FEMALE HYPERPROLACTINEMIA: ANALYSIS OF PRESENTATION AND DIAGNOSTIC EVALUATION. IS PITUITARY MAGNETIC RESONANCE IMAGING ALWAYS INDICATED?

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Abstract

Background: Hyperprolactinemia (HPRL) is the most common endocrine disorder of the hypothalamic-pituitary-ovarian axis. The most important and common cause is pituitary tumor.

Objectives: 1. Analysis of the presenting features. **2.** Role of MRI in the diagnostic evaluation of HPRL. **3.** MRI measurements and correlation between MRI findings and serum prolactin concentration (PRL) in Iraqi women. **4.** Literature review and work-up for HPRL.

Method: clinical assessment, basal PRL and pituitary and cranium MRI performed in a case-series study for 82 Iraqi HPRL female patients attending gynecologic clinic after excluding secondary HPRL.

Results: sub-fertility, galactorrhoea and menstrual irregularities were the commonest features. MRI abnormalities found in 41.46% of the patients. 88.24% were pituitary abnormalities. Their PRL was significantly higher than those with idiopathic HPRL (p=0.03). Right pituitary adenomas were more common than the left. The pituitary gland occupied 81.73% of the sella turcica in case of pituitary hyperplasia. There was no significant correlation between adenoma size and PRL (p=077), while there was significant positive correlation between pituitary and sella areas in those with normal MRI (p=0.007) as well as those with pituitary hyperplasia (p=0.04).

Conclusion: PRL of 18.5ng/ml considered as the cut-off value to perform high-resolution pituitary and cranium MRI. Primary pituitary hyperplasia may carry a risk of parasellar extension during pregnancy. There is positive correlation between pituitary and sella turcica sizes. MRI considered as the gold-standard imaging method for the pituitary while sella X-ray should be abandoned.

Key words: Hyperprolactinemia, Pituitary adenoma, Pituitary hyperplasia, MR imaging, MR measurement, Iraqi

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Introduction

Hyperprolactinemia (HPRL) is the most common endocrine disorder of the hypothalamic-pituitary-ovarian axis, occurring mostly in women, with a prevalence of 0.4-0.5% in unselected normal adult population to as high as 9-17% in women with reproductive disorders[1,2]. Hyperprolactinemia defined as serum prolactin (PRL) level above the normal range. This is considered as > 19 ng/ml[3], > 20-25 ng/ml[4,5] or > 30ng/ml[6].There is great deal of variability between laboratories in their analytic methods and ranges of normal. Unselected autopsy studies had shown pituitary tumors in 1.5-26.7%. Magnetic resonance imaging (MRI) signs of pituitary tumor found in 10% of normal population. However, clinically significant pituitary tumors affect the health of 8.2-20/100000 people[2, 3, 6-8]. The causes of HPRL fall into five categories:

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First: *Pituitary causes classified to:* Tumors secreting intact hormones that result in clinical syndromes of hormones hypersecretion. These tumors may secrete either *pure* hormones as PRL (termed prolactinoma which constitute 40% of pituitary tumors), growth hormone (GH), adrenocorticotrophic hormone (ACTH) or thyroid stimulating hormone (TSH) or may be *mixed* which express more than one hormone; Non-functioning tumors (non-secreting adenoma NSA) form 25-39% of pituitary tumors. They do not cause clinical syndromes of hormone hypersecretion but indeed produce either silent glycoprotein hormones or their subunits. They may present with functional HPRL. The cause of pituitary tumors is unknown and is not inheritable[8]; Pituitary hyperplasia i.e. global pituitary enlargement which is either primary or secondary to puberty, pregnancy, primary hypothyroidism with secondary HPRL, hypothalamic tumors as GH releasing hormone-secreting tumors or mental depression[3]. Pituitary incidentoloma represented 12% of pituitary tumors. It means incidentally discovered pituitary mass during imaging performed to evaluate conditions not linked to pituitary disease[3, 7, 9].

Second: *Non-pituitary sellar and parasella lesions with functional HPRL*: Structural lesions as empty sella, intrasellar cyst, tumours as craniopharangioma, germinoma, meningioma , chordoma, astrocytoma, lymphoma, metastatic tumors, glioma and vascular abnormalities as aneurysm; Non-structural lesions as sarcoidosis, cranial irradiation, stalk resection, lymphocytic hypophysitis[1,3,4,10].

