Investigation of the relationship between menstrual abnormalities after COVID-19 vaccination and adverse childhood experiences and the mediating effect of premenstrual disorders

Khishigbayar Uranbileg

Department of Medicine

The Graduate School, Yonsei University

Investigation of the relationship between menstrual abnormalities after COVID-19 vaccination and adverse childhood experiences and the mediating effect of premenstrual disorders

Directed by Professor Jeong-Ho Seok

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Khishigbayar Uranbileg

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This certifies that the Master's Thesis of
Khishigbayar Uranbileg is approved.

[Signature]

Thesis Supervisor : Jeong-Ho Seok

[Signature]

Thesis Committee Member#1 : Eunjoo Kim

[Signature]

Thesis Committee Member#2 : Soo Hyun Park

The Graduate School
Yonsei University

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<TABLE OF CONTENTS>

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

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Khishigbayar Uranbileg

Department of Medicine
The Graduate School, Yonsei University

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Women around the world have reported various types of adverse events, ranging from common vaccine side effects to menstrual abnormalities following administration of the COVID-19 vaccines. Although numerous studies have found an association between menstrual abnormalities and COVID-19 vaccination, the predictor factors and underlying mechanisms remain unclear. History of Adverse childhood experiences (ACEs) has been identified a contributing factor for premenstrual disorders (PMDs) in women of reproductive age. PMDs are considered gynecological disorders as they closely related to menstrual cycle; however, their relation to menstrual abnormalities following COVID-19 immunization has not been studied. This cross-sectional study aimed to investigate the relationship between ACEs and PMDs and menstrual abnormalities. 250 individuals enrolled through an online platform and completed 5 questionnaires. SPSS version 27 was used to perform descriptive statistics and logistic regression. Mediation analysis was done by using SAS version 9.4. In this study, three or more ACEs increased the odds of premenstrual dysphoric disorder (PMDD) by 5.7 times ($p<0.01$). A statistically significant difference was shown among PMD groups in women who experienced menstrual abnormalities ($p<0.05$). Women with PMDD were 2.3 more likely to experience menstrual abnormalities after COVID-19 vaccination ($p<0.05$), and PMDD showed a mediating effect on the relationship between menstrual abnormalities after COVID-19 vaccination and ACEs ($p<0.05$). Further studies are necessary to verify the plausible inflammation-

hyperimmune activity mechanism involving the HPA and the HPO axes in this indirect relationship. A follow-up study may explore the menstrual cycle characteristics of women with PMDD to test a hypothesis about whether women with PMDD frequently experience menstrual abnormalities by using a prospective tracking method.

Keywords: Adverse childhood experience (ACE), Premenstrual disorder (PMDs), Protective Vulnerable Factors Battery Test (PROVE-ACE), Premenstrual Screening Tool (PSST), COVID-19 vaccine

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I. INTRODUCTION

1. Menstrual cycle and immune system

Women of reproductive age cyclically experience menstruation, a normal physiological process of shedding the functional layer of the endometrium that occurs as a result of drastically decreased progesterone levels during the late luteal phase of the menstrual cycle[1]. The menstrual cycle is the period from the first day of menstruation to the day before the next menstruation and is governed by ovarian hormones, primarily by progesterone and estrogen, the end products of the hypothalamus-pituitary-ovary (HPO) axis[1]. Gonadotropin-releasing-hormone (GnRH) from the hypothalamus signals the synthesis and secretion of luteinizing hormone (LH) and follicular stimulating hormones (FSH) from the anterior pituitary, depending on menstrual cycle phase. During the follicular phase of the ovary, FSH stimulates estrogen producing-granulosa cells and follicular growth[1]. This phase occurs simultaneously with the proliferative phase of the endometrium in which estrogen induces epithelial proliferation to build up endometrial thickness[1]. This is followed by a significant increase in LH levels in the early luteal phase of the ovary, leading to ovulation[1]. Ovarian production of progesterone increases in response to this LH surge and prepares the endometrium for pregnancy by inhibiting estrogen-induced proliferation and allowing stromal cells to begin decidualization during the secretory phase of the

menstrual cycle[1]. If the released oocyte is not fertilized, ovarian hormones decline, resulting in menstruation[1].

The normal length of menstrual cycle length varies from woman to woman, but the average is from 21 to 35 days[1]. Menstrual bleeding usually lasts 2-6 days and normal menstrual flow is 20-60 ml[1]. The Federation of International Gynecology and Obstetrics (FIGO) classifies and defines abnormal uterine bleeding as follows: irregular menstrual bleeding (IMB) – the inconsistent onset of menstruation, heavy menstrual bleeding (HMB) – increased menstrual flow, intermenstrual bleeding – bleeding episodes that occur between regularly scheduled menstrual cycles, abnormal menstrual cycle frequency – shorter menstrual cycle <21 days or longer menstrual cycle > 35 days, and prolonged menstrual bleeding – menstruation that regularly lasts longer than 7 days[2].

Several components of female reproductive function, including follicular growth[3], ovulation[4], implantation[5], and endometrial repair[6], are influenced by the immune system. Immune cells, including T cells, natural killer (NK) cells, neutrophils, and antigen presenting cells (APCs) are distributed throughout the reproductive tract[7]. Fluctuation in ovarian hormones during the menstrual cycle phases have a significant impact on immune activity in the reproductive tract [7]. Endometrial CD 68^+ macrophages and CD 56^+ NK cells were found to increase during the secretory phase[7]. In addition, endometrial Th-1 cells are higher in the proliferative phase, but their numbers decrease under the influence of progesterone, which modulates $CD4^+$ T helper cell responses from Th-1 to Th-2 responses and promotes the production of anti-inflammatory cytokines (Interleukin 4 [IL-4], IL-5, and IL-10) during the secretory phase[3]. Depending on the type of estrogen receptor gene activation, menstrual cycle phase, estrogen level, and physiological or pathological condition, estrogen can activate both Th-1 response and Th-2 responses[3]. Ovulation and menstruation cause physiological inflammation with high proinflammatory cytokines (Tumor necrosing factor alpha [TNF-α], Interferon gamma [IFN-γ], IL-1β, IL-6, IL-8 IL-12) levels and inflammation marker C-reactive protein (CRP)[3].

2. COVID-19 vaccination and menstrual abnormalities

Developing a vaccine from scratch typically takes decades; however, COVID-19 vaccines were developed in less than a year[8]. Due to spread of the SARS-CoV-2 pandemic, Pfizer's vaccine was granted emergency use approval by the Food and Drug Administration in December 2020, becoming the first COVID-19 vaccine to receive such approval[9]. The major COVID-19 vaccines are classified into four categories based on their mechanism of delivery of the SARS-CoV-2 spike (S) protein, which is responsible for viral entry into target cells, endothelial damage, and proinflammatory cytokine release[3]. Conventional whole virus vaccines (e.g., Sinopharm, Sinovac, and Bharat Biotech) utilize an inactivated form of the entire virion as an antigen in which genetic material has been destroyed so it cannot infect cells and replicate but can still elicit an immune response[3]. Protein subunit vaccines (e.g., Novavax and Covax-19/Spikogen) are recombinant S protein vaccines with adjuvants to enhance the immunogenicity[3]. Viral vector-based vaccines (e.g., AstraZeneca, Johnson & Johnson, and Sputnik V) use adenovirus (the vector) with genetic code for S protein and deliver the genetic information into human cells to produce S protein as an antigen by their own cells[3]. Nucleic acid vaccines (Pfizer-BioNTech and Moderna) use a relatively new technology in which messenger RNA (mRNA), encapsulated in lipid nanoparticles, is inserted into host cells and provides the instructions for the cells to make S protein[3]. While the other technologies have been around for decades and have been used to develop vaccines against various viral agents (whole virus hepatitis A vaccine[10], Ebola vector vaccine[11], and hepatitis B protein subunit vaccine[12]), the SARS-CoV-2 mRNA vaccine is the first nucleic acid vaccine approved for commercial use.

