Neuroendocrinology Letters Volume 36 No. 1 2015
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Prolactin secretion in polycystic ovary syndrome (PCOS)

Konrad Szosland [1], Paweł Pawłowicz [2], Andrzej Lewiński [1,3]

1 Department of Endocrinology and Metabolic Diseases, Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland
2 1st Department of Obstetrics & Gynecology – Medical Centre of Postgraduate Education, Warsaw, Poland
3 Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland

Correspondence to: Prof. Andrzej Lewiński
Department of Endocrinology and Metabolic Diseases,
Rzgowska St. No. 281/289, 93-338 Lodz, Poland.
e-mail: alewin@csk.umed.lodz.pl

Submitted: 2015-01-23 Accepted: 2015-02-23 Published online: 2015-02-27

Key words: **polycystic ovary syndrome; prolactin; female infertility**

Neuroendocrinol Lett 2015; **36**(1):53–58 **PMID:** 25789595 NEL360115A11

Abstract

OBJECTIVES: Hyperprolactinemia and polycystic ovary syndrome (PCOS) are on the list of the most frequent causes of female infertility. Both pathologies are characterized in common by several clinical features. At the same time, there are essential discrepancies in medical literature on mutual relations between PCOS and hyperprolactinemia. The objective of our study was to answer several questions, e.g. about frequency of hyperprolactinemia in PCOS patients, typical concentrations of prolactin (Prl) in PCOS patients vs women without polycystic ovaries and/or an assessment of circadian Prl level profiles vs single Prl sampling, as regards diagnostic usefulness.
METHODS: The study was retrospective analysis of medical records of female patients in whom nine (9) points daily profile of prolactinemia had been performed.
RESULTS: Prl levels appeared to be slightly higher in women without PCOS but the difference did not reach a border of statistical significance. The incidence of elevated Prl concentrations in 8:00 AM and 11:00 AM samples was higher in women without PCOS than in PCOS patients (32.0% vs 16.3% – 8:00 AM, and 8.5% vs 4.6% – 11:00 AM, respectively). Also, elevated mean daily prolactinemia, assessed as area under the curve (AUC) of Prl concentrations, was more frequent in the group of women without PCOS than in those with PCOS (22.0% vs 13.9%).
CONCLUSIONS: Polycystic overy syndrome is not associated with higher levels of Prl, measured in daily profiles. Hyperprolactinemia does not seem to be more frequent in PCOS women than in healthy subjects and it should not be considered as characteristic feature of PCOS – both are distinct clinical entities. Prolactin concentrations should be assessed in each woman with PCOS suspicion because of certain common clinical signs in both disorders. Every woman diagnosed with PCOS and hyperprolactinemia should further be examined in terms of the actual causes of hyperprolactinemia because the coexistence of these two disease entities – as distinct – is also possible.

ORIGINAL ARTICLE

INTRODUCTION

Infertility is nowadays a very important problem, especially in highly developed countries; it can even be considered as a disease associated with development of civilization. Hyperprolactinemia and polycystic ovary syndrome (PCOS) are on the list of the most frequent causes of female infertility. Hyperprolactinemia is the most common pituitary oversecretion syndrome, both in females and in males. The incidence of hyperprolactinemia – defined as an excess of prolactin (Prl) in blood above laboratory reference limits – is difficult to assess because of the frequent lack of direct specific clinical symptoms or the presence of unspecific signs only. The prevalence of hyperprolactinemia (evertreated cases), is estimated on 20 per 100 000 male and approximately 90 per 100 000 female American patients; in women aged 25–34 yrs, the annual incidence of hyperprolactinemia has been reported to be 23.9 per 100 000 person years (Melmed *et al.* 2011). Occurrence of hyperprolactinemia in women presenting with fertility problems appears to be higher, reaching up to 5–14% (Souter *et al.* 2010; Lee *et al.* 2012).

Polycystic ovary syndrome is one of the most frequently diagnosed endocrinopathies in women. Prevalence of the syndrome in women in reproductive age is estimated in range from 6.5% to 8% (Lujan *et al.* 2008). According to currently used Rotterdam Criteria, PCOS is diagnosed when two (2) out of following three (3) signs/symptoms are fulfilled:

1. oligo- and/or anovulation;
2. clinical and/or biochemical signs of hyperandrogenism;
3. polycystic ovaries (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004);

Menstrual disorders, oligo/anovulation and resulting infertility are clinical features that PCOS and hyperprolactinemia share in common. For that reason, associations of PCOS with hyperprolactinemia have been an issue of several studies. Opinions on the relationship of PCOS and hyperprolactinemia widely vary: from the recognition of elevated levels of Prl as a disorder characteristic of PCOS on one hand, to the obligatory exclusion of hyperprolactinemia, in order to make a proper diagnosis of PCOS, on the other.

