Chapter

Graves' Disease and Pregnancy

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Abstract

Graves' disease is an autoimmune organ specific disease characterized by excessive production of hormones from the thyroid gland and by its diffuse enlargement. The growth and function of the thyroid gland are stimulated by autoantibodies directed against the thyroid-stimulating hormone receptor. Pregnancies complicated by Graves' disease are characterized with higher incidence of abortion, preterm delivery, low-birth- weight infants and neonatal mortality, as well as maternal complications such as heart failure, eclampsia and rarely thyroid storm. When fully controlled hyperthyroidism have excellent outcomes. Different therapeutic approaches are used in women with Graves' planning pregnancy and in those when the disease is diagnosed after they became pregnant. Thionamides are the first choice for treatment, with Propylthyouracil being preferred for the first trimester and Methimazole for the second and third trimester. Aplasia cutis and some other malformations were associated with methimazole use during pregnancy. Monitoring the effect of treatment should ensure keeping maternal FT4 in the high normal range. Block-and replace regimen is not recommended and rdioiodine therapy is absolutely contraindicated. Thyroidectomy may be considered before pregnancy or in rare cases in the second trimester. Iodine is avoided because of the risk of fetal hypothyroidism and goiter. The use of beta-blockers is contro-versial. Noenatal thyrotoxicosis may occur in association with maternal Graves' disease due to maternal TSAbs cross through the placenta.

Keywords: Graves' disease, pregnancy, thionamides, iodine, surgery

1. Introduction

Graves' disease (GD) is an autoimmune organ specific disease characterized by excessive production of hormones from the thyroid gland (hyperthyroidism) and by its diffuse enlargement. The growth and function of the thyroid gland are stimulated by autoantibodies directed against the thyroid-stimulating hormone (TSH) receptor (TSHR). Nevertheless, other autoantibodies against thyroid peroxidase (TPO) and thyroglobulin (Tg) may also be present, TSHR is the major autoantigen of Graves' disease, making antibodies against it (TRAb) the most characteristic for the disease. Graves' disease (GD) is the most frequent cause of thyrotoxicosis in iodine sufficient countries [1], although the exact frequency of GD in general population is difficult to be established and differs from country to country. A meta-analysis of various studies has estimated the general prevalence of GD to be around 1% [2], which makes it one of the most frequent clinically relevant autoimmune disorders. Graves' disease is a multifactorial disorder. Like

all autoimmune diseases, GD is characterized with the loss of immune tolerance to thyroid antigens and the initiation of a sustained autoimmune reaction caused by a complex interplay of genetic, hormonal and environmental factors. While detailed discussion of these factors is beyond the scope of this chapter, it is worth to mention that GD is typically a disease of women, with the female-to- male ratio ranges in different studies from 5 to 10 at any age [2, 3]. Autoimmune disorders are in general more prevalent in women and genetic and nongenetic factors may play role for that [4, 5]. Male hormones are considered to down-regulate immunity and thus play a protective role from autoimmunity, whereas the effect of estrogen is not always unequivocal [4, 5]. Despite this, little evidences in the literature are backing the role for sex hormones in the high prevalence of GD in women. Moreover thyroid autoimmunity often accompanies patients with Turner's syndrome, who have low estrogen levels [6]. Besides sex hormones, some genetic factors linked with the X chromosome could explain the epidemiologic evidence of a female preponderance in GD. In families with GD, a putative Graves' disease susceptibility locus on the long arm of X chromosome was located by an linkage analysis [7]. Inactivation of the X chromosome, an epigenetic phenomenon, has been suggested to determine the female predisposition to thyroid autoimmunity. One study showed that this phenomenon is more frequently observed in patients with GD or autoimmune thyroiditis than in healthy controls [8]. Never mind, what the predisposing factors for GD could be, pregnancy, itself, is a well-known risk factor for thyroid autoimmunity. Pregnancy can influence and change the course of a pregestational Graves' disease or can become a reason for the development of GD during the pregnancy or after delivery. The risk of development of GD in postpartum year increases fourfold to eightfold [9]. The reasons for this could be explained by the observed abrupt fall in the level of pregnancy-associated immunosuppressive factors immediately after delivery (rebound immunity) [9]. The factors involved in the immune alterations of the postpartum period may include, but are not limited to estrogen and progestin [9, 10]. Approximately 2–3% of all pregnancies are complicated by thyroid disease [11], making thyroid disorders the second most common significant pathology affecting women during pregnancy after diabetes mellitus [12]. Detailed understanding of the physiology, pathophysiology, diagnosis and treatment is required to limit the effects on both maternal and fetal health.

