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Quick Response Code:

Website: www.jehp.net
DOI: 10.4103/jehp.jehp_1200_21

Post-COVID-19 menstrual abnormalities and infertility: Repercussions of the pandemic

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Abstract:

While battling the life-threatening complications of COVID-19, its effect on the menstrual cycle and infertility has been somewhat ignored. This brief review aims on highlighting the importance of menstrual abnormalities being experienced during the post-COVID period and to make the clinicians aware about what to expect in regard of menstrual abnormalities by learning from various studies that have been conducted worldwide. This review article was written with systematic literature review with the help of data search machine such as PubMed, Scopus, Web of Sciences, and Google Scholar. A search strategy leads to the extraction of 160 related articles that after the removal of inappropriate and duplicate articles, 33 articles were selected for the review. To find other potentially relevant articles, the references of the extracted articles were thoroughly examined. The search was carried out using keywords including "COVID-19," "Menstrual abnormalities," and "Infertility." Using OR and AND, the keywords mentioned above were combined and then utilized in the search box of the databases. Articles published from January 2020 to September 2021 were included in this study. It includes worldwide data ranging from studies done in China, India, Ireland, Turkey, Jordan, and Germany. During the post-COVID period, there is a significant alteration in the sex hormones of females infected by COVID-19 which may manifest as menstrual cycle abnormalities such as decreased cycle length or prolonged menstrual cycle bleeding. It may also manifest as infertility due to ovarian failure due to suppression of ovarian function COVID-19 a novel coronavirus which is presently a pandemic has affected the world in manner reminding the world of 1918 Spanish flu. However, while battling the deadly pandemic, the clinicians should also be aware of the repercussions of the effect this infection has on multiple organs such as ovarian suppression leading to infertility, oligomenorrhea, or menorrhagia.

Keywords:

COVID-19, infertility, menstrual abnormalities

Introduction

Since the December of 2019, there was a sudden surge of patients acquiring pneumonia in Wuhan Province of China. At that time, there was discovery of severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) in the patients reporting with pneumonia and COVID-19 was then thought to be a pulmonary disease.^[1] However, as the infection emerged as a widespread pandemic, it slowly emerged as a multisystem disease effecting various system organs of the body starting from the nervous system to cardiovascular

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How to cite this article: Madaan S, Talwar D, Jaiswal A, Kumar S, Acharya N, Acharya S, *et al.* Post-COVID-19 menstrual abnormalities and infertility: Repercussions of the pandemic. *J Edu Health Promot* 2022;11:170.

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Received: 13-08-2021
Accepted: 19-10-2021
Published: 11-06-2022

system and gastrointestinal system to most recently emerging gynecological involvement of COVID-19.

During the exhausting pandemic of COVID-19, the gynecological care has somewhat taken a backseat with reduced reporting of menstrual abnormalities. With the ovarian suppression exerted by COVID-19, we postulate that there has been underreporting of post-COVID ovarian suppression, infertility, and menstrual abnormalities. COVID-19 has a long-lasting inflammatory effect which may last for several months postinfection with COVID-19 which is termed as long COVID syndrome. The effects exerted on ovary by COVID-19 are thought to be exerted due to this long COVID syndrome with long-lasting inflammation and also direct infiltration of the SARS-CoV-2 in the ovary, leading to its varied manifestations as a post-COVID sequela. Serious outcomes such as infertility and ovarian suppression need to be studied in detail to know the extent of impact COVID-19 can have on females contracting COVID-19. Infertility can be psychologically distressing for females in the pressure of achieving desired social roles. Infertility is a devastating experience inducing stress and affecting self-esteem. Therefore, COVID-19 can lead to serious gynecological issues such as infertility and menstrual abnormalities which impact the overall health of an individual as well as induce psychological stress associated with infertility. This review compiles data from studies conducted throughout the world thus describing the various changes in the reproductive system observed due to COVID-19 and the pathophysiology which is proposed to be causing them. These important findings can be used to diagnose and prevent menstrual disorders and infertility observed as a consequence of COVID-19. There are very few studies carried out on the implications; COVID-19 has on infertility and menstrual cycles making it an under discussed topic which needs further evaluation hence explaining the significance of our study.

