



Hyperthyroidism in the pregnant woman: Maternal and fetal aspects

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ARTICLE INFO

Keywords:

Pregnancy
Hyperthyroidism
Thyrotoxicosis
Gestational transient thyrotoxicosis
Graves' disease

ABSTRACT

Hyperthyroidism during pregnancy is uncommon. Nonetheless, prompt identification and adequate management of hyperthyroidism in a pregnant woman is essential, because uncontrolled thyrotoxicosis significantly increases the risk of maternal and fetal complications. Also, fetal prognosis may be affected by the transplacental passage of maternal thyroid stimulating antibodies or thyrostatic agents, both of which may disrupt fetal thyroid function. Birth defects have been reported in association with the use of antithyroid drugs during early pregnancy. Although rarely, offspring of mothers with Graves' disease may develop fetal/neonatal hyperthyroidism, the management of which requires a close collaboration between endocrinologists, obstetricians, and neonatologists.

Because of the above considerations, the management of pregnant and lactating women with hyperthyroidism requires special care, bearing in mind that both maternal thyroid excess *per se* and related treatments may adversely affect the newborn's health.

In this review we discuss the diagnosis and management of hyperthyroidism in pregnancy, along with the impact of thyrotoxicosis and medications on fetal outcome.

Introduction

Hyperthyroidism during pregnancy is uncommon, its prevalence ranging between 0.1% and 1% according to whether overt hyperthyroidism or also subclinical forms are considered [1,2].

Although infrequent, identification of hyperthyroidism in a pregnant woman is essential because unfavourable outcomes can occur in both the mother and the foetus. In general, subclinical hyperthyroidism is rarely associated with adverse gestational outcomes [3], whereas uncontrolled thyrotoxicosis significantly increases the risk of maternal and fetal complications, such as pregnancy-induced hypertension, maternal congestive heart failure, pregnancy loss, prematurity, low birth weight, stillbirth, intrauterine growth restriction [4], along with neurobehavioral disorders in offspring in later life [5].

Besides the severity of maternal hyperthyroidism, additional factors that may affect fetal prognosis include the transplacental passage of maternal TSH receptor antibodies (TRAb) or thyrostatic agents, both of which may disrupt fetal thyroid function.

Finally, the use of thionamide antithyroid drugs [methimazole (MMI), carbimazole (CM), and propylthiouracil (PTU)] has been linked to increased risk of birth defects and maternal liver injury.

Because of the above considerations, the management of pregnant and lactating women with hyperthyroidism requires special care,

bearing in mind that both maternal thyroid excess *per se* and related treatments may adversely affect the newborn's health.

In this review we discuss the diagnosis and management of hyperthyroidism in pregnancy, mainly focusing on gestational transient thyrotoxicosis (GTT) and Graves' Disease (GD), along with the impact of thyrotoxicosis and medications on fetal outcome.

Methods

The terms *hyperthyroidism* or *thyrotoxicosis* were used in conjunction with the terms *reproduction*, *pregnancy*, *anti-thyroid drugs*, *methimazole*, *carbimazole*, *propylthiouracil*, *obstetric outcomes*, *birth defects*, to search MEDLINE for articles published in English in the last 20 years (1998–2018). Additional papers were searched by scrutinizing the reference lists of previously published reviews and meta-analyses.

Hyperthyroidism in pregnant women

Causes of hyperthyroidism during pregnancy

The two most common causes of hyperthyroidism in pregnant women are Graves' disease (GD), due to thyroid stimulation by TRAbs, and gestational transient thyrotoxicosis (GTT) [1]. The latter results

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<https://doi.org/10.1016/j.jcte.2019.100190>

Received 3 March 2019; Received in revised form 10 April 2019; Accepted 11 April 2019

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from the transient increase in thyroid hormone output that occurs under the influence of elevated human chorionic gonadotropin (hCG) levels during early pregnancy [6]. Clinically the two forms may both present with classical thyrotoxic symptoms and signs, and a careful past history and physical evaluation, along with appropriate laboratory tests, are necessary for a proper differential diagnosis.

Less frequent causes of thyrotoxicosis in pregnancy include toxic multinodular goiter or solitary toxic thyroid adenoma [1]. The prevalence of these forms of hyperthyroidism is low in women of child-bearing age, as they mostly occur later in life [7].

