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The value of PRL in predicting prolactinoma in hyperprolactinemic PCOS

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Abstract

BACKGROUND: **To identify a serum prolactin (PRL) cut-off value indicative of a PRL-producing adenoma in women with Polycystic Ovarian Syndrome (PCOS) and hyperprolactinemia and characterize such patients.**

MATERIALS AND METHODS: **In the present retrospective case-control study the medical records of 528 PCOS women were reviewed. Pituitary magnetic resonance imaging (MRI) was performed in PCOS patients with PRL levels ≥94.0 ng/mL and/or symptoms suspicious of a pituitary adenoma (PA). Prolactinoma diagnosis was made in the presence of an MRI-identifiable PA with biochemical and radiological response to dopamine agonists. Receiver operating characteristic (ROC) curve analysis was performed to determine a serum PRL threshold that could identify hyperprolactinemic PCOS subjects with prolactinomas. Clinical, metabolic and endocrine parameters were also analysed.**

RESULTS: **Among 528 patients with PCOS, 60 (11.4%) had elevated PRL levels. Of 44 (73.3%) patients who had pituitary imaging, 19 had PAs, 18 normal MRI and 7 other abnormalities. Patients harboring prolactinomas had significantly higher PRL levels compared to patients without adenomas (median PRL 95.4 vs. 49.2 ng/mL, p<0.0001). A PRL threshold of 85.2 ng/mL could distinguish patients with prolactinomas with 77% sensitivity and 100% specificity [Area Under the curve (AUC) (95%) 0.91(0.8-1.018), p=0.0001]. PCOS women with prolactinomas were younger and had lower LH levels compared to women without prolactinomas.**

CONCLUSIONS: **In women with PCOS, PRL levels exceeding 85.2 ng/mL are highly suggestive of a prolactinoma warranting pituitary imaging. Pituitary MRI could also be considered in young PCOS patients with milder PRL elevation and low LH levels.**

Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrinopathy in women of reproductive age with a prevalence of 6-10% (1-3). Chronic oligo-anovulation and hyperandrogenism constitute the cardinal features of PCOS, while insulin resistance and hyperinsulinemia contribute substantially to its pathogenesis, clinical/biochemical manifestations and long-term sequelae (4). Current guidelines endorse the use of the Rotterdam criteria for diagnosing PCOS (5).

Elevated prolactin (PRL) levels have been reported with a prevalence ranging between 7-52% in PCOS attributed to the abnormal hormonal milieu as well as a relative dopamine deficiency (6-11). Hyperprolactinemia is also common in women of reproductive age (12), and may mimic the clinical phenotype of PCOS (6, 13, 14). Prolactinomas are the most frequent cause of non-puerperal endogenous hyperprolactinemia, accounting for 40% of all pituitary adenomas (14). Although PRL levels >250 ng/mL are highly indicative of a prolactinoma, a significant number of patients with mild to moderate elevations of PRL may still harbour a prolactinoma after excluding other causes of hypeprolactinemia (13, 14). This is particularly relevant in patients with PCOS and concomitant hyperprolactinemia as pathophysiology and their treatment may be different compared to normoprolactinemic PCOS (10, 15, 16). Magnetic resonance imaging (MRI) is the modality of choice for diagnosising pituitary adenomas, especially microadenomas (13). However, it has not been substantiated whether hypeprolactinemic PCOS patients should undergo pituitary MRI to exclude a prolactinoma based on serum PRL concentrations. This is of relevance as the presence of a pituitary microadenoma on pituitary MRI in PCOS patients with moderately elevated PRL concentrations may well represent an incidentaloma.

There is currently a paucity of data on the association between PCOS and prolactinomas (10, 17). In addition, since there is no clear cut-off value of serum PRL level that could be used to distinguish between functional hyperprolactinemia and the presence of a prolactinoma in PCOS, the criteria for further evaluation of such patients with pituitary imaging rely largely upon each clinician's threshold.

The aim of the present retrospective case-control study was the identification of a serum PRL cut-off value above which a pituitary MRI could be justifiable in hyperprolactinemic PCOS patients. We also aimed to identify clinical, metabolic and endocrine features of patients with PCOS and microprolactinomas and compare them to those of patients with PCOS and hyperprolactinemia without adenoma and normoprolactinemic PCOS subjects.

Materials and Methods

We retrospectively reviewed the records of 620 patients who attended the General Endocrine and PCOS Outpatient clinics at WISDEM Centre (Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism) and Centre for Reproductive Medicine (CRM), University Hospitals Coventry and Warwickshire NHS Trust (UHCW) for menstrual disorders, infertility or hirsutism between 2002 and 2016. The study was approved by the UHCW audit Department.

Out of 620 patients, 528 met at least two out of the three Rotterdam criteria for the diagnosis of PCOS, in the absence of other conditions with PCOS-like phenotype (5, 18). Patients without serum PRL measurement were excluded (Figure 1).

