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OPEN PEER REVIEW

Effectiveness of Pelvic Ultrasonography in the Diagnosis of Central Precocious Puberty and Its Differentiation from Similar Conditions

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

1 comment · 25 Jun 2022

Editor-in-Chief

MINOR REVISION 25 Jun 2022

Dear authors,
Before starting the review process for your article, it is necessary to clarify the following items:

Regarding the importance of “conflict of interest” clarification, the corresponding author should fill out the “ICMJE form” and upload it during the submission process. (The form is available in the “conflict of interest” section of the site:
https://brief.land/iranjradiol/knowledgebase/category/tree.html#conflicts_of_interest.html).

The references you used are old. Please use up-to-date relevant references.

If the author (Kosar Mohammadnejad) is a faculty member of Tehran University of Medical Sciences, this should be mentioned as a conflict of interest.
Regards

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reply to Comments

1. *I added a "conflict of interest" clarification.*
2. *I changed old references to up-to-date relevant references.*
3. *I highlight changes.*
4. *I mentioned and changed all figures and tables in the manuscript correctly.*

2 Revision 1

2 comments · 26 Jul 2022 – 3 Sep 2022

Referee 1 Reviewer

MAJOR REVISION 26 Jul 2022

Thanks to the authors for their submission to the IJR.
This manuscript must be substantially revised to address the following comments:

A. Title
1. Since the main goal of the study was to differentiate CCP from similar diseases, the inclusion of a healthy group is meaningless. Therefore, this group must be deleted and the title revised as follows: "Differential effectiveness of pelvic ultrasound in central precocious puberty from similar diseases"

B. Abstract
2. Lines 2-4 of the abstract introduction state: "Gonadotropin-releasing hormone stimulation test as the gold standard is used to differentiate CPP patients from other causes, but despite its high specificity, it has disadvantages such as low sensitivity,". However, the assumption is that the gold standard test is perfect; therefore, its sensitivity and specificity are 100 percent.
3. When the study's main goal is to differentiate CCP from similar diseases, the inclusion of a healthy group is meaningless. I think that it is better to merge the IPT and IPA groups into a control group and then make a comparison between the case (CCP) and control groups.
4. The study design is case-control, and this must be stated in the first sentence of the abstract and the full-text methods section.
5. The methods section of the abstract is very short. It must contain the time period and location of the study, inclusion and exclusion criteria, main variables, and statistical analysis.
6. The results section of the abstract must start with a presentation of the demographic and clinical characteristics of the sample; moreover, when each variable is compared between the case and control groups, its value in each group and the p-value must be presented in parentheses.
7. The conclusion is not supported by the present results of the study because the study's Youden index J is less than 0.5 and shows that it cannot be useful.

C. Full-Text

8. The methods and full-text sections must be reorganized using a similar study entitled "The Diagnostic Value of Pelvic Ultrasound in Girls with Central Precocious Puberty" as a template.
9. Statistical analysis: After running a univariate analysis, also use multivariate binary logistic regression to develop a combination of variables and use it in ROC analysis, because a combination of variables may be more useful.
10. The Total column must be deleted from tables 1 and 2.
11. ROC analysis must be presented in one table; moreover, the SE column must be deleted, and columns for positive and negative predictive values must be added. Furthermore, all indices must be presented with 95% confidence intervals.
12. This sentence in the last paragraph of the discussion is incorrect because this study is case-control.
13. The full-text conclusion is inappropriate and must be rewritten.

Editor-in-Chief MAJOR REVISION 3 Sep 2022

Dear authors,
Your article needs Major Revision.
Regards

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor in chief
Thank you for giving me the opportunity to submit a revised draft of my manuscript titled
Diagnostic efficacy of pelvic ultrasound in central precocious puberty in girls: a retrospective cohort study to *IRANIAN JOURNAL OF RADIOLOGY*. I appreciate the time and effort that you and the reviewers have dedicated to providing your valuable feedback on my manuscript. I am grateful to the reviewers for their insightful comments on my paper. I have been able to incorporate changes to reflect most of the suggestions provided by the reviewers. I have highlighted the changes within the manuscript.
Here is a point-by-point response to the reviewers' comments and concerns.

Comments from Reviewer 1

- Comment 1: *This article is not novel and my decision is rejected*

Response: I assure you that this article has never been done in Iran and the Middle East region, and the results of this article are different from the scales of precocious puberty in other regions. Therefore, considering the importance of the subject, conducting more studies in this field will help to create specific scales of precocious puberty for each region and will also lead to the creation of more data and information for future studies and meta-analyses.

