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Pregnancy in Women with Graves' Disease: Focus on Fetal Surveillance

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Abstract

Graves' Disease (GD) is one of the most common autoimmune conditions in women of reproductive age. The disorder is characterized by the presence of pathogenic immunoglobulins that bind the TSH receptors (TRAbs) and stimulate the production of thyroid hormones leading to hyperthyroidism (the occurrence of inhibiting or neutral antibodies being rare). Affected individuals can be treated by radioiodine therapy, surgical removal of the gland or by antithyroid drugs (ATDs). Thyroid stimulating immunoglobulins may persist for years after medical treatment, radioiodine therapy or surgical removal of the gland in those affected by GD and during pregnancy can cross the placenta and can act on the fetal thyroid gland resulting in the development of fetal and neonatal hyperthyroidism and sometimes to goiter. Antithyroid drugs used during pregnancy can also cross the placenta and may be teratogenic and act on the fetal thyroid gland, leading to fetal and neonatal hypothyroidism and goiter. This chapter will discuss specific aspects of GD during pregnancy and postpartum focusing on fetal and neonatal consequences related to this disorder.

Keywords: pregnancy, Graves' Disease, TRAb, anti-thyroid drugs, fetal goiter, fetal hypothyroidism, fetal hyperthyroidism

1. Introduction

Graves' Disease (GD) is one of the most common autoimmune conditions in women of reproductive age. Pathogenic immunoglobulins that bind the TSH receptors (TRAbs) are the hallmark of GD and stimulate the production of thyroid hormones leading to hyperthyroidism (the occurrence of inhibiting or neutral antibodies being exceptional). Treatment for affected individuals is either by radioiodine therapy, surgical removal of the gland or by antithyroid drugs (ATDs). TRAbs may persist for years after medical treatment, radioiodine therapy or surgical removal of the gland in those affected by Graves' Disease and during pregnancy can cross the placenta by hijacking the physiological maternal-fetal antibody transfer pathways [1] and can act on the fetal thyroid gland resulting in the development of fetal hyperthyroidism and sometimes to fetal goiter. Antithyroid drugs used during pregnancy can also cross the placenta and may be teratogenic and act on the fetal thyroid gland, leading to hypothyroidism and fetal goiter.

The maternal thyroid gland undergoes extensive changes during pregnancy and postpartum. These changes are supported by the interaction between the fetal-placental unit and the maternal endocrine system and are reflected in the thyroid

function tests, which differ from outside pregnancy as early as first trimester. Normal fetal development depends on maternally derived thyroid hormones (TH) at least until 16–18 weeks' gestation when the fetal thyroid starts to function [2].

This chapter will discuss specific aspects of Graves' Disease during pregnancy and postpartum with focus on its fetal and neonatal consequences.

2. Physiological changes of the thyroid gland and the thyroid hormone metabolism during pregnancy

The maternal thyroid gland and thyroid hormone metabolism undergo significant changes in pregnancy. The volume of the gland and its blood supply increase in pregnancy [3]. Plasma volume expands thus increasing total T4 and T3 pool size (T4 - thyroxine and T3 - tri-iodothyronine). The placenta produces estrogen that induces hepatic synthesis of thyroid-binding globulin (TBG), the main protein involved in serum transport of TH, thus increasing levels of total T4 (TT4) and T3 (TT3) in the maternal plasma. Thyroid hormone production is dependent of iodine supply so iodine metabolism needs to keep up with these changes, hence, there is an increase in iodine requirements during pregnancy to both meet the maternal and fetal demands and to overcome the increased clearance by the kidneys. The placenta also produces HCG (human chorionic gonadotropin), a glycoprotein hormone with molecular similarity of its α -subunit with TSH (thyroid stimulating hormone) which acts as an agonist of TSH raising transiently free T4 levels and decreasing serum TSH levels. These changes are more relevant to the first trimester, and, beyond it, maternal thyroid hormone levels gradually return to those seen in the nonpregnant state [4].

