Chapter 3

LH as a diagnostic criterion for polycystic ovary syndrome in patients with WHO II oligo/ amenorrhoea

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ABSTRACT

Elevated LH is common in polycystic ovary syndrome (PCOS), but is not part of the diagnostic criteria. LH concentrations are usually assessed in the early 'follicular' phase when it is suppressed, and therefore the prevalence is underestimated. In this study, LH is measured during the 'specific oligomenorrhoeic phase', when LH is least suppressed, and its importance as a diagnostic tool for PCOS is evaluated. Patients presenting with oligo- or amenorrhoea between 2002 and 2006 were selected, with the exclusion of women with WHO III oligoamenorrhoea, hyperprolactinaemia or with wrongly timed endocrine measurements. A total of 252 patients were included (198 oligo/amenorrhoeic PCOS patients and 54 oligo/amenorrhoeic controls). Mean LH concentrations were higher in PCOS patients than in controls (11.0 versus 4.1 IU/l, $P<0.001$). The receiver operating characteristics (ROC) curve showed an optimal cut-off for LH of ≥6.5 IU/l, resulting in a sensitivity of 84%, specificity of 78% and a likelihood ratio of 3.8, and elevated LH concentrations predicted PCOS accurately in 93%. In conclusion, elevated LH concentrations are found in a large majority of PCOS patients when measured at the appropriate time, and could be used as an additional diagnostic test to differentiate between oligo/amenorrhoeic PCOS patients and other causes of oligo- or anovulation.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility (Adams *et al*., 1986) and is characterized by symptoms of hyperandrogenism, oligo- or amenorrhoea, polycystic ovarian morphology, central obesity and insulin resistance. The presentation of PCOS symptoms is very heterogeneous, and this heterogeneity is the main reason for a continuous debate on the definition of PCOS (Azziz, 2005, 2006; Franks, 2006). Two definitions of PCOS are used today. The first, from 1990, the National Institutes of Health (NIH) criteria, defines PCOS by hyperandrogenism and oligo-ovulation. Recently a broader definition of PCOS was made in an ESHRE/ASRM consensus meeting, the 2003 Rotterdam criteria. This defines PCOS when at least two out of three features are present: (i) oligo- or anovulation (OA); (ii) clinical and/or biochemical signs of hyperandrogenism (HA); and (iii) polycystic ovaries (PCOM) (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2003). This results in four PCOS phenotypes, namely three groups with two criteria (OA + HA, OA + PCOM and HA + PCOM) and one group with all three criteria (OA + HA + PCOM). Both definitions exclude other aetiologies, such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome.

LH has been omitted from both diagnostic criteria as unnecessary (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2003). LH has been assessed as a diagnostic test to discriminate between women with PCOS and healthy controls, and the LH/FSH ratio in particular was found to be predictive (Turhan *et al*., 1999). Elevated LH is an inextricable feature of PCOS, found in about half of PCOS patients (Fauser *et al*., 1992; van Santbrink *et al*., 1997), but the large variety in reported prevalence, from 35 to 77% (Deutsch *et al*., 1978; Robinson *et al*., 1992), makes it difficult to use LH as a PCOS criterion. The cause of the high variability in prevalence of elevated LH is due to differences in the timing of LH sampling. Most studies measure LH in the early follicular phase (cycle day 3), but due to the intercycle variation of LH, the prevalence of high LH concentrations in PCOS is probably underestimated (van Hooff *et al*., 1999). Temporary normalization of LH concentrations occurs in the luteal and early follicular phase and after progesterone-induced withdrawal bleeding (Minakami *et al*., 1988; Anttila *et al*., 1992). The optimal time for measuring LH concentrations is when LH is minimally suppressed, and this is between at least 2 weeks from the start of the menstruation and at least 3 weeks before the next period. This phase is called the 'specific oligomenorrhoeic phase' (SOP) (van Hooff *et al*., 1999), and only exists in cycles longer than 35 days.

The aim of the present study was to evaluate the prevalence of elevated LH concentrations in adequately timed samples in oligo/amenorrhoeic PCOS patients and oligo/amenorrhoeic controls, and to assess the importance of LH as a diagnostic tool for PCOS.

