Thyroid autoimmunity in pregnancy – a problem of mother and child

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Abstract

Autoimmune thyroid diseases (AITD), including Hashimoto thyroiditis and Graves’ disease, are some of the most frequent autoaggressive entities occurring in females of childbearing age. Despite increasing knowledge about management of pregnant women with this type of thyroid disorders, they still constitute a significant problem in clinical practice. Due to widespread presence, unclear manifestation and possible negative repercussions for mother and her unborn progeny, coexistence of AITD and gravidaity remains a challenge for gynaecologists and endocrinologists. In the paper, the impact of AITD and accompanying thyroid dysfunction on both maternal health and outcome of pregnancy as well as current guidelines on screening and therapy of these conditions are discussed.

Key words: autoimmune thyroid disease, Hashimoto thyroiditis, Graves’ disease, hypothyroidism, hyperthyroidism, pregnancy

Autoimmune thyroid diseases (AITD), including Hashimoto thyroiditis (HT) and Graves’ disease (GD), are some of the most frequent autoaggressive entities occurring in females of childbearing age [1]. The prevalence of AITD ranges from 5 to 15% of population and women are affected 5-10 times more often than men [2]. Despite increasing knowledge about management of pregnant women with this type of thyroid disorder, important repercussions of these pathologies for both mother and a progeny are still a significant problem in clinical practice.

Physiological changes

Fundamental changes in function of maternal thyroid gland take place during pregnancy in order to achieve sufficient concentration of thyroid hormones in bloodstream. Profound alterations including increase in concentration of thyroxine-binding globulin (TBG) accompanied by intensification of thyroid hormones production, thyroid stimulating activity of human chorionic gonadotropin (hCG), iodine deprivation due to intensified glomerular filtration rate and placental transfer as well as increased deiodinases activity pose a challenge to maintain a fragile metabolic equilibrium [3]. Thyroid autoimmunity may easily disturb the process of adaptation, resulting in overproduction or insufficient delivery of thyroid hormones, eventually deteriorating pregnancy outcome.

Autoimmunity and hypothyroidism – impact on maternal health

Although iodine supplementation has been widely introduced, iodine deficiency is still the most common cause of hypothyroidism among women of reproductive age. However, when iodine intake is sufficient, autoimmunity plays the most significant role in disturbing thyroid hormonal production. With reference to recent studies, overall prevalence of AITD was established to be 7.8%, while autoimmunity features were shown in 5-20% of pregnant women.

Cell-mediated immune activity, underlying pathological process in HT triggers thyroid cells destruction, eventually leading to hypothyroidism. Although production of autoantibodies to thyroid peroxidase (TPO-Abs) and thyroglobulin (Tg-Abs) is secondary to actual etiology, their presence in bloodstream is vital in diagnosis, evaluation of the course of disease as well as in establishing prognosis [4]. Serum concentration of antithyroid autoantibodies attains maximum levels in the first trimester and then gradually decreases to the lowest value in the third one. With progress of gestation, while autoimmune process alleviates, surprisingly primarily euthyroid women frequently progress to hypothyroidism at term. In other words, gravidity imposes enormous strain on organism, which may not meet a challenge if increased gestational thyroid hormones demand cannot be provided [5]. Not only an inadequate serum concentration of hormones, but also presence of antithyroid autoantibodies itself is considered to aggravate pregnancy outcome. Generally, within a group of euthyroid females presenting with increased antithyroid autoantibodies concentration, pregnancy loss occurs more frequently comparing to the healthy ones [6]. Several obstetrical complications were reported in women with hypothyroidism, namely: increased miscarriage rate, gestation in-
duced hypertension, placental abruption and anaemia. Other research have shown increased likelihood of preterm delivery, low birth weight of the progeny, maternal postpartum haemorrhage as well as elevated ratio of caesarean sections [7]. The observation varies significantly between conducted studies, what may be partially elucidated by different research design. What is more important, discrepancies arise questions concerning association between complications alluded to above and thyroid gland hypofunction in pregnant women. AITD is both deteriorating pregnancy outcome and influencing adversely maternal health in a long-term manner. After delivery, as immunosuppression ceases, inducing a rebound of autoaggression, which subsequently disrupt newly established systemic balance.

Correlation between autoimmune activity during gravidity and postpartum thyroiditis (PPT) referred to as thyroid autoimmune malfunction emerging within the first year following delivery, is widely known [8]. Firstly, PPT emerges in 33-50% of women tested positively for TPO-Abs in the first trimester. Moreover, the higher foregoing decline in serum TPO-Abs concentration, the more severe the relapse. Usually, initially hyperthyroid patient, reverses to hypothyroidism in 3 to 12 months and finally recovers in the end of the year after delivery. Although in most cases the disorder has a transient character, approximately 25% of women will exhibit decreasing thyroid hormones serum concentration, requiring L-thyroxine supplementation within the forthcoming 10 years [9]. Females with coexisting diabetes mellitus type 1 are 3-fold more prone to PPT and the risk is even greater in subjects with high level of TPO-Abs [10].