Hyperprolactinemia, defined as PRL levels greater than the upper limit of normal (14) (UNL >23.6 ng/mL) in at least two different samples collected on two different days, was found in 76 patients (14.4%). Of these 76 patients 16 were excluded as hyperprolactinemia was attributed to another pathology (12 patients were receiving medications known to affect PRL levels, 2 were pregnant, and 1 had stress-related hyperprolactinemia. Screening for macroprolactin was performed in 19 patients with hyperprolactinemia and normal menstrual cycles and was positive in one. After exclusion of these 16 patients, 60 women were included in the hyperprolactinemic PCOS group of our study.

Further assessment with pituitary MRI was performed in patients with PRL levels ≥94.0 ng/mL (14), and in those with mild-to moderate persistent hyperprolactinemia and concomitant symptoms that could be attributed to a pituitary adenoma such as unaccounted headaches, prolonged amenorrhea and/or galactorrhea.

The diagnosis of prolactinoma was made in patients with hyperprolactinemia who had an MRI-identifiable pituitary adenoma that responded to treatment with dopamine agonists (DAs) with normalization of PRL levels and substantial reduction in the size or resolution of the adenoma on follow-up MRI scans (13, 14).

Only patients with microprolactinomas (measuring less than 10 mm) were included in our analysis. Subjects with adenomas who showed no response to treatment with DAs or other MRI abnormalities were excluded.

Clinical parameters: **Data collected included: age, body mass index (BMI=Kg/m^2), the presence of hirsutism/acne, galactorrhoea, and menstrual history. Oligomenorrhea was defined as cycles occurring at intervals greater than 35 days or less than 8 menstrual cycles per year. Amenorrhea was defined as the absence of menstrual cycles for more than 6 months (19).**

Biochemical parameters: **Fasting blood samples were obtained in the morning during early follicular phase in patients with regular menstrual cycles, 2 days after a 7-day progesterone-only pill course in patients with oligomenorrhea or randomly in patients with amenorrhea.**

The following parameters were recorded: serum concentrations of cholesterol, glycated hemoglobin A1c (HbA1c), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), PRL, Testosterone, dehydroepiandrosterone sulfate (DHEA-S), estradiol (E$_2$), sex hormone-binding globulin (SHBG). Free-androgen index (FAI) was calculated as follows: total testosterone (nmol/L) x 100/SHBG (nmol/L).

Assays: **PRL was measured using Prolactin II on Roche cobas e 602, which is a sandwich electrochemiluminescence immunoassay. The manufacturer states the assay has the following precision: 1.8% at 13.6 ng/mL, 1.4% at 41.1 ng/mL and 1.6% at 211.2 ng/mL. The laboratory has also established its own precision data: 1.97% at 2.0 ng/mL, 1.94% at 36.5 ng/mL and 1.59% at 83.2 ng/mL.**

Other measurements: **Assays were performed using an automated analyzer (Abbott Architect; Abbott Laboratories, Abbott Park, IL).**

Imaging studies: **Gadolinium-enhanced MRI scans of the pituitary were performed at the radiology department and were reviewed by the same radiologist (HM).**

Firstly, we aimed to identify a threshold for serum PRL that could distinguish hyperprolactinemic PCOS patients with microprolactinomas from those without. We also compared the clinical, metabolic and endocrine parameters of patients with PCOS and microprolactinomas (Group A) to those of patients with PCOS, hyperprolactinemia and normal MRI findings (Group B) and age- and BMI-matched PCOS patients with normal PRL levels (Group C).

Statistical Analysis

Comparisons of categorical variables between groups were performed using the Fisher's exact test. The non-parametric Mann-Whitney U test was used to compare not normally distributed continuous variables between two groups. Comparisons between three groups were assessed using the one-way ANOVA and Kruskal–Wallis tests, for normally and not-normally distributed variables respectively. The results were presented as a) mean±SD or median (range) for continuous variables with or without normal distribution, respectively b) frequency for categorical variables. Statistical analyses were performed using the statistical package PRISM 7. P-values <0.05 were considered as statistically significant. Receiver operating characteristic (ROC) curve analysis was performed in order to determine the cut-off value for serum PRL levels.

Results

Out of 60 patients with PCOS and concomitant hyperprolactinemia, 44 (73.3%) underwent MRI of the pituitary: 8/44 patients had serum PRL levels ≥94.0 ng/mL (range: 94.0-351.5 ng/mL) and 36/44 had mild-moderate hyperprolactinemia (PRL range: 25.3-93.7 ng/mL) and symptoms suspicious of a pituitary adenoma as previously defined. Four patients had minimal PRL elevations (25.3-31.1 ng/mL) and were imaged due to persistent headache and prolonged amenorrhea.