Dendritic cells (DCs) or other APCs take up the vaccine particles from the injection site or the draining lymph nodes and deliver both an antigenic and inflammatory signal to naïve T cells in the nearest lymph nodes[13]. Vaccine-induced type I IFN production by those DCs stimulates the development of proinflammatory Th1 cytokine-producing $CD4^+$ T cells, cytotoxic CD8+ effector T cells, and CD4+ T follicular helper cells, which support the

differentiation of B cells into neutralizing antibody producing-plasma cells[14]. The immune response to vaccination differs between genders mostly due to ovarian hormones[15]. The potent antiviral and immunostimulatory type I IFN-producing plasmacytoid DCs express estrogen receptor α, which is also expressed in macrophages, and have high sensitivity to estroge[15]. It is often observed that women have a higher number of natural killer T cells and CD+4 T cells compared with men[15,16]. Furthermore, women respond to antigenic encounters like vaccines or pathogens with higher antibody production[15]. For example: A half-dose of influenza vaccine administered to women resulted in the same amount of protective antibody production as a full dose administered to men[16]. Discrepancy of transcriptome and microbiome between genders provides the environmental factors that can affect the way sex hormones act during an immune response[15].

The Vaccine Adverse Event Reporting System (VAERS) was established in 1990 to detect potential safety problems with US licensed vaccines[17]. The Yellow Card Surveillance Scheme (YCSS) was designed to collect data on suspected vaccine-related adverse events from recipients of COVID-19 vaccines in the UK[18]. Various COVID-19 vaccine-related adverse events were reported, ranging from common side effects such as fever, headache, malaise, and injection site pain to rare and severe side effects such as vaccine-induced thrombotic thrombocytopenia and anaphylaxis[19]. Women were 1.9 times more likely to report these side effects than men[16]. In addition, in May 2021, fewer than 200 women reported menstrual abnormalities to VAERS following vaccination[17]. One year later the number substantially increased, and 39839 women made such reports to YCSS[18].

This was not the first time that women had reported menstrual abnormalities after vaccination. In the early 1910s, more than half of American nurses, who received typhoid vaccine, experienced temporary disturbances in their menstrual cycles[20]. Those who experienced menstrual disturbance also were more likely to have severe common vaccine side effects[20]. Subsequently, the majority of Japanese hospital workers also reported menstrual abnormalities, including menstrual delay, short menstrual cycle, and light flow

after receiving the first or second dose of the hepatitis B vaccine in the 1980s[21]. Recently, Gong L et al. found a statistical association between human papilloma virus vaccine (type 4 and 9) and IMB using VAERS data from 2006 to 2018[22].

Because the reports of menstrual abnormalities were based on passive reporting systems (VAERS and YCSS), that rely on individual reports, several studies have investigated the link between COVID-19 vaccination and menstrual abnormalities. A retrospective cohort study found that 358 participants who received the first and second doses within the same menstrual cycle experienced a mean menstrual delay of 2.38 days, with 10.6% of them experiencing a delay of eight days or more, which is a medically relevant condition according to FIGO classification[17]. However, it was also found that this alteration in menstrual cycle length was transient, and manifested for the two cycles following vaccination, and resolved without the need for medical intervention[17]. Prior to receiving the vaccine, 79 spontaneously (without the use of hormonal pills) menstruating women were enrolled in the prospective cohort[18]. Their menstrual cycles were then tracked for three consecutive cycles after vaccination[18]. The findings of the research were consistent with the retrospective cohort[18]. In addition to the report of menstrual delay, a large retrospective cohort study of 3972 Norwegian women demonstrated that the relative risk of HMB was 1.90 (95 % CI: 1.69-2.13) after the first vaccine dose and 1.84 (95 % CI 1.66-2.03) after the second dose[23].

Several cross-sectional studies around the world (Saudi Arabia, China, the Middle East and North Africa, Italy, the US, and the UK) also explored the relationship between menstrual cycle abnormalities and the COVID-19 vaccine, and their results have been summarized in a recent meta-analysis[24]. HMB was the most common menstrual abnormality, with a pooled prevalence of 24.2% (95% CI, 12.8-35.6%), followed by menstrual delay at 22.7% (95% CI, 13.5-32.0%), and shorter menstrual cycles at 16.2% (95% CI, 10.7-21.6%)[24]. Additionally, some cross-sectional studies reported worsening of premenstrual symptoms[19,25,26].

Although no causal relation has been reported in the literature regarding menstrual abnormalities and COVID-19, the predictors have been identified as increasing age, smoking, receiving the second dose of the vaccine, pregnancy history, and common vaccine side effects[27]. The use of combined hormonal contraceptives compared to progestogen-only or no contraception was found to protect against menstrual abnormalities. However, after adjusting for multiple factors, there was no significant difference between them[18]. The type of vaccine did not significantly affect the incidence of abnormalities, suggesting that any association is most likely a result of the immune response to vaccination rather than a specific vaccine component[19,24].

3. Adverse childhood experiences and their effects on immune system

Adverse childhood experiences (ACEs) refer to various trauma-causing events that occur before a person reaches the age of eighteen. Felitti et al. (1998) investigated the relationship between childhood abuse (including physical, psychological, and sexual) or household dysfunction (exposure to domestic violence, living with a household member with substance abuse, mental illness, or criminal record) and the leading causes of death in over 8,000 participants[28]. Over 50% of the study participants reported experiencing at least one ACE, with 6.2% of participants reporting four or more ACEs[28]. A dose-dependent response that the higher number of ACEs is associated with the higher probability of developing ischemic heart disease, cancer, and chronic bronchitis as well as their contributing factors, such as smoking, physical inactivity, obesity, and alcohol misuse[28]. Female participants had a higher prevalence of ACEs, with 8.5% of women reporting four or more ACEs compared to only 3.5% of men[28].

A follow-up study that used the original ACE study data found that women who experienced two or more ACEs were found to have a significantly higher risk of being hospitalized due to autoimmune disease (AD)[29]. For women, an increase in the ACE score was correlated with a 20% (p<.001) increase in the odds of hospitalization because of any AD, while this was only 10% for men[29]. Additionally, women had a 50% (p<.05) greater

likelihood of having a specific type of AD (Th2 mediated) compared to men[29]. A cohort study conducted on childhood maltreatment and psychiatric comorbidity in Immune-Mediated Inflammatory Disorders (IMIDs) revealed a significantly higher prevalence of childhood maltreatment in patients with IMIDs compared with healthy controls[30]. Of all ACE types, emotional abuse was found to be linked with higher odds of developing IMIDs (adjusted OR [aOR], 2.37; 95% confidence interval [CI], 1.15-4.89), and this association was observed only in female patients[30]. Chase et al. (2019) found a positive correlation between the total ACE score and the level of pro-inflammatory cytokine in peripheral IL-6 mRNA[31]. Furthermore, a meta-analysis study reported that individuals exposed to ACE had higher baseline peripheral levels of CRP (Fisher's *z*, 0.10; 95% CI, 0.05–0.14), IL-6 (*z*,0.08; 95% CI, 0.03–0.14) and TNF-α (*z*, 0.23; 95% CI, 0.14–0.32) than those not exposed to ACEs[32].

