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Research Article

The Role of Vitamin B6 in Reducing Serum Prolactin in Comparison to Cabergoline

Suha J Witwit*

Department of Obstetrics & Gynecology, College of Medicine, University of Babylon, Iraq

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ABSTRACT
Hyperprolactinemia is a common endocrine disorder of hypothalamic-pituitary axis. It affect about 4-17% of women in reproductive age & about 3-10% of patients with polycystic ovaries. Vitamin B6 is an effective prolactin inhibitor that is extremely cheap and safe.it exerts hypothalamic dopaminergic effect which causes a significant reduction in prolactin level. The aim of the study is To evaluate the effectiveness of vitamin B6 in reducing serum prolactin in Hyperprolactinemic patient. Compare this effect to that of cabergoline.

Keywords: hyperprolactinemia, vitamin B6, cabergoline.

INTRODUCTION

Hyperprolactinemia is the most common pituitary causes of amenorrhea. mildly elevated serum prolactin may be due to many causes like sleep, stress and recent breast examination[1]. Elevated serum prolactin level in many people remain unexplained & may represent hypothalamic-pituitary-ovarian axis disregulations & this is what is named idiopathic hyperprolactinemia[2]. Prolactin is one of an anterior pituitary hormone with it's principle physiological action of initiation & maintenance of lactation. In human reproduction, pathological hyperprolactinemia is commonly present as an ovulatory disorder& usually associated with secondary amenorrhea or oligomenorrhea, galactorrhea which occur in less than half of the patients[3]. Serum prolactin is higher in the afternoon than in the morning. Hence should preferably be assessed in the morning as it define when fasting serum level of more than 20ng\ml in men & more than 25 ng\ml in women[4]. Hyperprolactinemia is estimated to be present in 25% among women with galactorrhea& 9% of women with amenorrhea & high as 70% among women with both galactorrhea& amenorrhea. The prevalence is about 5% in those women who present with infertility[5]. Actual serum prolactin level is the net result of a complex balance between positive & negative stimuli derived from both endogenous & exogenous environment. many mediators of central, pituitary& peripheral origin play a role in regulation of prolactin production through direct or indirect effect on lactotrophic cells[6]. Hyperprolactinemia could be either physiological (due to sleep, pregnancy, stress, lactation & breast examination) or pathological due to pituitary adenoma, hypothalamic -pituitary stalk damage, systemic disease (hypothyroidism, chronic renal failure, liver cirrhosis) ,numerous drugs that either block dopamine receptors like tricyclic antidepressant drugs, antipsychotic & metachloropromide or drugs that inhibit formation of prolactin like methyldopa or selective serotonin re uptake inhibitors like fluoxetine[7]. Galactorrhea (inappropriate lactation) is a relatively common disorder that affect about 20-25% of women. it could be due to pituitary adenoma, breast stimulation, chest wall irritation, hypothyroidism & numerous drugs such as methyldopa, antipsychotic, tricyclic antidepressant drugs, metachloropromide, reserpine& ranitidine However there may be no identified cause with normal or raised serum prolactin and this is called idiopathic galactorrhea which occur in about 50% of women[8]. Vitamin B6 is a vital nutrient involved in many aspects of macronutrient metabolism, hemoglobin synthesis &formation, histamine synthesis& gene expression[9] as well as it involved in the synthesis & metabolism of amino acid & in the production of neurotransmitters such as dopamine, epinephrine , norepinephrine& serotonin, so it is the precursor for pyridoxine phosphate which is co factor for the enzyme aromatic amino acid decarboxylase which is necessary for the converting the precursor Levodopa (L dopa) into dopamine, adrenaline &noradrenaline so it has inhibitory effect on prolactin[10]**.** In high doses, vitamin B6 shown to have a major role in decreasing high blood sugar, high blood pressure, calcium channel blocker& as prolactin inhibitor in certain people by improving a functional deficiency of this vitamin that can occur[11]. Vitamin B6 is probably a common nutrient that has a role in reducing prolactin as it has inhibitory effect on serum prolactin as well as when selecting vitamin B6 supplement it is important to pay attention to the type of vitamin B6. For most people, the best choice of vitamin B6 is the natural form pyridoxine 5 phosphate (p5p) form[12]**.** Vitamin B6 has no side effect but high dose of it taking for several months may lead to nerve problem such as numbness in the toe& tingling in the fingers (peripheral neuropathy), also may cause sleep disturbance but these side effects are

