

Dear Editor,

Please find enclosed the edited manuscript in Word format under the file name: ESPS Manuscript NO: 2868-Review.

Title: Smoking and genital HPV infection in women attending cervical cancer screening in Greece

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated, and a "Comment" has been added at the end of the main text (page 10).

2 Revision has been made according to the suggestions of reviewers.

- (1) Reviewer 00742259 wrote: "The aim of the study does not fit with the conclusion. The authors wanted to investigate if smoking influences the course of HPV infection".

This is a very good comment. Unfortunately, we have erroneously stated in the Abstract that "Our aim was to investigate if smoking influences the course of HPV infection" (page 2, line 3). However, as mentioned in the "Introduction" section (in the last paragraph), the aim of the study was to investigate if smoking is associated with HPV infection. Hence the aforementioned sentence in the Abstract has been changed to "Our aim was to investigate whether smoking is associated with HPV infection". Furthermore, in order to avoid confusion to the readers, the following change has been made in the "Introduction" section, in the 2nd line of the last paragraph: "...may also influence the course of HPV infection..." has been changed to "may also influence HPV infection".

- (2) Reviewer 00742259 wrote: "The authors wanted to investigate if smoking influences the course of HPV infection. This suggests a study design with sequential HPV genotyping for the respective patients. In this way, one would be able to study the course of HPV infection. In fact, the authors found an association. -Smoking is regarded as a late effect during cervical carcinogenesis (Louie et al, CEBP 2011). This implies that smoking is not considered as an important factor for persistent HPV infections. The authors found a possible association, but unfortunately, they did not perform HPV genotyping at certain intervals to answer this question. They should comment on this."

The following comments have been added in the "Discussion" section (page 9, 3rd paragraph):

"A limitation of the present study, as well as of most relevant publications, is that HPV-DNA-testing was done only once for each woman. Sequential HPV genotyping of all participants, at certain intervals, could possibly show if smoking might also influence the course of HPV infection".

- (3) Reviewer 00742259 finally also wrote: It may be important for the readership to have more information about other important co-factors; age at first intercourse, number of sexual partners, oral contraceptive use, etc. This is important, because more information is needed to rule out bias. Is it possible that other risk factors for HPV infection were more prevalent in the young smoking HPV positive age group?"

The following comments have been added in the "Discussion" section (page 9, 3rd paragraph):

"Another limitation of the present study and most relevant publications is that possible co-factors, including age at first intercourse, number of sexual partners, oral contraceptive use have not been considered, and thus the possibility of bias cannot be ruled out."

- (4) Reviewer 00742113 wrote: "Interesting manuscript, excellent presented, to be published after adding a limitation paragraph before the conclusion."

A paragraph mentioning the limitations of this study has been added in the "Discussion" section, i.e. 3rd paragraph in page 9.

- (5) Reviewer 00742297 wrote: "Please list the primers used for PCR. Please figure out how to control the false positive ratio for PCR."

Details on primers and controls used for PCR have been added in the "Methods" section, under the subheading "*HPV DNA detection*" in pages 4 and 5 (last line of page 4 and lines 1-10 in page 5).

- (6) Reviewer 00742297 finally wrote: "Please mark the statistically significant on the Figure 1. 4. Please finish the figure legend for Fig 1."

Figure 1 shows the stratification of HPV-positive and HPV-negative women according to age and smoking intensity. As mentioned in page 6 (in the 1st line of the 3rd paragraph), there was no association between smoking intensity and hrHPV status. Hence, no statistically significant changes have been marked on Figure. 1. The figure legend is provided in page 24, and the following sentence has been added: "There was no statistically significant association between smoking intensity and hrHPV status."

3 References and typesetting were corrected

4. Three reviewers (00742259, 00742113 and 00398493) found previously that regarding language our manuscript was Grade A, whereas the other three reviewers (00730309, 00742250 and 00742297) gave Grade B. The manuscript has been now reviewed by two experts, and the language has reached Grade A. Hence, review by an English language editing company is not considered to be necessary.

Thank you again for publishing our manuscript in the *World Journal of Obstetrics and Gynecology*.

Sincerely yours,



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