OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:

Peer Review

Journal of Kermanshah University of Medical Sciences
Article DOI: https://doi.org/10.5812/jkums.86003
Published in: Journal of Kermanshah University of Medical Sciences: 23(1) ; e86003

Peer Review Report for "Is Morning Prolactin Level Sufficient for Diagnosis of Mild Hyperprolactinemia?"

Author(s): Hamid Ghasemi Basir, Zahra Razavi, mohammad chehreghani, Manoochehr Karami, Arash Dehghan

Review Timeline:

Submit Date:	2 Nov 2018
Revised Date:	8 Jan 2019
Accepted Date:	8 Jan 2019

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

جوابیه ایرادات وارد شده به مقاله ارسالی با عنوان: *"?Is morning prolactin level sufficient for diagnosis of mild hyperprolactinemia "* ID:86003	
نظرات کارشناس اول:	
ایراد	مواد و روشها : ایراد اساسی که به این مقاله وارد است اندازه گیری پرولاکتین بعد از ظهر تحت تاثیر عوامل مختلفی مانند استرس روزانه فعالیت وغذا خوردن قرار می گیرد واین عوامل عدد واقعی پرولاکتین را بالاتر گزارش می کنند و برای رفع این موارد مخدوش کننده توصیه میشود پرولاکتین صبح دوساعت بعد از بیدار شدن از خواب اندازه گیری شود واز دو روز قبل بیمار فراورده های حاوی کلسیم دریافت نکرده باشد
جواب	در این مطالعه برای بیماران، پرولاکتین در دو نوبت صبح وعصر اندازه گیری شد که در نوبت صبح کل شرایط مذکور شامل ناشتایی و فاصله نمونه گیری از زمان بیدار شدن لحاظ گردید و برای نوبت عصر استراحت قبل از نمونه گیری و حداقل فاصله چهار ساعته از وعده نهار مورد تاکید قرار گرفت: **در متن مقاله این دو موضوع مورد تاکید قرار گرفت:** It must be noted that sampling was performed in the fasting state and one hour after waking up with pre-analytical considerations including 30 min rest before sampling. Then in patients with normal MRI, a re-test was performed with a new sample at evening (5 to 7 pm), four-hours distance from lunch, in case of patient satisfaction for re-sampling with pre-analytical considerations including 30 min .rest before sampling **نکات قابل توجه:** • در مقاله ذیل در جنس مونث در هر دو نیمه سیکل قاعدگی به سطح پرولاکتین در نوبت عصر، در زنان سالم اشاره شده است که ناشی از اثر ترکیبی Circadian variation و Menstrual phase می باشد. Christopher J. Morris, Daniel Aeschbach, Frank A.J.L. Scheer. **Circadian System, Sleep and Endocrinology.** Mol Cell Endocrinol. 2012 February 5; 349(1): 91–104. Circadian variation in prolactin level was also present in women, but the characteristic of this rhythm was dependent on menstrual phase. In women studied during their follicular phase, prolactin levels **rose in the late biological afternoon**. In women studied in their luteal phase, prolactin concentrations **peaked in the late biological afternoon/early evening**. • در کتاب رفرانس HENRY'S Clinical Diagnosis AND Management BY Laboratory Methods در هر دو چاپ ۲۲ و ۲۳ ذکر شده است که حداکثر سطح سرمی پرولاکتین تحت تاثیر Diurnal Variation در ساعات اولیه صبح می باشد. • ضمنا در این کتاب بر تاثیر circadianدر اندازه گیری پرولاکتین تاکید شده

است:

PRL is secreted in a circadian fashion, with the highest levels attained during sleep. PRL is secreted in a pulsatile fashion, the amplitude and frequency of which not only vary throughout the day but are influenced by a variety of physiologic stimuli (e.g., stress, pregnancy, exercise). Because of these factors and a serum half-life of 26 to 47 minutes, **it had been recommended that when screening for hyperprolactinemia, three specimens be obtained at 20- to 30-minute intervals.** Each sample could either be analyzed separately and their results averaged, or alternatively an equal aliquot from each sample could be pooled into a single specimen for analysis. Current Endocrine Society guidelines recommend screening using a single determination, **collected at any time of day, reserving the option to follow the aforementioned recommendations if the diagnosis is in doubt** (Melmed et al, 2011).