*Author for Correspondence: su_sa_2006@yahoo.com

Table 1 A: Distribution of patients according to study variables.

Study variables	(Mean ± SD)	Range
Age (years)	(28.73± 7.58)	(15-43)
BMI (kg/m^2)	(25.45± 4.76)	(18-36)

Table 1 B: Distribution of patients according to study variables.

Study variables	N	%
Occupation		
House wife	34	56.7%
Employee	26	43.3%
Total	60	100.0%
Parity		
P0	21	35.0%
P1-P2	21	35.0%
P3-P4	15	25.0%
P5	3	5.0%
Total	60	100.0%

Table 2: Distribution of study participants according to study variables.

Study variables	N	%
History of infertility		
Positive	28	46.7%
Negative	32	53.3%
Total	60	100.0%
Type of infertility		
Primary	13	46.4%
Secondary	15	53.6%
Total	28	100.0%
History of PCOS		
Positive	26	43.3%
Negative	34	56.7%
Total	60	100.0%
History of galactorrhea		
Positive	23	38.3%
Negative	37	61.7%
Total	60	100.0%

transient& resolve once B6 therapy is stopped& these can be avoided by taking the activated form of B6 (p5p) so the dose either 50-200 mg of p5p or 300-1000mg of pyridoxine hydrochloride in divided doses[13]. Prolactin is one of the hormones that are produced in the anterior portion of the pituitary gland in both in woman &man, also it is produced from other sites in the body including immune cells, the uterus, prostate, brain, breast, skin & adipose tissue. It acts to encourage breast development & milk production especially during pregnancy & after delivery[14]. Many patients trying to decrease their prolactin level choose to use the prescribed drugs (bromocriptine & cabergoline) although they are effective in reducing prolactin, but these drugs are expensive & many people experience a lot of side effect in contrast to natural prolactin inhibitors(B6) are very cheap, no side effect& are so effective[15]. Dopamine agonists are the first line therapy for the majority of patients with hyperprolactinemia[16]. Cabergoline (Dostinex) is an ergot derivative which has been used to overcome the disadvantages that result from bromocriptine such as short half-life & adverse side effect as cabergoline should be taken only once or twice weekly[17]. Cabergoline has a greater selectivity& affinity for pituitary dopamine D2 receptors, low frequency of adverse effect& longer duration of action[5].

MATERIALS AND METHODS

A clinical trial was carried out at Babylon Teaching Hospital for Maternity and Children and outpatient clinic through the period of 1st of November 2017 till 1st of May 2018. This study involved a 60 women in reproductive age group with history of hyperprolactinemia subdivided into 3 groups 20 for each one.1st group received placebo, 2nd group received vitamin B6 300 mg in 3 divided doses and 3rd one received cabergoline 1mg\week. the period of therapy last for 1 month and then serum prolactin was re measured for all patients after 4 weeks. The primary outcome was the decline in serum prolactin & the secondary outcome was the comparative effect of vitamin B6 to that of cabergoline (Dostinex).

p-value of <0.001considerd statistically significant.

Study design

A clinical trial was carried out at Babylon Teaching Hospital for Maternity and Children and outpatient clinic through the period of 1st of November 2017 till 1st of May 2018. A total of 60 women with in reproductive age group with history of hyperprolactinemia were divided into 3 groups ,20 women for each.1st group (control) were received placebo, 2nd group were received vitamin B6 300 orally mg in 3 divided doses in form of tablet 50mg 2x3) & 3rd group were received cabergoline (Dostinex) 1mg/week. the period of therapy last for 4 weeks & then re measure serum prolactin for all patients.