There have been several possible mechanisms increasing Prl secretion that may occur in PCOS, as postulated by different authors. Hyperprolactinemia could be a consequence of altered dopamine turnover which might also deteriorate GnRH output, that – in turn – could result in abnormal ovary function and constitute a common cause for both PCOS and hyperprolactinemia. Out of peripheral hormones, the strongest effect have estrogens, which stimulate the synthesis and secretion of prolactin, as well as cell proliferation of lactotropic pituitary cells (Elias and Weiner 1984, Karasek *et al.* 2006). Consistently with early observations that estrogens stimulate Prl release (Ehara *et al.* 1976, Goh and Ratnam 1990, Katznelson *et al.* 1998), elevated estradiol levels in PCOS could result in increased Prl concentrations. However, currently available data on the role of estradiol in regulation of Prl secretion in humans, are controversial (Ben-Jonathan *et al.* 2008, Egli *et al.* 2010). The role of estrogens in excess – a well-known inducer of experimental prolactinomas in rodents – in humans has not been proven (Karasek *et al.* 2006, Ben-Jonathan *et al.* 2008). Because of the lack of consent in this matter, we decided to assess Prl levels in PCOS patients in our own clinical analysis.

The goals of the study were:

- comparison of Prl concentrations in PCOS women *vs* female patients without PCOS;
- assessment of frequency of hyperprolactinemia in PCOS patients *vs* women without PCOS;
- assessment of advantage of circadian profile assessment over single Prl sampling, especially in PCOS patients.

MATERIAL AND METHODS

The study was retrospective analysis comprising patients hospitalized in the Department of Endocrinology and Metabolic Diseases, Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland. The medical reports of female patients hospitalized for various reasons in the above Department were analysed. One hundred twenty seven (127) women were enrolled in whom circadian profile of Prl had been assessed. Among the study group, PCOS patients were selected, according to the diagnosis given in the reports. In our Department, PCOS is diagnosed, basing on The Rotterdam Criteria 2003. The diagnoses established earlier were not verified again for the analysis in the current study. Women with diagnosed pituitary tumors of prolactinoma type, and those receiving medications increasing Prl production and release from the pituitary were excluded from the analysis.

The routine procedure of Prl profile assessment in our Department included nine (9) Prl concentration assessments, every three (3) hours: 8:00 AM, 11:00 AM, 2:00 PM, 5:00 PM, 8:00 PM, 11:00 PM, 2:00 AM, 5:00 AM and repeatedly 8:00 AM. The blood samples had been obtained from cubital vein, using previously inserted cannula.

The Prl was assayed by electrochemiluminescence immunoassay method, using commercial "ECLIA" kit on cobas immunoassay analyzer, with the apper normal limit of prolactinema assayed by this method – 29 μg/l.

The area under the curve (AUC) of Prl concentrations was calculated in order to assess mean daily Prl secretion. The upper limit of AUC was assumed to be equal to 696. This value was calculated by substitution of 29 into the formula for AUC calculation and corresponded to the mean circadian Prl concentration of 29 μg/l. It

is noteworthy that the upper limit value of 29 μg/l, as accepted by us and by some other authors in non-pregnant females (Oner 2013), has been settled in order to avoid overdiagnosis of hyperprolactinemia in cases of accidental elevations of borderline Prl concentration. Below, we present the formula for AUC calculation:

$$AUC=0.5 * (\text{time between consecutive Prl assessments [h]}) * (Prl_{\text{first time point}} + 2 \Sigma Prl_{\text{intermediate time points}} + Prl_{\text{last time point}})$$

In our study, blood samples for Prl concentration assessment were collected every 3 hours, thus the formula was:

$$AUC=1.5 * (Prl_{\text{first time point}} + 2 \Sigma Prl_{\text{intermediate time points}} + Prl_{\text{last time point}})$$

RESULTS

In the entire study group of 127 females, mean age was 27.69±8.69 years (mean±SD; median value – 26 years), BMI – 25.78±6.45 kg/m^2 (median value – 24.5 kg/m^2). In this group, PCOS was diagnosed in 43 women. The PCOS subgroup age was 24.02±5.89 years (median – 23 years) and BMI – 25.39±5.89 kg/m^2 (median – 25.6 kg/m^2). In the subgroup of women without PCOS, mean age was 29.57±9.2 years (median value – 27 years), BMI – 25.98±6.75 kg/m^2 (median – 24 kg/m^2). The difference of age between the PCOS subgroup and the remaining women was statistically significant, $p<0.05$, namely, PCOS patients were younger.