MATERIALS AND METHODS

Patient and control population

All patients presenting with oligo- or amenorrhoea between October 1st, 2002 and April 1st, 2006, in the outpatient clinic of Reproductive Medicine of the VU University Medical Center in Amsterdam, The Netherlands were screened. For this retrospective anonymous evaluation, informed consent was waived by the Medical Ethics Board. The optimal time for LH measurements is in the specific oligomenorrhoeic phase (for definition, see Introduction), and for this reason only patients with an average cycle longer than 35 days were selected, with the exclusion of women with WHO III imminent or premature ovarian failure (FSH≥10 IU/l), hyperprolactinaemia (>0.60 IU/l), Cushing's syndrome, congenital adrenal hyperplasia and androgen-secreting tumours.

Patients were diagnosed as PCOS according to the Rotterdam classification, when at least two out of the three following criteria were present: OA, biochemical or clinical HA and PCOM (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2003). Controls consisted of oligo- or amenorrhoeic patients with none or one of the Rotterdam criteria listed above. Of the 392 screened oligo-/amenorrhoeic patients, 252 women were eligible for this study, consisting of 198 PCOS patients conforming to the Rotterdam criteria and 54 oligo-/amenorrhoeic control patients.

Screening

According to local protocol, all patients with oligo- or amenorrhoea underwent transvaginal ovarian ultrasound, were evaluated for clinical signs of hyperandrogenism and underwent laboratory screening during the specific oligomenorrhoeic phase.

Pelvic ultrasound examination

Transvaginal pelvic ultrasound was performed in both PCOS patients and controls. PCOM was confirmed when 12 or more follicles (2–9 mm) in each ovary and/or increased ovarian volume (>10 ml) were seen, conforming to the Rotterdam guidelines (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group', Human reproduction, 2004).

Hyperandrogenism

Patients were diagnosed with hyperandrogenism in the presence of clinical and/or biochemical signs of androgen excess. For assessing hirsutism, nine body areas were screened and a Ferriman-Gallwey score of ≥8 was regarded as clinical hyperandrogenism (Ferriman and Gallwey, 1961). Biochemical hyperandrogenism was diagnosed when testosterone was >2.5 nmol/l and/or androstenedione >9.0 nmol/l. The normal ranges were obtained from the manufacturers, re-

evaluated and confirmed in a local laboratory. Free testosterone concentrations could not be obtained, as sex hormone binding globulin was not measured.

Endocrine measurements

Laboratory screening was performed by the endocrine laboratory of the VU medical centre. Plasma LH concentrations were determined by immunometric assay (Delfia, Wallac, Turku, Finland), with a lower detection limit of 0.3 IU/l and an intra-assay coefficient of variation of 4% at a concentration of 2 IU/l and of 3% at more than 3 IU/l. Androstenedione was measured using radioimmunoassay (DSL, Webster, Texas, USA) with a lower detection limit of 0.5 nmol/l. Testosterone was analysed with a radioimmunoassay (Coat-A-Count; DPC, Los Angeles, USA) with a lower detection limit of 1.0 nmol/l. Oestradiol was determined by radioimmunoassay (DiaSorin, Saluggia, Italy) with a lower detection limit of 18 pmol/l. Progesterone was analysed using competitive immunoassay (Architect; Abbott Laboratories Diagnostic Division, Abbott Park, IL, USA) with a lower detection limit of 2 nmol/l.

Laboratory screening was performed during the specific oligomenorrhoeic phase. In practice, this meant that in patients with oligo/amenorrhoea, blood was sampled on cycle days 14 and 21, and once randomly in patients with amenorrhoea. Measurements that were retrospectively assessed as not performed within the specific oligomenorrhoeic phase were excluded (oestradiol ≥400 pmol/l and/or progesterone ≥5 nmol/l). When two or more adequately timed measurements were available, the measurement with the highest LH concentration was used in the analysis. Of the included patients, women with low LH (≤2.0 IU/l), FSH (≤2.0 IU/l) and/or oestradiol (≤80 pmol/l) concentrations were diagnosed as hypogonadotrophic (WHO I).