Even rarer causes of hyperthyroidism in pregnancy include subacute de Quervain's, painless and acute thyroiditis. Extrathyroidal sources of thyroid hormone, such as overtreatment with levo-thyroxine (LT4), factitious intake of thyroid hormone, struma ovarii and functional thyroid cancer metastases, may induce thyrotoxicosis, as well [1].

Changes in maternal thyroid economy during pregnancy

Physiological changes in thyroid economy take place from the very first weeks of gestation [8]. During the 1st trimester, the thyroid gland is directly stimulated by hCG that acts as a thyrotropic agonist [9], thus leading, near the end of the 1st trimester, to transient increase in free thyroid hormone levels. This event is mirrored by a transient decrease in serum TSH concentrations, with thyrotropin levels falling below the lower limit of the gestational specific reference range in about 15% of pregnancies [10]. As a consequence of high concentrations of circulating estrogens, serum thyroxine binding globulin (TBG) levels significantly increase from the 1st trimester of pregnancy and remain high until term. The increase in TBG concentrations is responsible for an increase in total T4 and T3 concentrations, and is accompanied by a contextual decrease in free thyroid hormone levels (~10 to 15%). This decrease is partially offset by an increase in thyroid hormone output (about 50% over gestation) induced by TSH, the concentrations of which, following the 1st trimester, show a slight but definite trend towards an increase in response to decreased serum free thyroid hormone levels [8]. The increased hormone production by the maternal thyroid gland is aimed at reaching a new equilibrium state (and ultimately guarantee maternal euthyroidism), and can be achieved provided that the gland is both anatomically and functionally intact and iodine intake adequate to the increased demands of pregnancy [11–13].

Because of the above changes, TSH levels during pregnancy are shifted downwards compared to non-pregnant population, especially during early gestation [8]. Detection of TSH levels below or near the lower limit of the reference range during the 1st trimester of pregnancy may not be indicative of maternal hyperthyroidism, as they are found in as many as 15% healthy women at this stage of pregnancy. Nonetheless, if a suppressed serum TSH is found, further biochemical investigations and accurate clinical evaluation should be performed to exclude/confirm hyperthyroidism [14,15].

Gestational transient thyrotoxicosis (GTT)

GTT refers to hyperthyroidism occurring in pregnant women without evidence of thyroid autoimmunity, which resolves spontaneously by the end of the 1st or early 2nd trimester of pregnancy [6]. Depending on the geographic area, GTT is estimated to occur in 1–5% of pregnancies, although prevalences as low as 0.3% in Japan or as high as 11% in Hong Kong have been reported [16–18].

GTT is deemed to be secondary to increased thyroid stimulation by hCG [19]. The structural homology between hCG and TSH molecules (as well as between their corresponding receptors) provides the basis for the thyrotropic action of hCG [9], the concentrations of which physiologically peak in the first 8 to 11 weeks of pregnancy, decrease thereafter, and remain in plateau up to pregnancy term. In most cases GTT is secondary to marked elevations of serum hCG (*i.e.*, twin or multiple pregnancies, hyperplacentosis, hydatidiform mole) [20], but it

may also be due to circulating hCG isoforms with increased thyrotropic activity and/or prolonged half-life [6,21]. Also, a heterozygous mutation of the TSH receptor (TSHR) gene, resulting in exchange of lysine for arginine at position 183 in the extracellular domain of the TSHR, has been reported as a rare cause of GTT (with normal serum hCG levels) due to thyroid hypersensitivity to hCG [22].

In accordance with the physiopathological role of hCG in thyroid hyperfunction, women affected with GTT have no history of hyperthyroidism prior to conception. Symptoms of thyrotoxicosis typically parallel hCG changes, and first occur by 4–9 weeks of gestation and remit by the end of the 1st or early 2nd trimester of pregnancy.