Third: *Secondary HPRL* to renal impairment, liver cirrhosis, primary hypothyroidism, lesions in dermatomes T 3-5 & mammary line, spinal cord tumors, seizures, ectopic PRL production by malignant lesion as bronchogenic carcinoma and PRL-enhancing drugs[1,10,11].

Fourth: *Physiological HPRL* in response to stress, sleep, food intake, sexual activity and nipple stimulation as well as in pregnancy and lactation. PRL is secreted in pulses every 20 minutes with a diurnal rhythm[1, 4, 10, 12].

Fifth: Lastly *idiopathic HPRL* in 32.8-61%, when no underlying cause is found[4,13,14].

The commonest features of HPRL are menstrual irregularity, galactorrhoea, infertility, pregnancy loss, loss of libido, acne and hirsutism, headaches and osteopenia. It is important to consider HPRL and pituitary adenoma in an expanded range of clinical situations. Baird's in his recent study[15] adds other troublesome complaints as physical and mental fatigue, mood disorder, sleep problem, unexplained pain, emotional behavior dysfunction and decline in sexual function.

HPRL alters the pattern of hypothalamic catecholamines and so suppresses pulsatile secretion of gonadotrophin releasing hormone thus blocking follicular stimulating (FSH) and leutinizing hormones (LH) by blunted or no response to estradiol. In addition, PRL inhibits gonadotrophin effect at ovarian level. There is hypoestrogenism and chronic hyperandrogenism[2,10].The increased mean intracellular pressure (MISP) contributes to the development of headaches even in those with microadenomas[16].

However, our understanding of HPRL has improved greatly since the availability of finer diagnostic imaging. MRI now regarded as the pituitary imaging method of choice that provides the most detailed information and

suggests pathological diagnosis, tumor vascularity and invasiveness to surroundings. It can be used during pregnancy and can be repeated.It has no ionizing radiation like computed tomogram (CT) which also provides less precise information[6], although tissue calcifications are better detected by CT[17]. Nevertheless, even MRI may have pit-falls i.e. false-positive results due to normal anatomic variations or imaging artifacts[7]. For pituitary and cranium, imaging the trend now is to use the high resolution MRI with dynamic contrast enhancement[3, 17].

The primary treatment of prolactinomas whether micro- or macro-adenomas and for idiopathic HPRL is medical therapy when indicated, while surgery is the first treatment for the non-PRL secreting and non-secreting pituitary adenoma as well as for the sellar and parasellar tumors[3,4].

Differentiation between prolactinomas and the other tumors is possible by immunohistochemistry study of the specimen after surgery. Since few prolactinoma patients are now submitted to surgery, dynamic tests of PRL in HPRL patients are useful in suggesting a pathological diagnosis of pituitary adenomas.

Dopamine antagonists domperidone[17], metoclopramide or perphenazine[2] stimulation tests give blunted PRL response in prolactinoma i.e. PRL 30/PRL 0<3 in comparison to PRL response of ≥3 in functional HPRL secondary to the other tumors. The blunted PRL increment of less than 30% after thyrotropin releasing hormone (TRH) stimulation test is typical of macroprolactinoma and excludes other pituitary adenoma, but the cut-off not yet established for microadenoma[3].

In prolactinoma when dopamine agonists are used as bromocriptine suppression test there is decrease of serum PRL by 70%[18].

Macroprolactin, a PRL aggregate with high molecular weight 150-170 Kda is active in vitro but has no or low biological activity in vivo. It is indistinguishable from the low molecular active PRL by routine assay but by special tests as chromatography and others[7,19,20]. Macroprolactinemia is present in 8-46% of HPRL. It found that 78-78.9% of those with macroprolactinemia had normal MRI[6,20] while the others have pituitary lesions.

Because MRI is expensive some studies[17,21] suggest the dynamic tests of PRL and macroprolactin assay in HPRL to be done first and then to select those who need the MRI. While others studies[2,4,6,19,20] concluded that pituitary imaging is necessary in the diagnostic evaluation of HPRL.