- **از مجموع این یافته ها می توان نتیجه گرفت** که در صورت شک بالینی به افزایش سطح سرمی پرولاکتین در شرایطی مثل AUB ، می توان از اندازه گیری چند نوبت پرولاکتین برای تشخیص دقیق استفاده کرد. ولی معمولا بیمار در یک نوبت مراجعه حاضر به چند نوبت نمونه گیری نمیشود و از طرفی در صورت نرمال بودن یک نوبت سطح سرمی پرولاکتین در صبح، احتیاجی به چند نوبت نمونه گیری نیست. بنابراین می توان در صورت مشکوک بودن به سطح پرولاکتین از اندازه گیری در دیگر ساعات شبانه روز به عنوان نوبت دوم بهره جست که با توجه به مقاله Morris نوبت عصر زمان قابل قبولی برای تکرار آزمایش در زنان بوده و ضمنا بیمار در دسترس می باشد.

در متن مقاله این موضوع مورد تاکید قرار گرفت و اضافه شد:

Circadian variation in prolactin level is also present in women, but is dependent on menstrual phase. During their follicular phase, prolactin levels rise in the late biological afternoon and in their luteal phase, prolactin concentrations peaked in the late biological afternoon/early evening.

In the study of Lewandowski et al. it has been claimed that a substantial proportion of patients found to have raised prolactin level on a single testing is subsequently found to have normal prolactin levels. It has been recommended that when screening for hyperprolactinemia, three specimens be obtained at 20- to 30-minute intervals. Each sample could either be analyzed separately or alternatively could be pooled into a single specimen. But usually the patient is not willing to sampled several times, at once testing time. On the other hand, if the morning serum prolactin level is normal in a single sampling, it is not necessary to sample several times. Endocrine Society guidelines recommend screening using a single determination, collected at any time of day, and reserving the above option for doubting condition.

در مورد ایراد وارده تحت عنوان ((اندازه گیری پرولاکتین بعد از ظهر تحت تاثیر عوامل مختلفی مانند استرس روزانه فعالیت وغذا خوردن قرار می گیرد و**این عوامل عدد واقعی پرولاکتین را بالاتر گزارش می کنند**)) ، این موضوع قابل ذکر است که اولا شرایط قبل از آزمایش لحاظ شده و تحت کنترل بود و ثانیا

	بر خلاف انتظار، نتایج مطالعه حاضر بدین شکل بود: **در متن مقاله این موضوع مورد تاکید قرار گرفته:** Mean value of morning and evening prolactin levels were 48.64 µg/L and 30.39 µg/L respectively with normal distribution. This difference was statistically significant (P value: < 0.001). (Table 1)
ایراد	یافته ها : به دلیل عوامل مخدوش کننده متفاوت معمولا پرو لاکتین صبح دقیق ترین روش برای اندازه گیری پرولاکتین می باشد
جواب	این موضوع که ((پرو لاکتین صبح دقیق ترین روش برای اندازه گیری پرولاکتین می باشد)) مورد بحث نمی باشد و در مطالعه حاضر نیز به آن تاکید شده است: **در متن مقاله این موضوع مورد تاکید قرار گرفته است:** It is important to emphasize, this study is not recommending to replace "normal evening prolactin level" instead of "mild morning elevated level" but, recommending to pay attention to the value of mild morning hyperprolactinemia defined as up to about twice the normal upper limit, especially in women without certain signs and symptoms of hyperprolactinemia including galactorrhea and pituitary adenoma. Also, it must be noted that mild morning hyperprolactinemia can be clinically significant in the absence of evening hyperprolactinemia when associated with certain clinical manifestations of hyperprolactinemia.
ایراد	بحث:هیچگونه مقاله ای که در این زمینه انجام شده باشد ذکر نشده است
جواب	بله این موضوع در قسمت بحث مورد اشاره واقع شده است: Effect of timing in prolactin sampling on decision to start treatment for patient with borderline values has not been investigated like this in previous studies that emphasizes on novelty of subject. البته خلاصه مقاله ارائه شده در 24th Joint Meeting of the British Endocrine Societies در مورخ 04 - 06 Apr 2005 در Harrogate, UK توسط KC Lewandowski, E Skowronska-Jozwiak, K Szosland & A Lewinski با عنوان: **Effect of timing of prolactin sampling on the incidence of spurious hyperprolactinaemia** تنها کار تحقیقاتی مشابه موجود است **در متن مقاله این موضوع مورد تاکید قرار گرفت و اضافه شد:**