2. Physiology of maternal and fetal thyroid in pregnancy

Pregnancy induces several major changes to thyroid morphology and physiology. Diagnosis of thyroid dysfunction during pregnancy is complicated by the hormonal changes that take place, posing specific challenges for both detection and management. During pregnancy, thyroid gland physiologically undergoes moderate enlargement, typically increasing in size between 10 and 40% of volume, and increasing of vascularization. This enlargement can be more pronounced if there is underling iodine deficiency [13]. At the same time there are transient, reversible after delivery, changes in thyroid hormone physiology and iodine metabolism. In early gestation, the thyroid gland is stimulated not only by TSH, but also by the alpha subunit of human chorionic gonadotropin (hCG), produced by the syncytiotrophoblasts of the developing placenta, which binds to and stimulates the TSH receptor, increasing thyroid hormone production and resulting in a subsequent reduction in serum TSH concentration [14]. Normally, hCG starts to rise from the very beginning of pregnancy and peaks at around 9–11 weeks of gestational age. Due to this, there is a parallel decrease in serum

TSH in the first trimester. Generally, TSH concentrations in pregnant women are lower than in non-pregnant women. Physiologically TSH concentrations fluctuate during different periods of gestation. During the first trimester, approximately 15% of healthy women have TSH level below the lower limit of the reference range of 0.4 mU/L [15, 16]. The percentage of women with suppressed TSH falls to about 10% in the second trimester, and 5% in the third trimester [17]. The upper limit of TSH reference range during pregnancy is also decreased by about 0.5–1.0 mU/L, in comparison to the typical nonpregnant TSH reference range and this downward shift usually occurs in the latter first trimester of pregnancy but typically not before week 7 [18]. Levels of hCG then decline until approximately 20 weeks of gestation and remain stable for the remainder of the pregnancy [19], which is followed by a slight increase of TSH levels. The level of decrease of TSH depends on number of the developing fetuses, because hCG concentrations are higher in multiple pregnancies than in singleton pregnancies, and downward shift in the TSH reference interval is greater in twin pregnancies [20]. The degree of the lowering of TSH concentrations during pregnancy varies significantly between different racial and ethnic groups, that is why the recommended by American Thyroid Association (ATA) trimester-specific reference ranges for TSH levels shown on **Table 1** [21], require determination of population-based trimester-specific reference ranges for serum TSH through assessment of local population data.

The reduction of the lower TSH reference range, observed during pregnancy should be regarded in the light of the data that even if this represents an undergoing subclinical hyperthyroidism, it has not been associated with adverse pregnancy outcomes. In a small percentage of women, TSH can be undetectable (<0.01 mU/L), but this is still represent a normal pregnancy. Therefore, a maternal TSH concentration that is low but detectable is likely not to be clinically significant [22].

Starting from the fourth week of gestation, the increase of estrogens causes the rise of circulating level of thyroid-binding globulin (TBG). Estrogens induce increase in the sialylation of the TBG, which is followed by a decrease of its hepatic clearance and by a prolongation of its serum half-life from 15 minutes to 3 days in comparison with the nonpregnancy time. TBG level reaches a plateau during mid-gestation and remain elevated until delivery. In the postpartum period TBG tend to normalize [23]. This rise of TGB level is followed by an increase of the total concentrations of thyroxine (TT4) and of triiodothyronine (TT3) in early pregnancy. There levels achieve a plateau early in the second trimester, at a concentrations value of 30–100% greater than prepregnancy [24]. To continue to maintain normal unbound thyroid hormone levels, thyroid gland needs to increase its thyroid hormone production. Some studies have reported a decrease, whereas others have stated even an increase of free T4 (FT4) and T3 (FT3) making the changes in free-hormone levels during pregnancy controversial. Despite this, pregnant women in general have lower free-hormone concentrations at term than nonpregnant women [17, 25, 26]. Because

	TSH range
First trimester	>0.1 mIU/L and < 2.5 mIU/L
Second trimester	>0.2 mIU/L and < 3.0 mIU/L
Third trimester	>0.3 mIU/L and < 3.0 mIU/L

TSH, thyroid-stimulating hormone.

Table 1.
Generalized trimester-specific reference ranges for TSH levels [21].

FT4 reference intervals in pregnancy vary widely between methods, interpretation of FT4 values requires method-specific as well as trimester-specific ranges.

The placenta is also an active player in thyroid hormone metabolism. It is a site for the inner ring deiodination of T4 and T3, generating the inactive iodothyronines, reverse T3 and 3,3′-T2, respectively, and thus modulating the amount of active hormone that passes to the fetus [27]. Because of the increased thyroid hormone requirements and iodine glomerular filtration rate during pregnancy [28], adequate iodine availability is strongly necessary to meet these needs. In iodine-replete regions, women are able to meet the increased demands of pregnancy. If adequate iodine is not available, TSH rises and consequently goiter develops [29]. Thyroid hormones play a vital role in the early embryogenesis. They are essential for neurodevelopment, somatic growth, and tissue differentiation. Because, organogenesis of fetal thyroid gland occurs by around 12-th week of gestation and the gland becomes functionally active approximately eight weeks later by the 20-th week of gestation, till then, the fetus fully relay on maternal T4, which is the only thyroid hormone that can cross the placenta. Fetal deiodinase converts maternal T4 to the bioactive T3The [30].