Because of its short and self-limiting course, GTT usually does not require specific treatment and milder forms are likely to remain unrecognised [6]. Exceptions include those cases characterized by more severe hyperthyroidism, which are frequently associated to nausea and vomiting or hyperemesis gravidarum (HG) [16]. The latter is reported to occur in 0.3–1.0% of pregnancies, and is defined as persistent vomiting, weight loss (at least 5% loss of prepregnancy weight), dehydration, ketonuria and serum electrolyte and acid-base abnormalities (hypochloremic alkalosis, hypokalemia, and hyponatremia) [23,24]. The latter is reported to occur in 0.3–1.0% of pregnancies, and is defined as persistent vomiting, weight loss (at least 5% loss of prepregnancy weight), dehydration, ketonuria and serum electrolyte and acid-base abnormalities (hypochloremic alkalosis, hypokalemia, and hyponatremia) [23,24]. Albeit extensively investigated, the pathogenesis of HG remains poorly understood, and hormonal, infectious and genetic factors, have all been indicated as potential causes [25]. Since HG is frequently associated with both clinical and biochemical hyperthyroidism, a causal role of hyperthyroxinaemia in the development of hyperemesis has been proposed. More likely, both thyrotoxicosis and HG might just concomitantly occur because of a common background, namely excessive hCG secretion/action, which induce hyperthyroidism through a direct thyroid hyperstimulation, and hyperemesis through as yet unidentified mechanisms [26].

Unless associated with HG, GTT is usually characterized by mild signs and symptoms of hyperthyroidism that often overlap those complained by women at early gestation, thus making diagnosis not immediately perceivable. In the absence of both personal and family history of GD or other autoimmune diseases, clinical diagnosis of GTT is usually suggested by the onset of thyrotoxic symptoms (palpitations, tremor, anxiety, nervousness, heat intolerance) within the 1st trimester of gestation, associated with weight loss (or lack to gain weight) and vomiting [15]. Interestingly, a slightly anticipated onset time of GTT as compared to GD has been reported, the respective median onset time of hyperthyroidism being at 12 and 13 gestational weeks [27].

Clinical findings on physical examination are usually unremarkable but may include all typical signs of thyrotoxicosis (tachycardia, hyperreflexia, hands tremors), whereas goitre is usually absent and no signs of Graves' orbitopathy are detectable.

Clinical diagnosis is confirmed by laboratory testing showing absence of serum TRAb, along with undetectable TSH and increased FT4 levels. Higher elevations in serum FT4 are usually observed in women with GTT associated with HG, in whom the severity of vomiting correlates with the degree of both FT4 and hCG concentrations [16]. By contrast, triiodothyronine (T3) is usually normal, or only slightly elevated in less than 20% of affected women. This finding is consistent with an enhanced peripheral conversion of T4, in response to caloric deprivation, to the inactive reverse triiodothyronine (rT3), the concentrations of which have been found to be increased in women with HG [28–30]. Also, since in GTT patients free T4 levels are usually more elevated than serum free T3, a decreased FT3/FT4 ratio has been proposed as a biochemical parameter useful for differentiating between GTT and active GD [31].

Although biochemical evidence of hyperthyroidism is usually associated with serum hCG levels of 100,000–500,000 IU/L, the diagnostic usefulness of serum hCG measurement is limited, unless gestational

trophoblastic diseases are suspected [32,33]. Analogously, thyroid ultrasonography is usually poorly informative, and it is mostly performed to distinguish GTT from GD.

Likely because of its short and self-limiting course, GTT is not associated with significant obstetrical complications and adverse neonatal outcomes. However, children born to mothers experiencing GTT complicated by severe hyperemesis and weight loss of > 5% of their pre-pregnancy weight have been reported to have significantly lower birth weight as compared to gestational-age matched infants born to unaffected mothers [6,34].

Concerning treatment, in most cases GTT does not require any treatment because of its spontaneous recovery within a few weeks. Antithyroid drugs are not indicated, since thyrotoxicosis usually recovers by 14–18 weeks of gestation, and the use of thionamides in early pregnancy increases the risk of birth defects. When GTT is associated with severe hyperemesis (> 5% weight loss, dehydration, and ketonuria), in addition to treatment with fluids and electrolytes, propranolol may be transiently given, because of its efficacy in reducing hyperemesis and symptoms of thyrotoxicosis [15].

