Mini Review

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Management of Fetal and Neonatal Graves' Disease

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Abstract
Fetal and neonatal autoimmune hyperthyroidism is a rare, serious but transient disorder. Early diagnosis and treatment are key objectives for an optimal prognosis and the well-being of the child. This review focuses on the management of these patients during the fetal and neonatal periods. We propose a diagnostic algorithm for high-risk pregnancies in mothers with current or past hyperthyroidism related to Graves' disease, involving repeated fetal thyroid gland assessments from 20 weeks of gestation onwards and maternal serum thyroid-stimulating hormone receptor antibody (TRAb) determination, with close monitoring if TRAb levels exceed 2 to 3 times the upper limit of the normal range. In fetuses with goiter, the main clinical issue is determining whether the cause is (1) maternal antithyroid drug (ATD) treatment that is appropriate for achieving normal maternal thyroid function but inappropriate and excessive for the fetus, resulting in hypothyroidism and necessitating a decrease in the ATD dose during pregnancy, or (2) the presence of TRAbs resulting in fetal thyroid stimulation and hyperthyroidism, requiring an increase in the maternal ATD dose. Methimazole/carbimazole treatment should be initiated as soon as possible during the neonatal period, carefully managed and maintained over a period of 1–3 months and then stopped when TRAb is no longer detectable in serum.

Introduction

Neonatal autoimmune hyperthyroidism (neonatal Graves' disease [GD]) is a rare but serious disorder that is generally transient, occurring in only about 2% of the offspring of mothers with GD. Cardiac insufficiency and mortality, intrauterine growth retardation, prematurity, craniostenosis, microcephaly, and psychomotor disabilities are the major risks in these infants, highlighting the importance of TRAb determination throughout pregnancy in women with GD and of the early diagnosis and treatment of fetal and neonatal hyperthyroidism. Antithyroid drugs (ATDs) are the treatment of choice for hyperthyroidism during gestation and the neonatal period, but their use during the teratogenic period of early pregnancy may be associated with a higher risk of birth defects and fetal hypothyroidism. Management of the mother, the fetus, and the neonate requires an experienced multidisciplinary team including adult and pediatric endocrinologists, obstetricians, and fetal radiologists.