Thyroid hormones are essential for normal development of the fetus and particularly of the fetal brain. The fetal thyroid gland only starts to produce adequate amounts of thyroid hormones in the second trimester; the first trimester fetus relies on maternal delivery of thyroid hormones to develop [2]. In the first part of pregnancy, before the fetal thyroid starts to work, T4 can be detected in fetal blood and brain, indicating that there is relevant transfer of maternal thyroid hormones to the fetus. The way maternal thyroid hormones are transferred across the placenta and in the fetal brain is not completely understood. Even though thyroid hormones are lipophilic, they can not passively cross the placenta nor the fetal blood–brain barrier because they are charged and thus can not cross a phospholipid bilayer [5]. Passage across the placenta and into the fetal brain is thought to be dependent on the function of several mechanisms [6] including: the existence of a specific transportation system, the function and expression of iodothyronine deiodinases (D) (enzymes that TH) in the placenta and fetal brain, and proteins within trophoblast and fetal brain which specifically bind TH. At the level of the placenta specific transporters capable of transporting maternal TH like monocarboxylate transporters MCT8 and MCT10 have been identified [6, 7]. Deiodinases found in the placenta in high concentration are D3, the main inactivating enzyme that catalyze monodiodination of T4 to reverse T3 and of T3 to T2, but also, D2, which the primary activating enzyme in tissues and locally catalyzes the monodeiodination of T4 to T3 [8]. The iodine released by this process might be used as a substrate by the fetus for the synthesis of its own thyroid hormones. D2 has been identified in the fetal brain [9] converting T4 to active T3, thus making it readily available. In the serum, TH are bound to liver-synthesized transportation proteins mainly TBG but also albumin and transthyretin. Transthyretin has been identified in the placenta and fetal choroid plexuses and is thought to play a role in transporting TH into the cells [10]. TSH does not cross the placenta and TSH in the fetal blood remains relatively constant throughout pregnancy between 4–8 mU/L [11]. The coordination and interplay between these systems ensures adequate availability of maternal TH to the fetus in a critical period of development (**Figure 1**).

Figure 1.
The interaction between the fetal-placental unit and the maternal endocrine system during pregnancy. TRH – Thyrotropin releasing hormone; TSH – Thyroid stimulating hormone; T3 – tri-iodothyronine; T4 – Thyroxine; HCG – human chorionic gonadotrophin; TBG – thyroid hormone binding globulin; D3 – type 3 iodothyronine deiodinase; D2 – type 2 iodothyronine deiodinase; rT3 – Reverse T3.

3. Thyroid function tests in pregnancy

The physiological changes occurring in the thyroid gland from the beginning of pregnancy reflect in changes of the thyroid function tests. International guidelines recommend that ideally, for each population, there should be available trimester specific normal ranges for TSH and maternal TH [4]. These data should be derived from studies in healthy pregnant women with no known thyroid disease, with no evidence of thyroid autoimmunity and with an adequate amount of iodine intake for each trimester of pregnancy. In the absence of such data, which in many clinical settings can be difficult to obtain, in order to determine normal first-trimester reference ranges for TSH it has been suggested that the lower limit of its reference interval used in the non-pregnant state can be reduced by 0.4 mU/L and the upper limit by 0.5 mU/L [4]. For a healthy young pregnant woman the upper limit of TSH would therefore correspond to a value of 4.0 mU/L in the first trimester. This downshifting of the normal TSH reference interval only applies to the first trimester values, between 7 and 12 weeks of pregnancy since in the second and third trimesters, TSH levels recover and intervals valid outside pregnancy could be used.

The second most common test used to investigate thyroid function outside as well as in pregnancy is free T4 (FT4). FT4 represents the thyroxine that is not bound to plasmatic proteins; it constitutes less than 0.1% of total T4 (TT4) but is the active form that is up taken by cells. Precise measurement of FT4 is difficult in pregnancy in part because of the limitation of the widely used commercial immunoassays to account for thyroid hormone concentration changes that occur under the influence of increased levels of TBG, nonesterified fatty acids and decreased albumin.

Therefore, it has been suggested that TT4 and the index of T4 are more accurate in determining shifts in thyroid hormone levels in pregnancy. With TT4 it is important to acknowledge that its level increases by 50% during weeks 7 to 16 and remain high thereafter throughout pregnancy. When the level of TT4 is determined before 16 weeks, an adjustment to the upper limit of the non-pregnancy interval by 5% per week between weeks 7 to 16 could be made. A TT4 measurement with reference value 1.5 times the non-pregnancy range may be used in second and third trimesters as discussed above. When trimester-specific FT4 values are not available, use of the reference range for non-pregnant patients is recommended [4, 12–14].

