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Subclinical Hypothyroidism and Gestational Hypertension: Causal or Coincidence?

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Thyroid hormone is critical in maintaining systemic homeostasis, as is demonstrated by the myriad of effects caused by thyroid hormone deficiency. Overt hypothyroidism can significantly disturb the cardiovascular system, resulting in alterations in left ventricular function, decreased cardiac output and increased systemic vascular resistance. The effects of subclinical hypothyroidism, defined as an elevated thyroid-stimulating hormone (TSH) level with normal serum thyroxine (T4) levels, on the cardiovascular system are less clear. While subclinical hypothyroidism has been linked to an increased risk of hypertension and cardiovascular mortality in some observational studies, other studies have found no difference in blood pressure between euthyroid subjects and subjects with subclinical hypothyroidism.(1, 2) The treatment in non-pregnant adults is also controversial and the most recent consensus guidelines from two major endocrinology societies recommend levothyroxine therapy for a TSH level of greater than 10, but that at levels lower than 10, treatment decisions should be made based on patient symptoms and other risk factors, such as the presence of anti-thyroperoxidase (TPO) antibodies.(3) There is no strong evidence to support treating patients with subclinical hypothyroidism and hypertension solely to improve blood pressure control.

Several alterations occur in thyroid hormone metabolism during pregnancy, making the diagnosis and management of hypothyroidism in pregnancy more complex. Serum thyroid binding globulin (TBG) levels increase in pregnancy and women with pre-existing hypothyroidism need escalating doses of levothyroxine due to the excess in TBG. Human chorionic gonadotropin, in addition, weakly stimulates TSH receptors, resulting in a transient physiologic increase in T4 and triiodothyronine (T3) concentrations, peaking at around 20 weeks gestation. The thresholds for abnormal TSH are, therefore, lower in pregnancy due to these physiologic changes.(3) Subclinical hypothyroidism is quite

common in pregnancy, occurring in up to 15% of pregnancies, while overt hypothyroidism is still rare (0.2%), likely due to the anovulation and diminished fertility seen with this condition.(4) Several case reports have described a preeclampsia-like syndrome in the setting of overt hypothyroidism, associated with very poor fetal outcomes.(5, 6) In a case series of pregnancy outcomes in women with both subclinical (n=12) and overt hypothyroidism (n=16), the authors found that preeclampsia occurred frequently in pregnancies complicated by overt hypothyroidism (n=7), but less commonly in women with subclinical hypothyroidism (n=2). A recent meta-analysis demonstrated that women with subclinical hypothyroidism were at increased risk for adverse pregnancy outcomes, including pregnancy loss and neonatal death, but they were not at an increased risk for gestational hypertension or preeclampsia. (7)

Drs. Ramtahal and Dhanoo, in this issue of the *Journal of the American Society of Hypertension*, describe an interesting case of a 25 year old primagravida who presented at 22 weeks gestation with significant elevations in blood pressure that required anti-hypertensive therapy. Her TSH level was 6 mIU/ml and the free T4 level was normal at 2.15 ng/dl, consistent with subclinical hypothyroidism. Notably, she did have a positive anti-TPO antibody and was started on levothyroxine therapy. Her blood pressure improved after the initiation of levothyroxine therapy, and remained normal until the end of pregnancy, off of medications. The authors conclude that the treatment with levothyroxine resulted in normalized blood pressure, and that this highlights the need to include subclinical hypothyroidism in the differential diagnosis of hypertension in pregnancy.

This case does bring up several interesting questions about the diagnosis of subclinical hypothyroidism in pregnancy and how levothyroxine therapy may interact with the physiologic changes of pregnancy. Universal screening for subclinical hypothyroidism and/or anti-TPO antibodies in pregnancy is not currently recommended, as it has not been shown to reduce adverse pregnancy outcomes.(8) The current case-finding strategy advocates screening women for thyroid dysfunction who are at 'high-risk' for developing overt hypothyroidism, such as women with a goiter, a strong family history of thyroid disease, morbid obesity, or other autoimmune conditions, such as Type 1 diabetes, along with several other conditions. The current level of evidence does not suggest that hypertension represents a 'high-risk' state that should trigger screening for thyroid disease in pregnancy, although subclinical hypothyroidism has been linked to hypertension in observational studies. The patient in this case report, however, did have a goiter, which should trigger testing for thyroid dysfunction, and had both subclinical hypothyroidism and anti-TPO antibodies, which would indicate the need for levothyroxine therapy. This case, in some respects, represents a success of the current case-finding strategy for thyroid dysfunction in pregnancy, with the gestational hypertension being a side issue. In the limited intervention trials of levothyroxine therapy in women with subclinical hypothyroidism, there has not been a clear benefit in reducing the risk of adverse pregnancy outcomes overall, nor of hypertensive disorders of pregnancy in particular, arguing against the routine treatment of subclinical hypothyroidism to prevent the development of hypertension.(9)(10)

Although screening for thyroid dysfunction in all women with hypertension in pregnancy may not be the current approach, it is still interesting to consider the physiology of this case

in particular, in which the patient's blood pressure improved after levothyroxine therapy. Levothyroxine has been shown to reduce markers of inflammation and improve endothelial function in subclinical hypothyroidism in both human and animal studies, so it is plausible that the levothyroxine therapy helped improve her blood pressure.(11, 12) An alternative explanation for her clinical improvement relates to the fact that blood pressure tends to decrease in mid-pregnancy. This patient's blood pressure improved by 24 weeks gestation, which may have been when her blood pressure would have naturally reached its nadir. Levothyroxine therapy, in addition, equilibrates very slowly and takes 4-6 weeks to reach steady state, suggesting that her improvement in 2 weeks was less likely to be due to the levothyroxine therapy and was more likely to be due to the natural course of hypertension in pregnancy. That being said, her blood pressure did not increase again in the third trimester, which could be attributed to the levothyroxine therapy, as the authors suggest. Despite the lack of clear evidence that treatment of subclinical hypothyroidism prevents the development of hypertensive pregnancy disorders, studies looking more closely at the hemodynamic effects of levothyroxine therapy in subclinical hypothyroidism may provide guidance to providers as to what effects they can expect, if any, on blood pressure reduction, and whether there is value in considering gestational hypertension a 'high-risk' condition, prompting an evaluation for thyroid dysfunction. In the high stakes state of pregnancy, where maternal and fetal health are paramount, any intervention that can improve pregnancy outcomes should be given full and thorough consideration.

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