Statistical methods

Statistical analysis was performed using SPSS software (version 12.0.1, Inc., Chicago, IL, USA). A P-value of <0.01 was considered significant (Mainland, 1984). In case of two independent groups, an independent Student's t-test was used to compare the normally distributed data, and for the comparison of three or more normally distributed groups variance analysis (ANOVA) was used in combination with the Bonferoni post-hoc test to identify differences between subgroups. To test the diagnostic value of LH a receiver operating characteristics (ROC) curve was plotted, using the Rotterdam criteria as a gold standard. An optimal cut-off point was identified by calculating its associated sensitivity plus specificity at each LH concentration. The Pearson correlation coefficient was used to evaluate the correlation between variables.

RESULTS

Of the 392 oligo/amenorrhoeic patients 252 women were eligible for this study, consisting of 198 PCOS patients conforming to Rotterdam criteria and 54 oligo-/amenorrhoeic control patients (Figure 1). In the PCOS group, 113 patients had oligomenorrhoea and 85 women suffered from amenorrhoea; the controls comprised 16 oligomenorrhoeic and 38 amenorrhoeic women (23 women with hypogonadotrophic oligo/amenorrhoea, 19 women with normogonadotrophic oligo/amenorrhoea and 12 women with cycle irregularities of an unknown cause). The majority of PCOS and control patients (148) had two adequately timed LH measurements. The clinical and hormonal features of both populations are shown in Table 1. The PCOS patients and controls were comparable for age and BMI. Mean LH concentrations (11.0 IU/l versus 4.1 IU/l) (Figure 2), FSH, oestradiol, testosterone and androstenedione were significantly higher in the PCOS patients compared with controls. A correlation was found by the Pearson correlation coefficient between LH concentrations and testosterone ($r=0.31$, $P<0.001$) and androstenedione concentrations ($r=0.22$, $P=0.004$) in PCOS patients only. No correlation was found between LH concentrations and age or BMI in PCOS patients or controls.

LH as a diagnostic test for PCOS

The value of LH as a diagnostic test for PCOS was assessed with a ROC curve, using Rotterdam criteria as a gold standard. A curve close to the left upper corner was seen (Figure 3), and several cut-off values of LH were analysed for its sensitivity and specificity (Table 2). An optimal cut-off point (highest specificity plus sensitivity) of LH was set at ≥6.5 IU/l. With this cut-off point, LH had a sensitivity of 84%, a specificity of 78%, positive and negative predicting values of 93 and 58% respectively and a likelihood ratio of 3.8. The area under the curve reached a value of 0.88 (0.83–0.93, 95% confidence interval). Assessment of the value of LH as a diagnostic test for the Rotterdam subgroups showed an optimal cut-off of ≥6.5 IU/l for patients with oligo/amenorrhoea and hyperandrogenism (1990 NIH criteria), with a sensitivity and specificity of 85 and 78% respectively. The area under the curve was 0.89 (0.84–0.94, 95% confidence interval). The subgroup with oligo/amenorrhoea and polycystic ovaries showed an optimal cut-off of ≥6.2 IU/l, resulting in a sensitivity of 90% and a specificity of 74%. The area under the curve reached a value of 0.89 (0.84–0.94, 95% confidence interval).

PCOS phenotypes

The Rotterdam criteria create four different PCOS phenotypes. Within the study population three phenotypic groups exist, women with all three criteria (OA, HA and PCOM) and two groups of patients with two out of the three criteria (OA + HA or OA + PCOM). Table 3 shows the mean hormone concentrations of these three groups of PCOS women and the controls. BMI was found to be higher in the PCOS group with all three diagnostic criteria compared with PCOS

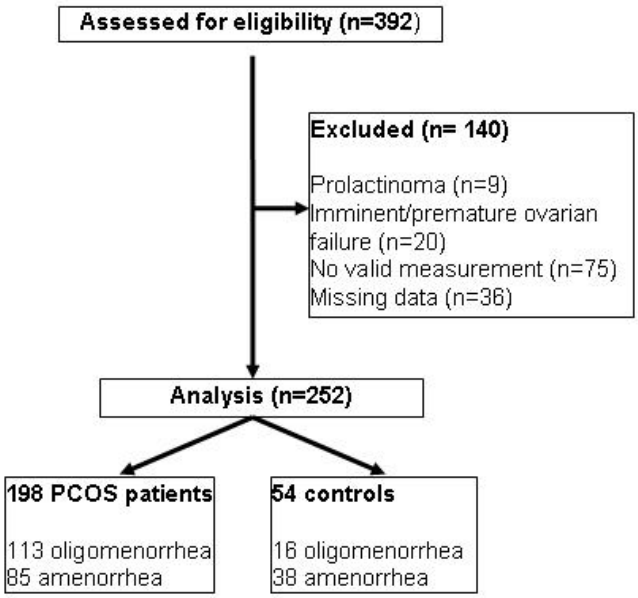

Figure 1. Flow chart of study enrolment.

