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Annales d'Endocrinologie
Annals of Endocrinology

Annales d'Endocrinologie 79 (2018) 636–646

Consensus

Graves' disease and pregnancy

Maladie de Basedow et grossesse

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Abstract

This section deals with the specificities of managing Graves' disease during pregnancy. Graves' disease incurs risks of fetal, neonatal and maternal complications that are rare but may be severe: fetal hyper- or hypothyroidism, usually first showing as fetal goiter, neonatal dysthyroidism, premature birth and pre-eclampsia. Treatment during pregnancy is based on antithyroid drugs alone, without association to levothyroxine. An history of Graves' disease, whether treated radically or not, with persistent maternal anti-TSH-receptor antibodies must be well identified. Fetal monitoring should be initiated in a multidisciplinary framework that should be continued throughout pregnancy. Neonatal monitoring is also crucial if the mother still shows anti-TSH-receptor antibodies at end of pregnancy or underwent antithyroid treatment. The risk of recurrence of hyperthyroidism in the weeks following delivery requires maternal monitoring. The long-term neuropsychological progression of children of mothers with Graves' disease is poorly known.

Keywords: Graves' disease; Multidisciplinarity; Teratogenicity; Fetal ultrasound; Neonatal monitoring; TRAB

Résumé

Ce chapitre aborde les particularités de la prise en charge de la maladie de Basedow pendant la grossesse. La maladie de Basedow expose à des complications fœtales, néonatales ou maternelles rares, mais parfois sévères parmi lesquelles l'hyperthyroïdie ou l'hypothyroïdie fœtale dont le goitre fœtal est généralement la première manifestation, les dysthyroïdies néonatales, l'accouchement prématuré et la pré-éclampsie. Le traitement de la maladie de Basedow chez la femme enceinte repose sur l'utilisation des antithyroïdiens seuls, sans association à la lévothyroxine. L'antécédent de maladie de Basedow, traitée radicalement ou pas, mais avec persistance d'anticorps anti-récepteur de la TSH maternels ne doit pas être méconnu. Une surveillance du fœtus doit être mise en place dans le cadre d'une prise en charge multidisciplinaire qui devra se poursuivre durant toute la grossesse. La surveillance du nouveau-né est également indispensable, dès lors que la mère conservait des anticorps anti-récepteur de la TSH en fin de grossesse, ou recevait un traitement antithyroïdien. Le risque de récidive de l'hyperthyroïdie dans les semaines suivant l'accouchement nécessite une surveillance maternelle. Enfin, le devenir neuropsychique à long terme des enfants nés de mère avec une maladie de Basedow reste mal connu.

Mots clés : Maladie de Basedow ; Multidisciplinarité ; Tératogénicité ; Échographie fœtale ; Surveillance néonatale ; TRAB

DOIs of original articles: https://doi.org/10.1016/j.ando.2018.08.005,
https://doi.org/10.1016/j.ando.2018.08.003,
https://doi.org/10.1016/j.ando.2018.09.003,
https://doi.org/10.1016/j.ando.2018.09.002,
https://doi.org/10.1016/j.ando.2018.08.002,
https://doi.org/10.1016/j.ando.2018.08.001
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https://doi.org/10.1016/j.ando.2018.08.004
0003-4266/

1. Diagnosis of Graves' disease and differential diagnoses

1.1. Assessment of thyroid function during pregnancy

Pregnancy alters thyroid function and morphology. The physiological reduction in TSH level during the first trimester may partly be due to thyroid hormone elevation secondary to follicular cell TSH-receptor stimulation by hCG [1,2]. The reduction begins in the 5th or 7th week of gestation, reaching a minimum between weeks 11 and 12 [3,4]. During the 2nd and 3rd trimesters, TSH levels progressively increase, while remaining within the normal range. Thyroid hormone levels usually decrease, but may be unchanged [5,6]. Compared to normal ranges for TSH, free T4 and free T3 in non-pregnant women, thyroid hormone profile during the first part, and especially the 1st trimester, of pregnancy resembles hyperthyroidism. Many studies have sought to determine normal values for TSH and free T4 per trimester; study population specificities, such as ethnicity, body-mass index, parity, iodine status and smoking, may affect these values [7–11]. Normal ranges vary from one kit to another, and it is recommended to report results as multiples of the median of the particular study population [11].

It is important to note that free T4 immunoassay is hampered in pregnancy by the increased TBG concentration and reduced albuminemia, as variation in protein concentrations can impact immunoassay [12]. Even with reference values on LC MS/MS (liquid chromatography - tandem mass spectrometry), reduction in free T4 is classically found during the 2nd and 3rd trimesters, making non-pregnant reference values inapplicable. Various American and European scientific societies have therefore published guidelines on the interpretation of thyroid assay during pregnancy [13–18]. Free T4 immunoassay is not recommended in first line by the American Thyroid Association or the Endocrine Society, which prefer LC MS/MS assay or a free T4 index based on total T4 and total T3, or total T4 and TBG. All guidelines, however, recognize that these techniques are not routinely available, and that, when there is no alternative, immunoassay should apply normal values according to trimester and geographical region.

