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Recurrent miscarriage causes are multiple, grouping genetic, anatomical, infectious and endocrine, or environmental factors, secondary to exposure to alcohol, smoking, consumption of toxic substances. Also autoimmunity is frequently associated with a history of repeated abortions.

The impact of thyroid diseases on pregnancy progress was the subject matter of numerous research groups. A significant association of the autoimmune thyroid disease with the risk of miscarriage is described in the literature.

Dysthyroidism is associated with an ovulatory cycles, subfertility or infertility. It is known that in the first 20 weeks of gestation, fetal thyroid is inoperative. Even though the formation of thyroid is described in the first 6-8 weeks of intrauterine development, the enzymatic apparatus necessary for thyroid hormone production is present only in the 8-10 week of pregnancy.
pregnancy. In the 12 week of gestation, the mechanism of iodine capitation in the thyroid is active. Normal functional triiodothyronine and tetraiodothyronine are synthesized and secreted only after the week 20 of gestation. Throughout the pregnancy, as much as 30% of the total thyroid hormones in the fetal blood are of maternal provenience. Because of this, normal brain and somatic fetal development are dependent on the maternal thyroid hormones. Physiologically, there is an increase of the thyroid maternal function for the increased materno-fetal needs.\textsuperscript{3,4}

The impression in the general population is that, once you are diagnosed with a thyroid disease, the probability of a pregnancy decrease significantly. Considering medicine in the ‘80’s, this was partially true, but nowadays this is totally false. Proper treatment of thyroid disease, make the evolution of a future pregnancy possible. Anyhow, recurrent abortion still remains a difficult to predict or treat association in the presence of autoimmune thyroid disease.

Many authors describe the possible link between thyroid autoimmunity and isolate or recurrent abortion.\textsuperscript{5,7} The presence of a positive titer of antithyroid antibodies associates a high risk of failure of in vitro fertilization techniques.\textsuperscript{8,9} The rate of successful pregnancies is lower (11 compared to 25%). Even if assisted pregnancy is obtained, the incidence of post FIV abortions is higher in the presence of antithyroid antibodies.\textsuperscript{10} Increased titers of antitiroperoxidase antibodies (Ac anti TPO) and/or anti Tireoglobulin antibodies (Ac anti Tg) are associated with a higher prevalence (17% compared to 8.4% and 13.3% versus 3.3%) of habitual abortion.\textsuperscript{11,12} The general risk of miscarriage is 3 to 5 times higher in the presence of the autoimmune thyroid disease.\textsuperscript{3,13}

Regarding the thyroid function, we can observe different situations: clinical manifest hypothyroidism (increased TSH values plus decreased peripheral hormones levels), subclinical hypothyroidism (isolated increased TSH levels), hyperthyroidism and asymptomatic form of autoimmune thyroiditis (isolated positive titer of antithyroid antibodies).

The presence of overt hypothyroidism, characterized with TSH changes along with decrease of the periphery hormonal levels, clinically manifest hypothyroidism is a jeopardy for the pregnancy development. Untreated hypothyroidism is associated with infertility, but also with a high rate of miscarriages.\textsuperscript{7} Some studies reveal an incidence of pregnancies stopped in evolution in women with untreated hypothyroidism, up to 60-71%.\textsuperscript{14} Obstetric events occur more frequently in case of late diagnosis or partial compensation under treatment with LT4.\textsuperscript{15-17} Given that, hypothyroidism, through various mechanisms, plays a role in spontaneous abortion, replacement treatment is advisable for these women.\textsuperscript{7} Proper compensation with LT4 treatment, which presupposes normalization of TSH titer, decreases the rate of possible complications: recurrent abortion rate decreases from 31.4% to 4% and successful pregnancy rate increases from 55% to 81% in case of patients that are not compensated correctly.\textsuperscript{14,18}

The definition of subclinical hypothyroidism is a rather controversial one. The consensus reached by AACE (American Association of Clinical Endocrinology), ATA (American Thyroid Association) and TES (Thyroid European Society) in 2004 recommends keeping the threshold value of TSH greater than 4.5 mU/mL, for defining subclinical hypothyroidism.\textsuperscript{19} Subclinical hypothyroidism affects 2-3% of women with evolving pregnancies.\textsuperscript{20} All other cases will benefit from active treatment. Subclinical hypothyroidism associates with a number of hypothalamo-hypophyseal-ovarian problems. There are some positive correlation between the levels of TSH, LH and testosterone in the early luteal phase. Also, slightly elevated TSH values associate with a lower rate of successful pregnancy.\textsuperscript{21} Also, untreated subclinical hypothyroidism causes negative effects on maternal health and fetal development. Surprisingly, the rate of spontaneous abortion in subclinical hypothyroidism is similar to that of the clinically manifest form of the disease (48%).\textsuperscript{14}