ACEs are proposed to cause chronic inflammation through alterations in the function of the hypothalamic-pituitary-adrenal axis (HPA)[30]. The innate immune system can be engaged in reaction to psychological stress similar to its response to physical stress[33]. Innate immune cells, including neutrophils, DCs, and macrophages, release pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFNs after being activated[34]. These cytokines initiated the release of corticotropin-releasing hormone (CRH) from the hypothalamus. This leads to the secretion of adrenocorticotropic (ACTH) hormone from the anterior pituitary gland[35]. ACTH then acts on the adrenal cortex, causing the release of primarily cortisol, glucocorticoids[35]. Cortisol acts as an anti-inflammatory hormone by downregulating the IL-2 receptor on the surface of T cell, necessary for initiating Th1 cellular immune response and T cell proliferation. Following its action, cortisol triggers negative feedback mechanism by binding intracellular glucocorticoid receptors, restraining the discharge of CRH, and enabling the body to restore homeostasis[35]. Repetitive, early, and severe adverse experiences have been linked to dysregulation of the HPA axis and dysfunction of glucocorticoid receptor[35]. ACEs are thought to cause DNA methylation, which, without changing DNA sequence, silences the activity of both the corticotropin-releasing hormone

receptor 1 (CRHR1) gene and FK506 binding protein 51 (FKBP5), a functional regulator of glucocorticoid receptors[35].

Cortisol is crucial for a normal menstrual cycle, and its levels fluctuate according to menstrual phases, adjusting to ovarian hormones[16]. Abnormal levels of cortisol exert inhibitory effects on LH secretion, estrogen activity, and progesterone synthesis[36]. Ovarian cells and endometrial cells express CRHR1 receptors, and their effect on CRH is responsible for various reproductive functions, including ovulation, follicular maturation, and decidualization[36]. Elevated CRH level suppresses GnRH secretion causing ovarian dysfunction and infertility[36].

4. Premenstrual disorders and immune system

Approximately 80-90% of women experience premenstrual symptoms, including physical, affective-cognitive, and behavioral symptoms such as depressed mood, irritability, anxiety, tension, difficulty concentrating, fatigue, bloating, and breast tenderness, which typically occur a week before menstruation starts[37]. If these premenstrual symptoms become more intense and regular during menstrual cycles, they may indicate the presence of core premenstrual disorders (PMDs), encompassing premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD)[38]. The diagnostic criteria for PMS, as mandated by the American Congress of Obstetricians and Gynecologists, require the presence of at least one affective or physical symptom that interferes with normal activities, occurring five days prior to menstruation, and ceasing within four days after menstruation, retrospectively for three consecutive cycles and prospectively for two consecutive cycles[38]. PMDD was initially introduced in the Diagnostic and Statistical Manual for Mental Disorders (DSM) IV in 1994, providing more specific criteria for what had previously been called late luteal phase dysphoric disorder in DSM III-R[39]. The current edition of the DSM (5th edition) has elevated PMDD’s diagnostic class from "conditions for further study" to

"depressive disorder." To meet the diagnostic criteria for PMDD, at least one affective symptom and five physical symptoms must be present during the last week before menstruation, improve after the onset, and disappear within one week after menstruation prospectively for two consecutive cycles[40].

The estimated prevalence rate of PMS and PMDD worldwide varies from 5.3% to 46.9% and from 1.1% to 14%, respectively. This variation is dependent on the diagnostic tool, sample size, and year of the study[41-43]. The prevalence of PMDs in South Korea also varies, with previous study results indicating rates of 16.9-25.5% for PMS and 2.4-11.7% for PMDD[44-48]. Furthermore, it has been reported that 69.3% of women with PMDs experience premenstrual symptoms before the age of twenty[49]. Accordingly, between 51-86% of adolescent girls reported experiencing premenstrual symptoms starting at about 15 years old of age (IQR: 14-16 years)[50]. The prevalence rate for PMS was found to be between 11.3-21.2%, while for PMDD it was between 3.2-8.3% among adolescent girls[50,51].

Considering early onset of premenstrual symptoms, several studies have explored the link between ACEs and PMDs. A population-based study conducted on Icelandic women showed that those who reported one ACE were about 43% more likely to have PMDs than those without ACE. Meanwhile, the prevalence of PMDs was over two times higher among women with four or more ACEs[52]. Additionally, a major prospective study by Bertone-Johnson et al. indicated that women who experienced emotional or physical abuse during their childhood had 2.6- and 2.1-fold increased odds of experiencing PMS, correspondingly, compared to those who did not have no such experiences[53]. A study of over 3000 Japanese women revealed that those who experienced childhood maltreatment had an increased risk of experiencing PMS with an OR of 1.39 (95% CI 1.15-1.68)[54].

The etiology of PMDs has been extensively researched; however, a clear cause has not yet been identified. Behavioral and psychological factors are thought to influence the type and severity of symptoms, but the precise roles of these elements remain unknown[55]. Recent

research suggests that premenstrual symptoms could be related to inflammation based on crosstalk between sex hormones and immune cells. Bertone-Johnson et al. found that women with PMS had two times greater levels of inflammatory cytokines IL-12 and IFN-γ that were twice as high as those of the control group after adjusting for physical or behavioral risk factors[56]. According to a recent systematic review, three studies demonstrate a significant difference in the inflammatory marker IL-1β levels between PMS group and the control groups[57]. A significant longitudinal study of 2939 women discovered that premenstrual mood and physical symptoms were linked to a higher level of high-sensitive CRP (>3 mg/L) (adjusted OR [aOR] 1.26-1.41)[58]. A randomized, double-blind, placebo-controlled trial of zinc, which is well-known for its anti-inflammatory and antioxidant properties, revealed that after a 12-week intervention with 30-milligram zinc gluconate, the treatment group experienced a significant reduction in psychological (p<0.01) and physical symptoms (p<0.05) of PMS compared to the placebo group[59].

A body of evidence suggests that the reported menstrual abnormalities are associated with COVID-19 vaccination, but a specific predisposing factor has not been explored except from sociodemographic factors. While PMDs are also considered gynecologic disorders as they closely associated with the menstrual cycle, the relationship between PMDs and menstrual abnormalities after COVID-19 vaccination has not yet been studied. Furthermore, given that ACE-exposed women are more likely to develop PMDs, it is possible that menstrual abnormalities can be related to ACEs. This study aimed to determine the mediating effect of PMDs on the relationship between ACEs and menstrual abnormalities following COVID-19 vaccine administration.

II. MATERIAL AND METHODS

1. Study Population

This retrospective cross-sectional study was conducted in April 2023. Women residing in South Korea were recruited through the online survey platform. Only panel users who provided informed consent were asked to complete the screening questionnaire, which assessed their gender, age, COVID-19 vaccination status, pregnancy, and any medical conditions that could affect the menstrual cycle. The inclusion criteria were (1) female; (2) reproductive age ranging from 19 to 39; (3) vaccinated with at least a single dose of COVID-19 vaccines. The exclusion criteria were (1) pregnant; (2) diagnosed with gynecological or hematological disorders (endometriosis, polycystic ovary syndrome (PCOS), adenomyosis, myoma, ovarian cancer, thyroid disease, liver disease, hemophilia, von Willebrand disease). The enrolled participants completed a comprehensive set of five questionnaires. The sample size of the study was determined by using population statistics, considering an 80% population representation with a 5% margin of error and a 95% confidence interval.