4. Graves' Disease in pregnancy

4.1 Incidence and pathophysiology

Graves' Disease is one of the most common causes of thyrotoxicosis in women of reproductive age. It has been reported in as much as 1 in 500 pregnancies [15] but is more frequent in the years prior and after conception. GD presents clinically in pregnancy as outside pregnancy with hyperthyroidism, goiter, ophthalmopathy. The condition is autoimmune and is characterized by the presence of abnormal autoantibodies (TRAbs) directed against the TSH receptor in the thyroid gland. These antibodies, unlike anti-thyroperoxidase and anti-tyroglobulin antibodies, do have a pathogenic role in the thyroid-related and extra-thyroidal manifestation of GD and in pregnancy can cross the placenta and act on the fetal thyroid gland [16]. TRAbs are the pathogenic hallmark of GD and are measurable in around 95% of patients with active Graves' hyperthyroidism but can also be found, sometimes in high levels, in patients with a history of treated GD [17]. TRAbs are usually of the stimulating type, but blocking or neutral autoantibodies have been described [18]. TRAbs can cross the placenta by hijacking normal physiological mechanisms of antibody transfer that become functional after 16 weeks of pregnancy and can get into the fetal blood and act on the fetal TSH receptor, therefore they also have a pathogenic role in the fetal consequences of maternal GD, especially when in high titers (> 2 to 3 times the upper limit of normal [4]).

The types of assays used in clinical settings for TRAb determination are relevant to pregnancy. There are two major methods to assess TRAbs in maternal blood: by using "receptor assays" and the newer "bioassays". Receptor or TSH Binding Inhibitory Immunoglobulin (TBII) assays detect serum autoantibodies that can block the binding of TSH to an in vitro prepared receptor. They are of three generations, with the third-generation TRAbs assays reaching very high sensitivity and specificity [19]. They do not measure antibodies' activity and can not distinguish between stimulating or blocking TRAbs types, hence they do not predict the phenotype of maternal or fetal GD and do not correlate well with the clinical and biochemical severity of the disease in neither mother nor the fetus [20]. The new bioassays are functional tests that characterize the biological properties of TRAbs – stimulating (TSAbs) or blocking (TBAbs). New bioassays are commercially available to measure either TSBIs or TBIs [21–23]. The functional activity of TRAbs relevant in pregnancy since, depending on their type, they can cause either hyperthyroidism or hypothyroidism in the fetus, for whom we do not readily have access to blood to assess fetal thyroid function as for the mother. Moreover, many women with a history of GD enter pregnancy in a euthyroid state either by taking medication (ATDs) or after undergoing surgery/radioiodine therapy, however, TSBIs and TBIs can stay elevated for years after these procedures. As stated by international guideline [4]. TRAbs should be determined during pregnancy for the following categories:

1. Pregnant women with recently diagnosed GD
2. Pregnant women known with GD and treated with ATDs
3. Women with a previous history of GD with past treatment by radioiodine or thyroidectomy
4. A previous history of delivering an infant with hyperthyroidism
5. Known history of thyroidectomy for treatment of hyperthyroidism in pregnancy

Fetal and neonatal hyperthyroidism has been reported in 1–5% of infants of mothers with GD [24]. In a follow-up study of 47 newborns of mothers with TRAbs during pregnancy, 9 infants developed hyperthyroidism and 5 required ATD medication [25]. A maternal TRAb serum concentration approximately 3 times the upper limit of normal for the assay in the second and third trimesters predicted neonatal hyperthyroidism with 100% sensitivity and 43% specificity [25]. A similar risk cut-off for TRAb level was also found in other studies [26]. It is therefore recommended to take into consideration determining TRAb levels at the initial thyroid function assessment during early pregnancy for those with a history of GD and maybe even in those that present for the preconceptional visit. TRAbs should definitely be measured at the first visit in pregnant women with previous GD that underwent radioiodine or surgery, in those requiring ATDs and in those that are first diagnosed with GD in pregnancy. If maternal TRAb is undetectable or low in early pregnancy, no further testing could be proposed. However, for those with elevated levels, repeated testing should occur at 18–22 weeks to guide fetal follow-up. If levels are persistently high at 18–22 weeks, repeat testing at 30–34 weeks guides neonatal monitoring [4].