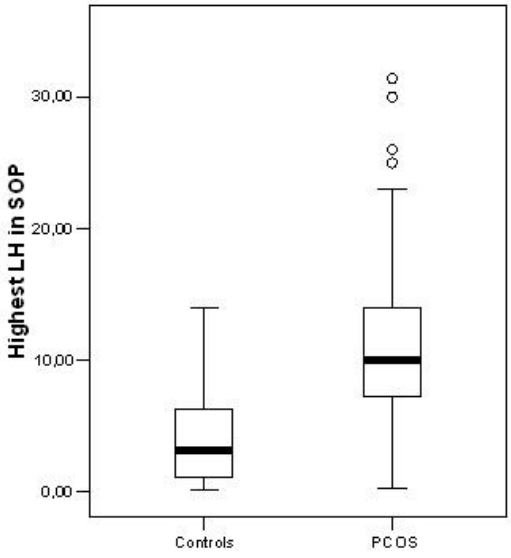

Figure 2. Box-and-whisker plot of the highest LH measured in the specific oligomenorrhoeic phase in oligoammenorrhoeic PCOS patients and controls. The upper line of the box represents the upper quartile, the thick line in the middle the median and the lower line of the box is the lower quartile.

Table 1. Comparison of characteristics and endocrine parameters in PCOS patients and controls.

	PCOS patients (n = 198)	Controls (n = 54)	P-value
Age (years)	27.9 ± 5.2 (*n* = 198)	28.6 ± 6.0 (*n* = 54)	NS
BMI (kg/m^2)	25.1 ± 6.0 (*n* = 190)	23.4 ± 7.4 (*n* = 51)	NS
LH (IU/l)	11.0 ± 5.0 (*n* = 198)	4.1 ± 3.4 (*n* = 54)	<0.001
FSH (IU/l)	5.7 ± 1.2 (*n* = 195)	4.9 ± 1.9 (*n* = 53)	0.004
LH/FSH ratio	2.0 ± 0.9 (*n* = 195)	0.8 ± 0.6 (*n* = 53)	<0.001
Oestradiol (pmol/l)	150.6 ± 64.4 (*n* = 189)	118.7 ± 79.1 (*n* = 54)	0.003
Testosterone (nmol/l)	1.8 ± 0.7 (*n* = 164)	1.2 ± 1.0 (*n* = 45)	0.001
Androstenedione (nmol/l)	8.5 ± 2.8 (*n* = 175)	5.1 ± 1.8 (*n* = 47)	<0.001
Prolactin (IU/l)	0.2 ± 0.2 (*n* = 113)	0.2 ± 0.3 (*n* = 32)	NS

NS = not significant
Values are mean ± SD.

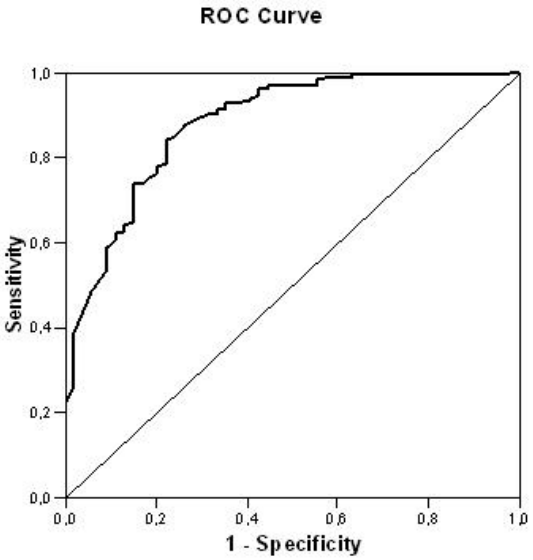

Figure 3. The receiver operating characteristic (ROC) curve for LH as a diagnostic test for oligo/amenorrhoeic PCOS patients, using the Rotterdam criteria as a gold standard. The area under the curve is 0.88.