1.2. Gestational hyperthyroidism

Diagnosing hyperthyroidism is the same during or not during pregnancy, although clinical signs typical of the 1st trimester, such as fatigue, nausea and weight-loss, have to be distinguished from those of thyrotoxicosis. Despite the difficulty of interpreting thyroid parameters during pregnancy, TSH assay should be the first-line examination for positive diagnosis, with free hormone assay if TSH levels are reduced. As the technique is readily accessible, automated free T4 immunoassay is recommended to assess the biological severity of the hyperthyroidism. Normal ranges should be trimester-specific as determined on each analyzer in each laboratory, and should be specified in the report; if such are not available, normal ranges taken from the recent literature should be used [6]. Evidence is lacking to recommend systematic assay of free T3 as well as free T4.

1.3. Graves' disease

Etiological diagnosis of hyperthyroidism related to Graves' disease can be straightforward. History of Graves' disease, whether cured or under treatment, before the conception makes diagnosis easier. Thrilling goiter or signs of Graves' orbitopathy also suggest diagnosis. Goiter is to be distinguished from physiological increase in thyroid volume during pregnancy. Anti-TSH-receptor antibodies usually confirm diagnosis and should be screened for: presence confirms Graves' disease and absence suggests transient gestational hyperthyroidism [13,17,18]. Anti-TSH-receptor antibody level also assesses risk of transplacental hyperthyroidism (see Section 3.2). In case of diagnostic uncertainty, Doppler ultrasound can explore for goiter or hypervascularized thyroid, but it should be stressed that this examination does not feature in the American or European guidelines [13,14,18] and has not been shown to discriminate between Graves' disease and other forms of hyperthyroidism during pregnancy [19,20].

Iodine-123 or technetium-99 m thyroid scintigraphy is contraindicated during pregnancy.

1.4. Differential diagnoses in Graves' disease

The main differential diagnosis in Graves' disease in the 1st trimester is transient gestational hyperthyroidism (TGH), at 1–3% of pregnancies: i.e., a higher rate than Graves' disease. It is secondary to the thyroid-stimulating effect of hCG in the 1st trimester. Concentrations of hCG > 200,000 U/L are associated with TSH < 0.2 mU/L in two-thirds of cases and with elevated free T4 in one-third; hCG > 400,000 U/L is systematically associated with TSH < 0.2 mU/L and, in 80% of cases, with elevated free T4. Suggested mechanisms comprise:

- increased quantity of hCG, as found in single or multiple pregnancy or in case of hydatidiform moles and choriocarcinoma;
- prolonged hCG elevation;
- hCG hypersensitivity, as in exceptional cases of TSH-R mutation [21,22].

It is often clinically difficult to distinguish TGH from Graves' disease, and anti-TSH-R antibody assay is recommended [13,17,18]. Other assays have been suggested: lower hCG and higher free T3/free T4 ratio in active Graves' disease than in TGH [23], or higher erythrocyte zinc concentration in TGH than in Graves' disease [24]; however, these data are not robust enough to found recommendations.

Hyperemesis gravidarum was reported in two-thirds of studies to be associated with low TSH and, also in two-thirds of studies, with higher free T4 levels [23]. The American College of Gynecologists and Obstetricians does not recommend assessing thyroid function in hyperemesis gravidarum in the absence of other signs of hyperthyroidism, as TGH regresses rapidly during the 2nd trimester [16], while other

scientific societies recommend thyroid hormone assessment and anti-TSH-R antibody assay [13,17,18].

Toxic nodule or toxic multinodular goiter are a rare cause of hyperthyroidism in pregnancy. Diagnosis is based on a hot aspect on scintigraphy, but this cannot be performed during pregnancy. Doppler ultrasound has not been assessed to diagnose toxic nodules in pregnancy, but can contribute to differential diagnosis. There are in fact no specific guidelines for exploration of these pathologies during pregnancy, which is performed as outside pregnancy except for the contraindication for scintigraphy.

The other causes of hyperthyroidism (De Quervain's subacute thyroiditis, Hashimoto's thyroiditis, factitious thyroid hormone intake) should also be considered in the absence of other etiology.

Recommendations

- R-1. It is desirable to have normal values for thyroid parameters according to trimester and to reference values during pregancy. 1/+++.
- R-2. Diagnosis of hyperthyroidism in pregnancy is based on TSH and free T4 assay, interpretation taking account of inherent physiological pregnancy changes. 1/+++.
- R-3. Diagnosis of Graves' disease is based on anti-TSH-R antibody assay. 1/+++.
- R-4. In hyperemesis gravidarum, thyroid assessment by TSH and free T4 assay is necessary to assess thyroid dysfunction. 1/++.
- R-5. Thyroid scintigraphy is contraindicated during pregnancy. 1/++.

2. Aspects concerning the mother

2.1. Maternal complications of hyperthyroidism during pregnancy

Hyperthyroidism during pregnancy may induce occasionnaly severe complications in the fetus (see Section 3 and Section 3.1) and mother. Studies have reported increased risk of pre-eclampsia [24] and heart failure [25–27]. Männistö et al. [26], in a large series of 417 hyperthyroid patients, reported significantly increased risk of pre-eclampsia (odds ratio, 1.78). There was also increased risk of premature labor (odds ratio, 1.40) and intensive care (odds ratio, 3.70). Medici et al. [28] reported significantly increased blood pressure elevation, while Männistö and Luewan found a non-significant increase [26,29].