The aims of the study of female:

1. Analysis of the presenting features.
2. Role of MRI in diagnosing the cause of HPRL with comparison to X-ray of pituitary fossa.
3. MRI measurements and correlation between MRI findings and PRL in Iraqi women.
4. Literature review and work-up for HPRL

Methods

This case-series study included 172 consecutive Iraqi women with PRL concentration higher than 14ng/ml, who were non-pregnant, non-lactating and not on hormonal contraception attending Al-Kadhmyia Teaching Hospital and private gynecologic and infertility clinics during the period from 1 June 2001 through the fifteenth of March 2003.

For all of them a second basal PRL assay in standardized conditions was performed. A fasting morning specimen drawn after suspending any sexual activity and nipple stimulation for at least four days. In spontaneously menstruating women, the sample drawn on the second or third day of the cycle. While in amenorrheic women,

pregnancy excluded by clinical assessment and pregnancy test before sampling. These measures were to reduce potential confounding physiological factors.

During medical history and examination, we looked for: PRL enhancing drugs, mammary line skin lesion or irritation at dermatomes T3-T5, features of renal, liver and thyroid dysfunction. For all the 120 patients with persistent HPRL, screening with blood urea, serum thyroxine and TSH performed.

Fifty-two women (30.23%) were found to have transient HPRL with the basal PRL ≤14ng/ml while the first PRL concentration mean was 16.67±1.38 (range 14.2-24ng/ml). Twenty-six patients(15.12%) were found to have possible secondary HPRL including: 14 (8.14%) with pharmacological HPRL using amitriptyline HCL, alphamethyldopa, digoxin, cortisteroid, danazol, diphenhydramine or cimetidine; 11(6.39%) had mammary line skin lesion or irritation (one herpes zoster, 3 breast pruritus and 7 used local methods for breast hair removal); one with high blood urea (70 mg/dl). None had chronic liver disease or primary hypothyroidism.

Those 26 patients with secondary HPRL with PRL concentration mean 19.2±2.01 range 14.5-29.3 ng/ml not presented in this study. Another 12 patients (6.98%) excluded from the study because they did not attend for the MRI. The remaining 82 women (47.67%) were the study group with HPRL (basal PRL>14ng/ml) who did not have any of the above factors and for whom pituitary and cranium MRI was performed. For the first thirteen patients lateral view X-ray of the pituitary fossa in addition to the MRI performed during the era when the MRI newly introduced to practice in this hospital. Then sella X-ray abandoned.

For the study group, detailed history and examination performed regarding symptoms possibility related to HPRL as menstrual irregularity, galactorrhoea, breast pain, sub-fertility with ovulatory factor, abortion, acne and hirsutism, dyspareunia and loss of libido. Also features of mass affect including headaches, visual symptoms, cranial neuropathies as third and sixth nerve palsy and cerebrospinal fluid (CSF) rhinorrhoea.

Clinical features of excess or deficiency of GH, ACTH and TSH looked for. Full ophthalmologic examination including visual field campimetry using Goldmann perimetry was requested for 50 patients desiring pregnancy as a base line, also for 5 patients with symptoms of mass effect and 5 with pituitary macroadenoma on MRI for whom neurosurgical opinion was also requested. Enquiry about previous brain trauma, postpartum hemorrhage and birth asphyxia made for those found to have empty sella on MRI.

Prolactin assay*:* PRL measured by immunoradiometric assay (IRMA, reference value for adult females 3.6-14 ng/ml; ImmunoTech, Bechman Coulter Company) with a sensitivity of 0.5 ng/ml, intra-assay and inter-assay variation were ≤2.8 and ≤ 8% respectively.

High Resolution Dynamic Contrast MRI Examination*:* MRI study was performed on 1.5 Tesla superconductive system (philips Gyroscan NTCS) with the use of dedicated phase array head coil. The used protocol included whole brain scan as survey by using T2 Turbo-spin-echo (Tse) axial and then dedicated scanning of: 1-The pituitary gland: Coronal and Sagittal planes T1 weighted Se, repetition time (TR) 625, echo time (TE) 13, slice thickness (SL) 1.5mm, 256x256 matrix, field of view(FOV) 180mm, number of excitation (NEX) 4 and intersection gap 0.3mm. 2-Coronal T2 weighted Tse, TR 6772, TE 150, SL 2mm, matrix

256x256, FOV 200 and NEX 4. 3- Dynamic contrast study on T1 coronal study after administration of 0.1 mmol/kg body weight gadolinium diethylene triamine pentaacetic acid (Gd-DTPA) intravenously.

