# Hypersecretion of luteinizing hormone in the polycystic ovary syndrome and a novel hormone 'gonadotrophin surge attenuating factor'

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## INTRODUCTION

Tonic hypersecretion of luteinizing hormone (LH) occurs only in women with the polycystic ovary syndrome (PCOS), which is a common condition affecting both fertility and pregnancy outcome. In particular, the finding of an elevated serum LH concentration has been associated with an increased risk of infertility and miscarriage. Several hypotheses exist to explain the mechanisms that lead to perturbed LH secretion. Treatment strategies have been developed to suppress serum LH levels, although whether they have a beneficial effect on conception and miscarriage rates is still uncertain.

## HYPERSECRETION OF LUTEINIZING HORMONE

Controversy surrounds the diagnosis of the polycystic ovary syndrome (PCOS), with different authors using various criteria to define the syndrome. In the UK it is generally now accepted that polycystic ovaries detected by ultrasound scan provide the unifying diagnostic criterion. The additional symptoms (oligo/amenorrhoea, obesity, hyperandrogenism) and biochemical disturbances (elevated serum concentrations of LH, androgens and insulin) may each occur together or in isolation with the ultrasound picture and hence result in the PCO syndrome.

The characteristics of 1741 patients with polycystic ovary syndrome were examined[1]. Of the patients, 38.4% were overweight (BMI>25 kg/m$^2$), 39.8% had an elevated serum concentration of LH (>10 iu/l) and 28.9% had an elevated serum testosterone concentration (>3.0 nmol/l). With respect to menstrual history: 47.0% had obligomenorrhoea; 29.7% had a normal menstrual cycle; 19.2% had amenorrhoea; 2.7% had polymenorrhoea; and 1.4% had menorrhagia. A number of women (63.4%) had not yet tested their fertility. Of the remaining women: 49% had primary infertility; 26% had secondary infertility; and 25% had proven fertility. The serum LH concentration of those with primary infertility was significantly higher than that of women with secondary infertility ($P<0.05$) and both were higher than the LH concentration of those with proven infertility ($P<0.05$). The rate of infertility increased if the serum LH concentration was greater than 10 iu/l. There was also a significant increase in the rate of cycle disturbance with serum LH concentrations greater than 10 iu/l.

It was first demonstrated in 1985 that oocytes obtained from women undergoing *in vitro* fertilization (IVF) who had a serum LH value greater than one standard deviation above the mean on the day of administration of hCG had a significantly reduced rate of fertilization and cleavage[2]. In a study of 538 patients undergoing IVF for conditions other than anovulatory infertility, polycystic ovaries were detected by ultrasound in 45.3% of those who miscarried compared with 31.4% of those with ongoing pregnancies ($P=0.0038$)[3]. In the patients with polycystic ovaries there was a highly significant reduction in the rate of miscarriage when buserelin was used to achieve pituitary desensitization (and hence suppression of LH) followed by stimulation with hMG compared with the use of clomiphene and hMG (15/74 versus 51/108, $P=0.0003$). There was no improvement in miscarriage rates with pituitary desensitization, however, in patients who did not have polycystic ovaries[3].

A field study of 193 women planning to become pregnant showed that raised mid-follicular phase serum LH concentrations were associated with both a lower conception rate (67%) and a much higher miscarriage rate (65%), compared with those in women with normal serum LH concentrations (88% and 12%, respectively)[4]. LH has a role in the suppression of the oocyte maturation inhibitor (OMI). Oocytes are maintained in the first meiotic division from their appearance in the ovary during intra-uterine life until just before ovulation, when oocyte maturation is completed, germinal vesicle breakdown occurs and the first polar body is extruded. Our hypothesis to explain the adverse effect of hypersecretion of LH on human fertility is that hypersecretion of LH during the follicular phase results in an elevated concentration of intrafollicular LH which in turn results in premature oocyte maturation, with subsequent ovulation of a prematurely matured egg. Thus, inappropriate release of LH may profoundly effect the timing of oocyte maturation such that the released egg is either unable to be fertilized, or if fertilized miscarries.

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## AETIOLOGY OF HYPERSECRETION OF LH

The precise mechanisms that control LH production and secretion have still to be fully determined. Furthermore, the reasons for hypersecretion of LH in women with the polycystic ovary syndrome also remain to be satisfactorily explained. Some studies have described an increase in both the pulse frequency and amplitude of LH release[5,6]. Whilst an elevation of pulse amplitude has been consistently demonstrated, many groups have failed to find an elevation of pulse frequency[7–11]. The differing conclusions of these separate studies may result from different study populations: alternatively, any differences in pulse frequency may be too small to represent an aetiological role for the hypothalamus in hypersecretion of LH. Most compelling are the data collected in women undergoing laparoscopic ovarian diathermy, in whom LH pulse amplitude decreased after the procedure but no change in the normal pulse frequency was detected[12,13]. Rossmanith *et al.*[12] found an attenuation of LH releasing hormone (LHRH)-stimulated LH secretion after laparoscopic ovarian diathermy, a result consistent with abnormalities in the production of an ovarian factor(s) that regulates LH secretion, rather than with the theory that the disorder starts at the level of either the hypothalamus or pituitary.