4.2 Differential diagnosis

Graves' Disease can rarely first manifest in the first trimester of pregnancy when it is important to be distinguished from gestational transient thyrotoxicosis (GTT) or in the postpartum when it should not be confused with the thyrotoxicosis phase of the postpartum thyroiditis (PPT). Gestational transient thyrotoxicosis is defined as hyperthyroidism of new-onset in the first trimester of pregnancy; it is usually associated with hyperemesis gravidarum and is mediated by the interaction of high level of HCG with the TSH receptor, hence it is expected to be more common with multiple gestation, hydatidiform mole and choriocarcinoma, where HCG levels are higher, but it can occur in any pregnant woman. In GTT there are no previous signs or symptoms of GD and importantly, TRAbs are not detectable. The condition is self-limiting and improves in the second trimester of pregnancy, therefore ATDs, which are known teratogenic, should be avoided. Supportive treatment with hydration, antiemetics, electrolyte replacement and occasionally a short-course of beta-blockers is sufficient [27]. Postpartum thyroiditis is characterized by inflammation secondary to autoimmunity (antithyroid peroxidase antibodies [TPO], anti-thyroglobulin antibodies) against the thyroid gland that manifests as new-onset thyroid dysfunction specifically developing in the first 12 months after a pregnancy in a previously euthyroid woman [28]. The condition typically ensues with a hyperthyroid state where the reservoir of thyroid hormones stored in the gland is released consequent to inflammation, followed by a hypothyroid state. The thyrotoxicosis state is more common in the first 6 months after delivery and again is different from GD because it lacks the presence of TRAbs and is generally

characterized by milder symptoms: palpitations, heat intolerance, fatigue and irritability. PPT is encountered in women with known TPO antibodies in the first trimester or in those with a personal or familial history of thyroid disease or other autoimmune conditions. It tends to recur after each pregnancy and in most cases the affected women recover their euthyroid function within 12 months, however, some of them may be persistently hypothyroid. PPT has a prevalence of about 5% [29]. Complete and partial hydatidiform moles as in gestational trophoblastic disease can sometimes present with thyrotoxicosis in pregnancy. This is more rare than previously believed. In a recent cohort-study, completed by a systematic review and meta-analysis of cases of hydatidiform moles in missed-miscarriages, in 295 women with a confirmed histological diagnosis of hydatidiform mole in the first trimester there were no cases of thyrotoxicosis [30]. However, in a review of 196 patients treated for gestational trophoblastic disease over a 5-years period at a major specialized center, 7% (14/196) patients had biochemical hyperthyroidism and 4 had clinical signs and symptoms of hyperthyroidism [31]. Causes of thyrotoxicosis in pregnancy are described in **Table 1** [27, 28, 32–36].

4.3 Clinical scenarios with Graves' Disease in pregnancy

There are several clinical scenarios related to pregnancy in women with Graves' Disease and they will be discussed in detail further.

4.3.1 Preparing for pregnancy in women with known Graves' Disease

Graves' Disease is common in women of reproductive age. Pregnancy should be carefully planned because both the characteristic pathogenic antibodies and the treatment of GD may be deleterious to the fetus. Also, uncontrolled GD may lead to unfavorable outcomes of pregnancy such as miscarriage, gestational hypertension, preeclampsia, preterm birth, fetal growth restriction, fetal intrauterine death, fetal and neonatal goiter, neonatal abnormal thyroid function with potential life-long disability for the infant. Contraception is strongly advised in women with newly diagnosed GD or in those with uncontrolled GD until euthyroidism is reached by treatment. Many patients will first be prescribed ATDs, however options of ablative therapy with I131 or surgery (total thyroidectomy) are also considered. These options should be discussed with women with GD in relation to how they may interfere with a potential pregnancy. Benefits and risks of options used for management of GD in women of reproductive age desiring a pregnancy are given in **Table 2** [4].

Gestational transient thyrotoxicosis
Hyperthyroid phase of postpartum thyroiditis
Graves' Disease
Toxic nodular goiter
Toxic adenoma
Thyroiditis
Excessive thyroid hormone drugs intake, factitious thyrotoxicosis
Gestational trophoblastic disease
Familial nonautoimmune hyperthyroidism

Table 1.
Causes of thyrotoxicosis in pregnancy and postpartum [27, 28, 32–36].

Approach	Benefits	Risks
ATDs	Euthyroidism in 1–2 months Gradual decrease of TRAb Easy to take, inexpensive Easy to discontinue or modify	Mild adverse effects: 5%, Severe adverse effects: 0.2% Birth defects (see below) Relapse after discontinuation: 50%–70%
Ablative therapy (I131)	Oral administration Reduction in goiter size Relapse rare	Repeat therapy at times Increase in TRAb for months to years – risk for the fetus Conception delayed for at least 6 months Worsening of orbitopathy Lifelong dependence of substitution with exogenous levothyroxine
Total thyroidectomy	Definitive treatment Autoimmunity gradually resolves Removal of the goiter	Surgical site complications: 5% Chronic hypoparathyroidism Permanent neck scar Life-long dependence of substitution with exogenous levothyroxine

Table 2.
Benefits and risks of the options for management of GD in women desiring a pregnancy. Adapted and modified from [4]; TRAb – TSH receptor antibodies.