In the study of Lewandowski et al. it has been claimed that a substantial proportion of patients found to have raised prolactin level on a single testing is subsequently found to have normal PRL levels. In the study of Lewandowski et al. it has been claimed that a significant proportion of patients have elevated PRL concentrations if blood sample is taken around the opening hours of the laboratory and finding of a raised PRL concentration usually generates unnecessary investigations. Although, in the study of Lewandowski et al. it has been alleged that individual diurnal variation of prolactin concentrations, when sampling is performed on the descending arm of the nocturnal peak of secretion, can leading to a raised PRL concentration and additional unnecessary investigations. In the study of Lewandowski et al. 55 women with symptoms of hyperprolactinemia and a mean age of 33.07±13 years were studied(17).They stated that the early morning (2, 5 and 8 am) average prolactin levels were more than 11, 14 and 17 o'clock. The main finding of our study (variations in morning and evening mean prolactin level) was close to what was stated by Lewandowski et al.	
نتيجه گيري :در حيطه اندوكرين موارد خفيف هيپر پرولاكتين كه علايم بالينی ندارد با شرط نرمال بودنMRI انديكاسيون درمان ندارد پس با اندازه گيری پرولاكتين بعد از ظهر هزينه اضافه به بيمار تحميل می شود و بار درمان اضافه هم بااين روش اندازه گيری كاسته نمی شود	ايراد
لازم به ذكر است كه همه بيماران مورد مطالعه علاوه بر افزايش سطح سرمی پرولاكتين صبحگاهی، مبتلا به AUB بوده و علامت دار محسوب ميشوند. **بر اساس نتايج بدست آمده در متن مقاله اين موضوع مورد تاكيد قرار گرفت و اضافه شد:** If prolactin levels are high at morning and evening, the treatment is emphasized more confidently, but if the evening level return to normal value, along with attention to increasing morning prolactin level, other causes of AUB should be considered carefully, especially in the absence of galactorrhea. Therefore, measurements of evening prolactin levels, leading to precision in choosing of treatment and can helps in the diagnosis of hyperprolactinemia. It should be noted that treatment of hyperprolactinemia is long and costly.	جواب
نظرات كارشناس دوم:	
چكيده فارسي و انگليسي : در قسمت بحث كه اظهار ميدارند يكبار نمونه گيری كافی نيست كاملاً درست است ولی نه در ساعات غير از Feartig و 2 ساعت پس از بيدار شدن	ايراد
در اين مطالعه برای بيماران، پرولاكتين در دو نوبت صبح وعصر اندازه گيری شد كه در نوبت صبح كل شرايط مذكور شامل ناشتايی و فاصله نمونه گيری از زمان بيدار شدن لحاظ گرديد و برای نوبت عصر استراحت قبل از نمونه گيری و حداقل فاصله چهار ساعته از وعده نهار مورد تاكيد قرار گرفت:	جواب

در متن مقاله این دو موضوع مورد تاکید قرار گرفت:

It must be noted that sampling was performed in the fasting state and one hour after waking up with pre-analytical considerations including 30 min rest before sampling.

Then in patients with normal MRI, a re-test was performed with a new sample at evening (5 to 7 pm), four-hours distance from lunch, in case of patient satisfaction for re-sampling with pre-analytical considerations including 30 min .rest before sampling

نکات قابل توجه:

- در مقاله ذیل در جنس مونث در هر دو نیمه سیکل قاعدگی به سطح پرولاکتین در نوبت عصر، در زنان سالم اشاره شده است که ناشی از اثر ترکیبی Circadian variation و Menstrual phase می باشد.

Christopher J. Morris, Daniel Aeschbach, Frank A.J.L. Scheer. **Circadian System, Sleep and Endocrinology.** Mol Cell Endocrinol. 2012 February 5; 349(1): 91–104.

Circadian variation in prolactin level was also present in women, but the characteristic of this rhythm was dependent on menstrual phase. In women studied during their follicular phase, prolactin levels **rose in the late biological afternoon**. In women studied in their luteal phase, prolactin concentrations **peaked in the late biological afternoon/early evening**.

