/L)) and the hormonal assays reconfirm the presence of autoimmune myxedema (Table 2), despite the fact she was on substitution treatment with a higher dose of levothyroxine than required calculated per body weight. Cervical ultrasound established the presence of a diffuse goiter, poorly vascularized on Doppler examination, without nodules, with a suggestive appearance of autoimmune thyroid disease (Figure 1).

We also performed a cardiological evaluation, the EKG showing the presence of a minor block of the right branch (RBBB) and diffusely flattened T waves, suggestive of myxedema. And the ophthalmological examination objectified the presence of active Graves ophthalmopathy, mainly right eye involvement, with the reduction of eyeballs motility in the superior-external quadrant, with exposure keratopathy, presence of diplopia and ocular hypertension.



Transversal view of the thyroid

Longitudinal view of the right lobe

Figure 1 - The patient's thyroid on ultrasound examination

Parameter (reference range)	**Value**	**Parameter** (reference range)	**Value**
TSH (0.5-4.5 µUI/mL)	107	**ATPO** (<5.61 UI/mL)	>1000
fT4 (9-19 pmol/L)	6.2	**TRAb** (<1.75 UI/L)	>40
T3 (80-200 ng/dL)	71.75	**25OHvitamin D** (20 – 100 ng/mL)	16.6

Table 2 – The hormonal evaluation results of our patient

Based on all clinical and paraclinical data, we concluded that we are in face of a patient with primary autoimmune myxedema associated with active Graves ophthalmopathy, minor RBBB, mild hypercholesterolemia, normochromic normocytic anemia, hepatic cytolysis syndrome and vitamin D deficiency.

We advised the patient to change the Levothyroxine tablets with oral solution to which we associated a combined levothyroxine-liothyronine preparation. She also received the indication to apply protective ophthalmic gel and eye drops to reduce intraocular hypertension.

The patient returned to control in January 2022. She noticed the improvement of her clinical condition, with increasing in exercise capacity, normalization of serum cholesterol and thyroid hormone levels, but with the persistence of elevated values of TSH and thyroid autoantibody titers (Table 3), without significant changes in terms of eye involvement.

Parameter (reference range)	**Value**	**Parameter (reference range)**	**Value**
TSH (0.5-4.5 µUI/mL)	36.98	**ATPO** (<5.61 UI/mL)	>1000
fT4 (9-19 pmol/L)	11.3	**TRAb** (<1.75 UI/L)	>39
T3 (80-200 ng/dL)	100.13		

Table 3 – Thyroid hormones evolution after the first month with the new treatment plan

DISCUSSION

We set out to present this case as it created a series of uncertainties. We have raised many questions starting with the history of the patient's disease: known as euthyroid in 2019, further to be diagnosed with thyrotoxicosis and active Graves ophthalmopathy in 2020, during the second trimester of pregnancy and later, throughout 2021 to be with persistent myxedema despite a significant increase of levothyroxine dose.

We asked ourselves: what could explain all these changes in thyroid function for this patient? Upon careful consideration, we concluded that the answer to this question is related to the increased titer of anti-TSH receptor antibodies or TRAbs. These antibodies are commonly found in autoimmune thyroid disease, not just Graves' disease, and play a unique role in the development of both autoimmune hyper and hypothyroidism [5]. Functionally, there are three types of anti-TSH receptor antibodies in this TRAbs family. Thus, depending on the ability to

generate intracellular cAMP by binding to the TSH receptor there is: TSAb (TSI), which stimulates thyroid function, TBAb (TBI), who blocks thyroid function and neutral antibodies [5], [7], [8]. Although the latter do not cause cAMP production, they are not so innocent, being able to activate a series of intracellular pathways with a role in maintaining the local inflammatory process [5]. It is important to note that most laboratories dose the anti-TSH receptor antibodies without making a functional distinction [8].

The most common mechanism involved in the onset of thyroid dysfunction in Hashimoto's thyroiditis is the cytotoxicity induced by T lymphocytes, but it appears that also the anti-TSH receptor antibodies play an important role [8]. The appearance of TRAb titers could explain the shifting phenomenon that can be encountered in autoimmune thyroid disease, namely the bidirectional shift hypothyroidism ↔ hyperthyroidism, which is partially correlated with the shift TBAb ↔ TSAb [5].

As mentioned at the beginning of the article, in pregnancy the prevalence of Graves' disease is significantly lower than of autoimmune hypothyroidism. Most often the cases are of patients known with Graves' disease before pregnancy. There is also the possibility of de novo diagnosis of Graves in pregnancy, often with onset in the first trimester [1], [4]. It can be difficult to make this diagnosis given the similarity between the symptoms of thyrotoxicosis and those induced by normal pregnancy [4], [9]. For these patients, presence of goiter or of extra thyroidal manifestations, such as ophthalmopathy may suggest the Graves' disease, the final diagnosis being established by the presence of a suppressed TSH with elevated levels of thyroid hormones and TRAbs titers [4], [5].

