



MATERNAL HYPOTHYROIDISM AND GESTATIONAL OBSTACLES

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AUTHOR'S CONTRIBUTION

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Commentary

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The developing embryo, fetus and neonates are reliant on the maternal quantity of thyroid hormones (THs) [1-20]. On the other hand, gestational hypothyroidism is the utmost common endocrine dysfunctions [21-23]. Also, thyroid deficiency is very common in women [24,25]. The elevation in the level of thyroid-stimulating hormone (TSH) during the first trimester of pregnancy can increase the frequency of miscarriage and perinatal loss [26]. In iodine-sufficient areas, the elevation in the concentration of thyroglobulin antibody (Tg-Ab+) or thyroid peroxidase antibody (TPO-Ab+) in pregnant women can cause chronic autoimmune thyroiditis and then gestational hypothyroidism [27,28], and vary the fetal thyroid activities [25,29]. Another cause of gestational hypothyroidism is the disruption in the activity of thyroid peroxidase (TPO), heme-containing enzyme (essential for TH synthesis) causing iron deficiency [30]. Thyroid antibodies during gestation with the euthyroid state (normal thyroid activity) can also cause miscarriage and premature delivery [31-33]. The subclinical hypothyroidism, with normal free thyroxine (fT4) level and high TSH level, is the most common during the pregnancy [34,35]. Subclinical hypothyroidism and overt hypothyroidism can

increase the risk of pregnancy loss and fetal death [32,36,37] and cause gestational hypertension, cardiac dysfunction, placental abruption, anemia, pre-eclampsia, fetal distress, congenital malformations, low birth weight, pre-term delivery, and postpartum hemorrhage [31,36,38]. In general, hypothyroidism was associated with morbid obesity and post-term delivery [39].

More specifically, the reduction in the THs during the early fetal period causes irreversible brain damage [40,41] and increases the risk of non-verbal cognitive disorders [42-44]. A severe deficiency of gestational THs causes neonatal sensory, motor, and cognitive dysfunctions, and produces long-lasting variations in neonatal brain structure [45,46]. As well, Thompson et al. [47] reported that subclinical hypothyroidism and maternal hypothyroxinaemia might cause neonatal intellectual disability. Fetal hypothyroidism can be attributed to disorders in synthesis, metabolism, and transport of maternal THs [48], and iodine deficiency [49,50]. In general, the maternal stress during the gestation can modulate the maternal thyroid function [51].