Of the remaining 16 patients, 14 displayed mild increases in their serum PRL levels (range: 23.8-35.4 ng/mL) in the absence of associated symptoms. A further 2 patients were claustrophobic and were unable to undergo MRI (PRL levels 47.3 and 51.0 ng/mL, respectively).

Of the 44 hyperprolactinemic PCOS patients who had pituitary imaging, 19 patients had pituitary adenomas, 18 had normal MRI findings and 7 other abnormalities (1 Rathke's cyst, 1 duplication and thickening of the pituitary stalk, 1 diffusely enlarged pituitary gland, 4 mild asymmetry of the pituitary gland with homogeneous or slightly inhomogeneous enhancement but no focal mass indentified). Median PRL levels in this latter group were 47.3 ng/mL (range: 39.3-75.3).

Among 19 patients with pituitary adenomas, 17 had microadenomas and 2 macroadenomas. The latter were initially referred for persistent headache, secondary amenorrhea and galactorrhea and were found to have non-functioning pituitary adenomas (NFPA) along with PCOS (PRL: 30.3 and 94.0 ng/mL) and were excluded from the analysis.

Out of 17 patients with microadenomas, 2 did not receive treatment with DAs (PRL: 71.1 and 74.7 ng/mL) and 2 showed no radiological response to treatment with DAs, i.e no reduction in tumour size on follow-up MRI scans besides normalization of their PRL levels (baseline PRL: 74.2 and 49.0 ng/mL). Thus, the diagnosis of a microprolactinoma could not be established based on the previously mentioned criteria and were excluded from analysis.

The remaining 13 women consisted Group A of our study, i.e PCOS patients with elevated PRL levels due to concomitant microprolactinomas (Figure 1). Median PRL levels in this patient group were 95.4 ng/mL (range: 48.3-351.5) (Table 2). Following initiation of treatment with DAs, all these patients with a provisional diagnosis of a prolactinoma obtained normalization/substantial reduction of their PRL levels along with a significant tumour reduction (n=9/13, 69.2%, median reduction: 47.2%, range: 25-100%) or resolution (n=4/13) of the previously noted pituitary adenoma.

Group B of our study consisted of 18 hyperprolactinemic PCOS subjects who had normal pituitary MRI (Figure 1). Median PRL levels in this patient group were 49.2 ng/mL (range: 25.3-84.3) (Table 2).

A further 30 age- and BMI-matched patients with PCOS and normal PRL levels (Group C) formed our control group.

A. Distribution of PRL levels in patients with PCOS and hyperprolactinemia and PRL thresholds as predictors of prolactinomas

Pituitary adenomas were identified in: 33.3% of patients with PRL levels ranging between 47.2-70.8 ng/mL (2/6), 44.4% with PRL levels between 70.8-94.0 ng/mL (4/9) and 100% with PRL levels ≥94.0 ng/mL (7/7). None of the patients with PRL values less than 47.2 ng/mL had an identifiable adenoma on MRI scan.

Patients harboring prolactinomas had significantly higher PRL levels compared to patients

with no adenomas (*P*<0.0001) (Table 2). Following initiation of treatment with DAs patients with prolactinomas responded with normalization or substantial decrease in serum PRL levels (median PRL post-treatment: 14.7 ng/mL, range: 1.2-26.4) and significant reduction in the size of adenoma on follow-up MRI scans (median pituitary adenoma size, pre- vs post-treatment: 7.7 vs 2.5 mm, *P*=0.005) (Table 1).

ROC curve analysis was performed in order to determine a cut-off value of serum PRL that could identify hyperprolactinemic PCOS subjects with adenomas. The Area Under the curve (AUC) value was 0.91, indicating a high accuracy. Several PRL cut-off values were analyzed in order to obtain acceptable sensitivity and specificity. A cut-off PRL value of 47.5 ng/mL could correctly identify all patients with prolactinomas, albeit with a low specificity (50%), as 9 out of 18 patients with no identifiable adenoma had PRL levels higher than 47.5 ng/mL [positive and negative predictive value (PPV) of 59.1% and (NPV) of 100% respectively]. A PRL threshold of 85.2 ng/mL could distinguish patients with prolactinomas with a sensitivity of 77% and a high specificity of 100% [AUC (95%)=0.91(0.8-1.018), *P*=0.0001] (PPV and NPV were 100% and 85.7%, respectively, diagnostic accuracy: 90.3%) [Figure 2(A) and (B)].

B. Comparisons between Groups A, B and C

Clinical, metabolic and endocrine features of patients in Groups A, B and C are shown in Tables 1 and 2.

1. Clinical parameters

Women in Group A were younger compared to women in Group B (*P*=0.03) (Table 1). No differences were observed in the frequency of clinical hyperandrogenism, menstrual irregularities or PCO morphology between the three groups and BMI or the frequency of galactorrhea between groups A and B.