***MRI Assessment**:* Sella turcica: size, antero-posterior (AP) diameter and height (HT) on sagittal view, the U-shaped configuration, walls and borders. Pituitary: position in the sella, the bean shaped configuration, superior border, size, AP diameter and HT on sagittal views, pituitary homogenisity before and after contrast enhancement, any circumscribed hypo- or hyper-intense area and dynamic sequence for any time differential in the enhancement of different pituitary areas.
Infundibulum (pituitary stalk): position and size. Optic chiasma: position, size and symmetry. Suprasella CSF spaces: symmetry and constriction. Cavernous sinus: symmetry, size and infiltration. Internal carotid arteries: symmetry, size, narrowing or expansion. Neurocranium: temporal lobe, hypothalamus and floor of third ventricle. Sphenoid sinus: margins especially the roof and pneumotization.
Diagnosis of pituitary adenoma and hyperplasia and the SIPAP classification as a grading system for extension was according to the imaging characteristics demonstrated in Ref. 3, 11, 22.23. In this study pituitary hyperplasia was diagnosed when both pituitary sagittal diameters AP and HT were >10mm and >8mm respectively with generalized pituitary heterogeneity with or without enhancement.

Statistical Analysis
Analysis of data was with the personal computer Microsoft Excel program. Results presented as frequencies. Mean and standard error of the mean (M±SEM) was calculated. Student *t-test* and ANOVA used as tests of significance taking $p \leq 0.05$ as significant value. Degree of association assessed by correlation coefficient *r* and linear regression analysis. Sensitivity, specificity and accuracy were calculated using the contingency two-by-two table.

Results

The results of the study group i.e. the 82 patients with HPRL who consulted the gynecologic clinics, for whom pituitary and cranium MRI was performed were presented.

Patients' characteristics: The results presented as M±SEM and (Min-Max).
Age (year) =31.37±0.96 (16-52); weight (kg) =69.93±1.78 (45-105); 10 (17.5%) were obese with BMI>30kg/m^2; 12 (15%) were unmarried; gravidity mean 1.42±0.25 (0-8); parity mean 0.93 (0-7); number of abortions mean 1.74±0.31 (1-6); primary sub-fertility duration (year) 4.83±1.01 (0.9-24); secondary sub-fertility duration (year) 4.82±0.92 (1-16).

Clinical features: The 82 patients had one or more of the features presented in Table 1. Their mean PRL was 39.64±2.47 (16.6-168).

Table 1: Frequencies of clinical features and PRL concentrations of the 82 HPRL patients

Features	Total 82 patients*		PRL ng/ml	
	Number	%	mean±SEM	Min-max
Sub-fertility§	50 (43)	71.43 (61.43)	39±2.52	19.6-118
1ry	32 (27)	45.71 (38.57)	39.82±3.22	19.6-110
2ndary	18 (16)	25.71 (22.86)	37.54±4.13	25.6-95
Galactorrhoea	38 (4)	46.34 (4.88)	41.6±4.48	18.5-168
Menstrual abnormality	31 (19)	37.8 (23.17)	45.47±5.19	22.6-168
Abortion§	19 (2)	27.14 (2.85)	43.29±7.62	22.6-168
Hirsutism/Acne	14 (3)	17.07 (3.66)	37.31±4.26	22.6-84.6
Breast pain	9 (3)	10.98 (3.66)	40.69±5.63	28-78.7
Headache	3 (0)	3.66 (0)	73.63±47.19	24.8-168
Visual symptoms	2 (0)	2.44 (0)	96.4±71.6	24.8-168
Dyspareunia/loss of libido	0	0		

*within parenthesis are the patients presenting symptoms

§ the denominator was 70 instead of 82 because the 12 unmarried patients were not included

Coexisting conditions: Some of the HPRL patients had also polycystic ovary syndrome (PCOS), uterine leiomyoma (LM) or goiter. Their results presented in Table 2. Of the 11 PCOS patients, only one had MRI abnormality. The remaining 10 with normal MRI had PRL concentration of 36.29±3.58, which compared with the PRL of 35.08±2.62 of the 38 patients who had neither PCOS nor MRI abnormality. Two tail student *t-test* revealed no significant difference (*t=0.27 df=20 p=0.79).*Of the 10 LM patients with HPRL 4 had MRI abnormalities. The remaining six LM patients with normal MRI had PRL concentration of 30.12±4.06, which compared with the 36.05±2.37ng/ml of the 42 patients with neither LM nor MRI abnormality. *t-test* revealed no significant difference (*t=1.26 df=9 P=0.24).* The two patients with HPRL and goiter were found to have neither hyper- nor hypo-thyroidism.

