TEACHING CASE REPORT

Management of hypothyroidism during pregnancy

The case: A 33-year-old woman had received a diagnosis of primary hypothyroidism when she was 23 years of age and had been taking an essentially stable dose of levothyroxine (0.112 mg/d) for at least 2 years. The patient began taking folic acid supplements (1 mg/d) 2 months before a natural, planned conception occurred. About 7 weeks before becoming pregnant, her thyroid stimulating hormone level was 5.95 mU/L, and the levothyroxine dose was increased to 0.116 mg/d. Pregnancy was confirmed by means of a urine home pregnancy test 4 weeks after her last menstrual period. At that time, the patient stopped taking folic acid supplements and, simultaneously with the levothyroxine, began taking prenatal multivitamins that contained iron (ferrous fumarate 60 mg), folic acid (1 mg) and other vitamins and minerals. Her thyroid stimulating hormone level was rechecked 8 weeks after her last menstrual period and was found to be elevated (40.75 mU/L), with a normal free thyroxine level (12.6 pmol/L); thus, the dose of levothyroxine was increased. Throughout her pregnancy, the dose of levothyroxine was adjusted multiple times in response to her thyroid stimulating hormone levels.

An ultrasound performed during week 16 of pregnancy showed live diamnionic, dichorionic fetuses. Labour was induced during week 37, and a vaginal delivery of healthy fraternal twin boys (2910 g and 2530 g) was performed. The patient did not receive levothyroxine therapy for 1 week after the delivery. Post partum, she resumed levothyroxine therapy (0.175 mg/d). On the basis of subsequent thyroid stimulating hormone levels, the levothyroxine dose was reduced to 0.125 mg/d, which resulted in normal thyroid stimulating hormone levels.

Maternal hypothyroidism has been reported to affect as many as 2.5% of pregnancies. Low concentrations of maternal thyroid hormones during early gestation delays neurodevelopment of the fetus and may lead to lower intelligence quotient scores compared with those of age-matched controls.[1] It has long been recognized that women with known primary hypothyroidism should have their thyroid stimulating hormone level checked at least once per trimester. The majority of pregnant women who have primary hypothyroidism require additional levothyroxine supplementation to achieve pre-conception thyroid stimulating hormone levels.[2,3] This dose increase may be required as early as the fifth week of gestation, which demonstrates the importance of early detection and supplementation during pregnancy. The increased levels of estrogen during pregnancy likely lead to increased levels of thyroxine-binding globulin, which may result in more bound, and less free, triiodothyronine and thyroxine. Thus, the patient is clinically hypothyroid.

Patients should be cautioned against simultaneous use of perinatal vitamins and levothyroxine.

It is quite common for primary hypothyroidism to be diagnosed among women in their child-bearing years, at a time when perinatal vitamin supplementation is often recommended. These supplements typically include, among other ingredients, folate, iron and selenium. However, patients should be cautioned against simultaneous use of perinatal vitamins and levothyroxine: a clinically significant reduction in levothyroxine efficacy can occur, probably caused by binding of levothyroxine with iron.[4] A clinical trial that included 14 patients with primary hypothyroidism reported a greater than 3 times increase in thyroid stimulating hormone levels (from 1.6 mU/L to 5.4 mU/L) after 12 weeks of simultaneous ferrous sulfate and levothyroxine therapy.[4] In vitro, if ferrous sulfate and levothyroxine are mixed, the result is a "poorly soluble purple complex"; this suggests that these drugs form an insoluble complex in the gastrointestinal tract, which thereby reduces the absorption of levothyroxine.

Our case is similar to others that have described the timing and magnitude of the increase in thyroid stimulating hormone levels and the changes in levothyroxine doses required during pregnancy.[2,3] In week 8 of pregnancy, our patient had a thyroid stimulating hormone level that was 8 times greater than the level during week 1, and the dose of levothyroxine was increased by 32% (last increase was during week 19). The literature suggests that levothyroxine requirements begin to change during the fifth week of pregnancy and stabilize by week 21. In addition, the magnitude of increase in thyroid stimulating hormone levels is 7–19 times the baseline level, with a corresponding 29%–48% increase in levothyroxine dose requirements. Despite the consistency of our case with other reports, the magnitude of the interaction between perinatal vitamins and levothyroxine therapy is uncertain.

