Ovarian function: a theory of relativity

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Kol and Homburg recently hypothesized in these pages that the change, rather than currently evaluated absolute hormone values, is important for biological processes. We fully agree, but wish, with this communication, to add to their concept: opposing forces, balancing each other, in order to maintain a system's stability, permeates nature. Loss of such equilibrium, in turn, results in systemic malfunctions with, at times, adverse consequences. Extrapolating to Kol and Homburg's hypothesis, this observation would suggest that not only changes in any given hormone carry biological messages, but that final message derives from hormonal ratios between hormones which oppose each other in physiological effects. In full concurrence to Kol and Homburg, this concept could give rise to better diagnosis and treatment of infertility problems.

Key words: ovarian function / physiological equilibrium / hormonal ratios / LH / FSH

As early as in the year 1933, Stein and Leventhal recognized the crucial importance of hormone balances for normal human reproduction. Their description of detrimental effects of excessive LH, in comparison with FSH levels, on folliculogenesis, in women with 'polycystic ovary syndrome', laid one of the cornerstones for successful assisted reproduction (Stein and Leventhal, 1935). The consequent description of the so-called 'two cells, two gonadotrophins—hypothesis' by Falck (1959), which codified the, since then, universally accepted concept of precise FSH/LH interaction as a prerequisite for normal follicular development and maturation, provided the basis for modern fertility treatments.

Since these groundbreaking works by Stein/Leventhal and Falck and associates, human reproduction has become to be seen as a complex system of interactions and feedback mechanisms, highly susceptible to disruption. We, however, also understand that the principle of duality, the presence of opposing forces, held in a normal equilibrium, is a mainstay of normal reproductive physiology. Examples are the activities of androgens and estrogens, FSH and LH, and activin and inhibin, all embedded in synergistic and antagonistic cascades of events which, even if only disturbed in a single component, can result in the breakdown of large components of the reproductive process.

Why are so many important issues unresolved?

The scientific literature in reproductive medicine is characterized by often greatly diverging opinions on even fundamental questions of daily clinical practice (Gleicher and Karande, 2000; Pehlivan et al., 2003; van Rooij et al., 2003). Why opinions on some of the most important issues in clinical reproductive medicine have remained so divergent is puzzling.

Kol and Homburg recently suggested that one important reason may lie in the profession's concentration on absolute hormone levels. They argue that what affects biological messaging are not absolute hormone levels but their change over, often, short time periods (Kol and Homburg, 2008).

Although we fully agree with their hypothesis, we feel that it mandates expansion since it still concentrates on the effects of single (hormonal) forces and fails to consider the importance of ratios between hormones with physiologically opposing functions, when analysing clinical outcome data. For example, to consider FSH without LH levels, or inhibin without activin, overlooks that the physiology of reproduction, like other systems of nature, is principally based on...
balanced interrelationships of opposing forces. As we affect one factor in this balance, its opposing counterpart has to be adjusted in parallel in order to maintain balance or, alternatively, the system becomes unbalanced.

The interplay of LH and FSH represents a good example: LH levels, alone, apparently do not demonstrate predictive value for IVF outcomes (Bjercke et al., 2005). We, however, previously reported that in women with diminished ovarian reserve (defined by basal FSH levels of 10.1–15.0 mIU/ml), high-normal LH levels (i.e. a low FSH/LH ratio) represented a good prognostic indicator and low-normal LH levels (high FSH/LH ratio) represented a comparatively poor indicator of oocyte yield (Weghofer et al., 2005). Liu and Greenblatt only very recently confirmed this initial report by demonstrating that an FSH/LH ratio ≥2 was significantly associated with poorer IVF cycle outcomes and increased cancellation rates (Liu and Greenblatt, 2008). These data, like the so-called threshold concept of Palermo and associates, who suggested that normal FSH levels, in the presence of unusually high LH, lead to lower pregnancy chances (Palermo, 2007), point towards a rather obvious need for ‘appropriate’ FSH/LH ratios to affect appropriate steroidogenesis.

Our concept of the importance of hormonal ratios, rather than absolute hormonal levels, an expansion of the hypothesis by Kol and Homburg, suddenly appears to explain why so many fundamental questions in reproductive medicine have remained unresolved: they simply may not have one single answer since every answer is relative, depending on where the balance of any given system lies. Finding the right point of balance may be further complicated by the patient’s age, her ovarian function or other factors that may require specific stratification and individualization of care.

**Clinical applications**

A number of additional examples for this concept come to mind: controlled ovarian stimulation, for example, clearly interferes with the balance of agonistic and antagonistic forces within the ovary and over-rides their endogenous patterns of control. One can speculate that women with normal ovarian function will be able to adjust, establish a new equilibrium and, consequently, conceive. Older patients with diminished ovarian reserve may, however, no longer be able to do so well and may require additional and/or different approaches to exogenous ovarian stimulation to reach a new equilibrium of ovarian function. For example, the literature suggests that younger women require more LH stimulation than older patients (Rekha et al., 1998). Older women may, in contrast, benefit more from progesterone substitution of the luteal phase since luteal phase progesterone appears to decrease with advancing age, reflective of increasing corpus luteum insufficiency (Malhi et al., 2005).