Inclusion criteria:1. women in reproductive age group 2. women with history of menstrual irregularity 3. History of PCOS 4. History of galactorrhea 5. History of infertility whether primary or secondary. Exclusion criteria: 1. Pregnancy 2. Lactation 3. History of hypothyroidism 4. Renal failure 5. History of certain drug therapy like antipsychotic & tricyclic anti depressive drugs. Questioner: include sociodemograpgic characteristic (name, age, occupation, parity, BMI, menstrual history: history of menstrual irregularity, amenorrhea, oligomenorrhea, history of acne, hisutism, any history of breast discharge, galactorrhea, any history of infertility whether primary or secondary, past medical history such as history of hypothyroidism &Renal failure as they excluded, drug history, family &social history. After a detailed history taken, general examination was performed. informed consent was taken from those who fulfilled the inclusion criteria then blood sample was taken for serum prolactin assessment.

Hormonal assay

Serum prolactin was assessed early in the menstrual cycle before ovulation with avoidance of any nipple or breast examination. by using a disposable syringe, venous blood samples (5ml) were collected in blood collecting tube, separate serum by centrifugation after standing whole

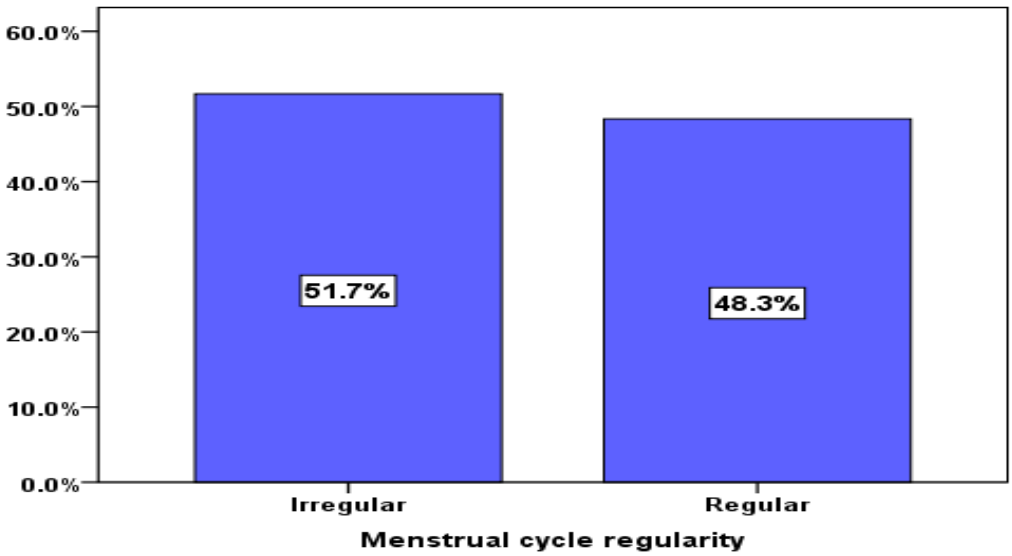

Figure 1: Distribution of patients according to menstrual cycle regularity.

Table 3: The mean differences of prolactin (ng/ml) before and after using of Placebo.

Study variable	Group	N	Mean ± SD	Paired t-test	P-value
Prolactin (ng/ml)	Before using of placebo	20	46.80 ± 10.77	-0.363	0.72
	After using of placebo	20	47.00 ± 10.78		

Table 4: The mean differences of prolactin (ng/ml) before and after using of B6.

Study variable	Group	N	Mean ± SD	Paired t-test	P-value
Prolactin (ng/ml)	Before using of B6	20	50.85 ± 16.82	11.05	<0.001*
	After using of B6	20	25.90 ± 10.65		

Table 5: The mean differences of prolactin (ng/ml) before and after using of Cabergoline.

