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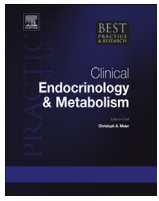

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Management of neonates born to mothers with thyroid dysfunction, and points for attention during pregnancy

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Thyroid hormone (TH) is indispensable for normal embryonic and fetal development. Throughout gestation TH is provided by the mother via the placenta, later in pregnancy the fetal thyroid gland makes an increasing contribution. Maternal thyroid dysfunction, resulting in lower or higher than normal (maternal) TH levels and transfer to the embryo/fetus, can disturb normal early development. (Maternal) thyroid dysfunction is mostly caused by autoimmune hypo- or hyperthyroidism, i.e. Hashimoto and Graves disease. Autoimmune hyperthyroidism is caused by stimulating TSH receptor antibodies (TSHR Ab), patients with autoimmune hypothyroidism may have blocking TSHR Ab. Maternal TSHR Ab cross the placenta from mid gestation and may cause fetal and transient neonatal hyper- or hypothyroidism. Anti-thyroid drugs taken for autoimmune hyperthyroidism cross the placenta throughout gestation, and may cause fetal and transient neonatal hypothyroidism. This review focusses on the consequences of maternal hypo- and hyperthyroidism for fetus and neonate, and provides a practical approach to clinical management of neonates born to mothers with thyroid dysfunction.

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Introduction

From early in gestation, the embryo and fetus need thyroid hormone (TH) for many developmental processes. Optimal TH levels are achieved by an intriguing collaboration between the mother and her developing child. Maternal TH has been shown to cross the placenta throughout pregnancy [1–3]. In addition, the embryonic thyroid gland produces small amounts of TH from around 10 to 11 weeks gestational age. However, only after the fetal hypothalamo-pituitary-thyroid (HPT) axis becomes functional, several weeks later - at approximately 20 weeks' gestation -, fetal TH production increases. Until that moment, embryo and fetus are dependent on small amounts of maternal TH obtained via the placenta [4,5]. There is substantial evidence that low as well as high maternal plasma TH concentrations early in pregnancy, probably resulting in abnormal embryonic/early fetal TH levels, are associated with impaired neurocognitive function in offspring [6,7]. In addition, abnormal fetal plasma TH concentrations during pregnancy may alter postnatal HPT axis functioning, not only in the neonatal period, but also long thereafter [8–10]. Low or high maternal plasma TH concentrations mostly result from maternal thyroid dysfunction, resulting in lower or higher than normal transplacental TH transport and, with that, lower or higher than normal embryonic/early fetal TH levels. Maternal dysfunction can be either hypo- or hyperthyroidism, with acquired disease - mainly thyroid autoimmunity - being a much more frequent cause than congenital disease. In addition to disease-related abnormal maternal TH concentrations influencing embryonic/early fetal TH levels, (early) fetal and neonatal thyroid function and TH levels can be disturbed by maternal thyroid autoantibodies, and by antithyroid drugs used by the mother for the treatment of hyperthyroidism. Because of considerable morbidity and even fatal outcome, fetal and neonatal hyperthyroidism are considered serious conditions, even though well-designed observational studies on their clinical and developmental outcome are lacking [11–13]. This review focusses on the consequences of maternal hypo- and hyperthyroidism for fetus and neonate, and provides a practical approach to the clinical management of neonates born to mothers with thyroid dysfunction.

Maternal thyroid dysfunction

Maternal thyroid dysfunction is mainly caused by autoimmune thyroid disease. The prevalence of autoimmune *hypo*thyroidism or Hashimoto disease, and autoimmune *hyper*thyroidism or Graves disease in women are approximately 0.3% and 0.5%, respectively [14]. In addition, at least 2–3% of healthy non-pregnant women of childbearing age have an elevated TSH, and 30–60% of pregnant women with an elevated TSH have detectable thyroid autoantibodies [15]. Treatment for hypothyroidism, whether it is caused by thyroid autoimmunity or not, consists of daily TH administration (levothyroxine, LT4). Autoimmune hyperthyroidism is usually treated "medically", with an antithyroid drug (methimazole [MMZ] or propylthiouracil [PTU]) plus or minus LT4 according to the "block and replace" or "titration" method. Like TH, antithyroid drugs can cross the placenta throughout pregnancy [16,17]. In addition to autoimmune hypothyroidism, maternal hypothyroidism can result from thyroidectomy or ablative ^{131}Iodine treatment for autoimmune hyperthyroidism (definitive treatment) or other thyroid disease, e.g. thyroid cancer or (multi-nodular) goiter [18]. Furthermore, maternal hypothyroidism can be a (much rarer) congenital disorder, i.e. (treated) congenital hypothyroidism. Most cases of congenital hypothyroidism are of primary origin and due to thyroid dysgenesis, e.g. thyroid athyreosis, ectopy or hypoplasia, but approximately 10–20% of cases result from an inborn error of thyroid hormone synthesis, also known as thyroid dyshormonogenesis [19]. Thyroid dyshormonogenesis is an autosomal recessive disorder with a 25% chance of recurrence. Thyroid dysgenesis does not seem to be a "classic" inheritable disease, but approximately 2% of cases occur familial [20]. Finally, maternal hypothyroidism can be central, i.e. due to hypothalamus-pituitary disease. Central hypothyroidism is characterized by a (too) low plasma FT4 concentration, in combination with a normal, low or slightly higher than normal TSH concentration. It can occur "isolated" or as part of multiple pituitary hormone deficiency, and can be congenital or acquired. In the past decades, a number of genetic causes of congenital central hypothyroidism have been discovered. With respect to heritability, most are autosomal recessive disorders, but some have an autosomal dominant or X-linked inheritance pattern [21]. Like maternal hypothyroidism, *hyper*thyroidism can also have non-autoimmune causes,

