Accepted Manuscript

Submission Date: 2022-10-12
Accepted Date: 2024-04-10
Accepted Manuscript online: 2024-05-02

American Journal of Perinatology Reports

FETAL HYPERTHYROIDISM SECONDARY TO MATERNAL BASEDOW-GRAVES DISEASE

JULIO SOTO BARROS, Bunio Weissglas, Gustav von Plesssing-Pierry, María Paz Del Solar, Carolina Peña-Villa, Ximena Flores, Mónica Arancibia, Laura Campos.

Affiliations below.

DOI: 10.1055/a-2317-9431

Please cite this article as: SOTO BARROS J, Weissglas B, von Plesssing-Pierry G et al. FETAL HYPERTHYROIDISM SECONDARY TO MATERNAL BASEDOW-GRAVES DISEASE. American Journal of Perinatology Reports 2024. doi: 10.1055/a-2317-9431

Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Fetal hyperthyroidism is a rare prenatal disease and can be life-threatening. The diagnosis is based on ultrasound in mothers with history of Basedow-Graves and elevation of TRAbs levels. The treatment consists of antithyroid drugs. We present a mother with Basedow-Graves disease, treated with radioactive iodine 16 years ago. She had an unplanned pregnancy at age 29 years, and an elevation of TRAbs (21 U/L) was found at the sixth week of pregnancy. At 22 weeks of gestation, fetal ultrasound displayed tachycardia, goiter, exophthalmos and suspicion of craniosynostosis, hence methimazole was started. Concomitantly, suppressed maternal TSH was found. Her daughter was born at 33 + 6 weeks showing clinical and laboratory findings of hyperthyroidism. Consequently, treatment with methimazole was prescribed. Normal thyroid function was documented in the mother after giving birth. Clear explanation has not been found for the alteration of maternal TSH during pregnancy.

Corresponding Author:
Dr. Gustav von Plesssing-Pierry, Universidad de Concepción, School of Medicine, Concepcion, Chile, gvonplessingp@outlook.com

Affiliations:
JULIO SOTO BARROS, Hospital Las Higueras, Pediatric Service, Talcahuano, Chile
JULIO SOTO BARROS, Universidad de Concepción, Department of Pediatrics, School of Medicine, Concepcion, Chile
Bunio Weissglas, Universidad de Concepción, School of Medicine, Concepcion, Chile
[...]
Laura Campos, Hospital Las Higueras, Pediatric Service, Talcahuano, Chile

FETAL HYPERTHYROIDISM SECONDARY TO MATERNAL BASEDOW-GRAVES DISEASE

Soto J[1,2], Weissglas B[3], von Plessing-Pierry G[3], del Solar MP[4], Peña-Villa C[5], Flores X[6], Arancibia M[2], Campos L[2].

[1]Department of Pediatrics, School of Medicine, Universidad de Concepcion, Concepcion, Chile

[2]Pediatric Endocrinology Unit, Pediatrics Service, Las Higueras Hospital, Talcahuano, Chile.

[3]Intern of Medicine, School of Medicine, Universidad de Concepcion, Concepcion, Chile.

[4]Department of Clinical and Preclinical Sciences, School of Medicine, Universidad Catolica de la Santisima Concepcion, Concepcion, Chile.

[5] Endocrinology Unit, Internal Medicine Service, Las Higueras Hospital, Talcahuano, Chile.

[6]Obstetric and Gynecologic Ultrasound Unit, Obstetrics and Gynecology Service, Las Higueras Hospital, Talcahuano, Chile

Corresponding author: Dra. Laura Campos, email: lauracampos720@gmail.com

ABSTRACT

Fetal hyperthyroidism is a rare prenatal disease and can be life-threatening. The diagnosis is based on ultrasound in mothers with history of Basedow-Graves and elevation of TRAbs levels. The treatment consists of antithyroid drugs. We present a mother with Basedow-Graves disease, treated with radioactive iodine 16 years ago. She had an unplanned pregnancy at age 29 years, and an elevation of TRAbs (21 U/L) was found at the sixth week of pregnancy. At 22 weeks of gestation, fetal ultrasound displayed tachycardia, goiter, exophthalmos and suspicion of craniosynostosis, hence methimazole was started. Concomitantly, suppressed maternal TSH was found. Her daughter was born at 33 + 6 weeks showing clinical and laboratory findings of hyperthyroidism. Consequently, treatment with methimazole was prescribed. Normal thyroid function was documented in the mother after giving birth. Clear explanation has not been found for the alteration of maternal TSH during pregnancy.