B. Metabolic and endocrine parameters

Serum PRL levels (pre-treatment) were significantly higher in Group A compared to Group B (*P*<0.0001).

In addition, LH levels were significantly lower in Group A compared to Groups B and C (A vs B: *P*=0.0063, A vs C: *P*=0.0001) (Figure 3). No differences were observed between the three groups with respect to biochemical and/or endocrine parameters (Table 2).

Discussion

The association between PCOS and prolactinoma was first described in 1979 in three patients presenting with hyperprolactinemia, infertility, a pituitary tumour and bilateral wedge resection of the ovaries for PCOS (20). Subsequently, further patients with galactorrhea, mildly elevated PRL levels and history of PCOS, were found to have prolactinomas (21, 22).

Since then, the frequency of pituitary adenomas among patients with PCOS and elevated PRL levels has been mentioned in only few small studies, overall ranging between 10-69% (7, 10, 23, 24). In our study, prolactinomas were identified in 21.7% of patients with PCOS and hyperprolactinemia and in 2.46% of all PCOS patients. Of note, the prevalence of ever treated hyperprolactinemia among female patients in a large cohort of patients in The Netherlands was 93.9/100,000 inhabitants (25). Thus, the association between PCOS and prolactinomas may not be a rare entity. However, there is limited information regarding the range of PRL levels in hyperprolactinemic PCOS patients and the prevalence of prolactinomas. Mild hyperprolactinemia in the absence of prolactinoma has been described in association with PCOS with a variable prevalence, mean PRL values ranging from 25.5±2.2 to 40.3±18.4 ng/mL and has been mainly attributed to a relative dopamine deficiency and the abnormal hormonal milieu (6-11, 26). Our analysis showed, that PCOS patients with prolactinomas had significantly higher PRL levels than hyperprolactinemic PCOS patients without adenomas (median PRL 95.4 vs. 49.2 ng/mL, $P<0.0001$). In addition, PRL levels ≥94.0 ng/mL were associated with prolactinomas in all cases. These findings are in accordance with previous studies (27, 28), suggesting that when other causes of hyperprolactinemia are excluded, PRL levels ≥4xupper normal limit make the possibility of functional hyperprolactinemia highly unlikely among PCOS patients and thus warrant further imaging investigations.

We tried to establish a cut-off PRL level that could predict the presence of a prolactinoma. A cut-off PRL value of 47.5 ng/mL could reliably identify all patients with PCOS and coexisting microadenomas albeit with low specificity and PPV of 59.1%, suggesting that a considerable number of women with PRL levels >47.5 ng/mL have no pituitary adenoma on MRI. Alternatively, PRL levels >85.2 ng/mL were associated with a 100% specificity and 77% sensitivity for discriminating hyperprolactinemic PCOS patients with prolactinomas from those without, as reflected by a high PPV of 100% and an acceptable NPV of 85.7%.

Taken together, it is prudent to suggest that MRI of the pituitary could be justifiable in patients with PCOS and elevated PRL exceeding 85.2 ng/mL.

The underlying mechanisms that might associate PCOS with prolactinomas have not yet been elucidated. Although the unopposed action of estrogens in PCOS patients could stimulate pituitary lactotrophs (20-22), an association between estrogens and the formation of prolactinomas or an increase in their volume is less clear (29). In addition, elevated PRL levels have been associated with alterations in steroidogenic enzyme activities, increased androgen production, insulin resistance, hirsutism and PCO morphology (6, 30-33), all of the above being essential components of the PCOS phenotype.

PCOS patients with prolactinomas had significantly lower LH levels compared to hyperprolactinemic PCOS patients without adenomas and normoprolactinemic PCOS. This finding may suggest that patients with PCOS and concomitant prolactinoma may have a different gonadotrophin profile from the "classic PCOS", which is often associated with LH excess (20, 22). In addition, women with PCOS and prolactinomas were younger than hyperprolactinemic PCOS patients without adenomas.

The main strength of the present study is that we accumulated data from a large number of unselected and well-characterized patients with PCOS. To our knowledge this is the first study aiming to delineate the clinical and biochemical profile of patients with PCOS and concurrent prolactinoma although there are some limitations with regards to the study design. Firstly, it is possible that the diagnosis of prolactinoma may have been missed in some cases, as 44 out of 60 hyperprolactinemic PCOS subjects were evaluated with pituitary MRI. However, the remaining patients presented mainly with mild elevations of PRL levels in the absence of symptoms, pointing towards functional hyperprolactinemia. Secondly, as this was a retrospective study, we had to deal with missing values in certain clinical and biochemical parameters and thus exclude them from our analysis. Furthermore, the number of patients with prolactinomas in both groups was relatively small. Similarly, larger studies are required in order to establish a cut-off level of serum PRL that could more accurately discriminate prolactinomas from functional hyperprolactinemia in patients with PCOS.

