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# Maternal Hypothyroidism-Milk Ejections: What is the Link?

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## HYPOTHESIS

The normal activity for the maternal hypothalamic-pituitary-thyroid axis (HPTA) isdynamic for the developing fetuses and neonates(Ahmed, 2011, 2012a,b, 2013, 2014, 2015a-c, 2016a-d, 2017a-v & 2018a-j; Ahmed et al., 2013a,b, 2014, 2015a,b &2018a,b; Ahmed and Incerpi, 2013;Van Hercket al., 2013; Ahmed and El-Gareib, 2014,Incerpi et al., 2014; Candelotti et al., 2015; De Vito et al., 2015; El-Ghareeb et al., 2016; Ahmed and El-Gareib, 2017), especially the function and activity of mammary gland (Varas et al. 2001 & 2002; Hapon et al. 2003 & 2007a,b; Ahmed et al., 2008; Campo Verde Arbocco et al. 2015 & 2016; Pennacchio et al., 2017). Thyroid hormones (THs) stimulate the signal transducer activator of transcription 5 (STAT5) proteins and ovarian hormone receptors-induced the differentiation of the mammary epithelial cell by their nuclear receptors (TRs) (Favre-Young et al., 2000; Zhao et al., 2005; Bagamasbad and Denver, 2011; Campo Verde Arbocco et al., 2015, 2016& 2017). More interestingly, THs, prolactin (PRL), glucocorticoids and ovarian hormones (estrogen and progesterone) can regulate the involution switch process in the mammary epithelial cell by activating several signaling pathways such as mitogen-activated protein kinase (MAPK) and JAK/STAT (Li et al., 1997; Lemay et al., 2007;Watson, 2009; Whyte et al.,2009; Bertucci et al., 2010; Bagamasbad and Denver, 2011; Zhao et al., 2012; Campo Verde Arbocco et al., 2017). Indeed, there is reduction in the expression of deiodinase type I [converts tetraiodothyronine (T4) to triiodothyronine (T3)] in the mammary gland to avoid the deleterious influence of any excessive in THs (Anguiano et al., 2004).

On the other hand, in the previous studies, several authors demonstrated the association between the thyroid dysfunction (hypothyroidism) and hindering the lactation mechanism (Hapon et al. 2003 & 2007a,b; Campo Verde Arbocco et al. 2015, 2016& 2017). This defect can be illustrated as the following (Hapon et al. 2003 & 2007b): (1) reduced the quality of milk nutrition quality; (2) dysfunction in the milk ejection due to the reduction in the response of oxytocin (OXT); (3) disorders in the accumulation of milk in the alveoli; (4) decreased the growth rate of the litter/pups and increased the litter mortality; (5) milk stasis and mammary involution (Rhoads and Grudzien-Nogalska, 2007; Bertucci et al. 2010; Campo Verde Arbocco et al., 2017); (6) disorders in the levels of all previous hormones and in the expression of their receptors; and (7) disturbance in the signaling of PRL and elevation in the signaling of PRL inhibitors including LIF and STAT3 (Campo Verde Arbocco et al., 2016).

From the previous data, I hypothesized that the maternal THs play active roles in the lactation process. The maternal hypothyroidism may directly or indirectly increase the risk of the premature mammary involution and destruction of the mammary tissue. The maternal hypothyroidism with suckling disorders may suppress the normal development. Thus, we can avoid these abnormalities if we controlling the activities of the maternal PRL, T3, T4, growth hormone (GH), and thyroid-stimulating hormone (TSH) during the gestation and lactation. Additional experiments are needed to identify the associations between the maternal hypothyroidism, lactation disorders and mammary carcinogenesis.

## References


[1] Ahmed, O.M., Abd El-Tawab, S.M., Ahmed, R.G., 2010. 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. 28, 437-454.

[2] Ahmed, O.M., Ahmed, R.G., 2012. Hypothyroidism. In A New Look At Hypothyroidism. Dr. D. Springer (Ed.), ISBN:978-953-51-0020-1), In Tech Open Access Publisher, Chapter 1, pp. 1-20.

[3] Ahmed, O.M., Ahmed, R.G., El-Gareib, A.W., El-Bakry, A.M., Abd El-Tawaba, S.M., 2012. 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. 30, 517–537.

[4] Ahmed, O.M., El-Gareib, A.W., El-bakry, A.M., Abd El-Tawab, S.M., Ahmed, R.G., 2008. Thyroid hormones states and brain development interactions. Int. J. Dev. Neurosci. 26(2), 147-209. Review.