KEYWORDS:
Fetal thyrotoxicosis; Graves' disease, Hyperthyroidism, Fetal

INTRODUCTION:

Thyroid hormones are essential for fetal development during pregnancy, particularly for fetal neurogenesis[1]. At the 10th week of pregnancy, the synthesis of fetal thyroid hormones starts, prior to which the fetus depends exclusively on maternal hormones.[2] Around 20 weeks of gestation, fetal TSH receptors begin to respond to TSH and TSH receptor antibodies (TRAb)[3]. TRAbs cross the feto-placental barrier and act on fetal TSH receptors and fetuses of mothers who have a history of active Graves Basedow Disease or treatment with thyroidectomy or radioiodine and currently being treated for hypothyroidism and who have high TRAb titers, may develop hyperthyroidism after this period [2,3]. Fetal hyperthyroidism is a rare and transient prenatal condition, however, it can have lethal consequences for the fetus if it is not investigated and treated immediately.[4] Diagnosis is based on antenatal Doppler ultrasound from 20 weeks of pregnancy in at risk mothers displaying signs of fetal thyroid dysfunction. The clinical and ultrasound manifestations are broad, ranging from tachycardia, goiter, growth retardation and amniotic fluid volume alterations to more serious consequences such as microcephaly, craniosynostosis, hydrops fetalis, heart failure, premature birth and stillbirth. [4–7] Once the diagnosis of fetal or maternal hyperthyroidism is made, the primary treatment is antithyroid drugs.[4]

CASE REPORT:

29-year-old primigravid mother was diagnosed with Basedow-Graves disease at age 13 years old and was treated with radioiodine at 14 years old, and developed post-treatment hypothyroidism. She showed progressive dysthyroid orbitopathy and underwent decompressive surgery at 19 years of age. Lately, she was referred to endocrinology in the context of her thyroid history and unintended pregnancy. Previously, she had been treated with levothyroxine 150 ug/day. Laboratory work-up showed elevated TRAbs levels at the sixth week of pregnancy (21 U/L, normal value <0.1 U/L), with normal levels of thyroid function test during the first trimester of pregnancy (Table 1). Repeated TRAbs levels at 18 weeks remained positive. At 22 weeks of gestation, a fetal ultrasound was performed, which showed suggestive signs of fetal hyperthyroidism, including tachycardia, goiter with increased central vascular flow, exophthalmus, and suspected craniosynostosis. Concomitantly a mild suppression in maternal TSH level was detected. TRAb typing was requested and the presence of stimulating antibody (TSI) was confirmed. Methimazole 10 mg was started which was later

increased to 20 mg according to ultrasound findings (Table 1). Interruption of pregnancy by cesarean section at 34 weeks due to progressive manifestations of fetal hyperthyroidism was decided, however, the pregnant woman went into labor at 33+6 weeks.

At birth her daughter had weight of 2660 g (-0.47 SD), height of 47.5 cm (1.2 SD), head circumference of 31.5 cm (-0.714 SD) and APGAR 8-9-9. Her physical examination revealed tachycardia, exophthalmus, bilateral palpebral retraction, and goiter. Treatment with methimazole 0.38 mg/kg/day and propranolol 1.5 mg/kg/day was immediately started. Thyroid function tests showed suppressed TSH, elevated free T4 (FT4) and T3. TRAbs levels were 9.187 IU/L. In the first hours of life, she presented respiratory distress syndrome, requiring CPAP for 15 hours, without hemodynamic instability. At 7 days of life, the dose of methimazole was increased to 0.68 mg/kg/day, progressing with slow normalization of thyroid tests. At 4 days of life, she presented hyperbilirubinemia with a cholestatic pattern and ursodeoxycholic acid and vitamin E were prescribed. Her abdominal and brain ultrasound were normal; Thyroid ultrasound showed slightly heterogeneous hypoechoic diffuse goiter without focal lesions. Skull X-ray ruled out craniosynostosis. At 17 days of life due to persistent elevation of FT4, methimazole dose was increased (0.83 mg/kg/day). She was discharged at 22 days of life.