Well-conducted treatment of hyperthyroidism reduces the risk of maternal complications [25,29].

Subclinical hyperthyroidism has no maternal impact affecting the pregnancy [28,30,31].

Recommendations

Proven maternal hyperthyroidism (elevated free T4 concentration) incurs a risk of sometimes severe maternal complications, and especially pre-eclampsia. Treatment of the hyperthyroidism reduces the risk of maternal complications.

- R-6. Proven maternal hyperthyroidism (elevated free T4 concentration) should be treated and corrected. 1/+++.
- R-7. It is not indicated to treat subclinical hyperthyroidism (isolated low TSH concentration). 1/+++.

2.2. Choice of treatment

The two families of antithyroid molecules on the market, imidazole and thiouracil derivatives, are comparable in their control of maternal hyperthyroidism, as shown by Wing and Momotani [32,33]. Time to recovery of euthyroid status is identical, although it was suggested that propylthiouracil crosses the placental barrier less; neonate and maternal TSH and free T4 concentrations are comparable for both molecules [33].

On the other hand, while antithyroid drugs are known to cross the placenta, the proportion of thyroxine crossing the place is lower. Thus a strategy associating an antithyroid drug to levothyroxine ("combined" or "block-replace" treatment) is contraindicated in pregnancy.

Thiouracil derivatives used to be preferred to imidazole derivatives for Graves' disease in pregnant patients, the latter being considered potentially teratogenic. However, recent studies suggested that propylthiouracil could also cause fetal malformation: moreover, it induces liver toxicity that has been greatly discussed in the recent literature. Thus, several warnings against using any antithyroid drugs in pregnant patients have recently been published. The first report of possible thiamazole-related teratogenicity was made by Greenberg in 1987 [34], and several cases of congenital malformation following in-utero thiamazole were subsequently published, associating esophageal and/or choanal atresia, scalp abnormalities, minor facial bone abnormalities and retarded psychomotor development. A recent registry report and a study of pregnant women receiving antithyroid drugs for Graves' disease confirmed that early exposure to thiamazole was associated with increased risk of fetal malformation compared to a non-exposed population [35,36]. A Japanese study of more than 6000 pregnant women, including 1426 receiving thiamazole and 1578 propylthiouracil in the first trimester, found significantly higher rates of congenital malformation in the thiamazole group as compared to controls: 4.1% versus 2.1% [36], with an odds ratio of 2.28 (95%CI: 1.54–3.33); rates with propylthiouracil, on the other hand, were comparable to those in controls (1.9%). Andersen's registry data [35] confirmed higher risk of congenital malformation following in utero imidazole exposure (9.12%, versus 5.66% for controls), and also

reported significantly more frequent malformation, mainly in the head and neck, with propylthiouracil (7.98%) [35]. Moreover, prolonged follow-up of children with in-utero propylthiouracil exposure diagnosed further cases of malformation, overlooked neonatally, most of which required surgical correction; these malformations concerned the head and neck or urinary system, with odds ratios of respectively 4.92 (95%CI: 2.04–11.86) and 2.73 (95%CI: 1.22–6.07) [37].

Even before Andersen's report [35] suggesting teratogenicity, propylthiouracil had been implicated in sometimes very severe hepatitis [38], with a safety warning put out by the FDA (http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm209256.htm).

In 2012, the Endocrine Society recommended propylthiouracil during the first trimester, switching to an imidazole derivative for the 2nd and 3rd trimesters [13]. Their recent registry data led Laurberg and Andersen [39] to recommend stopping antithyroid drugs, when possible, at the beginning of pregnancy, between weeks 6 and 10, under close monitoring of biological parameters. In case of non-controlled hyperthyroidism or recurrence at end of treatment, they suggest that propylthiouracil is to be used in first line during the first trimester, as associated congenital malformations seem less severe than with imidazole derivatives. It should be stressed that this strategy runs a risk of recurrence of hyperthyroidism and that consequences for the mother and fetus have not as yet been assessed in any studies.

When antithyroid molecules are switched, dose-equivalences have been published [40] (http://www.sfendocrino.org/article/571/choix-d-un-antithyroidien-de-synthese-et-equivalences-recommandations-sfe-grt), but close biological monitoring remains indispensable.

Iodine-131 is contraindicated during pregnancy.

Surgery is reserved for serious allergy to antithyroid drugs and to poor control of maternal hyperthyroidism. It should preferably be performed during the 2nd trimester.