After his thyroid gland becomes active and starts to produce hormones, fetal thyroidal turnover of iodine increases and becomes much higher than that in adults [30]. Fetal iodine store, which exclusively depends from maternal intake, must be continuously refilled. Iodine homeostasis, following fluctuating metabolic needs varies across the different trimesters. After parturition, maternal iodine continues to be the only source of iodine to the breast-fed neonate. Sodium Iodine symporter (NIS) is present in breast tissue and is responsible for concentrating iodine in colostrum and breast milk [31].

3. Thyroid autoimmunity in pregnancy

In around 10% of the women with childbearing potential thyroid antibodies could be found and they represents the most common autoimmune disease. Stagnaro-Green et al. in 1990 first demonstrated an association between pregnancy loss and thyroid antibodies. They showed, that there was a 2-fold increase in the risk of pregnancy loss (17% vs. 8.4%) in women with thyroid antibodies [32]. One meta-analysis discovered, that the presence of thyroid antibodies in pregnant women was connected with a 4-fold increased risk of miscarriage in cohort studies, and a 1.8-fold increased risk in case–control studies [33]. The association of thyroid autoimmunity and preterm birth is not unambiguously as the studies showed conflicting results. Some found significant association [33–36], while others [37] didn't show such correlation.

Following the changes of the activity of the immune system through pregnancy, the activity of Graves' disease fluctuates. Concomitant changes of the TSH receptor antibody (TRAb) levels, generally reflecting the clinical course of the disease, are observed [38]. During the first trimester TRAb levels are usually elevated with a subsequently fall to even undetectable values during the second and third trimesters and may increase again postpartum [39, 40]. Due to this pattern of fluctuations of TRAb levels, exacerbation of the clinical symptoms of Graves' disease may occur in the first trimester of gestation, followed by a remission in the second and third trimesters, because of the observed immune tolerance [41]. The decrease in TRAb levels, rather than increases in inhibitory anti-TSH receptor antibodies determines this clinical pattern [39]. From a clinician's point of view, the dosage of antithyroid drugs can be reduced or even discontinued late in gestation and restarted in the postpartum period [41].

4. Hyperthyroidism and pregnancy

Hyperthyroidism is defined as an excessive production of thyroid hormones caused by immune or nonimmune thyroid disease. Hyperthyroidism is less common than hypothyroidism, but nevertheless, it represents a great challenge for the physician, pregnant woman and developing fetus. Specific knowledge is required by healthcare providers and a team approach is necessary to provide the best possible cares for pregnant women with GD. Caring physicians (gynecologists, endocrinologists, cardiologists) must be aware of the symptoms of thyrotoxicosis, often overlapping with the pregnancy itself and of specific changes of the thyroid hormones during pregnancy. Knowing the fact, that any pregnancy complicated with hyperthyroidism carries a greater risk for complications for both mother and developing fetus, proper diagnosis and treatment are necessary. Adequate decisions about when to start treatment and with what to start are required, following the ancient principle of *primium non nocere*. Although our therapeutic approaches didn't change very substantially during the last fifty years, our understanding of the pathophysiology, hormonal changes, immunology and obstetric outcomes have changed dramatically. We still have at our disposal only two types of antithyroid drugs (ATD) (see later in the text), which are the same that had been in use since the 1950's and still remain the cornerstone of treatment of GD in pregnancy. Rarely, other approaches are necessary, like surgery during the second trimester. Radioiodine ablation is absolutely contraindicated. Close monitoring of thyroid hormone levels and frequent adjustment of the dose are necessary to avoid both overdosage or subdosage of antithyroid drugs.

The reasons for thyrotoxicosis during pregnancy can be divided in such typical for all patients and such specific for the pregnancy. The common causes for thyrotoxicosis include: Graves' disease, chronic thyroiditis, painless thyroiditis, subacute thyroiditis, toxic adenoma, multinodular goiter; excessive levothyroxine (LT4) intake and drug induced thyrotoxicosis caused by iodine, amiodarone, lithium. The causes of thyrotoxicosis specific for the pregnancy are: gestational transient thyrotoxicosis, multiple gestations, trophoblastic disease, hyperplacentosis, hyperreactio luteinalis [22]. Grave's disease and gestational transient thyrotoxicosis (GTT) account for the majority of hyperthyroidism in pregnancy. Graves' disease affects 0.2% of pregnant women [42]. Thyrotoxicosis during pregnancy could affect both pregnant woman and developing fetus. Hyperthyroidism may cause both maternal complications such as heart failure, eclampsia and thyroid storm and also higher incidence of abortion, preterm delivery, low-birth-weight infants and neonatal mortality [43]. Distinguishing between different causes of hyperthyroidism is relevant, because some of them, like GTT, are transient, lead to mild thyrotoxicosis and do not require treatment with antithyroid drugs and are not associated with adverse pregnancy outcomes [44]. The Endocrine Society recommends that screening for thyroid conditions in pregnancy is performed in women >30 years, those with previous personal or family history of thyroid disease, women with issues with conception and existing autoimmune conditions [45].

