Differentiation of pathologic/neoplastic hypercortisolism (Cushing's syndrome) from physiologic/non-neoplastic hypercortisolism (formerly known as pseudo-Cushing's syndrome): Letter to the Editor

Murray Thomson

The University of Sydney, The School of Life and Environmental Sciences, New South Wales, Australia

Correspondence should be addressed to M Thomson

Email
murray.thomson@sydney.edu.au

I enjoyed reading Prof. Findling and Prof. Raff's recent review article on hypercortisolism (1), and this letter provides further discussion on one sentence in that article. The review states that 'CRH-binding protein also increases during pregnancy, which may prevent the stimulatory effects of placental CRH on the maternal pituitary gland (67 (2), 68 (3), 69 (4)).' The references cited at the end of the aforementioned statement, however, do not report that plasma levels of CRH-binding protein increase during pregnancy, and indeed, CRH-BP plasma levels decrease in the last few weeks of pregnancy so the stimulatory effects of placental CRH on the maternal pituitary gland may be increased at this time. Sasaki and coworkers wrote, 'CRH-binding protein did not increase during pregnancy' (3) in reference to the paper by Suda and coworkers, which reported that the amount of binding of radiolabeled CRH to CRH-BP in pregnant women's plasma (the plasma had been stripped of endogenous CRH) does not significantly change throughout pregnancy or become significantly different from non-pregnant controls (2). When endogenous CRH was not pre-stripped from plasma, levels of radiolabeled CRH binding to the CRH-BP stayed relatively stable for the first two trimesters, and then progressively decreased to reach approximately 40% of control non-pregnant levels shortly before parturition (2). The authors concluded that, (1) rises in CRH secretion from the placenta may have been displacing the radiolabeled CRH from the CRH-BP in later pregnancy plasma samples that did not have endogenous CRH removed, (2) the assay that they used does not show actual concentrations of CRH-BP and (3) the results suggest that hypothetically, even if there was a rise in CRH-BP levels at the end of pregnancy (noting that cortisol-binding protein levels

show this pattern) that their assay did not reveal, it would be small (2).

Linton and colleagues were the first to develop a radioimmunoassay (RIA) so they could directly measure CRH-BP levels during pregnancy. In their 1993 paper titled, 'Corticotropin releasing hormone-binding protein (CRH-BP): plasma levels decrease during the 3rd trimester of normal human pregnancy', these authors used their new RIA to disprove the hypothesis that CRH-BP plasma levels may show a small and previously undetectable rise late in pregnancy (5). Instead, this group showed that the levels of CRH-BP in pregnant women stayed relatively stable during the first and second trimester (and were not significantly different from non-pregnant controls during this phase), and then decreased in the third trimester. Later studies each showed a similar pattern of CRH-BP plasma levels during pregnancy (6, 7). In a study of 59 women in whom CRH and CRH-BP were measured every 10 days in the 180 days prior to birth, the drop in CRH-BP levels in the last four weeks of pregnancy was quantified as falling significantly from 2074 ± 279 pmol/L at 30 days before birth to 927 ± 164 pmol/L at 10 days prior to birth (6). There is now widespread recognition that CRH-BP levels rapidly decrease in the last weeks of pregnancy (8, 9, 10, 11, 12).

The question of whether there is a transient and modest rise in CRH-BP plasma levels prior to the rapid decline in late pregnancy has not been so reproducibly answered. There is one published study with a sample size of 14, that has shown that that halfway through the second semester plasma CRH-BP levels in the pregnant women in this cohort were not significantly different to non-pregnant levels, however, a small (27.7%) but significant increase in CRH-BP plasma levels between weeks 18 and 30 of

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gestation was observed (13). After the 30-week time point, CRH-BP plasma levels showed the usual decline and in 4 women who were sampled to close to parturition, levels fell to 49% of that seen at week 16 (13).

CRH-BP attenuates CRH activity on pituitary cells, ACTH release from cultured pituitary cells stimulated with 319 pM CRH was reduced by approximately 45% by the presence of 337 pM CRH-BP and raising the concentration of CRH-BP to 2.7 nM (an 8.5-fold excess of molecules in comparison to the CRH concentration tested) increased the attenuation of 319 pM CRH bioactivity to 76% (14). The CRH-BP pattern of relative stability in the first 36 weeks of pregnancy, followed by a rapid decrease in the last 4 weeks, dramatically contrasts to that shown by plasma CRH levels that progressively rise to reach 1000 fold or higher prior to labor (4, 6). McLean and colleagues have pointed out that the important point to note here is that for the first 36 weeks of pregnancy, the levels of CRH-BP are vastly higher than that of CRH but the falling levels of CRH-BP in the last few weeks of pregnancy with a concurrent exponential rise in CRH levels results in CRH molecules outnumbering CRH-BP molecules in the plasma by up to 3 to 1 and therefore placental CRH has a higher potential for bioactivity during this time (6, 12). Because CRH in the plasma can stimulate the pituitary (15, 16), higher levels of placental CRH unbound to CRH-BP may allow more placental CRH to interact with pituitary receptors in late pregnancy.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this article.