Graves' disease (GD) in pregnancy

GD is the most common cause of hyperthyroidism in women of childbearing age, occurring before pregnancy in 0.4–1.0% women and in approximately 0.2% pregnant women [1]. The pathogenesis of hyperthyroidism due to GD in a pregnant woman is the same as in non-pregnant patients, as it results from thyroid overstimulation by TRAbs.

As for other autoimmune diseases, GD typically improves during the 2nd and 3rd trimesters, and often relapses in the post-partum period. This evolution mostly reflects the pattern of changes in TRAb levels occurring during gestation, as a result of the tolerogenic state that takes place during normal pregnancy [35]. Gestational immune tolerance, ultimately aimed at avoiding the fetus to be rejected as foreign tissue while maintaining the mother and fetus protected against infections, involves a complex interplay between hormonal factors, immunological molecules of trophoblastic origin and specific T-cell subsets (regulatory T [T_{REG}] cells) generated within the maternal decidua. Besides maintaining fetal alloantigen tolerance, T_{REG} cells migrating to the maternal circulation indirectly induce a state of generalized and transient immune-suppression, which explains either the observed amelioration of GD during pregnancy or the rare *de novo* gestational onset of GD [13,36–38]. However, although clinical and biochemical features of thyrotoxicosis usually improve with the progression of pregnancy, a transient worsening of hyperthyroidism during the 1st trimester due to the thyroid-stimulating activity of hCG is not infrequently observed [39,40]. Finally, following delivery, the abrupt fall of T_{REG} cells provides an explanation for the rebound of post-partum thyroid autoimmunity, with either worsening or re-exacerbation of GD [38].

Clinical and biochemical diagnosis of GD in pregnancy

From a diagnostic point of view, women with a history of GD already known prior to conception obviously pose no problems. In contrast, diagnosis of GD first occurring during pregnancy may be difficult, because many clinical symptoms of hyperthyroidism such as palpitations, sleeplessness, anxiety, fatigue, are nonspecific and may be overlooked or interpreted as normal pregnancy symptoms. However, symptoms and signs like failure to gain weight or weight loss despite an increased food intake, presence of goiter, or ocular changes are highly suggestive of a diagnosis of hyperthyroidism due to GD in a pregnant patient [15,41].

Clinical diagnosis of hyperthyroidism may be confirmed only by findings of elevated serum thyroid hormone concentrations and suppressed serum TSH levels. If biochemical hyperthyroidism is detected, measurement of TRAbs is indicated, since the presence of these antibodies discriminates GD from other causes of gestational

hyperthyroidism [15].

Beyond their diagnostic utility, the determination of these antibodies has clear prognostic significance for the fetus. In fact, TRAbs can cross the placenta and induce abnormal fetal thyroid gland stimulation, similar to that occurring in the mother [42–44]. In general, the risk of fetal or neonatal thyrotoxicosis is greater in infants born to mothers with GD of recent onset, in whom TRAb titers are usually higher than in those with less recent illness or in those who previously underwent ablative therapy (radioiodine or thyroidectomy) [45,46]. The latter, however, may have TRAb titers persistently elevated even long after ablative therapy, and the recommendation is to measure maternal TRAbs in early pregnancy in these women. In all circumstances, namely current or past history of GD, if high TRAb titers (> 5 IU/L or 3 times the upper limit of normal) in the first trimester are found, TRAb measurement should be repeated at weeks 18–22, and once again in late pregnancy (weeks 30–34), if elevated at midgestation [15].

Maternal and fetal adverse events of GD

Prompt recognition and appropriate treatment of GD in pregnancy is necessary to prevent serious consequences both in the mother and in the fetus. By contrast, subclinical hyperthyroidism is not associated with adverse obstetric effects [3].

Two severe complications in pregnant women with uncontrolled thyrotoxicosis are thyroid storm and congestive heart failure. Thyroid storm is a very rare, life-threatening emergency that may occur in women with undertreated or undiagnosed severe hyperthyroidism and concurrent precipitating factors such as labor, surgical delivery, infections or trauma. It is characterized by altered mental status, hyperthermia, widened pulse pressure, tachycardia, left ventricular dysfunction, and multi-organ failure. Because of its rarity, the actual incidence of gestational thyroid storm is not assessed [47,48]. By contrast, heart failure has been reported to occur in about 10% of pregnant women with severe untreated hyperthyroidism, a rate that is much higher than that observed in non pregnant patients [49]. The increased risk of congestive heart failure in thyrotoxic pregnant women would result from an increased cardiac workload imposed by the cumulative effect of thyrotoxic and pregnancy-induced cardiovascular changes and coexistent obstetric complications (severe preeclampsia, haemorrhages, anemia, etc) that precipitate the heart failure [49].