Because of possible influence of age on Prl secretion and Prl concentrations, the group of women without PCOS was adjusted according to the age to the PCOS group for further comparison. Out of 84 women without PCOS, 59 subjects were enrolled to the final comparison, aged 25.24±5.36 years (median – 24 years). The value of BMI in the PCOS-free group – after adjustment according to the age – was 24.52±5.35 kg/m^2 and it did not differ significantly from BMI in the PCOS group ($p>0.05$).

The Prl concentrations in 9 particular time points and AUC of Prl concentrations in PCOS and PCOS-free groups were compared. None of the values differed significantly (Table 1). The mean daily Prl secretion calculated as AUC of Prl concentrations also did not differ significantly between groups, being 580.62±236.17 (551.81) in women without PCOS and 516.55±249.99 (453.17) in PCOS group (Figure 1).

The number of patients that could be diagnosed as "hyperprolactinemia" on the basis of 8:00 AM Prl concentration in the group without PCOS was 19 (i.e., 32% of the group); mean prolactinemia in these subjects was 43.93±15.05 μg/l (median – 42.36 μg/l). In PCOS group hyperprolactinemia at 8:00 AM was found in 7 subjects (16.3% of the group), mean prolactinemia in these subjects was 38.71±10.69 μg/l (median – 36.28 μg/l). According to the assessment of prolactinemia at 11:00 AM in the PCOS-free group only 5 hyperprolactinemic subjects were found (8.5% of the group) with mean Prl concentration 39.18±15.22 μg/l (median – 32.9 μg/l). In PCOS group prolactinemia over 29 μg/l at 11:00 AM was found only in 2 subjects (4.6% of the group) – in one of them – 29.3 μg/l and in the second one – 54.9 μg/l.

The area under the curve of Prl concentrations above 696, indicating hyperprolactinemia, was found in 13 subjects (22% of the group) without PCOS. Mean daily Prl secretion was 913.95±235.78 (median – 813.390). In the PCOS group, AUC above 696 was found in 6 subjects (13.9%). Mean daily Prl secretion was 1019.73±281.96 (median – 933.02).

The cumulative linear plots of Prl concentrations in both groups during 24 h are presented in the Figure 2.

DISCUSSION

Polycystic ovary syndrome and hyperprolactinemia are both common causes of secondary amenorrhoea in women being in reproductive age. The studies on

Tab. 1. Prolactin concentrations in women without PCOS and in the group of PCOS patients during daily profile.

Time	Prl concentration [μg/l] mean±SD (median value)		
	Women without PCOS	PCOS patients	
8:00 AM	26.83±14.95 (23.21)	22.07±10.04 (21.0)	$p>0.05$
11:00 AM	15.14±10.06 (12.05)	13.88±8.65 (11.69)	
2:00 PM	17.15±15.39 (12.3)	14.52±9.44 (12.0)	
5:00 PM	19.59±12.47 (15.2)	16.80±11.45 (13.9)	
8:00 PM	22.12±17.41 (18.1)	18.93±12.61 (14.22)	
11:00 PM	21.61±11.15 (19.99)	20.03±12.47 (16.0)	
2:00 AM	37.12±17.19 (34.62)	35.55±20.26 (30.91)	
5:00 AM	32.53±15.13 (29.7)	32.41±16.52 (25.6)	
8:00 AM second day	29.72±17.19 (26.43)	26.08±11.40 (25.0)	

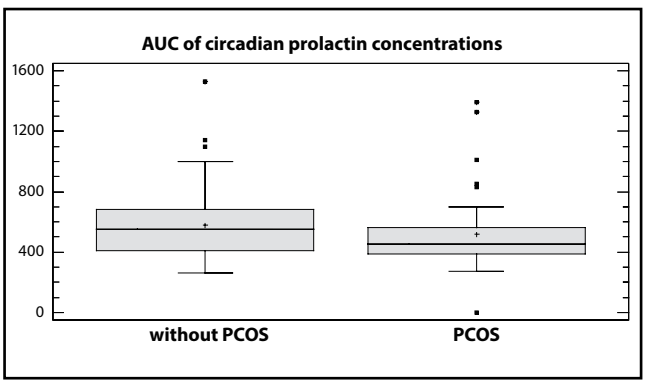

Fig. 1. Comparison of AUC (areas under curve) of Prl concentration in women without PCOS and in the group of PCOS patients.