In her follow-up at age 2 months 5 days, the infant showed resolution of cholestasis, normalization of thyroid function with an adequate growth and weight gain, therefore methimazole, ursodeoxycholic acid and vitamin E were suspended and levothyroxine was prescribed due to transient hypothyroidism secondary to methimazole (Table 2). Ophthalmology evaluation reported regression of palpebral retraction with persistence of mild exophthalmos and her fundoscopic exam was normal. Nonetheless, dysphagia was suspected due to history of choking with feeding and saliva. She was evaluated by neurology and central hypotonia and an increased in her head circumference were noted (Figure 1). MRI displayed triventricular hydrocephalus and type 1 Chiari malformation and she underwent endoscopic ventricular cisternostomy at 12 months of age. She progressed with psychomotor developmental retardation, speech being predominantly affected. Brainstem evoked response audiometry (BERA) was normal. At age 15 months, she underwent a new neurologic procedure owing to pseudomeningocele and a plasty of a cerebrospinal fluid non-communicating fistula in the subgaleal space. She has been receiving speech therapy and has shown improvement in this area. Her growth has been adequate during follow-up (Figure 1).

DISCUSSION:

The most common management scenario in children of mothers with maternal hyperthyroidism due to Graves' disease is neonatal hyperthyroidism with several cases being described in the literature. Due to the severe consequences of fetal hyperthyroidism[8], screening during pregnancy is mandatory in mothers with a history of active Graves' disease or those who have been treated with radioiodine and/or thyroidectomy[4]. Laboratory work-up with TRAbs and thyroid function levels immediately after pregnancy diagnosis is suggested in the literature[4,9]. If TRAbs are negative, no further follow-up is required. Conversely, if TRAbs are positive, repeated levels should be requested at 18-22 weeks of pregnancy. If TRAbs remains positive at that time, new levels should be determined at 30-34 weeks of pregnancy. In addition, an obstetric ultrasound should be performed starting at 20-24 weeks of gestation every 4-6 weeks.[9]

To the best of our knowledge, 15 cases of fetal hyperthyroidism have been reported in the literature (Table 3). Six of those cases had a history of maternal radioiodine treatment for Graves' disease several years prior to pregnancy. This is consistent with data showing that high levels of TRAbs have been observed 5 years after treatment with I131, in contrast to thyroidectomy.[10] In our case, TRABs remained positive after 16 years of radioiodine therapy.

Regarding maternal thyroid function at the time of pregnancy diagnosis, our patient was receiving levothyroxine showing normal thyroid function, which was similar to another seven case reports (Table 3).

Ultrasound and measurement of maternal TRAbs were used as diagnostic methods for fetal hyperthyroidism in concordance with 12 others reports. However, cordocentesis has also been described as a diagnostic tool following ultrasound suspicion of fetal hyperthyroidism in most of the cases. In our case, cordocentesis was not performed due to maternal and fetal risks, fetal death being the most feared.[11]

In our patient, diagnosis was based on ultrasound findings of fetal tachycardia, goiter with central hyperemia, exophthalmus, and suspicion of craniosynostosis. Whereas in the cases previously reported (Table 3), goiter was described in 6 fetuses and fetal tachycardia in 13. Furthermore other signs observed were advanced bone maturation, oligohydramnios, IUGR, pleural effusion, pericardial effusion, among others.[4–7]

Once diagnosis of fetal hyperthyroidism is confirmed, mothers should receive low-dose antithyroid drugs: propylthiouracil (PTU) during the first trimester of pregnancy, transitioning to methimazole or carbimazole

later. Fetal hypothyroidism is the most risky complication of this management.[4,6,9]

