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Research Article

Menstrual Cycle Changes after the Covid-19 Vaccine: A Case-Control Study in Saudi Arabia

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Abstract

Background

Various side effects of the COVID-19 vaccine, such as fatigue, have been reported. However, there has been a recent increase in reports of menstrual cycle changes among women. This study assessed the effect of the COVID-19 vaccine on the menstrual cycle of Saudi women.

Material & Methods

In this case-control study, data were based on an interview questionnaire used to collect all the requested information. Data were collected between November–December 2021 from 500 healthy Saudi females between 20–40 years. We included all women who reported having a normal menstrual cycle before being vaccinated against COVID-19.

Result

A total of 65.6% of participants reported having significant changes in their cycle in terms of period timing, blood flow, and pain following the first and 65.6.% following the second COVID-19 vaccination doses. Both the mRNA and adenovirus vectored COVID-19 vaccines affected the cycle similarly. The induced COVID-19 vaccine menstrual cycle abnormality is a short-term effect lasting less than three months after the first and second dose.

Conclusion

There are reported side effects of the COVID-19 vaccine, however, changes in the menstrual cycle have not been reporte Our study assume that the menstrual cycle changes observed in study's participants were unlikely to be caused by reason other than the COVID-19 vaccine, since we excluded all participants with medical interventions, medical conditions, and the age range that might affect the menstrual cycle. Although this effect is a short-term effect, the exact mechanism behir this phenomenon must be investigated.

Key words: COVID-19; COVID-19 vaccine; menstrual cycle

Introduction

The World Health Organization (WHO) announced the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; also known as COVID-19) on March 11, 2020. COVID-19 originated in Asia and spread worldwide [1]. The latest WHO update shows that there are approximately 250 million confirmed cases and 5 million deaths worldwide due to COVID-19 (1). COVID-19 became a global pandemic and caused a worldwide crisis that led to international lockdowns of different levels of stringency [1]. Several methods were implemented to prevent the spread of the virus, including quarantine, social distancing, disinfection drives, and the use of protective masks. These procedures have had an adverse psychological and economic impact and have led to controversies between the healthcare community and political decision-makers [2]. Therefore, rapid progress was made in terms of exploring the genomic sequence of the viral RNA, diagnostic tools, experimental treatments, and methods of protection from SARS-CoV-2. Although several potential therapies with promising results were being developed to treat severe forms of COVID-19, restrictions were applied to prevent the spread of the virus, and antiviral treatments were utilized to address public health needs [2].

By September 2020, pharmaceutical companies worldwide were competing in the development and commercialization of effective COVID-19 vaccines, with over 124 vaccine proposals employing various strategies to design and produce the vaccine. Of these, only 10 vaccines successfully reached the phase 1 trial stage [2]. Various vaccines have been approved by the United States Food and Drug Administration and have been distributed and used worldwide. Among these, only the Pfizer and AstraZeneca vaccines were initially approved and used in Saudi Arabia. The Pfizer/BioNTech vaccine (BNT162b2) uses mRNA viruses to encode the modified spike protein stabilized in its pre-fusion conformation. The Oxford–AstraZeneca vaccine is a chimpanzee adenovirus-vectored vaccine ChAdOx1 nCoV-19 (AZD1222) [3]. Both vaccines have been effective and safe in preventing COVID-19 in clinical trials and are now used worldwide [1].

There is considerable interest in exploring the effect of various COVID-19 vaccines on the human body [4]. Numerous researchers are investigating different side effects of the COVID-19 vaccine such as fever, headache and vaccine-induced cross-reactivity in specific disease conditions. The Medicines and Healthcare products Regulatory Agency (MHRA) of the UK has reported some common side effects of the COVID-19 vaccine, such as a sore arm, fever, and fatigue (from the weekly summary of yellow card reporting). However, primary care clinicians and reproductive health workers have been continuously reporting changes in the menstrual cycle of women, including unexpected bleeding [4]. One study has linked the COVID-19 vaccine to an increased menstrual cycle length in women [5]. An investigation of the possible connection between COVID-19 vaccines and menstrual changes may enhance our understanding of the mechanism and thereby help prevent this adverse effect.

