**CLINICAL VIGNETTE**

# Thyroid and Bone Disease Before Pregnancy

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***Case Presentation***

A 47-year-old premenopausal woman with a history of infertilty and hypothyroidism presented to endocrinology with concerns about laboratory test results and "low bone mass". The patient was started on levothyroxine 75 mcg once daily 4 years prior to presentation when she was undergoing in-vitro fertilization. She continued levothyroxine therapy during pregnancy, but subsequently stopped the medication after normal postpartum thyroid function tests. She was now ready to undergo another in-vitro fertilization for second pregnancy and was concerned about a high-normal thyroid stimulating hormone (TSH) level of 4.09 mcIU/mL (0.3-4.7).

The patient also reported a history of low bone mineral density, requiring denosumab therapy, which was initiated in Mexico. She was told by her previous endocrinologist that she had osteopenia and had received 2 doses of denosumab injections, 8 months apart, with the most recent dose 5 months prior to presentation. She reported no history of fractures or height loss. She had no history of kidney stones, prior high dose or long-term steroid use, or heavy alcohol or tobacco use. She had no family history of osteoporosis or thyroid disease. She was lactose intolerant, but drank soy milk and consumed seafood and dark, leafy green vegetables. She took 3,000 IU vitamin D supplement and 2,500 mcg biotin supplement daily.

Her bone density scan done prior to her first denosumab injection showed T score of -1.9 and Z score of -1.3 at the lumbar spine (L3-L4), T score of -2 and Z score of -1.8 at the total hip, T score of -2.2 and Z score of -2 at the femoral neck. Her bone density scan done before the second denosumab injection at another facility showed T score of -1.2 and Z score of -0.6 at the lumbar spine, T score of -1.9 and Z score of -1.5 at the total hip, and T score of -1.9 and Z score of -1.4 at the femoral neck. The patient's outside records were carefully reviewed and she was reassured that she had normal bone mineral density based on prior Z-scores from her bone density scans. The patient was interested in undergoing in-vitro fertilization and was recommended to wait 6 months after denosumab injection before embryo transfer. The patient was also counseled on the risk of rebound vertebral fractures after stopping denosumab.

With regards to her thyroid function, the patient was asked to stop her biotin supplement and obtain repeat laboratory testing. After stopping 2,500 mcg daily biotin supplement for 5 days, thyroid peroxidase antibody level was <9 IU/mL (<=20), and thyroglobulin antibody level was <0.9 IU/mL (<4), TSH was 2.25 mcIU/mL and free T4 was 1.34 ng/dL (0.8-1.7). She was advised not to restart levothyroxine treatment.

***Discussion***

Biotin, vitamin B7, is a water-soluble vitamin which has become a popular nutrient supplement for presumptive health benefits, such as improvement in hair and nail health, neuropathy, and multiple sclerosis. However, taking high doses of biotin can interfere with laboratory testing, as immunoassays commonly use biotinylated antibodies or analogues. These have the advantage of detecting low analyte levels, but in the setting of excessive biotin concentration in the blood, results can be falsely low in sandwich immunoassay or falsely high in competitive immunoassay.[1] Ingestion of 10 mg per day of oral biotin for 1 week can cause clinically significant changes in hormone test results, including parathyroid hormone, TSH, and free thyroxine hormone levels. Falsely abnormal hormone levels returned to normal 2 days after stopping up to 300 mg/day of biotin. The American Thyroid Association recommends that patients stop biotin supplement for 2 days before getting thyroid function measured with blood testing.[2]

The reference range of TSH is population and trimester-specific, and in general, an upper reference limit of 4 mU/L, which is a reduction of 0.5 mU/L from the nonpregnant TSH upper reference limit.[3] There is mixed data regarding whether there is a significant difference in pregnancy outcomes, including preterm delivery, miscarriage, preeclampsia, and neurocognitive outcomes in the offspring of mothers treated with levothyroxine with TSH in the reference range compared to those with elevated TSH levels. Some studies have shown improved maternal and fetal outcomes in cases where the mother had elevated thyroid peroxidase antibody levels.[4,5] For those with normal (or negative) thyroid peroxidase antibody levels, levothyroxine therapy is only indicated for those with TSH above 4 mU/L. Stopping biotin and repeating the thyroid function tests resulted in a significantly lower TSH levels well below 4 mU/L in our patient with negative thyroid peroxidase antibody. The patient was recommended not to take levothyroxine which would not have any beneficial effects in future pregnancy but may have risk for harmful effects, such as thyrotoxicosis.

The second important topic in our case is the effect of osteoporosis drugs on pregnancy. The literature on antiresorptive treatment in pregnancy is scant, and the few available studies have been on women with pregnancy and lactation-associated osteoporosis (PLAO). PLAO is a rare condition, where women with presumable low bone mass pre-pregnancy experience increased bone turnover due to loss of minerals through the placenta and the breast.[6,7] As a result, women commonly experience back pain due to bone marrow edema or vertebral fractures. Women with fragility fractures due to PLAO are recommended antiresorptive therapy with bisphosphonates or denosumab, but due to the risk on the fetus and the newborn, therapy is recommended after the patient completes breast-feeding.

Bisphosphonates cross the placenta, and animal studies have shown decreased fetal bone growth, survival, and birth weight.[8] A review by Green and Pappas examined 65 cases of human mother-infant pairs with exposures to bisphosphonate prior to or during pregnancy. They reported decreased birth weights and gestational age in some but not all pairs, which was not statistically significant.[9] There were no reported cases of abnormal development of the offspring at follow up. There was one case of bilateral talipes equinovarus due to unclear etiology, and several cases of late-onset neonatal hypocalcemia presenting approximately at 1week after birth with tetany and seizures, associated with high phosphate intake. In cases of known bisphosphonate exposure in utero, the infant should be screened for hypocalcemia.

Denosumab is a monoclonal antibody that inhibits bone resorption by targeting RANK-ligand, an essential mediator of osteoclast formation and survival. The literature on the effects of denosumab in pregnancy and fetus is more limited than that of bisphosphonates. In a study assessing effects in monkeys, in-utero exposure to denosumab resulted in decreased long bone length, long bone fractures due to a reduction in cortical thickness and dental dysplasia secondary to growth impairment of the mandible, increased risk of stillbirth, and growth abnormalities.[10] The Food and Drug Administration has recommended the use of contraception for at least five months after the last dose of denosumab.[11] Our patient had low bone mineral density for age based on Z score less than or equal to -2. With isolated low Z score without fracture history of other risk factors, she did not have any indication to start pharmacologic therapy for low bone mineral density. She was inappropriately given two doses of denosumab prior to establishing care at UCLA. She was recommended to wait at least 6 months after her last dose of denosumab to undergo in-vitro fertilization, as there are potential harmful effects of denosumab on the skeletal health of the fetus.

## REFERENCES


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