Ethical consideration

This study was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (IRB No.3-2023-0041). The privacy and the rights of the participants were fully protected.

2. Assessment of Premenstrual Disorders:

Prospective evaluation is an effective means of accurately diagnosing PMDs. However, keeping a premenstrual symptom diary for over two months can be challenging for participants. According to DSM-V, premenstrual symptoms must be confirmed by prospective daily ratings during at least two symptomatic cycles. Additionally, a provisional diagnosis may also be made before this confirmation[40]. A survey conducted

among primary care physicians and gynecologists in the United States revealed that only 11.5% of physicians performed prospective recording of premenstrual symptoms for diagnosing PMDs. The percentage was lower among Japanese physicians, at 8.4%[60]. In a recent survey of 2,500 patients undergoing PMDD treatment, based on diagnostic methods other than prospective daily charts accounted for more than half of the cases[37]. The Premenstrual Symptoms Screening Tool (PSST) is a self-administered questionnaire developed to address the need for a reliable and rapid screening tool for PMD as defined by DSM-IV criteria[61]. The questionnaire consists of 14 (#1-#14) items that cover affective-cognitive, behavioral, and physiological symptoms and 5 (A-E) items on interference with daily functioning[61]. The interference with daily functioning and distress differentiates PMDD and moderate/severe PMS from no/mild PMS. The distinction between PMDD and moderate/severe PMS, which impede day-to-day functioning, is based on the presence of affective symptoms and the number other symptoms[61]. PSST is widely used measure in global studies, adapted to many languages and modified per requirements. For the Korean version, moderate symptomology was excluded from the rating scale, due to a concern in translation; nonetheless, it maintained good validity and reliability (Cronbach's α 0.82)[45].

3. Assessment of Adverse Childhood Experiences

The **Pro**tective and **V**ulnerable factors batt**e**ry test (PROVE) was developed to thoroughly evaluate depressive symptoms and related protective-vulnerable factors to screen for depression and mental status. PROVE–ACE is among its five subsections and Ju-Yeal Lee et al examined its validity and reliability (Cronbach's α 0.95)[62]. PROVE-ACE is a self-reported scale intended to assess adverse childhood experiences before the age of 18. The long-form questionnaire consists of 52 items, each rated on scale of 0 (never), 1 (rarely), 2 (sometimes) to 3 (often) to assess the frequency of 6 types of ACES, while the short 12-item binary questionnaire examines the presence or absence of 10 ACE types. The study employs both frequency and binary methods for assessing the 6 types of ACEs, including domestic violence, emotional abuse, physical abuse, physical neglect, sexual abuse, and

bullying. The utilization of both questionnaires increases the overall reliability and validity of the study. If the score of the long-form questionnaire indicated possible exposure to the specific adverse experience but could not meet the cutoff score (Table 1), the binary question of the short-form questionnaire was considered because participants who answered yes provided the details of the experiences. This binary evaluating method was also used for parental separation, natural disaster/accident, death of a loved one, and kidnapping. The cumulative scores of ACE scores were classified into four categories (0, 1, 2, and ≥3) for multinomial logistic regression analysis. The PROVE-ACE was chosen over the Adverse Childhood Experience International questionnaire (ACE-IQ) and Childhood Trauma Questionnaire (CTQ) in this study because it is self-reported, detailed, and foremost culturally accustomed to Koreans.

Table 1. Cut-off scores of the PROVE-ACE long-form questionnaire

Type of adverse experience	Number of items	Cut-off score
1. Emotional abuse	5	≥9
2. Neglect	12	≥9
3. Physical abuse	7	≥7
4. Sexual abuse	10	≥3
5. Domestic violence	10	≥9
6. Bullying	8	≥8

4. Covariates:

Sociodemographic data were collected from participants, including age, education level, marital status, pregnancy history, employment type, income status, and behavioral risk factors including smoking and drinking. Furthermore, age of menarche, menstrual duration, menstrual cycle length, menstrual cycle logging into application and oral contraceptive use were also collected. Menstrual cycle length was classified into five categories: <21 days,

22-25 days, 26-30 days, 31-34 days, and 35< or more days. Education levels were categorized as high school, community college, university, graduate school. Marital status options included single, married, divorced, widowed and other. Employment status was classified as full-time worker, part-time worker, contract worker, student, housewife, and other. Income levels were grouped into low, middle, and high bracket. For smoking habits, participants were classified as non-smokers, current smokers, and past smokers if they had not smoked in a year. Alcohol consumption was categorized as non-drinker, light drinker, heavy drinker, or past drinker if they have not consumed alcohol in a year.

5. COVID-19 vaccine-related questionnaire :

The questionnaire was modified from the existing questionnaire after the literature review by the author[19]. It comprises 9 items covering number of COVID-19 vaccine doses, vaccine type, severity of common vaccine side effects and type of menstrual abnormalities after COVID-19 vaccination, changes in premenstrual symptoms, onset of menstrual abnormalities by menstrual cycle measurement, onset of menstrual abnormalities by vaccination dose measurement, duration of menstrual abnormalities, and type of interventions for menstrual abnormalities. The severity of common vaccine side effects was categorized as none, mild, moderate, or severe. Those who reported moderate or severe side effects are considered to have common vaccine side effects. Menstrual abnormalities were classified as IMB, HMB, light menstrual flow, abnormal frequency of menstrual cycles, experience of premenstrual symptoms, or other. Interventions were categorized as hospital visits, home remedies, no interventions, or other.

6. Data analysis

SPSS version 27 (Chicago, IL) was used to perform descriptive statistical methods, including the calculation of mean, standard deviation, and frequency of distribution depending on the type of variable to describe sociodemographic, menstrual, PMDs, ACE, COVID-19 vaccination-related characteristics. A **multiple logistic regression analysis** was performed to determine association between the number of ACEs on PMDs. Age, menarche age, use of hormonal contraceptives, marital status, smoking, alcohol consumption, and employment status were included in the multivariate model. A **Chi-square test** was conducted to identify variables that show a significant difference between individuals who experienced menstrual abnormalities after receiving COVID-19 vaccine and those who did not. **Binary logistic regression** was used to calculate the OR of identified variables (marital status, pregnancy history, PMD type, and common vaccine side effects) upon experiencing menstrual abnormalities respectively in the bivariate model. In the multivariate Model 1, the four variables were mutually adjusted. In the multivariate Model 2, age and status of smoking were adjusted in addition to Model 1 variables.

Mediation analysis was performed by SAS version 9.4 (SAS Institute, Cary, NC, USA) to determine the mediating effect of PMDs in the relationship between ACEs and menstrual abnormalities after COVID-19 vaccination. Age, pregnancy history, smoking, hormonal contraceptives and common vaccine side effects were adjusted in the multivariate model.

III. RESULT

Out of 1379 participants who finished the screening questionnaire, 250 met the inclusion criteria and were included in this study. The program on the platform mandates that all questions be answered, making in 250 participants available for analysis. Table 2 displays the sociodemographic and menstrual characteristics of the participants. The average age of the subjects was 29.05 years, with standard deviation of 5.1 years. Over the half of the participants (58.8%) were graduated from university. Moreover, the majority of women were employed (64.2%), single (74.0%), and had a middle income (77.2%). 78.4% of the participants responded to be without pregnancy history. While around 15% of the women were non-drinkers, a significantly larger proportion (82.8%) were non-smokers.

