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FETAL GOITRE IN MATERNAL GRAVES' DISEASE

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Abstract

Fetal goitre is found in about 1 in 5,000 births, usually in association with maternal Graves' disease, due to transplacental passage of high levels of thyroid stimulating antibodies or of anti-thyroid drugs. A goitre can cause complications attributable to its size and to the associated thyroid dysfunction. Fetal ultrasound examination allows easy recognition of the goitre but is not reliable in distinguishing between fetal hypo- and hyperthyroidism. Assessment of the maternal condition and, in some cases, cordocentesis provide adequate diagnosis of the fetal thyroid function. First-line treatment consists of adjusting the dose of maternal anti-thyroid drugs. Delivery is aimed at term. In cases with large goitres, caesarean-section is indicated.

Key words: Graves' disease, fetal goitre, fetal thyroid, pregnancy.

INTRODUCTION

The thyroid gland undergoes extensive changes during pregnancy, delivery and lactation. These changes are supported by the interaction between the fetal-placental unit and the maternal endocrine system (Fig. 1) and are reflected in the thyroid function tests, which differ from outside pregnancy as early as first trimester. During pregnancy, there is an increase in thyroid binding globulin which leads to increased levels of serum thyroid hormones (T4 - thyroxine and T3 - tri-iodothyronine); the placenta produces hCG (human chorionic gonadotrophin), a glycoprotein hormone with molecular similarity of its α-subunit with TSH (thyroid stimulating hormone) which acts as an agonist of TSH raising transiently free T4 levels and decreasing serum TSH levels; plasma volume expands thus increasing total T4 and T3 pool size; in the placenta, type 3 iodothyronine deiodinase is highly expressed converting T4 into inactive reverse T3 and thus controlling the availability of T3 and T4 to the fetus and increasing requirements for maternal hormone production; the gland itself may increase in size up to 40% in some women thus decreasing serum thyroglobulin. Also, iodine clearance is increased during pregnancy making hormone production in iodine deficient areas potentially insufficient (1).

Changes in the thyroid hormones during pregnancy relate to the necessity of delivering thyroxine to the fetus, especially to the fetal brain. Maternal T4 is effectively metabolised into inactive reverse T3 by the placenta, however a small but physiologically relevant amount of T4 is still transferred to the fetus and this is essential for normal fetal development (2). Normal fetal brain development depends on maternal derived T4 at least until 16 weeks' gestation when the fetal thyroid starts to produce the thyroid hormones.(3) In the fetal brain deiodinase type 2 is found in high levels and is responsible for converting T4 to active T3, thus making it readily available (3). In healthy women thyroid physiological changes happen seamlessly, however in cases with uncorrected thyroid dysfunction there may be deleterious effects on the fetus during pregnancy such as development of fetal hypo- or hyperthyroidism or fetal goitre and long term neurodevelopmental sequalae (4).

Along with gestational and preexisting diabetes, thyroid disorders are the most common endocrine disorders in pregnant women (5). Hypothyroidism, either clinical or subclinical, is encountered in about 2-3% of pregnant women (6). Thyrotoxicosis is also common and is usually due to Graves' disease, but during the first part of pregnancy may also be the consequence of elevated hCG levels (7) (gestational transient thyrotoxicosis) and is often associated with hyperemesis gravidarum.

This review will only discuss maternal Graves' disease and its fetal consequences and will focus on the management of prenatally detected fetal goitre in the case of maternal Graves' disease.

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Graves' disease during pregnancy

Graves' disease is an autoimmune disorder characterised by the presence of immunoglobulins that bind the TSH receptors in the thyroid gland and stimulate the production of thyroid hormones leading to hyperthyroidism (the occurrence of inhibiting antibodies being exceptional). Affected individuals are treated by radioiodine therapy or surgical removal of the gland followed by the administration of the synthetic thyroid hormone levothyroxine. Some patients are treated by anti-thyroid drugs, such as propylthiouracil, carbimazole and methimazole; these drugs inhibit the enzyme thyroperoxidase which facilitates the addition of iodine to tyrosine in the production of thyroglobulin (Fig. 1), an essential step in the formation of thyroid hormones.