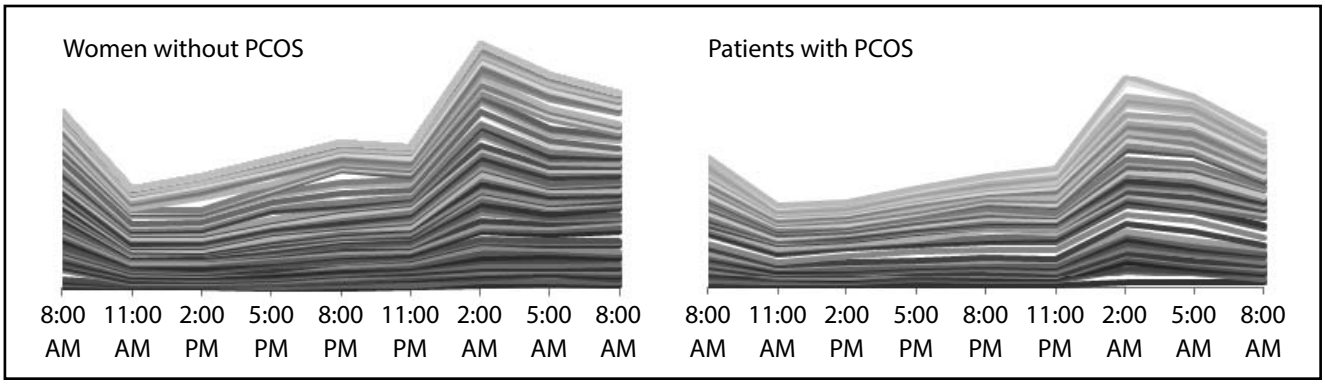

Fig. 2. Cumulative daily profiles of Prl concentrations in women without PCOS and in the group of PCOS patients.

mutual relationships between PCOS and hyperprolactinemia bring many controversial results.

In this study, we have analysed prolactinemia at 8:00 AM, as well as at 11:00 AM and AUC of Prl concentration. It has been observed by us that significant proportion of patients have Prl concentrations above the upper limit of the reference range at 8:00 AM and normal prolactinemia later on during the day (Lewandowski *et al.* 2005, Szosland *et al.* 2015 – in press).

The AUC appears the most reliable tool of circadian prolactinemia assessment. The cumulated curves of Prl concentrations confirm that 8:00 AM fasting prolactinemia appears to be higher than any other point measurement in the daytime. The peak of Prl secretion occurred in both groups at 2:00 AM and it was in concordance with findings of other authors and with well-established circadian Prl rhythm (Kok *et al.* 2006).

No significant difference between prolactinemia in women with PCOS and those without PCOS was found in our study. The Prl concentrations appeared slightly higher in the group without PCOS but no statistical significance was recorded. In the group in question, Prl concentrations were much more dispersed than in the PCOS group. This observation could be foreseen, as the group without PCOS included representation of women with various pathological conditions, while the PCOS group was much more homogenous. The only heterogeneity in this group could possibly be dependent upon different subtypes/presentations of PCOS that – however – were not distinguished in our study. We did not verify PCOS diagnoses established earlier, neither we did analyse which out of obligatory signs/symptoms (acc. to Rotterdam criteria) were present in the particular subjects involved in the study.

In the present study, the mean age of women without PCOS turned out to be a bit older than the mean age of patients with PCOS, while – as mentioned above, in subdivision "Results" – mean Prl concentrations in PCOS-free group were higher than in women with PCOS. Keeping in mind that Prl levels in women decrease steadily with age (Vekemans and Robyn 1975), data juxtaposition, i.e. slightly lower Prl levels in younger PCOS group – speaks against relation between PCOS and hyperprolactinemia. Nevertheless, in spite of adjustment of PCOS-free group according to the age to the PCOS women, still the mean daily Prl secretion calculated as AUC was slightly higher in women without PCOS (however, no statistical difference was recorded, Figure 1).