Table 2: Frequencies of coexisting conditions and PRL concentration in the 82 HPRL patients

Condition	Total 82 patients		PRL ng/ml	
	Number	%	mean±SEM	Min-max
Polycystic ovary syndrome	11	13.41	35.38±3.37	22.6-50.7
Uterin leiomyoma	10	12.2	30.7±2.75	16.6-45.1
goitre	2	2.44	32±2.9	29.1-34.9

Pituitary MRI Characteristics: MRI findings and their correlation to prolactinemia values presented in Table 3 and Table 4. Of the 48 normal MRI i.e.idiopathic HPRL patients 2 (4.2%) had normal variations: one with left local asymmetry of the pituitary gland and the other with left sided pituitary stalk. Another two had incidental findings in the form of nasopharangeal polyp in one and left sphenoid sinus mucocele in the other. Three (10%) of the 30 patients with MRI abnormality showed convexity or bulge of the upper pituitary margin. In 2 (8.4%) MRI with pituitary adenoma the adenoma areas 99mm^2, 276mm^2 were larger than their sella areas 90 mm^2, 258mm^2 respectively with suprasellar extension grade 1 according to SIPAP classification but no pressure on optic chiasma. One MRI with pituitary microadenoma showed shift of the lower pituitary stalk.

The mean pituitary area, mean sella area and their percentage ratio calculated for the 48 women with normal pituitary MRI and for the 5 women with pituitary hyperplasia. Results revealed

69.79±3.32 mm^2, 107.15±4.83 mm^2 and 65.13% vs. 139.75±38.8 mm^2, 171±38.9 mm^2 and 81.73% respectively.

Only one patient with macroadenoma had restricted visual field and treated medically under the supervision of the neurosurgeon. Opened cranial surgery done with removal of the meningioma and the cerebellar cyst. The latter revealed heamangioblastoma tumor.

Table 3: Pituitary and cranium MRI findings in the 82 HPRL patients

MRI findings	Total 82 patients		PRL ng/ml		P value
	Number	%	mean±SEM	Min-max	
Normal*	48	58.54	35.33±2.19	16.6-110	0.03
Abnormal	34	41.46	45.45±4.87	18.5-168	
Pituitary abnormality§	30	36.59	46.35±5.28	18.5-168	
Microadenoma	20		45.51±7.09	18.5-168	0.57
Right	11				
Left	9				
Macroadenoma	5		57.76±13.68	29.5-95	
Right	4				
left	1				
Hyperplasia	5		38.32±4.68	28-53.9	
Non-pituitary brain abnormality	4	4.88			
Meningioma	1		26.3		
Cerebellar cyst	1		21.7		
Empty sella¤	2		53.4		

***** Those HPRL patients with normal MRI considered to have idiopathic HPRL

§ Microadenoma means: its largest diameter < 10 mm while macroadenoma ≥ 10 mm

¤ One empty sella associates microadenoma

Table 4: Pituitary gland, pituitary adenoma and sella measurements of the 82 HPRL patients

	MRI findings	M±SEM	Min-Max
Normal pituitary	AP(mm)	10.58±0.31	8-16
	HT(mm)	6.61±0.29	4-10
	AREA(mm^2)	69.79±3.32	32-105
Microadenoma	AP(mm)	5.43±0.54	2.2-9.7
	HT(mm)	4.37±0.45	1.2-8.8
	AREA(mm^2)	27.1±5.11	4.2-77.44
Macroadenoma	AP(mm)	16.24±2.19	11-23
	HT(mm)	8.58±1.10	5.1-12
	AREA(mm^2)	146.15±36.2	62.22-276
Hyperplasia	AP(mm)	12±1.08	9-14
	HT(mm)	11.25±2.29	8-18
	AREA(mm^2)	139.75±38.8	81-252
Sella	AP(mm)	1192±0.25	9-16
	HT(mm)	9.37±0.3	6-18
	AREA(mm^2)	113.24±5.32	54-270

AP=antero-posterior diameter HT=height

Correlation Study: These presented in Table 5 and Figure 1.

