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A confusing situation in the clinic practice: Isolated maternal hypothyroxinemia

Zekeriya Keskin[1]

[1] Şarkışla State Hospital, Clinic of Internal Medicine, Sivas, Turkiye

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Abstract

Isolated maternal hypothyroxinemia (IMH) is a common problem in the clinic practice. There is a normal maternal thyroid stimulating hormone (TSH) level with a low maternal free thyroxine (FT4) level. The aim of this review is to explain IMH in the light of current literature and to contribute to clinicians in the management of IMH. Iodine deficiency is the most important factor in etiology. The effects of IMH on the pregnant women and the fetus are not clear. However, it is a serious concern among clinicians, especially considering the importance of the effect of thyroid hormones on fetal brain development. As for the treatment of IMH, the number of studies conducted is not sufficient and there is no consensus and evidence on levothyroxine treatment. However, there is a consensus on iodine supplementation and it is recommended to take 250 mg of iodine daily. As a result, IMH is a problem that should be taken seriously during pregnancy and care should be taken regarding its diagnosis and treatment. Additionally, more research is needed on the effects and treatment of IMH on pregnant women and fetal health.

Key Words: Isolated maternal hypothyroxinemia, Thyroid hormone, Pregnant, Fetus, Iodine deficiency

Klinik pratikte kafa karıştıran bir durum: İzole maternal hipotiroksinemi

Özet

İzole maternal hipotiroksinemi (İMH) klinik pratikte sık görülen bir sorundur. Düşük anne serbest tiroksin (FT4) düzeyi ile birlikte normal bir anne tiroid stimulan hormon (TSH) düzeyi mevcuttur. Bu derlemenin amacı İMH'nin güncel literatür eşliğinde gözden geçirilmesi ve İMH'nın yönetiminde klinisyenlere katkıda bulunmaktır. Etyolojide en önemli etken olarak iyot eksikliği bulunmaktadır. İMH'nın gebe ve fetüs üzerindeki etkileri net değildir. Ancak tiroid hormonlarının özellikle fetal beyin gelişimi üzerindeki etkisinin önemi düşünüldüğünde klinisyenler arasında ciddi bir endişe kaynağıdır. İMH tedavisinde ise yapılan çalışma sayısı yeterli olmayıp levotiroksin tedavisi konusunda fikir birliği ve kanıt yoktur. Ancak iyot takviyesi konusunda görüş birliği vardır ve günlük 250 mg iyot alınması önerilir. Sonuçta İMH gebelikte ciddiye alınması gereken, tanı ve tedavisi konusunda dikkatli olunması gereken bir problemdir. Ayrıca İMH'nın gebe ve fetüs sağlığı üzerine etkileri ve tedavisi konusunda daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: İzole maternal hipotiroksinemi, Tiroid hormonu, Gebe, Fetüs, İyot eksikliği

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Address for correspondence/reprints:

Zekeriya Keskin

Telephone number: +90 (536) 686 69 14

E-mail: zekeriyakeskinsh@gmail.com

INTRODUCTION

Thyroid hormones are very important for the healthy maintenance of pregnancy and fetal development. Placental and fetal development are related to maternal thyroid hormones. Untreated maternal hypothyroidism poses a high risk for pregnancy and the baby (1). In the first trimester, thyroid hormones are supplied from the mother to the fetus via the placenta. Although thyroid hormone is secreted from the fetus in the second trimester, most of the hormones are provided by the mother. Therefore, hypothyroidism, especially in the first trimester, seriously affects the growth of the fetus. Hypothyroidism during pregnancy; includes clinical hypothyroidism, isolated maternal hypothyroxinemia (IMH) and subclinical hypothyroidism (2). IMH is defined as a normal maternal thyroid-stimulating hormone (TSH) level with a maternal free thyroxine (FT4) level below the 5th or 10th percentile of the reference range (3).

The prevalence of IMH has been tried to be determined by various studies, and it varies between 1.3% and 23.9% due to reasons such as different gestational ages, iodine deficiency status and ethnic differences. It has been detected more frequently in countries with iodine deficiency and in countries where specific reference ranges for pregnant women are not applied (4).