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In conclusion, the long-term effects of maternal hypothyroidism during the gestation may represent a risk factor for the fetal and neonatal development especially regarding the cardiac and neurodevelopmental disorders. Thus, the ideal regulation of maternal thyroid function during or before pregnancy is significant not only for the health of women but also for the health of fetus and neonates. Further research is required to determine the developmental, biochemical, and behavioral dysfunctions produced by gestational hypothyroidism in fetus and newborn.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Candelotti E, De Vito P, Ahmed RG, Luly P, Davis PJ, Pedersen JZ, Lin H-Y, Incerpi I. Thyroid hormones crosstalk with growth factors: Old facts and new hypotheses. *Immun., Endoc. & Metab. Agents in Med. Chem.* 2015;15:71-85.
2. De Vito P, Candelotti E, Ahmed RG, Luly P, Davis PJ, Incerpi S, Pedersen JZ. Role of thyroid hormones in insulin resistance and diabetes. *Immun., Endoc. & Metab. Agents in Med. Chem.* 2015;15:86-93.
3. El-bakry AM, El-Ghareeb AW, Ahmed RG. Comparative study of the effects of experimentally-induced hypothyroidism and hyperthyroidism in some brain regions in albino rats. *Int. J. Dev. Neurosci.* 2010;28:371-389.
4. Incerpi S, Hsieh M-T, Lin H-Y, Cheng G-Y, De Vito P, Fiore AM, Ahmed RG, Salvia R, Candelotti E, Leone S, Luly P, Pedersen JZ, Davis FB, Davis PJ. Thyroid hormone inhibition in L6 myoblasts of IGF-I-mediated glucose uptake and proliferation: new roles for integrin $\alpha\beta 3$. *Am. J. Physiol. Cell Physiol.* 2014;307:C150-C161.
5. Van Herck SLJ, Geysens S, Bald E, Chwatko G, Delezie E, Dianati E, Ahmed RG, Darras VM. Maternal transfer of methimazole and effects on thyroid hormone availability in embryonic tissues. *Endocrinol.* 2013;218:105-115.
6. Ahmed OM, Abd El-Tawab SM, Ahmed RG. Effects of experimentally induced maternal hypothyroidism and hyperthyroidism on the development of rat offspring: I- The development of the thyroid hormones-neurotransmitters and adenosinergic system interactions. *Int. J. Dev. Neurosci.* 2010; 28:437-454.
7. Ahmed OM, Ahmed RG, El-Gareib AW, El-Bakry AM, Abd El-Tawab SM. Effects of experimentally induced maternal hypothyroidism and hyperthyroidism on the development of rat offspring: II-The developmental pattern of neurons in relation to oxidative stress and antioxidant defense system. *Int. J. Dev. Neurosci.* 2012;30:517-537.
8. Ahmed OM, El-Gareib AW, El-bakry AM, Abd El-Tawab SM, Ahmed RG. Thyroid hormones states and brain development interactions. *Int. J. Dev. Neurosci.* 2008;26(2):147-209. Review.
9. Ahmed RG. Perinatal 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin exposure alters developmental neuroendocrine system. *Food Chem. Toxicology.* 2011;49:1276-1284.
10. Ahmed RG. Early weaning PCB 95 exposure alters the neonatal endocrine system: Thyroid adipokine dysfunction. *J. Endocrinol.* 2013;219(3):205-215.
11. Ahmed RG. Hypothyroidism and brain developmental players. *Thyroid Research J.* 2015;8(2):1-12.
12. Ahmed RG. Gestational dexamethasone alters fetal neuroendocrine axis. *Toxicology Letters.* 2016;258:46-54.
13. Ahmed RG. Maternal bisphenol A alters fetal endocrine system: Thyroid adipokine dysfunction. *Food Chem. Toxicology.* 2016; 95:168-174.
14. Ahmed RG. Perinatal hypothyroidism and cytoskeleton dysfunction. *Endocrinol Metab Syndr.* 2017;6:271. DOI: 10.4172/2161-1017.1000271
15. Ahmed RG. Is there a connection between maternal hypothyroidism and developing autism spectrum disorders? *ARC Journal of Neuroscience.* 2018;3(1):5-8. DOI:<http://dx.doi.org/10.20431/2456-057X.0301002>
16. Ahmed RG, Abdel-Latif M, Ahmed F. Protective effects of GM-CSF in experimental neonatal hypothyroidism. *International Immunopharmacology.* 2015;29:538-543.
17. Ahmed RG, Abdel-Latif M, Mahdi E, El-Nesr K. Immune stimulation improves endocrine and neural fetal outcomes in a model of maternofetal thyrotoxicosis. *Int. Immunopharmacol.* 2015;29:714-721.
18. Ahmed RG, El-Gareib AW. Maternal carbamazepine alters fetal neuroendocrine-cytokines axis. *Toxicology.* 2017;382:59-66.