Pituitary and cranium MRI vs. sella turcica X-ray: Of the 13 patients who had sella X-ray in addition to the MRI, six X-rays showed abnormal findings in the form of calcifications, ballooning or doubling of the floor, erosion of the floor or clinoid process. Calculation from the 2*2 Table 6 revealed 12.5% sensitivity of the sella X-ray, 16.67% specificity and the overall accuracy of only 15.71%.

Table 5: correlation between pituitary and cranium findings and other parameters

MRI findings	Variables		Statistical tests		
	Independent(X)	Dependent(Y)	r	p	n
Pituitary adenoma	Adenoma area(mm^2)	PRL(ng/ml)	0.06	0.77	25
Pituitary hyperplasia	Pituitary area(mm^2)	PRL(ng/ml)	0.4	0.51	5
Normal pituitary	Pituitary area(mm^2)	PRL(ng/ml)	0.28	0.11	33*
Pituitary adenoma	Age(year)	Adenoma area(mm^2)	0.2	0.35	25
Normal pituitary	Age(year)	Pituitary area(mm^2)	0.3	0.09	33*
Normal pituitary	Gravidity	Pituitary area(mm^2)	0.15	0.44	30*
Normal pituitary	Parity	Pituitary area(mm^2)	0.01	0.96	30*
Pituitary hyperplasia	Sella area(mm^2)	Pituitary area(mm^2)	0.96	0.04	5
Normal pituitary	Sella area(mm^2)	Pituitary area(mm^2)	0.46	0.007	33*

r=correlation coefficient p=significant value n=sample size

* In 15 HPRL patients with normal pituitary MRI, the pituitary diameters not measured. The gravidity and parity not mentioned in three of them

Figure 1:correlation between MRI normal pituitary & sella areas

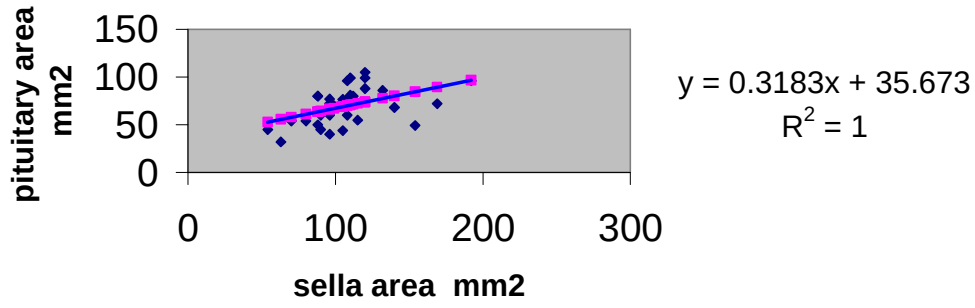

Table 6: Two-by-two table between pituitary MRI and sella X-ray findings

		MRI findings		
		Abnormal	Normal	Total
X-ray findings	Abnormal	*a* 1	*b* 5	6
	Normal	*c* 7	*d* 1	8
	Total	7	6	14

a=true positive b=false positive c=false negative d=true negative

Discussion

with NSAs. Patients lost weight during PRL lowering therapy. In addition, he found that recent weight gain is an indication to measure serum PRL as it may be the presenting symptom of HPRL. In Dublin's study[14] drug-

The entire study group was in reproductive age. 17.54% of them were obese. Green[24] found that the mean weight is significantly higher (P=0.007) in those with prolactinomas than those

LH as well as PRL. Therefore, the central basal hypothalamic deficiency of dopaminergic activity leads to the increased LH/FSH ratio and PRL in PCOS HPRL patient.

PRL produced by human endometrium, myometrium and uterine leiomyoma. Insulin-like growth factor and others mediate this production. Proliferative phase leiomyomas contain elevated levels of PRL in vivo and synthesize PRL in vitro[27]. Could leiomyoma be the source of the high PRL in patients with idiopathic HPRL? The answer may be "NO" as we found no significant difference in PRL level in those with idiopathic HPRL whether they had leiomyoma or not (p=0.24).