We have recently found that some women with hypogonadotrophic hypogonadism also have polycystic ovaries detected by pelvic ultrasound. When these women were treated with pulsatile LHRH to induce ovulation they had significantly higher serum LH concentrations during the follicular phase than women with hypogonadotrophic hypogonadism and normal ovaries who were treated in the same way[14]. Furthermore, the elevation of LH concentrations preceded the rise of serum oestradiol concentrations. Thus, hypersecretion of LH still occurs when the hypothalamus has been replaced by an exogenous LHRH pulse generator (i.e. the LHRH pump), with a fixed LHRH pulse interval of 90 min (equivalent to the pulse interval of the normal early follicular phase). These studies suggest that hypersecretion of LH involves a perturbation of ovarian-pituitary feedback, rather than of hypothalamic pulse regulation.

Insulin is facilitatory to pituitary LH secretion[15] and it has been suggested that the common association between insulin resistance and the PCOS may result in a direct effect of hyperinsulinaemia driving the gonadotroph to hypersecrete LH. In our clinical practice, however, it is often slim, non-hyperinsulinaemic women with polycystic ovaries who hypersecrete LH[16].

It is the abnormal ovary which is central to the PCOS[17], so it is reasonable to explore whether an ovarian disturbance might effect pituitary secretion of LH. The polycystic ovary over-secretes androgens, which are metabolized to oestrogens (oestradiol in the ovary but principally oestrone in the extra-glandular body fat). Exogenously administered androgens do not result in an elevation of either LH pulse amplitude or frequency, whether administered acutely or long term. Indeed supraphysiological levels of testosterone suppress LH secretion[18].

Oestrogens sensitize the pituitary to gonadotrophin (Gn)RH and also enhance self-priming by GnRH, which increases pituitary sensitivity and reserve[19]. It has been proposed that hypersecretion of LH is the consequence of the elevated circulating oestrone levels found in women with the PCOS. The administration of exogenous oestrone to women with normal or polycystic ovaries over periods of 5–15 days did not, however, increase serum LH levels or the sensitivity of the pituitary to exogenously administered GnRH[20]. Ovarian peptide hormones have important effects on pituitary gonadotrophin secretion. Inhibin and its related peptides act primarily on follical-stimulating hormone (FSH) secretion. Inhibin secretion does not appear to be disturbed in the PCOS[21]. The fact that the normal mid-cycle LH surge is sometimes attenuated when the ovary is stimulated to produce many follicles has led to the proposition that there is a substance of follicular origin which suppresses the GnRH-induced release of LH from the pituitary. This substance has yet to be characterized but it appears to be a peptide and is different from inhibin. It has been termed gonadotrophin surge attenuating or inhibitory factor (GnSAF or GnSIF)[22,23]. GnSAF appears to act at the level of the pituitary. Deficiency of GnSAF, or another ovarian LH inhibitory factor, has been postulated to result in hypersecretion of LH[24]. We are currently exploring this hypothesis, which may explain how disordered feedback from the polycystic ovary results in abnormalities in gonadotrophin secretion. Preliminary data indicates that GnSAF is a novel hormone which inhibits gonadotrophin secretion *in vitro* and does not appear to be a member of the inhibin family as it is not immunoneutralized by an anti-inhibin antibody[25].

## CONCLUSIONS

Polycystic ovaries can be detected in about 20% of the population[26] and of those who have the polycystic ovary syndrome, about 40% hypersecrete LH. As many as 50% of women attending infertility clinics may have polycystic ovaries, although not necessarily symptoms of the polycystic ovary syndrome. Of the endocrine and metabolic sequelae of the PCOS, it is hypersecretion of LH that has the most significant impact on fertility and miscarriage, possibly by disturbing the timing of oocyte maturation. Hypersecretion of LH is only found in women with the PCOS and, despite much debate, there is still no satisfactory explanation for its aetiology. Strategies to suppress LH secretion during

ovulation induction regimens include the use of GnRH agonists and laparoscopic ovarian diathermy. It appears likely that these two treatments have a beneficial effect on miscarriage rates, but this has still be conclusively demonstrated in prospective, randomized trials.

## REFERENCES


1 Balen AH, Conway GS, Kaltsas G, *et al.* Polycystic ovary syndrome: The spectrum of the disorder in 1741 patients. *Hum Reprod* 1995 (in press)

2 Stanger JD, Yovich JL. Reduced in-vitro fertilisation of human oocyte from patients with raised basal luteinising hormone levels during the follicular phase. *Br J Obstet Gynaecol* 1985;**92**:385–93

3 Balen AH, Tan SL, MacDougall J, Jacobs HS. Miscarriage rates following in vitro fertilisation are increased in women with polycystic ovaries and reduced by pituitary desensitisation with buserelin. *Hum Reprod* 1993;**8**:959–64

4 Regan L, Owen EJ, Jacobs HS. Hypersecretion of luteinising hormone, infertility and miscarriage. *Lancet* 1990;**336**:1141–4