[5] Ahmed, R.G., 2011. Perinatal 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin exposure alters developmental neuroendocrine system. Food Chem. Toxicology, 49, 1276–1284.

[6] Ahmed, R.G., 2012a. Maternal-newborn thyroid dysfunction.In the Developmental Neuroendocrinology, pp. 1-369. Ed R.G. Ahmed. Germany: LAP LAMBERT Academic Publishing GmbH & Co KG.

[7] Ahmed, R.G., 2012b. Maternal-fetal thyroid interactions, Thyroid Hormone, Dr. N.K. Agrawal (Ed.), ISBN: 978-953-51-0678-4, In Tech Open Access Publisher, Chapter 5, pp. 125-156.

[8] Ahmed, R.G., 2013. Early weaning PCB 95 exposure alters the neonatal endocrine system: thyroid adipokine dysfunction. J. Endocrinol. 219 (3), 205-215.

[9] Ahmed, R.G., 2014. Editorial: Do PCBs modify the thyroid-adipokine axis during development? Annals Thyroid Res. 1(1), 11-12.

[10] Ahmed, R.G., 2015a. Chapter 1: Hypothyroidism and brain development. In advances in hypothyroidism treatment.Avid Science Borsigstr.9, 10115 Berlin, Berlin, Germany. Avid Science Publications level 6, Melange Towers, Wing a, Hitec City, Hyderabad, Telangana, India. pp. 1-40.

[11] Ahmed, R.G., 2015b. Hypothyroidism and brain developmental players.Thyroid Research J. 8(2), 1-12.

[12] Ahmed, R.G., 2015c. Editorials and Commentary: Maternofetal thyroid action and brain development. J. of Advances in Biology; 7(1), 1207-1213.

[13] Ahmed, R.G., 2016a. Gestational dexamethas one alters fetal neuroendocrine axis. Toxicology Letters, 258, 46–54.

[14] Ahmed, R.G., 2016b. Neonatal polychlorinated biphenyls-induced endocrine dysfunction. Ann. Thyroid. Res. 2 (1), 34-35.

[15] Ahmed, R.G., 2016c. Maternal iodine deficiency and brain disorders. Endocrinol. Metab.Syndr.5, 223.http:// dx.doi.org/10.4172/ 2161-1017.1000223.

[16] Ahmed, R.G., 2016d. Maternal bisphenol A alters fetal endocrine system: Thyroid adipokine dysfunction. Food Chem. Toxicology, 95, 168-174.

[17] Ahmed, R.G.,2017a. Developmental thyroid diseases and GABAergic dysfunction. EC Neurology 8.1, 02-04.

[18] Ahmed, R.G., 2017b. Hyperthyroidism and developmental dysfunction.Arch Med. 9, 4.

[19] Ahmed, R.G.,2017c. Anti-thyroid drugs may be at higher risk for perinatal thyroid disease. EC Pharmacology and Toxicology 4.4, 140-142.

[20] Ahmed, R.G.,2017d. Perinatal hypothyroidism and cytoskeleton dysfunction. Endocrinol MetabSyndr 6, 271.doi:10.4172/2161-1017.1000271

[21] Ahmed, R.G.,2017e. Developmental thyroid diseases and monoaminergic dysfunction. Advances in Applied Science Research 8(3), 01-10.

[22] Ahmed, R.G.,2017f.Hypothyroidism and brain development.J. Anim Res Nutr.2(2), 13.

[23] Ahmed, R.G.,2017g. Antiepileptic drugs and developmental neuroendocrine dysfunction: Every why has A Wherefore.Arch Med 9(6), 2.

[24] Ahmed, R.G.,2017h. Gestational prooxidant-antioxidant imbalance may be at higher risk for postpartum thyroid disease. Endocrinol MetabSyndr 6, 279. doi:10.4172/2161-1017. 1000279.

[25] Ahmed, R.G.,2017i. Synergistic actions of thyroid-adipokines axis during development. EndocrinolMetabSyndr 6, 280. doi:10.4172/ 2161-1017.1000280.

[26] Ahmed, R.G.,2017j. Thyroid-insulin dysfunction during development. International Journal of Research Studies in Zoology 3(4), 73-75. DOI: http://dx.doi.org/10.20431/2454-941X.0304010.

[27] Ahmed, R.G.,2017k. Developmental thyroid diseases and cholinergic imbalance. International Journal of Research Studies in

Zoology 3(4), 70-72. DOI: http://dx. doi.org/10 .20431/2454-941 X.03 040 09.