Antithyroid drugs, thionamides propylthiouracil (PTU), carbimazol and methimazole (MMI) have been the traditional mode of treating GD. These drugs inhibit the enzyme thyroperoxidase which facilitates the addition of iodine to tyrosine in the production of thyroglobulin (**Figure 1**), an essential step in the formation of thyroid hormones. ATDs have their advantages, however, when it comes to preparing for pregnancy, counseling on the continuation of treatment and on what drugs should be preferred is of great use. ATDs can have adverse effects to the mother, but during pregnancy, they can cross the placenta and affect the fetus. Use of ATDs in the first trimester of pregnancy has been linked with congenital malformations. Later usage may lead to fetal/neonatal hypothyroidism and goiter. Carbimazol and methimazole administration during the first trimester and especially between 6 to 10 weeks has been associated in epidemiological and case-report studies with a pattern of anomalies (carbimazole/methimazole embryopathy) characterized by dysmorphic facies, choanal atresia, aplasia cutis congenita and other skin defects, heart and gastrointestinal abnormalities and abdominal wall defects [37]. Prudently, many authorities recommend for pregnant women with GD on ATDs, that PTU should be used in the first trimester and MMI thereafter. While PTU has a very small risk of maternal liver toxicity, it could be preferred in the first trimester, however, switching from one ATD to another at the beginning of pregnancy is not an easy process and it may lead to worsening in control of the thyroid function which in itself may increase the chance of congenital anomalies [37]. Recent reports show that PTU also is not devoid of the risk of congenital anomalies. In a Danish study, 2–3% of children exposed to PTU presented facial anomalies, necks cysts and urinary tract abnormalities, often requiring surgery in later life [38].

Women with GD treated with I131 before at least six months prior to conception who are in an euthyroid state had similar outcomes of their pregnancies as healthy controls in a retrospective study [39]. Obviously, I131 is contraindicated in pregnancy and women undertaking this treatment should prove a negative pregnancy test 48 hours prior to it [4].

Total thyroidectomy is the definitive treatment for GD but it can lead to surgical complications such as recurrent laryngeal nerve paralysis and hypoparathyroidism.

Hypoparathyroidism is the most common complication after total thyroidectomy and is usually underrecognized. In a recent retrospective study of patients undergoing total thyroidectomy for benign thyroid conditions, the incidence of transient hypoparathyroidism was 43.3% and permanent was 13.4%. In patients with GD chronic hypoparathyroidism developed in 27.3% [40]. Entering pregnancy with hypoparathyroidism has its own potential risks for both mother and the fetus [41].

A preconceptional visit should ideally be planned for women with known GD of reproductive age that are considering pregnancy. This consultation should be given by a team of physicians that includes an endocrinologist and a maternal-fetal medicine specialist/obstetrician with experience in dealing with GD during pregnancy. Women with GD seeking pregnancy should be euthyroid – exhibit normal levels of thyroid hormones for at least 1–2 months successively. It may be sensible that in patients who underwent thyroidectomy but especially in those previously treated with I131 ablative therapy, TRAb titers be assessed at the preconceptional visit, since the level of these antibodies could interfere with fetal thyroid development in the second half of pregnancy and they can remain increased many months even years. Pregnancy could be postponed if the levels are very high. For those with a total thyroidectomy, parathyroid function should be checked if not assessed before. For women with GD, other autoimmune conditions should be looked for and a thorough clinical exam complemented in specific cases with targeted tests should be prescribed. A recent systematic review and meta-analysis found overt polyautoimmunity in 14% of patients with autoimmune thyroid disease. Most common autoimmune conditions associated with GD were type 1 diabetes mellitus and autoimmune gastritis, but rheumatological, dermatological and neurological autoimmune disorders could also be found in GD affected patients [42]. Folic acid is usually recommended to these women in the preparation of pregnancy.