Recommendations

- R-8. Treatment of Graves' disease during pregnancy is based on antithyroid drugs. As levothyroxine shows less passage across the placenta, only the adapted-dose strategy is recommended. If combined treatment was implemented before the pregnancy, it is essential to stop levothyroxine and continue with only antithyroid drugs at adapted dose. 1/+++.
- R-9. Malformation was reported following in utero imidazole-derivative exposure, and, more recently and with lower frequency and severity with propylthiouracil. Propylthiouracil which is also implicated in rare but severe cases of hepatitis. Thus, in hyperthyroidism requiring treatment, it is recommended to prescribe propylthiouracil for the 1st trimester then switch to an imidazole-derivative. The switch during pregnancy can destabilize thyroid balance and requires closer biological monitoring. If clear improvement in hyperthyroidism allows dose reduction and possible cessation of antithyroid drugs during pregnancy, continuing propylthiouracil may be considered. 1/++.
- R-10. If antithyroid drugs are switched during pregnancy, thyroid monitoring should be reinforced. 1/++.
- R-11. Surgery is reserved for allergy to antithyroid drugs or poor control of maternal hyperthyroidism. It is preferably performed during the 2nd trimester. 1/++.
- R-12. Radio iodine therapy is contraindicated in pregnancy. 1/++.

2.3. Monitoring means and objectives: normal values for TSH, free T3 and free T4 in pregnancy

Treatment of hyperthyroidism during pregnancy aims to correct symptoms of thyrotoxicosis and prevent maternal and fetal complications (Section 2.1 and Section 3.1). It is not justified in subclinical maternal hyperthyroidism.

Antithyroid treatment should be initiated at 50–150 mg daily for propylthiouracil, 5–10 mg for thiamazole [41], and 5–15 mg for carbimazole [42] (http://www.sfendocrino.org/article/571/choix-d-un-antithyroidien-de-synthese-et-equivalences-recommandations-sfe-grt). These are approximate doses, to be adapted to clinical specificities, and notably hyperthyroidism severity, and at term.

Thyroid assessment should be closely monitored, 2 weeks after initiation then every 2–4 weeks throughout pregnancy or for as long as antithyroid treatment is continued. Umbilical and maternal free T4 concentrations seem to be correlated at end of pregnancy: according to Momotani et al., they should be identical when antithyroid treatment was stopped during pregnancy, but with lower umbilical levels when treatment was continued until delivery [43]. The authors concluded that the optimal dose maintains maternal free T4 in or just above the upper range of normal (as established in a non-pregnant population). TSH levels may remain low throughout pregnancy, in which case they cannot guide dose adaptation [33]. There is no correlation between maternal dose and fetal thyroid status.

Immunomodulation accompanying pregnancy leads to improvement in hyperthyroidism during the 2nd trimester, with apparent remission of Graves' disease [44]. When dose has been reduced and the minimal dose (50 mg/day for propylthiouracil, 5 mg/day for carbimazole) maintains maternal clinical euthyroid status with normalized free T4 concentration decreasing on 2 successive assays, treatment termination may be considered.

Rare but severe cytolytic hepatitis reported under propylthiouracil led to an FDA safety warning. The risk/benefit ratio for propylthiouracil during the 1st trimester is nevertheless better than for imidazole-derivatives; the Summary of Product Characteristics states that, if liver enzyme levels become significantly

abnormal during treatment, treatment should be immediately stopped, which requires liver monitoring, despite there being no evidence for this.

Recommendations

- R-13. Treatment of Graves' disease during pregnancy should follow the adapted-dose strategy, with 1/++.
- R-14. Antithyroid treatment monitoring during pregnancy should be close: initially every 2 weeks, then every 2–4 weeks according to progression. 1/++.
- R-15. Antithyroid treatment monitoring during pregnancy is based on free T4 and TSH assay. TSH levels may remain low; free T4 levels should be kept in the upper range of normal. 1/++.
- R-16. When, at minimum antithyroid dose, the clinical situation is satisfactory and normalized maternal free T4 decreases on 2 successive assays, treatment termination may be considered. 2/++.
- R-17. Despite the lack of convincing evidence, transaminases should be monitored every 2–4 weeks during propylthiouracil treatment. Patients should be advised to avoid other hepatotoxic drugs and to consult in case of digestive signs. 2/+.

2.4. *Graves' disease progression after pregnancy*

In the postpartum period, immune rebound may induce onset or recurrence of Graves' disease; this needs to be distinguished from the hyperthyroid phase of postpartum autoimmune thyroiditis. In women of child-bearing age, onset of Graves' disease is in the postpartum period in 40% of cases [45]. Anti-TSH and anti-microsomal antibodies at the beginning of pregnancy in euthyroid subjects are predictive of postpartum Graves' disease [46]. In case of difficult diagnosis, 3rd-generation anti-TSH-R antibody assay shows excellent sensitivity and negative predictive value in differentiating Graves' disease from postpartum thyrotoxicosis [47,48]. If scintigraphy is to be performed, the tracer should be technetium-99^{m} or iodine-123, which have relatively short half-lives, allowing breast-feeding after a period in which breast milk is discarded [49].