Materials and Methods

Study design and setting

The present study is a systematic review of all the publications which are related to the menstrual abnormalities and infertility associated with COVID-19. This study is based on the guidelines drafted by Preferred Reporting Items for Systematic Reviews and MetaAnalyses. Electronic databases were searched extensively to find relevant articles. The following databases were searched: PubMed, Web of Science, Scopus, and Google Scholar. For each electronic database, expressions and words were used from a controlled vocabulary (MESH and others) along with free text searching strategy. To find other potentially relevant articles, the references of the extracted articles

were thoroughly examined. The search was carried out using keywords including "COVID-19," "Menstrual abnormalities," and "Infertility." Using OR and AND, the keywords mentioned above were combined and then utilized in the search box of the databases.

Study participants and sampling

To select eligible articles, the following inclusion criteria were considered:

- Studies published in English language
- Studies with full-length article accessible free of cost
- Studies which were published with focus on menstrual abnormalities and infertility following COVID-19.

Exclusion criteria included the studies which were published in languages other than English, with full-length articles not available along with articles which were editorials and letter to editor. In addition, the articles based on obstetric complications arising in COVID-19 were also excluded. To obtain authoritative information, only the articles which were from peer-reviewed journals were short listed for this review. Articles with no clear methodology were also excluded from this review.

After the initial search, 160 articles which were relevant could be identified. Thereafter, all the duplicate and irrelevant articles were excluded after reviewing their titles and abstracts. Thirty-three articles were finally shortlisted after screening and evaluation [Figure 1].

Data collection tool and technique

Synthesis thematic approach was used to analyze and collect information and to identify the themes. The authors analyzed the articles in three stages: (1) extraction of all the findings and coding of findings for each study that was analyzed, (2) grouping of the findings was done according to the similarity to confirm if the findings confirmed refute or extend each other, and (3) abstraction was done for the findings. The initial synthesis was done by conducting separate synthesis of each of the article format followed by preparation of extraction datasheet by one of the author. The accuracy and the shortcomings of the datasheet were analyzed by rest of the authors.

Ethical consideration

Guidelines set by committee on publication ethics on good publication practice were followed. There were no conflicts of interests. There was early agreement on the precise roles of the contributors, and on matters of authorship and publication.

Results

It is a well-known phenomenon for virus to affect the female reproductive system. This is the prime reason