Uncontrolled overt hyperthyroidism also adversely affects fetal health. Since the presence of thyroid autoantibodies is associated with an increased rate of obstetrical complications [13], it is unclear whether maternal thyrotoxicosis *per se* or the underlying autoimmunity may be responsible for this adverse events. However, a study comparing obstetrical outcomes in women with resistance to thyroid hormone (RTH) and in unaffected control mothers, showed a significantly increased rate of miscarriages in the former. In addition, highly significant reduction in birth weight was found in unaffected infants born to RTH mothers compared to both RTH children born to RTH mothers and healthy children born to control mothers. According to the authors, their findings indicate that high levels of maternal thyroid hormone can exert direct toxic effects on fetal development, which are not manifested in fetuses harbouring the mutation because of a reduced sensitivity to thyroid hormone [50].

The pathogenic relevance of hyperthyroidism in the occurrence of obstetrical complications is also demonstrated by studies showing the highest incidence of complications among women with the poorest control of hyperthyroidism and the lowest incidence in those adequately treated. Data from case studies [51–54] and large population studies [55–57] collectively show hyperthyroidism during pregnancy to be associated with increased risk of fetal loss, fetal growth restriction, preterm birth and low birth weight. All the above complications have also been reported to occur in fetuses of euthyroid mothers who were previously ablated for GD by surgery or radioiodine therapy, and with persistently high TRAb levels inducing isolated fetal hyperthyroidism

[58].

Fetal and neonatal hyperthyroidism in offspring of GD mothers

As stated above, maternal TRAbs are able to cross the placenta and have the potential to induce fetal hyperthyroidism. The likelihood that this event will happen ultimately depends on maternal TRAbs, and the higher the maternal TRAb concentrations, the higher the risk for the fetus to develop hyperthyroidism [59]. However, ATDs also cross the placenta and are effective on fetal thyroid, and thus when the mother is treated the net effect on fetal thyroid hormone production will eventually depend on the balance of TRAb stimulation and ATD inhibition.

The risk of fetal hyperthyroidism is estimated to be very low, with only 1% of children of GD mothers described as having hyperthyroidism [60,61]. Nonetheless, fetuses of GD mothers with uncontrolled hyperthyroidism in the second half of gestation, and/or with high TRAb levels need to be closely monitored to allow proper fetal management. Fetal thyroid ultrasonography has been proven to be extremely sensitive and specific for detecting intrauterine thyroid dysfunction [42]. Ultrasonographic signs suggestive of fetal hyperthyroidism include goitre, sustained heart rate > 160–170 bpm, accelerated bone maturation, growth restriction, oligo/polyhydramnios [60]. Cordocentesis can be used to measure fetal thyroid hormone directly, but its use is limited to selected cases due to the potential risks associated with this procedure [15].

Because of the persistence of maternal TRAb in the infant's circulation (half-life around 2 weeks), 1–5% of infants of mothers with high TRAb levels are at risk of developing neonatal hyperthyroidism [62]. In newborns of mothers treated with ATDs until delivery, hyperthyroidism may not clinically manifest until these drugs are cleared from the neonatal circulation.

Although typically transient, overt neonatal hyperthyroidism should be adequately treated to limit short- and long-term morbidity, and neonatal thyroid function monitored until

hyperthyroidism resolves [63]. Following the disappearance of maternal TRAbs from the newborn's circulation, a phase of neonatal central hypothyroidism may also occur, likely because of the prolonged suppression of pituitary TSH production during fetal and neonatal hyperthyroidism [64].

Treatment of GD in the pregnant woman

Thionamide antithyroid drugs (ATDs) are the mainstay of treatment for overt gestational hyperthyroidism due to GD, since radioiodine therapy is obviously contraindicated and thyroidectomy, though feasible, should be reserved for highly selected cases [15,65].