5. Graves' disease and pregnancy

As it has been already discussed, generally there are three scenarios in which Graves' disease may affect a pregnancy. *First*, women with preexisting active Graves'disease. *Second,* women in remission, who may experience a relapse during pregnancy. *Third*, Graves' disease may occur for the first time during gestation [46].

The women with prepregnancy active disease (either treated or untreated) may undergo exacerbation during the first trimester. Those, with previously diagnosed GD, who stayed in clinical remission and remained euthyroid throughout the whole pregnancy, hyperthyroidism may recur in the postpartum period. We must be very careful in this situation, because this may represent either the thyrotoxic phase of postpartum thyroiditis (PPT) or in up to 25% or relapse of Graves' disease. Even in those with PPT, Graves' disease may recur after resolution of PPT, triggered by the destruction of the thyrocytes [47].

5.1 Diagnosis

Diagnosis should begin with taking complete case history, medical history and family history. The clinical diagnosis of hyperthyroidism may be *difficult* because pregnancy is itself a hypermetabolic state with symptoms of palpitations and heat intolerance. In addition, patients will usually have increased irritability, decreased exercise tolerance, heat intolerance, fatigue and increasing shortness of breath during physical activity. The examination usually reveals the presence of a diffuse goiter, sometimes with a bruit or thrill and eye changes. The clinician must recognize this constellation of symptoms so that the patient can be appropriately screened for hyperthyroidism. Once, hormonally hyperthyroidism has been established, it is very important to go deeper into the specific reason which causes it, because all types of thyrotoxicosis are characterized with similar changes of thyroid hormones. Different reasons for hyperthyroidism during pregnancy require different therapeutic approaches. Some are self-limiting and do no require treatment with ATD but only follow up.

5.2 Differential diagnosis

The most common cause of nonautoimmune hyperthyroidism is gestational transient thyrotoxicosis (GTT), defined as transient hyperthyroidism, limited to the first trimester of pregnancy. It is associated with hyperemesis gravidarum (HG) and is characterized by elevated serum FT4 and suppressed or undetectable serum TSH. It is differentiated from Graves' disease by the absence of anti-TSH-receptor antibody (TRAb) [48]. Hyperemesis gravidarum often presents in the first trimester of pregnancy with severe nausea and vomiting [49]. It may result in dehydration and ketonuria. Thyroid hormones return to their normal trimester specific reference ranges within 15 weeks, due to resolution of vomiting. Initially FT4 normalized spontaneously; however, serum TSH may remain suppressed for several other weeks and does not require ATD therapy, because this condition is self-limiting [50]. Rarely, for example in the case of dual or triple pregnancy, connected with very high level hCG, the use of ATD is required due to the severity of symptoms. For the clinical practice, it is very important to differentiate between GTT and Graves' disease. The presence of goitre, thyroid eye disease (Graves' orbitopathy) and TRAbs in Graves' disease and their absence in GTT can help for proper diagnosis. Because in both conditions there are similar changes of TSH (low) and FT4(high) levels, using a free T3/free T4 ratio could be discriminatory. Often the patients with gestational thyrotoxicosis have significantly lower or even normal T3 values [51].

Subclinical hyperthyroidism, defined as a serum TSH concentration below the lower limit of reference range, with FT4 and FT3 concentrations within normal reference range, affects up to 1.7% of pregnant women. This condition has not been found to be associated with adverse outcomes and doesn't require ATD therapy [31].

5.3 Laboratory

The usual findings from the laboratory studies show low, below the trimester-specific 95% lower confidence limit, TSH level together with elevated serum thyroid hormone (FT4 and FT3) concentrations. We should always consider the fact that up to 50% of women with hyperemesis gravidarum may have similar changes of theh hormonal levels (suppressed serum TSH level and/or elevated FT4) [52]. An elevated free T3 index or free T3 level may be the most clinically useful test to distinguish hyperthyroid patients from those with hyperemesis gravidarum as less than 15% of hyperemetic women have elevations in these measures. TSH receptor antibodies are usually detectable and may also be of diagnostic utility. High levels of TRAb cross placental barrier [53]. and the risk of fetal and neonatal thyrotoxicosis increases with TSRAb values 3–5 times above normal [54, 55].

