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Adverse outcome of T3-predominant maternal Grave's disease during pregnancy in the mother and the offspring

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Maternal hyperthyroidism can result in a seriously adverse foetal/neonatal outcome, most frequently caused by Grave's disease (GD) in a pregnant mother.

Neonatal hyperthyroidism is a rare but life threatening condition. The impact of excessive thyroid hormone production on growth and brain development may be dramatic.

Some patients have high serum free triiodothyronine (FT3) levels with a normal free thyroxine (FT4) level. This condition is known as T3-predominant GD. Approximately 10–12% of GD patients are T3-predominat GD [1–3].

We present the case of a pregnant woman with an infant with T3-predominant GD.

A female neonate was born by spontaneous vaginal delivery at 36 + 5/7 weeks of gestation to a 29-year-old gravida 2 mother with GD diagnosed in the third trimester.

The mother manifested clinical symptoms characteristic of hyperthyroidism: sweating, irritability, and hot spells. Foetal tachycardia was diagnosed. The thyroid function test showed suppressed thyroid-stimulating hormone (TSH) and elevated serum FT4 levels. Methimazole (MMI) was initiated due to the diagnosed GD. The infant was a female, weighing 2780 g, with an Apgar score of 10. On admission she presented no hyperthyroid features. After birth, parental fluid was administered due to polycythaemia (hematocrit: 73%). Tachycardia was observed; electrocardiogram showed: arrhythmia with supraventricular tachycardia (220 bpm); enlargement of atria (Fig. 1). A dose of 2 mg/kg/day propranolol was administered. On the 4th day of life (DOL4) a blood thyroid test showed elevated FT4 and suppressed TSH (Tab. 1). The heart rate normalised, but hyperexcitability, diarrhoea, staring, and tachypnoea were observed. Echocardiography revealed heart failure (fraction shortening: 25%). Thyroid ultrasound examination indicated goitre with hypervascularity and thyroid volume 3 times larger than normal (Fig. 2), estimated by the ellipsoid method at 4.2 cm^3 [range volume (RV): 0.76–1.35 cm^3] [5]. Repeat blood sampling confirmed a diagnosis of neonatal hyperthyroidism. On DOL9 a course of propylthiouracil (PTU) was initiated. Propranolol was tapered to 1 mg/kg due to cardiac failure, and discontinued after 2 weeks. Liver enzymes were within normal limits. Her condition was improving. The infant was discharged on DOL19. Following discharge PTU was gradually tapered until 6 weeks of age. At 10 weeks of life the TSH level normalised, the thyrotropin receptor antibodies (TRAb) level decreased, and the FT3 level was slightly above the upper limit with FT4 normalisation. After propranolol withdrawal tachycardia (180–200 bpm) returned and metoprolol was given until 6 months of age.

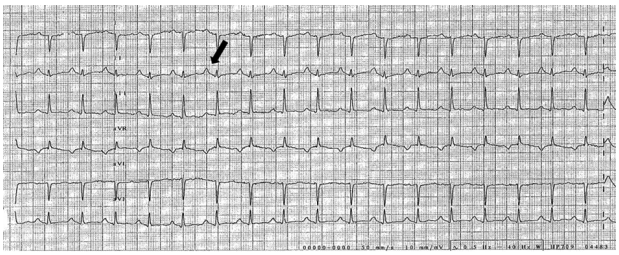

Figure 1. *Supraventricular tachycardia and enlargement of both atria (arrow)*

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Table 1. *Infant's thyroid hormones results*

Age at time of collection DOL	TSH (0.8–5.42) mIU/L	FT4 (10.94–23.68) pmol/L	FT3 (3.39–6.47) pmol/L	TRAb < 1.5 IU/L
4th	0.0003	64.56		27.01
6th	0.0016	44.92		
10th	0.0011	69.66	13.37	
14th	0.0051	25.94		
18th	0.0018	14.61	6.36	
23rd	1.45	8.96	5.26	
28th	0.052	10.87	6.62	
38th	0.027	16.06	7.40	14.22
50th	0.10	9.57	4.15	
64th	0.27	16.78	6.49	
182nd	0.88	13.10	5.52	
302nd	0.715	13.32	6.64	
604th	0.418	15.40	4.85	
740th	0.87	16.78	6.69	

DOL — day of life; TSH — thyrotropin; FT4 — free thyroxine; FT3 — free triiodothyronine; TRAb — thyrotropin receptor antibody

Presently, the 5-year-old child remains euthyroid with appropriate development and growth. The infant's thyroid hormone results are given in Table 1.

A 29-year-old mother remained on 45 mg metamizole daily, with the TSH level supressed and normal FT4 level. On DOL11 after delivery a physical examination showed signs of hyperthyroidism. Suspecting a T3-predominant GD due to suppressed TSH, normal value of FT4, elevated FT3: 6.28 pmol/L (RV: 2.63–5.71 pmol/L), and high TRAb level: > 40.0 IU/L; (RV: < 1.5), we instituted propranolol to inhibit the peripheral T4 to T3 conversion. Finally, the FT3 and FT4 normalised while TSH remained suppressed.

GD occurrence in pregnancy deserves particular attention. Foetal/neonatal hyperthyroidism develops due to transplacental passage of maternal TRAbs [1, 3]. The TRAb level may increase and remain elevated for months/years in women with a history of ablative therapy [3].

Persistently elevated TRAb levels during pregnancy are prognostic of foetal dysfunction, and a high TRAb level in the third trimester is a risk factor of neonate hyperthyroidism [4].

Neonatal hyperthyroidism is usually self-limiting over 1–3 months as the maternal immunoglobulin levels decrease.

In our patient, we did not assess the thyroid function tests from the cord blood, which might have delayed the diagnosis and treatment of hyperthyroidism. We assumed T3-predominant GD when signs of hyperthyroidism persisted despite treatment. T3-predominat GD promotes the activity of 1 iodothyronine deiodinase (D1) in the thyroid gland, generating T4-to-T3 conversion [1–3]. The typical features of T3-predominant GD include high FT3-to-FT4 ratio, high TRAb level, and large goitre size [3].

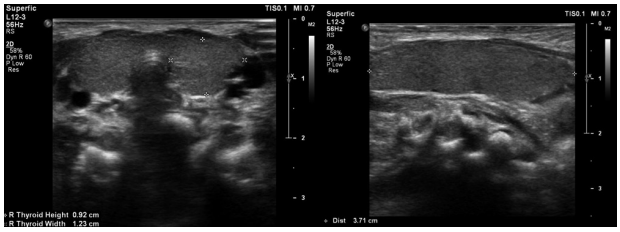

Figure 2. *Goitre, diameters of one of the enlarged lobes of the thyroid gland*

In our case, treatment with antithyroid drugs (ATDs) adjusted the FT4 level to the normal range; however, the mother presented clinical signs of thyrotoxicosis probably associated with a high FT3 level. Unlike MMI, PTU suppresses D1 activity, leading to T4-to-T3 conversion [1, 2]. With PTU not recommended in children due to PTU-induced severe hepatitis, its administration is sometimes necessary to normalize the thyroid function [3,4]. Apart from PTU, there are also other drugs such as steroids or b-blockers, the pharmacological action of which suppresses the conversion of T4 to T3 [2].

The block-replacement therapy is not beneficial for the foetus due to the fact that ATDs migrate faster via the placenta than levothyroxine.

In conclusion, while an effective treatment is available for pregnant women and infants with thyroid-related disorders, cases of T3-predominant GD might be challenging to manage. There is thus a need to measure FT3 serum and evaluate the FT4:FT3 ratio to administer appropriate management.

Conflict of interest
None declared.

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