

Incidence of elevated LH/FSH ratio in polycystic ovary syndrome women with normo- and hyperinsulinemia

Banaszewska B, Spaczyński RZ, Pelesz M, Pawelczyk L

Division of Infertility and Reproductive Endocrinology
Department of Gynecology and Obstetrics, Poznan University of Medical Sciences, Poznań, Poland

Abstract

Purpose: The aim of this study was to determine the incidence of abnormal LH/FSH ratio in women with polycystic ovary with normo- and hyperinsulinemia and to assess the influence of elevated LH/FSH ratio on selected endocrine and biochemical parameters.

Material and methods: One hundred nineteen polycystic ovary syndrome women in reproductive age hospitalized between 1996 and 2000 in Division of Infertility and Reproductive Endocrinology at Poznan University of Medical Sciences were selected for the study. In all selected women LH and FSH serum levels were determined and LH/FSH ratio was calculated. These groups became the subject of a detailed clinical, hormonal and metabolic analysis, which was performed between 6th and 10th day of a natural or induced menstrual period.

Results: LH/FSH ratio greater than 2 was accepted as abnormal, and it was found in 54 women (45.4%; I group). Normal gonadotropin ratio was detected in 65 women (55%; group II). Statistically significant differences were noted between groups with normal and elevated LH/FSH ratio in the following parameters: BMI (body mass index), serum insulin, and LH levels. Further analysis revealed that the majority of women with elevated insulin concentrations belong to the group with normal LH/FSH ratio.

Conclusions: LH/FSH ratio is not a characteristic attribute of all PCOS women: in the present study this abnormality was detected in a subpopulation smaller than 50%. Most of the PCOS women with normal gonadotropin ratio belong to a group of patients suffering from hyperinsulinemia and obesity. Patients with hyperinsulinemia and

excess of LH constitute a selected and distinct subgroup with increased adrenal androgenic activity.

Key words: polycystic ovary syndrome, hyperinsulinemia, LH, LH/FSH ratio.

Introduction

Polycystic ovary syndrome [PCOS] affects approximately 5-10% of women in the reproductive age. It is characterized by hyperandrogenemia and clinical signs of androgenisation: hirsutism, acne with seborrhea, menstrual disorders with anovulation, and infertility. Additionally, the affected women may suffer from overweight or obesity of androgenic type (abdominal) with a typical waist to hip ratio (WHR) over 0.85 [11,12,18]. In polycystic ovary syndrome both the initial stadium of follicle growth, that is recruitment, and the growth with subsequent selection and domination proceeds irregularly. It results in the accumulation of a large number of small ovarian follicles producing predominantly androgens in thecal cells, with impaired aromatization to estrogens [1,8]. The exact pathogenic mechanism of PCOS is unknown. There are many hypothesis concerning causes of PCOS development and the concurrent coexistence of many interdependent disorders is also possible. Most attention is paid to the hypersecretion of LH and insulin resistance as well hyperinsulinemia. The oldest theory emphasized the relation between thecal cells stimulation with LH and the consequent androgen overproduction [3,8,20]. Lutropin is the best known androgen synthesis stimulator. However last decade brought new hypothesis emphasizing the role of insulin and insulin-like growth factor I (IGF-I) system [15,17].

Insulin resistance and hyperinsulinaemia were usually linked with diabetes mellitus type II (NIDDM) and obesity. Insulin resistance and secondary hyperinsulinemia are perceived as the main cause for the development of PCOS. Most probably insulin resistance in polycystic ovary syndrome is caused by post-receptor defects and it affects most frequently

ADDRESS FOR CORRESPONDENCE:
Division of Infertility
and Reproductive Endocrinology
60-535 Poznań, ul. Polna 33
fax: +48 61 8419612

patients with obesity. Ovarian morphologic abnormalities include theca and stroma hypertrophy and atresia of granulosa cells.

To date the pathogenic relationship between hypothalamic-pituitary system and insulin resistance in polycystic ovary syndrome have remained unexplained. Meanwhile there is still controversy over essential diagnostic investigations in PCOS. LH/FSH ratio greater than 2 has been considered as “gold standard” in PCOS diagnosis for a long time. Taking this into account it is an intriguing problem to recognize the role of LH and the possible associations with hyperinsulinemia and furthermore to evaluate the usefulness of gonadotropin ratio in PCOS diagnosis.

The aim of this study was:

1. To determine the incidence of abnormal LH/FSH ratio in women with polycystic ovary syndrome and with normoinsulinemia or hyperinsulinemia
2. To assess effects of increased LH/FSH ratio on remaining endocrine and biochemical parameters.

Study subjects

One hundred nineteen polycystic ovary syndrome women in reproductive age hospitalized between 1996 and 2000 in Division of Infertility and Reproductive Endocrinology at Poznan University of Medical Sciences were recruited to the study. PCOS was diagnosed on the grounds of the following clinical findings: testosterone >0.8 ng/mL, menstrual disorders – oligomenorrhoea or amenorrhoea, acne or hirsutism (>8 points according to Thomas and Ferriman scale).

