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The possible role of human placental lactogen in worse outcomes of differentiated thyroid cancer in pregnancy

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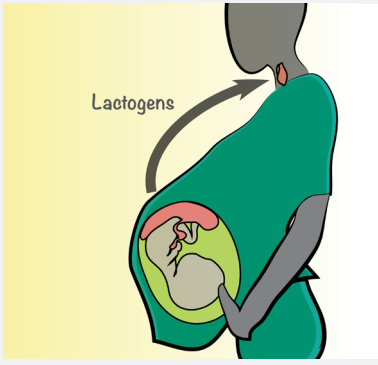

Illustration by Eloïse Kremer

ABSTRACT Lactogens comprise three closely related peptide hormones: human growth hormone (hGH), human placental lactogen (hPL), and human prolactin (hPRL). hPRL and hGH originate from the pituitary and hPL is secreted by syncytiotrophoblasts of the placenta. Levels of hPL vary during pregnancy; it can be detected from the sixth week of gestation, increases steadily in the first and second trimesters, and peaks at a constant level in the third. hPL expression has been reported in testicular, ovarian, and breast cancers. Of the endocrine tumors, differentiated thyroid cancer (DTC) is the most frequently seen and commonly occurs in younger women and pregnancy has the potential to exacerbate thyroid cancer progression or recurrence. Although hGH binds well to GH receptors (GHR) and PRL receptors (PRLR), hPRL only binds to PRLR. hPL per se has no specific receptor yet it is able to bind to PRLRs with a high affinity regardless of its low (23%) structural homology to PRL. Paradoxically, hPL binds weakly to GHR even though they have significant (85%) amino acid sequence homology. We hypothesized that high levels of hPL could explain the worse outcomes of DTC in pregnancy. A possible mechanism could be that hPL binds GHR–PRLR in thyroid tissue and promotes tumor growth. Alternatively, the high affinity of hPL for PRLRs expressed in thyroid cancer may account for these results. Conversely, hPL binding to GHR, albeit weakly, might also play a role in worsened outcomes. Additional studies must be performed in order for the pathophysiologic mechanisms to be elucidated.

INTRODUCTION The most frequently seen endocrine tumor is differentiated thyroid cancer (DTC) and it is common in younger women[1]. Numerous factors are known to induce thyroid cell growth in the course of normal pregnancy[2]. Human chorionic gonadotropin, which is especially increased in the first trimester of pregnancy, directly but temporarily stimulates the thyroid gland. This stimulatory effect may partially account for pregnancy-related thyroid enlargement[3].

Increased concentrations of estrogen may have a negative impact in thyroid cancer growth, but this remains controversial[4,5]. Magri *et al.* proposed that estrogen receptor-β negativity, estrogen receptor-α positivity, and high expression of androgen receptor in thyroid cancer were associated with a more aggressive phenotype[6]. Relative iodine deficiency during gestation can also have an effect on stimulation of thyroid tissue growth[3]. It is reasonable to propose that pregnancy may increase the risk of thyroid cancer progression or recurrence because normal thyroid growth and thyroglobulin production are induced by pregnancy[7]. In a recent study, Mesutti *et al.* indicated that pregnant women have higher rates of DTC persistence/recurrence, which lends support to the argument that pregnancy has a negative impact on patients with DTC; however, no differences were found between the groups regarding estrogen receptor pattern, sodium/iodide symporter (NIS) expression, and B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutations. Consequently, the authors concluded that additional future studies were required because the underlying causes were yet to be revealed[8].

HYPOTHESIS We hypothesize that high levels of hPL could explain the worse outcomes of DTC in pregnancy.

SUPPORTING ARGUMENTS ***a. Human placental lactogen and pregnancy.*** Lactogens comprise three closely related peptide hormones: human growth hormone (hGH), human placental lactogen (hPL), and human prolactin (hPRL)[9]. The tertiary structures of these hormones are comparable and their functions overlap[10]. hPRL and hGH principally originate from the pituitary and hPL, known as chorionic somatomammotropin hormone (CSH), is secreted by syncytiotrophoblasts of the placenta. Levels of hPL vary during pregnancy; it can be detected from the sixth week of gestation,

increases steadily in the first and second trimesters, and peaks at a constant level in the third. Serum levels of hPL display slight changes throughout the day. Induced hyperglycemia or hypoglycemia do not affect serum hPL. Its half-life is approximately 30 min and it immediately disappears from the blood after labor[11,12]. hPL stimulates mammary gland development and lactogenesis and directly affects fetal growth and metabolism[13]. At term, no other protein hormone has greater levels than maternal serum hPL[14].