Different ATD strategies have been indicated, according to whether GD is first diagnosed in pregnancy, or pregnancy occurs in a woman already receiving ATDs for GD. In both cases the therapeutic goal is to control maternal hyperthyroidism in order to prevent obstetrical and medical complications (see paragraph *Maternal and fetal adverse events of GD*).

When GD is first diagnosed in pregnancy, decision to prescribe ATDs should be based on a careful risk–benefit assessment on an individual basis, taking into account either the severity of maternal hyperthyroidism or the potential deleterious effects of ATDs on the fetus [65,66]. In general, starting doses of ATDs during pregnancy are within the range of 200–400 mg daily for PTU or 10–20 mg daily for MMI [15]. If ATD therapy is started during the first trimester, PTU is preferred over MMI because the risk for severe birth defects is lower [67]. Following initiation of therapy, close monitoring of maternal thyroid function should be performed, and ATD dosage adjusted to maintain maternal thyroid hormone levels in the upper reference range [15] (see paragraph *Effects of maternal ATD therapy on the fetal thyroid*).

Management of women already treated with ATDs before pregnancy depends on the severity and activity of GD when pregnancy establishes.

In general, discontinuation of antithyroid medications may be considered for women without large goiters or positive TRAbs, who had been receiving ATDs for at least 6 months prior to becoming pregnant and are euthyroid on low MMI or PTU doses (≤ 5 –10 mg/day and ≤ 100 –200 mg/day, respectively) [15,68]. Conversely, women in whom the risk of recurrence of thyrotoxicosis is estimated to be high if ATDs were to be discontinued, should be maintained on medical therapy (PTU in the first trimester, MMI thereafter) at the lowest dosage useful to maintain thyroid hormone levels in the upper reference range [15,68]. In both circumstances, i.e. if treatment is either suspended or continued, close monitoring of maternal thyroid function (every 1–2 weeks over the course of 1st trimester, and every 2–4 weeks during the 2nd and 3rd trimester) is needed to guide further management (conservative or interventional), bearing in mind that both hyperthyroidism and overtreatment may have deleterious effects on the fetus. Since pregnancy is usually associated with attenuation in both immunological and biochemical features of GD, most women with active GD prior to conception may withdraw their therapy in the last trimester [15,68].

Effects of maternal ATD therapy on the fetal thyroid

The use of ATDs in pregnancy poses specific difficulties, because all available ATDs (MMI, CM, PTU) can cross the placenta, and therefore have the potential to cause fetal hypothyroidism [69]. Early studies suggested that placenta was less permeable to PTU than to MMI [70], and accordingly PTU has been long regarded as the preferred ATD for treating hyperthyroidism in pregnancy. However, subsequent studies using in vitro perfusion techniques failed to demonstrate differences in placental transfer kinetics of PTU and MMI [71], and both compounds were reported to exert similar effects on fetal thyroid function [72].

Data from studies examining a dose response relationship between maternal ATD dose and fetal/neonatal thyroid function have produced conflicting results, with some showing a direct correlation between maternal dosage and fetal thyroid function [71,73,74], and others reporting no correlation [72,75–78]. Differences in individual bioavailability of the administered drug, as well as in the transplacental transfer of maternal TRAbs that stimulate the fetal thyroid, are among the factors that may account for the above discrepancies. Levels of circulating maternal thyroid hormones have been shown to better correlate with fetal thyroid function. ATD doses adequate to maintain maternal FT4 in the upper normal to mildly thyrotoxic range are associated to normal fetal thyroid function in more than 90% of neonates, whereas for maternal FT4 levels in the lower two thirds of the normal non-pregnant reference range, more than one third of neonates have free T4 levels in the hypothyroid range [78]. In other words, doses of ATDs sufficient to maintain euthyroidism in the mothers may result excessive for their fetuses, which suggest that fetal thyroid may be more sensitive to thionamides compared to maternal thyroid [72]. This being the case, current guidelines recommend the use of the lowest effective dose of MMI or PTU to maintain maternal serum FT4/TT4 at or moderately above the upper limit of the reference range [15,68].

