Point-by-point responses.

Title: Utilization of cervical cancer screening by cytology and the burden of epithelial abnormalities

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Dear Editor,

Thank you for taking the time and effort to consider our manuscript. We thank our peer-reviewers panel who provided valuable comments. We have considered all comments and revised the manuscript. We include a point by point responses to all comments.

Reviewer Comments:  
  
Reviewer 1

The authors report their 42-year long study of cervical cytology in Greater Cairo, Egypt. Such studies and data are vital in understanding the cervical cancer control efforts in resource-constrained countries that have a higher burden of cervical cancer.

Authors’ Response: Thank you for emphasizing the importance of this work in understanding the cervical cancer control efforts in resource-constrained countries that have a higher burden of cervical cancer.

There are a few concerns that need to be addressed, as detailed below:

Authors’ Response: [All comments of reviewer 1 need pathologists to reply]

1. The Bethesda system of classification of cervical smears has evolved over the time period in this study. The authors need to include in their methodology as to how this evolution in terminology was incorporated in the results. This is important because categories such as AGUS were replaced by AGC-NOS and AGC-FN having different clinical implications.

2. Since 42 years is a long period, we assume that at least a proportion, even though small, of women might have had a repeat cervical smear. The authors should specify how were the repeat smears in the same woman included in the study?

3. The percentage utilization of cervical cancer screening services should be depicted, if possible. This would help understand the temporal trend in the uptake of screening services. Mere numbers of cervical smears do not provide this information.

4. In Table 2, the cervical cytology results are depicted as per TBS 2014. The categories of AGC-NOS and AGC-FN were introduced in 2001 only. Were all the smears reviewed by the authors for classification as per TBS 2014? If not, how were the smears reported as AGUS reclassified as per the TBS 2014?

5. In Figures 2 and 3, the color coding of graphs has not been explained.

Authors’ Response: Color coding has been added.

6. "Epithelial abnormalities were significantly more common in women who underwent routine check-ups than in symptomatic women". Does this include 11414 routine asymptomatic and 30352 symptomatic women? The numbers should also be given.

Authors’ reponse: Yes. "Epithelial abnormalities were significantly more common in women who underwent routine check-ups (11414) (6.4%) than in symptomatic women (30352) (4.4%) “. The rate is higher in routine when compared to all other (symptomatic and not reported) cases 6.4% vs 5.3% (even after adding 53354 “not reported” as they attended the clinic repeatedly)

7. "The yearly number of screened women was positively associated with the observed LSIL". Is this association for the total number of women screened? Is there any difference in the association for symptomatic and asymptomatic women?

Authors’ response: Yes, this association is for all screened women, and the association was among symptomatic but not among routine cases

8. "Furthermore, these abnormalities were more prevalent among women who underwent the screening process at a relatively advanced age than among their counterparts". There is no data supporting this statement.

Authors’ response: Thank you for this comment. Data added in Table.

9. "The yearly utilization of cervical screening by cytology was positively associated with LSIL and negatively associated with invasive lesions". The utilization of cervical screening should not be used in this sentence, since only the numbers screened are being used. The utilization rate has not been calculated.

Authors’ response: Done. we modified the wording.

10. "This finding suggests that routine cervical cancer screening may be more effective in detecting precancerous changes than relying solely on the presence of symptoms." This is a bold statement and should be modified. We do not know if the rate of specific infections in cervical smears was higher among symptomatic women. The sentence may be modified to "This finding can provide support to the cervical cancer control efforts by providing evidence on the benefit of routine screening rather than only when symptoms arise."

Authors’ response: We agreed to tone down the sentence.

11. "we found that women older than 60 had the highest prevalence of epithelial abnormalities". This data has not been provided in the manuscript.