4.3.2 *Pregnancy in women with Graves' Disease on anti-thyroid drugs*

For many women with Graves' Disease ATDs are a good choice of treatment gradually inducing remission of autoimmunity. Drugs can be stopped after 1–2 years of trial, and even though, hyperthyroidism will eventually develop in almost 50% of these patients, reactivation of TRAb positivity is not usually expected. In a prospective study on 218 patients with GD treated for 12 months with ATDs, only 5% of those that were TRAb-negative with treatment became hyperthyroid within 8 weeks after stopping the medication [43]. It has therefore been suggested that, under good clinical judgment, in women with GD on ATDs that become pregnant and that are considered in remission, drugs could be stopped at least during the first trimester of pregnancy, especially between weeks 6 to 10, the major teratogenic period [4]. This approach is very different from what is recommended for other autoimmune conditions in early pregnancy where discontinuation of the chronic medication is strongly discouraged. Clinical assessment and thyroid function tests are recommended frequently in these patients and if relapse is diagnosed and ATD therapy is required, PTU is the preferred drug during the first trimester. The risk of rapid relapse of hyperthyroidism after stopping ATDs during early pregnancy is higher in women that were treated less than 6 months, in those that required more than 5 mg MMI per day to remain euthyroid, in those with suppressed or low levels of TSH, in those with large goiters, with orbitopathy and those with high levels of TRAbs [44].

In women where ATDs can not be discontinued during pregnancy, MMI is usually changed with PTU for the first trimester and reintroduced thereafter. Some women will have a worsening of their symptoms with GD in the first trimester and

improvement later in pregnancy. Many pregnant women will not require ATDs by the third trimester as autoimmunity subsides characteristically in pregnancy. Normal THS levels and disappearance of maternal TRAb guide the decision to stop ATDs. If this is not done, there is a risk of overtreatment that can lead to hypothyroidism in the fetus (see below).

4.3.3 When Graves' Disease is first diagnosed in pregnancy

Uncontrolled maternal hyperthyroidism is associated with adverse maternal, fetal and neonatal outcomes [4]. When GD is first diagnosed during pregnancy, thionamides are the mainstay of treatment and they should be prescribed to achieve an euthyroid state. Beta-adrenergic blockers, which are generally considered safe in pregnancy, are also prescribed to control the hypermetabolic state until patients become euthyroid on ATDs. I131 is contraindicated in pregnancy and thyroidectomy, if required should ideally be performed in the second trimester. Thyroidectomy is considered for those women that have contraindications to ATDs, are not compliant with drug therapy, and in women where euthyroidism is not achieved despite large doses of ATDs. Preparation for surgery with beta-blockers and a short course of potassium iodide solution (50–100 mg/day) is permitted during pregnancy [4]. TRAb levels decrease slowly after surgery, therefore, continuation of monitoring should be in place for the remainder of pregnancy, since these antibodies can cross the placenta when in high titers (> 3 times the upper reference for the assay) and render the fetus hyperthyroid despite euthyroidism in the mother. Initial doses of ATDs for GD diagnosed in pregnancy depend on the severity of the symptoms and the degree of hyperthyroxinemia. During pregnancy MMI is prescribed at doses between 5–30 mg/d, typically in an average patient about 10–20 mg; CMZ at 10–40 mg/d and PTU at 100–600 mg/d (typically the average dose for PTU in an average patient is 200–400 mg/d). The beneficial effects of the drugs are seen gradually over weeks as the reservoir of hormones stored in the thyroid gland is consumed. The risk of maternal side effects from ATDs is not increased during pregnancy and is similar with one would expect in the non-pregnant state. Allergic skin reactions are the most common side effects while severe agranulocytosis and liver failure are rarely expected. Because of its potential risk of liver hepatotoxicity and liver transplant, some authorities recommend that the use of PTU should be limited to the first trimester of pregnancy and considered for use thereafter for those with MMI allergy and for those in thyroid storm [4]. The greatest concern however, with ATDs use in pregnancy remains their potential teratogenic effect and their risk of inducing fetal and neonatal hypothyroidism by crossing the placenta. Beta-blockers are considered safe in pregnancy even in the first trimester [45]. Usual doses for pregnancy are 10 to 40 mg of propranolol every 6 to 8 hours for several weeks. There is a concern related to fetal growth, fetal bradycardia and neonatal hypoglycemia with long term use of some beta-blockers [46], however propranolol and metoprolol have a more favorable safety profile than other beta-blockers during pregnancy [47].

Thyroid function tests could be carried out every 2 to 4 weeks in these patients at the beginning of the ATDs course and every 5 to 6 weeks after reaching an euthyroid state. When specific population lab values for pregnancy by trimester are not available, it is recommended to use the reference ranges for nonpregnant patients [4]. [See Thyroid function tests in pregnancy above]. The aim of GD treatment is to maintain maternal TT4/FT4 values at or just above the pregnancy specific upper limit of normal on the lowest effective dose of ATDs, to avoid potential harm to the fetus. Worthy of mentioning, ATDs are considered more potent in the fetus than in the mother, hence, in a well controlled mother, we could expect hypothyroidism in the fetus.