Each of the three lactogens binds to PRLRs, which is a feature exclusive to humans. hGH binds to PRLRs and GHRs but in many species PRL binds exclusively with PRLRs. hPL per se has no specific receptor, yet it is able to bind to PRLRs with a high affinity regardless of its low (23%) structural homology to PRL. Paradoxically, hPL binds weakly to GHR even though they have significant (85%) amino acid sequence homology[15-18].

b. Human placental lactogen and cancer

hPL expression has been reported in testicular and ovarian cancers[19-21]. Immunoreactive hPL has been determined in the serum of some patients with breast cancer but not in those with benign breast disease or healthy men and women[22,23]. Presence of hPL in breast cancer has a negative influence on prognosis for patients[22]. Contrary to these findings, one study did not find hPL in the serum of patients with breast cancer[24]. The amplification of CSH genes in breast cancers was shown to be related to aneuploidy, lymph node metastases, and overexpression of the Her2/neu oncogene. Moreover, immunohistochemical labelling of hPL in carcinomas further demonstrates the relationship with gene amplification[25].

hPL is increased in histologic sections as well as serum with placental site trophoblastic tumors[26]. Xiong *et al.* reported that the expression of placental hormones including human chorionic gonadotropin (hCG), human placental lactogen, and pregnancy-specific 1-glycoprotein in invasive moles and choriocarcinomas were associated with the degree of tumor malignancy, biologic behaviour, and grading of trophoblastic cell differentiation[27]. Remadi *et al.* described a case of placental site trophoblastic tumor with pulmonary metastasis that exhibited a preponderance of hPL positive cells[28]. Breast carcinoma with choriocarcinomatous features that demonstrate hCG and hPL expression is a rare variant of breast carcinoma characterized by atypical malignant cells, which are morphologically similar to choriocarcinoma cells[29]. hPL was detected in 19 of 97 (20%) lung tumor tissue sections in one study[30]. The ectopic production of hPL may provide a specific marker for cancers in men and non-pregnant women[31]. The low efficacy of cancer therapy and continuous growth of breast and prostate tumors is thought to be caused by activation of anti-apoptotic processes through long-term exposure to circulating and/or locally-produced lactogens[32]. The frequency of immunoreactive hPLs in endometrial cancer is higher than in endometrial hyperplasia[33].

Wu ***et al.*** reported that hGH expression alone or combined with hPRL expression in patients with mammary or endometrial carcinoma was related to worse relapse-free survival and overall survival[34]. Costa *et al.* reported that PRLR expression was detected in 76.1% of all thyroid cancers[35].

GH has metabolic and growth-promoting effects in various tissues of humans. Although hGH binds to hGHRs and hPRLRs, hPRL only binds to hPRLRs. GHRs and PRLRs combine and form heterodimers in breast cancer cells and this increases the likelihood of hPL binding to these receptors and promoting growth[36]. Previous studies reported that ovine placental lactogen (PL) heterodimerized the extracellular domains of ruminant GHRs and PRLRs[37,38]. Langenheim *et al.* showed that humans could form PRLR-GHR heterodimers, which provided connections for signal transduction[39].

CONCLUSION GHR–PRLR heterodimerization in breast cancer cells augments the probability of hPL binding to such a hybrid receptor and promoting growth. We hypothesize that high levels of hPL could explain the worse outcome of DTC in pregnancy. A possible mechanism is that hPL binds GHR–PRLR in thyroid tissue and promotes tumor growth. High affinity of hPL for PRLR which is expressed in thyroid cancer could explain worse outcomes. Although weak, the binding of hPL to the hGH receptor may have a negative effect on outcomes. GH and PRL are potent oncogenes and hPL exerts its effects via the same receptors. hPL may have oncogenic action as a consequence of exerting its effect via the same receptors. Additional studies are required to elucidate the pathophysiologic mechanisms.**H**

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CONFLICTS OF INTEREST Authors declare no conflicts of interest.

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REFERENCES

1 Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA. 2006;295:2164–2167.
http://dx.doi.org/10.1001/jama.295.18.2164

2 Smallridge RC, Glinoer D, Hollowell JG, Brent G. Thyroid function inside and outside of pregnancy: what do we know and what don't we know? Thyroid. 2005;15:54–59.
http://dx.doi.org/10.1089/thy.2005.15.54

3 Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology.
Endocr Rev. 1997;18:404–433.
http://dx.doi.org/10.1210/edrv.18.3.0300

4 Bonacci R, Pinchera A, Fierabracci P, Gigliotti A, Grasso L, Giani C. Relevance of estrogen and progesterone receptors enzyme immunoassay in malignant, benign and surrounding normal thyroid tissue. J Endocrinol Invest. 1996;19:159–164.
http://dx.doi.org/10.1007/BF03349859

5 Lee ML, Chen GG, Vlantis AC, Tse GM, Leung BC, van Hasselt CA. Induction of thyroid papillary carcinoma cell proliferation by estrogen is associated with an altered expression of Bcl-xL. Cancer J. 2005;11:113–121.