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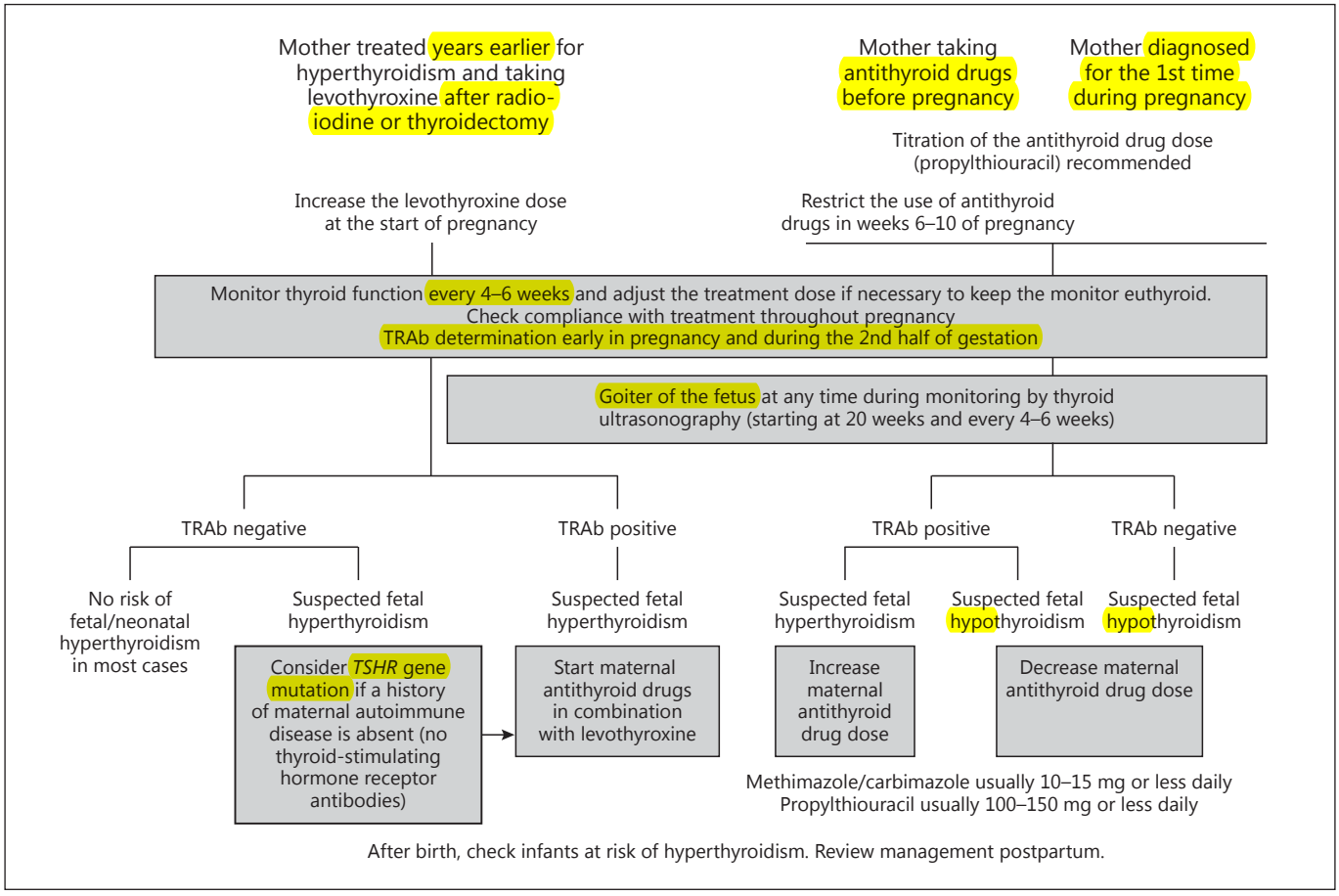

Fig. 1. Management algorithm for at-risk pregnancies in mothers with current or past hyperthyroidism mostly due to Graves' disease.

Pathogenesis

Autoimmune fetal and neonatal hyperthyroidism is commonly caused by the passage across the placenta of maternal stimulating antibodies directed against the thyroid-stimulating hormone (TSH) receptor antibodies (TRAbs). These antibodies stimulate the adenylate cyclase in fetal thyrocytes, leading to the hypersecretion of TH. The prevalence of hyperthyroidism in pregnancy is about 0.2%, with most cases due to GD. Graves' thyrotoxicosis generally improves in the second half of pregnancy due to decreases in the serum TRAb concentration but it then worsens after delivery [1]. The preservation of normal fetal TH status, which is essential to ensure normal brain development, is a complex issue in cases of maternal gestational autoimmune GD. High levels of antibody transmission are associated with the occurrence of fetal thyrotoxicosis. Fetal hyperthyroidism may develop when fetal TSH receptors become physiologically responsive to TSH and to TRAbs during the second half of gestation at around week 20, mostly in women with high levels of TRAbs. It may also occur in children of mothers who were treated years earlier for GD but still have circulating TRAbs. Thus, all pregnant women with GD and euthyroid pregnant women with a history of GD (and/or receiving long-term levothyroxine treatment after radioiodine or thyroidectomy related to GD) should undergo TRAb determinations at the beginning of pregnancy. If TRAbs are detected, the fetus should be considered at risk of developing thyrotoxicosis and monitored accordingly (Fig. 1) [1, 2].