including subacute thyroiditis or toxic multinodular goiter. Besides these acquired disorders, hyperthyroidism can be a rare congenital disease, caused by activating mutations of the genes encoding the thyroid-stimulating hormone receptor (*TSHR*) or the Gs-alpha (*GNAS1*). Activating *TSHR* mutations inherit in an autosomal dominant way, activating *GNAS1* mutations are somatic mutations [22]. Thyroid hormone overproduction can also result from generalized resistance to TH caused by usually autosomal dominant mutations of the gene encoding the TH receptor beta (*THRB*) [22,23].

Autoimmune thyroid disease

Autoimmune *hypo*thyroidism or Hashimoto disease is characterized by chronic thyroiditis and thyroid destruction. It can present with goiter or atrophy, and often results in (subclinical) hypothyroidism. Typical IgG class autoantibodies to thyroperoxidase (TPOAb) can be detected in almost all patients with autoimmune hypothyroidism [24]. Autoimmune *hyper*thyroidism or Graves disease is characterized by TH overproduction caused by circulating IgG autoantibodies binding to, and stimulating the thyrotropin (TSH) receptor: TSAb [25]. In time, in some patients with autoimmune hyperthyroidism TSAb may disappear and be replaced by Ab that do not stimulate, but block binding of TSH to its receptor: TBAb. Furthermore, TSAb and TBAb may co-occur [26,27]. Most currently used laboratory tests do not discriminate between TSAb and TBAb, but only measure the amount of Ab that inhibits binding of TSH to the TSH receptor: TSHRAb [28]. Many patients with autoimmune hyperthyroidism also have circulating TPOAb, reflecting concomitant autoimmune thyroiditis [29]. In addition to TPOAb, a small percentage of patients with autoimmune hypothyroidism have circulating TSHRAb. In most patients they are of the "blocking" type: TBAb, but incidentally they may be replaced by stimulating Ab: TSAb [26,27]. Maternal immunoglobulins, including TPOAb, TSAb and TBAb, can cross the placenta from mid gestation [30]. However, during pregnancy thyroid autoimmunity is usually suppressed, resulting in decreasing thyroid autoantibodies concentrations and, with that, lower maternofetal transfer [31].

Maternal autoimmune thyroid disease, and fetal/neonatal thyroid (dys-)function

Of the two autoimmune thyroid diseases, maternal autoimmune hyperthyroidism has a greater potential impact on fetal and neonatal thyroid function than maternal autoimmune hypothyroidism. However, autoimmune hypothyroidism and subclinical hypothyroidism are more frequent conditions with some important points of attention.

Maternal autoimmune hypothyroidism

In many (just) pregnant women with autoimmune hypothyroidism, the diagnosis is made before pregnancy, and these women will be treated with LT4. If LT4 is dosed properly, it is likely that most fetuses will be provided with adequate amounts of TH throughout pregnancy. Maternal TPOAb can cross the placenta, but do not influence fetal or neonatal thyroid function [15,32]. Ten to 20% of pregnant women with autoimmune hypothyroidism have circulating TBAb [29]. From mid gestation on, these TBAb can cross the placenta, inhibit fetal TH production and cause fetal and transient neonatal hypothyroidism [33]. Yet, the incidence of transient neonatal hypothyroidism due to TBAb seems very low. The first reported incidence by Brown et al., derived from neonatal screening data, was 1 in 180,000 [34]. Later reported incidences ranged between 1 in 84,700 and 1 in 310,000 [35,36]. If severe enough, TBAb related transient congenital hypothyroidism will be detected by neonatal screening, and when treated properly with LT4, affected neonates have an excellent neurodevelopmental prognosis. Given a half-life of approximately two to four weeks of maternal IgG class immunoglobulins in neonates, transient usually means no longer than three to four months [37]. However, if autoimmune hypothyroidism arises just before or early in pregnancy, is not (clinically or biochemically) recognized, and is accompanied by the presence of circulating TBAb that cause fetal hypothyroidism, neurodevelopment of the fetus may be impaired resulting in irreversible postnatal developmental delay. Fortunately, this seems to be quite a rare problem illustrated by only a few published case reports [38,39]. Another rarity is transient neonatal hyperthyroidism in neonates born