6 Magri F, Capelli V, Rotondi M, Leporati P, La Manna L, Ruggiero R *et al.* Expression of estrogen and androgen receptors in differentiated thyroid cancer: an additional criterion to assess the patient's risk. Endocrine-Related Cancer. 2012;19:463–471.
http://dx.doi.org/10.1530/ERC-11-0389

7 Leboeuf R, Emerick LE, Martorella AJ, Tuttle RM. Impact of pregnancy on serum thyroglobulin and detection of recurrent disease shortly after delivery in thyroid cancer survivors. Thyroid. 2007;17:543-547.
http://dx.doi.org/10.1089/thy.2007.0020

8 Messuti I, Corvisieri S, Bardesono F, Rapa I, Giorcelli J, Pellerito R *et al.* Impact of pregnancy on prognosis of differentiated thyroid cancer: clinical and molecular features. Eur J Endocrinol. 2014;10(170):659-666.
http://dx.doi.org/10.1530/EJE-13-0903

9 Idelman G, Jacobson EM, Tuttle TR, Ben-Jonathan N. Lactogens and estrogens in breast cancer chemoresistance. Expert Rev Endocrinol Metab. 2011;6:411-422.
http://dx.doi.org/10.1586/eem.11.19

10 Keeler C, Dannies PS, Hodsdon ME. The tertiary structure and backbone dynamics of human prolactin. J Mol Biol. 2003;328:1105–1121.
http://dx.doi.org/10.1016/S0022-2836(03)00367-X

11 Walsh ST, Kossiakoff AA. Crystal structure and site 1 binding energetics of human placental lactogen. J Mol Biol. 2006;358:773–784.
http://dx.doi.org/10.1016/j.jmb.2006.02.038

12 Samaan N, Yen SC, Friesen H, Pearson OH. Serum placental lactogen levels during pregnancy and in trophoblastic disease. J Clin Endocrinol Metab. 1966;26:1303–1308.
http://dx.doi.org/10.1210/jcem-26-12-1303

13 Walker WH, Fitzpatrick SL, Barrera-Saldaña HA, Resendez-Perez D, Saunders GF. The human placental lactogen genes: structure, function, evolution and transcriptional regulation. Endocr Rev. 1991;12:316–328.
http://dx.doi.org/10.1210/edrv-12-4-316

14 Handwerger S. New insights into the regulation of human cytotrophoblast cell differentiation. Mol. Cell Endocrinol. 2010;323:94–104.
http://dx.doi.org/10.1016/j.mce.2009.12.015

15 Ben-Jonathan N, Lapensee CR, Lapensee EW. What can we learn from rodents about prolactin in humans? Endocr Rev. 2008;29:1–41.
http://dx.doi.org/10.1210/er.2007-0017

16 Lowman HB, Cunningham BC, Wells JA. Mutational analysis and protein engineering of receptor-binding determinants in human placental lactogen. J Biol Chem. 1991;266(17):10982-8.

17 Peterson FC, Brooks CL. Different elements of mini-helix 1 are required for human growth hormone or prolactin action via the prolactin receptor. Protein Eng Des Sel. 2004;17:417–424.
http://dx.doi.org/10.1093/protein/gzh051

18 Kelly PA, Tsushima T, Shiu RP *et al.* Lactogenic and growth hormone-like activities in pregnancy determined by radioreceptor assays. Endocrinology. 1976;99:765–774.
http://dx.doi.org/10.1210/endo-99-3-765

19 Fukunaga M, Ushigome S. Malignant trophoblastic tumors: immunohistochemical and flow cytometric comparison of choriocarcinoma and placentalsite trophoblastic tumors. Hum Pathol. 1993;24:1098–1106.
http://dx.doi.org/10.1016/0046-8177(93)90190-R

20 Monteiro JC, Barker G, Ferguson KM, Wiltshaw E, Neville AM. Ectopic production of human chorionic gonadotrophin (hCG) and human placental lactogen (hPL) by ovarian carcinoma. Eur J Cancer Clin Oncol. 1983;19:173–178.
http://dx.doi.org/10.1016/0277-5379(83)90414-5

21 Sesterhenn IA, Davis CJ Jr. Pathology of germ cell tumors of the testis. Cancer Control. 2004;11:374–387.

22 Horne CH, Reid IN, Milne GD. Prognostic significance of inappropriate production of pregnancy proteins by breast cancers. Lancet. 1976;2:279–282.
http://dx.doi.org/10.1016/S0140-6736(76)90731-5