5 Rebar R, Judd HL, Yen SCC, Rakoff J, Vandenberg G, Naftolin F. Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. *J Clin Invest* 1976;**57**:1320–9

6 Burger CW, Korsen T, Van Kessel H, Van Dop PA, Caron FJM, Schoemaker J. Pulsatile luteinizing hormone patterns in the follicular phase of the menstrual cycle, polycystic ovarian disease (PCOD) and non PCOD secondary amenorrhoea. *J Clin Endocrinol Metab* 1988;**61**:1126–32

7 Baird DT, Corker CS, Davison DW, Hunter WM, Michie EA, Van Look PFA. Pituitary ovarian relationships in polycystic ovary syndrome. *J Clin Endocrinol Metab* 1977;**45**:798–809

8 Kazer RR, Kessel B, Yen SS. Circulating luteinizing hormone pulse frequency in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1987;**65**:233–6

9 Sagle M, Kiddy D, Mason HD, Dobriansky D, Polson DW, Franks S. Evidence for normal hypothalamic regulation of LH in ovulatory women with the polycystic ovary syndrome. In: Rolland R, Heineman MJ, eds. *Neuroendocrinology of Reproduction* Amsterdam: Excerpta Medica, 1987

10 Venturoli S, Porcu E, Fabbri R, *et al.* Episodic pulsatile secretion of FSH, LH, prolactin, oestradiol, oestrone and LH circadian variations in polycystic ovary syndrome. *Clin Endocrinol* 1988;**28**:93–107

11 Murdoch AP, Diggle PJ, White MC, Kendall-Taylor P, Dunlop W. LH in polycystic ovary syndrome: reproducibility and pulsatile secretion. *J Endocrinol* 1989;**121**:185–91

12 Rossmanith WG, Keckstein J, Spatzier K, Lauritzen C. The impact of ovarian laser surgery on the gonadotrophin secretion in women with polycystic ovarian disease. *Clin Endocrinol* 1991;**34**:223–30

13 Gadir AA, Khatim MS, Mowafi RS, Alnaser HMI, Alzaid HGN, Shaw RW. Hormonal changes in patients with polycystic ovarian disease after ovarian electocautery or pituitary desensitization. *Clin Endocrinol* 1990;**32**:749–54

14 Schachter M, Balen AH, Patel A, Jacobs HS. Hypogonadotropic patients with ultrasonographically detected polycystic ovaries have aberrant gonadotropin secretion when treated with pulsatile gonadotropin releasing hormone—a new insight to the pathophysiology of polycystic ovary syndrome. *Fertil Steril* 1995 (in press)

15 Adashi EY, Hsueh AJW, Yen SSC. Insulin enhancement of luteinising hormone and follicle stimulating hormone release by cultured pituitary cells. *Endocrinology* 1981;**108**:1441–9

16 Conway GS, Honour JW, Jacobs HS. Heterogeneity of the polycystic ovary syndrome: clinical, endocrine and ultrasound features in 556 patients. *Clin Endocrinol* 1989;**30**:459–70

17 Jacobs HS. Polycystic ovaries and polycystic ovary syndrome. *Gynecol Endocrinol* 1987;**1**:113–31

18 Spinder T, Spijkstra JJ, van den Tweel JG, *et al.* The effects of long term testosterone administration on pulsatile luteinizing hormone secretion and on ovarian histology in eugonadal female to male transsexual subjects. *J Clin Endocrinol Metab* 1989;**69**:151–7

19 Wang CR, Lasley BL, Lein A, Yen SSC. The functional changes of the pituitary gonadotrophs during the menstrual cycle. *J Clin Endocrinol Metab* 1976;**42**:718–28

20 Chang RJ, Mandfdel FP, Lu JK, Judd HL. Enhanced disparity of gonadotropin secretion by estrone in women with polycystic ovarian disease. *J Clin Endocrinol Metab* 1982;**54**:490–4

21 Buckler HM, McLachlan RI, MacLachlan VB, Healy DL, Burger HG. Serum inhibin levels in polycystic ovary syndrome: basal levels and response to luteinising hormone-releasing hormone agonist and exogenous gonadotrophin administration. *J Clin Endocrinol Metab* 1988;**66**:798–803

22 Sopelak VM, Hodgen GD. Blockade of the estrogen-induced luteinising hormone surge in monkeys: a nonsteroidal, antigenic factor in porcine follicular fluid. *Fertil Steril* 1984;**41**:108–13

23 Messinis IE, Templeton A, Baird DT. Endogenous luteinising hormone surge during superovulation induction with sequential use of clomiphene citrate and pulsatile human menopausal gonadotrophin. *J Clin Endocrinol Metab* 1985;**61**:1076–80

24 Balen AH, Jacobs HS. Gonadotrophin surge attenuating factor: a missing link in the control of LH secretion? *Clin Endocrinol* 1991; **35**:399–402

25 Balen AH, Er J, Rafferty B, Rose M. Evidence that gonadotrophin surge attenuating factor is not inhibin. *J Reprod Fert* 1995 (in press)

26 Polson DW, Wadsworth J, Adams J, Franks S. Polycystic ovaries: a common finding in normal women. *Lancet* 1988;**i**:870–2


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