Study variable	Group	N	Mean ± SD	Paired t-test	P-value
Prolactin (ng/ml)	Before using of Cabergoline	20	56.15 ± 17.22	8.11	<0.001*
	After using of Cabergoline	20	21.60 ± 10.83		

blood at room temperature, then taking 50 micron of the serum through the pipette for prolactin assessment using a commercially available kits (MAGLUMI Fully-auto chemoiluminescence immunoassay (CLIA) analyzer including maglumi 800 through snib device.

Reference Range of serum prolactin

in women from 1-25 ng /ml & in men 1-20 ng/ml

conversion factor: 1ng/ml=21.2munit/l (PRL-V5 EU 2017-07.

Data retrieved from the patient during treatment include pretreatment level of serum prolactin, post treatment level & any reported side effect of therapy.

Statistical study: Data Analysis

Statistical analysis was carried out using SPSS version 20. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Independent samples t-test was used to compare means between two groups. Paired t-test was used to compare means for paired readings. A p-value of ≤ 0.05 was considered as significant.

All groups were comparable in their demographic criteria. There was 12(60%) of women in 2nd group who treated with vitamin B6 got decrease in serum prolactin, mean decline in serum prolactin was(25.90 ± 10.65), p-value was<0.001 which is statistically significant and this effect was comparable to that obtained by using a potent dopaminergic drug, cabergoline in 3rd group in which there was decline in serum prolactin in 15 patients(75%) & mean decline in serum prolactin was (21.60 ± 10.83) & P-value was <0.001 which is also statistically significant. No significant side effect was reported in all study groups. Data for those patients were collected & included in the groups to which the patients were divided. Those groups were comparable with regard to maternal age, parity& BMI.

Table 1 shows the distribution of patients according to study variables including (age BMI, occupation and Parity) Figure 1 shows the distribution of patients according to menstrual cycle regularity. About (51.7%) of patients presented with irregular cycle.