5.4 Pregnancy outcomes

Maternal hyperthyroidism is associated with increased morbidity for both mother and fetus. Prior to the development of ATD, only about 50% of hyperthyroid women were be able to conceive. About in half of those who conceived, spontaneous miscarriage and premature delivery occurred [56]. The degree and duration of hyperthyroidism strongly correlate with pregnancy outcomes for both mother and fetus. The highest risk was reported in those with uncontrolled or poorly controlled disease and a decreased risk in those appropriately treated with ATD. Established thyrotoxicosis during gestation or before a planned pregnancy, requires appropriate treatment, because in cases with uncontrolled maternal hyperthyroidism in the first trimester, the period of embryogenesis, there is an increased risk for congenital malformations (imperforate anus, polydactyly, harelip) [57]. The use of ATD during this period itself is not associated with a higher incidence of structural anomalies. For optimal pregnancy outcomes it is very important to keep maternal hyperthyroidism under control, avoiding the development of drug induced hypothyroidism, understanding the crucial significance of thyroid hormones for the normal embryogenesis. Significantly, subclinical hyperthyroidism, has not been found to be associated with adverse pregnancy outcomes and doesn't require antithyroid therapy [22]. Pregnancy complications reported in hyperthyroid women vary in frequency in different studies and include: miscarriage from 8 to 10–21% [58, 59], preterm delivery [58, 60, 61] from 3 to 14% to 21–88%, preeclampsia [60] from 2–11%, heart failure [61] from 3–63%, stillbirth [58, 61] from 0% -7 to 50%, small for gestational age [59, 62] and thyroid storm during delivery.

5.5 Treatment

Unfortunately, because the cause of the immune dysregulation in Graves' disease remains unclear, the available treatments are directed at the thyroid gland rather than the underlying autoimmunity. In general, the available therapies include: Antithyroid drugs, surgery and radioiodine, with predominant use of ATD in pregnancy hyperthyroidism, surgery in exception, during the second trimester and iodine ablation being absolutely contraindicated. Because the degree of hyperthyroidism can vary from patient to patient, those who are relatively asymptomatic may remain undiagnosed and untreated till the delivery, when usually aggravation of thyrotoxicosis is observed. Even when they had been properly diagnosed, they may do not want to accept the diagnosis and ask whether specific treatment is really necessary, fearing of possible side effects of the drugs both for them and for their developing fetuses. Usually they consider their complaints to be related with

the pregnancy itself. Those with overt hyperthyroidism require restoration of a euthyroid state because of potentially negative outcomes, both for the mother and the fetus. Fully controlled hyperthyroidism substantially decrease the potential risk for these negative outcomes and at the same time is not a reason for recommending abortion.

Therapeutic approaches differ from case to case. In the *first* scenario, when GD is preceding pregnancy, the woman will be advised to conceive after restoration of euthyroidism. Taking into account patent's plan for the time of the future pregnancy, treatment with thionamide drugs is started, and the treatment continues throughout the whole pregnancy. In this case, the patient should be fully aware of the possible side effects of ATD, both for the mother and fetus and of the need for frequent monitoring of thyroid hormones levels. To avoid this an if the woman with GD is willing to postpone her future pregnancy, than alternatively radioiodine ablation can be offered. Pregnancy should be delayed for at least 4 months after radioiodine therapy, but a longer period, 6 months or even a year, is usually required for restoring euthyroid state and establishing the necessary stable dose of the inevitable postablational replacement therapy with thyroid hormones. Surgery may also be considered as an alternative because of more rapid restoration of euthyroidism.

In the *second* scenario, if GD is diagnosed during pregnancy, ATD are almost the only therapeutic option. Radioiodine is absolutely contraindicated, because it may result in congenital hypothyroidism and may cause malformations. Thyroidectomy is restricted to exceptional cases.

In the *third* scenario, if GD is established after delivery and when the possibility of transient, self-limiting destructive thyrotoxicosis has been excluded, it is prudent to start thionamide treatment. In this case breast feeding should be stopped, because of the risk for development of neonatal hypothyroidism (see below). Radioiodine ablation with its delayed effect of achieving euthyroidism, the need for concomitant use of ATD to control symptoms in some cases and the need for isolation for several days, usually is not well accepted by the mothers. Surgery is an option in patients who experienced side effects of ATD use, or found it difficult to adhere to the prescribed drugs, either due to the number of pills or to the frequency of their intake.

Decision to initiate ATD treatment depends on the severity of the clinical symptoms and the pretreatment levels of FT4, FT3 and TSH. In mild cases with Graves' disease, when FT4 values are at or slightly above the reference range, treatment may be withheld with a subsequent monitoring of the thyroid status as long as there is a satisfactory clinical progression of pregnancy. In other words, the pregnant woman with Graves' disease should be kept in slight *subclinical hyperthyroidism*, because there are no reported gestational adverse effects of maternal subclinical hyperthyroidism [63]. The goal of treatment is to keep the patient euthyroid, using the lowest possible dose of antithyroid drugs necessary to maintain FT4 levels in the upper one-third of the normal non pregnant range or up to 10% above the normal range [64]. This level will ensure fetal euthyroidism, because FT4 in the mother's serum correlates with fetal FT4 levels in cord blood [65]. Maternal serum T3 levels may not be as helpful because there is no correlation with fetal thyroid function [66] The dose should be adjusted every 2–4 weeks to maintain a serum FT4 of 1.7 to 2.0 ng/L and TSH at or just below at the 95% confidence interval trimester-specific lower limit [67]. The presence of detectable TSH is an indication to decrease ATD dose [60]. A low TSH level is not a reliable index to judge the adequacy of treatment, because it doesn't promptly reflect the changes in thyroid function like FT4. It is important to monitor TSH level, because a high level always indicates over dosage of ATD and the need for proper dosage correction of the drugs. Because of

the expected immunosuppression during the second and third trimester, a partial and transient remission of Grave's disease may occur and appropriate reduction of the dose or even discontinuation of ATD could be done. Otherwise excessive doses of ATDs, indeed, may affect fetal thyroid function, with the development of hypothyroidism and/or goiter [68, 69]. Relapse of the hyperthyroidism is frequent in postpartum period [70].