Recurrence of Graves'-related hyperthyroidism may require resumption of antithyroid treatment, which may also be continued throughout and after pregnancy. This leaves the question of breast-feeding. The pharmacokinetics of propylthiouracil (short half-life, strong binding to plasma proteins, and low liposolubility) entail less passage into breast milk than with imidazole-derivatives [50]. Experimental data showed low excretion of propylthiouracil into breast milk, at 0.025% of the oral dose [51]. Thiamazole breast-milk concentrations, in contrast, are comparable to those in plasma [52]. Clinical data are sparse, but suggest no harmful impact on physical and intellectual development or thyroid status of children breast-fed by mothers treated with thiamazole, even in case of iatrogenic hypothyroidism [53,54]. In breast-feeding women, propylthiouracil has no impact on the baby's thyroid status, except at the highest doses (750 mg/day), where slight TSH elevation may ensue. Propylthiouracil used to be preferred to imidazole-derivatives during breast-feeding, even though the most recent American guidelines indicate that both propylthiouracil and imidazole can be administered during lactation [55]. It is recommended to avoid breast-feeding under propylthiouracil but if this is not possible, the infant needs to be monitored. In France, in 2018, the Vidal database contraindicated carbimazole during breast-feeding. Thiamazole may be used, but with a ceiling of 10 mg/day, and should be accompanied by neonate thyroid function monitoring.

Recommendations

- R-18. In Graves' disease, hyperthyroidism in remission during pregnancy shows risk of postpartum recurrence. Endocrine monitoring and systematic control of TSH at 1, 3 and 6 months are recommended after delivery. 1/+++.
- R-19. Experimental and clinical data on the impact of maternal antithyroid therapy on breast-fed infants are reassuring, but antithyroid drug Summaries of Product Characteristics nevertheless either contraindicate (carbimazole) or restrict (propylthiouracil, thiamazole) use during breast-feeding. Breast-feeding under antithyroid drugs requires pediatric monitoring. 2/++.

2.5. *Pregnancy preparation: choice of antithyroid drug; when to opt for radical treatment and by what means?*

In view of the fetal risk associated with anti-TSH-R antibodies and antithyroid drugs and the risk of maternal hyperthyroidism, the pregnancy projects of women under treatment for Graves' disease need to be discussed [40]. The teratogenicity of imidazole-derivatives and propylthiouracil and the means of adapting and monitoring antithyroid drugs have been raised in Section 2.2. The risk of liver toxicity under propylthiouracil is lower than the teratogenic risk of thiamazole, and imidazole-derivatives should be replaced by propylthiouracil in young women intending pregnancy [40]. The risks and restrictions associated with antithyroid drugs may also make it worth discussing radical treatment, by radioiodine or thyroidectomy, especially in situations at high risk of transplacental dysthyroidism: i.e., anti-TSH-R antibody elevation, especially if the stimulatory activity is strong [56], necessity of high antithyroid

doses or history of fetal dysthyroidism in previous pregnancy. Radical radioiodine treatment contraindicates pregnancy during the following 6 months, and may also exacerbate thyroid autoimmunity and induce anti-TSH-R antibody elevation [57]; anti-TSH-R antibodies will also take longer to disappear after isotopic than surgical treatment. Thus, in case of pregnancy project, radioiodine is not the first treatment choice. Postponing pregnancy until anti-TSH-R antibodies become negative is another option. All of this information should be discussed individually with the patient, to enable an informed decision according to the risk/benefit ratio, which partly depends on how long she is prepared to wait before becoming pregnant.

Recommendations

- R-20. Women of child-bearing age with Graves' disease need to be informed about fetal risks and management of hyperthyroidism during pregnancy. 1/+++.
- R-21. Pregnancy is contraindicated for the 6 months following radioiodine therapy. 1/++.
- R-22. In case of radical therapy with pregnancy project, total thyroidectomy may be preferable to radioiodine treatment due to faster decrease in anti-TSH-R antibody levels. 2/++.

3. Aspects concerning the child

Fetal/neonatal hyperthyroidism is rare, at 1 in 50,000 neonates. It is usually transient, and affects 1–2% of neonates born to mothers with Graves' disease [58]. Most cases of congenital hyperthyroidism implicate transfer of thyroid-stimulating immunoglobulins (TSI) from mother to fetus. When the fetal thyroid gland becomes functional, TSH receptor stimulation by TSI induces in-utero thyrotoxicosis, which may persist until 4 months of life, when the TSIs disappear from the infant's blood.

Anti-TSH-R antibodies may also be present and transferred to the fetus from mothers with Graves' disease. Impact depends on the balance between their inhibitory action and the stimulatory action of TSI. In practice, only anti-TSH-R antibodies are routinely assayed, on 2nd generation radioreceptor TRAK assay, which is sufficient to identify women whose fetus is at risk of fetal or neonatal dysthyroidism. Risk factors [59] comprise:

- hyperthyroidism in Graves' disease diagnosed during pregnancy;
- Graves' disease patient under antithyroid treatment during pregnancy;
- euthyroid patient under antithyroid treatment with residual anti-TSH-R antibodies;
- personal history of surgical or radioiodine ablative treatment, which may lead to anti-TSH-R antibodies being overlooked or persisting.

Neonatal thyroid dysfunction is usually preceded by fetal thyroid dysfunction. Thus, good treatment during pregnancy is essential to avoid premature mortality and long-term neurologic sequelae [57]. Thyroid hormones are critical in brain development, and too low or too high a free T4 level may impact long-term intellectual development [60], and fine maternal balance in Graves' disease is essential to normal fetal neurologic development.