The average age of menarche was 12.6±1.4 years old, and the mean duration of menstruation was 5.89±2.0 days. Of the participants, 94.8% reported to have normal menstrual cycle length, and 78% recorded their menstrual cycle information using their preferred applications.

Participants were categorized into groups their based on PSST score, including a no/mild PMS group (60.8%), moderate/severe PMS group (21.2%), and PMDD group (18%).

Table 2. Sociodemographic and menstrual characteristics *N*, number (%) or mean ± standard deviation

All	***N*=250**
Age	29.0±5.1
Education level	
High school	23(9.2)
Community college	59(23.6)
University	147(58.8)
Graduate school	21(8.4)
Income	
Low	12(4.8)
Middle	193(77.2)
High	45(15.1)
Employment status	
Employed	162(64.2)
Unemployed	30(10.5)
Others	58(19.7)
Marital status	
Single	185(74.0)
Married	59(23.6)
Divorced	6(2.4)
Pregnancy history	
Yes	54(21.6)
No	196(78.4)
Alcohol consumption	
None	35(14.0)
Low	149(59.6)
High	66(26.4)
Smoking	
Never	207(82.8)
Ever	17(6.8)
Current	26(10.4)
Menarche age	12.6±1.4
Menstrual duration	5.89±2.0
Menstrual cycle length	
>21	9(3.6)
22-25	62(24.8)
26-29	155(62.0)
30-34	20(8.0)
35<	4(1.6)
Menstrual cycle logging	
Yes	196(78.4)
No	54(21.6)

Those who reported experiencing at least one ACE compromised 78.8% of the participants; they most commonly experienced domestic violence (49.2%), followed by sexual abuse (30.0%), bullying (26.5%), emotional abuse (22.0%), parental separation (20.8%), neglect (17.6%), physical abuse (16.8%), death of a loved one (12.4%), and accident (8.8%). Kidnapping was the least reported type of ACE, at 3.2%. The frequency of participants who had three or more types of ACEs was 33.2%.

The majority of participants (97.6 %) were fully vaccinated two or more doses. More than half of the participants (56.8%) were vaccinated with Pfizer for all doses. Of the participants, 22.8% received different types of vaccines and 20.4% were vaccinated with Moderna for all doses. Common vaccine side effects were reported in 26.4% of the participants. The women who experienced menstrual abnormalities constitutes 36.4% of the participants, of them 47.2% had IMB, 20.8% experienced HMB. The other menstrual abnormalities included menstrual delay (14.4%), light menstrual flow (9.8%), multiple symptoms (4.5%), and worsening of premenstrual symptoms (3.3%). 47% of the women noticed menstrual abnormalities following the first dose. 12.5% of the women experienced menstrual abnormalities every time they receive COVID-19 vaccination. 67% of the women spotted menstrual abnormalities in the following menstrual cycle after vaccination. The menstrual abnormalities had been observed for three or more menstrual cycles in the 44% of women. The majority of the women who experienced menstrual abnormalities did not seek medical intervention and only 12.5% of them visited hospital mostly due to IMB and menstrual delay.

The number of Adverse childhood experiences are associated with Premenstrual disorders

Table.3 presents the bivariate model examining the association between PMDs and ACEs, revealing that experiencing three or more ACEs increased the likelihood of moderate/severe PMS by 3.1 times (p=0.019) and PMDD by 5.7 times (p=0.003). The multivariate model showed that three or more ACEs significantly increased of the odds of moderate/severe PMS and PMDD (OR 3.8, p=0.012; OR 8.5, p=0.001). An increase in age of menarche was associated with 1.2-fold increase in the odds of experiencing moderate/severe PMS. In addition, married participants were 73% less likely to experience PMDD compared to those who were single.

Table 3. Bivariate model of the association between adverse childhood experiences (ACEs) and moderate/severe premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) compared to no/mild PMS, number (%)

	Moderate/Severe PMS				**PMDD**			
	***N* (%)**	**OR**	**95% CI**	***p***	***N* (%)**	**OR**	**95% CI**	***p***
Number of ACEs								
0	7(13.2)	Ref			4(8.9)	Ref		
1	14(22.6)	1.90	0.72-5.19	0.205	8(15.6)	1.90	0.53-6.81	0.319
2	11(20.8)	2.53	0.87-7.37	0.087	11(24.4)	4.44	1.28-15.41	0.019*
≥3	21(39.6)	3.15	1.20-8.21	0.019*	22(48.9)	5.77	1.82-18.23	0.003**

OR, odds ratio; *p*, probability; CI, Confidence interval; Ref, reference
* p<0.05
**p<0.01

Table 4. Multivariate model of the association between adverse childhood experiences (ACEs) and moderate/severe premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) compared to no/mild PMS

	Moderate/severe PMS			PMDD		
	OR	95% CI	*p*	OR	95% CI	*P*
Number of ACEs						
0	Ref					
1	2.90	0.99-8.50	0.052	2.62	0.68-10.01	0.158
2	2.73	0.88-8.42	0.081	5.29	1.43-19.56	0.012**
≥3	3.85	1.35-10.99	0.012**	8.57	2.47-29.72	0.001***
Age	0.98	0.90-1.06	0.658	0.97	0.88-1.06	0.059

Age at menarche	1.29	1.02-1.62	0.032*	1.16	0.89-1.50	0.251
Hormonal contraceptive						
No	Ref					
Yes	0.59	0.26-1.34	0.214	0.79	0.34-1.84	0.588
Marital status						
Single	Ref					
Married	0.46	0.17-1.24	0.127	0.27	0.81-0.90	0.033*
Divorced	0.82	0.07-9.50	0.875	0.91	0.07-11.04	0.944
Employment						
Unemployed	Ref					
Employed	0.93	0.30-2.89	0.907	0.90	0.30-2.75	0.866
Others	2.39	0.69-8.17	0.165	1.51	0.42-5.36	0.517
Smoking						
No	Ref					
Yes	2.26	0.92-5.52	0.072	0.33	0.08-1.28	0.334
Alcohol consumption						
None	Ref					
Low	0.63	0.24-1.68	0.366	0.51	0.19-1.34	0.178
High	0.42	0.13-1.37	0.154	0.52	0.16-1.66	0.272

OR, odds ratio; *p*, probability; CI, Confidence interval; Ref, reference
* p<0.05
**p<0.01
***p<0.001

PMDD is associated with menstrual abnormalities after COVID-19 vaccination

No statistically significant differences were observed between participants with or without menstrual abnormalities in terms of age, education level, income, employment status, alcohol consumption, smoking, menarche age, menstrual duration, menstrual cycle length and ACE score among after receiving COVID-19 vaccines. However, there was a significant difference in marital status (*p*=0.01), pregnancy history (*p*=0.01), PMDD (*p*=0.01), and common vaccine side effects (*p*=0.02), as shown in Table 5.