Moreover, association between the postpartum depression and AITD during pregnancy is also well-proven. On the whole, presence of TPO-Abs in gravidity is positively correlated with subsequent depression symptoms, occurring after delivery. Depression is very common, but most patients do not attend clinical evaluation. What is more, the disorder remains often undiagnosed. TPO-Abs cannot be treated as a screening tool for depression, but once measured should be used to identify women at risk for depression [11].

Pregnancy may be seen as a challenge for the organism. Some authors suggest that disturbance occurring in this period could provide information about efficiency of systemic regulations, thereby creating prognosis for the forthcoming life. Impact of thyroid dysfunction and AITD present in pregnancy on later maternal morbidity was evaluated in several prospective studies. Specifically, authors imply that abovementioned factors may be predictive for cardiovascular problems and mortality, even if evaluated at young age. Results disclosed possible association of overt hypothyroidism and subsequent diabetes morbidity in later life, but no connection with cardiac disorders was found [12].

To sum up, consequences of thyroid dysfunction during pregnancy are not clearly established. However, despite significant connection between autoimmunity and aggravation of pregnancy outcome or maternal health seems to be relevant, universal screening is not recommended. Targeted evaluation is suggested in high-risk groups, including those with family or personal history of thyroid disease, thyroid autoimmune disease, symptoms of impaired thyroid function, diabetes mellitus type 1, history of head and neck irradiation, positive thyroid autoantibodies and infertility [13].

Autoimmunity and hyperthyroidism – impact on maternal health

Hyperthyroidism during gravidity is less common than hypothyroidism, with an incidence estimated at 0.1-1% of pregnant women. The most important cause is GD, which occurs in 85% of females with apparent symptoms of thyroid hormones overproduction [14]. Gestational transient thyrotoxicosis (GTT) is the another frequent etiology. Other diseases such as toxic nodular goitre accounts for less than 5% of hyperthyroid women [15].

Some analyses suggest the association between gestational thyrotoxicosis and hyperemesis gravidarum. During early gravidity patients suffering from hyperemesis have significantly lower levels of TSH than pregnant women not affected by this disorder [16].

The diagnosis of GD in pregnancy may be difficult due to non-specific symptoms such as tachycardia, moist skin, irritation, heat intolerance and insomnia, which are present also in healthy pregnant women. Moreover, physiological alterations in thyroid hormonal status make it even more complex. Distinctive presentation with orbitopathy and dermopathy rarely occurs [17].

Important tool to distinguish between most common GD and GTT, is measurement of antithyroid autoantibodies titre. Differential diagnosis is vital, according to less severe, transient and highly related to hCG levels character of GTT, comparing to GD, associated with the risk for foetal health and requiring antithyroid drug administration in case of overt thyrotoxicosis. Thus, all pregnant women presenting with symptoms of hyperthyroidism should undergo TSH, free thyroxine (fT4), free triiodothyronine (fT3) as well as TPO-Abs, Tg-Abs and anti-
TSH receptor autoantibodies (TR-Abs) serum concentration evaluation [18]. TR-Abs circulating in bloodstream, the hallmark for GD, are capable of stimulating both maternal and foetal thyroid function and growth. Activity of autoimmune process in GD fluctuates with progression of pregnancy. Disorder usually emerges or aggravates in the first trimester, while in second gradual improvement can be noticed, leading frequently to spontaneous remission in late pregnancy. Relapse usually occurs in postpartum period, when natural immunosuppression typical for pregnancy ceases [4]. Above-mentioned alterations are more probably simultaneous with changes in stimulating antibodies titres rather than elevation in inhibiting ones.

Interaction between TR-Abs and TSH-receptor, depends on the sort of present antibodies (stimulating, blocking or neutral). Thyrotropin binding inhibiting immunoglobulins (TBII) assay, which is the most popular method used in measurement of antithyroid antibodies, unfortunately cannot distinguish TR-Abs types. Thyroid stimulating assay (TS-Abs), available only in specialized centres is capable of differentiation antibodies on the basis of cAMP marking [17]. Both TR-Abs and antithyroid drugs (ATD) pass the placental barrier, having an impact on progeny. Occasionally, women and child with inhibiting TR-Abs may develop hypothyroidism, instead of thyroid hormone overproduction [19].