Teratogenicity of maternal ATD therapy

Another important point to be addressed when considering the use of thionamides in pregnancy is related to the potential of teratogenicity of these drugs. In particular, both MMI and CM have been repeatedly reported to be associated with several birth defects and malformations, including aplasia cutis congenita, coanal atresia, tracheo-oesophageal fistula, omphalocele and other less common abnormalities [79,80].

A large retrospective case-control study involving almost 6000 children born to mothers affected with GD, and either treated with MMI/PTU or never receiving ATDs showed a significantly higher rate of major anomalies among children of MMI-treated mothers than in non exposed infants (4.1% vs 2.1%). Conversely, no differences were found

in the incidence rates of malformations between children born to PTU-treated mothers and controls [81]. Similarly, a meta-analysis of 10 studies involving 5059 participants indicated that exposure to MMI/CM significantly increased the incidence of neonatal congenital malformations compared to both exposure to PTU (OR 1.90) and no ATD exposure (OR 1.88), whereas no differences were found between PTU and no ATD exposure [82]. At variance with the above findings, in a Danish nationwide cohort study, exposure to either MMI/CM or PTU in early pregnancy was associated with an increased risk of birth defects (MMI/CM adjusted OR 1.66; PTU adjusted OR 1.41;), although the spectrum of birth defects differed according to MMI/CM and PTU exposure [83]. By contrast, other studies failed to find any significant correlation between gestational exposure to thionamides and congenital abnormalities [84–86]. In particular, a retrospective analysis of insurance claims data including almost one million pregnancies showed the rates of congenital defects (per 1000 infants) associated with ATD use to be 55.6 for MMI, 72.1 for PTU, and 65.8 for untreated women with thyrotoxicosis, compared to 58.8 among women without thyrotoxicosis. In addition, there was an overall 13% increased risk of any congenital anomaly among infants of mothers with thyrotoxicosis compared to women without a diagnosis of thyrotoxicosis [85]. Also, a Swedish nationwide register-based cohort study including almost 700,000 live-born children found no significant differences in the cumulative incidence of birth defects in children exposed to MMI (6.8%) or PTU (6.4%) vs non-exposed (8.0%). Nonetheless, analysis for subtypes of birth defects showed differences in the spectrum of abnormalities associated with these two compounds, with an increased incidence of septal heart defects in offspring exposed to MMI, and of ear and urinary system malformations in those exposed to PTU [86]. In general, the latter seems to be safer than MMI, in that birth defects associated with the use of PTU during pregnancy tend to be less severe than those observed after MMI/CM exposure [67]. On the other hand, because of the reported risk of severe hepatotoxicity in patients exposed to PTU, the use of this drug for the treatment of hyperthyroidism in pregnancy should be limited to the 1st trimester (i.e. during the period of organogenesis) and PTU switched to MMI/CM from the 2nd trimester onwards, in order to minimize the risk of both PTU-related hepatotoxicity and birth defects [15,68,87,88].

Alternative therapies

Alternative therapies for GD in pregnancy include thyroidectomy, potassium iodide and β -blocking drugs.

Thyroidectomy is indicated when the woman is not compliant with ATDs, or when these medications are ineffective (uncontrolled hyperthyroidism with doses as high as 40–60 mg daily of MMI or 800–1200 mg daily of PTU), or not tolerated, or there is a large goiter causing compressive symptoms. When deemed necessary, thyroidectomy can be performed most safely in the 2nd trimester, and both beta-blocking agents and a short course of potassium iodide solution are recommended in preparation for surgery [15].

Potassium iodide has also been effectively used to treat mild gestational hyperthyroidism in Japan [89,90]. However, data on safety and efficacy of such therapy in populations with iodine intake lower than in Japan are limited, and this modality of treatment is not presently recommended for GD during pregnancy [15].

Finally, propranolol may be transiently given, because of its efficacy in reducing symptoms of thyrotoxicosis. Although this drug has no teratogenic effects, its use should be limited because chronic use has been reported in association with intrauterine growth restriction [1].

Preconception counseling

Owing to the complexity of maternal and fetal management of gestational GD and the potential for related serious adverse events, a preconception counseling should be systematically offered to women of

reproductive age with a history of GD [15,68]. This should be aimed at making the woman fully aware of the potential risks and benefits of the different GD therapeutic options, while taking into account the woman's plans to conceive. Also, women should be informed about the need of regular medical visits and serial thyroid blood tests during pregnancy, as well as about the risks of uncontrolled hyperthyroidism on pregnancy.