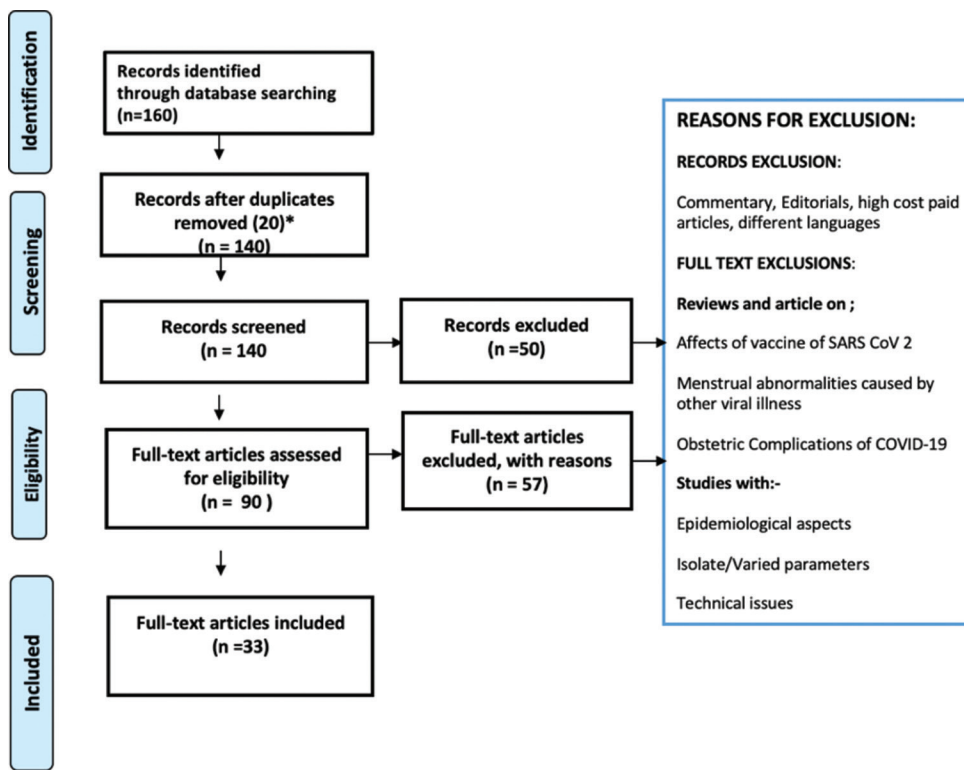


Figure 1: Method of data collection

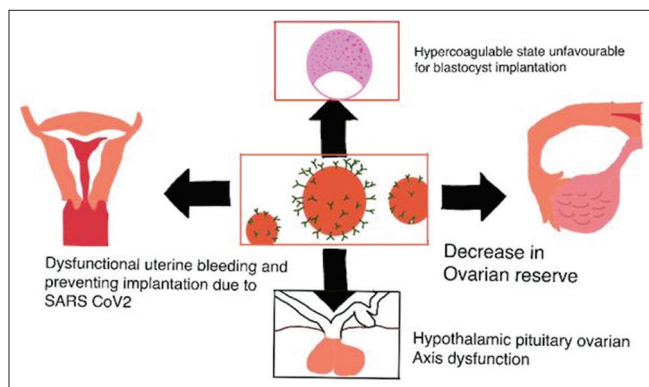


Figure 2: Various mechanisms of menstrual abnormalities and infertility associated with COVID-19

for females with hepatitis B and hepatitis C virus infection to develop reproductive dysfunction in the form of pregnancy loss as well as infertility. Menopause was found to occur earlier in females with human immunodeficiency virus infection. Hantavirus infection has also shown to affect female fecundity in animals.^[2] However, very few studies have been conducted on COVID-19-associated menstrual changes and its impact on female fertility. The various mechanisms of menstrual abnormalities and infertility associated with COVID-19 has been shown in figure 2. The result of this review have been summarised in Table 1.

Discussion

Menstrual changes reported post-COVID-19

It was found that post-COVID-19, there was an upsurge of menstrual abnormalities such as prolonged cycles and decreased volume of menstruation.^[3] A few patients also reported to have shortened or disordered menstrual cycles as well as increased volume of menstruation.^[4] It was found that menstrual changes were observed more commonly in patients of COVID-19 with systemic complications arising out of COVID.^[5] This suggests that menstrual changes which are often neglected by the treating clinicians are more common to be seen in patients with multisystem dysfunction. Hence, there is massive underreporting of menstrual abnormalities which otherwise seems to be a very common problem associated with COVID-19.

Sex hormone changes in COVID-19

Assessment of sex hormones is often neglected in patients with COVID-19, however, it was found that some patients with COVID-19 had abnormal levels of sex hormones.^[6] There was inappropriately high concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) seen in patients with COVID-19.^[7] This points toward ovarian suppression which might be linked to COVID-19. When placed in stress, ovarian function is often suppressed to ensure