Authors’ response: Done. Data added in Table

12. "Over a 42-year period, the prevalence of SIL abnormalities decreased from 6.9–4.3% for LSILs and from 1.2–0.13% for HSILs. The relative frequency of preinvasive abnormalities (ASC, LSIL, and HSIL) started at approximately 10% in 1981 and decreased to 5% in 2022. " The prevalence of cervical intraepithelial lesions would make sense with data of percentage utilization of screening services. As seen in Figure 1, number of screened has reduced over years.

Authors’ response: We have modified the wording to be more accurate.

13. Since the study spans a very long period. I would be interested in knowing the practice of cervical cytology. Is it a one-tier screening or two-tier screening method? Has anything changed over the years?

Authors’ response: It was 2 tiers. Tier 2 was confirmation by colposcopy and guided biopsy from aceto-white areas in our unit, we did not include the total results of colposcopy as it was introduced later in our unit. Some of the patients were referred after colposcopy to other lab for pathological examination, others don’t respond.

Reviewer 2

I read with great interest the Manuscript, which falls within the aim of this Journal. In my honest opinion, the topic is interesting enough to attract the readers’ attention.

Authors’ Response: Thank you for the praise.

Methodology is accurate and conclusions are supported by the data analysis.

Authors’ Response: Thank you for the praise.

Nevertheless, authors should clarify some point and improve the discussion citing relevant and novel key articles about the topic. Authors should consider the following recommendations:

- Manuscript should be further revised by a native English speaker.

- Inclusion/exclusion criteria should be better clarified.

- The authors have not adequately highlighted the strengths and limitations of their study. I suggest clarifying these points. - What are the actual clinical implications of this study? it is important to report the results obtained by the authors in the context of clinical practice and to adequately highlight what contribution this study adds to the literature already existing on the topic and to future study perspectives.

Authors’ Response: [For pathologists to reply]

Reviewer 3

I read with great interest the Manuscript titled “Utilization of cervical cancer screening by cytology and the burden of epithelial abnormalities: A tertiary-center 42-year study”. In my opinion, this topic analyzed is interesting enough to attract readers’ attention.I suggest a few recommendations.

I suggest a round of language revision, in order to correct few typos and improve readability.

Authors’ Response: Thank you. Done.

Considering the state of art of this topic, it would be interesting to consider and discuss these important points about cervical diseases, referring to: Tullio Golia D’Augè , Ilaria Cuccu, Andrea Etrusco, Antonio D’Amato, Antonio Simone Laganà, Ottavia D’Oria, Giorgio Bogani, Violante Di Donato, Ludovico Muzii, Andrea Giannini. State of the art on HPV-related cervical lesions. doi: 10.36129/jog.2024.161

Authors’ Response: Thank you. Done.

In cervical cancer management is crucial an efficacy prevention. I suggest reading and adding recent evidence about HPV-related lower genital tract lesions and the potential role of anti-HPV vaccination. I would be glad if the authors discuss this important point, referring to PMID: 37978580.

Authors’ Response: Thank you. Done.

Because of these reasons, the article should be revised and completed. Considering all these points, *I think it could be of interest to the readers and, in my opinion, it deserves the priority to be published after minor revisions*.

Authors’ Response: Thank you for the encouraging comment.

Reviewer 4  
The authors report their experience with screening for cervical lesions in a population treated at the Cairo University Hospital.

The results are not impressive, since around 5% of the samples analyzed showed cytological changes, and the majority of them were minimal lesions.

They are not informed whether there are diagnostic quality control criteria, nor whether the cases were confirmed by biopsy.

Authors’ Response: Abnormal cytology was confirmed by biopsy either in the same unit or referred to a private facility. We did not include the diagnostic accuracy based on biopsies in this paper and we acknowledged this in the limitations.

The study does not bring anything new to international cervical cancer prevention guidelines. Perhaps the work can support local protocols for women's health care.

Authors’ Response: This work is important to inform national policy, but it would help other LMIC countries with limited resources.  
  
Reviewer 5  
The study is very good covering a long period and good number of cases. The manuscript is well written.

Authors’ Response: Thank you for the praise.

However kindly check the keywords and revise.

Authors’ Response: Keywords have been revised.