In our case, due to suppressed maternal TSH without having modified levothyroxine dose concomitant with manifestation of fetal hyperthyroidism on the ultrasound, methimazole was started at 22 weeks of gestation. Abnormal levels of TSH were normalized postpartum. TSH suppression is rare in a pregnant woman with history of hypothyroidism secondary to radioactive iodine ablation. Additionally, an improvement in clinical and laboratory manifestations during pregnancy have been reported in Th1-predominant autoimmune diseases in pregnancy, such as Graves' disease, which make the hypothesis of reactivation of maternal hyperthyroidism as a cause of this TSH level abnormality unlikely.[12]

On the other hand, hCG-induced maternal TSH receptor activation could not explain the suppression of TSH in our patient since this phenomenon began in the second trimester of pregnancy.[13]

Other less common causes of TSH suppression in pregnancy are those related to autonomous secretion of thyroid hormones, destruction of thyroid follicles, and extrathyroidal sources of thyroid hormones.[14] These were also ruled out, considering the absence of a history of nodular goiter, viral or bacterial infection, anterior cervical pain, among others.

We hypothesized that the suppression of maternal TSH was due to a transplacental transfer of thyroid hormones from the fetus to the mother. This was suspected since TSH values began to fall concomitantly with the onset of ultrasound manifestations of fetal hyperthyroidism at the time when fetal thyroid hormone secretion begins, especially considering that TSH suppression was corrected postpartum.

Monocarboxylate transporter 8 (MCT8) could play a fundamental role in the transport of thyroid hormones of fetal origin towards the maternal circulation. This transporter is present in the placenta in both apical and basal membranes of maternal and fetal endothelial cells, in addition to the villous stroma and a potent and specific affinity for T3 has been described.[15]

Another mechanism that may support the theory of bidirectional transport is reverse T3 (T3r), which is synthesized by the fetal thyroid and is transported from the fetus to the maternal circulation through the placenta,[16] showing 40 times greater affinity for placental nuclear binding sites than T4 and 63 times greater than T3.[17] However, it has

been observed that T3r is functionally inactive and does not generate serum TSH modifications,[18] so if T3r played any role it would be indirect and due to other mechanisms not yet established.

In summary, no clear explanation was found for the suppression of TSH during pregnancy in our patient. Further studies addressing transport or metabolism mechanisms of thyroid hormones are needed.

CONCLUSION

Healthcare providers must be alert to the eventual development of fetal hyperthyroidism in any mother with a history of GBD, even when she has received definitive treatment (surgery or radioiodine) several years before pregnancy, since the production of TRAbs antibodies can persist for a long time. Therefore it is important that the entire care team for a pregnant woman inquire about maternal thyroid history and apply a protocol for monitoring TRAbs and ultrasound and, if necessary, treatment with antithyroid drugs.

FOUNDING SOURCES

We did not receive any financial support for this report.

ACKNOWLEDGEMENT

We would like to acknowledge the motivation and participation of Dr. Laura Campos to make the publication of this case report possible.

CONFLICT OF INTEREST

None of the participants of this research declare any conflict of interest.

TABLES AND FIGURES:

Table 1. Maternal-fetal evaluations since the beginning of the pregnancy.

GA	6 W	12 +4 W	18 +3 W	22+4 W	24 +3 W	27+ 4 W	30+2 W	33 W	33 +6 W	Normal reference ranges
TSH	0,2 91	0,524	1,2	0,22	0,015	0,02	0,0011			0,3-4,2 uUI/mL
FT4	1,3	1,31	1,3	1,09	1,33	0,9	1,26			0,7-1,48 ng/dL
T4	10,3	9,81	10	11,4	12,9	11,2	10			<16 weeks: 5,5-11,5 ug/dL >16 weeks: 8,25-15,25 ug/dL
TRABS	21,3		16,4		18,7 (TSI)*					< 0,1 U/L
Treatment	LVT150 ug	LVT 150 ug	LVT 150 ug	LVT 150 ug, Methimazole 10mg	LVT 150 ug, Methimazole 15mg	LVT 150 ug, Thiamazole 20 mg	LVT 150 ug, Methimazole 20 mg		Preterm Labor	
Fetal US		HR: 153xmin AF normal		Fetal tachycardia, goiter with central hypervascularization. Long bones >p90.	Sinus tachycardia, goiter improvement	Fetal tachycardia, goiter, exophthalmus	Similar goiter, normocardia, exophthalmus	Suspected craniosynostosis, HR: 160xmin		
Mother's Physical examination						Exophthalmus, HR: 95xmin Tremor (+)				

GA: Gestational age. LVT: Levothyroxine TSH: Thyroid-Stimulating Hormone FT4: Free Thyroxine T4: Thyroxine TRABS: Thyrotropin Receptor Antibodies.