Autoimmune fetal and neonatal hyperthyroidism must be distinguished from other, less frequent mechanisms of non-autoimmune congenital hyperthyroidism

[3]. Non-autoimmune neonatal hyperthyroidism due to an activating mutation of the TSH receptor gene or McCune Albright syndrome (activating mutation of the *Gsα* gene) is a very rare disease. Molecular abnormalities of the TSH receptor, leading to its constitutive activation, may be responsible for severe permanent congenital fetal and postnatal hyperthyroidism. Germline mutations are found in cases of hereditary autosomal dominant hyperthyroidism, and de novo mutations may cause sporadic congenital hyperthyroidism. The clinical course of these diseases requires careful management. Even with high doses of ATDs to control severe congenital thyrotoxicosis, thyroid nodules may develop, and goiter enlargement may occur early in life, necessitating subtotal thyroidectomy followed by radioiodine therapy. Autonomous adenomas with autonomous TH secretion due to somatic mutations of the TSH receptor gene and abnormally high levels of constitutive TSH receptor activity remain exceptional and are much rarer in neonates and children than in adults. Surgical excision of the nodule definitively cures the hyperthyroidism.

This review focuses on the management of autoimmune hyperthyroidism during the fetal and neonatal periods.

Clinical Manifestations

Fetal hyperthyroidism is almost invariably followed by neonatal hyperthyroidism. Neonatal autoimmune hyperthyroidism is generally transient, and it occurs in only about 2% of the offspring of mothers with GD. However, it is associated with a risk of mortality and immediate and long-term morbidity. Fetal and neonatal thyroid function may be disturbed to various extents by the presence of TRAbs, the use of ATDs, and maternal TH status. If the maternal disease is untreated or poorly controlled, goiter, intrauterine growth retardation, oligohydramnios, prematurity, and fetal death may occur [4]. Tachycardia, hyperexcitability, poor weight gain in children with a normal or large appetite, goiter, staring and/or eyelid retraction and/or exophthalmia, small anterior fontanel, advanced bone age, hepatomegaly and/or splenomegaly are the most frequently observed clinical features during the neonatal period. Cardiac insufficiency is one of the major risks in these infants. Biological abnormalities of the liver may also be observed in the absence of cardiac insufficiency. Craniosynostosis, microcephaly, and psychomotor disabilities may occur in severely affected infants [3, 5].

Diagnosis and Management

During Pregnancy

The early diagnosis and treatment of fetal hyperthyroidism or hypothyroidism are crucial and highlight the importance of TRAb determination throughout pregnancy in women with GD. Current guidelines recommend TRAb determination early in pregnancy and during the second half of gestation, starting from 20–24 weeks of gestation, with close monitoring if TRAb levels exceed 2–3 times the upper limit of the normal range [6]. These at-risk pregnancies should be monitored carefully, with repeated ultrasound examinations of the fetal thyroid gland [7]. The experience of the ultrasound operator is also crucial to the management of pregnancy in women with GD. Fetal thyroid width and circumference should be determined from 20 weeks of gestation onwards [8]. In fetuses with goiter, the main clinical issue is determining the cause: maternal ATD treatment appropriate for achieving normal maternal thyroid function but inappropriate and excessive for the fetus, resulting in hypothyroidism and necessitating a decrease in the ATD dose, or fetal thyroid stimulation by maternal GD, with the presence of TRAbs resulting in fetal thyroid stimulation and hyperthyroidism, requiring an increase in the maternal ATD dose (Fig. 1).

Fetal ultrasound scans are a noninvasive tool for detecting fetal thyroid dysfunction. Such scans should be performed monthly, from 20 weeks of gestation onwards, to screen for goiter and evidence of fetal thyroid dysfunction in pregnant women with GD testing positive for TRAbs and/or receiving ATDs. Thyroid gland enlargement is the starting point for the diagnosis of thyroid dysfunction, and ultrasound scans are also used to assess the presence and vascularity of goiter. A positive signal at the periphery of the thyroid gland has been shown to be associated with fetal hypothyroidism, whereas a positive signal throughout the gland is linked to fetal hyperthyroidism [7]. Assessments of fetal bone maturation (advanced bone maturation in cases of fetal hyperthyroidism, with a distal femoral center seen before the normal physiological appearance of this structure at a gestational age of 32 weeks; delayed bone maturation, with no visible distal femoral center after 32 weeks of gestation in cases of fetal hypothyroidism) and fetal heart rate (greater than 160/min in cases of fetal hyperthyroidism) may also facilitate the diagnosis of hypo- or hyperthyroidism, guiding the choice of the most appropriate treatment (Fig. 1) [2]. Invasive examinations, such as fetal blood collection or amniotic fluid sampling, are not usually required and