- در کتاب رفرانس HENRY'S Clinical Diagnosis AND Management BY Laboratory Methods در هر دو چاپ ۲۲ و ۲۳ ذکر شده است که حداکثر سطح سرمی پرولاکتین تحت تاثیر Diurnal Variation در ساعات اولیه صبح می باشد.

- ضمنا در این کتاب بر تاثیر circadianدر اندازه گیری پرولاکتین تاکید شده است:

PRL is secreted in a circadian fashion, with the highest levels attained during sleep. PRL is secreted in a pulsatile fashion, the amplitude and frequency of which not only vary throughout the day but are influenced by a variety of physiologic stimuli (e.g., stress, pregnancy, exercise). Because of these factors and a serum half-life of 26 to 47 minutes, **it had been recommended that when screening for hyperprolactinemia, three specimens be obtained at 20- to 30-minute intervals.** Each sample could either be analyzed separately and their results averaged, or alternatively an equal aliquot from each sample could be pooled into a single specimen for analysis. Current Endocrine Society guidelines recommend screening using a single determination, **collected at any time of day, reserving the option to follow the aforementioned recommendations if the diagnosis is in doubt** (Melmed et al, 2011).

- **از مجموع این یافته ها می توان نتیجه گرفت** که در صورت شک

	بالینی به افزایش سطح سرمی پرولاکتین در شرایطی مثل AUB ، می توان از اندازه گیری چند نوبت پرولاکتین برای تشخیص دقیق استفاده کرد. ولی معمولا بیمار در یک نوبت مراجعه حاضر به چند نوبت نمونه گیری نمیشود و از طرفی در صورت نرمال بودن یک نوبت سطح سرمی پرولاکتین در صبح، احتیاجی به چند نوبت نمونه گیری نیست. بنابراین می توان در صورت مشکوک بودن به سطح پرولاکتین از اندازه گیری در دیگر ساعات شبانه روز به عنوان نوبت دوم بهره جست که با توجه به مقاله Morris نوبت عصر زمان قابل قبولی برای تکرار آزمایش بوده و ضمنا بیمار در دسترس می باشد. **در متن مقاله این موضوع مورد تاکید قرار گرفت و اضافه شد:** Circadian variation in prolactin level is also present in women, but is dependent on menstrual phase. During their follicular phase, prolactin levels rise in the late biological afternoon and in their luteal phase, prolactin concentrations peaked in the late biological afternoon/early evening. In the study of Lewandowski et al. it has been claimed that a substantial proportion of patients found to have raised prolactin level on a single testing is subsequently found to have normal prolactin levels. It has been recommended that when screening for hyperprolactinemia, three specimens be obtained at 20- to 30-minute intervals. Each sample could either be analyzed separately or alternatively could be pooled into a single specimen. But usually the patient is not willing to sampled several times, at once testing time. On the other hand, if the morning serum prolactin level is normal in a single sampling, it is not necessary to sample several times. Endocrine Society guidelines recommend screening using a single determination, collected at any time of day, and reserving the above option for doubting condition.
ایراد	کلیدواژه‌ها: بهتر است morning level اضافه شود
جواب	اضافه شد **Keywords:** Prolactin, Hyperprolactinemia, Morning level
ایراد	مقدمه: در قسمت مقدمه پاراگراف دوم13-14 day rate مبهم است . چنین Circardian مشخص است که منظور در شبانه روز است (از طرفی هم نیمه عمر PRL حدود min50 است که ترشحات ضربانی خیلی در اندازه گیری آن موثر نیست .
جواب	برای رفع ابهام عبارت فوق به شکل زیر تغییر یافت: (with about 13 -14 time in one day) ضمنا در کتاب رفرانس HENRY’S Clinical Diagnosis AND Management BY Laboratory Methods در هر دو چاپ ۲۲ و ۲۳ بر تاثیر circadianدر اندازه گیری پرولاکتین تاکید شده است: PRL is secreted in a circadian fashion, with the highest levels attained during sleep. PRL is secreted in a pulsatile fashion, the amplitude and frequency of