In conclusion, PRL levels exceeding 85.2 ng/mL in women with PCOS are suggestive of a PRL-producing adenoma and warrant pituitary imaging. In addition, pituitary MRI could be justifiable in young PCOS patients with milder PRL elevation, low LH levels and concomitant symptoms suspicious of a pituitary adenoma. Further studies are needed to better elucidate the pathophysiological mechanisms linking PCOS and prolactinoma.

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Figure Legends

Figure 1. **Schematic representation of patients' distribution in our study groups.**

PCOS= Polycystic ovary syndrome; CAH= Congenital adrenal hyperplasia; PRL= Prolactin; MRI= Magnetic resonance imaging; NFPA=Non-functioning pituitary adenoma; DAs= Dopamine agonists

*=referred for headaches, secondary amenorrhea and galactorrhea

 **=no reduction of the tumour size on follow-up MRI scans after initiation of treatment with DAs

Figure 2: (A) **Range of serum PRL levels in hyperprolactinemic PCOS patients with and without prolactinomas** (B) **ROC curve analysis, showing sensitivity and specificity of**

different serum PRL cut-off values that could distinguish hyperprolactinemic PCOS patients with prolactinomas from those without.

ROC= Receiver operating characteristic; PRL= Prolactin; PCOS: Polycystic ovary syndrome; AUC= Area under the curve; IQR= Interquartile range; CI= Confidence interval

Figure 3. **LH levels were lower in Group A compared to Group B and C (A vs B: *P*=0.0063; A vs C: *P*=0.0001).**

LH= Luteinizing hormone

Table 1. **Baseline clinical and imaging characteristics in 3 PCOS study groups**

	Group A	Group B	Group C	*P* values
Patients (n)	**13**	**18**	**30**	
Age (years)				*P*=0.12
Mean ± SD	**26±5.4**	**29.8±4.6**	**28.7±4.9**	*Group A vs B: P=0.03*
				Group A vs C: *P*=0.13
				Group B vs C: *P*=0.33
BMI (Kg/m^2)				*P*=0.13
Mean ± SD	**35.0±8.3**	**28.8±8.8**	**30.7±7.8**	**Group A vs B: *P*=0.15**
				Group A vs C: *P*=0.13
				Group B vs C: *P*=0.26

Table 1. **Baseline clinical and imaging characteristics in 3 PCOS study groups (cont.)**

	Group A	Group B	Group C	*P* values
Age at menarche (years)				*P*=0.44
				Group A vs B: *P*=0.8
Median (range)	**12.0 (11-15)**	**12.0 (11-16)**	**13.5 (11-15)**	**Group A vs C: *P*=0.16**
				Group B vs C: *P*=0.65
Clinical hyperandrogenism (n)	**7/13**	**11/12**	**17/22**	**Group A vs B: *P*=0.07**
				Group A vs C: *P*=0.25
				Group B vs C: *P*=0.38

Menstrual irregularities (n)	12/13	15/16	26/28	Group A vs B: *P*=0.8 Group A vs C: *P*=0.9 Group B vs C: *P*=0.9
PCO morphology (n)	10/10	11/14	25/27	Group A vs B: *P*=0.2 Group A vs C: *P*=1.0 Group B vs C: *P*=0.3

Table 1. Baseline clinical and imaging characteristics in 3 PCOS study groups (cont.)

Galactorrhea (n)	5/11	7/11	Group A vs B: *P*=0.6
Size of adenoma (mm) pretreatment* median (range)	7.7 (4.0-9.0)		*P=0.005*
Size of adenoma (mm) posttreatment** median (range)	2.5 (0-6)		

PCOS=Polycystic ovary syndrome; Group A= PCOS patients with microprolactinomas; Group B= PCOS patients with hyperprolactinemia and normal pituitary magnetic resonance imaging (MRI); Group C=PCOS patients with normal PRL levels; SD= standard deviation; BMI= Body mass index; vs= versus.

*Size of pituitary adenoma in Group A before initiation of treatment with dopamine agonists.