should be reserved for rare cases in which the diagnosis is dubious or intra-amniotic thyroxine injection is required to treat a secondary fetal hypothyroid state [2] if hypothyroidism persists 2–4 weeks after ATD dose reduction, with propylthiouracil (PTU) ≤100 mg/day or methimazole/carbimazole (MMI/CMZ) (CMZ is a precursor of MMI) with CMZ ≤10 mg/day. A combination of maternal criteria (TRAb titers, ATD use, and dose) and fetal criteria (thyroid Doppler signal, fetal heart rate, and bone maturation) is used to distinguish between fetal hypothyroidism and hyperthyroidism [7].

During the Neonatal Period

The prenatal response to treatment, based on fetal status and the results of thyroid function tests carried out on cord blood at birth, may validate the prenatal treatment strategy but is not predictive of subsequent neonatal thyroid dysfunction. Remarkably, only a minority of neonates born to mothers with gestational autoimmune thyroid disease have disturbed TH levels [7, 9, 10]. Neonates from mothers testing negative for TRAbs during the second half of gestation (with negative tests on cord blood) can be discharged and require no further follow-up [9, 11]. Hyperthyroidism may develop in neonates within 2–5 days of birth if TRAbs persist after the clearance of transplacentally transmitted ATDs from the mother. A threshold value for a maternal second-generation thyroid binding inhibitory immunoglobulin assay of 5 IU/L during the second half of gestation and delivery has recently been identified for defining risk situations for fetal and neonatal hyperthyroidism [12]. A close relationship has been demonstrated between serum maternal TRAb levels at the end of gestation and the levels of these antibodies in the serum of the neonate. If TRAbs are detectable, thyroid function tests should be repeated in the first week of life (every 2 days), even if normal (or high TSH levels due to excessive ATD treatment in late gestation) results were obtained with cord blood. Most cases of neonatal autoimmune hyperthyroidism are diagnosed within the first 2 weeks of life [11]. Neonates born to mothers with very low TRAb levels (less than 2–3 times the upper limit of the normal range; values depending on the assay, but usually below 5 IU/L) may have serum FT4 levels at about the 95th percentile on days 2–5, with these levels subsequently decreasing to within the normal range during the second week of life [10]. A strong suspicion of neonatal autoimmune hyperthyroidism when TRAbs are detectable and present at high levels (more than 3 times the upper limit of the normal range; generally >5 IU/L) in cord blood and free TH levels are high in the first 2–4 days after delivery (FT4 levels above the upper limit of the normal range for age, ≥40 pmol/L) should lead to the initiation of ATD treatment in the infant shortly after birth to prevent the development of clinical hyperthyroidism, thereby protecting the infant from the serious consequences of this condition. In rare cases, transient neonatal hypothyroidism may occur for 1–2 weeks due to the simultaneous presence of maternally transmitted thyrotropin receptor-blocking antibodies (TBAbs), and an imbalance in TSAb and the TBAb levels. Neonatal hyperthyroidism then occurs, in which TRAbs predominate, highlighting the need for repeated measurements of serum TH levels during the first 2–4 weeks of life in some cases, depending on serum TRAb levels. Less widely available third-generation bioassays determining the levels of thyroid-stimulating or blocking immunoglobulins through the monitoring of cyclic adenosine monophosphate production may be used in these cases.

Treatment

During Gestation

ATD treatment is commonly used to achieve euthyroidism in women with GD. However, both MMI/CMZ and PTU are associated with an increase in the prevalence of birth defects (including maternal agranulocytosis and liver failure, both of which are usually very rare), but the spectrum of malformations differs between these drugs [13]. Exposure to MMI/CMZ during the teratogenic period of pregnancy (6–10 weeks of gestation, corresponding to weeks 4–8 of embryonic development) is associated with a higher risk of choanal atresia, omphalocele, esophageal atresia, omphalomesenteric duct abnormalities, aplasia cutis congenital, nipple, and eye malformations. The birth defects associated with PTU exposure are milder and appear to be restricted to face and neck malformations. Exposure to MMI/CMZ or PTU is also associated with a higher risk of malformations of the urinary system [14]. Such birth defects are observed in about 3% of the neonates, and some birth defects may be detected later, resulting in a total prevalence of about 6% at 2 years of age. It has, therefore, recently been suggested that the use of ATDs at 6–10 weeks of gestation should be limited as much as possible to decrease the risk of birth defects [15].