which not only vary throughout the day but are influenced by a variety of physiologic stimuli (e.g., stress, pregnancy, exercise). Because of these factors and a serum half-life of 26 to 47 minutes, **it had been recommended that when screening for hyperprolactinemia, three specimens be obtained at 20- to 30-minute intervals.** Each sample could either be analyzed separately and their results averaged, or alternatively an equal aliquot from each sample could be .pooled into a single specimen for analysis	
مواد و روشها : الف- نمونه Evening در چه ساعتی از شب اندازه گیری می شود . evening یک تعریف دارد که باید ذکر شد .	ایراد
Material and Method: Then in patients with normal MRI, a re-test was performed with a new sample **at evening (5 to 7 pm)** in case of patient satisfaction for re-sampling **with pre-analytical considerations**. including 30 min rest before sampling	جواب
مواد و روشها : ب- تمام بیماران با PRL کمتر از 2 برابر نرمال چرا Imaging انجام شده است ؟ مگر آدنوم های هیپوفیز پرولاکتین در این اندازه و مقدار ایجاد می کنند (البته این ایراد بر مقاله نیست ولی هزینه سرسام آوری ایجاد می کند و قبل از انجام تحقیق باید توصیه می شد)	ایراد
در نظر کارشناس اول در ایراد آخر اینگونه ذکر شده است: (در حیطه اندوکرین موارد خفیف هیپر پرولاکتین که علایم بالینی ندارد با شرط نرمال بودنMRI اندیکاسیون درمان ندارد) ✓ لازم به ذکر است که تمامی افراد مورد مطالعه علامت دار و مبتلا به AUB بودند و از طرفی MRI برای تعیین تکلیف وجود یا عدم وجود اندیکاسیون درمان با توجه به نظر فوق تخصص غدد لازم دانسته شده. ✓ از طرفی این **موضوع جز طراحی طرح تحقیقاتی بوده** و برای تعمیم به همه افراد نمی باشد. ✓ ضمنا هدف اصلی این مطالعه مشخص کردن موارد کم اهمیت **hyperprolactinemia** و ارایه **راهکار برای تشخیص این موارد** و **کاهش هزینه های تشخیصی غیر لازم** است.	جواب
بحث: الف- پاراگراف اول معولاً بطور روتین پرولاکتین یک تا 8 ساعت پس از بیدار شدن اندازه گیری می شود و ممکن است قبل از این ساعت تا mg50 هم افزایش یابد که درست است ولی هدف مقاله در آخرین خط همین پاراگراف محسوب نمی شود .	ایراد
به منظور تفهیم موضوع مورد بحث این پاراگراف به این شکل اصلاح شد: Often prolactin is measured in the early morning hours along with other tests that require fasting and is affected by the **physiological** morning peak. So, it can be falsely higher than the normal range **and in symptomatic patients with AUB, can leading to unnecessary treatment. In the study of Lewandowski et al. it has been claimed that a significant proportion of patients have elevated PRL concentrations if blood sample is taken around the opening hours of the laboratory and finding of a raised PRL concentration usually generates unnecessary investigations.** The aim of this study is **evaluation of the importance of mild morning hyperprolactinemia in patients with AUB,** in the absence of certain signs and symptoms **of hyperprolactinemia** including	جواب