Graves' disease is found in 1 in 500 pregnant women (8). During pregnancy, thyroid stimulating immunoglobulins can cross the placenta by using the physiological maternal-fetal antibody transfer pathways (9) and can act on the fetal thyroid gland resulting in the development of fetal hyperthyroidism and sometimes to fetal goitre. Thyroid stimulating immunoglobulins may persist for years after medical

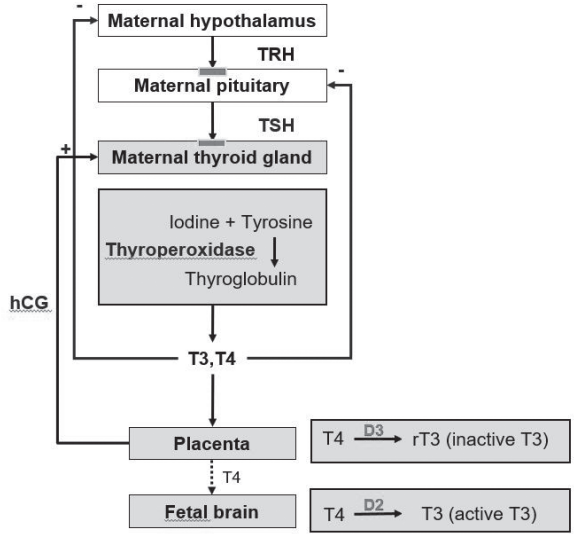

Figure 1. Production of thyroid hormones and its control. The hypothalamus produces thyroid releasing hormone (TRH) which stimulates the pituitary gland to release thyroid stimulating hormone (TSH) which acts on TSH receptors on the thyroid gland and stimulates the production of thyroid hormones. They in turn control their production through negative feedback on both the hypothalamus and pituitary gland. During pregnancy, the placenta produces human chorionic gonadotrophin (hCG) which stimulates the TSH receptor. Placenta controls the availability of maternal thyroid hormones to the fetus through the enzyme iodothyronine deiodinase type 3 (D3) which inactivates T4 and T3. A small, but physiologically relevant amount of T4 is transferred from the mother to the fetus. This is essential for normal early neurological fetal development. Within the fetal brain, deiodinase type 2 is specifically expressed and converts T4 into active T3.

treatment, radioiodine therapy or surgical removal of the gland in those affected by Graves' disease. Therefore, indications for testing for thyroid stimulating immunoglobulins in pregnant women with known Graves' disease include (a) mothers with untreated or drug-treated hyperthyroidism in pregnancy, (b) a previous history of Graves' disease with past treatment with radioiodine or total thyroidectomy, (c) a previous history of delivering an infant with hyperthyroidism, or (d) a known history of thyroidectomy for the treatment of hyperthyroidism in pregnancy. A level of antibodies of 3 times the upper limit of normal is an indication for establishing close follow-up of the fetus (10). Anti-thyroid drugs used during pregnancy can also cross the placenta and may be teratogenic and act on the fetal thyroid gland, leading to hypothyroidism and fetal goitre. If possible, it is recommended that anti-thyroid medication is avoided in the first trimester of pregnancy and this can be achieved in some stable cases of Graves' disease as the general autoimmunity decreases during pregnancy (11). However, when treatment is necessary, propylthiouracil is generally favoured due to its safer fetal profile compared to carbimazole and methimazole which have been associated with development of aplasia cutis, choanal and oesophageal atresia, abdominal wall defects and ventricular septal defects. After the first trimester, consideration can be given to switching to carbimazole or methimazole to decrease the risk of liver failure in the mother (10).

Fetal goitre

The exact incidence of fetal goitre is not known but it may be up to 1 in 5,000 births, usually, but not exclusively, in association with maternal Graves' disease (12). Thus, the incidence of Graves' disease during pregnancy is about 1 in 500 (8) and incidence of fetal goitre in mothers with treated or untreated Graves' disease is about 10% (13-17).