5.5.1 Antithyroid drugs

ATD are the first choice for treatment of Graves' disease during pregnancy. Propylthiouracil (PTU) and methimazole (MMI) are equally effective in the management of hyperthyroidism during pregnancy. Propylthiouracil and methimazole inhibit thyroid hormone synthesis by interfering with intrathyroidal iodine utilization and the iodotyrosine coupling reaction, both of which are catalyzed by thyroid peroxidase. Antithyroid drugs do not directly affect iodine uptake or hormone release by the thyroid. Because of this, the clinical and hormonal improvement is delayed for 10-14 days after their implementation in the therapeutic regimen. PTU, but not methimazole, inhibits the conversion of T4 to T3 in peripheral tissues, thus theoretically it can ensure faster alleviation of the symptoms and reaching the desired levels of FT4. In clinical practice this is not considered relevant. Comparative study showed that methimazole generally normalizes serum T4 and T3 levels faster than PTU [71]. Both antithyroid agents are well absorbed from the gastrointestinal tract. They differ in their ability to bind to proteins in circulation, with PTU being strongly protein-bound, mainly to albumin, at physiologic pH, while methimazole binding to proteins is negligible [72]. Other studies have found that both drugs readily cross the placenta [73, 74]. The serum half-lives of PTU and methimazole are 1 and 4 to 6 hours, respectively. The intrathyroidal duration of action of both drugs is longer than that. Both drugs are metabolized in the liver and their metabolites are excreted by the kidney. However, so far there are no data, that the doses used to treat hyperthyroidism generally need to be altered in patients with liver or kidney disease. This characteristic, apart from their side effects, may determine the choice of the antithyroid drug in pregnancy and lactation, since PTU crosses the placenta and breast epithelium less readily than methimazole. So it is reasonable to begin therapy with PTU because there are no reported cases of PTU-associated aplasia cutis. However, if a woman cannot tolerate PTU for any reason, experience side effects does not want to take the prescribed number of pills (PTU usually requires multiple daily dosages, whereas MMI can often be given once daily), MMI may be substituted. The initial dose rarely exceeds more than 450 mg of PTU or 30 mg of MMI daily in order to achieve the predefined levels of FT4 and TSH. The median time, usually seven to eight weeks, to normalization of the maternal FT4 index for both PTU and MMI is equal [75], but improvement in these parameters may be seen earlier at three to four weeks. This fact, makes clinically relevant to reassess maternal FT4 or total T4 at an interval of three to four weeks and to adjust ATD dosage appropriately based upon the current levels of thyroid hormones. We should keep in mind, that maternal serum TSH levels may remain suppressed for several weeks after normalization of thyroid hormone levels. So measuring TSH level is not helpful early in treatment, and may mislead us to continue with the unnecessary high dose of ATD, causing drug induced hypothyroidism and thus depriving the developing fetus from crucially important maternal T4 delivery. As was discussed above, due to the changes of the activity of Graves' disease throughout pregnancy, determined by fluctuations of TRAbs concentrations, in the late second and third trimesters the dose of ATD can be reduced or even stopped by 32 to 34 weeks of gestation in 30% of women [76]. Of course, the

same spectrum of adverse effects related to ATD therapy in the nonpregnant state applies to use during gestation.

Both drugs are showing similar fetal outcomes, in terms of thyroid function. The risk for congenital abnormalities had been considered to be higher in MMI than in PTU.

Aplasia cutis and also other malformations have been reported in the offspring of mothers who had taken methimazole during pregnancy [67, 77]. Aplasia cutis is a congenital localized absence of skin that occurs spontaneously in approximately 1 in 2000 births [78]. Many years, the fear from the possible development of this complication had restricted the use of methimazole during pregnancy, nevertheless, there is no definitive proof that MMI is actually responsible for the condition. Additional possible congenital malformation in children exposed to MMI during the first trimester of pregnancy are choanal and esophageal atresia, minor facial abnormalities and psychomotor delay, which either isolated or associated with aplasia cutis define the so called methimazole embryopathy [67, 77].