Table 1:Result of the review

Article Title	Authors	Source	Year	Method	Finding
SARS-CoV-2 and the reproductive system: known and the unknown!!	Sharma I, Kumari P, Sharma A, Saha S	PubMed, Scopus, Web of Science	2021	Review	SARS-CoV-2 seems to have the potential of affecting both male and female reproductive tracts
SARS-CoV-2 infection risk assessment in the endometrium: viral infection-related gene expression across the menstrual cycle	Castillo I, Leon P, Peiro A <i>et al</i>	PubMed, Scopus	2020	Cross Sectional Study	Endometrial tissue is likely safe from SARS-CoV-2 cell entry based on ACE2 and TMPRSS2 expression, but susceptibility increases with age. Further, TMPRSS4, along with BSG-mediated viral entry into cells, could imply a susceptible environment for SARS-CoV-2 entry via different mechanisms
Single-cell transcriptome analysis of the novel coronavirus (SARS-CoV-2) associated gene ACE2 expression in normal and non-obstructive azoospermia (NOA) human male teste	Liu X, Chen Y, Tang W <i>et al.</i>	PubMed, Scopus	2020	Cross Sectional Study	CE2 expressing cells existed in almost all testis cell types and Sertoli cells had highest expression level and positive cells ratio
COVID-19 pandemic effect on early pregnancy: are miscarriage rates altered, in asymptomatic women?	Olshika K, Perel A, Steiner N <i>et al</i>	PubMed, Scopus	2021	retrospective cohort study	The COVID-19 pandemic environment does not seem to affect early first-trimester miscarriage rates in asymptomatic patients
Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age	Li K, Chen G, Hou H <i>et al</i>	PubMed, Scopus	2021	retrospective cross-sectional study	Nearly one-fifth of patients exhibited a menstrual volume decrease or cycle prolongation. The menstruation changes of these patients might be the consequence of transient sex hormone changes caused by suppression of ovarian function that quickly resume after recovery
The role of androgens in COVID-19	Moradi F, Behnaz E, Anari A	PubMed Scopus	2020	Review	Angiotensin-converting enzyme 2 (ACE-2) acts as a functional receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and male hormones are effective in the ACE-2 passageway and simplify SARS-CoV-2 entry into host cells
The impact of the COVID-19 Pandemic on Women's Reproductive Health	Phelan N, Behan L, Owens L	PubMed, Scopus	2021	Digital Survey	The COVID-19 pandemic has severely impacted the reproductive health of women
Effect of the COVID-19 pandemic on female sexual behaviour	Yuksel B, Ozgor F	Pubmed, Scopus, Web of Science	2020	Observational Study	The pandemic is associated with a decrease in the desire for pregnancies and decreased female contraception and increased menstrual disorders
Impact of COVID-19 and other virus on reproductive health	Baitha O, Deeb T, Zoubi Emissary E <i>et al.</i>	Pubmed, Scopus, Web of science	2020	Review	Viral infection by HPV, HSV, GIV, HBV, HCV and MuV challenges the reproductive health and can be considered as a risk factor for development of infertility
Potential Risks of SARS CoV 2 infection on reproductive health	Li R, Yin T, Fang F <i>et al.</i>	Pubmed, Scopus	2020	Review	The potential pathogenicity and attack of COVID-19 on testicular tissues, ovarian tissue and granulosa cells might affect the functioning of testes and ovary , spermatozoa production , oocyte quality and pregnancy outcomes
Assessment of SARS-CoV-2 in human semen-a cohort study	Holtmann N, Edimiris P, Andree M <i>et al.</i>	PubMed, Scopus	2020	Cohort Study	A mild COVID-19 infection is not likely to affect testis and epididymis function, whereas semen parameters did seem impaired after a moderate infection
Expressions and significances of the <i>angiotensin-converting enzyme 2</i> gene, the receptor of SARS-CoV-2 for COVID-19	Fu J, Zhou B, Zhang L <i>et al.</i>	PubMed, Scopus, Web of Science	2020	Cross Sectional Study	ACE2 expression distributions were organ-specific, mainly in kidney, male testis, female breast, and the cardiovascular and gastrointestinal systems. Thus, SARS-CoV-2 infection may most likely affect male infertility.
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and its effect on gametogenesis and early pregnancy	Singh B, Gornet M, Sims H <i>et al</i>	PubMed, Scopus, Web of Science	2020	Meta Analysis	In females, an alteration of the ACE2 cascade via SARS-CoV-2 infection could lead to impairment in important follicular and luteal processes

normal functioning of other organ systems which are essential for life and amenorrhea has also been previously reported in acute diseases. This explains infertility and decreased menstruation in patients with COVID-19 which may be linked to ovarian suppression due to acute stress of COVID-19 infection and multiple organ dysfunction. This also supports the presence of menstrual changes in patients with more severe involvement of multiple organ systems which was clinically witnessed by various studies.

There has been documentation of difference in response to inflammation by different sex which can be attributed to sex steroid hormones.^[8] Age-related decrease in sex hormones is also associated with more severe COVID-19 infection which might be associated with higher mortality witnessed in the elderly with COVID-19. Sex hormones have shown to mitigate inflammatory response and thus the increase in sex hormones in COVID-19 can be a response to decrease the inflammation associated with cytokine storm. Hormone replacement therapy has thus been studied as a potential therapy to mitigate inflammation in COVID-19.