to mothers with autoimmune hypothyroidism [40–42]. In these mothers, TBAb may have been replaced by TSAb. This condition is not detected by neonatal screening. A frequently asked question is if a newborn baby of a mother with autoimmune hypothyroidism treated with LT4 should undergo thyroid function testing. Considering the harmlessness of TPOAb for fetal and neonatal thyroid function, the rarity of TBAb induced transient neonatal hypothyroidism, and probable detection of this problem by neonatal screening, the answer is "no". However, and this can't be stressed enough, women with newly diagnosed autoimmune hypothyroidism who can (still) have children, should be properly counseled about increasing the LT4 dose and thyroid function testing frequency when (becoming) pregnant, aiming at optimal FT4 (and TSH) levels guided by a proper LT4 treatment guideline [15]. Timely increasing the LT4 dose will prevent embryonic and early fetal TH deficiency, and optimizing FT4 levels will prevents fetal TH deficiency or excess later on. This also applies to most other causes of acquired and congenital hypothyroidism. The only exception to this rule is acquired hypothyroidism due to thyroidectomy or ablative ^{131}Iodine treatment for autoimmune hyperthyroidism (definite treatment). This will be discussed in the next paragraph.

Maternal autoimmune hyperthyroidism

In contrast to autoimmune hypothyroidism, maternal autoimmune *hyper*thyroidism can have a much greater impact on the embryonic and fetal TH state, and on neonatal thyroid function than maternal hypothyroidism. Just like in women with hypothyroidism treated with LT4, TH concentrations in women with hyperthyroidism treated with an antithyroid drug plus or minus LT4 may be suboptimal – too low or high - resulting in lower or higher than normal maternofetal TH transport. Furthermore, maternal TSAb and anti-thyroid medication can cross the placenta (from mid gestation onwards and throughout pregnancy, respectively), inhibiting late embryonic and (early) fetal TH production (anti-thyroid medication), and overstimulating the fetal thyroid gland resulting in fetal hyperthyroidism from mid gestation onwards (TSAb) [43,44]. Finally, fetal hyperthyroidism may be followed by neonatal hyperthyroidism, but also by central hypothyroidism. Neonatal hyperthyroidism occurs in less than 5% of neonates born to mothers with autoimmune hyperthyroidism, corresponding to an incidence of approximately 1 in 50,000 neonates [15]. The incidence of central hypothyroidism may even be somewhat higher: 1 in 35,000 [45]. All this is illustrated on the basis of three scenarios.

Scenario 1 - the pregnant woman diagnosed with autoimmune hyperthyroidism in the past, who received definitive treatment

The *first scenario* is the pregnant woman diagnosed with autoimmune *hyper*thyroidism in the past, who received definitive treatment for recurrent or persistent TSAb induced hyperthyroidism (long) before the current pregnancy. Because of acquired *hypo*thyroidism following thyroidectomy or ^{131}I administration she is treated with LT4. Just like in (autoimmune and other causes of) hypothyroidism, this poses a risk of under- or overtreatment, and thus a risk of embryonic and early fetal TH deficiency or excess. A second problem is the potential presence of TSAb. After definitive treatment for autoimmune hyperthyroidism, TSAb production may go on for many years. The chance of ongoing production is higher in women who underwent ^{131}I treatment than in women who underwent thyroidectomy [46–48]. Fortunately, during pregnancy thyroid autoimmunity is usually suppressed, resulting in decreasing TSAb concentrations and, with that, lower transplacental transfer [31]. If TSAb are present, persist past mid gestation and cross the placenta, they can cause fetal hyperthyroidism. If TSAb persist until the end of gestation, they can cause (transient) neonatal hyperthyroidism. TSAb can be replaced by TBAb that may (partly) counteract the stimulating effect of TSAb. If TBAb prevail over TSAb, theoretically they may even cause (late) fetal, and transient congenital hypothyroidism [27,31]. Especially given the severity and potential harmfulness of TSAb induced fetal and neonatal hyperthyroidism, pregnant women with a medical history of autoimmune hyperthyroidism should be tested for the presence of TSHRAb in the first trimester of pregnancy. If absent or low - bearing in mind that pregnancy suppresses thyroid autoimmunity - the risk of fetal and neonatal hyperthyroidism after mid gestation is negligible and further testing is not necessary. If present, testing should be repeated at mid

gestation. If TSHRAb are then absent or low, no further action is required. If however TSHRAb are still present, the risk is increased and the fetus should be examined and followed for signs and symptoms of hyperthyroidism. If a presumptive diagnosis of hyperthyroidism is made, the fetus should be treated with an antithyroid drug via the mother. At the same time the mother's TH levels should be kept in the upper level of the reference interval to prevent suboptimal maternofetal TH transport [49]. Recently, Banigé et al. determined optimal maternal TSHRAb concentration cut-offs predicting fetal and neonatal dysthyroidism (FD and ND, respectively; FD included fetal hyper- and hypothyroidism, ND included neonatal hyper- and hypothyroidism). The presence of FD was best predicted by a maternal TSHRAb concentration ≥2.5 times the upper limit of the reference interval. In this study, TSHRAb were measured using a second-generation human assay with a reference interval upper limit of 1.0 IU/L [48]. If maternal TSHRAb are still present late in the third trimester of pregnancy, the newborn should be examined for signs of hyper- and hypothyroidism, and cord blood should be taken for measurement of the thyroid function and presence of TSHRAb. Subsequently, the newborn should be followed up according to a clear and effective screening protocol, and results should be assessed according to a diagnostic algorithm consisting of clear decision rules with respect to whether to treat or not, and — given the transient character of the neonatal hyperthyroidism -, when to stop further screening or treatment (Fig. 1).