[28] Ahmed, R.G.,2017l. Thyroid diseases and developmental adenosinergic imbalance.Int J ClinEndocrinol 1(2), 053-055.

[29] Ahmed, R.G.,2017m.Maternal anticancer drugs and fetal neuroendocrine dysfunction in experimental animals.EndocrinolMetabSyndr 6, 281.doi:10.4172/2161-1017.1000281.

[30] Ahmed, R.G.,2017n. Letter: Gestational dexamethasone may be at higher risk for thyroid disease developing peripartum. Open Journal Of Biomedical & Life Sciences (Ojbili) 3(2), 01-06.

[31] Ahmed, R.G.,2017o. Deiodinases and developmental hypothyroidism. EC Nutrition 11.5, 183-185.

[32] Ahmed, R.G.,2017p. Maternofetal thyroid hormones and risk of diabetes. Int. J. of Res. Studies in Medical and Health Sciences 2(10), 18-21.

[33] Ahmed, R.G.,2017r. Association between hypothyroidism and renal dysfunctions. International Journal of Research Studies in Medical and Health Sciences 2(11), 1-4.

[34] Ahmed, R.G.,2017s.Maternal hypothyroidism and lung dysfunction. International Journal of Research Studies in Medical and Health Sciences 2(11), 8-11.

[35] Ahmed, R.G.,2017t.Endocrine disruptors; possible mechanisms for inducing developmental disorders.International journal of basic science in medicine (IJBSM)2(4), 157-160.

[36] Ahmed, R.G.,2017u. Maternal thyroid hormon es trajectories and neonatal behavioral disorders. ARC Journal of Diabetes and Endocrinology 3(2), 18-21.

[37] Ahmed, R.G.,2017v. Maternal thyroid dysfunction and neonatal cardiac disorders. Insights Biol Med. 1, 092-096.

[38] Ahmed, R.G.,2018a. Maternal hypothyroidism and neonatal testicular dysfunction. International Journal of Research Studies in Medical and Health Sciences 3(1), 8-12.

[39] Ahmed, R.G.,2018b. Maternal hypothyroidism and neonatal depression: Current perspective. International Journal of Research Studies in Zoology 4(1), 6-10. DOI: http://dx.d oi.org/10 .20431/2454-941X.0401002.

[40] Ahmed, R.G.,2018c. Non-genomic actions of thyroid hormones during development. App ClinPharmacolToxicol: ACPT-108. DOI: 10.29011/ACPT-109. 100008.

[41] Ahmed, R.G.,2018d. Maternal thyroid function and placental hemodynamics. ARC Journal of Animal and Veterinary Sciences 4(1), 9-13. DOI:http://dx.doi.org/10.20431/2455-2518.04 01002.

[42] Ahmed, R.G.,2018e.Interactions between thyroid and growth factors during development. ARC Journal of Diabetes and Endocrinology 4(1), 1-4. DOI: http://dx.doi.org/10.20431/ 2455-5983.0401001.

[43] Ahmed, R.G.,2018f. Maternal thyroid hormones and neonatal appetite. ARC Journal of Nutrition and Growth 4(1), 18-22. DOI: http://dx.doi.org/10.20431/2455-2550.0401005.

[44] Ahmed, R.G.,2018g. Genomic actions of thyroid hormones during development. ARC Journal of Diabetes and Endocrinology 4(1), 5-8. DOI: http://dx.doi.org/10.20431/2455-5983. 0401002.

[45] Ahmed, R.G.,2018h. Dysfunction of maternal thyroid hormones and psychiatric symptoms.American Research Journal of Endocrinology. 2(1), 1-6.

[46] Ahmed, R.G.,2018i. Is there a connection between maternal hypothyroidism and developing autism spectrum disorders? ARC Journal of Neuroscience 3(1), 5-8. DOI: http://dx.doi.org/10.20431/2456-057X. 030100 2.

[47] Ahmed, R.G.,2018j. Maternal thyroid dysfunctions and neonatal bone maldevelopment.American Research Journal of Endocrinology (in press) xx-xxx.

[48] Ahmed, R.G., Abdel-Latif, M., Ahmed F., 2015a.Protective effects of GM-CSF in experimental neonatal hypothyroidism. International Immunopharmacology 29, 538–543.

[49] Ahmed, R.G., Abdel-Latif, M., Mahdi, E., El-Nesr, K., 2015b. Immune stimulation improves endocrine and neural fetal outcomes in a model of maternofetal thyrotoxicosis. Int. Immunopharmacol. 29, 714-721.