Thyroid stimulating immunoglobulins in maternal Graves' disease can cross the placenta and act on the fetal thyroid gland resulting in the development of fetal hyperthyroidism and in some cases of fetal goitre. However, most cases of fetal thyroid goitre are the consequence of fetal hypothyroidism due to trans-placentally derived anti-thyroid drugs used for the treatment of maternal hyperthyroidism. (13-15).

Less common causes of fetal goitre are inadequate or excessive iodine availability (18) or congenital thyroid dyshormonogenesis due to defects in genes involved in the pathway of thyroid hormone production (19).

Ultrasound diagnosis

Fetal goitre can be diagnosed prenatally by ultrasound with the demonstration of an anterior cervical echogenic mass of variable size (Fig. 2). Large fetal goitres may lead to obstruction of fetal swallowing with consequent polyhydramnios; the neck may be hyperextended. As with other causes of obstructive polyhydramnios (duodenal stenosis, oesophageal atresia) this becomes evident usually after 24 weeks and places the pregnancy at risk for pre-term birth. With fetal goitre there may also be a higher risk of birth dystocia because of the inadequate head flexion during labour and increased incidence of neonatal breathing problems and difficulties in intubation.

Fetal goitre can cause complications attributable not only to the size of goitre itself, but also to thyroid dysfunction. Ultrasound is not a reliable tool to distinguish between fetal hyper- and hypothyroidism. In some cases of fetal hyperthyroidism there can be associated intrauterine growth restriction with accelerated bone maturation, tachycardia, intrauterine death by cardiac failure or thyrotoxicosis and craniosynostosis (20, 21). Severe fetal hypothyroidism can delay bone maturation (22) and there may be impaired growth and bradycardia.

There are usually no other associated structural anomalies and the incidence of chromosomal or genetic anomalies is not increased in fetal goitres in maternal Graves' disease. Fetal thyroid dyshormonogenesis is inherited as an autosomal recessive condition and therefore there is a 25% risk of recurrence.

Management

In most cases of fetal goitre assessment of the maternal condition can help decide whether the cause is fetal hypothyroidism or hyperthyroidism. In uncertain cases, cordocentesis and measurement of fetal blood thyroid hormones and TSH can help distinguish between hypothyroidism, with low thyroid hormones and high TSH, due to anti-thyroid drugs or congenital dyshormonogenesis, and hyperthyroidism, with high thyroid hormones and low TSH, due to thyroid stimulating immunoglobulins (13, 23). Normal ranges for the thyroid hormones level in the fetal blood and a discussion on the method of their assessment has been previously reported (24, 25).

In fetal hypothyroid goitre the first-line of treatment is to reduce or even discontinue maternal anti-thyroid medication aiming to maintain maternal blood thyroxine levels in the upper level of the gestational age-specific normal range (Fig. 3)(10). It should be noted that Graves' disease, like most other autoimmune disorders, improves during pregnancy and consequently requires less medication (26, 27). The second-line of treatment is intra-amniotic injection of levothyroxine (100 μg / kg) every 1-2 weeks until delivery at term (13, 28). The goitre usually decreases in size within a few days after the first course of treatment. Subsequent injections are given depending on sonographic evidence of re-enlargement of the gland or serial measurements of levels of thyroid hormones in amniotic fluid or fetal blood (13, 29, 30).