Table 5. Characteristics of participants with and without menstrual abnormalities after COVID-19 vaccination

Characteristics	No menstrual abnormalities (n=159; 63.6%)	Menstrual abnormalities (n=91; 36.4%)	χ^2	***P***
Age (years)				
19-24	32 (20.1)	13 (14.2)		
25-29	46 (28.9)	34 (37.3)	5.50	0.66
30-34	44 (27.6)	31 (34.0)		
35-39	37 (23.2)	13 (14.2)		
Education level				
High school	14 (8.8)	9 (9.9)		

Community college	39 (24.5)	20 (22.0)	0.53	0.88
University	92 (57.9)	55 (60.4)		
Graduate school	14 (8.8)	7 (7.7)		
Income				
Low	10 (6.3)	2 (2.2)		
Middle	117 (73.6)	76 (83.5)	3.85	0.77
High	32 (20.1)	13 (14.3)		
Employment status				
Employed	100 (62.9)	63 (69.2)		
Unemployed	19 (11.9)	10 (11.0)	1.12	0.56
Others	40 (25.2)	18 (19.8)		
Marital status				
Single	109 (68.6)	76 (83.5)		
Married	45 (28.3)	14 (15.4)	6.85	0.01**
Divorced	5 (3.1)	1 (1.1)		
Pregnancy history				
Yes	42 (26.4)	12 (13.2)	5.98	0.01*
No	117 (73.6)	79 (86.8)		
Alcohol consumption				
None	29 (18.2)	10 (11.0)		
Low	95 (59.7)	54 (59.3)	3.32	0.07
High	35 (22)	27 (29.7)		
Smoking				
Never	129 (81.1)	78 (85.7)		
Ever	18 (11.3)	8 (8.8)	0.86	0.37
Current	12 (7.5)	5 (5.5)		
Menarche age				
Normal	129 (81.1)	82 (90.1)	3.54	0.07
Abnormal (≥10;15≤ years)	30 (18.9)	9 (9.9)		
Menstrual duration				
Normal	108 (67.9)	54 (60.0)	1.58	0.21
Abnormal (7≤ days)	51 (32.1)	36 (40)		
Menstrual cycle length				
Normal	150 (94.3)	86 (94.5)	0.17	0.77
Abnormal (≥21;35≤ days)	9 (5.7)	5 (5.5)		
ACE score				
0	31 (19.5)	22 (24.2)		
1	41 (25.8)	25 (27.5)	1.60	0.22
2	30 (18.9)	18 (19.8)		
≥3	57 (35.8)	26 (28.6)		
PMDs				
No/mild PMS	103 (64.8)	49 (53.8)		
Moderate/Severe PMS	36 (22.6)	17 (18.7)	8.69	0.01*
PMD	20 (12.6)	25 (27.5)		
Common vaccine side effects				
Yes	34 (21.4)	32 (35.2)	5.65	0.02*
No	125 (78.6)	59 (64.8)		

χ^2 , chi-square; *p*, probability
* p<0.05
**p<0.01

The bivariate model showed that married women were 56% less likely to have menstrual abnormalities after COVID-19 vaccination compared to single women (p=0.018). Women who had conceived at least once were 1.3 times more likely to experience menstrual abnormalities than those who had never conceived (p=0.016). Menstrual abnormalities were 2.6 times more common in the PMDD group than in the no/mild PMS group after COVID-19 immunization (p=0.005). Those who experienced common vaccine side effects were 1.9 times more likely to experience menstrual abnormalities than those who did not (p=0.018). In the multivariate model 1, only PMDD was found to be 2-fold increase the odds of menstrual abnormalities (p=0.041). In the multivariate model 2, compared with 19-24 age group, women in 30-34 age group were 2.8-fold more likely to experience menstrual abnormalities. PMDD remained significantly increase (OR, 2.3; p= 0.024) the likelihood of showing menstrual abnormalities (Table 6.)

Table 6. The odds of experiencing menstrual abnormalities after COVID-19 vaccination

	Bivariate		**Multivariate**			
			Model 1		Model 2	
	OR	*P*	OR	*p*	OR	*p*
Marital status						
Single	Ref		Ref		Ref	
Married	0.44	0.018*	0.62	0.309	0.59	0.290
Divorced	0.28	0.259	0.39	0.436	0.39	0.437
Pregnancy history						
Yes	Ref		Ref		Ref	
No	2.32	0.016*	1.44	0.461	1.46	0.453
PMDs						
No/mild PMS	Ref		Ref		Ref	
Moderate/severe PMS	0.99	0.983	0.95	0.883	1.0	0.922
PMDD	2.62	0.005**	2.09	0.041*	2.3	0.024*
Common vaccine side effects						
No	Ref		Ref		Ref	
Yes	1.99	0.018*	1.75	0.067	1.8	0.059
Smoking						
No					Ref	
Yes					0.78	0.543
Age						
19-24					Ref	
25-29					2.0	0.082
30-34					2.8	0.019*
35-39					1.3	0.532

OR, odds ratio; *p*, probability; Ref, reference
* p<0.05
**p<0.01

PMDD is the mediator in the relationship between ACEs and menstrual abnormalities after COVID-19 vaccination

Table 7. displays the mediation effect of moderate/severe PMS compared to no/mild PMS, and there was no statistically significant indirect effect on the relationship between ACEs and menstrual abnormalities after COVID-19 vaccination both bivariate (*p*=0.848) and multivariate models (*p*=0.897).

Table 7. The mediating effect of moderate/severe premenstrual syndrome (PMS) on the relationship between Adverse childhood experiences (ACEs) and menstrual abnormalities compared to no/mild PMS

	Moderate/severe PMS			
	Bivariate		**Multivariate**	
	β (95% CI)	*p*	β (95% CI)	*p*
1. ACE score → moderate/severe PMS	0.146(−0.035 to 0.326)	0.1134	0.150(−0.045 to 0.345)	0.1314
2. moderate/severe PMS → Menstrual abnormalities	0.015(−0.136 to 0.166)	0.8477	0.010(−0.145 to 0.166)	0.8969
3. Direct (ACE score→ Menstrual abnormalities)	−0.164(−0.321 to −0.008)	0.0391*	−0.171(−0.335 to −0.006)	0.0416*
4. Indirect effect	0.0022(−0.020 to 0.024)	0.8489	0.0015(−0.022 to 0.025)	0.8972

β, comparable coefficient; CI, Confidence interval; *p*, probability;
* p<0.05

Compared to women with no/mild PMS, PMDD showed a statistically significant indirect effect on the relationship between ACEs and menstrual abnormalities both bivariate (*p*=0.010) and multivariate models(*p*=0.024). The total effect was lower than the indirect effect and not statistically significant. (Table 8; Figure 1).