A recent cohort study that included U.S. residents, aged 18–45 years, with normal menstrual cycle lengths, investigated their menstrual cycle data using the "Natural Cycles" application for three cycles before the vaccine dose and one cycle after receiving the vaccine. They also compared vaccinated and unvaccinated women. This study reported that the COVID-19 vaccination leads to a small change in the cycle length but not in the length of menses [5]. Reports on social media about the disturbance of the menstrual cycle after the COVID-19 vaccination may also lead to vaccine hesitancy [6].

The menstrual cycle is considered a sensitive vital sign in women, a marker of possible underlying medical conditions, and an effective tool to assess hormonal development normalcy and exclude dangerous abnormalities, such as inflammatory bowel disease [7]. Unfortunately, all of the current trials on the COVID-19 vaccines did not study the effect of the vaccines on the menstrual cycle, and only a small number of women had self-reported menstruation-related changes in response to the vaccines. Therefore, it is very important to investigate the effects and characterize the changes in the menstrual cycle that occured after the COVID-19 vaccine. The findings of this investigation may help women in overcoming their hesitancy and fears that the COVID-19 vaccine may disrupt their hormone levels. Successful COVID-19 vaccination programs rely on clear research findings on the adverse effects of the COVID-19 vaccines.

The present study aimed to investigate the association between the COVID-19 vaccines and the occurrence of menstrual cycle changes and to determine the adverse effects of the vaccine on the menstrual cycle of Saudi women. Furthermore, the study aimed to confirm whether the COVID-19 vaccine-related adverse effects are short-term or long-term. This will help women plan for potentially altered cycles. Collectively, this study aims to help clarify the doubts that women have by providing them with robust information about the COVID-19 vaccine, which can help them overcome their apprehensions regarding the vaccine.

Materials & Methods

This case-control study, conducted between November and December 2021, quantitatively assessed the effect of the COVID-19 vaccine on the menstrual cycle of women in Saudi Arabia. The estimated sample size (n= 500) was derived from the online Raosoft sample size calculator and this study included a healthy participants who were aged 20–40 years, vaccinated against COVID-19, and reported a normal menstrual cycle before receiving the vaccine. In contrast, women that were pregnant, receiving medications, and those with pre-existing medical conditions were excluded [10].

The data were based on an interview questionnaire used to collect all the requested information from Saudi women. Participation was voluntary and informed consent was obtained from the participants. Participants were recurited from different public areas in universities, hospitals, and malls. A total of 40–50 participants were recrutied from each site. The study adhered to the tenants of the Declaration of Helsinki. In addition, the study was approved by the ethics committee of the King Saud University (approval on Research Project No. E-21-6345).

A questionnaire consisting of questions which were either close-ended or multiple choices was used. The questionnaire included information about demographics detials, medication, disease, vaccine, time of vaccine administration, menstrual cycle status before and after vaccination, menstrual irregularity, type of menstrual irregularity (timing, bleeding, and pain), and the time of the observed change [12].

Data were collected in excel 2016 and statistically analyzed by using Statistical Package for Social Studies (SPSS 22; IBM Corp., New York, NY, USA). To assess the relationship between variables, qualitative data was expressed as percentages, and the chi-squared test ($\chi 2$) was used. p-value of <0.05 was considered statistically significant.

Results

Our study included 500 women, all of whom were healthy, aged 20-40 years, and had received two doses of the COVID-19 vaccine (Table 1). Nearly two-thirds of the participants reported an irregularity (in timing, bleeding, and pain) in their menstrual cycle after the first and second doses of the COVID-19 vaccine (Figure 1).