The optimal maternal TSHRAb concentration cut-off for predicting the emergence of ND is less clear. Banigé et al. found that ND was best predicted by a maternal TSHRAb concentration ≥5.9 times the upper limit of the reference interval. However, based on a systematic review of available studies van Dijk et al. suggested a lower cut-off value; in their analysis the presence of neonatal hyperthyroidism was best predicted by a maternal TSHRAb concentration ≥3.7 times the upper limit of the reference interval [48,50]. The study by Banigé et al. was not included in the systematic review. Yet, given the seriousness of neonatal hyperthyroidism choosing the lower cut-off seems reasonable. So, in this scenario, optimal care of the fetus consists of careful dosing of LT4 throughout pregnancy, if necessary repeatedly measuring maternal TSHRAb and, if present at mid gestation, examining and following up the fetus for signs and symptoms of hyperthyroidism. After birth, the neonate should be repeatedly examined and tested for (the risk of developing) hyperthyroidism. If neonatal hyperthyroidism is diagnosed, antithyroid drug plus or minus LT4 treatment should be started to bring and maintain TH concentrations within the reference interval. Treatment can be stopped when TSHRAb have disappeared, usually three months after birth.

Scenario 2 - the pregnant woman diagnosed with autoimmune hyperthyroidism more recently and treated with an antithyroid drugs plus or minus LT4

The *second scenario* is the pregnant woman who has been diagnosed with autoimmune hyperthyroidism more recently and is treated with an antithyroid drug plus or minus LT4. Properly guided by her treating doctor, after becoming pregnant she is treated with PTU only. Just like in scenario one, maternal TH levels (PTU regulated in this scenario) may be too low or high with the risk of embryonic and early fetal TH deficiency or excess. Also like in scenario one, TSAb may cause fetal hyperthyroidism after mid gestation (see the first scenario). However, in this scenario the mother's antithyroid medication poses an extra risk. If dosed too high it may impair fetal TH production and cause fetal goiter [48]. If at the same time maternal TH levels and maternofetal TH transport are lower than desirable, fetal growth and development are at risk. If dosed too low, maternal TH levels and maternofetal TH transport may be higher than normal, also putting fetal growth and development at risk. Optimal care in this scenario consists of careful dosing of PTU throughout pregnancy, avoiding too low or high TH concentrations, following maternal TSHRAb concentrations and, if present at mid gestation, examining and following the fetus for signs and symptoms of hyperthyroidism. In addition, extra attention should be paid to signs and symptoms of antithyroid drug induced fetal hypothyroidism. In the context of maternal antithyroid drug use, goiter more often indicates fetal hypothyroidism than hyperthyroidism [48].

If maternal TSHRAb are still present late in the third trimester of pregnancy, the newborn should be examined for signs of hyper- and hypothyroidism, like in scenario 1. Cord blood should be taken for