3.1. Fetal complications

There is a high risk (15%) of fetal and neonatal thyroid dysfunction in case of maternal anti-TSH-R antibodies and/or antithyroid drug use during the last trimester [57]. In normal fetal thyroid gland development, thyroid hormones are synthesized after 10–12 weeks, and TSH receptors become functional around 20 weeks, enabling fetal thyroid stimulation by TSH and also by maternal anti-TSH-R antibodies [61,62], which may be transferred via the placenta, stimulating the fetal thyroid gland and inducing hyperthyroidism in the 2nd half of pregnancy [59,63,64]. Antithyroid drugs may also cross the placenta, inducing fetal hyperthyroidism; diagnosis can be suspected on fetal goiter seen on ultrasound. Maternal TSH does not cross the placenta, unlike free T4 and free T3.

Consequently, fetuses of mothers with Graves' disease may develop either hyper- or hypo-thyroidism. Early diagnosis and treatment are essential to avoid premature birth, miscarriage [65] or permanent neurologic sequelae due to hyperthyroidism, or intellectual deficit due to hypothyroidism [66]. Goiter is the most effective sign of fetal dysthyroidism and can be detected by standardized ultrasound measurements according to gestational age [67].

Fetal hyperthyroidism can be suspected in case of advanced bone maturation or thyroid hypertrophy with central vascularization. In case of retarded intrauterine growth with fetal tachycardia (which may be accompanied by heart failure), premature birth is frequent.

Fetal hypothyroidism can be suspected in case of goiter with peripheral hypersignal on Doppler, retarded bone maturation and excessive active fetal movement or excess amniotic fluid.

Malformation may be induced by antithyroid drugs, as described above (Section 2.2).

3.2. Monitoring: TRABs and risk threshold; biologic activity; ultrasound; indication of percutaneous umbilical blood sampling

In pregnant women with past or present Graves' disease, anti-TSH-R antibodies should be assayed at the beginning of pregnancy; in case of presence, monitoring should be intensive, while otherwise obstetric follow-up can be normal [18]. When anti-TSH-R antibodies are present or the mother is under antithyroid drugs, monthly ultrasound scan with fetal thyroid analysis should be undertaken from 20 weeks' amenorrhea. Anti-TSH-R antibody level exceeding 5 IU/L in the 2nd trimester is a risk factor for fetal and neonatal hyperthyroidism [56]. In centers equipped for bioassay, the thyroid-stimulating

Recommendations

- R-23. Fetuses of mothers with Graves' disease may develop hyperthyroidism, by transplacental passage of anti-TSH-R antibodies, or hypothyroidism, by passage of antithyroid drugs. 1/++.
- R-24. Goiter is the most effective sign of fetal dysthyroidism and can be detected on standardized ultrasound measurement according to gestational age. 1/+++.
- R-25. Fetal hyperthyroidism can be suspected in case of goiter, retarded intrauterine growth and fetal tachycardia, which is a late sign of severe hyperthyroidism. 1/++.
- R-26. The therapeutic objective is to prevent fetal hyperthyroidism thanks to early diagnosis of thyroid fetal hypertrophy and adapting maternal treatment, and to prevent fetal hypothyroidism due to antithyroid drug overdose or unjustified association to levothyroxine ("combined" maternal treatment is contraindicated). 1/++.
- R 27. Effective treatment of fetal dysthyroidism is essential to avoid premature mortality and long-term neurologic lesions. 1/+++.

activity of anti-TSH-R antibodies can be measured to discriminate patients at higher risk of fetal hyperthyroidism, indicated by concentrations >5 IU/L associated with strong thyroid-stimulating activity [56]; in this case, ultrasound monitoring should be stepped up, notably with repeated fetal thyroid scan. As the quality of ultrasound scanning is operator-dependent, it is strongly recommended that mother and fetus be followed in a multidisciplinary expert center. However, considering all fetal thyroid abnormalities (hyperthyroidism, hypothyroidism and thyroid hypertrophy), this threshold may need to be lowered in the light of a recent study reporting a maternal threshold of >2.5 IU/L for risk of fetal thyroid abnormality [68]. If anti-TSH-R antibodies are absent up to the 3rd trimester and no antithyroid drugs are needed, no specific neonatal monitoring is required.

Ultrasound measurement of fetal thyroid perimeter and/or diameter identifies fetuses at risk of thyroid dysfunction, with values beyond the 95th percentile for gestational age [59,67].

In case of fetal goiter, a combination of criteria distinguishes hyper- from hypo-thyroidism [57]:

- maternal: anti-TSH-R antibodies >5 IU/L; free T4 level correlates between mother and fetus and may be contributive for antithyroid drug treatment during the 3rd trimester;
- fetal: growth, heart rhythm, active movement (hypothyroid fetuses being paradoxically more active), bone maturity (points of distal femoral ossification), and fetal thyroid Doppler ultrasound.

No signs, however, are pathognomonic for a given situation.

Fetal blood sampling should be considered in case of fetal goiter when non-invasive exploration or progression under treatment or change in treatment have failed to determine fetal thyroid functional status. The indication should be confirmed by a multidisciplinary team, given the associated risk of fetal morbidity and mortality.