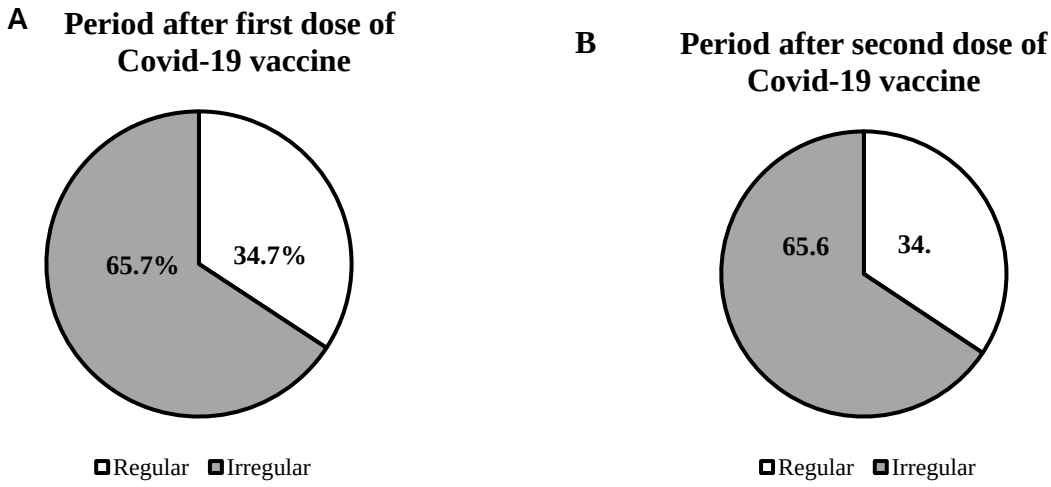

Figure 1: This pie chart displays the percentage of women that had irregular periods after the first (**a**) and second doses (**b**) of the COVID-19 vaccine. There is a significant difference between the percentages of women who reported regular and irregular periods after the two doses of the COVID-19 vaccine (*p*-value < 0.001).

Irregularity of the Menstrual Cycle

A normal menstrual cycle is characterized by anovulatory cycles, fixed timing of the period, menstrual flow, and pain. In our study, menstrual cycle irregularity was classified, and its percentage was assessed in the study participants that had received two doses of the COVID-19 vaccine. More than one-third of the participants (38% following the first dose and 40% following the second dose) had been experiencing a change in the period timing after the COVID-19 vaccine for either a prolonged or short interval. Around half (52% following both the first and second doses) of the participants reported a change in the amount of bleeding, including excessive menstrual flow. Nearly half of the participants (52% following both the first and second doses) reported changes in the pain associated with their period (Figure 2).