Impact of COVID-19 on ovarian reserve

To determine the effect of COVID-19 on ovarian reserve the patients have been tested in various studies for anti-mullerian hormone levels. Granulosa cells of small antral and preantral ovarian follicles are responsible for secretion of anti-Mullerian hormone and its deficiency directly depicts decreased ovarian reserve.^[9] Levels of anti-Mullerian hormone are not affected by the menstrual cycle, exogenous sex hormones, or pregnancy. Deficiency of anti-Mullerian hormone detected in post-COVID period depicts the decreased ovarian reserve due to COVID-19 which might ultimately result in infertility. Another school of thought is that there is presence of angiotensin convertase enzyme 2 (ACE 2) receptor on the ovarian follicles.^[10] SARS-CoV-2 exerts its effect through modulation of these ACE 2 receptors which were earlier thought to be present only in the pulmonary system. However, the presence of ACE 2 receptors on ovarian follicles has now clearly been established and expression of ACE 2 receptors on the ovarian follicles is essential for maturation of these follicles along with ovulation, modulation of luteal angiogenesis and degeneration, and it also influences the regular changes which are observed in endometrial tissue and embryo development.^[5] ACE2 mRNA transcripts have been detected in the ovaries of women of reproductive age group as well as postmenopausal women.

ACE2 receptor has been found in stroma and granulosa cells as well as oocytes in immature rat ovaries, the expression of which is enhanced in antral and preovulatory follicles.^[11] Its presence in the antral follicle

might explain the reduced anti-Mullerian hormone in post-COVID patients. ACE 2 receptors are also expressed on the vagina, placenta, and uterus. This explains another postulate of reduced ovarian reserve where SARS-CoV-2 directly invades the ovarian follicles using these ACE 2 receptors leading to infertility and various menstrual abnormalities.

Effect of COVID-19 on the endometrium

Angiotensin II plays a dual role in the vascular bed and regeneration of the endometrium and it also initiates menstruation through vasoconstriction of spiral artery.^[12] The balance between angiotensin II and Ang (1-7) could regulate the myometrium activity and regeneration of endometrium.^[13] Furthermore, angiotensin II increases the proliferation of epithelial cells of the uterus and stroma cells and enhances the fibrosis of endometrium.

Therefore, angiotensin II is essential for regular menstrual cycles and alteration in the receptors of angiotensin II may thus lead to dysfunctional uterine bleeding and hyperplasia of the endometrium.^[14] Furthermore, extensive expression of ACE 2 might be correlated with metastasis and prognosis of endometrial carcinoma.^[15] Therefore, the interaction of SARS-CoV-2 with ACE 2 receptors present in the endometrium may be a prime reason for menstrual abnormalities being witnessed after COVID-19 infection.

Role of inflammatory cytokines

There is a role of immune dysregulation in COVID-19. The immune response against SARS-CoV-2 is shown to involve all the components of immune system that combined together appear to be responsible for elimination of the virus and recovery from the infection.^[16] However, such strong immune responses are responsible for the disease's progression to an even more severe as well as lethal process. Interleukin-6 is emerging as a key cytokine involved in the inflammatory response seen in COVID-19.^[17] Interleukin-6 along with other cytokines such as interleukin-8 and tumor necrosis factor alpha triggers a procoagulant state which is unfavorable for blastocyst or fetus in a normal uterus of human.^[18,19] This might explain another reason for the infertility associated with COVID-19.

Role of basigin receptor

Besides, ACE 2 receptor another receptor responsible for SARS-CoV-2 invasion is basigin (BSG) receptor.^[20] This basigin receptor mediates the entry of SARS-CoV-2 into the host cells. Basigin receptor is expressed in the uterus as well as granulosa and stroma cells of the ovary.^[21] Basigin receptor normally plays a crucial role in the development of follicles, formation of corpus luteum, and implantation of the embryo. Thus, modulation of this receptor in COVID-19 might contribute to infertility.