During pregnancy there is a dynamic change in terms of TRAbs levels. These are explained by the fact the pregnancy induces a state of immunosuppression, which is why the levels of thyroid autoantibodies tends to decrease as the pregnancy progresses [5]. But these quantitative changes can be very variable [1]. Most often the TRAb level starts to drop after the 20th week of gestation reaching values below upper normal limit. However, there may be patients in whom the decrease in TRAb levels is not so obvious or even absent, especially in those with levels over 4-5 times the upper normal limit [5].

Pregnancy also causes a series of qualitative changes in TRAbs, in addition to those quantitative. Thus, it is possible the functional shift from the stimulation activity to the blocking activity of TRAb. The level of TSAb gradually decreases in the second part of pregnancy, but with the possibility of increasing after birth, a mechanism that would explain the recurrence of hyperthyroidism 4-8 months after birth [5]. It is worth mentioning that TRAb level dosing is useful in making differential diagnosis of Graves' disease versus other cause of thyrotoxicosis like postpartum thyroiditis [1], [10]. Postpartum thyroiditis is a condition with a prevalence of 5-10% cases in the first year after birth. TRAb will be positive in all patients with Graves' disease and absent in postpartum thyroiditis [4].

Returning to the present case, during the pregnancy the patient was diagnosed with Graves' disease, confirmed by the presence of thyrotoxicosis, associated with thyroid goiter and ophthalmopathy. Subsequently, there was a functional shift of anti-TSH receptor antibodies from the stimulatory to the blocking ones, with the installation of the autoimmune myxedema identified after birth. At the same time, patient noticed a worsening of ophthalmopathy, which was the main reason why she came to our clinic. As previously mentioned, thyroid eye disease is a major extrathyroidal manifestation of Graves' disease, but it can also occur in patients with euthyroid function or chronic autoimmune thyroiditis [8]. According to the 2021 EUGOGO guide, high serum TRAb concentrations of more than 5 times upper normal limit are associated with the presence of ophthalmopathy in patients with Graves' disease, but also with Hashimoto's thyroiditis [11]–[21]. According to the same guide, there are several factors that have a negative impact on Graves' ophthalmopathy, such as thyroid dysfunction, both hyperthyroidism and hypothyroidism or smoking. Regarding smoking, it is considered a risk factor in the onset of Graves' ophthalmopathy and in delaying or limiting the response to immunosuppressive therapy. Thus, recommending patients to quit smoking may

have a beneficial effect on the prognosis of Graves' ophthalmopathy [11]–[21].

CONCLUSION

In conclusion, it is important to note that Graves' disease and autoimmune myxedema are part of the spectrum of autoimmune thyroid disorders, more often encountered in women than in men. It should also be considered that the onset of pregnancy may alter the course of autoimmune thyroid disease in women of childbearing age. That is why we want to emphasize the importance of regular monitoring of patients known or diagnosed with autoimmune thyroid disease in pregnancy, because their clinical course may be unpredictable.

REFERENCES

[1] E. K. Alexander et al., "2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum," Thyroid, vol. 27, no. 3, pp. 315–389, Mar. 2017, doi: 10.1089/thy.2016.0457.

[2] J. C. Galofre and T. F. Davies, "Autoimmune Thyroid Disease in Pregnancy: A Review," J Womens Health, vol. 18, no. 11, pp. 1847–1856, Nov. 2009, doi: 10.1089/jwh.2008.1234.

[3] "Hyperthyroidism In Pregnancy - StatPearls - NCBI Bookshelf." https://www.ncbi.nlm.nih.gov/books/NBK559203/ (accessed Jan. 08, 2023).

[4] L. de Groot et al., "Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline," J Clin Endocrinol Metab, vol. 97, no. 8, pp. 2543–2565, Aug. 2012, doi: 10.1210/jc.2011-2803.

[5] I. Bucci, C. Giuliani, and G. Napolitano, "Thyroid-Stimulating Hormone Receptor Antibodies in Pregnancy: Clinical Relevance," Front Endocrinol (Lausanne), vol. 8, Jun. 2017, doi: 10.3389/fendo.2017.00137.

[6] A. Gheorghisan-Galateanu, "Not Just Hashimoto's Thyroiditis," Acta Endocrinologica (Bucharest), vol. 15, no. 4, pp. 537–538, 2019, doi: 10.4183/aeb.2019.537.