4.4 Fetal and neonatal consequences

Fetal and neonatal outcomes of GD are related to the control of the maternal hyperthyroid state, the presence or absence of TRAbs and the effect of ATDs. Uncontrolled maternal thyrotoxicosis can negatively influence how pregnancy progresses. TRAbs, when in high levels can cross the placenta and lead to fetal hyperthyroidism and goiter and ATDs, by also crossing the placenta, can lead to fetal hypothyroidism and goiter. When assessing a fetus in a mother with GD, a maternal-fetal specialist checks with the use of ultrasound the fetal neck in both gray-scale and color doppler, looking for signs of fetal goiter. Assessment of fetal growth, Doppler studies for assessment of fetal oxygenation, bones, heart rate, amniotic fluid volume are also performed. The exact incidence of fetal goiter is not known but it may be up to 1 in 5,000 births, usually, but not exclusively, in association with maternal Graves' Disease [48]. It has been estimated from different studies that the incidence of fetal goiter with either hypo- or hyperthyroidism in mothers with treated or untreated Graves' Disease is about 10% [49–53]. Fetal hypothyroidism is found more frequently than fetal hyperthyroidism in mothers with GD because of the inadequate use of ATDs [50, 51]. Fetal goiter can be diagnosed prenatally by ultrasound with the demonstration of an anterior cervical echogenic mass of variable size. (**Figure 2**) Large fetal goiters may lead to obstruction of fetal swallowing with consequent polyhydramnios and an increased risk of preterm birth; the neck may be hyperextended. As with other causes of obstructive polyhydramnios (duodenal stenosis, esophageal atresia) this becomes evident usually after 24 weeks' gestation. With fetal goiter there may also be a higher risk of birth dystocia because of the inadequate head flexion during labor and increased incidence of neonatal breathing problems and difficulties in intubation. Fetal goiter harbors thyroid dysfunction. Ultrasound is not a reliable tool to distinguish between fetal hyper- and hypothyroidism. In some cases of fetal hyperthyroidism there can be associated intrauterine growth restriction with accelerated bone maturation, tachycardia, intrauterine death by cardiac failure or thyrotoxicosis and craniosynostosis [54, 55]. In severe fetal hypothyroidism there can be a delay in bone maturation [56] and there may be impaired growth and bradycardia. There are usually no other associated structural anomalies and the incidence of chromosomal or genetic anomalies is not increased in fetal goiters in maternal Graves' Disease. In terms of management, in most cases of fetal goiter, assessment of the maternal condition can help decide whether the cause is fetal hypothyroidism or hyperthyroidism. In uncertain cases,

Figure 2. Ultrasound imaging of a fetal thyroid goiter (A in gray scale, B with color doppler). Courtesy of the Fetal Medicine Foundation, reproduced with permission.

cordocentesis and measurement of fetal blood thyroid hormones and TSH can help distinguish between hypothyroidism, with low thyroid hormones and high TSH, due to ATDs and hyperthyroidism, with high thyroid hormones and low TSH, due to TRAbs [49, 57]. Normal ranges for the thyroid hormones level in the fetal blood have been previously reported [58, 59].

In fetal hypothyroid goiter the first-line of treatment is to reduce or even discontinue maternal ATD medication aiming to maintain maternal blood thyroxine in the upper level of the gestational age-specific normal range. As noted before, GD, similar to other autoimmune conditions, improves during pregnancy and consequently requires less medication. The second-line of treatment is intra-amniotic injection of levothyroxine (100 µg/kg) every 1–2 weeks until delivery at term [49, 60]. The goiter usually decreases in size within a few days to weeks after the first course of treatment. Subsequent injections are given depending on sonographic evidence of re-enlargement of the gland or serial measurements of levels of thyroid hormones in amniotic fluid or fetal blood [49, 61, 62].

