Letter to the Editor

Oestrogen-selective modulation of FSH and LH secretion by pituitary gland

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Sir,

We read the interesting article by Forward *et al* (2004) on the clinical and endocrine data for goserelin plus anastrozole in premenopausal women with advanced breast cancer. The authors presented interesting data regarding serum gonadotropin (FSH and LH) levels and androgen (testosterone, DHEAS and androstenedione) levels in 13 patients treated with the GnRH agonist, goserelin, plus the selective oestrogen receptor modulator, tamoxifen, followed by goserelin plus the aromatase inhibitor, anastrozole. The authors found that goserelin and tamoxifen led to a 90% fall in FSH levels down to 1.0 IU/L at 6 months ($P < 0.001$). Once the therapy was changed to goserelin and anastrozole, there was a significant rise in the mean FSH level to 7.8 IU/l at 12 months ($P < 0.0001$). Introduction of goserelin and tamoxifen resulted in an 89% reduction in mean LH levels (pretreatment vs 6 months = 19.9 vs 0.3 IU/l; $P = 0.01$), but with substitution of tamoxifen by anastrozole, no significant change in LH levels occurred.

With regard to androgen levels, the authors found a significant fall in testosterone and androstenedione, but not DHEAS, levels in association with substitution of tamoxifen by anastrozole.

In their explanation for these observations, the authors suggested that the rise in FSH was due to release of a negative feedback as a result of further reduction in oestradiol levels upon the introduction of an aromatase inhibitor, or a rebound phenomenon from coming off tamoxifen. Regarding the significant decline in androgen levels (testosterone and androstenedione), contrary to what is expected (a rise due to potential substrate accumulation secondary to inhibition of the aromatase enzyme), the authors provided little in the way of discussion.

We would like to propose a possible mechanism for the endocrine changes found in this study. Regarding the differential changes in gonadotropins (rise in FSH levels while LH levels remained suppressed) with substitution of tamoxifen by the aromatase inhibitor, anastrozole, we believe that involvement of the activin/inhibin/follistatin system could explain these changes.

Accumulating evidence suggests that oestrogen can modulate gonadotropin production through a direct effect on pituitary cells, independent of GnRH. This effect is thought to be mediated through the activin/inhibin/follistatin system (DePaolo, 1997; Nett *et al*, 2002; Welt *et al*, 2002; McNeilly *et al*, 2003). Activins are produced by a wide variety of tissues including the pituitary gland,

and are specifically by gonadotropes (Roberts *et al*, 1989). Activins stimulate synthesis of FSH by a direct action on the gonadotropes (Mason *et al*, 1989). Follistatin, also produced by the pituitary gland, is an activin-binding protein and may decrease FSH synthesis by sequestering activin (Mather *et al*, 1993). Oestrogen was found to selectively suppress FSH production but not LH through an increase in follistatin/inhibin and a decrease in activin, independent of GnRH (Shupnik and Rosenzweig, 1991; DiGregorio and Nett, 1995; Baratta *et al*, 2001), mainly through activin suppression (Baratta *et al*, 2001).

Testosterone has been found to have the opposite effect of oestrogen on pituitary FSH (but not LH) production, that is, an increase in FSH by the gonadotropes. This effect was found to be mediated through locally produced activins (Burger *et al*, 2004). Potentially, testosterone may accumulate at the tissue level as a result of aromatase inhibition even in the absence of measurable changes in the serum. Such locally accumulated testosterone could exert a stimulatory effect on FSH production by the anterior pituitary through an activin-mediated effect. The reason why a more suppressive effect on FSH production occurred with the antioestrogen tamoxifen is probably related to its selective oestrogen receptor modulation effect, known to exert antioestrogenic effects at the level of the hypothalamus, but oestrogenic effects at the level of the pituitary gland (Gonzalez *et al*, 2000).

The significant decline in testosterone and androstenedione, but not DHEAS, in the face of aromatase inhibition is much harder to rationalise. It is possible that inhibition of oestrogen locally in the hypothalamus and pituitary by the aromatase inhibitor, together with GnRH receptor downregulation by goserelin, resulted in profound combined suppression of LH levels, especially at the level of bioactivity, which is not totally reflected in the immunoassay results.