[7] K. Michalek, S. A. Morshed, R. Latif, and T. F. Davies, "TSH receptor autoantibodies," Autoimmun Rev, vol. 9, no. 2, pp. 113–116, Dec. 2009, doi: 10.1016/j.autrev.2009.03.012.

[8] G. Napolitano, I. Bucci, G. di Dalmazi, and C. Giuliani, "Non-Conventional Clinical Uses of TSH Receptor Antibodies: The Case of Chronic Autoimmune Thyroiditis," Front Endocrinol (Lausanne), vol. 12, Nov. 2021, doi: 10.3389/fendo.2021.769084.

[9] J. Orgiazzi, "ANTI–TSH RECEPTOR ANTIBODIES IN CLINICAL PRACTICE," Endocrinol Metab Clin North Am, vol. 29, no. 2, pp. 339–355, Jun. 2000, doi: 10.1016/S0889-8529(05)70135-3.

[10] A. Cocoloș et al., "RIEDEL'S THYROIDITIS: A RARE DIAGNOSIS THAT RARELY REQUIRES THYROID SURGERY," Journal of Surgical Sciences, vol. 5, no. 1, pp. 38–41, 2018.

[11] P. P. LIMONE et al., "Graves' orbitopathy: a multidisciplinary approach," The Quarterly Journal of Nuclear Medicine and Molecular Imaging, vol. 65, no. 2, Apr. 2021, doi: 10.23736/S1824-4785.21.03350-1.

[12] S. Mbarek, F. Abid, W. Ammari, W. Alaya, A. Mahmoud, and R. Messaoud, "Graves' Orbitopathy: Report of 82 cases.," Tunis Med, vol. 99, no. 2, pp. 243–251, Feb. 2021.

[13] M. Jamshidian-Tehrani, A. Kasaei, Z. Mahdizad, M. A. Fard, and M. Aminizade, "Effect of Smoking on Retinal Thickness and Vascular Density in Thyroid Eye Disease," Korean Journal of Ophthalmology, vol. 35, no. 5, pp. 376–382, Oct. 2021, doi: 10.3341/kjo.2021.0059.

[14] M. J. Schatz, B. C. McGeehan, M. G. Maguire, and C. A. Briceño, "Tobacco counseling in the setting of thyroid eye disease," Arq Bras Oftalmol, vol. 85, no. 1, 2022, doi: 10.5935/0004-2749.20220003.

[15] J. Schovanek et al., "Adipocytokines in Graves' orbitopathy and the effect of high-dose corticosteroids," Adipocyte, vol. 10, no. 1, pp. 456–462, Jan. 2021, doi: 10.1080/21623945.2021.1980258.

[16] V. K. Patel, L. Padnick-Silver, S. D'Souza, R. K. Bhattacharya, M. Francis-Sedlak, and R. J. Holt, "Characteristics of Diabetic and Nondiabetic Patients With Thyroid Eye Disease in the United States: A Claims-Based Analysis," Endocrine Practice, vol. 28, no. 2, pp. 159–164, Feb. 2022, doi: 10.1016/j.eprac.2021.11.080.

[17] J. Cao, Y. Su, Z. Chen, C. Ma, and W. Xiong, "The risk factors for Graves' ophthalmopathy," Graefe's Archive for Clinical and Experimental Ophthalmology, vol. 260, no. 4, pp. 1043–1054, Apr. 2022, doi: 10.1007/s00417-021-05456-x.

[18] T.-Y. Hou, S.-B. Wu, H.-C. Kau, and C.-C. Tsai, "The Role of Oxidative Stress and Therapeutic Potential of Antioxidants in Graves' Ophthalmopathy," Biomedicines, vol. 9, no. 12, p. 1871, Dec. 2021, doi: 10.3390/biomedicines9121871.

[19] P. Cerri, B. Shahida, M. Lantz, and T. Planck, "Serum CYR61 Levels are Associated with Graves' Ophthalmopathy and Smoking in Patients with Graves' Disease," Hormone and Metabolic Research, vol. 54, no. 03, pp. 168–174, Mar. 2022, doi: 10.1055/a-1743-2988.

[20] J. K. Aranyosi et al., "Different Effects of Cigarette Smoke, Heated Tobacco Product and E-Cigarette Vapour on Orbital Fibroblasts in Graves' Orbitopathy; a Study by Real Time Cell Electronic Sensing," Molecules, vol. 27, no. 9, p. 3001, May 2022, doi: 10.3390/molecules27093001.

[21] L. Bartalena et al., "The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy," Eur J Endocrinol, vol. 185, no. 4, pp. G43–G67, Oct. 2021, doi: 10.1530/EJE-21-0479.