In fetal hyperthyroid goiter the treatment is administration of ATDs to the mother [63]. Occasionally, the mother should also be given levothyroxine, as the dose of ATDs can be appropriate for the fetus but could lead to hypothyroidism in the mother (one of the few occasions block and replace therapy is used) [4]. The fetal goiter usually decreases in size after initiation of the treatment, but if this does not occur measurement of levels of thyroid hormones in fetal blood [24] may be needed and the dose of ATDs adjusted. Follow-up should be arranged depending on the clinical context, but generally at every 2–4 weeks to monitor fetal growth, size of the tumor, fetal heart rate, amniotic fluid volume and cervical length (for the prediction of risk of preterm birth). Delivery in the case of fetal goiter should take place in a hospital with neonatal intensive care capacities and pediatric surgery facilities, ideally around 38 weeks. With large goiters, where there is hyperextension of the neck, cesarean section is preferred for delivery. An EXIT (ex utero intrapartum treatment) procedure may be required to access and stabilize neonatal breathing while maintaining placental flow through the umbilical cord from the mother [24]. Adequately treated fetal thyroid goiters generally have good prognosis. However, fetal hyperthyroidism may lead to neonatal thyrotoxicosis [64] and, to long term intellectual impairment [65] while fetal hypothyroidism may result in long term abnormal psychomotor development [66].

Neonatal thyroid function abnormalities are frequent in newborns of mothers with GD. In a recent study in 32 newborns from mothers with GD, 3 cases had hypothyroidism and 2 had hyperthyroidism despite not showing a goiter. These affected babies all had higher levels of TRAbs in their cord blood at delivery and in the follow-up tests [67]. Newborns of mothers with GD can present with hyperthyroidism but also with central or primary hypothyroidism. There are no clear guidelines as to how these neonates should be followed, but most authorities do recommend testing for TRAbs in the cord blood/blood with subsequent discharge of negative testing newborns. FT4 and TSH can be performed at 3 to 5 days of life and repeated at 10 to 14 days. For hyperthyroid newborns MMI and beta-blockers can be used [68]. Maternal TRAbs passed to the newborn will be cleared from the neonates' serum within weeks to months as in the case of other maternal autoimmune conditions [48].

4.5 The postpartum in women with GD

Worsening of GD, relapse or need for increased medication do occur after delivery even in mothers that were previously under remission [69, 70] and women should be counseled and informed about this. Pregnant women with

positive TRAbs in early pregnancy are at high-risk of developing postpartum GD. Postpartum GD usually occurs after 3 months from delivery and this helps in differentiating it from other forms of thyrotoxicosis specific to this period that tend to develop earlier. Women with known GD before or during pregnancy should be regularly checked with thyroid function tests in the postpartum. Treatment options for postpartum GD are the same as for any GD patient. ATDs are an initial good choice since in many instances GD postpartum can be transient and mothers can continue breastfeeding on them. Both MMI (up to maximal recommended dose of 20 mg/d) and PTU (up to maximal dose of 450 mg/d) can be safely administered in breastfeeding mothers [4]. Monitoring the infants for appropriate growth and development routinely is advised [4]. It may be necessary to check the infants' thyroid function when antithyroid drugs are administered at higher doses. Medication should be taken just after breastfeeding, which should provide a 3 to 4 hours lactating free interval [71]. Considering the possibility of side effects of severe hepatic injury of PTU in mothers and infants [72], and high incidence of general side effects with PTU [73], MMI is the preferred drug in the treatment of breastfeeding women. The use of I131 is strictly contraindicated during lactation. If circumstances require it I123, when available can be used in lactating women. The half-life of I123 is 13 hours so breast milk should be pumped and discarded for 3–4 days until the radioactive iodine has cleared from the body [74]. Similarly, Tc-99 m pertechnetate administration requires breast milk to be pumped and discarded during the day of testing [4].

5. Conclusions

Graves' Disease is frequent in women of reproductive age and in pregnancy. It can lead to maternal, fetal and neonatal complications with potential long-term sequels. For those with known GD before pregnancy a preconception plan should be made to ensure optimal timing for pregnancy when GD is well under control. Management options for GD and their implications to pregnancy should be discussed. TRAbs are the pathogenic hallmark of GD and they can cause harm to the fetus and the neonate by crossing the placenta. Antithyroid drugs are traditionally used to treat GD, however in pregnancy they can be teratogenic and they can induce fetal and neonatal hypothyroidism by placental passage. Fetal ultrasound during pregnancy is helpful for fetal assessment and for diagnosing fetal goiter. The type of fetal thyroid dysfunction when goiter is associated can be usually deduced by assessing the maternal state. Fetal treatment is in most cases achieved by treating the mother – increasing or decreasing ATDs. Neonatal assessment in newborns of mothers with known GD is recommended. Maternal GD, like other autoimmune conditions can flare in the postpartum, therefore, the mother should also be under supervision. Breastfeeding is allowed in women on regular doses of ATDs.

Conflict of interest

The author declares no conflict of interest.

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