PRL is two folds higher in tumoral HPRL than secondary HPRL[29]. This also proved in our study, the mean PRL in MRI abnormality group was 45.45 ± 4.87 ng/ml (Table 3) vs. 19.2±2.01 in those with secondary HPRL. Table 3 showed the significantly higher PRL level in those with pituitary and brain MRI abnormality than those with idiopathic HPRL (P=0.03). This is consistent with Dr. Reba findings[18]. As PRL of 18.5ng/ml was the minimal value for those HPRL with pituitary and brain lesions (Table 3), this figure may be suggested to be considered as the cut-off value at or above it MRI is indicated. In Ref 3 a patient with pituitary adenoma had even a PRL level of 18ng/ml. The mean PRL level in those with pituitary lesions was 46.35±5.28 in our study while in other studies it was 61±16.6[20], 62±13[29] and 79.9±63.6[6].

The results of Table 3 can be compared with Cano et al. study[13] of MRI findings in HPRL which were: pituitary adenoma in 40.6%, questionable nodule in 4.7%, homogenous gland (i.e. pituitary hyperplasia) in 12.5%, 9.4% empty sella and 32.8% normal pituitary gland while Hauche et al study[6] revealed 6.2% pituitary macroadenoma, 32.8% microadenoma and 61% normal induced, HPRL is found in 16% vs. 8.14% in our study which may be explained by the more common use of neuroleptic drugs in developed countries.

The prevalence of HPRL varies according to patient selection and presenting symptom[10]. Our study included patients attending gynecologic clinic: subfertility was the commonest clinical feature followed by galactorrhoea and menstrual abnormality (Table 1) while in other studies[3,10,14] menstrual abnormalities was the commonest followed by galactorrhoea then subfertility but these studies include male and female patients presenting to endocrine centers. We should stress that not all HPRL women have galactorrhoea; it ranges between 40.5-67.4%[3,10,14]. Only 25% of those with galactorrhoea have HPRL[10]. It was found that 20-30% of those with menstrual abnormality had HPRL vs. only 10% of those regularly menstruating[10,21]. Thirty percent of patients with infertility have HPRL[10].There was no significant difference (P=0.14) in PRL concentration between the different clinical features of HPRL (Table 1). PRL level indeed correlates with the severity of the symptoms rather than the type of the symptom[25].

The association between polycystic ovary syndrome (PCOS) and HPRL remains controversial. In one study[10] HPRL was found in 17% of PCOS patients. PCOS found in 13% of the study group (Table 2). There was no significant difference in PRL level in those with idiopathic HPRL whether they had PCOS or not (P=0.79). It seems that these two conditions may coexist and they have independent origin[26]. However, Dr. Luciano 10 explained the relationship between PCOS and HPRL: First, the high oestrone of PCOS stimulates PRL; second, dopamine inhibits the release of

response to treatment on follow-up MRI[22].

It seems that women with HPRL present to the gynecologist early. In this study, no one with pituitary adenoma had suprasellar significant extension, invasion or compression as manifested by MRI, full ophthalmologic and neurological examination. Because of the vague presenting features of HPRL in men, they tend to present late with larger prolactinomas and at older age than women[3]. If we assume that microadenoma increases in size with time to change to macroadenoma then we should find increasing adenoma size with increasing women age but this was not found(r=0.2, p=0.35)Table 5. This is supported by the fact that microadenomas tend to remain the same size[18] and in less than 5% the tumor enlarges slowly; while macroadenomas are already established at time of presentation and in 25% significant tumor growth occurs during follow-up[1,9,12,18]. Adverse pregnancy out-come occurs in <5% in microadenoma as compared to 40% in macroadenoma patients[5]. In those with normal pituitary MRI no correlation (r=0.3, p=0.09) between age and pituitary size was demonstrated in women of reproductive age; while pituitary size is larger in pubertal girls and smaller in postmenopausal women[23].