In fetal hyperthyroid goitre the treatment of choice is administration of anti-thyroid drugs to the mother (Fig. 3)(31). Occasionally, the mother should also be given levothyroxine, as the dose of anti-thyroid drug can be appropriate for the fetus but could lead to hypothyroidism in the mother (16). The fetal goitre usually decreases in size within a few days after

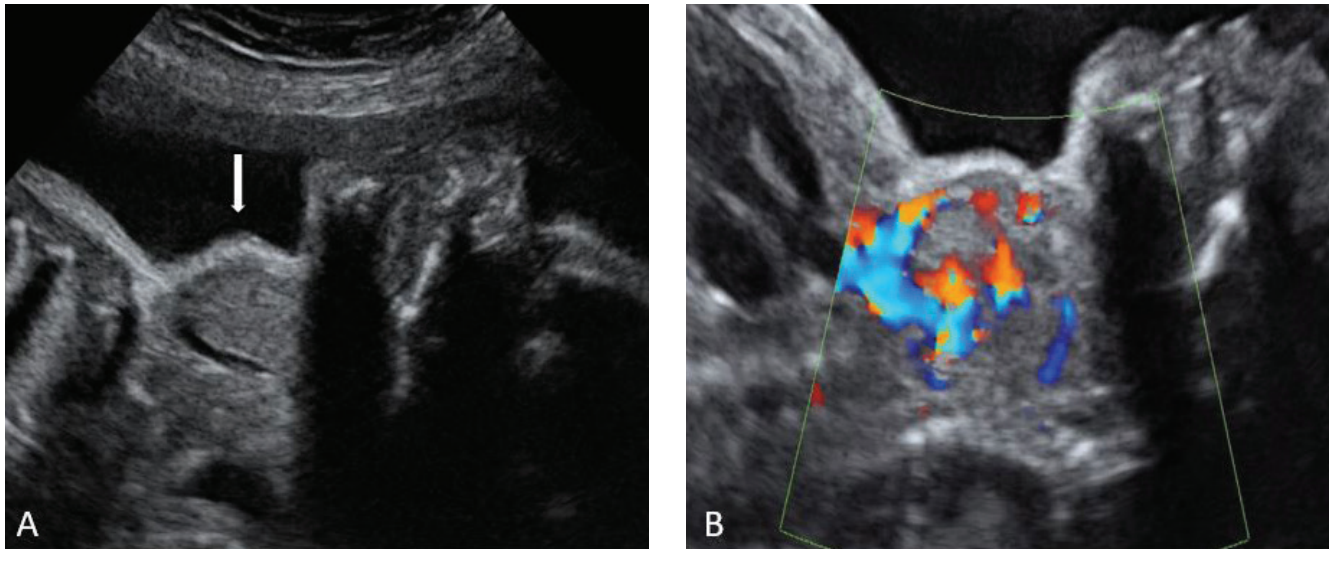

Figure 2. A. Fetal goitre (arrow) in a mother with Graves' disease. B. Diffuse hypervascularity on fetal doppler examination of the same case.

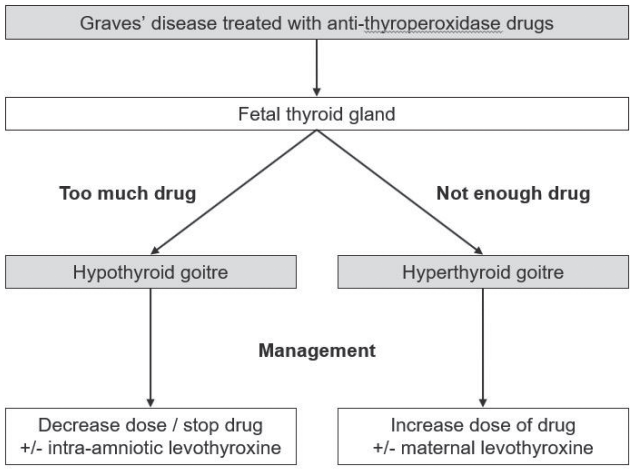

Figure 3. Management of fetal thyroid in maternal Graves' disease.

the initiation of treatment, but if this does not occur measurement of levels of thyroid hormones in fetal blood (32) may be needed and the dose of anti-thyroid drugs given to the mother adjusted as necessary.

Follow-up should be arranged depending on the clinical context, but generally at every 4 weeks to monitor fetal growth, size of the tumour, fetal heart rate, amniotic fluid volume and cervical length.