Because there are no reports of aplasia cutis in association with PTU, this drug is preferred by some physicians. Growing data from the literature for the causative roll of PTU for acute liver injury, had limited the use of the drug only during the first trimester of the pregnancy due to its lower risk for congenital malformations. Before pregnancy and during the second and third trimester methimazole is preferred, considered to be less hepatotoxic. Pregnancy itself does not appear to alter the maternal pharmacokinetics of MMI, although serum PTU levels may be lower in the latter part of gestation compared to the first and second trimesters [71].

The treatment of Graves' disease during pregnancy should aim to achieve normalization of FT4 and FT3 levels with strict monitoring of maternal thyroid function at an appropriate intervals. Careful surveillance of fetal development to optimize fetal outcomes is also important, and this makes the team approach with a close collaboration between endocrinologist and obstetrician crucial. Apart from monitoring the laboratory parameters, there are clinical signs of improvement, that include maternal weight gain, decrease in pulse rate and appropriate fetal growth, that should be followed up. Clinical signs and laboratory values must always be considered together when a therapeutic decision is necessary, and if for example, there is a detected lack of maternal weight gain in conjunction with mild elevations in thyroid hormone levels, the initiation of a low dose of ATD should be considered.

5.5.1.1 Antithyroid drugs: effect on the Fetus

In pregnancies complicated with concomitant Graves' disease, fetal thyroid status is influenced by two maternal factors, both of which cross the placenta: maternal ATD dosage and maternal TRAb activity. There are two potentially opposing influences on fetal thyroid function by maternal TRAb, because they can be with either stimulating or blocking effect on the developing fetal thyroid gland. Different assays for maternal TRAb exist. Some, like one of the most commonly used radioreceptor assay does not distinguish between blocking and stimulating antibodies, so their peripheral effect can be estimated only by assessing the thyroid function [79]. The currently available bioassay is the thyroid stimulating immunoglobulin (TSI), which measures the generation of cyclic adenosine monophosphate by cells that express TSH receptor when incubated with the patient's serum [66].

Because both PTU and MMI can cross the placenta and they may decrease fetal thyroid hormone production The dose–response relationship between maternal ATD dose and neonatal thyroid function is controversial, as some studies have

reported a direct correlation [66, 69, 80] and others have not demonstrated this [64, 69, 73]. There are data showing that ATD drugs even at low daily dosages (PTU ≤ 100 mg, MMI ≤ 10 mg) at term may affect the fetal thyroid function. An elevated cord TSH level was found in 23% of babies born to such PTU-treated mothers and in 14% of those treated MMI [81]. There is an individual variability in serum PTU and MMI levels after a standard oral dose and that could partly explain the observed lack of correlation between maternal dosage and fetal thyroid function [81, 82]. Transplacental passage of maternal TRAb resulting in excessive fetal thyroid stimulation is the second factor that can influence fetal thyroid function. Usually, this becomes clinically relevant at 24 to 26 weeks, of gestation. Maternal levels reflect the degree of fetal exposure [83]. At term there is a strong correlation between maternal and cord TRAb levels with development of neonatal hyperthyroidism. Clinically relevant is to measure the maternal TRAb levels at term, because the combination of continued use of maternal ATD therapy with low maternal TRAb levels may lead to elevated serum TSH levels in approximately 50–60% of infants [80]. This shows how important is to adjust appropriately the maternal ATD dosage during pregnancy especially when maternal immune thyroid stimulation is low. In nonimmune types of thyrotoxicosis, like toxic adenoma for example, dose relationship between ATD and the risk of suppression of the fetal thyroid function is more profound, since there is no contribution of fetal thyroid stimulation by the maternal immune system. Therefore, it is not surprising that fetal thyroid status is not strictly correlated with maternal ATD dosage. Inappropriately high doses of ATD may result in development of fetal or neonatal goiter, which in the most severe cases if markedly enlarged at birth may cause respiratory distress. In the past, due to the concomitant iodide therapy and ATD, goiter occurred more frequently. The combined inhibitory effect on the fatal thyroid gland of iodide and ATD resulted in the development of goiter. One clinical approach is to perform a fetal utrasound in all women who are still taking relatively high ATD doses at 26 to 28 weeks (PTU ≥450 mg/day, MMI ≥30 mg/day) [84]. If a fetal goiter is detected this could be due to either fetal hyperthyroidism, transplacental passage of stimulating TRAbs, or to fetal hypothyroidism caused by transplacental passage of maternal ATD therapy. In both situations intrauterine growth retardation may occur. The presence of fetal tachycardia (160–180 beats per minute) and advanced fetal bone age is highly suggestive of hyperthyroidism [85, 86]. When caused by maternal ATD use, a quick resolution within two weeks after birth of the neonatal goiter is observed, reflecting the discontinuation of drug exposure [69]. Therefore, stopping maternal ATD therapy and monitoring the fetal goiter by ultrasound is advisable. Other therapeutic approach for treatment of the fetal goiter due to maternal ATD exposure includes intra-amniotic levothyroxine injections [87, 88], but because it was done concomitantly with lowering of the maternal PTU dose, it is difficult to estimate the relative importance of each factor on the resolution of the fetal goiter. The cessation of maternal ATD therapy alone may result in decrease in the fetal goiter assessed ultrasonographically [89]. Discontinuation or decreasing the dose of ATD therapy is crucial in cases where hypothyroidism is suspected because of transplacental ATD passage. Fetal goiter must be followed with sequential ultrasounds and if no reduction in size, within two to three weeks, occurs, fetal thyroid function should be determined by performing periumbilical blood sampling, and intra-amniotic levothyroxine therapy should considered if necessary. Several studies have reported no cognitive and somatic defects in development of children exposed to maternal ATD in utero [90–93] and this was so even after accounting for higher dosage or first trimester exposure. These were cross sectional studies that measured cognitive development by intelligence quotient. Therefore, it is unknown if transient, or more subtle developmental changes might have been present.