RESULTS

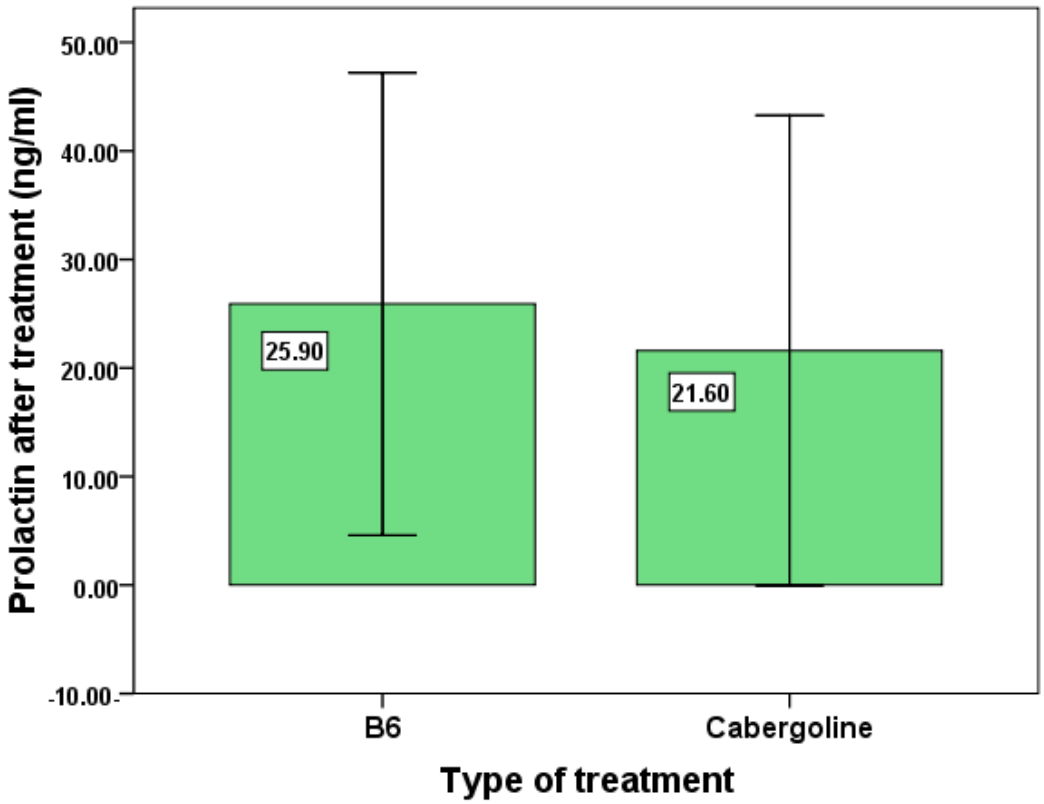

Figure 2: Mean differences of prolactin (ng/ml) after treatment according to type of treatment.

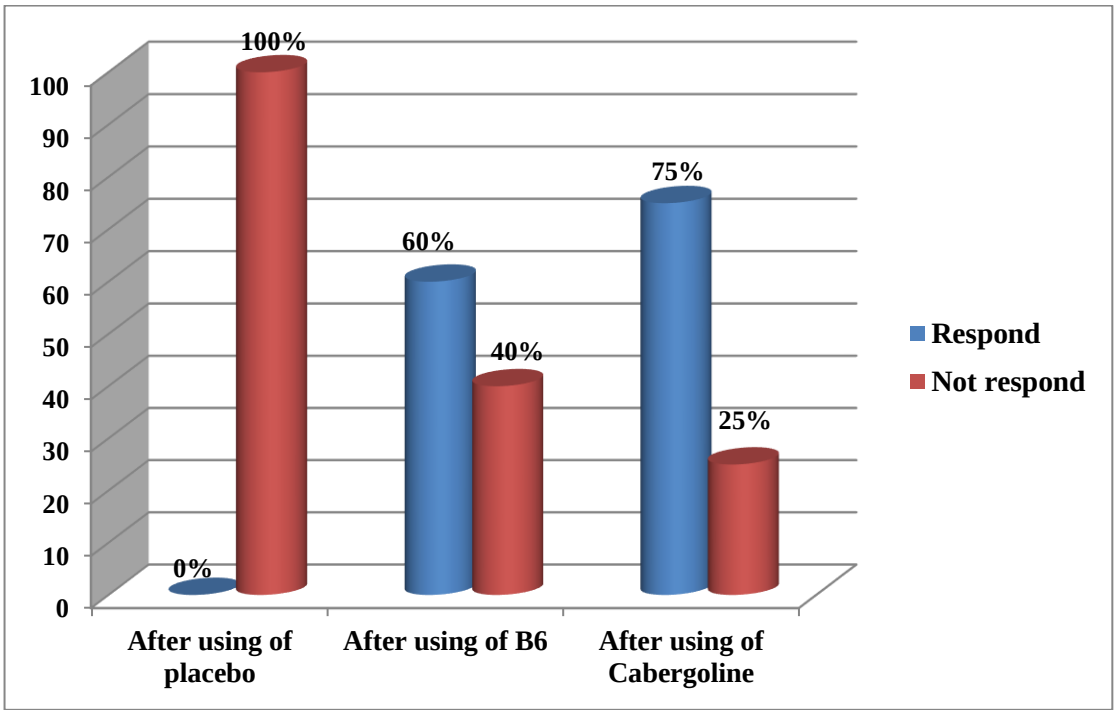

Figure 3: The association between type of treatment and response of patients.

Table 2 shows the distribution of patients according to study variables including (history of infertility, history of PCOS and history of galactorrhea).

About 46.7% of women in this study had history of infertility& about half of them are primary infertility. also about 43.3% of patients had history of PCOS while 38.3% presented with history of galactorrhea.