In pregnant women with known Graves' disease, treated or untreated, thyroid stimulating immunoglobulins should be determined in the beginning of pregnancy and later in the second and third trimester. If the level is 3 times the normal range, close follow-up should be initiated from the second trimester onwards (10). Ultrasound scan, carried out every four weeks, should include examination of the fetal neck, monitoring of the fetal growth and Doppler studies for assessment of fetal oxygentation.

Delivery

Delivery in the case of fetal goitre should take place in a hospital with neonatal intensive care capacities and pediatric surgery facilities, ideally around 38 weeks. With large goitres, where there is hyperextension of the neck, caesarean section is the preferred method of delivery. An EXIT (ex utero intrapartum treatment) procedure may be required to access and stabilize neonatal breathing while maintaining placental flow through the mother.

Prognosis

Adequately treated fetal thyroid goitres generally have good prognosis. However, fetal hyperthyroidism may lead to neonatal thyrotoxicosis (33) and, in association with craniosynostosis, to long term intellectual impairment (20) while fetal hypothyroidism may result in long term abnormal psychomotor development (34).

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Brent GA. Maternal thyroid function: interpretation of thyroid function tests in pregnancy, Clin Obstet Gynecol 1997;40:3-15.
2. Patel J, Landers K, Li H, Mortimer RH, Richard K. Thyroid hormones and fetal neurological development. J Endocrinol 2011; 209(1):1-8.
3. Obregon MJ, Calvo RM, Del Rey FE, de Escobar GM. Ontogenesis of thyroid function and interactions with maternal function. Endocr Dev 2007; 10:86-98.
4. Lazarus JH. Thyroid function in pregnancy. British Medical Bulletin 2011; 97(1): 137-148.
5. Panaitescu AM, Peltecu G. Gestational Diabetes. Obstetrical Perspective. Acta Endo (Buc) 2016, 12 (3): 331-334.
6. Neale DM, Cootauco AC, Burrow G. Thyroid disease in pregnancy. Clin Perinatol 2007; 34(4):543-557.
7. Goodwin TM, Montoro M, Mestman JH. Transient hyperthyroidism and hyperemesis gravidarum: clinical aspects. Am J Obstet Gynecol 1992; 167:648–652.
8. Cooper DS, Laurberg P. Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol 2013; 1: 238-249.
9. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG Placental Transfer in Healthy and Pathological Pregnancies. Clinical and Developmental Immunology 2012; 13: 2012-2025.
10. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017; 27(3):315-389.
11. Nedrebo BG, Holm PI, Uhlving S, Sorheim JI, Skeie S, Eide GE, Husebye ES, Lien EA, Aanderud S. Predictors of outcome and comparison of different drug regimens for the prevention of relapse in patients with Graves' disease. Eur J Endocrinol 2002; 147: 583–589.
12. Panaitescu AM, Nicolaides K. Maternal autoimmune disorders and fetal defects. J Matern Fetal Neonatal Med 2017; 18:1-9.
13. Bliddal S, Rasmussen AK, Sundberg K, Brocks V, Feldt-Rasmussen U. Antithyroid drug-induced fetal goitrous hypothyroidism. Nat Rev Endocrinol 2011; 7:396-406.
14. Burrow GN. Neonatal goiter after maternal propylthiouracil therapy. J Clin Endocrinol Metab 1965; 25:403-408.
15. Volumenie JL, Polak M, Guibourdenche J, Oury JF, Vuillard E, Sibony O. Management of fetal thyroid goitres: a report of 11 cases in a single perinatal unit. Prenat Diagn 2000; 20:799-806.
16. Luton D, Le Gac I, Vuillard E, Castanet M, Guibourdenche J, Noel M, Toubert ME, Léger J, Boissinot C, Schlageter MH, Garel C, Tébeka B, Oury JF, Czernichow P, Polak M: Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. J Clin Endocrinol Metab 2005; 90:6093–6098.
17. Rosenfeld H, Ornoy A, Shechtman S, Diav-Citrin O. Pregnancy outcome, thyroid dysfunction and fetal goitre after in utero exposure to propylthiouracil: a controlled cohort study. Br J Clin Pharmacol 2009; 68: 609-617.