19. Ahmed RG, El-Gareib AW, Shaker HM. Gestational 3,3',4,4',5-pentachlorobiphenyl (PCB 126) exposure disrupts fetoplacental unit: Fetal thyroid-cytokines dysfunction. *Life Sciences*. 2018;192:213–220.
20. Ahmed RG, Incerpi S. Gestational doxorubicin alters fetal thyroid–brain axis. *Int. J. Devl. Neuroscience*. 2013;31:96–104.
21. Santos SO, Loureiro SM, Alves IG. Experimental gestational hypothyroidism evokes hypertension in adult offspring rats. *Auton. Neurosci*. 2012;170:36–41.
22. Ahmed RG. Maternal hypothyroidism and neonatal depression: Current perspective. *International Journal of Research Studies in Zoology*. 2018;4(1):6-10.
DOI: <http://dx.doi.org/10.20431/2454-941X.0401002>
23. Jeddi S, Zaman J, Ghasemi A. Effect of fetal hypothyroidism on tolerance to ischemia-reperfusion injury in aged male rats: Role of nitric oxide. *Nitric Oxide*. 2016;55–56:82–90.
24. Triggiani V, Iacoviello M, Monzani F. Incidence and prevalence of hypothyroidism in patients affected by chronic heart failure: Role of amiodarone. *Endocr Metab Immune Disord Drug Targets*. 2012;12:86–94.
25. Ghanbari M, Ghasemi A. Maternal hypothyroidism: An overview of current experimental models. *Life Sciences*. 2017;187:1–8.
26. Hernández M, López C, Soldevila B, Cecenarro L, Martínez-Barahona M, Palomera E, Rius F. Impact of TSH during the first trimester of pregnancy on obstetric and fetal complications: Usefulness of 2.5 mIU/L cut-off value. *Clin Endocrinol (Oxf)*; 2018.
DOI: 10.1111/cen.13575
27. Yim CH. Update on the management of thyroid disease during pregnancy. *Endocrinol. Metab*. 2016;31:386–391.
28. Alexander EK, Pearce EN, Brent GA. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27:315–389.
29. Seror J, Amand G, Guibourdenche J, Ceccaldi PF, Luton D. Anti-TPO antibodies diffusion through the placental barrier during pregnancy. *PLoS One*. 2014;9:e84647.
30. Mei Z, Cogswell ME, Looker AC. Assessment of iron status in US pregnant women from the National Health and nutrition examination survey (NHANES), 1999–2006. *Am. J. Clin. Nutr*. 2011;93:1312–1320.
31. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *Journal of Clinical Endocrinology and Metabolism*. 2006; 91(7):2587–2591.
32. Castillo Lara M, Vilar Sánchez Á, Cañavate Solano C, Soto Pazos E, Iglesias Álvarez M, González Macías C, Ayala Ortega C. Hypothyroidism screening during first trimester of pregnancy. *BMC Pregnancy Childbirth*. 2017;17(1):438.
DOI: 10.1186/s12884-017-1624-x
33. De Leo S, Pearce EN. Autoimmune thyroid disease during pregnancy. *Lancet Diabetes Endocrinol*; 2017 Dec 12.
pii: S2213-8587(17)30402-3.
DOI: 10.1016/S2213-8587(17)30402-3
34. Vaidya B, Anthony S, Bilous M. Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? *Journal of Clinical Endocrinology and Metabolism*. 2007;92:203–207.
35. Negro R, Mestman JH. Thyroid disease in pregnancy. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2011;25:927–943.
36. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. *Journal of Clinical Endocrinology and Metabolism*. 2010;95(9):E44–E48.
37. Johns LE, Ferguson KK, Cantonwine DE, Mukherjee B, Meeker JD, McElrath TF. Subclinical changes in maternal thyroid function parameters in pregnancy and fetal growth. *J Clin Endocrinol Metab*; 2017.
DOI: 10.1210/jc.2017-01698
38. Krassas GE, Poppe K, Glinioer D. Thyroid function and human reproductive health. *Endocrine Reviews*. 2010;31:702–755.
39. Ezzeddine D, Ezzeddine D, Hamadi C, Abbas HA, Nassar A, Abiad M, Ghazeeri G. Prevalence and correlation of hypothyroidism with pregnancy outcomes among lebanese women. *J Endocr Soc*. 2017;1(5):415-422.
DOI: 10.1210/js.2017-00014
40. Henrichs J, Bongers-Schokking JJ, Schenk JJ. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *Journal of Clinical Endocrinology and Metabolism*. 2010;95:4227–4234.
41. Li Y, Shan Z, Teng W. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their

- children at 25–30 months. *Clinical Endocrinology (Oxford)*. 2010;72:825–829.
42. Berbel P, Mestre JL, Santamaría A. 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;19:511–519.
43. Velasco I, Carreira M, Santiago P. Effect of iodine prophylaxis during pregnancy on neurocognitive development of children during the first two years of life. *Journal of Clinical Endocrinology and Metabolism*. 2009;94:3234–3241.
44. Glinoe D, Spencer CA. Serum TSH determinations in pregnancy: how, when and why? *Nature Reviews Endocrinology*. 2010;6:526–529.
45. Pakkila F, Mannisto T, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Vaarasmaki M, Jarvelin MR, Moilanen I, Suvanto E. The impact of gestational thyroid hormone concentrations on ADHD symptoms of the child. *J. Clin. Endocrinol. Metab*. 2014;99:E1–8.
46. Willoughby KA, McAndrews MP, Rovet JF. Effects of maternal hypothyroidism on offspring hippocampus and memory. *Thyroid* 2014;24:576–584.
47. Thompson W, Russell G, Baragwanath G, Matthews J, Vaidya B, Thompson-Coon J. Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis. *Clin Endocrinol (Oxf)*; 2018. DOI: 10.1111/cen.13550.
48. Grasberger H, Refetoff S. Genetic causes of congenital hypothyroidism due to dysmorphogenesis. *Curr. Opin. Pediatr*. 2011;23:421–428.
49. Hashemipour M, Hovsepian S, Kelishadi R. Permanent and transient congenital hypothyroidism in Isfahan-Iran. *J. Med. Screen*. 2009;16:11–16.
50. Kapil U. Health consequences of iodine deficiency. *Sultan Qaboos Univ. Med. J*. 2007;7:267–272.
51. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. *Neuroscience*. 2017;342:68–100.