galactorrhea or pituitary adenoma.	
بحث: ب- پاراگراف 2 بهتر است ساعت evening را ذکر نمائید .	ایراد
اصلاح شد: The mean serum level of prolactin was 48.64 µg/L in the morning and 30.39 µg/L in the evening (5-7pm).	جواب
بحث: ج- مقایسه با مطالعات دیگر مشابهت ندارد . با وجود اینکه مطالعه فوق نمی تواند پیشنهاد قاطعی برای درمان بیماران با AVB . افزایش پرولاکتین و مقایسه در دو زمان متفاوت داشته باشد ولی در حد یک مطالعه و یک ایده قابل تامل است .	ایراد
خلاصه مقاله ارائه شده در 24th Joint Meeting of the British Endocrine Societies در مورخ 04 - 06 Apr 2005 در Harrogate, UK توسط KC Lewandowski, E Skowronska-Jozwiak, K Szosland & A Lewinski با عنوان: **Effect of timing of prolactin sampling on the incidence of spurious hyperprolactinaemia** تنها کار تحقیقاتی مشابه موجود است: It is recognized that **a substantial proportion of patients found to have raised prolactin (PRL) level on a single testing is subsequently found to have normal PRL levels.** Though this is often attributed to stress or medication factor, it should be noted, that PRL secretion displays **diurnal variation with a nocturnal peak in the late-night/early morning hours**. In our study we tested the hypothesis, that **in some patients raised PRL levels in the morning may reflect individual diurnal variation of PRL secretion**. Subjects & Methods: We assessed serum PRL concentrations tested at 2.00, 5.00, 8.00, 11.00, 14.00 and 17.00 hours in 55 female patients (age (mean±SD) 33.07±13 years, BMI 25.3±5.2 kg/m2) referred to our Department with the history of galactorrhoea and/or menstrual irregularities. Results: In 12 of 55 patients (21.8%) **we confirmed significantly raised PRL levels on serial sampling, with evidence of either macro- or microadenoma** on pituitary MRI scan in 6 patients (10.9%). In the remaining 43 patients (78.2%) PRL levels were significantly higher at 2.00 ((mean±SEM) 35.59±2.21 ng/mL), 5.00 (32.87±2.22 ng/mL) and 8.00 hours (30.65±2.19 ng/mL) than at 11.00 (18.62±2.27 ng/mL), 14.00 (21.18±2.39 ng/mL) and 17.00 hours (22.05±2.24 ng/mL), respectively, $p<0.05$. With the upper normal limit of our assay around 29 ng/mL we found PRL levels above this limit in 11 out of 43	جواب

patients (25.6%) at 8.00 hours. All of those subjects were subsequently found to have normal PRL concentrations later during the day.

Conclusion: Significant proportion of patients have PRL concentrations above the upper limit on the reference range if **blood sample is taken around the opening hours of the laboratory**. This might be explained by **individual diurnal variation** of PRL concentrations, **when sampling is performed on the descending arm of the nocturnal peak of PRL secretion.** As **finding of raised PRL concentration usually generates additional, and often unnecessary, investigations**, we postulate that sampling for PRL should be delayed till mid-morning

در مقاله ما، به نتایج و نتیجه گیری این مطالعه در قسمت های مختلف اشاره شده است

در متن مقاله این مطالب مورد تاکید قرار گرفت و اضافه شد:

In the study of Lewandowski et al. it has been claimed that a substantial proportion of patients found to have raised prolactin (PRL) level on a single testing is subsequently found to have normal PRL levels.

In the study of Lewandowski et al. it has been claimed that a significant proportion of patients have elevated PRL concentrations if blood sample is taken around the opening hours of the laboratory and finding of a raised PRL concentration usually generates unnecessary investigations.

Although, in the study of Lewandowski et al. it has been alleged that individual diurnal variation of prolactin concentrations, when sampling is performed on the descending arm of the nocturnal peak of secretion, can leading to a raised PRL concentration and additional unnecessary investigations.

In the study of Lewandowski et al. 55 women with symptoms of hyperprolactinemia and a mean age of 33.07±13 years were studied(17).They stated that the early morning (2, 5 and 8 am) average prolactin levels were more than 11, 14 and 17 o'clock. The main finding of our study (variations in morning and evening mean prolactin level) was close to what was stated by Lewandowski et al.

ضمنا در متن مقاله این موضوع نیز مورد تاکید قرار گرفت و اضافه شد:

If prolactin levels are high at morning and evening, the treatment is emphasized more confidently, but if the evening level return to normal value, along with attention to increasing morning prolactin level, other causes of AUB should be

considered carefully, especially in the absence of galactorrhea. Therefore, measurements of evening prolactin levels, leading to precision in choosing of treatment and can helps in the diagnosis of hyperprolactinemia. It should be noted that treatment of hyperprolactinemia is long and costly. در مورد جمله آخر داور محترم ((با وجود اینکه مطالعه فوق نمی تواند پیشنهاد قاطعی برای درمان بیماران با AVB . افزایش پرولاکتین و مقایسه در دو زمان متفاوت داشته باشد ولی **در حد یک مطالعه و یک ایده قابل تامل ا ست**)) : ضمن تشکر از نظرات سازنده هر دو داور، این مطلب دقیقا موضوع مورد نظر است، شاید این مطالعه بتواند در طراحی مطالعات قویتر در آینده کمک کننده باشد.	

OPEN PEER REVIEW

Revision (1)