Mean Differences of Prolactin Before and After Using of Placebo

Table 3 shows mean differences of prolactin (ng/ml) before and after using of Placebo. There were no

significant differences between means of prolactin before and after using of Placebo.

Mean Differences of Prolactin Before and After Using of B6

Table 4 shows mean differences of prolactin (ng/ml) before and after using of B6. There were significant differences between means of prolactin before and after using of B6.

Mean Differences of Prolactin Before and After Using of Cabergoline

Table 5 shows mean differences of prolactin (ng/ml) before and after using of Cabergoline. There were significant differences between means of prolactin before and after using of Cabergoline.

Mean Differences of Prolactin after treatment According to type of treatment

Figure 2 shows mean differences of prolactin (ng/ml) after treatment according to type of treatment including (using of B6 and using of Cabergoline). There were no significant differences between means of prolactin after treatment by using of B6 or using of Cabergoline.(t=1.266, P=0.213).

Figure 3 shows the association between type of treatment and response of patients. There was significant association between type of treatment and response of patients. (x^2=25.45, P=< 0.001*).

DISCUSSION

An excess prolactin level, is a commonly encountered clinical disorder. management of this condition depend heavily on the cause & on the effect it has on the patient[5]. Normal prolactin level may differs slightly among different laboratories because some lab. use different measurements or may test different specimens. Unlike other tropic hormone secreted by frontal portion of pituitary gland, prolactin secretion is controlled primarily by inhibition from hypothalamus & it is not subjected to negative feedback directly or indirectly by peripheral hormones. It exercises self-inhibition by a counter-curved flow in the hypothalamus dopamine as well as cause suppression of the GnRH, thus negatively modulate the release of pituitary hormones responsible for gonadal function[3]. No discernible difference was detected in serum prolactin in group one who treated with placebo as shown in table -3- and this disagree with a clinical study which viewed that prolactin level may retained to normal in some patients who didn't receive treatment[5]. Those patients in group 2 who treated with 300 mg of vitamin B6 in 3 divided doses show that 12 (60%) of them got benefit of treatment as mean decrease in serum prolactin was (25.90 ± 10.65) as shown in table -4- and this is agree with another study which show that taking 300 mg of vitamin B6 twice daily lowered prolactin level & slightly but significant raise in growth hormone level[18]. Also this goes with another study which showed a single 300 mg of B6 exert a hypothalamic dopaminergic effect which cause a significant reduction of plasma prolactin[13].

Bigozzi M. reported the effect of administration of 300 mg of B6(pyridoxine chloride) on circulatory level of pituitary hormone including dopamine, show that there is a 52% suppression of prolactin level &18%reduction in LH hormone & 31.5% increase in growth hormone level. These finding suggest dopaminergic mediation[19]. Table -5- shows that there was15 (75%)of patient got decline in serum prolactin after treatment with cabergoline & this is agree with a large comparative double blind study in female with idiopathic hyperprolactinemia which show that cabergoline was significantly more effective in inhibition prolactin secretion & restoring the menstrual cycle & had a slightly superior tolerability[20]. Johen Verhelst reported in his study which done on 455 patients with high serum prolactin treated with cabergoline that there is normalization of it's level in 80% of patients with history of idiopathic hyperprolactinemia ,micro adenoma, macro adenoma& visual field impairment[21]. In our study, only one patient develop side effect with cabergoline in form of headache and hypotension which subside spontaneously & this is disagree with another study which reported that 13% of patients develop side effect of cabergoline therapy[20]. No case treated with 300 mg of vitamin B6 develop side effect while other study show that taking B6 in dose of 300 mg or more is toxic on the long term use for more than 4 weeks[22]. On the hand taking vitamin B6 at 600-900mg /day for many weeks can cause side effect such as nerve numbness & body instability but these side effect are transient & disappeared once this drug is stopped[22]. The effect of vitamin B6 in current study was comparable to that of cabergoline as shown in figure -2-.