TSI: thyroid stimulating immunoglobulin. AF: Amniotic fluid. HR: Heart rate.

Age	0	4 d	7 d	10 d	13 d	17 d	20 d	22 d	1 m 5 d	1 m 17 d	2 m 5 d	2 m 11 d	2 m 25 d
GA						36 + 3			38 + 5	3 d	19 d	25 d	1 m 9d
Weight (gr)	2660	2130	2090	2205	2270	2345	2390	2380	3100	3510	4040		
Height (cm)	47.5 cm									53.5	55		
TSH (mUI/mL)	0.027		<0.015					15	<0.01	<0.01	0.33	629	<0.01
FT4 (ng/dL)	5.59	6.37	5.07	3.63	3.22	3.48	3.03	2.27	1.0	0.7	0.4	0.54	1.7
T3 (ng/m L)	3.54	2.88	3.32	3.89	4.1		3.6		2.0	1.1	0.9	129 ng/dl	
TRABS (UI/L)		9.187					6.88					0.19 UI/L	
Therapy	Methimazole 0.5-0.5 mg (0.38 mg/kg/d	↓Propranolol 1-1 mg due to bradychardi a,	↑Methimazole 1-0.5 mg (0.7 mg/kg/d) Propranol			↑Methimazole 1-1 mg (0.83 mg/kg		Propranol suspension,	↓Methimazole 1-0.5 mg (0.48 mg/kg/d), ursodiol ,	↓Methimazole 0.5-0.5 mg (0.28 mg/kg/d)	Methimazole suspension	LVT 25 ug (6 ug	LVT suspension

	) Propranol ol 2-2 mg (1.5 mg/kg/d)	start of ursodiol and Vitamin E	ol 2-2 mg			/ d) Propanolol 2-2 (1.67 mg/kg/d)		ursodiol 25 mg c/8h (20 mg/kg/d)	vitamin E suspension			/kg/d)	

Table 2. Clinical and laboratory follow-up of the Newborn

References values: TRAbs (VR <1.5), T4l (0.78-2.19), T3 (0.97-1.7) y TSH: (0.9 - 7.7)