Fetal hyperthyroidism can be prevented by administering ATDs to the mother. PTU and MMI/CMZ cross the placenta and are equally effective for treating hyperthyroidism in pregnancy. PTU is the most widely used

Table 1. Management for neonates with autoimmune hyperthyroidism

Determine TRAb in cord blood: high risk of neonatal hyperthyroidism if TRAb >5 IU/L; FT4, TSH levels: may validate the prenatal strategy but are not predictive of subsequent thyroid function
Repeated measurements of serum thyroid hormone levels during the first 2 weeks of life: days 3, 5, 7, 10, and 15
Physical examination: check for malformations
Admission to hospital for the first week of life
Initiate MMI/CMZ treatment as soon as possible: 0.5–1 mg/kg/day divided into 2–3 doses The dose should be decreased when serum FT4 levels are within the reference range
Propanolol: 2 mg/kg/day divided into 2 doses, for 2 weeks
Repeated measurement of serum TH levels weekly until stable, and then every 2 weeks
Dose titration should be preferred, but "block-and-replace" (levothyroxine) strategies may be considered in some cases
Safety of breast feeding
Treatment should be stopped when TRAb is no longer detectable in serum (1–3 months, depending on initial level)
Outcome: check for craniosynostosis, transient central hypothyroidism, long-term neuropsychological development

TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid-stimulating hormone; TH, thyroid hormone; MMI, methimazole; CMZ, carbimazole.

during pregnancy, generally with a shift onto this drug from MMI/CMZ shortly before conception [15]. The fetus benefits directly from the maternal ingestion of these drugs, which cross the placenta and act on the fetal thyroid gland. However, these drugs may also expose the fetus to the risk of hypothyroidism, and small doses (usually no more than 100–150 mg PTU or 10–15 mg MMI/CMZ daily) are, therefore, recommended during the second half of gestation (Fig. 1).

During the neonatal period

MMI/CMZ is preferred (0.5–1 mg/kg/day, depending on the initial severity of the disease, in 3 divided doses). Propanolol (2 mg/kg/day, in 2 divided doses) can also be used to control tachycardia during the first 1–2 weeks of treatment. It is usually possible to decrease the ATD dose progressively, according to the TH levels. Levothyroxine may be added to the regimen, but as later in life dose titration should be preferred over "block-and-replace" approaches. The disease is transient and may last from 1–3 months, until maternal TRAbs are eliminated from the infant's bloodstream. Mothers can breastfeed while taking ATDs (usually with a MMI/CMZ dose of <20 mg per day, or a PTU dose <300 mg per day), with no adverse effects on the thyroid status of their infants [16]. The management for neonates with autoimmune hyperthyroidism is summarized in Table 1.

Outcome

Craniosynostosis (premature fusion of 1 or more cranial sutures causing an abnormal head shape and restricting skull growth) is rarely reported but should be diagnosed through clinical examination and imaging studies and managed as early as possible to improve neurocognitive outcome. Transient central hypothyroidism due to thyroid regulatory system impairment as a result of inadequately treated maternal GD is rare [17] but may become apparent after the clearance of ATDs. It requires levothyroxine treatment for several weeks and highlights the need for careful monitoring of thyroid function after the resolution of neonatal hyperthyroidism.

Despite the favorable outcome, follow-up studies are required to evaluate the long-term neuropsychological, emotional, and behavioral functioning of children with neonatal hyperthyroidism. Individual assessment during preschool years should be considered in all patients, especially in those with severe fetal and neonatal hyperthyroidism.

Disclosure Statement

J.L. has no conflicts of interest to declare.

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