Table 8. The mediating effect of premenstrual dysphoric disorder (PMDD) on the relationship between Adverse childhood experiences (ACEs) and menstrual abnormalities compared to no/mild PMS

	PMDD			
	Bivariate		**Multivariate**	
	β (95% CI)	*p*	β (95% CI)	*p*
1. ACE score → PMDD(a)	0.365(0.194 to 0.535)	<.0001***	0.439(0.245 to 0.634)	<.0001***
2. PMDD → Menstrual abnormalities (b)	0.249(0.098 to 0.399)	0.0012**	0.212(0.052 to 0.371)	0.0092**
3. Direct (ACE score → Menstrual abnormalities) (c')	−0.161(−0.314 to −0.008)	0.0391*	−0.168(−0.330 to −0.006)	0.0416*
4. Indirect effect(a x b)	0.090(0.021 to 0.160)	0.0104*	0.093(0.012 to 0.174)	0.0248*
5. Total effect (c=axb+c')	-0.072(-0.221 to 0.081)	0.3592	-0.062(-0.218 to 0.094)	0.436

β, comparable coefficient; CI, Confidence interval; *p*, probability;
* p<0.05
**p<0.01
***p<0.001

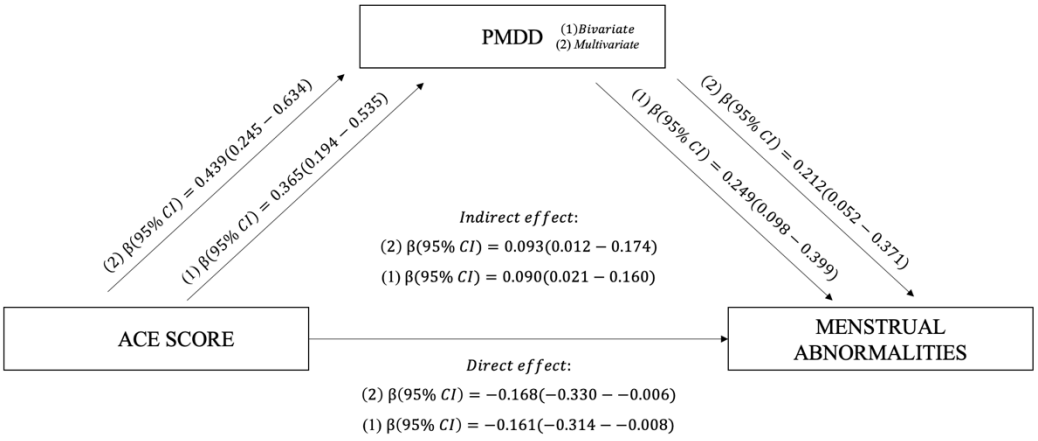

Figure 1. The mediating effect of PMDD on the relationship between ACE score and menstrual abnormalities after COVID-19 vaccination compared to no/mild PMS

Compared to both no/mild PMS and moderate/severe PMS, PMDD continued to show a statistically significant indirect effect on the relationship on the relationship between ACEs and menstrual abnormalities both bivariate (p=0.011) and multivariate models (p=0.024) (Table 9, Figure 2).

Table 9. The mediating effect of PMDD on the relationship between ACEs and menstrual abnormalities compared to both no/mild PMS and moderate/severe PMS

	PMDD			
	Bivariate		**Multivariate**	
	β (95% CI)	*P*	β (95% CI)	*p*
1. ACE score → PMDD(a)	0.328(0.166 to 0.490)	<.0001***	0.407(0.218 to 0.595)	<.0001***
2. PMDD → Menstrual abnormalities (b)	0.245(0.100 to 0.389)	0.0009**	0.209(0.056 to 0.363)	0.0076**
3. Direct (ACE score → Menstrual abnormalities) (c')	−0.160(−0.312 to −0.008)	0.0396*	−0.167(−0.328 to −0.006)	0.0416*
4. Indirect effect(a x b)	0.0803(0.018 to 0.142)	0.0110*	0.0850(0.011 to 0.159)	0.0240*
5. Total effect (c=axb+c')	-0.079(-0.228 to 0.069)	0.293	-0.069(-0.223 to 0.085)	0.379

β, comparable coefficient; CI, Confidence interval; *p*, probability;
* p<0.05
**p<0.01
***p<0.001

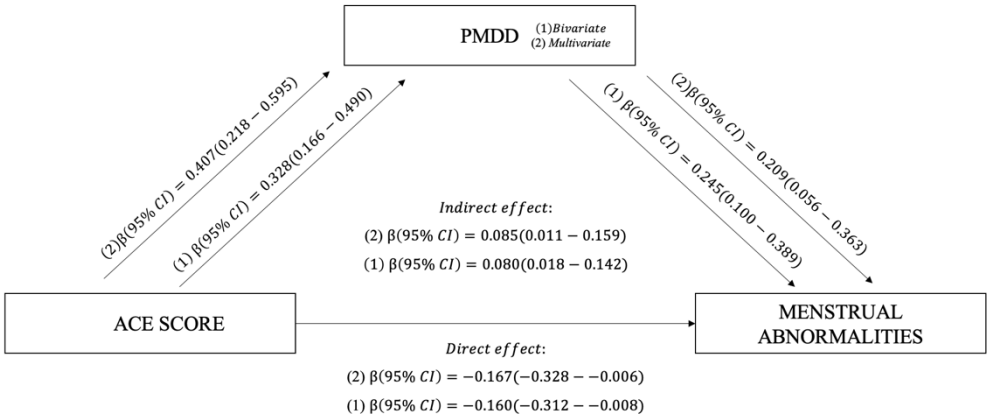

Figure 2. The mediating effect of PMDD on the relationship between ACE score and menstrual abnormalities after COVID-19 vaccination compared to both no/mild PMS and moderate/severe PMS

IV. DISCUSSION

To the best of the author's knowledge, this study is the first to investigate the relationship between ACEs and menstrual abnormalities after COVID-19 vaccination, and the mediating effect of PMDs. The current prevalence rate of PMS is similar to previous studies, but a higher rate of PMDD was discovered when compared to both Korean and international studies[41-48]. It is possible that the rise in PMDD among Korean women is linked to the substantial effect of the COVID-19 pandemic has had on mental health in recent years. The global incidence of major depressive disorders and anxiety disorders has reportedly increased by 27.6% and 25.6%, respectively[63]. A previous Korean study[64] that included both genders reported a lower prevalence of ACEs compared to this study, which may be due to females experiencing a wider range of ACEs than males[65]. However, a similar ACE prevalence was reported in a population-based study of Icelandic females[52], providing further validation of this study's result.

In line with previous research on the relationship between PMDs and ACEs, a dose-dependent response was observed – women who had experienced more ACEs were more likely to suffer from severe premenstrual symptoms than those without ACEs[52,54]. However, the OR was notably higher than that of other studies, which could have been influenced by the method of ACE assessment and an increased awareness of ACEs among women. The PROVE-ACE included ten types of ACEs with detailed questions about the experiences. In contrast, another Asian study[54] utilized five types of ACEs with dichotomous questions. The concept of childhood maltreatment among Koreans has changed over the years. Culturally, harsh treatment of children was not considered a violation of their rights, and it was often used for disciplinary purposes. In recent years, reports of childhood maltreatment in Korean media have raised awareness regarding different forms of ACEs.

This study found that more than one-third of the participants experienced menstrual abnormalities after receiving the COVID-19 vaccines, which was consistent with the result of a cohort study[23], but it was relatively low compared with other cross-sectional

studies[19,26,66]. The most prevalent type of menstrual abnormality was IMB, followed by HMB and menstrual delay, which was different from the result that HMB was the most occurring type in the recent meta-analysis[24]. The cross-sectional study in the UK, which included approximately 5000 women, found that smoking and not using estradiol-containing contraceptives were risk factors for experiencing menstrual abnormalities after COVID-19 vaccination[70]; however, this study did not find a significant difference in menstrual abnormalities between participants who used hormonal contraceptives or had a history of smoking and those who did not. The comparatively lower usage of hormonal contraceptives and cigarettes among Korean women, in contrast to British women, may have influenced the discrepant outcome[71,72]. Furthermore, this study revealed significant differences in marital status, common vaccine side effects, and pregnancy history among women who experienced menstrual abnormalities and those who were not.