Table 2. Various LH cut-off points and their sensitivity and specificity.

LH threshold concentration (IU/l)	Sensitivity (%)	Specificity (%)
6.0	89	70
6.5	84	78
7.0	78	80
7.5	74	85
9.0	59	91
10.5	49	94

women with OA and PCOM. By definition, testosterone and androstenedione were higher in the two PCOS groups with clinical or biochemical hyperandrogenism. The rest of the endocrine environment was comparable among the three PCOS groups, but significantly different from the controls. The prevalence of elevated LH (≥6.5 IU/l) in the PCOS group with all three diagnostic criteria was 87%, in the group with OA and HA 77%, 84% in the PCOS patients with OA and PCOM, and 22% in the controls.

Oligomenorrhoea versus amenorrhoea

The 113 PCOS women with oligomenorrhoea and the 85 PCOS patients with amenorrhoea are compared in Table 4. All features are comparable between these two groups. In the control group, LH was found to be significantly higher in the oligomenorrhoeic women than in amenorrhoeic patients (6.7 ± 3.4 and 3.0 ± 2.8 respectively, $P < 0.001$). The remaining hormonal values were comparable between the oligo- and amenorrhoeic control group (data not shown).

DISCUSSION

This study assessed the prevalence of elevated LH concentrations in adequately timed samples and its importance as a tool in the diagnosis of PCOS. High serum LH concentrations are often found in PCOS patients, and this is an inextricable feature of PCOS. An increased amplitude and frequency of pituitary LH pulses is seen in PCOS patients (Waldstreicher *et al*., 1988), and it is postulated that LH hypersecretion is caused by insufficient gonadotropin surge attenuating factor (GnSAF) production resulting in increased pituitary priming (Balen and Jacobs, 1991; de Koning *et al*., 2001). Besides causing ovulation and luteinization, LH is known to stimulate ovarian androgen production (Havelock *et al*., 2004), and is seen as one of the main causes for hyperandrogenism in PCOS patients. The role of elevated LH concentrations in the pathogenesis of PCOS is unclear, and the question remains if it is part of the cause of PCOS or is a result of the endocrine and cycle disturbances.

Table 3. Comparison of characteristics and endocrine parameters in PCOS patients with OA + HA + PCOM, OA + HA, OA + PCOM and controls.

	OA + HA + PCOM[a] (n = 102)	**OA + HA[b] (n = 34)**	**OA + PCOM[c] (n = 62)**	**Controls[d] (n = 54)**	**P-value (ANOVA)**
Age (years)	27.7 ± 4.8 (*n* = 102)	26.9 ± 6.7 (*n* = 34)	29.0 ± 4.8 (*n* = 64)	28.6 ± 6.0 (*n* = 54)	NS
BMI (kg/m^2)	26.1 ± 6.3 (*n* = 98)[c]	25.5 ± 6.9 (*n* = 34)	23.0 ± 4.3 (*n* = 58)[a]	23.4 ± 7.4 (*n* = 51)	0.009
LH (IU/l)	11.4 ± 4.7 (*n* = 102)[d]	10.2 ± 5.1 (*n* = 34)[d]	10.7 ± 5.3 (*n* = 62)[d]	4.1 ± 3.4 (*n* = 54)[a,b,c]	<0.001
FSH (IU/l)	5.8 ± 1.1 (*n* = 101)[d]	5.5 ± 1.2 (*n* = 34)	5.8 ± 1.4 (*n* = 60)[d]	4.9 ± 1.9 (*n* = 53)[a,c]	0.002
LH/FSH ratio	2.0 ± 0.9 (*n* = 101)[d]	1.9 ± 1.2 (*n* = 34)[d]	1.8 ± 0.9 (*n* = 60)[d]	0.8 ± 0.6 (*n* = 53)[a,b,c]	<0.001
Testosterone (nmol/l)	2.0 ± 0.7 (*n* = 93)[c,d]	1.8 ± 0.7 (*n* = 26)[c,d]	1.2 ± 0.3 (*n* = 45)[a,b]	1.2 ± 1.0 (*n* = 45)[a,b]	<0.001
Androstenedione (nmol/l)	9.5 ± 2.7 (*n* = 95)[c,d]	8.7 ± 2.9 (*n* = 30)[c,d]	6.3 ± 1.4 (*n* = 50)[a,b]	5.1 ± 1.8 (*n* = 47)[a,b]	<0.001
DHEAS (mmol/l)	5.7 ± 2.2 (*n* = 77)[d]	5.6 ± 2.1 (*n* = 25)	4.7 ± 2.3 (*n* = 41)	4.4 ± 1.8 (*n* = 34)[a]	0.008

HA = hyperandrogenism; NS = not significant; OA = oligo- or amenorrhoea; PCOM = polycystic ovarian morphology.