In all selected women LH and FSH serum levels were determined and LH/FSH ratio was calculated. LH/FSH ratio >2 was accepted as abnormal. In both groups with normal and increased LH/FSH ratio insulin serum levels were determined in fasting state. These groups became the subject of a detailed clinical, hormonal and metabolic analysis, which was performed between 6th and 10th day of a natural or induced menstrual period.

Assays

Testosterone, LH, FSH, and prolactin were measured by specific chemiluminescence assays (Chiron Diagnostics GmbH, Fernwald, Germany). Serum levels of insulin were determined with ELISA assay – Enzymun Test Insulin (Boehringer Mannheim, Germany). Sex hormone binding globulin (SHBG) was measured by specific radioimmunoassay (Orion Diagnostica, Espoo, Finland).

Statistical analysis

Results are presented as arithmetical mean with standard deviation. Statistical analysis was done using Student's t-test after confirmation of the normal distribution. Differences at $p < 0.05$ were considered statistically significant.

Table 1. Comparison of insulin concentration, LH, FSH, LH/FSH ratio and BMI in women with elevated and normal gonadotropin ratio.

Parameter	PCOS with LH/FSH >2 (n=54)	PCOS with LH/FSH <2 (n=65)	p <
BMI (kg/m ²)	24.4 \pm 5.3	27.1 \pm 7.1	0.05
Insulin (μ U/mL)	11.2 \pm 7.5	16.9 \pm 10.5	0.001
LH (mU/mL)	14.7 \pm 6.8	6.1 \pm 3.0	0.0001
LH/FSH ratio	2.8 \pm 1.1	1.1 \pm 0.4	0.0001

Figure 1. Incidence of hyperinsulinemia in women with elevated gonadotropin ratio.

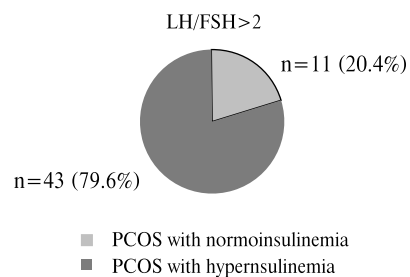
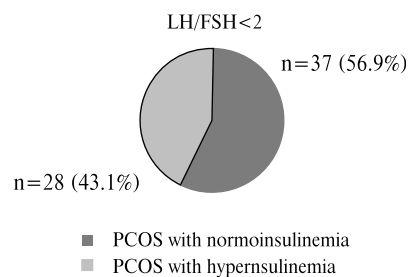


Figure 2. Incidence of hyperinsulinemia in women with normal gonadotropin ratio.



Results

Elevated LH/FSH ratio (LH/FSH >2) was found only in 45.4% of the studied PCOS women (54 out of 119).

Statistically significant differences were noted between groups with normal and elevated LH/FSH ratio in the following parameters: BMI, serum insulin, and LH levels (Tab. 1). However, there was no difference between groups with abnormal and normal gonadotropin ratio in total testosterone concentrations (1.01 \pm 0.3 ng/mL versus 1.02 \pm 0.4 ng/mL) and SHBG levels (48.89 \pm 28.4 versus 44.2 \pm 36.9 nmol/L). Also the average menstrual cycle length was similar in both groups: 54.2 \pm 28.7 days in a group with LH/FSH ratio >2 and 64.4 \pm 38.0 days in a group with normal gonadotropin ratio.

Having divided each group into patients with normo- and hyperinsulinemia it turned out, that the majority of women with elevated insulin concentrations belong to the group with normal LH/FSH ratio (Fig. 1, 2). Identification of subgroups with normo- and hyperinsulinemia among groups with normal and elevated LH/FSH ratio allowed for detection of significant differences in many parameters as demonstrated in Tab. 2.

Table 2. Clinical and endocrine parameters in normo- and hyperinsulinemic PCOS women according to gonadotropin ratio.

Parameter	PCOS with LH/FSH >2 (n=54)			PCOS with LH/FSH < 2 (n=65)		
	Normo-insulinemia (n=43)	Hyper-insulinemia (n=11)	p<	Normo-insulinemia (n=37)	Hyper-insulinemia (n=28)	p<
BMI (kg/m ²)	22.8±3.4	32.0±5.6	0.0001	23.3±4.0	33.0±7.0	0.0001
Hirsutism (points)	9.3± 3.9	10.0±2.5*	NS	8.8±4.6	7.3±4.4	NS
Testosterone (ng/mL)	1.0±0.3	1.0± 0.2	NS	1.1±0.4	1.0±0.3	NS
SHBG (nmol/L)	52.7±29.2	30.1±13.5*	0.05	57.7±41.2	20.9±8.0	0.001
FTI	9.0±5.9	15.4±10.8	0.001	10.1±9.6	20.1±12.0	0.001
Insulin (μU/mL)	8.4±3.5	25.7±6.3	0.001	9.4±4.5	27.1±7.5	0.001
LH (mU/mL)	13.9±5.7	17.8±9.5	NS	6.0±3.1	6.2±2.9	NS
FSH (mU/mL)	5.5±1.8	6.0±1.4	NS	5.8±2.0	5.9±1.5	NS
LH/FSH	2.7±1.1	3.0±1.3	NS	1.0±0.5	1.0±0.6	NS
DHEAS (μmol/L)	363.5±162	510±218*	0.05	419±178	367.2±139	NS