Hyperthyroidism, when untreated or under insufficient control, may result in serious maternal complications, including preeclampsia, elevated risk of congestive heart failure or thyroid storm. Moreover, preterm delivery, placental abruption and miscarriages appear considerably more often among thyrotoxic mothers [5].

Regarding postpartum period as mentioned above relapse of GD can be observed, as well as PPT. Adversely to GD, PPT usually do not require antithyroid treatment, thus it is of paramount importance to measure TR-Abs serum concentration in order to differentiate between those entities [20].

Pregnant female diagnosed with GD, are usually divided into subgroups due to dissimilar course of the disease, need for treatment and risk for neonatal hyperthyroidism, namely women: (1) under antithyroid therapy diagnosed primarily during pregnancy or before, (2) in remission after previous antithyroid treatment, (3) with a history of GD cured with thyroid surgery or iodine administration and (4) with a history of thyroid dysfunction identified in the progeny [15]. According to international consensus, TR-Abs should be measured at least once – by the end of the second trimester – in mothers from all groups except the second one, due to low risk of recurrence and neonatal GD. European recommendations include additional measurement of TR-Abs in the last trimester in the (1) group, while in the (3) group it is suggested to assess TR-Abs in the first trimester: if negative, no further evaluation is needed, if positive, repeated TR-Abs measurement in the third trimester together with foetal monitoring is recommended. Monotherapy with antithyroid drug at minimal effective doses is recommended during pregnancy for women suffering from GD and overt hyperthyroidism, while patients with subclinical hyperthyroidism, presenting with suppressed TSH level and normal free thyroid hormones, require entirely close monitoring [21].

The foetus and thyroid autoimmunity

Thyroid autoimmune disorders occurring during pregnancy has been widely described to potentially endanger not only mother but also her unborn offspring [22]. Insufficient supply of thyroid hormones to the foetus, especially in the early stages of gestation, may result in severe impairment of child development [23]. On the other hand, congenital foetal hyperthyroidism caused by transplacental passage of TR-Abs is also described to have a substantial influence on an infant and pregnancy outcome [24-27]. The possible adverse impact of ATD on the foetal thyroid function in mothers with GD is also noteworthy [24, 25].

Autoimmunity and hypothyroidism – impact on foetus

The thyroid gland is the first of endocrine glands to develop during organogenesis [28]. The foetal synthesis of thyroid hormones starts around 10 to 12 weeks of pregnancy, but its blood level remains insignificant until 20th week of gestation [29]. Therefore, especially during the first half of pregnancy, foetus obtains major proportion of its thyroid hormones from the maternal circulation system. The presence of some amounts of thyroxine in cord blood of newborns with genetic incapacity to synthetize thyroid hormones described by Vulsma et al. confirmed the ability of thyroxine to cross the placenta [30]. Even after midgestation, the need for maternal thyroid hormones remains significant [31]. Maintenance of this specific maternal-foetal thyroid hormone balance seems to be crucial for proper development of brain and other organs.

The published data strongly implies the direct influence of hypothyroxinaemia on deficits in foetal neurodevelopment [23, 31-33]. The earliest time examined,
when thyroid hormone receptors are present in the human foetus is by 8 weeks of gestation [34]. The stimulation of these receptors promotes the differentiation of neural stem cells, regulates the migration of neurons and affects the maturation of other tissues [35]. Since it was published in the research by Lavado-Autric et al. that early maternal hypothyroxinaemia alters histogenesis and cerebral cortex cytoarchitecture of the rats foetuses, we may assume that there is parallel influence on the neurodevelopment in human progeny [36]. Pop et al. described the direct correlation between the decreased IQs of children and low thyroxine blood concentration observed in their mothers, comparing to the control subjects [37]. According to a prospective population-based research performed in China clinical maternal hypothyroidism at the early stages of gestation is responsible for increased foetal loss, low birth weight, and congenital circulation system malformations, while subclinical hypothyroidism was associated with increased foetal distress, preterm delivery, poor vision development and neurodevelopment delay [38].

Recently adverse outcome of late maternal hypothyroxinaemia was described by Berbel et al. This article also suggests the need for thyroid hormones treatment of preterm neonates, to compensate for the interruption of the maternal hormones supply, because thyroid may not yet be sufficiently mature to produce the appropriate amounts of T4 [31]. Thus, according to the published data, even after onset of foetal thyroid gland hormonal production, maternal T4 is still essential for normal development of the offspring. An important issue is that female patients who already receive L-thyroxine supplementation require 30 to 50% higher doses during pregnancy to stay euthyroid and prevent the adverse effects on the foetus [39]. This stems directly from described above maternal physiological changes in the thyroid function during pregnancy and prevents inadequate (too low comparing to the needs) thyroxine transfer to the child.