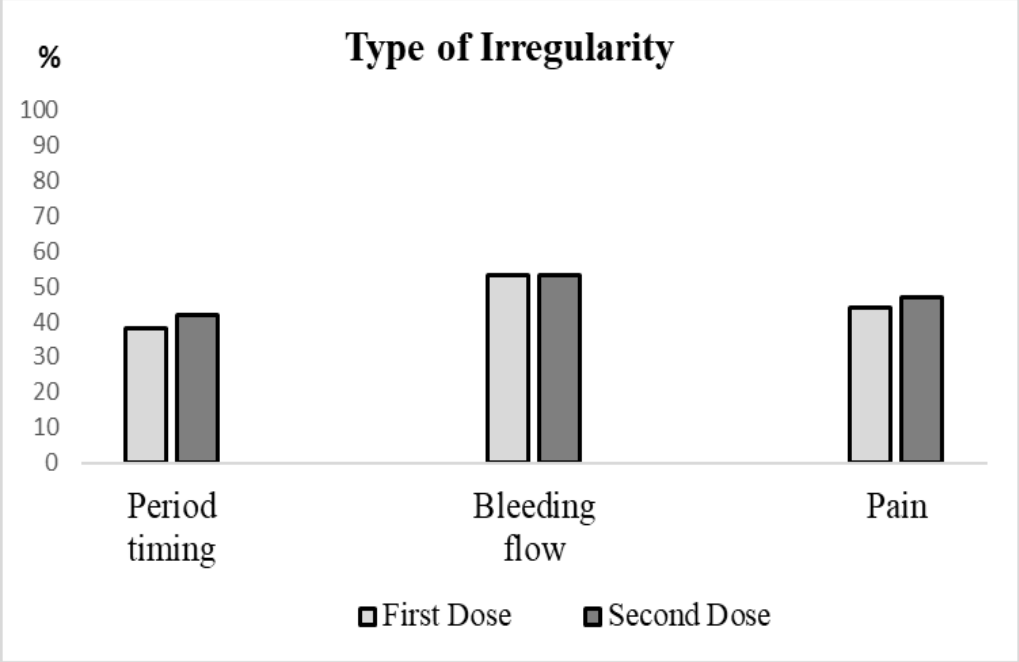

Figure 2: The percentages of menstrual irregularity after the first and second doses of the COVID-19 vaccine. The various types of irregularities involving blood flow, period timing, and pain occurred at a similar rate in women after the first and second dose of the COVID-19 vaccine.

Menstrual Cycle Abnormality After Both the mRNA and Adenovirus-Vectored COVID-19 Vaccines

Among the 500 participants, 78% were vaccinated with BNT162b2, while 21% were vaccinated with AZD1222. Despite the different formulations of Pfizer (New York, United States of America) and AstraZeneca, both vaccines showed a similar impact on the menstrual cycle, where the p-value was >0.05 (Figure 3).

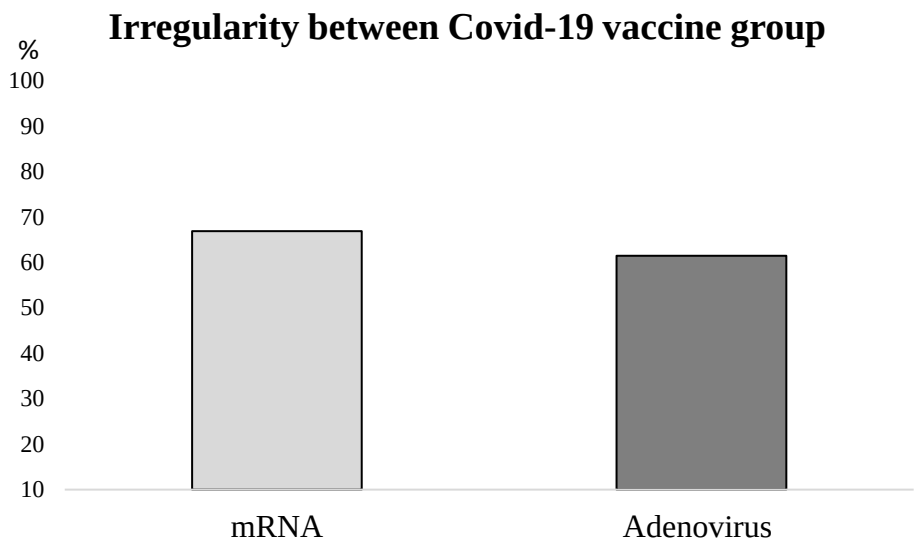

Figure 3: The menstrual irregularity caused by both the mRNA and adenovirus-vectored COVID-19 vaccines were similar in women, $p>0.05$.

The menstrual cycle abnormality induced by the COVID-19 vaccine is a short-term effect. After the first dose, 97% of the participants reported that the effect lasted for less than 3 months, and only 3% reported that the effect lasted for 3 months to one year. Furthermore, after the second dose, 96% of the participants reported that the effect lasted for less than 3 months, and only 3.7% reported that the effect lasted for 3 months to one year.

Association Between the Time of the Vaccine and the Menstruation Period

Most participants with an adverse effect did not report the time of the vaccination (if whether it was during their period or after their period), as they could not recall the timing. However, the abnormality in the menstrual cycle was observed in 38% of the participants who reported that the vaccine was not taken during their periods or in the week before their periods, compared to the 45% of participants who reportedly received the vaccine during their period.

