Leptin Involvement in Reproductive Performance

Dear Dr. Visek:

In their interesting article, Shaw et al. (1997) show that the poor reproductive outcomes observed in rats consuming a cafeteria diet are due to the high fat content and occur despite adequate protein, vitamin and mineral dietary levels. The authors claim that the exact mechanisms involved in these findings remain unknown and point to the possibility of macronutrient partitioning disorders leading to energetic inhibition of reproduction.

Numerous studies have revealed an association between nutritional status, adiposity and reproductive maturity. Extremes of body mass are associated with disturbances of reproductive function in women. On the one hand, obese women exhibit a high incidence of oligo- or amenorrhea and infertility (Green et al. 1988). At the other extreme, women with a low percentage of body fat, such as trained distance runners, ballet dancers and patients with anorexia nervosa, often are infertile (De Souza and Metzger 1991). Although it is acknowledged that the maintenance of reproductive function in adults is physiologically coupled to nutrition and energetics, how this linkage is accomplished at the cellular and molecular levels remains unknown. In this sense, leptin—a recently identified 16-kDa protein hormone produced by adipocytes that increases general metabolism and decreases appetite, body weight and fat stores—may provide some clues (Fellemynounter et al. 1995).

Leptin-deficient ob/ob mice are infertile. Injection of leptin into these mice increased the levels of circulating gonadotropins, promotes ovarian follicular development, and restores fertility (Chehab et al. 1996). In addition, normal prepubertal female mice injected with leptin showed accelerated reproduction, vaginal opening, onset of the first estrous cycle, and maturation of reproductive tissues concomitant with changes in luteinizing hormone and 17β-estradiol levels (Chehab et al. 1997).

To the other extreme, excessive leptin concentrations are also associated with disrupted fertility. Women with polycystic ovary syndrome (PCOS) show oligo- or amenorrhea, obesity and insulin resistance, symptoms reminiscent of those observed in leptin-deficient ob/ob mice. However, in this case, serum leptin concentrations are increased (Brzechffa et al. 1996). It is possible that women with the PCOS produce a less potent form of leptin, or they may have diminished response to leptin at the target cell level. This could be caused by mutant receptors, transport problems or deficiencies in intracellular signaling.

Leptin resistance has been shown in mutant db/db mice that lack functioning leptin receptors and in diet-induced obesity (Caro et al. 1996). In this sense, high circulating levels of immunoreactive leptin may be a compensatory response to the absence of functional receptors as well as to decreased leptin bioactivity or signaling. Another explanation may be supplied by the finding that supraphysiological leptin concentrations do not trigger maximal effects. Thus, under physiological circumstances leptin stimulates gonadotropin release by both hypothalamic and pituitary actions. However, the highest leptin concentration tested decreased gonadotropin secretion (Yu et al. 1997). This may be explained by a saturation of receptors by supraphysiological leptin concentrations and receptor down-regulation as a defence mechanism.

Observations linking very low adiposity with impaired reproductive function have led to the critical fat hypothesis that relates an ideal percentage of body fat to sexual maturation. Because leptin levels reflect adipose mass, extreme changes in body fat may alter leptin levels below or above a threshold range necessary for correct signaling to the reproductive axis. Perhaps leptin is not the primary signal that initiates the onset of puberty but rather acts in a permissive fashion, as a metabolic gate, to allow pubertal maturation to proceed, if and when metabolic resources are deemed adequate (Cheung et al. 1997).

Gema Fruhbeck
Dunn Clinical Nutrition Centre,
Cambridge CB2 2DH, U.K.

LITERATURE CITED