Effect of COVID-19 of hypothalamic pituitary gonadal axis

The hypothalamic pituitary gonadal axis plays a crucial role in regulation of the human reproductive system. The anterior portion of pituitary is responsible for the production of LH and FSH, and the gonads are responsible for the production of estrogen and testosterone; the hypothalamic pituitary gonadal axis regulates female menstrual cycle. The positive loop of feedback between estrogen and LH is responsible to prepare the follicles in the ovary for ovulation and to prepare the uterus for implantation.

The hypothalamus and pituitary both have ACE 2 receptors and can be sites of SARS-CoV-2 infection if the virus is able to invade the brain.^[22] It is postulated in some studies that SARS-CoV-2 can enter the brain through the olfactory pathway where it enters the brain through cribriform plate which is porous.^[23] The virus may then enter the hypothalamus as the blood-brain barrier is permeable in proximity of this structure. Furthermore, infection of the hypothalamus might result in hypophysitis which would also disturb the hypothalamic pituitary gonadal axis, thereby leading to menstrual abnormalities and infertility.^[24]

Functional hypothalamic amenorrhea and lifestyle changes during the pandemic

Functional hypothalamic amenorrhea is also being reported in patients with COVID-19, there is chronic anovulation which is not due to any underlying cause but is associated with energy deficit, anxiety and mood disorders.^[25] Functional hypothalamic amenorrhea has long-term consequences of health of the patients, leading to subfertility, increased risk of cardiovascular diseases, psychiatric disorders, and osteoporosis. There was a significant increase in incidence of missed periods which might be explained by functional hypothalamic amenorrhea due to psychological distress and also increased amount of exercise.^[26] Will these missed periods ultimately lead to chronic anovulation is yet to be determined as COVID-19 is a new infection and the long term effects of COVID-19 are yet unknown.

Women who earlier had a history of missed periods are more prone to have amenorrhea during the pandemic.^[27] As many women have gained weight and have reported their diet to get worsen during the pandemic, this amenorrhea is not only related to stress but also to obesity and worsening of polycystic ovarian disease due to increase in body weight.

Premenstrual syndrome in COVID-19

Various patients with COVID-19 have reported worsening of symptoms of premenstrual syndrome.^[28]

Premenstrual syndrome is reported more in women with high psychological stress.

Premenstrual syndrome can significantly affect patients health and is associated with impairment of various activities of daily life and mental health disorders such as anxiety, postnatal, and perimenopausal depression. Many patients with COVID-19 reported periods to be heavy and more painful with a significant difference than before COVID-19 infection.^[29] Again, this can be attributed to increased level of stress and psychological distress along with low mood all of which are being witnessed during the pandemic. A few studies have also found patients to experience hypoactive sexual disorder where symptoms last for a period of more than 6 months and these symptoms are accompanied with distress.^[30] Reduced sexual desire has been associated with depression and anxiety. The psychological impact of pandemic along with environmental factors has also contributed in inducing psychological distress precipitating premenstrual symptoms and a number of coping strategies have been tried for the same.^[31,32]

Male infertility linked with COVID-19

The semen analysis of patients with COVID-19 did not show any viral RNA.^[33] However, stress, anxiety, and other psychological factors may impact the sperm count in male patients who contract COVID-19. The presence of ACE 2 receptors on the testis can also be linked to a subfertility and decreased sperm count associated with COVID-19.^[34,35] However, this requires further studies to verify.

Limitation and recommendation

A limitation of this review of literature remains the study selection phase. In this review, the studies published in English language were included and potentially relevant articles published in other languages could not be selected for review. Furthermore, certain articles on our topic which were not free to access and were costly to subscribe could not be included in our study.

We suggest regular screening of females of reproductive age group who contract COVID-19 infection so that they undergo regular follow-up and to report any kind of abnormalities in their menstrual cycles as there are a number of factors which influence the menstrual cycle as well as fertility post-COVID-19

Conclusion

SARS-CoV-2 may infect the ovary, uterus, and vagina through ubiquitous expression of ACE 2. This may lead to disturbance of functions of the female reproductive system, leading to infertility and various menstrual disorders. We strongly suggest that patients of COVID-19 should be evaluated for fertility after recovery.

Acknowledgments

The authors would like to thank all those who cooperated in collecting and analyzing the data.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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