Comments from Reviewer 2

- Comment 1: *In the background section of the abstract (line 8), the term CPP-like is used and it seems that it is better to define the study groups instead.*

Response: I agree with this comment. Therefore, I changed it to isolated premature thelarche (IPT) and isolated premature adrenarche (IPA).

Comment 2: *In line 278, the importance of the thickness and echogenicity of the endometrium is discussed based on the results of the study, while in the results and tables, there is no mention of the endometrial echogenicity.*
Response: I agree with this comment. Therefore, I added endometrial thickness values.

Comment 3: *about the endometrial thickness, although the difference in the numbers is statistically significant, according to table 2, the average thickness in patients with CPP was about 1 mm, which does not seem to be significant in practice. It seems better to provide more information about endometrial thickness in practical measurements in text or tables.*
Response: I agree with this comment. However, according to the results, using higher values for endometrial thickness to make a distinction, is associated with very low sensitivity, so the best value

for endometrial thickness abstracted from ROC curves is 1 mm, although this number has low sensitivity in comparison with other criteria. (Table 3 and Table 4).

Comments from Reviewer 3

Comment 1: *Since the main goal of the study was the differentiation of CCP from like disease, the inclusion of a healthy group is meaningless. Therefore, this group must be deleted and the title revised to this form "Differential effectiveness of pelvic ultrasound in central precocious puberty from similar diseases"*

Response: In CPP like conditions, isolated premature thelarche (IPT) and isolated premature adrenarche (IPA), according to the definition, the only clinical symptom is either thelarche or pubarche without uterine or ovary enlargement or evidence of the effect of estrogen on the uterus, in other word thelarche and pubarche in presence of uterine enlargement will be CPP not CPP like.

For example, in a child, she has isolated premature thelarche, she only has thelarche, and the characteristics of the uterus are not different from those of a pre-pubertal child, so it makes sense to compare the size and characteristics of the uterus with a pre-pubertal child.

Comment 2: *In lines 2-4 of the abstract introduction mentioned "Gonadotropin-releasing hormone stimulation test as the gold standard is used to differentiate CPP patients from other causes, but despite its high specificity, it has disadvantages such as low sensitivity," Whereas, the assumption is that the gold standard test is perfect; and so, its sensitivity and specificity is 100 percent.*

Response: You have mentioned an important point here. The ideal gold standard test has 100% sensitivity and 100% specificity. Of course, in practice, there is no ideal gold standard test, and we try to use a test that is close to the ideal as much as possible. For CPP, it is what it is and there is no better "gold standard" test. Of course, it should be noted that to ensure the initial diagnosis, the patients were followed up for two years, and we did not limit ourselves to GNRH stimulation for the absolute diagnosis of precocious puberty.

Comment 3: *When the study main goal is to differentiate CCP from like diseases, including of healthy group is meaningless. I think that it is better to be merged IPT, and IPA groups as control; and then, make a comparison between the case (CCP) and the control group.*

Response: As I mentioned earlier, In CPP-like conditions, the only clinical symptom is either thelarche or pubarche without uterine enlargement. So basically, in terms of pelvic ultrasound, there should not be any difference between a normal healthy girl with CPP-like conditions.

Comment 4: The design of study is case-control and it must be added in first sentence of abstract and full-text method.

Response: I agree with this comment. Therefore, I changed the design of the study in abstract and full text to a case-control study.

Comment 5: The abstract method is very short. It must contain the time period and location of the study, inclusion and exclusion criteria, main variables, and statistical analysis.

Response: I agree with this comment. Therefore, I changed the abstract method as you wish.

Comment 6: *The abstract results must start with a presentation of the demographic and clinical characteristics of samples; moreover, when each variable is compared between case and control, its value in each group and p-value must be presented in the parenthesis.*

Response: I agree with this comment. Therefore, I changed the abstract results as you wish.

Comment 7: According to the present results of the study, the conclusion is not supported; because the Youden index J of the study is less than 0.5 and shows that it can't be useful.
Response:
I agree with this comment. Therefore, I changed the conclusion as

'In this study, we evaluate the ultrasound parameters of females in relation to precise clinical and laboratory data. A comparison of all ultrasound parameters in different groups showed that only uterine volume (with a youden index of more than 0.5), is a good predictor of central precocious puberty. On the other hand, we found that uterine transverse diameter and F/C ratio are not useful as a predictor in differentiating CPP patients from other patients but have good sensitivity and specificity values.'

As you also noted the only parameter that has youden index of more than 0.5 is a uterine volume which is cited in the conclusion.

Comment 8. Method and full-text sections must be reorganized using by a similar study entitled "The Diagnostic Value of Pelvic Ultrasound in Girls with Central Precocious Puberty" as a template.