5.5.2 Beta-adrenergic blockers

Considering the relation between thyroid hormones and sympathetic nervous system, beta-adrenergic blocking agents may be used transiently to control adrenergic symptoms, while waiting for ATD therapy to decrease thyroid hormone levels. The fact, that combined use of ATD and propranolol in comparison with ATD alone was related with a higher rate of spontaneous first trimester miscarriages, although the similar levels of thyroid hormone [94], beta-blockers should be used for short period and with caution.

5.5.3 Iodides

As was previously discussed, chronic use of iodides during pregnancy has been associated with hypothyroidism and goiter in neonates, sometimes in severe cases resulting in asphyxiation because of tracheal obstruction [95]. Iodides should not be used as a first line therapy in women with Grave's because of the well-known dual effect of iodine upon the thyroid function and the risk for provocation of a latent autoimmune disorder and also for aggravation of the thyrotoxicosis increasing the iodine store in an already hyperfunctioning thyroid gland. Iodides could be used transiently if needed in preparation for thyroidectomy.

5.5.4 Surgery

Subtotal thyroidectomy for Graves' disease is rarely considered during pregnancy. The reasons for such treatment could be the need to use high levels of ATD (PTU 450 mg/day, MMI 40 mg/day) to control the clinical symptoms and thyroid hormonal levels, if compressive symptoms due to goiter size develop or if a patient is allergic to ATD therapy or noncompliant to the therapeutic regiment. The surgery is usually performed in latter half of the second trimester. The surgery in the first trimester is relatively contraindicated, because that this is the time of the highest spontaneous abortion rate and surgery and anesthesia could possibly further increase the risk, but if clinically indicated subtotal thyroidectomy may be done in some specific cases [96].

5.5.5 131I therapy

The use of 131I therapy is completely contraindicated in pregnancy. The most vulnerable for the fetus period to 131I therapy is that after 12 weeks gestation, because at this period the fetal thyroid begins to concentrate radioiodine at higher rate than the maternal thyroid and other fetal tissues are generally more radiosensitive [97]. It is essentially important to exclude pregnancy in all women prior to radioiodine therapy. The therapeutic administration of 131I to a nursing mother is contraindicated and lactation should be stopped immediately if this occurs.

5.6 Lactation

Because the ATD present in breast milk in sufficient concentrations that can influence infant's thyroid, their use in breast-feeding women was considered contraindicated. Due to the ability of PTU to bind more tightly with protein than MMI, less amount of PTU is available in the milk. The ratio of milk to serum levels is found to be lower for PTU (0.67) [98] than for MMI (1.0) [99], moreover the amount of ingested drug secreted in breast milk is approximately six

times higher for MMI than for PTU (0.14 vs. 0.025% of the ingested dose) [99]. Despite this, the fetal thyroid function assessed in newborns breast-fed by mothers treated with ATD with daily doses of PTU (50–300 mg), MMI (5–20 mg), or carbimazole (5–15 mg) for periods ranging from three weeks to eight months, remained normal, even in overtreated women with elevated serum TSH levels [100]. Data from the literature show that ATD therapy (PTU 300 mg/day, MMI 20 mg/day) may be considered relatively safe during lactation [100]. Generally, PTU would be preferred than MMI, because of its less availability in breast milk. It is wise the drug to be taken by the mother after a feeding. So far, there are no reports of the development of ATD side-effects in an infant breast fed by a mother treated with ATD [101].

Abbreviations

GD	Graves' disease
TSH	Thyroid-stimulating hormone
TSHR	Thyroid-stimulating hormone receptor
GTT	Gestational transient thyrotoxicosis
ATD	Antithyroid drugs
hCG	Chorionic gonadotropin
TBG	Thyroid-binding globulin
TT4	Total thyroxine
TT3	Total triiodothyronine
FT4	Free thyroxine
FT3	Free triiodothyronine
rT3	Reverse triiodothyronine
NIS	Sodium Iodine symporter
TRAb	TSH receptor antibody
PPT	Postpartum thyroiditis
PTU	Propylthiouracil
MMI	Methimazole
HG	Hyperemesis gravidarum

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