The aim of this review is to examine IMH which is commonly seen in the clinic practice and where there is often confusion in its management, in the light of current literature and to contribute to clinicians in the management of IMH.

Thyroid Gland Physiology During Pregnancy

During pregnancy, the demand for the mother's thyroid hormones increases significantly. Human chorionic gonadotropin (HCG), secreted by the placenta, increases thyroid hormone production by directly stimulating the TSH receptor. Thus, a decrease in TSH and a small, temporary increase in FT4 occurs in the first trimester. Since thyroid binding globulin (TBG) synthesis increases 2.5 times under the influence of estrogen, more thyroid hormone production is needed to maintain adequate FT4 levels (5). Additionally, there is increased renal clearance of iodine, an important element of thyroid hormones. It increases thyroid gland production by approximately 50% to compensate for the increased thyroid hormone need during pregnancy. In order to achieve this increase, the maternal thyroid gland must have sufficient iodine support and also there must be no significant underlying autoimmunity problem (6).

Etiology of IMH

The etiology of IMH is not fully determined and understood. Potential risk factors for IMH include iodine deficiency, increased affinity of TBG to thyroxine, increased placental 5-deiodinase type 3 activity, and placental angiogenic factors (7). Thyroid autoimmunity has not been identified as a risk factor (4). Additionally, many studies have

determined that obesity creates a predisposition to IMH and that negative metabolic parameters like fasting plasma glucose, triglycerides and plasma glucose and insulin resistance (HOMA-IR), are associated with IMH (4,8,9).

Effects of IMH on Pregnant and Baby

The effects of IMH during early pregnancy are not clear. However, there are concerns about its negative effects on both mother and baby. While overt hypothyroidism is associated with obstetric complications such as fetal losses, preeclampsia, spontaneous miscarriages, and gestational hypertension, there is no consensus on the perinatal effects of IMH (10). In two studies conducted with large study groups, no relationship was found between IMH and adverse perinatal events (11,12). In a study conducted with 2864 pregnant women, pregnant women in the 1st trimester and 2nd trimester were examined separately, and no association of IMH with pregnancy outcomes was found (13).

There are studies with findings contrary to these studies. In a study conducted with more than 10,000 patients, IMH in the first trimester was associated with premature birth and macrosomia, while IMH in the second trimester was associated with gestational diabetes mellitus (14). In a study conducted in China, it was observed that IMH may increase maternal hypertensive events (15). There are also studies showing that IMH causes preterm birth (16,17).

When looking at its effects on the baby, there are studies showing that IMH causes macrosomia (14,15,18). On the contrary, IMH has also been shown to cause low birth weight. Additionally, in the same study, IMH was associated with fetal distress and musculoskeletal anomalies (19).

Considering the importance of the effects of thyroid hormones on fetal brain development, especially in the first trimester, it is thought that IMH may have a negative effect on fetal brain development in this period (20). In two studies, it was stated that there was a decrease in the psychomotor test scores of children of mothers diagnosed with IMH, especially in the first trimester (21,22). Contrary to these views, there are studies showing that IMH does not affect the neurodevelopment of babies (19,23).

Treatment

There is no consensus and evidence on the treatment of IMH, just like there is no consensus on the clinical effects of IMH. As a general precaution, it is recommended to take daily 150 mg og iodine for those who are not pregnant and planning pregnancy, and 250 mg of iodine for the pregnant and breastfeeding women (24). Pregnant women with hypothyroidism are recommended to measure TSH levels every 4 weeks in the first half of pregnancy and at least once between the 26th and 32nd weeks (25). There is no definitive treatment method in the treatment of IMH, and iodine supplementation is generally

recommended. There is not enough evidence for the use of levothyroxine and there are conflicting results (26).