Values are mean ± SD.

a-d: Significant differences between groups are indicated by superscripts (Bonferoni post-hoc test).

Table 4. Comparison of characteristics and endocrine parameters in oligo- and amenorrhoeic PCOS patients.

	Oligomenorrhoea (n = 113)	**Amenorrhoea (n = 85)**
Age (years)	28.5 ± 5.4 (*n* = 113)	27.2 ± 4.8 (*n* = 85)
BMI (kg/m^2)	25.9 ± 6.3 (*n* = 106)	24.0 ± 5.5 (*n* = 84)
LH (IU/l)	11.3 ± 5.0 (*n* = 113)	10.5 ± 4.9 (*n* = 85)
FSH (IU/l)	5.8 ± 1.2 (*n* = 111)	5.6 ±1.2 (*n* = 84)
Testosterone (nmol/l)	1.7 ± 0.7 (*n* = 88)	1.8 ± 0.8 (*n* = 76)
Androstenedione (nmol/l)	8.1 ± 3.0 (*n* = 99)	8.9 ± 2.6 (*n* = 76)
LH/FSH ratio	2.0 ± 0.9 (*n* = 111)	1.9 ± 1.0 (*n* = 84)

There were no significant differences between the two groups of patients.

Values are mean ± SD.

The more severe forms of PCOS seem to be associated with higher LH concentrations. Previous studies show that follicle number and ovarian volume are positively related to LH (Pache *et al*., 1993; Balen *et al*., 1995; Fulghesu *et al*., 2006), and more severe cycle disturbances and an increased infertility rate were found with increasing LH concentrations in PCOS patients (Balen *et al*., 1995). Furthermore, with increasing age and decreasing number of follicles, PCOS patients regain regular menstrual cycles (Elting *et al*., 2000) and concomitantly show lower LH concentrations (Bili *et al*., 2001). A more pronounced decrease in LH concentrations is also seen in PCOS women responding to ovarian surgery to induce ovulation than in non-responders (Hendriks *et al*., 2007; Youssef and Atallah, 2007). Thus, 'overcoming' PCOS and regaining regular menstrual cycles through ovarian surgery or by increasing age is accompanied by decreasing LH concentrations. Sufficient GnSAF production through adequate folliculogenesis could lower the pituitary sensitivity and subsequently cause lower LH production. In the PCOS woman, LH hypersecretion could be (partly) an expression of inadequate folliculogenesis, rather than a cause of the cycle disturbance. This is supported by the finding that regularly ovulating PCOS patients (with hyperandrogenism and polycystic ovarian morphology) show lower LH concentrations than patients with irregular cycles (Dewailly *et al*., 2006; Welt *et al*., 2006). Furthermore, it was recently demonstrated that LH stimulates anti-Müllerian hormone (AMH) production in ovarian cells from PCOS patients (Pellatt *et al*., 2007) and subsequently can contribute to an arrest in folliculogenesis and development of the syndrome. It seems that high LH concentrations, besides being a common feature in PCOS, also reflect the severity of the syndrome.

In this study, elevated LH concentrations were found in a large majority of oligo-/amenorrhoeic PCOS patients, when measured during the specific oligomenorrhoeic phase. The reported prevalence in the literature of elevated LH concentrations in PCOS patients varies between 35 and 77% (Deutsch *et al*., 1978; Robinson *et al*., 1992), but this study found a prevalence as high as 84%. This discrepancy can probably be fully explained by the intercycle variation of LH and the chosen timing of LH sampling. Most studies measure LH in the early 'follicular' phase, but due to suppression of LH concentrations during this phase by previous progesterone exposure, the prevalence of elevated LH concentrations is underestimated. LH is minimally suppressed during the specific oligomenorrhoeic phase, and a higher prevalence of elevated LH concentrations is found when LH is measured during this specific phase.