The third category of cases, is composed by cases with euthyroidism with positive antithyroid antibody titers, especially anti-tiroperoxidase high titers. These patients should be monitored in the first weeks of pregnancy because of the risk of hypotroidism development that will affect both mother and fetus.\textsuperscript{22} This group of patients has increased risk of miscarriage and premature births.\textsuperscript{7} Age also can contribute as an independent risk factor in this problem because the prevalence of patients with positive antibody titers increases with age: 10.7% (group 25-29 years), 14.2% (30-34 years group), respectively 26.2% for women over 35 years.\textsuperscript{23}

In the case of hyperthyroidism there is a physiological hyperthyroid response, that can mimic Hashitoxicosis, but also it can be overt true hyperthyroidism secondary to activation/relapse of autoimmune hyperthyroidism.\textsuperscript{24} Hyperemesis gravidarium, present in up to 10-20% of normal pregnant women, appears in the first 12 weeks of gestation, can mimic hyperthyroidism but is no thyroid disease.\textsuperscript{25} The effect is secondary to the mild stimulating effect of the human chorionic...
gonadotropic hormone. Typically these women do not need any antithyroid treatment. A more severe form of the same mechanism is hyperemesis gravidarum. Treatment with an antithyroid drug is not needed, due to the spontaneously remission of symptoms with the progression of pregnancy, secondary to the normalization of T4 levels by 14 to 20 weeks’ gestation.

Untreated and uncontrolled overt hyperthyroidism may result in high incidence of spontaneous abortion, preterm labor with low birth-weight babies or stillbirths. The autoimmune disease is the most common form of hyperthyroidism. Association pregnancy – Graves disease can be as a recidive of a previous treated Graves disease, exacerbation of a treated disease, due to beta-hCG effect, or new diagnostic of hyperthyroidism.

The fetal risk in Graves’ disease is described in cases with very high TRAb titers that are able to cross the placentral barrier and can induce, as in adults, overt Graves’ disease. The threshold value for TRAb titer as an indicator for the risk of neonatal hyperthyroidism of the fetus, is considered ones higher than 500% of basal activity. The physiological changes in maternal immunity, explain the amelioration of the hyperthyroidism symptoms during pregnancy, and the postpartum relapse of the autoimmune process. Antibody titers decrease in the second half of pregnancy because of immunomodulation of pregnancy, followed by a possible flare during the postpartum period. That is why the best time of evaluation TSH receptor antibodies is between 24 and 28 weeks.

Ethiopathogenetic mechanisms of association of thyroid autoimmune disease, with different levels of thyroid function, and pregnancy influence, are not fully elucidated. There are several theories. One of them considers that the autoimmune thyroid disease is a marker of autoimmune hyperactivity that rejects the “non-self” represented by the fetus. It is possible that thyroid autoantibodies exert a direct effect on trophoblast development with a vicious development. There are theories that consider autoimmune thyroiditis a consequence of increased lymphocytes T activation. Patients with antecedents of habitual abortions show an increased number of endometrial T lymphocytes.

Expression of the antithyroid antibodies may be an epiphenomenon that reflects an autoimmune imbalance, causing the rejection of the product of conception. This hypothesis is supported by the existence of an increased number of CD5/20-positive B lymphocytes in women with a history of recurrent miscarriages.

Aberrant autoimmune recognition of thyroglobulin and fetal antigens by maternal anti Tg antibodies can be a source of the initiation of the abortion.

Gonadal steroid synthesis by oocytes depends on an adequate level of thyroid hormones. T3 modulates the regulating action of LH and FSH on steroid biosynthesis, thyroid hormones increase and enhance estrogenic responses, for example pituitary prolactin production. It is not clear whether the T3-dependent mechanism, or the production of T3 changes in the autoimmune thyroid disease. The tendency of TSH is to increase progressively during pregnancy evolution, from an average of 1.7 μU/mL (week 12) to 3.5 μU/mL (week 38), 19% of the group becoming hypothyroidic as the pregnancy evolves. The presence of antithyroid antibodies, is associated with a subtle hormonal thyroidal deficiency, even in cases with “normal” TSH values. Also in the presence of autoimmune thyroiditis, history of recurrent abortion is associated with higher mean values of TSH.

The third hypothesis takes into consideration the relationship between the autoimmune thyroid disease and infertility. Subfertility defers pregnancy for 3-5 years, age being an independent risk factor for spontaneous abortions. Mechanisms remain largely speculative, being insufficiently demonstrated. The three main hypotheses mentioned above do not exclude each other. They can coexist and contribute to increase the risk of repeated abortions in case of association with the autoimmune thyroid disease.

Subclinical hyperthyroidism in pregnancy, due to autoimmune thyroid antibodies is the most difficult to diagnose situation.