While the European Thyroid Association (ETA) states that IMH treatment can be considered in the first trimester, the American Thyroid Association (ATA) does not recommend any specific treatment (27). Only 2 randomized controlled trials have investigated the effects of levothyroxine treatment on IMH. In one of these studies, 526 pregnant women with IMH were included in the study. Control groups, treated with levothyroxine and not treated with levothyroxine groups were compared. Children born later were screened with comprehensive tests until the age of 5, and no significant neurodevelopmental difference was observed between the two groups (28). The other study was conducted with 411 pregnant women with IMH and it was determined that levothyroxine treatment did not create a significant difference in cognitive functions in children (29). However, in these two studies, the fact that the treatment was given in late gestational weeks was considered a limitation. Contrary to these studies, Auso et al. was observed in an animal model study evaluating IMH, that early levothyroxine treatment affected the neurodevelopment of offspring born to hypothyroxinemic mothers (30). A recent review focused on the negative effects of IMH on children's cognitive and psychosocial development, and recommended iodine supplementation as a precaution (31). Similarly, two different reviews have stated that IMH negatively affects pregnancy and newborn health. In addition, levothyroxine treatment was not thought to be beneficial. (32,33). For this reason, more studies are needed on the treatment of IMH with levothyroxine.

In a study investigating the effect of iodine supplementation on IMH, iodine supplements were given to pregnant women during the late pregnancy period, between the 4th and 6th and between the 10th-12th weeks. In this study, no neurodevelopmental delay was observed in the children of pregnant women who received iodine supplementation between the 4th and 6th weeks compared to the other two groups (34). Although levothyroxine treatment in the treatment of IMH is controversial, there is a consensus on iodine supplementation (26).

CONCLUSION

IMH is a frequently encountered problem in the clinic practice. Iodine deficiency is generally defined as the biggest risk factor. There is no consensus on its consequences and treatment for pregnant and baby health. This creates confusion among clinicians. Considering the effects of thyroid hormones on the fetal brain, serious concerns arise. However, the effects of IMH on pregnancy and the fetus have not been definitively demonstrated. The number of studies on treatment is limited and the effectiveness of levothyroxine treatment has not been proven, however, iodine

supplementation is recommended. As a result, IMH is a problem that should be taken into account during pregnancy and care should be taken regarding its diagnosis and treatment. Additionally, more research is needed on the effects and treatment of IMH on pregnant and fetal health.

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REFERENCES

1. Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol. 2017;13(10):610-622.
2. Furnica RM, Lazarus JH, Gruson D, Daumerie C. Update on a new controversy in endocrinology: isolated maternal hypothyroxinemia. J Endocrinol Invest. 2015;38(2):117-123.
3. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21(10):1081-125.
4. Dosiou C, Medici M. Management of Endocrine Disease: Isolated maternal hypothyroxinemia during pregnancy: knowns and unknowns. Eur J Endocrinol. 2017;176(1):R21-R38.
5. Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med. 1994;331(16):1072-1078.
6. Glinoer D. Pregnancy and iodine. Thyroid. 2001;11(5):471-481.
7. Furnica RM, Gruson D, Lazarus JH, Maiter D, Bernard P, Daumerie C. First trimester isolated maternal hypothyroxinaemia: adverse maternal metabolic profile and impact on the obstetrical outcome. Clin Endocrinol (Oxf). 2017;86(4):576-583.
8. Gowachirapant S, Melse-Boonstra A, Winichagoon P, Zimmermann MB. Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient

pregnant women. Matern Child Nutr. 2014;10(1):61-71.