Continuing with the LH/FSH ratio as an example for our argument in favour of an expansion of Kol and Homburg’s hypothesis, these authors astutely cited contradictions in LH levels in the assessment of ovarian function as one example for their thesis (Kol and Homburg, 2008). LH can, indeed, also be viewed as an example of the kind of hormonal disequilibrium our expanded concept refers to. Shrim et al., for instance, describe the FSH/LH ratio as an integral marker for the assessment of ovarian reserve (Shrim et al., 2006), whereas, as Bjercke et al. recently suggested, LH levels, after pituitary suppression, are not at all predictive of ovarian function (Bjercke et al., 2005). As Kol and Homburg also noted (Kol and Homburg, 2008), its short half-life of only ~20 min and its dependence on consistent GnRH pulsatility (Speroff and Kase, 1999) make LH especially vulnerable to disturbances. Within the context of hormonal equilibriums, LH should, therefore, be especially dependent on levels of other hormones, such as FSH and, possibly, androgens. One, indeed, within such a context, expects LH to function ‘properly’ only within a satisfactory constellation of other interacting hormones. In the absence of such balance, it may even exert harmful effects.

Such variations of responses to even constant LH levels, though at varying levels of other hormones, antagonistic to LH activity, potentially very well explain contradictory data in the literature. By combining in one study patients with, and without, proper LH/antagonist balances, the numerically dominant patient group will determine outcome. If both groups are of equal size, they may very well balance out and give the erroneous impression of absent effects. We actually demonstrated this, when reporting a significant reduction in oocyte numbers in women with relatively high basal FSH and relatively low basal LH levels, compared with patients with equal levels of FSH but relatively higher (though still normal) LH values (Weghofer and Feichtinger, 2006). Confirming Bjercke et al. (2005), basal LH alone was, however, not predictive of ovarian function (Weghofer and Feichtinger, 2006).

LH alone was, thus, not predictive of ovarian function. In combination with its opposing hormone, FSH, it was, however, suggested that normal ovarian function may not be dependent on either hormone alone, but dependent on an equilibrium of both.

**The law of relativity**

The sum of all of these observations strongly supports the notion that what constitutes normal hormone levels is relative and that different clinical circumstances call for different normal hormone levels in efforts to maintain or re-establish equilibrium.

As also discussed by Kol and Homburg (2008), this law of relativity can in addition explain contradictory results with profound GnRH suppression (Penarubia et al., 2003; De Placido et al., 2005). For example, it is very reasonable to assume, in full agreement with Kol and Homburg, that profound suppressive effects of GnRH are not primarily a consequence of LH suppression, but reflect abilities, or inabilities, of the endocrine system to establish a new equilibrium that takes into account the relative lack of LH during pituitary suppression.

All of this suggests that it may be time to abandon the concept of sufficiently accurate single ovarian function parameters and, instead, turn towards potential interplays of hormones. The literature, indeed, provides ample examples for such an approach: contrast the lack of predictive value of basal LH levels, alone, on ovarian function with the clinical relevance of FSH/LH ratios, as described by Mukherjee et al. (1996). Or, consider the controversy over FSH levels as a single criterion to exclude patients from fertility treatment (Toner, 2004) and contrast these data with results obtained by simultaneously evaluating FSH and inhibin levels (Yong et al., 2003) or the FSH/E2 ratio (Ranieri et al., 1998). Estradiol levels, alone, offer less than in combination with progesterone (Younis et al., 2001), and the addition of androgens, as suggested by Frattarelli and associates (Frattarelli and Peterson, 2004), may even further improve predictive values.
Conclusions

Human reproduction represents a highly complex network of autocrine and paracrine interrelationships between hormones and cytokines. It, thus, in many ways mimics the human immune system, which in a similar fashion maintains equilibrium, even though constantly challenged. Jerne’s idiotypic network theory a few decades ago explained how the body protects itself from runaway immunological reactions in response to outside stimuli, always striving for a return to equilibrium (Jerne, 1984). Our hypothesis presented here suggests that the human hormonal system, very likely, also constantly strives for such equilibrium.

Such a concept, of course, has considerable potential significance for our understanding of reproductive physiology, but also for routine infertility treatments. It means that effects of hormones, which interact with each other, will fluctuate in response to auto- and paracrine environments and, of course, in response to therapeutic interventions. As already noted by Kol and Homburg, absolute hormone levels, therefore, need to be interpreted with caution (Kol and Homburg, 2008) and hormone should be seen as only relative, rather than absolute. Such a relative interpretation of laboratory results is already well established in prenatal diagnosis (Babbur et al., 2005).

Like the hypothesis by Kol and Homburg (2008), our expanded concept should be easily confirmed if re-establishment of hormonal equilibriums will achieve superior clinical success rates. In addition, however, this concept, hopefully, will also be able to explain many of the contradictions that have plagued the reproductive medicine literature for much too long.

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