Women on ATDs who plan a pregnancy, should be advised to delay conception until a stable euthyroid state is reached. This reduces the risks of hyperthyroidism-related obstetrical complications and allows antithyroid drugs discontinuation once pregnant in a substantial number of cases. Also, if pregnancy is expected to occur within a short timeframe, switching from MMI to PTU prior to conception may be advisable to minimize fetal exposure to MMI during the period of organogenesis [15].

Women on medical therapy with poorly controlled hyperthyroidism even on high doses of ATDs, should be considered for a definitive therapy for hyperthyroidism prior to conception. Both thyroidectomy and radioactive iodine ablation (RAIA) are effective means of permanently controlling hyperthyroidism, and the choice between the two modalities is mostly influenced by coexisting medical conditions and patient preference [51]. In the setting of hyperthyroidism during pregnancy, additional specific considerations should be made. In particular, while the majority of patients with GD after surgical therapy experience a gradual decrease in circulating TRAbs, a transient increase in TRAb titers after RAIA may occur, with TRAb levels remaining persistently elevated for months to years [91]. A very recent study showed the incidence of neonatal hyperthyroidism to be 8.8% and 3.6% among the newborns born to mothers with GD who conceived within 6–12 months and 18–24 months after RAI, respectively [92]. This being the case, women with very elevated TRAb levels prior to conception should be better addressed to thyroidectomy than to RAIA, as TRAb levels tend to decrease more rapidly (within months to one year), and only rarely remain elevated for years. In any case, following either surgery or RAIA women should be advised to measure TRAbs and TSH prior to conception, and to avoid pregnancy if TRAbs are still high or if TSH is elevated (> 2.5 mU/L) on levothyroxine therapy.

Conclusions

Management of hyperthyroidism during pregnancy requires close maternal and fetal surveillance. Thyroid hormone excess is a risk factor for obstetrical and fetal complications and should be adequately controlled throughout pregnancy. However, because of the potential hazard to the fetus with the use of ATDs during pregnancy, special care should be taken to avoid both untimely or excessive fetal exposure to these drugs. Maternal hyperthyroidism due to GD poses the fetus at risk of hyperthyroidism because maternal antibodies enter the fetal compartment and may exert their effect on fetal thyroid. Women of reproductive age with GD should be routinely offered preconception counseling, and pregnancy should be postponed until hyperthyroidism is adequately controlled. Importantly, high maternal TRAb levels may even persist for years beyond resolution of hyperthyroidism in women definitively treated for GD by radioiodine or surgery, which requires measurement of TRAb prior to or upon becoming pregnant also in women with past history of GD.

Although rarely, offspring of mothers with GD may develop fetal/neonatal hyperthyroidism, the management of which requires close collaboration between endocrinologists, obstetricians, and neonatologists.

Current guidelines provide invaluable assistance for clinical practice, as a number of specific questions relating to the management of maternal hyperthyroidism during pregnancy are comprehensively addressed. Nonetheless, a survey investigating whether and to what extent the clinical practice relating to the management of hyperthyroidism during pregnancy was consistent with available guidelines, showed

inconsistencies mainly in the treatment of women with GD planning pregnancy, the choice and monitoring of ATDs in pregnant women, treatment of GTT and the choice of ATDs in lactating women [93]. This being the case, efforts should be made to encourage a wider implementation of evidence-based diagnostic and therapeutic strategies, in order to reduce maternal and fetal risks related to both hyperthyroidism and antithyroid drug use during pregnancy.

There are currently some critical issues in the therapeutic management of pregnant hyperthyroid women that need to be addressed. These include the identification of upper free-T4 cut-off values that may confidently be considered safe for the fetus, as some evidence has been provided showing that maternal free-T4 concentrations even within the higher end of the normal range might have detrimental effects on child neurodevelopment [94]. Also, further studies evaluating the safety of alternative therapies for hyperthyroidism in pregnancy (i.e., potassium iodide) are advisable, as current evidence suggests the use of both MMI and PTU to be associated with an increased risk of embryopathies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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