The therapeutically approach of this cases, regarded as a prophylactic attitude in case of future pregnancies derives from this ethiopathogenetic facts. In case of a future wanted pregnancy, identifying patients with thyroid disease by screening is important. Secondary their supervision and treatment will decreases the incidence of adverse events for both mother and fetus. All women with increased risk should be evaluated. Nowadays the universal screening is not recommended due to financing problems, ideally universal screening should be considered.

Ideally, as we monitor TSH in case of pregnancy loss or assisted reproduction procedure, we should add thyroid antibodies in this algorithm. It is a matter of cost and not of clinical usefulness this universal screening.

According to American Endocrine Society, the risk categories are the following: presence of personal history of thyroid disease: hypothyroidism,
hyperthroidism, postpartum thyroiditis, lobectomy, positive family history of thyroid diseases or thyroid interventions, presence of clinical goiter, women with antecedent positive titers of antithyroid antibodies, presence of suggestive signs or symptoms of thyroid dysfunction, positive diagnostic of type 1 diabetes mellitus, known personal autoimmune diseases. Any woman diagnosed with infertility is considered a possible indicator of thyroid autoimmunity disease. Personal history of irradiation of the head and neck region should be screened very careful. A positive history of miscarriage should be screened for thyroid autoimmunity and thyroid hormonal function. The questions remains: what means “normal” TSH.

The tendency is to recommend the universal screening, because it is much more cost-effective. There are some controversies regarding therapeutic approach, once the presence of autoimmune thyroid is stated. Current recommendations address all the above mentioned categories of patients.

In case of clinical hypothyroidism, diagnosed antepartum, there is a consensus (ATA, ETA, AACE, ENDO) regarding supplemental therapy.

In case of antenatal diagnosis, a titration of replacement doses of 30-50% is necessary to maintain and obtain normal TSH values. The optimal values of TSH in the first trimester of pregnancy are 2.5 μM/mL, respectively 3 μM/mL in the 2nd and 3rd trimesters of pregnancy. In the case of pregnancy “normal” TSH values periodical repeating of tests every 30-40 days is needed.

The treatment is continued postpartum, even in case of breastfeeding, usually in doses employed before pregnancy. In case of subclinical hypothyroidism, in case of pregnancy, immediate treatment is established. The questions remains: what means “normal” TSH. Although under “nonpregnant conditions” subclinical hypothyroidism definition uses a TSH value higher than 4.5 μM/mL, there is a increasing body of evidence considering the risk of miscarriage in cases with TSH values between 2.5 and 4.5 μM/mL. Women who had antibodies but were given levothyroxine had pregnancy loss rates similar to the antibody-negative control population. Women with otherwise unexplained previous pregnancy losses probably should be treated if their TSH level is above 2.5 μM/mL and/or they have a positive test for antibodies.

ATA recommendations for asymptomatic autoimmune thyroiditis are: monthly follow up for early diagnosis of hypothyroidism. Thyroid hormone therapy, with normalization of TSH values, cancels the increased risk of complications. The TSH threshold remains an issue.

The few cases with autoimmune hyperthyroidism during pregnancy with slightly suppressed values of TSH in early pregnancy, one should distinguish between real hyperthyroidism and side effects of beta hCG hyper secretion. In case of a clinically obvious hyperthyroidism, synthesis antithyroid therapy remains the treatment of choice. The goal is to use the lowest possible dosage of antithyroid medication necessary to maintain the free T4 index in the upper one-third of the reference range or just above the normal range. Therapy should not be interrupted before week 32, as the hyperthyroidism may relapse.

Subtotal thyroidectomy is recommended in case of severe hyperthyroidism, which does not respond to treatment or requires very high doses of therapy, cannot tolerate treatment, development of a very large goiter requiring high dosages of antithyroid drugs, or allergy to both antithyroid drugs. Iodine therapy is not recommended due to high incidence of neonatal goiter and hypothyroidism.

Active monitorisation with dosing of TRAB is recommended in selected cases: previous neonatal hyperthyroidism, active disease despite antithyroid medication, thyroidectomy during pregnancy, fetal tachycardia or presence of fetal goiter at ultrasonography.

CONCLUSIONS

The following factors put women at increased risk for thyroid problems: age over 30, living in an area with known iodine insufficiency, personal or family history of thyroid problems, including goiter, type 1 diabetes, history of miscarriage, infertility, or preterm delivery, obesity, previous medication with lithium or amiodarone.

In case of recurrent miscarriage we should consider testing for autoimmune thyroid disease that is responsible for up to 10% of cases.

In cases with TSH higher than 10 μM/mL supplemental therapy is recommended without any further investigation.

In cases of high TSH values (higher than 2.5 μM/mL) treatment is recommended if FT4 levels are decreased or there is a positive titer of anti TPO antibodies.

Active screening and team work should be the key for a correct management of these cases.

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