CONCLUSION

vitamin B6 has an effect in reducing serum prolactin in hyperprolactinemic one and it is cheap, available, effective with no side effect.

REFERENCES

1. Adam Balen, 2012. polycystic ovarian syndrome and secondary amenorrhea. Dewhurst's textbook of obstetric gyn. 513-532.
2. Shlomo Melmed et. al. 2011**.** Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. Volume 96, Issue 2.
3. Abha Majumdar& Nisha Sharma. 2013. Hyperprolactinemia, Journal of Human Reproductive Science;6(3):168-175
4. Hall breich U, et. al. 2003. Elevated prolactin level in patient with schizophrenia, mechanism & related adverse effect, psychneuroendocrine 28:53-67.
5. Omar Serri, 2003. Constance L.Chik, Ehud Ur and Shereen Ezzat. Diagnosis & Management of Hyperprolactinemia,CMAJ 160;9(16)575-581.
6. Freeman ME, et. al. 2000. Prolactin: Structure, Function &Regulation of secretion, Physiol Review 80(4):1523-631.
7. Daria La Torre and Alberto Falorni. 2007. Pharmacological causes of hyperprolactinemia, Dove Press Journal, 3(5):929-951.
8. Kristin S. Pena, M.D. and JO Ann Rosenfeld, M. D. 2001. Evaluation & Treatment of Galactorrhea, American Family Physician 63(9):1763-1771.

9. Yvonne Lamers, et. al. 2009. Vitamin B-6 restriction tends to reduce the red blood cell glutathione synthesis rate without affecting red blood cell or plasma glutathione concentrations in healthy men and women, The amarican journal of clinical nutrition, 90(2): 336–343.
10. David O. Kennedy , B Vitamins and the Brain: Mechanisms, 2016 Feb. Dose and Efficacy, Nutrients. 8(2): 68
11. Edward Clements 2012. Prolactin Inhibitors Supplements Set,
12. Song-Guang Ren and Shlomo Melmed, 2006. Pyridoxal Phosphate Inhibits Pituitary Cell Proliferation and Hormone Secretion.Endocrinology. 147(8):3936-3942.
13. Terry Graedon 2012. Vitamin Overdose Damages Nerves, The people pharmacy.
14. Kerstin Foitzik Ewan A.Langan RalfPaus 2009. Prolactin and the Skin: A Dermatological Perspective on an Ancient Pleiotropic Peptide Hormone,Journal of Ivestigative Dermatology, vol 129,issue9;p:1071-1087.
15. Sabuncu T, Arikan E, Tasan E, Hatemi H. 2001. Comparison of the effects of cabergoline and bromocriptine on prolactin levels in hyperprolactinemic patients, Internal Medicine Volume 40 Issue 9 Pages 857-861.
16. Mancini T Casanueva FF,Cinstina A. 2007. Hyperprolactinemia & prolactinoma, Endocrinology &Metabolism Clinic of North America 37(1):76-99
17. Dan L. Longo et. al. Vitamins& trace minerals: deficiency &excess, Harrison's Principles of Internal Medicine, 18e;p 2887.
18. Barletta C, et. al. 1984. influence of administration of pyridoxine on circadian rhythm of plasma adrenocorticotropic hormone, cortisol prolactin& somatotropine in normal subject; Boll Soc Ital Biol Sper. 28;60(2):273-8.
19. M. Bigozzi, et. al. 2014. Effect of vitamin B6 on the serum concentration of pituitary hormone in normal human & under pathological conditions.
20. Torre DL, Falorni. 2007. Pharmacological causes of hyperprolactinemia, Therapeutics & Clinical Risk Management. vol3(5):929-951
21. Johen Verhelst, Roger Abs. Dominique Majter. 1999. Cabergoline in treatment of hyperprolactinemia, The Journal Of Clinical Endocrinology& Metabolism, vol 84, issue 7;p .2518-2522.
22. Cheap Dostinex 2014. Mega doses of vitamin B6 & vitamin E, Personal Expression, Marinera.