23 Sheth NA, Suraiya JN, Sheth AR, Ranadive KJ, Jussawalla DJ. Ectopic production of human placental lactogen by human breast tumors. Cancer. 1977;39(4):1693-9.
http://dx.doi.org/10.1002/1097-0142(197704)39

24 Monteiro JC, Biswas S, Al-Awqati MA, Greening WP, McKinna JA, *et al.* Serum levels of human placental lactogen and pregnancy-specific beta 1-glycoprotein in breast cancer. Br J Cancer. 1982;46:279–282.
http://dx.doi.org/10.1038/bjc.1982.193

25 Latham C, Zhang A, Nalbanti A, Maner S, Zickert P, Blegen H *et al.* Frequent coamplification of two different regions on 17q in aneuploid breast carcinomas. Cancer Genet Cytogenet. 2001;127:16–23.
http://dx.doi.org/10.1016/S0165-4608(00)00427-1

26 Kim SJ. Placental site trophoblastic tumour. Best Pract Res Clin Obstet Gynaecol. 2003;17:969-984.
http://dx.doi.org/10.1016/S1521-6934(03)00095-6

27 Xiong YY, Zeng J, Tang ZJ. Expression of human chorionic gonadotropin, human placental lactogen and pregnancy-specific 1-glycoprotein in malignant trophoblastic neoplasms. Zhonghua Fu Chan Ke Za Zhi. 1994 Oct;29(10):610-613,638.

28 Remadi S, Lifschitz-Mercer B, Ben-Hur H *et al.* Metastasizing placental site trophoblastic tumor: immunohistochemical and DNA analysis. 2 case reports and a review of the literature. Arch Gynecol Obstet. 1997;259(2):97-103.
http://dx.doi.org/10.1007/BF02505316

29 Saigo PE, Rosen PP. Mammary carcinoma with ''choriocarcinomatous'' features. Am J Surg Pathol. 1981;5:773–778.
http://dx.doi.org/10.1097/00000478-198112000-00006

30 Harach HR, Skinner M, Gibbs AR. Biological markers in human lung carcinoma: an immunopathological study of six antigens. Thorax. 1983;38(12):937-941.
http://dx.doi.org/10.1136/thx.38.12.937

31 Weintraub BD, Rosen SW. Ectopic production of human chorionic somatomammotropin by nontrophoblastic cancers. J Clin Endocrinol Metab. 1971;32:94-101.
http://dx.doi.org/10.1210/jcem-32-1-94

32 Jacobson EM, Hugo ER, Tuttle TR, Papoian R, Ben-Jonathan N. Unexploited therapies in breast and prostate cancer: blockade of the prolactin receptor. Trends Endocrinol Metab. 2010;21:691-698.
http://dx.doi.org/10.1016/j.tem.2010.08.004

33 Ikarashi T, Takeuchi S. Immunohistochemical localization of placental proteins and tumor-associated antigens in endometrial cancer and endometrial hyperplasia. Nihon Sanka Fujinka Gakkai Zasshi. 1987;39:1634-40.

34 Wu ZS, Yang K, Wan Y *et al.* Tumor expression of human growth hormone and human prolactin predict a worse survival outcome in patients with mammary or endometrial carcinoma. J Clin Endocrinol Metab. 2011;96(10):E1619-29.
http://dx.doi.org/10.1210/jc.2011-1245

35 Costa P, Catarino AL, Silva F *et al.* Expression of prolactin receptor and prolactin in normal and malignant thyroid: a tissue microarray study. Endocr Pathol. 2006;17(4):377-86.
http://dx.doi.org/10.1007/s12022-006-0009-x

36 Xu J, Zhang Y, Berry PA, *et al.* Growth hormone signaling in human T47D breast cancer cells:potential role for a growth hormone receptor-prolactin receptor complex. Mol Endocrinol. 2011;25(4):597–610
http://dx.doi.org/10.1210/me.2010-0255

37 Biener E, Martin C, Daniel N *et al.* Ovine placental lactogen-induced heterodimerization of ovine growth hormone and prolactin receptors in living cells is demonstrated by fluorescence resonance energy transfer microscopy and leads to prolonged phosphorylation of signal transducer and activator of transcription (STAT)1 and STAT3. Endocrinology. 2003;144(8):3532-40.
http://dx.doi.org/10.1210/en.2003-0096

38 Herman A, Bignon C, Daniel N *et al.* Functional heterodimerization of prolactin and growth hormone receptors by ovine placental lactogen. J Biol Chem. 2000;275:6295–6301.
http://dx.doi.org/10.1074/jbc.275.9.6295

39 Langenheim JF, Chen WY Development of a novel ligand that activates JAK2/STAT5 signaling through a heterodimer of prolactin receptor and growth hormone receptor. J Recept Signal Transduct Res. 2009;29:107–112.
http://dx.doi.org/10.1080/10799890902845252