Recommendations

- R 28. Anti-TSH-R antibody assay should be performed at start of pregnancy; in case of presence, monitoring should be intensive. 1/+++.
- R-29. Anti-TSH-R antibody concentration >5 IU/L on 2nd generation assay in the 2nd trimester indicates risk of fetal and neonatal hyperthyroidism; ultrasound monitoring should be intensified, with monthly fetal ultrasound as of 22 weeks' amenorrhea. This rhythm should be adapted according to onset of fetal thyroid hypertrophy. 1/++.
- R-30. As the quality of fetal thyroid ultrasound scanning is operator-dependent, mother and fetus should be followed in a multidisciplinary expert center. 1/++.
- R-31. Fetal goiter is defined by dimensions beyond the 95th percentile according to gestational age. 1/+++.
- R-32. Fetal blood sampling should be considered only in case of fetal goiter when non-invasive exploration or progression under treatment or change in treatment have failed to determine fetal thyroid functional status. The indication should be confirmed by a multidisciplinary prenatal diagnostic center. 1/++.

3.3. Indications and treatment modalities (intra-amniotic levothyroxine injection, fetus-targeting maternal antithyroid drugs)

Prenatal treatment is effective in improving fetal and neonatal thyroid function.

In proven fetal hypothyroidism, reducing the maternal antithyroid drug dose should be enough to normalize fetal thyroid function. Intra-amniotic administration of levothyroxine has been reported, but is to be discussed in a multidisciplinary team meeting in an approved prenatal care center [57,59]. Levothyroxine injected into the amniotic fluid is taken up by the fetus, restoring euthyroid status [66]. It also avoids the progression of a goiter that would compromise a natural delivery.

In fetal hyperthyroidism, fetal treatment via maternal antithyroid therapy improves fetal and neonatal progression. Propylthiouracil is to be preferred to thiamazole during the 1st trimester (see Section 2.2 and Section 2.5) [69,70]. In the 2nd and 3rd trimesters, carbimazole may be used if necessary.

Recommendations

- R-33. Prenatal treatment is effective in correcting fetal and neonatal thyroid dysfunction.
- R-34. In fetal hypothyroidism secondary to maternal antithyroid therapy, dose should be reduced. 1/++.
- R-35. Intra-amniotic administration of levothyroxine may be considered for persistent hypothyroidism despite adapted maternal treatment, after confirmation by fetal blood sampling, which needs to be validated by a multidisciplinary prenatal diagnostic center. 2/+.
- R-36. Fetal hyperthyroidism is treated via maternal antithyroid therapy. 1/++.

4. Neonatal and post-partum follow-up

4.1. Neonatal assessment: umbilical blood? frequency?

There is no risk of neonatal hyperthyroidism when maternal anti-TSH-R antibodies were negative throughout pregnancy, with or without antithyroid drug treatment [71]. It is usually transient, but with 27% morbidity and 1.2% mortality [26]. The major risk is heart failure, but liver dysfunction (jaundice, hepatitis), coagulopathy, pulmonary hypertension, craniostenosis, microcephaly or mental retardation may also occur. Mortality is now mainly related to prematurity and the consequent intensive care.

If the mother is under antithyroid drugs, transient neonatal hyperthyroidism may be delayed, with onset at 10 days of life at most. Neonates are usually initially asymptomatic, although there may be increased excitability and appetite with insufficient weight gain, vomiting or diarrhea, fever and sweats, or erythema. Tachypnea may occur in case of heart failure or pulmonary hypertension. Sinus tachycardia is frequent, sometimes associated with arrhythmia but rarely with high blood pressure. Clinical goiter is found in 50% of cases.

Umbilical blood thyroid hormone levels at birth are not predictive of neonatal hyperthyroidism, corresponding as they do only to fetal thyroid function. Anti-TSH-R antibodies > 2 IU/L in umbilical blood, however, identifies neonates at risk of hyperthyroidism, about one-third of whom will require treatment [72]. In a recent retrospective study of 417 women with Graves' disease and anti-TSH-R antibodies, a threshold concentration of > 6.8 IU/L in the neonate was predictive of thyroid dysfunction [68].

Rapid increase in T4 levels, beyond the upper normal limit for age, between umbilical blood assay and 3–5 days' postnatal life is predictive of neonatal hyperthyroidism [72].

Clinical signs appear later than biological signs, and carbimazole treatment should be initiated on onset of the latter, usually at 0.5 mg/kg/day initially, associated to propranolol in case of poorly tolerated tachycardia. If hypothyroidism develops, according to age-related normal values [72–74], levothyroxine can be added after case-by-case discussion.

Disappearance of anti-TSH-R antibodies indicates cure and possible termination of levothyroxine and antithyroid drugs.

In rare cases, inadequate treatment of maternal Graves' disease can lead to persistent thyrotropic insufficiency in the neonate, with non-elevated TSH and low free T4 at birth [75,76]. In extreme cases, prolonged maternal thyroid hormone elevation may inhibit normal fetal thyroid gland development, leading to congenital thyroid hypoplasia [77].