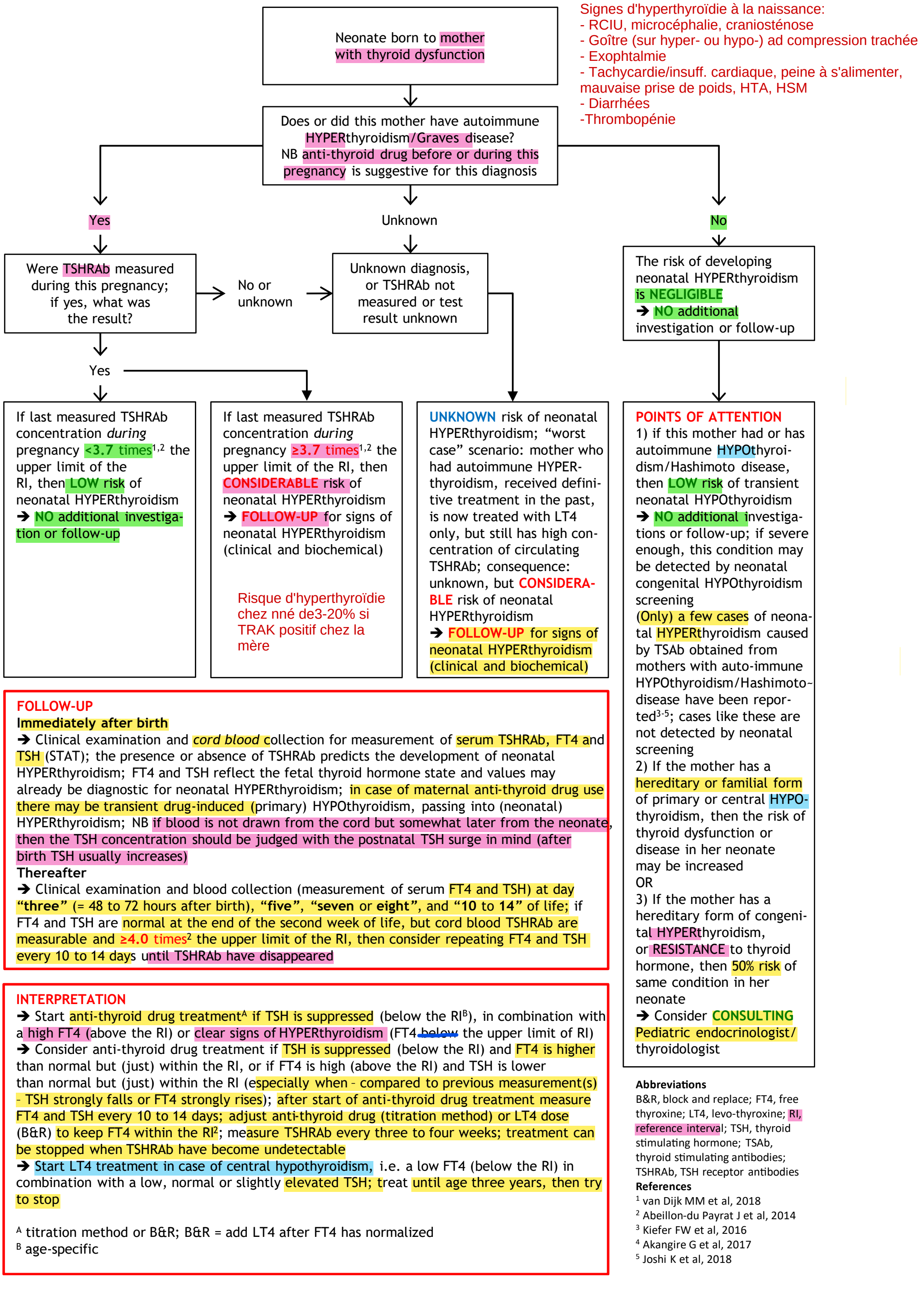

Fig. 1. The neonate born to a mother with thyroid dysfunction - Screening protocol, and diagnostic and treatment algorithm.

NB:
- Hyper- ou hypo- thyroidie transitoire si sur traitement médicamenteux maternel excessif vs trop faible ou anti-thyroidien
- Hypothyroïdie prolongé si hyperthyroidie maternelle non traité durant la grosses --> perturbation de la matiration du système Tç/TSH chez enfant

measurement of the thyroid function and presence of TSHRAb. Also like in scenario 1, the newborn should be followed up according to a screening protocol and diagnostic algorithm (Fig. 1).

It is important to note that at, and during the first days after birth the neonate may be biochemically hypothyroid because of circulating maternal antithyroid medication. Because both PTU and MMZ are quickly cleared from the neonatal circulation (duration of action 12–24 h, and 36–72 h, respectively), this primary hypothyroidism is of a short-term nature, usually taking no longer than a few days [11].

Scenario 3 - central hypothyroidism in neonates born to mothers with inadequately treated or undiagnosed autoimmune hyperthyroidism

Since the late 1980s, a number of case reports and series have been published reporting neonates diagnosed with central hypothyroidism – i.e. TH deficiency due to insufficient production of thyroid-stimulating hormone (TSH) - born to mothers with undiagnosed or inadequately treated autoimmune hyperthyroidism during pregnancy. In many of these babies, the diagnosis central hypothyroidism was made in the neonatal period, during clinical and biochemical follow-up because of known autoimmune hyperthyroidism of their mothers [51–54]. In other babies, the central hypothyroidism was detected by the (nationwide) T4-based neonatal congenital hypothyroidism screening program [9]. In some of these babies their central hypothyroidism was the first clue to their mothers' autoimmune hyperthyroidism. The most likely cause of the central hypothyroidism is exposure of the fetal HPT axis to higher-than-normal TH concentrations impairing its physiologic maturation during intrauterine life [9]. The high fetal TH concentrations probably result from higher than normal transplacental maternofetal TH transport (because of suboptimal or not treated maternal hyperthyroidism), and maternal TSAb crossing the placenta and stimulating the fetal thyroid gland (that is insufficiently or not inhibited because of insufficient or no maternal anti-thyroid drug treatment). The most likely reason why these neonates develop central hypothyroidism and not hyperthyroidism is that during the last part of pregnancy their TSHRAb/TSAb concentration has decreased or that their TSHRAb have become predominantly TBAb instead of TSAb [52]. Recent research - animal and human studies – sheds some light on the probable pathogenesis of this form of central hypothyroidism. Transgenic zebrafish embryos early exposed to elevated TH show thyrotrope cell death, with cell numbers slowly recovering following removal of excess TH. This suggests that TH exposure during a critical period of pituitary development may have long-term implications for the functional reserve of TSH production [55]. Fetuses exposed to the high TH levels of mothers with generalized resistance to TH caused by *THRB* gene mutations have suppressed TSH [56]. Adult humans and mice without resistance to TH, born to mothers with resistance to TH and thus exposed to high maternal TH in utero, showed persistent central resistance to TH, as evidenced by preserved responses of serum TSH to thyrotropin releasing hormone when treated with T3. In the mice, anterior pituitary TSH-β and deiodinase 3 (D3) mRNAs were increased. Since the D3 enzyme protects the fetus from maternal T3 excess and the D3 gene is imprinted, increased expression of the D3 gene may be a long-lasting and even permanent epigenetic effect [10]. Although neonatal central hypothyroidism resulting from maternal autoimmune hyperthyroidism was considered a transient disorder [52,54], it may persist in up to 30% of affected children, and even change into mild primary hypothyroidism with a smaller than normal thyroid gland [57]. Just like sporadic primary and central congenital hypothyroidism, neonatal central hypothyroidism due to maternal autoimmune hyperthyroidism is an indisputable indication for LT4 treatment [58].