Since, as alluded to above, chronic autoimmune thyroiditis is the most frequent cause of hypothyroidism in pregnancy in populations without iodine deficiency, it also plays the most important role in disturbances in foetal neurodevelopment in most European countries [4].

Another interesting issue is foetal hypothyroidism and goitre development as a result of ATD therapy during pregnancy. A large goitre may cause polyhydramnios and hyperextension of the child’s neck and head, complicating labour and vaginal delivery [40]. The danger of trachea obstruction in the neonate may result in asphyxia and death. Propylthiouracil (PTU) is a well-documented potential goitrogen, causing impairment in thyroid hormone synthesis in mothers treated for GD as well as in the progeny [41]. In most cases dose reduction is sufficient to regain proper foetal thyroid function and reduce the size of goiter, but occasionally direct supplementation of thyroxine to the foetus is needed. Treatment with intra-amniotic installation of thyroxine following cordocentesis, that delivers the most precise assessment of foetal thyroid status, has already been performed by Davidson et al. more than 20 years ago. This type of direct foetal therapy allows oral ingestion of the hormone, but also creates risks of repeated amniocentesis [24, 40].

**Autoimmunity and hyperthyroidism – impact on foetus**

Hyperthyroidism exerts significant adverse effect on pregnancy outcome and the foetus as well. It is proven to be associated with an increased risk of miscarriage, premature birth, intrauterine growth retardation, foetal demise, maternal hypertension and thyroid storm [38]. The most frequent cause of maternal hyperthyroidism during pregnancy is GD, as described previously [14]. Moreover, TR-Abs produced by the mother may also cross the placenta and stimulate the foetal thyroid, resulting in congenital intrauterine hyperthyroidism. That transfer increases especially during the second half of gestation and that is when symptoms of thyroid hormones excess in the foetus occur [26, 42]. Signs like excessive heart rate, the presence of foetal goitre and growth abnormalities should be monitored regularly from midpregnancy onward. Accelerated maturation of the femoral ossification centre has also been reported [43].

Recently overt hyperthyroidism was also associated with hearing dysplasia [38]. The possible role of autoimmunity in the pathogenesis of hearing impairment in patients diagnosed with AITD has been suggested [44].

Using ATD of the thionamide type prevents the increased risk of thyrotoxicosis due to GD. Unfortunately, such treatment not only may expose foetus to hypothyroidism but also be the cause of malformations itself. According to Dussault et al. maternal ingestion of PTU was responsible for 25% of transient neonatal hypothyroidism detected during screening for congenital hypothyroidism [45].

Until recently the recommended drug for GD during pregnancy was PTU, mostly because widely used methimazole (MMI) has been associated with cutis aplasia and choanal atresia in progenies and the fact, that PTU pas-
ses less easily through the placenta [46]. However, data are not clear. 17-fold greater risk of choanal atresia comparing to the general population was found while other birth defects were attributed to thyrotoxicosis itself, not MMI use [47]. Momotani et al. on the other hand found no association between MMI use and congenital defects [48]. Despite no reports about birth abnormalities, one should take under consideration the increased risk of liver failure (both foetal and maternal) associated with radioiodine treatment, that are contraindicated during pregnancy. Another important issue is achieving euthyroidism in women already diagnosed with AITD during gestation. Another important issue is achieving euthyroidism in women already diagnosed with AITD during pregnancy. Treatment of such patients is also problematic, due to possible side effects of ATD and the difficulties to keep the thyroid hormone levels in the values optimal for the future in- pregnancy outcome, however the additional autoimmune factor connected with HT and GD makes the risk even higher. The antibody passage through the placenta itself causes clear manifestation and possible negative effects for mother and her offspring, AITD and gravidity coexistence remains a challenge for both gynaecologists and endocrinologists. Both under- and overproduction of thyroid hormones have an adverse influence on the pregnancy outcome, however the additional autoimmune factor connected with HT and GD makes the risk even higher. The antibody passage through the placenta itself causes multiplicity of damages to the unborn child and worsen the gestation prognosis. On the other hand, treatment of such patients is also problematic, due to possible side effects of ATD and the difficulties to keep the thyroid hormone levels in the values optimal for the future infant development. Although the routine screening of thyroid disorders in pregnancy is not recommended, vigilance especially concerning women from so called groups of risk may be helpful to prevent problems during gestation. Another important issue is achieving euthyroidism in women already diagnosed with AITD and thyroid dysfunction before the conception as a prevention of possible adverse effects and due to wider therapeutic possibilities, including surgical therapy and radioiodine treatment, that are contraindicated during pregnancy.

References


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