Response: In CPP-like conditions, isolated premature thelarche (IPT) and isolated premature adrenarche (IPA), according to the definition, the only clinical symptom is either thelarche or pubarche without uterine or ovary enlargement or evidence of the effect of estrogen on the uterus, in other word thelarche and pubarche in presence of uterine enlargement will be CPP not CPP like.

For example, in a child, who has isolated premature thelarche, she only has thelarche, and the characteristics of the uterus are not different from those of a pre-pubertal child, so it makes sense to compare the size and characteristics of the uterus with a pre-pubertal child. So basically, in terms of pelvic ultrasound, there should not be any difference between normal healthy girls with CPP-like conditions.

Comment 9. Statistical analysis: After running univariate analysis, also used of multivariate binary logistic regression for developing a combination of variables and using it in ROC analysis. Because a combination of variables may be more useful.

Response: You have mentioned an important point here. but as you see our study and all of the similar studies for precocious puberty are tried to find a single test to verify patients from other groups in which a clinician could use it simply in the office to determinate patients, the way you suggested has a good value however use it in the clinical background in that way is very hard for clinicians.

Comment 10. The total column must be deleted from 1 and 2 tables.

Response: I agree with this comment. Therefore, I deleted the Total columns from 1 and 2 tables, as you wish.

Comment 11. Roc analysis must be presented in one table; moreover, the SE column must be deleted, and columns for positive and negative predictive values must be added. Furthermore, all indices must be presented with %95 confidence intervals.

Response: I agree with this comment. Therefore, I changed it as you wish.

Comment 12. This sentence of the last paragraph of the discussion is incorrect; because this study is case-control.

Response: I agree with this comment. Therefore, I changed it as you wish.

Comment 13. The full-text conclusion is inappropriate and must be re-write.

Response: I agree with this comment. Therefore, I rewrite the full-text text conclusion as you wish.

Response to Associate Editor

Thank you for giving me the opportunity to submit a revised draft of my manuscript. I assure you that this article has never been done in Iran and the Middle East region, and the results of this article are different from the scales of precocious puberty in other regions. Therefore, considering the importance of the subject, conducting more studies in this field will help to create specific scales of precocious puberty for each region and will also lead to the creation of more data and information for future studies and meta-analyses.

I completely revised and restructured the article structure according to the valuable comments of the methodological reviewer and you.

We look forward to hearing from you in due time regarding our submission and to respond to any further questions and comments you may have.

Sincerely,

N.R .M.D

Corresponding author, Radiologist

3 Revision 2

2 comments · 16 Oct 2022 – 11 Dec 2022

Referee 1 Reviewer

ACCEPT 16 Oct 2022

This manuscript has now been appropriately revised based on the methodological comments. Therefore, it is acceptable for publication in IJR.

Editor-in-Chief

MINOR REVISION 11 Dec 2022

Dear authors,
Your article needs Minor Revision.
Regards

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Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor in chief
Thank you for allowing me to submit a revised draft of my manuscript titled Diagnostic efficacy of pelvic ultrasound in central precocious puberty in girls: a retrospective cohort study to IRANIAN JOURNAL OF RADIOLOGY. I appreciate the time and effort you and the reviewers have dedicated to providing valuable feedback on my manuscript. I am grateful to the reviewers for their insightful comments on my paper. I have been able to incorporate changes to reflect most of the suggestions provided by the reviewers. I have highlighted the changes within the manuscript.
Here is a point-by-point response to the associate editor's comments and concerns.

Comments from associate editor 2
1-please correct lines 17 and 18: "All cases were of Persian ethnicity and were classified by clinical and laboratory findings". Sentences should be written in the past tense, so the later sentence should be: "Pelvic ultrasonography parameters were evaluated ……" and so on.
Sentences corrected as you wish.

2-this sentence is unclear: "In order of best parameters for differentiating CPP compared to study groups, uterine volume ……" it could be written as: "The best parameters for differentiating CPP compared to study groups were uterine volume (a cut-off of 1.40, 75.27% sensitivity,75.56% specificity), transverse diameter (a cut-off of 13.5 mm, 72.04% sensitivity, 71.11% specificity) and F/C ratio (a cut-off of 0.98, 78.49% sensitivity, 70% specificity)."
Sentences corrected as you wish.

3-please add an objective part to the paper according the o journal format.
Objective part added and highlighted as you wish.

4-please add sequential numbers to titles and subtitles [based on journal format].
Sequential numbers to titles and subtitles [based on journal format as you wish.

5-in line 98, please correct: "iatrogenic or"
Sentences corrected as you wish.

6-in line 135, please change are to were [past tense]. Please follow this advice for all method section. There are other similar problems in the text.
Sentences corrected as you wish.

7-please change "Statistics" subtitle to Statistical Analysis.
Statistics subtitle changed to Statistical Analysis as you wish.