** Size of pituitary adenoma in Group A following initiation of treatment with dopamine agonists.

Table 2. **Metabolic and endocrine parameters in 3 PCOS study groups**

	Group A	Group B	Group C	*P* values
Patients (n)	**13**	**18**	**30**	
Hba1c (%)				**P=0.8**
median (range)	**5.6 (5.0-5.7)**	**5.6 (5.4-5.9)**	**5.5 (4.9-7.5)**	**Group A vs B: P=0.7**
				Group A vs C: P=0.9
				Group B vs C: P=0.57
Chol (mg/dL)				**P=0.22**
median (range)	**239 (131-255)**	**208 (131-263)**	**166 (124-278)**	**Group A vs B: P=0.41**
				Group A vs C: P=0.11
				Group B vs C: P=0.36

Table 2. **Metabolic and endocrine parameters in 3 PCOS study groups (cont.)**

	Group A	Group B	Group C	*P* values
TSH (mIU/L)				**P=0.37**
median (range)	**1.93 (0.87-3.13)**	**2.88 (0.38-4.18)**	**1.98 (0.38-5.21)**	**Group A vs B: P=0.63**
				Group B vs C: P=0.2
				Group A vs C: P=0.38
Testosterone (ng/dL)				**P=0.74**
				Group A vs B: P=0.64

median (range)	51.9 (0.58-77.8)	57.6 (17.3-147.0)	53.3 (11.5-172.9)	Group A vs C: *P*=0.43
				Group B vs C: *P*=0.89
SHBG (nmol/L)				*P*=0.12
median (range)	23.8 (13.3-47.4)	38 (10.7-158.3)	25.9 (1.4-72.1)	Group A vs B: *P*=0.2
				Group A vs C: *P*=0.7
				Group B vs C: *P*=0.06

Table 2. Metabolic and endocrine parameters in 3 PCOS study groups (cont.)

FAI				*P*=0.2
median (range)	5.67 (4.43-20.3)	3.21 (1.39-19.54)	7.04 (1.14-59.8)	Group A vs B: *P*=0.2
				Group A vs C: *P*=0.9
				Group B vs C: *P*=0.09
DHEA-S (µg/dL)				*P*=0.6
median (range)	365.3 (155.0-405.9)	202.9 (73.8-383.8)	232.5 (95.9-483.4)	Group A vs B: *P*=0.43
				Group A vs C: *P*=0.4
				Group B vs C: *P*=0.7
LH (mIU/mL)				*P=0.0012*
median (range)	3 (0.8-8.3)	7.0 (2.1-20)	9.5 (3.0-53.0)	*Group A vs B: P=0.0063*
				Group A vs C: P=0.0001

Group B vs C: *P*=0.17

Table 2. Metabolic and endocrine parameters in 3 PCOS study groups (cont.)

FSH (mIU/mL)				**P=0.7**
median (range)	5 (2.0-12.7)	5 (2.0-7.0)	5 (3.0-8.0)	Group A vs B: *P*=0.6
				Group A vs C: *P*=0.4
				Group B vs C: *P*=0.75
Estradiol (pg/mL) median (range)	35.2 (17.2-100.0)	67.3 (16.9-140)	54.0 (20.2-221.8)	**P=0.3** Group A vs B: *P*=0.36
				Group A vs C: *P*=0.19
				Group B vs C: *P*=0.56

Table 2. Metabolic and endocrine parameters in 3 PCOS study groups (cont.)

PRL (ng/mL)				*P <0.0001*
median (range)	95.4* (48.3-351.5)	49.2 (25.3-84.3)	9.15 (4.1-23.4)	*Group A vs B: P<0.0001*
				Group A vs. C: P<0.0001
				Group B vs C: P<0.001