18. Sasaki Y, Kikuchi A, Murai M, Kanasugi T, Isurugi C, Oyama R, Sugiyama T. Fetal goiter associated with preconception hysterosalpingography using an oil-soluble iodinated contrast medium. Ultrasound Obstet Gynecol 2016; 49: 275-276.
19. Rubio IG, Medeiros-Neto G. Mutations of the thyroglobulin gene and its relevance to thyroid disorders. Curr Opin Endocrinol Diabetes Obes 2009; 16:373-378.
20. Daneman D, Howard NJ. Neonatal thyrotoxicosis: intellectual impairment and craniosynostosis in later years. J Pediatr 1980; 97:257–259.
21. Heckel S, Favre R, Schlienger JL, Soskin P. Diagnosis and successful in utero treatment of a fetal goitrous hyperthyroidism caused by maternal Graves' disease. A case report. Fetal Diagn Ther 1997; 12:54–58.
22. Avni EF, Rodesch F, Vandemerckt C, Vermeylen D. Detection and evaluation of fetal goitre by ultrasound. Br J Radiol 1992; 65:302–305.
23. Kilpatrick S. Umbilical blood sampling in women with thyroid disease in pregnancy: Is it necessary? Am J Obstet Gynecol 2003; 189:1-2.
24. Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler J, McGregor AM. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus. N Engl J Med. 1991; 324(8):532-536.
25. Thorpe-Beeston JG, Nicolaides KH. Fetal thyroid function. Fetal Diagn Ther. 1993; 8(1):60-72.
26. Momotani N, Noh J, Oyanagi H, Ishikawa N, Ito K. Antithyroid drug therapy for Graves' disease during pregnancy. Optimal regimen for fetal thyroid status. N Engl J Med 1986; 315: 24-28.
27. Smyth PP, Wijeyaratne CN, Kaluarachi WN, Smith DF, Premawardhana LD, Parkes AB, Jayasinghe A, de Silva DG, Lazarus JH. Sequential studies on thyroid antibodies during pregnancy. Thyroid 2005; 15:474-477.
28. Bliddal S, Rasmussen ÅK, Sundberg K, Brocks V, Skovbo P, Feldt-Rasmussen U. Graves' disease in two pregnancies complicated by fetal goitrous hypothyroidism: successful in utero treatment with levothyroxine. Thyroid 2011; 21:75-81.
29. Munoz JL, Kessler AA, Felig P, Curtis J, Evans MI. Sequential Amniotic Fluid Thyroid Hormone Changes Correlate with Goiter Shrinkage following in utero Thyroxine Therapy. Fetal Diagn Ther 2016; 39:222-227.
30. Nachum Z, Rakover Y, Weiner E, Shalev E. Graves' disease in pregnancy: prospective evaluation of a selective invasive treatment protocol. Am J Obstet Gynecol 2003; 189:159-165.
31. Polak M. Thyroid disorders during pregnancy: impact on the fetus. Horm Res Paediatr 2011; 76 Suppl 1:97-101.
32. Polak M, Leger J, Luton D, Oury JF, Vuillard E, Boissinot C, Czernichow P. Fetal cord blood sampling in the diagnosis and the treatment of fetal hyperthyroidism in the offsprings of a euthyroid mother, producing thyroid stimulating immunoglobulins. Ann Endocrinol (Paris) 1997; 58:338-342.
33. Bruinse HW, Vermeulen-Meiners C, Wit JM. Fetal treatment for thyrotoxicosis in non-thyrotoxic pregnant women. Fetal Ther 1988; 3:152–157
34. Rovet J, Ehrlich R, Sorbara D. Intellectual outcome in children with fetal hypothyroidism. J Pediatr 1987; 110:700-704.