8-it is better the authors add in stat. analysis section that the normality of continuous variables were checked before analysis and the appropriate stat. tests were chosen based on the normality of data.
Normality test of continuous variables were added as you wish.

9-please add full term of abbreviations in first usage and then, abbreviate in later instances; for example, F/C ratio or, in line 180, it should be one-way ANOVA.
I added full term of abbreviations in first usage and then, abbreviate in later instances as you wish.

10-in footnote of tables 1 and 2, it is unknown what are a and b? the authors mentioned: “Dissimilar values (a, b) in each row are significantly different based on the Tukey's Test in post-hoc analysis.” But referring the table, it is unknown for which comparison, “a” refer to a dissimilarity and for which comparison, “b” refers to a dissimilarity? Please explain and clarify. [Please mention clearly which values are statistically different compared to the other groups]
I agree with you and explained all marks completely in tables footnote.

11-please correct [lines 188-191]: “According to our one-way ANOVA and post hoc analysis, CPP patients had significantly increased uterine fundus AP diameter, uterine body AP diameter, F/C ratio, uterine length, uterine volume, endometrial thickness and transverse uterine diameter compared to other classified groups ($p<0.001$) (Fig 1)”
Sentences corrected as you wish.

12-please explain full term of all abbreviations in foot note of tables for example, it is unknown what is F/C, AP, …. In table 2.
I agree with you and explained full term of all abbreviations in foot note of tables.

13-the authors mentioned: “Checking the equality of the ROC area of each parameter against a "gold standard" ROC curve” they followed this approach in other parts of paper for example in explaining Rocgold. I think this approach in writing is wrong. Uterine volume has only the best AUC and we cannot assume or name it as gold. In methodology, the term gold [in gold standard method of a diagnostic test study] has a certain defined definition and we cannot name other variables as gold. So, For example, the authors can change the above mentioned sub-title as: “Checking the equality of the ROC area of Sonographic measurements against Uterine Volume as the Best and most Accurate measurement” [or something like this]. I recommend the authors follow such approach and correct the corresponding parts of paper.

I agree with you and Sentences corrected as you wish.

14-please change 0.000 in table 5 to <0.001.
Numbers corrected as you wish.

15-please correct Yu J et al to Yu et al.
Phrase corrected as you wish.

16-the part mentioned in lines 266-270 are unclear. Please correct and re-write.
I agree with you and Sentences corrected and rewritten as you wish.

17-writing style is not appropriate in some parts and reader should read the sentence to the end to find out what is the meaning of sentence; for example, in lines 277-282. They can write for example this part as: “These findings are in close similarity with Yu et al. findings that in a cut-off point of 7.6 for transverse uterine diameter, showed a sensitivity of 71% and specificity of 56.5% (26), De Vries et al. study that in a cut-off of point of 15 for transverse uterine diameter, showed a sensitivity of 67.9% and a specificity of 100% (27), Badouraki et al. study that in a cut-off point of 1.05 for F/C ratio, showed a sensitivity of 82.4% and a specificity of 81.8% (25), and Binay et al. study that in a cut-off point of 0.98 for F/C ratio, showed a sensitivity of 91.9% and a specificity of 87.3% (29).”
I agree with you and Sentences corrected and rewritten as you wish.

18-please correct in lines 191-2: At the end, we compared all ultrasonography parameters with the uterine volume ROC curve, that was selected based on its highest area under the ROC curve with acceptable sensitivity and specificity”.
Sentences corrected as you wish.

19-please correct: Our study has some limitations due to ….
Sentences corrected as you wish.

20-please add in statistical analysis part that the selected cut off points were chosen based on youden index.
I added sentence as you wish.

21-please change method titles to patients and methods
Phrase corrected as you wish.

22-Table 5 legend is better as: “Comparison of Receiver–Operating Characteristics (ROC) Curve Area of each Parameter against ROC Curve Area of Uterine Volume as the Best Differentiating Parameter”
Sentence corrected as you wish.

23-please correct table 1 and 2 legend as: “Comparison of Pelvic Ultrasonography Parameters Between Groups” and “Comparison of Demographic characteristics and hormonal laboratory values between groups”
[please capitalize the first characters of the words in table legends.
Sentence corrected as you wish.

I completely revised and restructured the article structure according to the valuable comments of the methodological reviewer and you.
We look forward to hearing from you in due time regarding our submission and to respond to any further questions and comments you may have.
Sincerely,

N.R .M.D

Corresponding author, Radiologist

4 Revision 3

1 comment · 21 Dec 2022

Editor-in-Chief

ACCEPT 21 Dec 2022

Dear authors,
Your article is acceptable for publication in IJR.
Regards