PCOS=Polycystic ovary syndrome; Group A= PCOS patients with microprolactinomas; Group B= PCOS patients with hyperprolactinemia and normal pituitary magnetic resonance imaging (MRI); Group C=PCOS patients with normal PRL levels; vs= versus; HbA1c= glycated
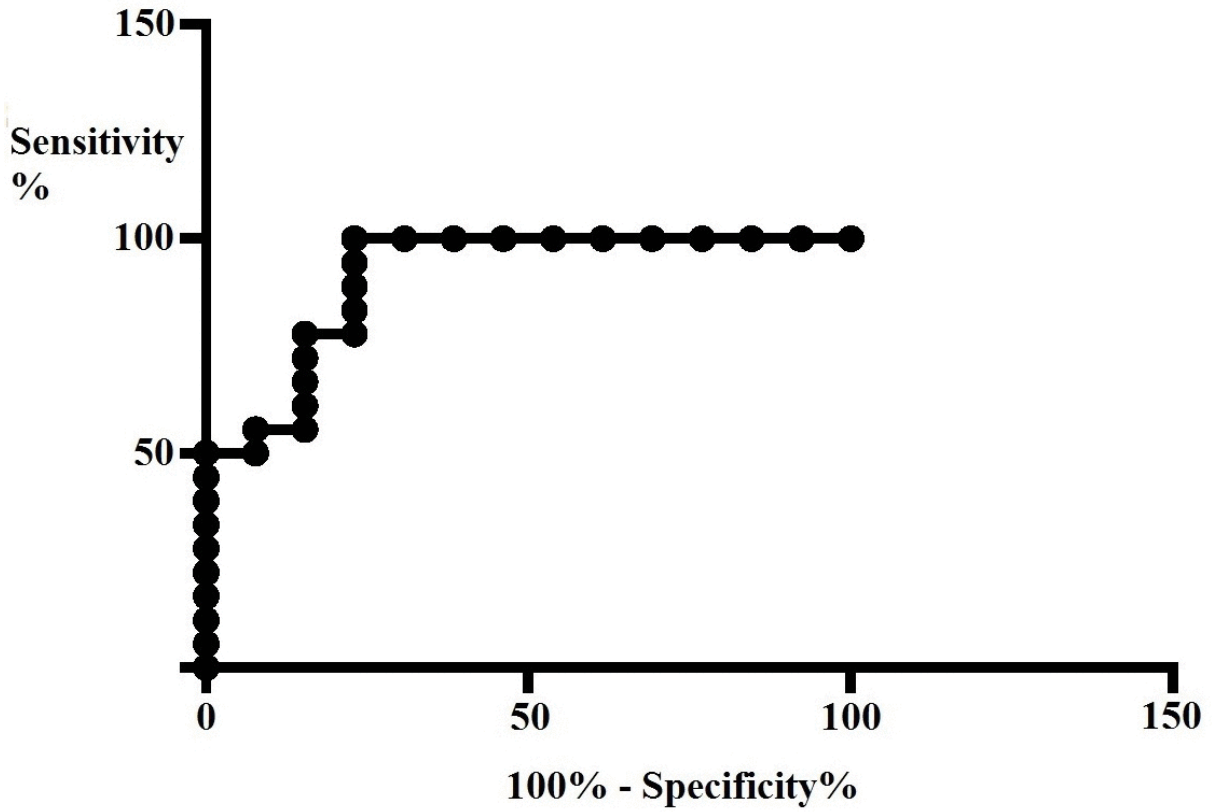
hemoglobin A1c; TSH= Thyroid-stimulating hormone; SHBG= Sex hormone-binding globulin; FAI= Free-Androgen Index; DHEA-S= Dehydroepiandrosterone sulfate; LH= Luteinizing hormone; FSH= Follicle-stimulating hormone; PRL= Prolactin.

*PRL values in Group A before initiation of treatment with dopamine agonists.