Maternal non-autoimmune hypo- and hyperthyroidism, and maternal thyroid dysfunction of unknown origin

If maternal hypothyroidism results from thyroidectomy or ablative ^{131}Iodine treatment for acquired non-autoimmune conditions like thyroid cancer or (multinodular) goiter, from acquired central hypothyroidism, or from non-hereditary or non-familial forms of primary or central congenital hypothyroidism, then neonates born to such mothers do not have an increased risk of thyroid dysfunction or disease. Of course, maternal LT4 treatment poses the risk of under- or overtreatment and with that a risk of embryonic and early fetal TH deficiency or excess, just like in the aforementioned scenarios.

However, if maternal hypothyroidism results from hereditary or familial primary or central congenital hypothyroidism, then the risk of thyroid dysfunction or disease in these mothers' neonates may be increased, depending on the specific (genetic) cause. In such cases, it is advisable to arrange a prenatal consultation with a clinical geneticist or (pediatric) endocrinologist experienced in hereditary thyroid or pituitary disease. Congenital hyperthyroidism due to *TSHR* gene mutations and generalized resistance to TH caused by *THRB* gene mutations both inherit in an autosomal dominant way. So, newborns of affected mothers have a 50 percent risk of having the same condition. A special challenge is the neonate born to a mother with thyroid dysfunction of unknown origin. Pediatricians and pediatric endocrinologists are often asked for advice when nothing more is known than that the neonate's mother uses “thyroid medication” - mostly only LT4 -, or “has a thyroid disorder”. Since this may be a mother who underwent ablative ^{131}Iodine treatment for autoimmune hyperthyroidism, and is now using LT4 for subsequent hypothyroidism, her newborn baby may be at risk of having or developing hyperthyroidism as a result of TSAb. So, as long as the maternal precise diagnosis is unknown, the neonate should be assessed like neonates born to mothers with autoimmune hyperthyroidism.

The neonate born to a mother with thyroid dysfunction - screening protocol and diagnostic algorithm

The first step in the assessment of a neonate, recently born to a mother with thyroid dysfunction, is to track down the maternal diagnosis (Fig. 1). If it is certain that it was/is not autoimmune hyperthyroidism/Graves disease, then additional investigation or follow-up is not necessary. In neonates born to mothers with autoimmune *hypo*thyroidism/Hashimoto disease, TBAb induced transient primary hypothyroidism is a rare condition. If present, it may be detected by neonatal congenital hypothyroidism screening. The same applies to (also rare) hereditary or familial occurring primary congenital hypothyroidism (affecting the mother, and maybe the neonate). Whether and how to treat primary congenital hypothyroidism should be guided by an appropriate guideline or protocol, like the 2014 European Society for Paediatric Endocrinology Consensus Guidelines on Screening, Diagnosis, and Management of Congenital Hypothyroidism [59]. In case of maternal carriership of a mutation in one of the genes causing central congenital hypothyroidism it is advisable to test for this diagnosis, especially in case of X-linked forms affecting boys (by measurement of serum of plasma FT4 and TSH). For an overview of genetic causes of primary and central congenital hypothyroidism, see the reviews by Zwaveling-Soonawala et al., and by Peters C et al. [19,21]. If the mother had or has autoimmune *hyperthyroidism*/Graves disease, then the mother's medication and last measured TSHRAb concentration (preferably late in the third trimester) should be tracked down. If the last maternal TSHRAb concentration was <3.7 times the upper limit of the reference interval [50], then the chance that the neonate has or may develop hyperthyroidism is so small that additional investigation or follow-up is *not* indicated. If the last TSHRAb concentration was ≥3.7 times the upper limit of the reference interval or this result is not available, then cord blood should be taken for measurement of TSHRAb, TSH and FT4, and the neonate should be examined for signs of hyperthyroidism. The presence and level of cord blood TSHRAb will predict the (near-future) development of neonatal hyperthyroidism. Cord blood TSH and FT4 levels will reflect the interaction between the fetal/neonatal HPT axis, TSHRAb, and maternal antithyroid drug that crossed the placenta preceding delivery (if used by the mother) [11]. Banigé et al. also determined the optimal neonatal TSHRAb concentration cut-off predicting ND (measured in cord blood, or venous blood taken between days zero and five). The presence of ND was best predicted by a neonatal TSHRAb concentration ≥6.8 times the upper limit of the reference interval (measured by a second-generation human assay with a reference interval upper limit of 1.0 IU/L) [48]. However, Abeillon-du Payrat found a lower number. In their analysis neonatal hyperthyroidism was best predicted by a neonatal TSHRAb concentration ≥4.0 times the upper limit of the reference interval (measured between one and three days post-delivery) [60]. Given the severity of neonatal hyperthyroidism, it seems reasonable to use the lower cut-off. If the mother used an antithyroid drug during pregnancy, TSH will usually be high to very high, and FT4 normal to low, depending on the antithyroid drug dose. In our experience, a high cord blood TSH in combination with a low FT4 in a neonate born to