It is important to mention that the evidence presented above came mainly from animal studies. However, if we can extrapolate from the available animal data, it is pertinent here to point out another potential mechanism for aromatase inhibitors to enhance the efficacy of controlled ovarian hyperstimulation (COH) protocols, as we have recently reported (Mitwally and Casper, 2002, 2003, 2004). The ability of the aromatase inhibitors to increase endogenous FSH production by the anterior pituitary, even with pituitary GnRH receptor downregulation (as in the present publication by Forward *et al*), is an exciting approach to improve the outcome of ovarian stimulation particularly in poor responders in *in vitro* fertilisation protocols. We believe this area of aromatase inhibitor use warrants further investigation.

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REFERENCES

- Baratta M, West LA, Turzillo AM, Nett TM (2001) Activin modulates differential effects of estradiol on synthesis and secretion of follicle-stimulating hormone in ovine pituitary cells. *Biol Reprod* **64**: 714–719
- Burger LL, Haisenleder DJ, Aylor KW, Dalkin AC, Prendergast KA, Marshall JC (2004) Regulation of luteinizing hormone-beta and follicle-stimulating hormone (FSH)-beta gene transcription by androgens: testosterone directly stimulates FSH-beta transcription independent from its role on follistatin gene expression. *Endocrinology* **145**(1): 71–78
- DePaolo LV (1997) Inhibins, activins, and follistatins: the saga continues. *Proc Soc Exp Biol Med* **214**: 328–339
- DiGregorio GB, Nett TM (1995) Estradiol and progesterone influence the synthesis of gonadotropins in the absence of GnRH in the ewe. *Biol Reprod* **35**: 166–172
- Forward DP, Cheung KL, Jackson L, Robertson JF (2004) Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. *Br J Cancer* **90**(3): 590–594
- Gonzalez D, Bellido C, Aguilar R, Garrido-Gracia JC, Hernandez G, Alonso R, Sanchez-Criado JE (2000) Luteinizing hormone secretion elicited in a ligand-independent activation of progesterone receptor manner at pituitary level in the rat: differential effect of two selective estrogen receptor modulators. *Neurosci Lett* **289**(2): 111–114
- Mason AJ, Berkemeier LM, Schmelzer CH, Schwall RH (1989) Activin B: precursor sequences, genomic structure and *in vitro* activities. *Mol Endocrinol* **3**: 1352–1358
- Mather JP, Roberts PE, Krummen LA (1993) Follistatin modulates activin activity in a cell- and tissue-specific manner. *Endocrinology* **132**: 2732–2734
- McNeilly AS, Crawford JL, Taragnat C, Nicol L, McNeilly JR (2003) The differential secretion of FSH and LH: regulation through genes, feedback and packaging. *Reprod Suppl* **61**: 463–476
- Mitwally MFM, Casper RF (2002) Aromatase inhibition improves ovarian response to follicle-stimulating hormone in poor responders. *Fertil Steril* **77**: 776–780
- Mitwally MFM, Casper RF (2004) Aromatase inhibition decreases FSH dose needed during controlled ovarian hyperstimulation: a controlled prospective trial. *J Soc Gynecol Invest* **11**(6): 406–415
- Mitwally MFM, Casper RF (2003) Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulation in women with unexplained infertility. *Hum Reprod* **18**(8): 1588–1597
- Nett TM, Turzillo AM, Baratta M, Rispoli LA (2002) Pituitary effects of steroid hormones on secretion of follicle-stimulating hormone and luteinizing hormone. *Domest Anim Endocrinol* **23**: 33–42
- Roberts V, Meunier H, Vaughan J, Rivier J, Rivier C, Vale W, Sawchenko P (1989) Production and regulation of inhibin subunits in pituitary gonadotropes. *Endocrinology* **124**: 552–554
- Shupnik MA, Rosenzweig BA (1991) Identification of an estrogen-responsive element in the rat LH beta gene. DNA–estrogen receptor interactions and functional analysis. *J Biol Chem* **266**: 17084–17091
- Welt C, Sidis Y, Keutmann H, Schneyer A (2002) Activins, inhibins, and follistatins: from endocrinology to signaling. A paradigm for the new millennium. *Biol Med (Maywood)* **227**(9): 724–752