In women with normal MRI no correlation was found between pituitary area and previous gravidity (r=0.15, p=0.44) or parity (r=0.01, p=0.96) (Table 5). Although there is, 2% and 5% increase in height and width of pituitary gland respectively 2-6 months postpartum as compared to non-pregnant control but the difference is not statistically significant[30]. Post-pregnancy PRL returns to pre-pregnancy level in HPRL women yet it is significantly lower in parous than pituitary .It seams that right pituitary adenomas are more common than left. It was 15 vs. 10 in our study, and twice as frequent in the right as left in Gspones et al study[3].

The relation between PRL level and adenoma size not settled yet. We found no significant difference (P=0.57) in PRL concentration between those with micro- and macroadenoma (Table 3). In addition, there was no correlation between PRL concentration and each of adenoma area(r=0.06 P=0.77) and normal MRI pituitary area(r=0.28 P=0.11) (Table 5). In Arafah et al study[16] PRL levels correlated positively with the MISP but the tumor size did not correlate with MISP or PRL level. While in other studies there is relatively linear relationship between degree of PRL elevation and the size of "True Prolactinoma"[4,13]. Indeed, PRL level correlates positively with the vascular density in prolactinoma. MRI can diagnose pituitary adenoma and its size but not its type. Not all adenomas are secretary and not all secretary adenomas are “True Prolactinomas”. In those with non-PRL, producing mass there is usually large mass and mild functional HPRL[4], which is explained by secondary interruption of the normal PRL inhibiting dopamine traveling via the portal blood vessels down the pituitary stalk due to either compression by the mass or due to increased MISP, which impairs portal blood flow[16].

In women of childbearing age the normal pituitary MRI sagittal diameters are: AP 8-10 (< 10 mm) HT 3.5-8 (2-6 mm) Ref 23 and 29 respectively. The normal sella turcia MRI sagittal diameters are: AP 11-16 mm and HT 8-10 mm[23]. These are comparable to our results in table 4. Variation in different populations is possible. Indeed for each patient more than one diameter basic measures of the pituitary adenoma is necessary to diagnose growth and

ng/ml[3] and >100 ng/ml[2] are 100% diagnostic of "True macroprolactinoma".

Third: If milder HPRL of ≤85 ng/ml is associated with MRI pituitary mass, further dynamic tests of PRL are required to differentiate prolactinomas, which treated primarily medically from other pituitary and brain tumors, which require surgery. Dynamic tests alone do not differentiate tumor induced functional HPRL from idiopathic HPRL. Therefore, they cannot replace MRI.

Fourth: 21.1-22% of those with macroprolactinemia have prolactinomas, usually microprolactinomas[6,20]. Therefore, MRI still indicated to diagnose them with follow-up of their mass effect. However, there is no need to treat those who have macroprolactinemia as they do not have clinical features of HPRL.

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nulliparous normoprolactinemic women[5].

There were no previous reports on pituitary size and its correlation with sella turcica size. We found the correlation to be highly significant between pituitary area and sella area in normal pituitary MRI cases (r=0.46, p=0.007) and significant in pituitary hyperplasia (r=0.96, p=0.04) (Table 5, Figure 1). According to our results, the pituitary area occupied 65.13% of the sella turcica in those with normal pituitary vs. 81.73% in those with primary pituitary hyperplasia. As the pituitary doubles its size during pregnancy[1] and increases by 120% in the third day postpartum[31], we may suggest that primary pituitary hyperplasia to be another indication for pre-pregnancy dopamine agonist therapy in order to shrink the pituitary size in a manner similar to the management of macroadenoma. No sufficient information regarding primary pituitary hyperplasia found in all the literatures reviewed in this study.

Simple sella turcica x-ray should be abandoned as a test for the pituitary because of its low sensitivity, specificity and accuracy (Table 6). Interpretation of sella X-ray is vague and incorrect[1,12].

From the results of this study and from reviewing literatures the following work-up suggested in the diagnostic evaluation of female HPRL:

First: whenever clinical features of HPRL are present, basal PRL should be measured and secondary HPRL should be diagnosed before treating the symptoms in order not to miss serious diseases and pituitary or brain tumors.

Second: Then if the basal PRL is > 18.5 ng/ml (as suggested from our study), MRI is indicated in order to differentiate pituitary macro- and microadenoma, pituitary hyperplasia or other brain tumors. MRI diagnosis of pituitary macroadenoma and PRL of > 85

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