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References

- Findling JW & Raff H. Diagnosis of endocrine disease: differentiation of pathologic/neoplastic hypercortisolism (Cushing's syndrome) from physiologic/non-neoplastic hypercortisolism (formerly known as pseudo-Cushing's syndrome). *European Journal of Endocrinology* 2017 **176** R205–R216. (<https://doi.org/10.1530/EJE-16-0946>)
- Suda T, Iwashita M, Tozawa F, Ushiyama T, Tomori N, Sumitomo T, Nakagami Y, Demura H & Shizume K. Characterization of corticotropin-releasing hormone binding protein in human plasma by chemical cross-linking and its binding during pregnancy. *Journal of Clinical Endocrinology and Metabolism* 1988 **67** 1278–1283. (<https://doi.org/10.1210/jcem-67-6-1278>)
- Sasaki A, Shinkawa O & Yoshinaga K. Placental corticotropin-releasing hormone may be a stimulator of maternal pituitary adrenocorticotrophic hormone secretion in humans. *Journal of Clinical Investigation* 1989 **84** 1997–2001. (<https://doi.org/10.1172/JCI114390>)
- Thomson M. The physiological roles of placental corticotropin releasing hormone in pregnancy and childbirth. *Journal of Physiology and Biochemistry* 2013 **69** 559–573. (<https://doi.org/10.1007/s13105-012-0227-2>)
- Linton EA, Perkins AV, Woods RJ, Eben F, Wolfe CDA, Behan DP, Potter E, Vale WW & Lowry PJ. Corticotropin releasing hormone-binding protein (CRH-BP): plasma levels decrease during the 3rd trimester of normal human pregnancy. *Journal of Clinical Endocrinology and Metabolism* 1993 **76** 260–262. (<https://doi.org/10.1210/jcem.76.1.8421097>)
- McLean M, Bisits A, Davies J, Woods R, Lowry P & Smith R. A placental clock controlling the length of human-pregnancy. *Nature Medicine* 1995 **1** 460–463. (<https://doi.org/10.1038/nm0595-460>)
- Petraglia F, Florio P, Benedetto C, Gallo C, Woods RJ, Genazzani AR & Lowry PJ. High levels of corticotropin-releasing factor (CRF) are inversely correlated with low levels of maternal CRF-binding protein in pregnant women with pregnancy-induced hypertension. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 852–856. (<https://doi.org/10.1210/jcem.81.2.8636316>)
- Vannuccini S, Bocchi C, Severi FM, Challis JR & Petraglia F. Endocrinology of human parturition. *Annales d'Endocrinologie* 2016 **77** 105–113. (<https://doi.org/10.1016/j.ando.2016.04.025>)
- Vitale SG, Laganà AS, Rapisarda AMC, Scarale MG, Corrado F, Cignini P, Butticiè S & Rossetti D. Role of urocortin in pregnancy: an update and future perspectives. *World Journal of Clinical Cases* 2016 **4** 165–171. (<https://doi.org/10.12998/wjcc.v4.i7.165>)
- Zhou F, Zhang L, He MM, Liu ZF, Gao BX & Wang XD. Corticotropin-releasing hormone expression in patients with intrahepatic cholestasis of pregnancy after ursodeoxycholic acid treatment: an initial experience. *Current Medical Research and Opinion* 2014 **30** 1529–1535. (<https://doi.org/10.1185/03007995.2014.907560>)
- Florio P, Woods RJ, Genazzani AR, Lowry PJ & Petraglia F. Changes in amniotic fluid immunoreactive corticotropin-releasing factor (CRF) and CRF-binding protein levels in pregnant women at term and during labor. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 835–838. (<https://doi.org/10.1210/jcem.82.3.3807>)
- McLean M & Smith R. Corticotrophin-releasing hormone and human parturition. *Reproduction* 2001 **121** 493–501. (<https://doi.org/10.1530/rep.0.1210493>)
- Perkins AV, Eben F, Wolfe CDA, Schulte HM & Linton EA. Plasma measurements of corticotrophin-releasing hormone-binding protein in normal and abnormal human pregnancy. *Journal of Endocrinology* 1993 **138** 149–157. (<https://doi.org/10.1677/joe.0.1380149>)
- Linton EA, Behan DP, Saphier PW & Lowry PJ. Corticotropin-releasing hormone (CRH)-binding protein: reduction in the adrenocorticotropin-releasing activity of placental but not hypothalamic CRH. *Journal of Clinical Endocrinology and Metabolism* 1990 **70** 1574–1580. (<https://doi.org/10.1210/jcem-70-6-1574>)
- DeBold CR, DeCherney GS, Jackson RV, Sheldon WR, Alexander AN, Island DP, Rivier J, Vale W & Orth DN. Effect of synthetic ovine corticotropin-releasing factor: prolonged duration of action and biphasic response of plasma adrenocorticotropin and cortisol. *Journal of Clinical Endocrinology and Metabolism* 1983 **57** 294–298. (<https://doi.org/10.1210/jcem-57-2-294>)
- Stalla GK, Hartwimmer J, von Werder K & Muller OA. Ovine (o) and human (h) corticotrophin releasing factor (CRF) in man: CRF-stimulation and CRF-immunoreactivity. *Acta Endocrinologica* 1984 **106** 289–297. (<https://doi.org/10.1530/acta.0.1060289>)

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