Furthermore, it is important to realize that investigators often compare PCOS patients to a 'healthy' control group, which might cause a bias (Bloom *et al*., 2006). In daily practice, the clinical question usually is whether or not the oligo-/amenorrhoeic woman has PCOS, and due to the oligo/amenorrhoeic control group, this study is a close reflection of the daily clinical situation.

To obtain at least one adequately timed LH sample, oligomenorrhoeic women should be screened at cycle days 14 and 21 and amenorrhoeic women once randomly. Assessment of progesterone can be added to ensure that ovulation has not occurred. This regimen has been used for years in the study centre, and is not difficult to use in practice. In spite of the variable length of the cycle in oligo/amenorrhoeic patients and the fact that the adequacy of timing can only be evaluated in retrospect, implementing this schedule for laboratory screening is successful in the majority of cases.

The diagnostic potency of LH was assessed in this study, and the results indicate that LH could be used as a diagnostic test to differentiate between PCOS and other causes of oligo- or amenorrhoea. The ROC showed a curve close to the left upper corner and a satisfactory area under the curve of 0.88. Furthermore, a single elevation of LH concentrations in oligo-/amenorrhoeic women predicted PCOS accurately in 93%, when using the optimal cut-off point in this assay of ≥6.5 IU/l, and a high sensitivity of 84% and a fair specificity of 78% were found. LH appeared to be a good diagnostic test in all PCOS subgroups created by the Rotterdam criteria. Taking LH as a single diagnostic criterion for PCOS, 84% of PCOS patients according to Rotterdam criteria would be diagnosed as PCOS and 22% of controls; thus 38% of patients would be diagnosed differently.

Choosing a threshold value with specificity above 90% resulted in a substantial loss of sensitivity, and therefore was not found to be suitable as a cut-off value. It is important to remember that the PCOS diagnosis is made after the exclusion of other diseases, like congenital adrenal hyperplasia, androgen secreting tumours and Cushing's syndrome (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2003). Excluding patients with WHO III amenorrhoea or hyperprolactinaemia is important before interpreting the LH concentrations, because these causes of cycle disturbances can also increase LH concentrations and mimic PCOS.

The possibility of using LH as a diagnostic test for oligo-/amenorrhoeic PCOS does not directly imply that it should be used. The current Rotterdam criteria give rise to four different phenotypes of PCOS patients, and introducing an extra criterion would only increase the diversity, which would be undesirable. Due to the heterogeneity of the syndrome, no single criterion of the Rotterdam consensus, or LH, can be used as a single test to diagnose PCOS. Furthermore, LH measurements can only be timed in the specific oligomenorrhoeic phase in oligo-/amenorrhoeic patients and LH concentrations are probably lower in regularly ovulating PCOS patients, limiting its diagnostic potency in this subgroup. However, LH has been shown to be frequently elevated, and is possibly a reflection of the severity of the syndrome; therefore, the importance of LH in PCOS should not be ignored.

The clinical applicability of LH is limited to oligo-/amenorrhoeic patients. In these patients, elevated LH concentration(s) in the specific oligomenorrhoeic phase predicts PCOS accurately in 93%. This does not imply that LH can be directly used as a surrogate for ultrasound or hyperandrogenism, but it could be used as a secondary parameter in case of uncertainty of diagnosis (inconclusive ultrasound or problems in diagnosing clinical hyperandrogenism) or in situations where (transvaginal) ultrasound is less available or not desired (virgin patients). In these cases, LH offers an objective and cheap additional test costing around €8. Furthermore, future research should include adequately timed LH measurements to evaluate its prognostic potential for successful treatment, chances of ongoing pregnancy, etc. Additional benefits for LH measurements may arise in future when further clinical applications are found.

In conclusion, elevated LH concentrations are found in a large majority of PCOS patients, when measured at the appropriate time. Due to the high positive predictive value, LH could be used as an additional diagnostic test to differentiate between PCOS and other causes of oligo- and anovulation. The prevalence and importance of high LH concentrations in PCOS seems to be underestimated, and its importance within the diagnosis of PCOS and future research should be re-established.

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