* p<0.05 in comparison to a group with hyperinsulinemia and LH/FSH <2

Discussion

Polycystic ovary syndrome is a subject of continuous studies concerning both pathogenesis, diagnostics methods, and therapeutics procedures. Nowadays, most attention is focused on the role of insulin resistance and hyperinsulinemia in development of the syndrome [10]. However, one problem remains important and controversial: how many PCOS women are affected by hyperinsulinemia. In the presented study of 119 women with ovarian hyperandrogenism, 33% of the subjects had elevated insulin serum levels. Literature data reports incidence of hyperinsulinemia and insulin resistance at 40% to 60% [9,13]. Insulin resistance is strongly associated with androgenic type of obesity (abdominal). In our study majority of patients with hyperinsulinemia presented with BMI>25, and the mean value in this group was over 30 kg/m².

At the end of 1980s LH/FSH ratio was still perceived as a "gold standard" for diagnosis of PCOS, and the coexistence of insulin resistance and hyperinsulinemia was only emerging as a potential pathogenic factor. The overproduction of LH and consequently the incorrect LH/FSH ratio is nowadays considered not to be a characteristic attribute of all PCOS patients. In this study elevated gonadotropin ratio was found only in 45.4 % of patients. Some studies assess the incidence of elevated LH/FSH ratio at even 94%. In 1975, Berger was the first to emphasize that one can differentiate a separate type of PCOS with normal gonadotropin level. At that time it was not associated with insulin resistance. Nowadays it is believed that elevated LH level occurs more rarely in a group of patients with insulin resistance and hyperinsulinemia, than in group without hyperinsulinemia. This observation was confirmed in a presented group of women, in which normal gonadotropin ratio 1:1 was observed in up to 72% of patients with hyperinsulinemia. One may speculate that additionally to, that is considered to be a strongest androgen production stimulator, in women with normal LH level additional stimulators of steroidogenesis exist. Most probably it is insulin and IGF-I. Thus it could have been expected that the most severe clinical symptoms and greater androgen concentration would appear in women with hyperinsulinemia and overproduction of LH. However, the mean

testosterone levels in the studied women, were independent of insulin and LH concentrations. Hirsutism of greater severity was observed in a group of women with hyperinsulinemia and LH/FSH ratio >2 when compared with women with hyperinsulinemia and normal gonadotropin ratio.

Interestingly, PCOS women with hyperinsulinemia and overproduction of LH, had significantly higher serum levels of dehydroepiandrosterone sulphate. In the remaining groups DHEAS concentration was normal. It is still not fully understood how insulin influences the adrenal androgen secretion. The negative correlation between insulin levels and dehydroepiandrosterone sulphate production have been found. On the other hand there are also studies that do not confirm correlation between insulin activity and adrenal androgen production [2].

Another interesting observation concerned sex hormone binding globulin. Remarkably lower SHBG concentration was noted in patients with hyperinsulinemia, in comparison to the group without elevated insulin. Majority of available studies confirm low sex hormone binding globulin concentrations in women with insulin resistance and hyperinsulinemia. The negative influence of insulin on SHBG production in liver is well known [5,14,16]. It was unanticipated, though, to find significant differences in SHBG concentration in hyperinsulinemic groups with normal and high LH levels. In a group with elevated LH/FSH ratio SHBG globulin was higher than in a group with normal LH concentrations. It could be hypothesized that the excess of LH may reduce the influence of insulin on SHBG production. It is also interesting, that in the presented study, despite the higher index of free testosterone in women with hyperinsulinemia, clinical symptoms of hyperandrogenism were approximately similar in both of the groups. It is difficult to fully explain these results, we may only speculate that androgen peripheral activity was weakened by aromatization of androgens to estrogens, mainly to estron in excessively developed adipose tissue of those women.

PCOS is a very heterogeneous disorder of different phenotypes. In summary we would like to point out that: 1) LH/FSH ratio is not a characteristic attribute of PCOS women, 2) most of PCOS women with normal gonadotropin ratio belong to a subgroup of patients with hyperinsulinemia and obesity,

3) patients with hyperinsulinemia and excess of LH constitute probably a separate subpopulation with increased adrenal androgenic activity. Possibly, this is the group, in which two different pathogenic mechanisms interweave and present a characteristic clinical pictures of these women.

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