Discussion

Herein, we investigated the type and prevalence of COVID-19 vaccine-related menstrual cycle changes in Saudi women in a case-control study. The number of studies that have linked the COVID-19 vaccine and menstrual cycle abnormalities is relatively low compared to those reporting other vaccine side effects [4]. Our study has added to the existing information on this topic as we confirmed that the COVID-19 vaccine caused irregular menstrual cycles in about 65% of the Saudi women in this study. Importantly, this study aimed to provide an ideal setting to differentiate between the menstrual changes caused by pre-existing medical conditions and those that occur due to the vaccine. Our participants were unlikely to report changes in their menstrual cycle caused by any reason other than the COVID-19 vaccine since the study excluded participants receiving medical interventions, those with pre-existing medical conditions, those in an age range that could affect the menstrual cycle, pregnant women, those with endocrine disorders, polycystic ovary syndrome, hyperprolactinemia, obesity, adrenal and ovarian tumors [8,9]. Additionally, women on insulin, Roctane Electrolyte capsules, hormonal, cardiac, and blood pressure control drugs, and psychotropic medications were excluded [10].

Additionally, this study identified irregularities in the blood flow, period timing, and pain of the menstrual cycle after the COVID-19 vaccine. The menstrual irregularities can either be a single change or combined changes in blood flow, period timing, and pain. Since the participants were between 20–40 years of age, they could seek counsel, recognize abnormal cycle variations, and clearly understand menstrual patterns in terms of blood flow, timing, and pain. Also, the study included only women between 20–40 years of age because women under 20 years of age are adolescents, and abnormal menstrual patterns are expected in adolescents [10], and women over 40 years of age experience menopausal symptoms and are expected to have abnormalities in their menstrual cycle [10].

Furthermore, the menstrual irregularities reported after receiving both the mRNA and adenovirus-vectored COVID-19 vaccines were similar. This might be indicates to a correlation, and the effect is more likely a result of the immune response to the vaccination than to a specific vaccine component. It is well-known that the menstrual cycle can be affected by stimuli related to immune activation, including viral infections. Menstrual cycle changes occur in 25% of the women infected with COVID-19 [11]. In the past, it has been documented that the vaccination against human papillomavirus (HPV) was also linked with menstrual changes [11]. Two concepts explain the biological mechanisms behind the link between menstrual cycle changes and immune stimulation. First, immune stimulation influences the hormones controlling the menstrual cycle [11]. Second, immune cells in the uterus that control the cyclical build-up and breakdown of the endometrium could act as mediators that produce this effect [11]. However, there is still a need to investigate the exact mechanism by which the COVID-19 vaccine affects the menstrual cycle.

Lastly, the menstrual cycle changes induced by the COVID-19 vaccine are short-term, and usually do not last for more than three months. Only 3% of the participants reported that this effect lasted for up to one year. There is COVID-19 vaccine hesitancy among young women due to the misinformation that it could affect their fertility and induce menstrual cycle changes. It has been proved that the COVID-19 vaccination does not affect fertility in women, and clinical trials have reported the same pregnancy rates in vaccinated and unvaccinated groups [8]. Therefore, our study results can help women overcome their fears of vaccination. Also, this important information will particularly help women predict their menstrual cycle after vaccination.

The long period between the first and second dose and the survey time was the key limitation of our study. Also, many participants chose the option "I do not remember" as an answer to some questions, especially the questions regarding the time of receiving the COVID-19 vaccine, where it was hard for participants to remember if it was during, before, or after their period.

Conclusion

The findings reveal that these menstrual irregularities could be either a single change or a combination of changes involving blood flow, period timing, and pain. Additionally, the effects are short-term and occur irrespective of the type of COVID-19 vaccine. A better way to study these effects is to compare the rates of menstrual changes in vaccinated and unvaccinated women; however, this could not be done due to mandatory government regulations. Moreover, this study assessed only the percentage of affected vaccinated women in Saudi Arabia. In the future, COVID-19 vaccine clinical trials should provide information about the effects of the vaccine on the menstrual cycle and possible associated health concerns on females at a global scale. Future studies should aim to monitor participants from the period before the COVID-19 vaccine is received until their menstrual cycle returns to normal. Finally, many participants in our study have reported hair loss and effects on their memory that need to be investigated further.

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Conflict of interest: The authors have no conflict of interest to disclose.

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