a mother with "active" Graves disease treated with an antithyroid drug is not a reason for immediate start of LT4 treatment. FT4 will quickly rise (TSAb present) or normalize (TSHRAb absent) when the antithyroid drug is eliminated by the kidneys (PTU t ½ ≈ 1,5 h, methmazole t ½ ≈ 2–6 h). If the mother did *not* use an antithyroid drug during pregnancy but TSHRAb are present, TSH and FT4 levels will reflect their net intrinsic activity: a low TSH in combination with a high FT4 indicates TSAb induced hyperthyroidism, and a high TSH in combination with a low to normal FT4 indicates TBAb induced hypothyroidism. Even more rarely, a balanced mixture of TSA and TBAb may be associated with initially normal TSH and FT4 concentrations. Cord blood TSH and FT4 levels do not predict the development of neonatal hyperthyroidism, only the presence (or absence) of TSHRAb does [11]. If neonatal hyperthyroidism is diagnosed, treatment should be started to prevent adverse effects (see next paragraph). If cord blood TSH and FT4 concentrations do not point to hyperthyroidism (yet), then the neonate should be followed-up for clinical and biochemical signs of hyperthyroidism, with measurement of TSH and FT4 at day three (= 48–72 h after birth), five, seven or eight, and 10 to 14 of life [60]. If neonatal hyperthyroidism develops during this period, then treatment should be started. If there are no or not yet biochemical or clinical signs of hyper- (or hypo)thyroidism, and cord blood TSHRAb are <4.0 times the upper limit of the reference interval, then follow-up can be stopped [61]. However, if cord blood TSHRAb are ≥4.0 times the upper limit of the reference interval, it is advisable to continue clinical and biochemical follow-up, e.g. every ten to 14 days until TSHRAb have disappeared. The reason for this careful approach is the rare occurrence of transient hyperthyroidism beyond the first weeks of life in neonates with an initial "balanced" mixture of TBAb and TSAb, but in whom TBAb are cleared more quickly than TSAb. How long TSHRAb remain detectable is closely related their concentration in the first days of life. Recently, Banigé et al. drafted the following equation between TSHRAb and its duration of elimination: TRAb elimination time (day) = 7.28 + 2.88 × log (TSHRAb) + 11.62 log (TRAb^2) [60].

Neonatal hyperthyroidism - treatment

Treatment is indicated when there is biochemical evidence of neonatal hyperthyroidism, i.e. a low TSH (<0.9 mIU/L between days three and seven of life) in combination with a high or high normal FT4 plus clinical signs supporting this diagnosis [61]. Clinical signs are irritability, poor drinking, perspiration, insufficient weight gain, wide open eyes, warm and moist skin, hyperthermia, tachycardia, tachypnea, respiratory "distress", and goiter. Treatment should be strongly considered when TSH and FT4 are low and high, respectively, but clear symptoms are (still) absent. It should be noted that, with respect to TSH and FT4 concentrations, the neonatal period is a rather dynamic period. Normally, shortly after birth TSH abruptly increases. Within the first 30 min after birth, neonates experience the so-called TSH surge secondary to cold-induced thyrotropin releasing hormone release. This stimulates T4 production with FT4 peaking at approximately day three of life, and slowly deceasing thereafter. Treatment consists of the anti-thyroid drug MMZ in a dose of approximately 0.5 (0.2–1.0) mg per kg per day in two to three divided doses plus or minus LT4 in a dose of 8–10 μg per kg per day in one daily dose (both orally) according to the "block and replace" or "titration method" [11]. LT4 should be added (block and replace)/the MMZ dose should be lowered (titration) when FT4 has decreased to within the age-specific reference interval (thyroxine t ½ at this age ≈ 3–4 days). The advantage of titration is a lower total daily dose, a disadvantage is a less stable FT4 concentration. An advantage of block and replace is a more stable FT4 concentration, a disadvantage is a generally somewhat higher total daily dose of antithyroid drugs possibly associated with more side effects. In case of severe hyperthyroidism accompanied by sympathetic hyperactivity, treatment can be expanded by adding propranolol 2 mg per kg per day in two divided doses orally. In case of hemodynamic instability, potassium iodide (Lugol's iodine, one drop three times per day; one drop contains approximately 5 mg iodine plus iodide) and prednisolone can be added (2 mg per kg per day in one or two divided doses orally) [11]. Treatment should be monitored by clinical examination and measurement of TSH and FT4 every ten to 14 days, and measurement of TSHRAb every three to four weeks. Treatment can be stopped when TSHRAb have become undetectable.