Reference ranges: HbA1c: values <6.5%; Cholesterol: <193 mg/dL, TSH: 0.27-4.2 mIU/L; Testosterone: <51.9 ng/dL; SHBG: females: 26-110 nmol/L; FAI: females: <6; DHEA-S: females: 15-19 years (y): 66.4-369.0 µg/dL, 20-24y: 147.6-405.9 µg/dL, 25-34y: 99.6-339.5 µg/dL; 35-44y: 62.7-339.5 µg/dL; LH: Follicular phase: 2-13 mIU/mL; FSH: Follicular phase: 3-12 mIU/mL; Estradiol: females: Follicular phase: 24.5-195.1 pg/mL; PRL: <23.6 ng/mL. Conversion factors between conventional and International System of units (SI) were as as follows: Hba1c: % = [0.09148 × mmol/mol] + 2.152; Cholesterol: mg/dL = mmol/L÷ 0.0259; Testosterone: ng/dL = nmol/L÷ 0.0347; DHEA-S: µg/dL = µmol/L÷ 0.0271; FSH: mIU/mL = IU/L ÷ 1; LH: mIU/mL = IU/L ÷ 1; Estradiol: pg/mL = pmol/L ÷ 3.67; Prolactin: ng/mL = nmol/L ÷ 0.04348.
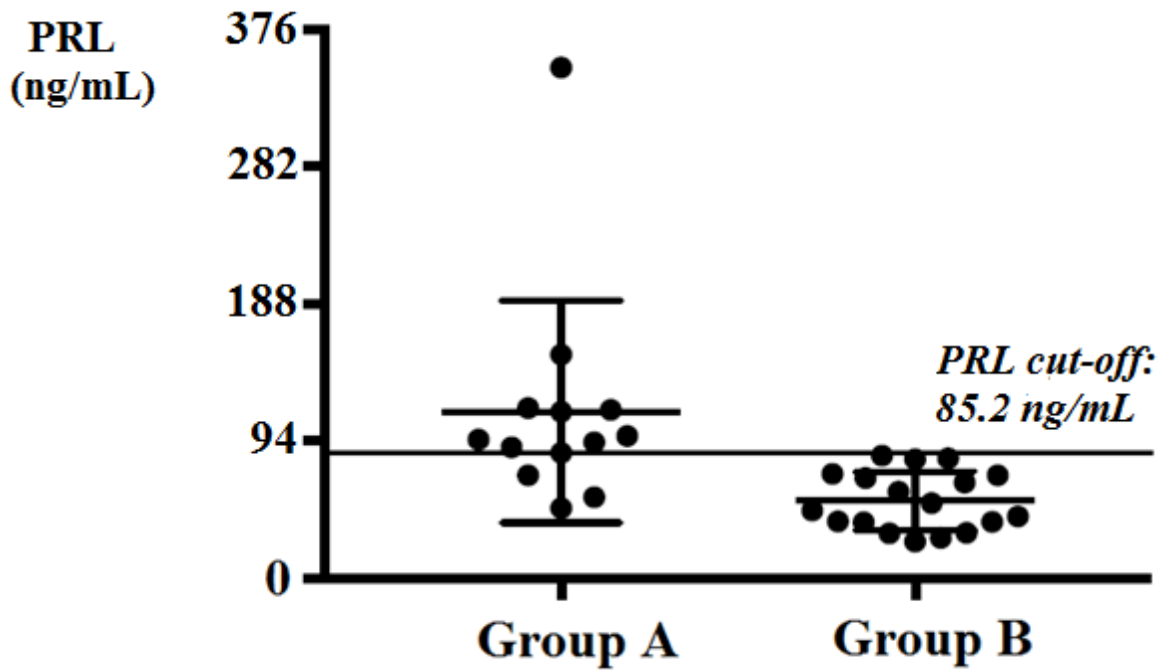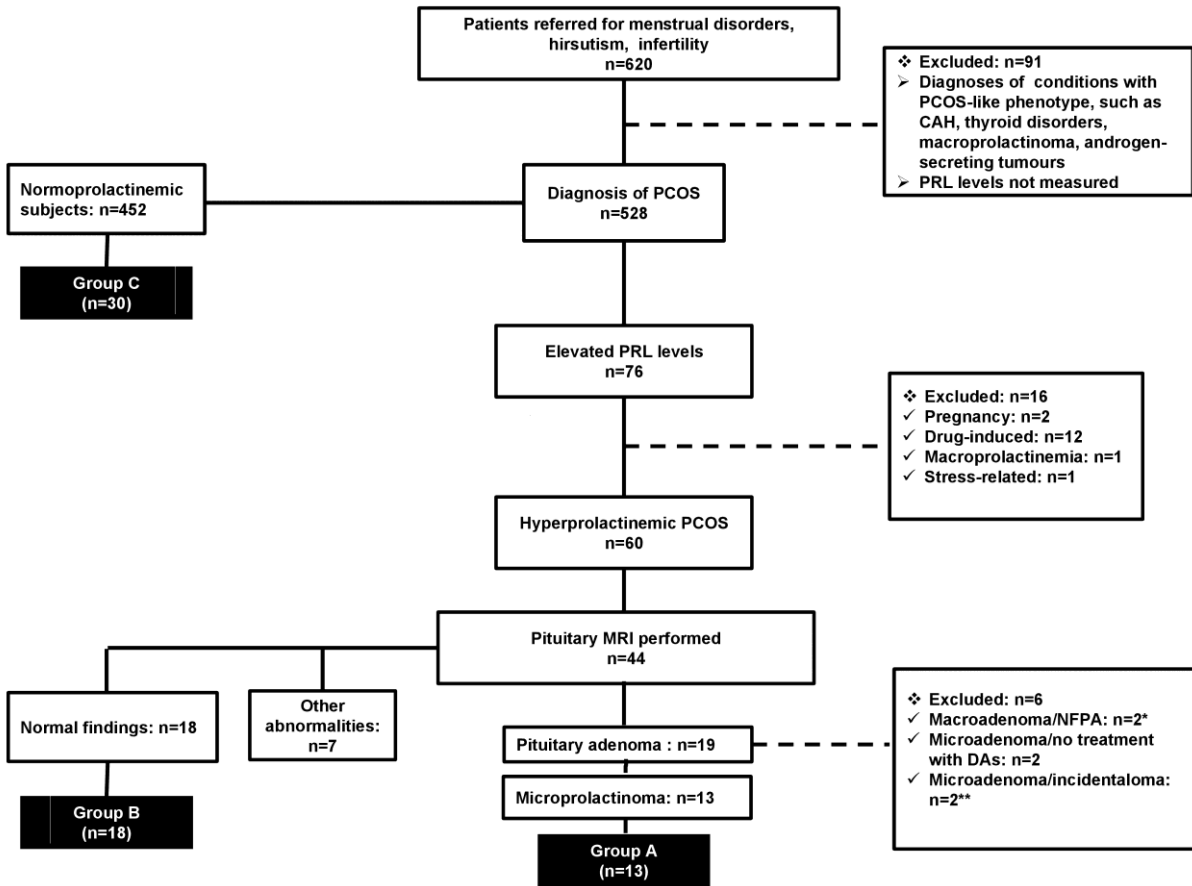
ROC Curve

AUC median (IQR) 95CI=0.91(0.8-1.018), P=0.0001

LH
(mIU/mL)

A vs B: p= 0.0063
A vs C: p= 0.0001