Similarly to us, also the Taipei authors found no statistical difference between prolactinemia in women with PCOS and without PCOS; though, they hypothesized reverse relation – frequent occurrence of PCOS in hyperprolactinemic women (Su *et al.* 2011).

The occurrence of Prl serum concentrations above the upper reference limit in our study was higher in women without PCOS than in PCOS group. The incidence of hyperprolactinemia in our PCOS patients was similar to that found by Filho *et al.* (2007). We agree with opinion of these authors that PCOS patients with increased Prl levels should be investigated for other causes of hyperprolactinemia, because hyperprolactinemia is not a clinical manifestation of PCOS. In the study on young women with menstrual disorders (Lee *et al.* 2012), prevalence of hyperprolactinemia in PCOS subjects, diagnosed according to the Rotterdam criteria, was 7.9% and appeared lower than that found in our study (13.9%), which can reflect the differences between examined populations.

The opinions about relations of PCOS and hyperprolactinemia in current scientific literature are discrepant. There were authors who suggested that functional hyperprolactinemia could occur even in 25% of women with PCOS (Amzar *et al.* 2013); in the light of our present results, we cannot confirm that observation.

Association between PCOS and hyperprolactinemia can sometimes be clinically difficult to analyse, as hyperprolactinemia and hyperandrogenism can occur quite independently; moreover, sometimes the evaluation is even more complicated as it takes place in macroprolactinemia states (Taghavi and Sedigheh 2008). Certainly, the relation between PCOS and hyperprolactinemia is not fully understood and it remains a topic of debate.

It has been speculated whether the increased level of androgens in hyperandrogenic–hyperprolactinemic women is the cause or the consequence of hyperprolactinemia. Hyperandrogenism has been considered to be the cause, since it has been hypothesized that androgens have the potential to weaken the hypothalamic dopaminergic tone; in certain clinical circumstances, hyperandrogenism can be secondary to hyperprolactinemia (Finken *et al.* 2013).

Herein, the observation by Schroeder *et al.* (2004) should be recalled who found lower fasting prolactinemia in PCOS patients with altered reaction to hyperglycemia (lack of decrease of prolactinemia observed in healthy group) and hypoglycemia (significant increase to values almost 10 times above the baseline).

In our opinion, hyperprolactinemia in PCOS syndrome is not so frequent disorder. Before it is considered to be a consequence of hyperandrogenemia, all other possible reasons of elevated Prl concentrations have to be excluded. It is to be stressed the diagnosis of PCOS does not exclude possibility of simultaneous prolactinoma existence (Yavasoglu *et al.* 2009).

If hyperprolactinemia is not a clinical manifestation of PCOS, it means that the patients with PCOS and increased Prl levels should be investigated for other causes of hyperprolactinemia (Agbaht *et al.* 2009). Our results support such a point of view.

In the present study, subjects receiving any medication of known potential to increase prolactinemia have been excluded. However, it is possible that in some cases the high prevalence of hyperprolactinemia in PCOS may be a result of medication affecting process of Prl secretion.

In summary, we can draw the following conclusions:

1. Incidence of hyperprolactinemia in PCOS women is not more frequent in comparison to women without PCOS; thus, hyperprolactinemia should not be considered a feature of polycystic ovary syndrome, as both are distinct clinical entities.
2. The possibility of prolactinemia should be taken into consideration in every woman with suspicion of PCOS, because of some common clinical signs of both disorders.
3. Each subject with diagnosed PCOS and hyperprolactinemia should be diagnosed towards other reasons of hyperprolactinemia because the coexistence of these two pathological conditions is possible.

ACKNOWLEDGEMENT

This study was financially supported by the Medical University of Lodz, Poland (503/1-107-03/503-01).