4.2. Progression of children of mothers with Graves' disease

Clinical data suggest that maternal hyperthyroidism can impact the child's long-term neuropsychological development:

- thyroid hormones are found in various fetal fluids during the first weeks of gestation [78];
- placental deiodinases seem insufficient to protect the fetus against excess thyroid hormone: TSH is sometimes inhibited in children of mothers resistant to thyroid hormones [65];
- maternal gestational hyperthyroidism can inhibit the thyrotropic axis in the neonatal period, impairing thyroid status in the young child [77,79].

The thyroid status of children whose mothers showed hyperthyroidism during pregnancy may be affected by gestational thyroid status. In a study that did not specifically focus on hyperthyroidism during pregnancy, maternal TSH concentration accounted for 4% of the variance in the child's TSH level at 6 years, and gestational free T4 accounted for 2.9% of the variance in free T4 at the same age [80].

The only studies available concern the intellectual and psychomotor progression of children of mothers under antithyroid treatment for Graves' disease. They found no intellectual impairment in childhood or young adulthood; but these mothers were considered euthyroid, and the main study objectives were to analyze the fetal impact of thiamazole, rather than neurologic development [81–83].

Three recent studies relaunched the debate concerning the consequences of gestational hyperthyroidism. The Generation R study, with 3839 mother/child pairs, analyzed the correlation between maternal TSH and free T4 levels at 13 weeks of pregnancy and the child's IQ at a median 6 years of age [60]; there was a significant inverted U-curve correlation between maternal free T4 and children's IQ. Taking only children whose mothers showed free T4 within the normal range for gestational age, the association was no longer significant, although the risk of IQ < 85 remained significantly elevated. There was also an

Recommendations

- R-37. In case of anti-TSH-R antibodies during pregnancy, there is risk of neonatal hyperthyroidism, especially with levels exceeding 5 IU/L on 2nd generation assay. 1/+++.
- R-38. TSH, free T4 and anti-TSH-R antibodies should be systematically assayed in umbilical blood if the mother shows anti-TSH-R antibodies or is under antithyroid drugs. These assays indicate antenatal status and/or treatment and guide postnatal monitoring. 1/++.
- R-39. There is no risk of neonatal hyperthyroidism when anti-TSH-R antibodies were absent in the mother throughout pregnancy. 1/++.
- R-40. Umbilical blood anti-TSH-R antibodies are associated with high risk of neonatal hyperthyroidism: monitoring should be continued, in teamwork with a pediatric endocrinologist. 1/++.
- R-41. Normal thyroid levels (TSH and free T4) in umbilical blood at delivery are not predictive of neonatal hyperthyroidism. 1/++.
- R-42. Rapid increase in free T4, beyond the age-related upper limit of normal, between umbilical sampling and 3–5 days' postnatal life is predictive of neonatal hyperthyroidism. 1/++.
- R-43. Carbimazole treatment should be initiated at 0.5 mg/kg/day at onset of biological signs, to be interpreted in the light of age-related normal values, associated to propranolol in case of clinical signs.
- R-44. In case of neonatal hyperthyroidism, carbimazole should be continued until anti-TSH-R antibodies become negative. 1/++.
- R-45. Low free T4 at birth associated with low or non-elevated TSH level requires monitoring in teamwork with a pediatric endocrinologist. 2/++.

inverted U-curve between gestational free T4 levels and cerebral cortex and gray matter volume on MRI in the child at 8 years of age. These findings were not confirmed in a Finnish cohort, which did, however, find greater difficulty in learning math in 16 year-old children of hyperthyroid mothers [84]. Extra risk of attention deficit/hyperactivity disorder in children of mothers with hyperthyroidism during pregnancy was also reported, although it seemed only to apply to mothers with hyperthyroidism diagnosed and treated during the 2 years following delivery [85].

Mechanisms underlying these effects may concern elevated maternal thyroid hormone levels, presence of anti-TSH-R antibodies, antithyroid drug effects, and variations in fetal thyroid status over the trimesters of pregnancy, especially when maternal antithyroid treatment is continued. It is thus difficult to conclude whether maternal hyperthyroidism in Graves' disease (or Graves' disease itself) during pregnancy affects the child's long-term neuropsychological development. The studies do, however, stress the importance of normal free T4 levels during pregnancy.

Recommendations

- R-46. There is insufficient evidence that maternal hyperthyroidism during pregnancy alters the intellectual, psychological or behavioral development of children and young adults. 1/++.
- R-47. It is presently recommended to keep free T4 levels within the normal range in women treated for Grave's' disease during pregnancy. 1, and expert opinion / ++.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The authors thank Michele d'Herbomez (faculté de médecine, université de Lille, France, centre de biologie-pathologie-génétique, département de biochimie, CHRU de Lille, France), Kris Poppe (Endocrine Unit, centre hospitalier universitaire Saint-Pierre, Brussels, Belgium), Jérome Massardier (hospices civils de Lyon, hôpital Femme–Mère–Enfant, service d'obstétrique) and Laurent Meyer (centre d'endocrinologie et maladies métaboliques, 24, avenue de la Paix, 67000 Strasbourg) for re-editing.

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