When a patient with primary hypothyroidism is planning a pregnancy, it seems reasonable to proactively implement a plan to avoid exacerbation of

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the hypothyroidism. Early in the pregnancy, the fetus is completely dependent on maternal triiodothyronine and thyroxine. Further, the pharmacodynamic effect of levothyroxine does not manifest until the patient has been taking it for 4–6 weeks. As such, the practical solution offered by Alexander and colleagues seems reasonable:[2] upon confirmation of pregnancy, the current dose of levothyroxine should be increased by 29%, or the equivalent of 2 additional doses per week. They suggest that this dose be continued until thyroid function testing is performed. It is prudent that health care providers inform patients of the potential interaction between perinatal vitamins and levothyroxine to avoid any potential reduction in levothyroxine efficacy.

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Clinical Vistas

Upper-extremity deep-vein thrombosis in an elderly man

A 79-year-old man presented after a week of pleuritic-type chest pain, dyspnea and a swollen, painful left arm. His past medical history included benign prostatic hypertrophy, vitiligo, hearing loss and a combat wound to the chest experienced 58 years earlier, with a bullet left in situ adjacent to the aortic arch near the superior vena cava. His sole medication was sildenafil. He reported that for the past 2 months he had engaged in vigorous exercises for up to 30 minutes a day that involved the shoulder girdle (demonstrated with his right, healthy arm in Fig. 1) and that he had had no recent injuries to the left arm. The patient was right handed.

Physical examination revealed a general nonpitting edema of his left arm and forearm and marked superficial venous engorgement. Some reddening of the arm was noted, with moderate pain during movement in all directions. Doppler ultrasonography revealed a thrombus in the left subclavian, jugular, axillary and brachial veins. A CT of the chest did not reveal pulmonary embolism or a source of external pressure at the thoracic outlet.

The patient had no personal or family history suggestive of thrombophilia. However, he was found to be heterozygous for both factor V Leiden and methyltetrahydrofolate reductase C677T mutations. Results of tests for other causes of thrombophilia (including protein S, C, antithrombin III and prothrombin G20210A mutations) were negative. The result of an initial anticardiolipin IgG antibody test was low positive, but that of a repeated test was negative. Apart from vitiligo, no signs of autoimmune disorders were present.

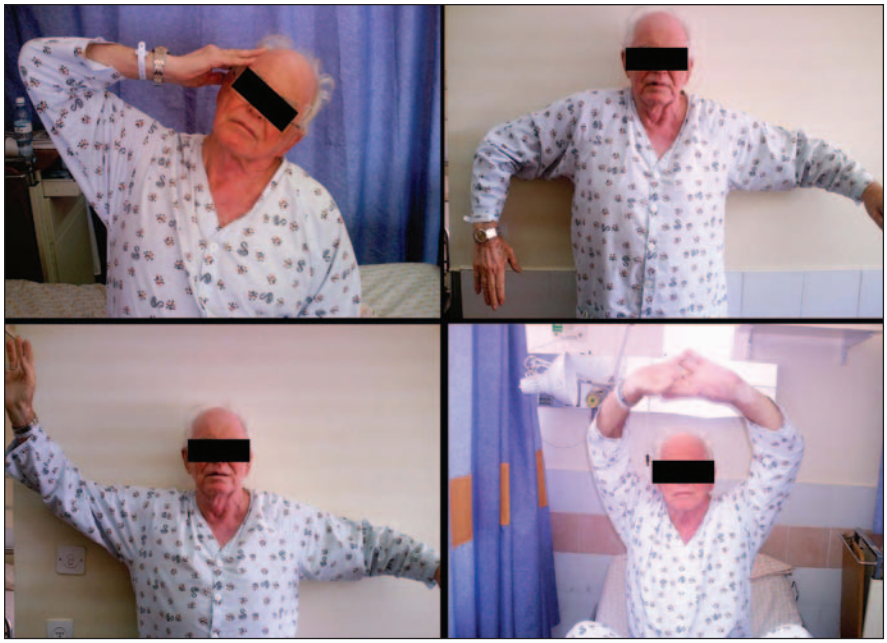

Fig. 1: Patient demonstrating exercises he had been performing that involved abduction movements of the arm, known to trigger effort-induced deep-vein thrombosis of the upper extremity. (The patient is using his right arm for the demonstration, to avoid potential detachment of thrombus fragments in his left arm.)

Enoxaprin and warfarin therapy were started, with rapid and complete resolution of symptoms. Follow-up during the next 6 months was unremarkable.

Deep-vein thrombosis of the upper extremity occurs infrequently, constituting only 10% of all deep-vein thromboses.[1] The majority of cases

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