REFERENCES

1 Agbaht K, Yerlikaya H, Demir O. Gullu S (2009). Hyperprolactinemia in polycystic ovary syndrome. Endocrine Abstracts. **20:** P653.
2 Amzar D, Balas M, Golu I, Vizitiu A, Stana L, Gurban C *et al.* (2013). Functional hyperprolactinemia in polycystic ovary syndrome: incidence and correlation with hormonal parameters. Endocrine Abstracts. **32:** P914.
3 Ben-Jonathan N, LaPensee CR, LaPensee EW (2008). What can we learn from rodents about prolactin in humans? Endocr Rev. **29:** 1–41.
4 Egli M, Leeners B, Kruger THC (2010). Prolactin secretion patterns: basic mechanisms and clinical implications for reproduction. Reproduction. **140:** 643–654.
5 Ehara Y, Siler TM, Yen SS (1976). Effects of large doses of estrogen on prolactin and growth hormone release. Am J Obstet Gynecol. **125:** 455–458.
6 Elias KA, Weiner RI (1984). Direct arterial vascularisation of estrogen-induced prolactin secreting anterior pituitary tumours. Proc Natl Acad Sci USA. **81:** 4549–4553.
7 Filho RB, Domingues L, Naves L, Ferraz E, Alves A, Casulari LA (2007). Polycystic ovary syndrome and hyperprolactinemia are distinct entities. Gynecol Endocrinol. **23:** 267–272.
8 Finken MJ, Boersma B, Rotteveel J (2013). Hyperprolactinemia and hyperandrogenism in an adolescent girl presenting with primary amenorrhea. Eur J Obstet Gynecol Reprod Biol. **166:** 230–231.
9 Goh HH, Ratnam SS (1990). Effect of estrogens on prolactin secretion in transsexual subjects. Arch Sex Behav. **19:** 507–516.
10 Karasek M, Pawlikowski M, Lewiński A (2006). Hyperprolactinemia: causes, diagnosis, and treatment [in Polish]. Endokrynol Pol - Polish J Endocrinol. **57:** 656–662.
11 Katznelson L, Riskind PN, Saxe VC, Klibanski A (1998). Prolactin pulsatile characteristics in postmenopausal women. J Clin Endocrinol Metab. **83:** 761–764.
12 Kok P, Roelfsema F, Langendonk JG, de Wit CC, Frölich M, Burggraaf J *et al.* (2006). Increased circadian prolactin release is blunted after body weight loss in obese premenopausal women. Am J Physiol Endocrinol Metab. **290:** E218–E224.
13 Lee D-Y, Oh Y-K, Yoon B-K, Choi D (2012). Prevalence of hyperprolactinemia in adolescents and young women with menstruation-related problems. Am J Obstet Gynecol. **206:** 213.e1–5.
14 Lewandowski KC, Skowronska-Jozwiak E, Szosland K, Lewinski A (2005). Effect of timing of prolactin sampling on the incidence of spurious hyperprolactinaemia. Endocrine Abstracts. **9:** P223.
15 Lujan ME, Chizen DR, Pierson RA (2008). Diagnostic criteria for polycystic ovary syndrome: pitfalls and controversies. J Obstet Gynaecol Can. **30:** 671–679.
16 Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA *et al.* (2011). Diagnosis and treatment of hyperprolactinemia: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. **96:** 273–288.
17 Oner G (2013). Prolactin and infertility. In: Prolactin, eds. György M. Nagy and Bela E. Toth. InTech, chap. 9: pp. 147–166.
18 Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group (2004). Revised 2003 consensus on diagnostic criteria and longterm health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. **19:** 41–47.
19 Schroeder AK, Tauchert S, Ortmann O, Diedrich K, Weiss JM (2004). Differential responds of prolactin secretion to hyperglycaemia and hypoglycaemia in healthy women and in women with polycystic ovary syndrome. Fertil Steril. **82** suppl 2: s297–298.
20 Souter I, Baltagi LM, Toth TL, Petrozza JC (2010). Prevalence of hyperprolactinemia and abnormal magnetic resonance imaging findings in a population with infertility Fertil Steril. **94:** 1159–62.
21 Su HW, Chen CM, Chou SY, Liang SJ, Hsu CS, Hsu MI (2011). Polycystic ovary syndrome or hyperprolactinaemia: a study of mild hyperprolactinaemia. Gynecol Endocrinol. **27:** 55–62

22 Szosland K, Stasiak M, Lewiński A (2015). Hyperprolactinemia diagnostics – dilemmas over optimal selection of prolactinemia time points – analysis of 138 patients. AAEM [in press].
23 Taghavi M, Sedigheh F (2008). Macroprolactinemia in patients presenting with hyperandrogenic symptoms and hyperprolactinemia. Int J Endocrinol Metab. **3:** 140–143.
24 Vekemans M, Robyn C (1975). Influence of age on serum prolactin levels in women and men. Br Med J. **4:** 738–739.
25 Yavasoglu I, Kucuk M, Coskun A, Guney E, Kadikoylu G, Bolaman Z (2009). Polycystic ovary syndrome and prolactinoma Association Inter Med. **48:** 611–613.