Practice points

- Maternal anti-TPO and TSHR Ab cross the placenta from mid-gestation; anti-TPO Ab do not harm fetal thyroid function, but stimulating and blocking TSHR Ab do, and may cause fetal and (transient) neonatal hyper- or hypothyroidism, respectively;
- Neonatal hypothyroidism caused by blocking TSHRAb is quite a rare problem, and does not justify screening of all pregnant women with (a medical history of) autoimmune hypothyroidism for the presence of TSHRAb; fortunately, if severe enough this type of congenital hypothyroidism will be detected by neonatal screening;
- Given the severity of fetal and neonatal hyperthyroidism, pregnant women with (a history of) autoimmune hyperthyroidism should be screened for presence of TSHRAb;
- If maternal TSHRAb are present at mid gestation with a concentration $\geq$2.5 times the upper limit of the reference interval, then the fetus should be examined and followed for signs and symptoms of hyperthyroidism; if hyperthyroidism is diagnosed, the fetus should be treated with an anti-thyroid drug via the mother;
- If, during gestation, the last measured maternal TSHR Ab is $\geq$3.7 times the upper limit of the reference interval, then the neonate should be examined for signs of hyperthyroidism, and cord blood should be taken for measurement of the thyroid function and presence of TSHR b; subsequently, the neonate should be followed-up according to a clear and effective screening protocol with decision rules about when to start (and stop) anti-thyroid drug plus or minus LT4 treatment, and when to discontinue follow-up;
- Special attention should be paid to neonates born to mothers who are treated with LT4 for hypothyroidism of unknown cause; these mothers may have hypothyroidism resulting from definitive treatment for autoimmune hyperthyroidism, and their neonates may be at risk of fetal and neonatal hyperthyroidism; therefore, these neonates should also be examined and tested shortly after birth for the presence of neonatal hyperthyroidism.

Research agenda

- Well-designed observational studies on the clinical and developmental outcome of TSHRAb related fetal and neonatal hyperthyroidism are lacking;
- The same applies to optimal treatment of TSHRAb related neonatal hyperthyroidism, for example when to treat, and the choice between antithyroid drug plus or minus LT4 treatment.

Summary

Maternal thyroid dysfunction is mostly caused by autoimmune hypo- or hyperthyroidism. Autoimmune hyperthyroidism is caused by stimulating TSH receptor antibodies (TSHRAb), patients with autoimmune hypothyroidism usually have anti-TPO Ab and may have blocking TSHRAb. Maternal anti-TPO and TSHRAb cross the placenta from mid gestation. Anti-TPO Ab do not harm fetal thyroid function, but stimulating and blocking TSHRAb do, and may cause fetal and (transient) neonatal hyper- or hypothyroidism, respectively. Anti-thyroid drugs taken for autoimmune hyperthyroidism cross the placenta throughout gestation, and may cause fetal hypothyroidism and goiter, and transient neonatal/congenital hypothyroidism. Neonatal hypothyroidism caused by blocking TSHRAb is quite a rare problem, and does not justify screening of all pregnant women with (a medical history of) autoimmune hypothyroidism for the presence of TSHRAb. Given the severity of fetal and neonatal hyperthyroidism, pregnant women with (a history of) autoimmune hyperthyroidism should be screened for presence of TSHRAb. If maternal TSHRAb are present at mid gestation with a concentration $\geq$2.5 times the upper limit of the reference interval, then the fetus should be examined and followed for signs and symptoms of hyperthyroidism. If, during gestation, the last measured maternal TSHR Ab is $\geq$3.7 times the upper

limit of the reference interval, then the neonate should be examined for signs of hyperthyroidism shortly after birth, and cord blood should be taken for measurement of the thyroid function and presence of TSHR Ab. Subsequently, the neonate should be followed-up according to a clear and effective screening protocol with decision rules about when to start (and stop) anti-thyroid drug plus or minus LT4 treatment, and when to discontinue follow-up. Sometimes neonates born to mothers with autoimmune hyperthyroidism develop central hypothyroidism due to high fetal thyroid hormone concentrations suppressing the hypothalamus-pituitary-thyroid axis. Special attention should be paid to neonates born to mothers who are treated with LT4 for hypothyroidism of unknown cause. These mothers may have hypothyroidism resulting from definitive treatment for autoimmune hyperthyroidism, and their neonates may be at risk of fetal and neonatal hyperthyroidism.

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