[50] Ahmed, R.G., Davis, P.J., Davis, F.B., De Vito, P., Farias, R.N., Luly, P., Pedersen, J.Z., Incerpi, S., 2013a. Nongenomic actions of thyroid hormones: from basic research to clinical applications. An update. Immunology, Endocrine & Metabolic Agents in Medicinal Chemistry, 13(1), 46-59.

[51] Ahmed, R.G., El-Gareib, A.W. 2014.Lactating PTU exposure: I- Alters thyroid-neural axis in neonatal cerebellum. Eur. J. of Biol. and Medical Sci. Res. 2(1), 1-16.

[52] Ahmed, R.G., El-Gareib, A.W., 2017.Maternal carbamazepine alters fetal neuroendocrine-cytokines axis. Toxicology 382, 59–66.

[53] Ahmed, R.G., El-Gareib, A.W., Incerpi, S., 2014. Lactating PTU exposure: II- Alters thyroid-axis and prooxidant-antioxidant balance in neonatal cerebellum. Int. Res. J. of Natural Sciences 2(1), 1-20.

[54] Ahmed, R.G.,El-Gareib, A.W., Shaker, H.M., 2018a.Gestational 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126) exposure disrupts fetoplacental unit: Fetal thyroid-cytokines dysfunction. Life Sciences 192, 213–220.

[55] Ahmed, R.G., Incerpi, S., 2013. Gestational doxorubicin alters fetal thyroid–brain axis. Int. J. Devl. Neuroscience 31, 96–104.

[56] Ahmed, R.G., Incerpi, S., Ahmed, F., Gaber, A., 2013b. The developmental and physiological interactions between free radicals and antioxidant: Effect of environmental pollutants. J. of Natural Sci. Res. 3(13), 74-110.

[57] Ahmed, R.G.,Walaa G.H., Asmaa F.S., 2018b.Suppressive effects of neonatal bisphenol A on the neuroendocrine system.Toxicology and Industrial Health Journal (in press).

[58] Anguiano, B., Rojas-Huidobro, R., Delgado, G., Aceves, C., 2004. Has the mammary gland a protective mechanism against overexposure to triiodothyronine during the peripartum period? The prolactin pulse down-regulates mammary type I deiodinase responsiveness to norepinephrine. J. Endocrinol. 183, 267-277.

[59] Bagamasbad, P., Denver, R.J., 2011. Mechanisms and significance of nuclear receptor auto- and cross-regulation. Gen. Comp. Endocrinol. 170, 3-17.

[60] Bertucci, P.Y., Quaglino, A., Pozzi, A.G., Kordon, E.C., Pecci, A., 2010. Glucocorticoid induced impairment of mammary gland involution is associated with STAT5 and STAT3 signaling modulation. Endocrinology 151, 5730-5740.

[61] Campo Verde Arbocco, F., Persia, F.A., Hapon, M.B., Jahn, G.A., 2017. Hypothyroidism decreases JAK/STAT signaling pathway in lactating rat mammary gland. Molecular and Cellular Endocrinology 450, 14-23.

[62] Campo Verde Arbocco, F., Sasso, C.V., Actis, E.A., Carón, R.W., Hapon, M.B., Jahn, G.A., 2016. Hypothyroidism advances mammary involution in lactating rats through inhibition of PRL signaling and induction of LIF/STAT3 mRNAs. Molecular and Cellular Endocrinology 419, 18-28.

[63] Campo Verde Arbocco, F., Sasso, C.V., Nasif, D.L., Hapon, M.B., Jahn, G.A., 2015.Effect of hypothyroidism on the expression of nuclear receptors and their coregulators in mammary gland during lactation in the rat.Mol. Cell Endocrinol. 412, 26-35.

[64] Candelotti, E., De Vito, P., Ahmed, R.G., Luly, P., Davis, P.J., Pedersen, J.Z., Lin, H-Y., Incerpi, I., 2015. Thyroid hormones crosstalk with growth factors: Old facts and new hypotheses. Immun., Endoc.&Metab. Agents in Med. Chem., 15, 71-85.

[65] De Vito, P., Candelotti, E., Ahmed, R.G., Luly, P., Davis, P.J., Incerpi, S., Pedersen, J.Z., 2015.Role of thyroid hormones in insulin resistance and diabetes.Immun., Endoc.&Metab. Agents in Med. Chem., 15, 86-93.

[66] El-bakry, A.M., El-Ghareeb, A.W.,Ahmed, R.G., 2010.Comparative study of the effects of experimentally-induced hypothyroidism and hyperthyroidism in some brain regions in albino rats.Int. J. Dev. Neurosci. 28, 371-389.