Figure 1. Height, weight and head circumference growth charts

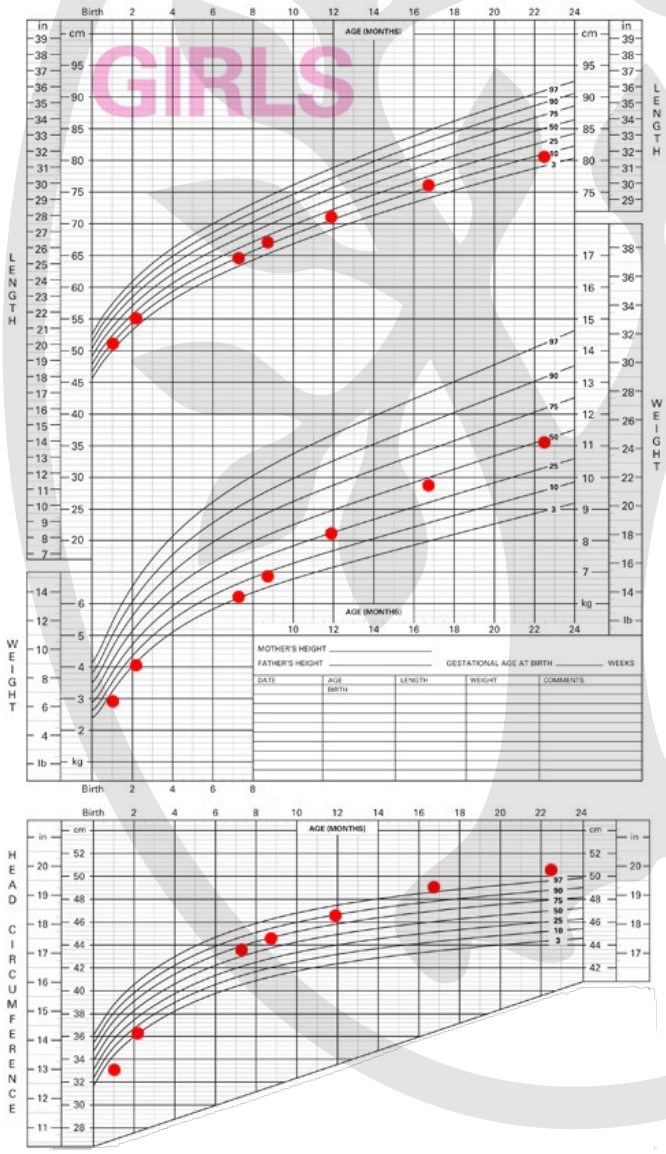

Table 3. Diagnosis and management of previous cases of fetal hyperthyroidism reported in the literature.

Case report			Prenatal maternal treatment	Total thyroidectomy + LT4	Maternal thyroid function and/or TRABs/TSIab	Gestational age at diagnosis (weeks)	Diagnosis	US diagnosis	Fetal goiter, tachycardia facial edema, pleural and pericardial effusion, IUGR, Hydrops, Oligohydramnios	Treatment	MMI
Srisupundit et al. 2008		1		Thyroidectomy	Euthyroidism	28	US+FBS		Tachycardia	PTU	
Lembet et al. 2004	Wallace et al. 1995	1		Radioiodine TT >3 years	Euthyroidism TSI> 500%	32	US		Tachycardia		PTU
	Wenstrom et al. 1990	2	PTU + Propanolol	Radioiodine TT	Hypothyroidism TSI >500%	29	US		Tachycardia, IURG, Olygohydramnios		PTU
					Hypothyroidism	26	FBS	Fetal goiter, Intrauterine growth restriction (IUGR) and Olygohydroamnios.		PTU	
				Radioiodine TT	Hyperthyroidism TRAb 467 UI/l	TSI: 500%	23	FBS	(-)		MMI
Spoke and Martin et al.2020	Haidi and Sstrickland 1995	1	Radioiodine TT + desecated thyroid extract and LT4	Radioiodine TT + PTU	Hyperthyroidism Hypothyroidism	iTSI:470%	30	US + FBS	Fetal goiter, tachycardia and pericardial effusion	Fetal goiter, tachycardia. MMI at week 23.	PTU
	Porroco and Bloch 1990	1	Thyroidectomy		Euthyroidism TSI> 500%		25	FBS	Tachycardia	PTU since week 25	PTU
Luton et al. 1996	Vali et al. 1998	1	Thyroidectomy		Hyperthyroidism TSI> 100%		22	US	Fetal goiter		Carbimazole
	Belfar et al. 1991	2	Partial thyroidectomy	PTU + Propanolol	TRAb 297 UI/L	Euthyroidism.	24	26	US + FBS	Fetal goiter, pericardial effusion and advance in bone maturation.	Tachycardia	PTU	PTU
	Pekonen et al. 1994	1	Thyroidectomy		Euthyroidism.		31	US	Thyroid cyst, tachycardia.		Carbimazole
	Hatjis	1	Partial thyroidectomy	Radioiodine	Euthyroidism TRAb 459 UI/L	Hypothyroidism TSI:770%	25	26	FBS US	Fetal goiter, fetal tachycardia	Fetal goiter, tachycardia,	PTU	PTU
Donnelly et al. 2015		1		Thyroidceotmy + LT4		Euthyroidism	18	US	Fetal goiter, tachycardia, bone maturation acceleration in proximal and distal tibial epiphysis and dilated cardiomegaly.		PTU

1993		TT				IUGR, olygohydramnios.	
Heckel et al 1997	1	(-)	Hyperthyroidism TSI> 500%	28	US + FBS	Fetal goiter, tachycardia.	Carbimazole