9. Knight BA, Shields BM, Hattersley AT, Vaidya B. Maternal hypothyroxinaemia in pregnancy is associated with obesity and adverse maternal metabolic parameters. Eur J Endocrinol. 2016;174(1):51-57.
10. Wang S, Teng WP, Li JX, Wang WW, Shan ZY. Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. J Endocrinol Invest. 2012;35(3):322-325.
11. Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. Obstet Gynecol. 2007;109(5):1129-1135.
12. Hamm MP, Cherry NM, Martin JW, Bamforth F, Burstyn I. The impact of isolated maternal hypothyroxinemia on perinatal morbidity. J Obstet Gynaecol Can. 2009;31(11):1015-1021.
13. Chen L, Yang H, Ye E, Lin Z, Peng M, Lin H, et al. Insignificant Effect of Isolated Hypothyroxinemia on Pregnancy Outcomes During the First and Second Trimester of Pregnancy. Front Endocrinol (Lausanne). 2020 ;16(11):528146.
14. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, et al. Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol. 2008;112(1):85-92.
15. Su X, Zhao Y, Cao Z, Yang Y, Duan T, Hua J. Association between isolated hypothyroxinaemia in early pregnancy and perinatal outcomes. Endocr Connect. 2019;8(4):435-441.
16. Yang X, Yu Y, Zhang C, Zhang Y, Chen Z, Dubois L, et al. The Association Between Isolated Maternal Hypothyroxinemia in Early Pregnancy and Preterm Birth. Thyroid. 2020;30(12):1724-1731.
17. Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SM, et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. J Clin Endocrinol Metab. 2013;98(11):4382-90.
18. Gong X, Liu A, Li Y, Sun H, Li Y, Li C, et al. The impact of isolated maternal hypothyroxinemia during the first and second trimester of gestation on pregnancy outcomes: an intervention and prospective cohort study in China. J Endocrinol Invest. 2019;42(5):599-607.
19. Su PY, Huang K, Hao JH, Xu YQ, Yan SQ, Li T, et al. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in

China. J Clin Endocrinol Metab. 2011;96(10):3234-41.

20. Lavado-Autric R, Ausó E, García-Velasco JV, Arufe Mdel C, Escobar del Rey F, Berbel P, et al. Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny. J Clin Invest. 2003;111(7):1073-82.
21. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. Clin Endocrinol (Oxf). 2010;72(6):825-9.
22. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf). 2003;59(3):282-288.
23. Craig WY, Allan WC, Kloza EM, Pulkkinen AJ, Waisbren S, Spratt DI, et al. Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. J Clin Endocrinol Metab. 2012;97(1):E22-8.
24. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, 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.
25. Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. J Clin Endocrinol Metab. 2010;95(7):3234-3241.
26. López-Muñoz E, Mateos-Sánchez L, Mejía-Terrazas GE, Bedwell-Cordero SE. Hypothyroidism and isolated hypothyroxinemia in pregnancy, from physiology to the clinic. Taiwan J Obstet Gynecol. 2019;58(6):757-763.
27. Taylor PN, Muller I, Nana M, Velasco I, Lazarus JH. Indications for treatment of subclinical hypothyroidism and isolated hypothyroxinaemia in pregnancy. Best Pract Res Clin Endocrinol Metab. 2020;34(4):101436.
28. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. N Engl J Med. 2017;376(9):815-825.
29. Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med. 2012;366(6):493-501.
30. Ausó E, Lavado-Autric R, Cuevas E, Del Rey FE, Morreale De Escobar G, Berbel P. A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration. Endocrinology. 2004;145(9):4037-4047.

31. Grossklaus R, Liesenkötter KP, Doubek K, Völzke H, Gaertner R. Iodine Deficiency, Maternal Hypothyroxinemia and Endocrine Disrupters Affecting Fetal Brain Development: A Scoping Review. Nutrients. 2023;15(10):2249.
32. Han Y, Gao X, Wang X, Zhang C, Gong B, Peng B, et al. A Systematic Review and Meta-Analysis Examining the Risk of Adverse Pregnancy and Neonatal Outcomes in Women with Isolated Hypothyroxinemia in Pregnancy. Thyroid. 2023;33(5):603-614.
33. Zhuo L, Wang Z, Yang Y, Liu Z, Wang S, Song Y. Obstetric and offspring outcomes in isolated maternal hypothyroxinaemia: a systematic review and meta-analysis. J Endocrinol Invest. 2023;46(6):1087-1101.
34. Berbel P, Mestre JL, Santamaría A, Palazón I, Franco A, Graells M, et al. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. Thyroid. 2009;19(5):511-9.