[67] El-Ghareeb, A.A., El-Bakry, A.M., Ahmed, R.G., Gaber, A., 2016.Effects of zinc supplementation in neonatal hypothyroidism and cerebellar distortion induced by maternal carbimazole. Asian Journal of Applied Sciences 4(04), 1030-1040.

[68] Favre-Young, H., Dif, F., Roussille, F., Demeneix, B.A., Kelly, P.A., Edery, M., de Luze, A., 2000.Cross-talk between signal transducer and activator of transcription (Stat5) and thyroid hormone receptor-beta 1 (TRbeta1) signaling pathways. Mol. Endocrinol. 14, 1411-1424.

[69] Hapon, M.B., Motta, A.B., Ezquer, M., Bonafede, M., Jahn, G.A., 2007a. Hypothyroidism prolongs corpus luteum function in the pregnant rat. Reproduction 133, 197-205.

[70] Hapon, M.B., Simoncini, M., Via, G., Jahn, G.A., 2003. Effect of hypothyroidism on hormone profiles in virgin, pregnant and lactating rats, and on lactation. Reproduction 126, 371-382.

[71] Hapon, M.B., Varas, S.M., Gimenez, M.S., Jahn, G.A., 2007b. Reduction of mammary and liver lipogenesis and alteration of milk composition during lactation in rats by hypothyroidism. Thyroid 17, 11-18.

[72] Incerpi, S., Hsieh, M-T., Lin, H-Y., Cheng, G-Y., De Vito, P., Fiore, A.M., Ahmed, R.G., Salvia, R., Candelotti, E., Leone, S., Luly, P., Pedersen, J.Z., Davis, F.B., Davis, P.J., 2014. Thyroid hormone inhibition in L6 myoblasts of IGF-I-mediated glucose uptake and proliferation: new roles for integrin αvβ3. Am. J. Physiol. Cell Physiol. 307, C150–C161.

[73] Lemay, D.G., Neville, M.C., Rudolph, M.C., Pollard, K.S., German, J.B., 2007. Gene regulatory networks in lactation: identification of global principles using bioinformatics. BMC Syst. Biol. 1, 56.

[74] Li, M., Liu, X., Robinson, G., Bar-Peled, U., Wagner, K.U., Young, W.S., Hennighausen, L., Furth, P.A., 1997. Mammary-derived signals activate programmed cell death during the first stage of mammary gland involution. Proc. Natl. Acad. Sci. U. S. A. 94, 3425-3430.

[75] Rhoads, R.E., Grudzien-Nogalska, E., 2007.Translational regulation of milk protein synthesis at secretory activation. J. Mammary Gland. Biol. Neoplasia 12, 283-292.

[76] Van Herck, S.L.J., Geysens, S., Bald, E., Chwatko, G., Delezie, E., Dianati, E., Ahmed, R.G., Darras, V.M., 2013.Maternal transfer of methimazole and effects on thyroid hormone availability in embryonic tissues.Endocrinol. 218, 105-115.

[77] Varas, S.M., Jahn, G.A., Gimenez, M.S., 2001. Hyperthyroidism affects lipid metabolism in lactating and suckling rats. Lipids 36, 801-806.

[78] Varas, S.M., Munoz, E.M., Hapon, M.B., Aguilera Merlo, C.I., Gimenez, M.S., Jahn, G.A., 2002.Hyperthyroidism and production of precocious involution in the mammary glands of lactating rats. Reproduction 124, 691-702.

[79] Watson, C.J., 2009. Immune cell regulators in mouse mammary development and involution. J. Anim. Sci. 87, 35-42.

[80] Whyte, J., Bergin, O., Bianchi, A., McNally, S., Martin, F., 2009. Key signalling nodes in mammary gland development and cancer. Mitogen-activated protein kinase signalling in experimental models of breast cancer progression and in mammary gland development.Breast Cancer Res. 11, 209.

[81] Zhao, H., Huang, M., Chen, Q., Wang, Q., Pan, Y., 2012. Comparative gene expression analysis in mouse models for identifying critical pathways in mammary gland development. Breast Cancer Res. Treat. 132, 969-977.

[82] Zhao, X., Lorenc, H., Stephenson, H., Wang, Y.J., Witherspoon, D., Katzenellenbogen, B., Pfaff, D., Vasudevan, N., 2005. Thyroid hormone can increase estrogen-mediated transcription from a consensus estrogen response element in neuroblastoma cells. Proc. Natl. Acad. Sci. U. S. A. 102, 4890-4895.

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