REFERENCES:

1. Eng L, Lam L. Thyroid function during the fetal and neonatal periods. *Neoreviews*.

   2020;21(1):e30-e36. doi:10.1542/neo.21-1-e30

2. Polak M, Legac I, Vuillard E, Guibourdenche J, Castanet M, Luton D. Congenital hyperthyroidism: The fetus as a patient. *Horm Res*. 2006;65(5):235-242. doi:10.1159/000092454

3. Léger J, Carel JC. Diagnosis and management of hyperthyroidism from prenatal life to adolescence. *Best Pract Res Clin Endocrinol Metab*. 2018;32(4):373-386. doi:10.1016/j.beem.2018.03.014

4. Léger J. Management of Fetal and Neonatal Graves' Disease. *Horm Res Paediatr*. 2017;87(1):1-6. doi:10.1159/000453065

5. Luton D, Le Gac I, Vuillard E, et al. Management of Graves' disease during pregnancy: The key role of fetal thyroid gland monitoring. *J Clin Endocrinol Metab*. 2005;90(11):6093-6098. doi:10.1210/jc.2004-2555

6. León MC. Hipertiroidismo en el embarazo . Recién nacido hijo de madre con Enfermedad de Graves Hyperthyroidism in pregnancy . Newborn of mother with Graves disease. *Rev Española Endocrinol Pediatr*. 2013;5(2):35-40.

7. Kurtoğlu S, Özdemir A. Fetal neonatal hyperthyroidism: Diagnostic and therapeutic approachment. *Turk Pediatr Ars*. 2017;52(1):1-9. doi:10.5152/TurkPediatriArs.2017.2513

8. Spoke C, Martin C. Maternal Graves Disease and Abnormal CYP2D6 Genotype with Fetal Hyperthyroidism. *AACE Clin Case Reports*. 2020;6(4):e161-e164. doi:10.4158/ACCR-2019-0517

9. Alexander EK, Pearce EN, Brent GA, et al. 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. doi:10.1089/thy.2016.0457

10. Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Törring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: A 5-year prospective randomized study. *Eur J Endocrinol*. 2008;158(1):69-75. doi:10.1530/EJE-07-0450

11. Tongsong T, Wanapirak C, Kunavikatikul C, Sirirchotiyakul S, Piyamongkol W, Chanprapaph P. Fetal loss rate associated with cordocentesis at midgestation. *Am J Obstet Gynecol*. 2001;184(4):719-723. doi:10.1067/mob.2001.111716

12. Somers EC. Pregnancy and autoimmune diseases. *Best Pract Res Clin Obstet Gynaecol*. 2020;64:3-10. doi:10.1016/j.bpobgyn.2019.11.004

13. Kobaly K, Mandel SJ. Hyperthyroidism and Pregnancy. *Endocrinol Metab Clin North Am*. 2019;48(3):533-545. doi:10.1016/j.ecl.2019.05.002

14. Cooper DS, Laurberg P. Hyperthyroidism in pregnancy. *Lancet Diabetes Endocrinol*. 2013;1(3):238-249. doi:10.1016/S2213-8587(13)70086-X

15. James SR, Franklyn JA, Kilby MD. Placental transport of thyroid hormone. *Best Pract Res Clin Endocrinol Metab*. 2007;21(2):253-264. doi:10.1016/j.beem.2007.03.001

16. Blackburn S. Maternal-Fetal thyroid interactions. *J Perinat Neonatal Nurs*. 2009;23(4):312-313. doi:10.1097/JPN.0b013e3181bfdc56

17. Banovac K, Ryan EA, O'Sullivan MJ. Triiodothyronine (T3) nuclear binding sites in human placenta and decidua. *Placenta*. 1986;7(6):543-549. doi:10.1016/S0143-4004(86)80140-0

18. Schmidt RL, Lopresti JS, McDermott MT, Zick SM, Straseski JA. Does Reverse Triiodothyronine Testing Have Clinical Utility. An Analysis of Practice Variation Based on Order Data from a National Reference Laboratory. *Thyroid*. 2018;28(7):842-848. doi:10.1089/thy.2017.0645