The previous study[19] reported that women who experienced menstrual abnormalities were more likely to report common vaccine side effects such as high fever, headache, and malaise, which possibly indicate a robust systematic immune activation. The increase in body temperatures is associated with enhanced production of Type I IFNs and pro-inflammatory cytokines, as well as the activation of APCs production in the bone marrow and their subsequent migration. Moreover, a previous large study conducted in the US demonstrated that prior pregnancy represents a risk for heavy bleeding after receiving the COVID-19 vaccines[68]. Among PMD groups, there was a significant difference in menstrual abnormalities. PMDD exhibited a strong association with menstrual abnormalities and a mediating effect on the relationship between ACEs and menstrual abnormalities after COVID-19 vaccination compared to other PMD groups. Mersel et al. found that marital status was associated with menstrual cycle disturbance following COVID-19 vaccination[27]. The study's current finding showed that married women are less likely to develop PMDD at a rate of only 8.4% and experience menstrual abnormalities at a rate of 23.7% after COVID-19 vaccination; although, most of these women reporting at least one ACE, with a third of them reporting three or more ACEs. Adults who have ACEs history tend to develop

insecure attachment styles[74], which potentially related to different types of anxiety regardless of whether they have avoidant, ambivalent, and disorganized types[73]. On the other hand, married women could have formed a secure attachment with their partners, making them feel safe and protected, and thus, less anxious and vigilant when confronted with stressors.

Compared to the control group, women diagnosed with PMDD reported significantly higher levels of stress occurring in daily life and high arousal negative affect towards stressors specifically during the late luteal phase[75]. Likewise, women with PMDD exhibited acoustic startle response comparable to healthy controls during the follicular phase, but during the late luteal phase, their startle response increased, indicating that women with PMDD have elevated stress reactivity to environmental cues before menstruation. Heightened response to environmental stimuli was also shown among women who carry one or more short alleles of the 5-HTTLPR polymorphism[77]. This gene polymorphism is associated with reduced transcriptional efficiency of the serotonin transporter and is found in women with PMDD who have neuroticism-related personality traits, such as somatic trait anxiety, stress susceptibility, and mistrust[78]. Additionally, recent research suggests that women with PMDD have alteration in sensitivity to normal hormonal fluctuations[76] and naturally occurring inflammation during the late luteal phase. Taken together, dysfunction in subcortical regions, primarily the amygdala, hippocampus, and striatum that may result from ACEs, can activate hypervigilance to threats, leading to abnormal perception of both internal (hormonal fluctuation or inflammation) or external stimuli (angry faces and acoustic startle). This can be linked to potentiation of negative valence systems that are related to PMDD symptoms.

The type of menstrual abnormality can be influenced by the timing of vaccine administration[67], and it might associated with the immune system activity. A large-scale study showed that doses given in the follicular phase were associated with menstrual delay while doses given in the luteal phase resulted in a shorter menstrual cycle[67]. TNF-α is one

of the earliest pro-inflammatory cytokines to be produced when encountered with SARS-CoV2 virus S protein, whether it is from vaccination or infection, and stimulates inflammatory response[18]. The activation of the HPA axis, triggered by pro-inflammatory cytokines, possibly causes interference with the HPO axis that controls the menstrual cycle[18]. The HPO axis dysfunction may involve prolongation of follicular recruitment and suppression of endometrial functional layer growth and then resulting in menstrual delay or IMB[67]. Lee et al. reported that 70.5% of transgender men, who suppress menstruation with long-acting reversible contraception, and 66% of postmenopausal women, who were over 55 years old and have not menstruated for over a year, experienced breakthrough bleeding after COVID-19 vaccine administration[68]. HMB, intermenstrual bleeding, and breakthrough bleeding can be linked to the effects of pro-inflammatory cytokines on the coagulative pathway. Pro-inflammatory cytokines activate tissue factor expression, which binds and stimulates coagulating factor VII to make tissue factor-VIIa complexes and then activate clotting factors X and IX, on endothelial cells or macrophages[69]. Therefore, hemorrhagic problems like uterine bleeding result from the simultaneous depletion of coagulation factors and platelets.

The menstrual cycle is an essential health indicator in women and can be influenced by various factors. Short-term menstrual cycle interruption can result from vaccination, infection, strenuous physical activity or dietary restrictions, while prolonged menstrual cycle disruption is often associated with endocrinopathies and gynecological disorders[19]. A study found that participants with endometriosis, PCOS, and adenomyosis were prone to report HMB following COVID-19 immunization than those without reproductive disorders[64]. Women who had a preexisting endometriosis reported experiencing earlier-than-usual menstruation, while those with PCOS were more likely to experience lighter flow after administration of the COVID-19 vaccines[18]. It is worth noting that intermenstrual bleeding, light flow, and HMB are symptoms of endometriosis, PCOS, and adenomyosis respectively. Therefore, previous studies may have had women report their usual menstrual cycle experiences[18,68]. Likely, women with PMDD possibly reported IMB and menstrual

delay following COVID-19 vaccination, as they commonly experience such abnormalities. Muhaidat et al. reported that menstrual abnormalities resolved within a month in 86.8% of women who experienced them[19]. Additionally, 93.6% of participants in the UK study experienced menstrual abnormalities for less than three months[65]. However, nearly half of the participants in this study reported experiencing menstrual abnormalities for over four months, indicating that menstrual abnormalities are common symptoms among women with PMDD. It should be considered that menstrual abnormalities became more evident or exacerbated following local or systemic inflammatory activity in response to vaccination.

Children who were maltreated not only had greater levels of CRP and other pro-inflammatory cytokines, but they also displayed a robust inflammatory response, with increased cytokine production in response to stress[33]; thus, it can be argued that exposure to various ACEs could activate local immune cells within the endometrium or systemic immune cells, predisposing them to be hypersensitive to stress. The heightened inflammatory reactivity is an adaptive process that readies the body to respond efficiently to both physical and psychological stress and promote survival[33]. When foreign antigens from vaccines trigger a response in women with PMDD, who have history of ACEs, they exhibit heightened immune reactivity characterized by activation of the HPA axis, followed by disruption of the HPO axis. Consequently, they showed increased vulnerability to IMB after receiving the COVID-19 vaccines.

While carefully designed, this study does have limitations. Although this study found indirect relationship between ACEs and menstrual abnormalities, which is mediated by PMDD, the causal relationship cannot be defined to due to the cross-sectional study design. Also, it failed to obtain the data on the timing of vaccination during menstrual cycle due to the limitation of the retrospective study design. The questionnaires were self-administered and retrospective which could lead to recall bias. Due to the comparatively low number of instances reported to authorities compared to today, the retrospective technique may, nonetheless, be appropriate for obtaining information on ACEs. To minimize the recall bias

of the PSST or menstrual abnormalities after COVID-19, inquiry of menstrual cycle tracking applications use was included, and the majority of women responded to questionnaire based on their menstrual cycle information recorded in the menstrual/health applications. The sample size is relatively small compared to similar studies, but population difference should be considered. Nevertheless, the minimum required number for performing inferential statistics has been met.

The present study provides new insights into the effects of ACEs on women's reproductive health, with an emphasis on inflammation and immune reactivity involving the HPA and the HPO axes. Previous studies[52,54], which found a relationship between ACEs and PMDs, supported hypotheses either serotonin pathway or the HPA axis. Considering that ACEs have impact on various biological pathways involving stress, immunity, and ovarian hormones. Furthermore, several physiological pathways are identified for the pathogenesis of PMDs. It is challenging to decide on which of the systems is more relevant to the relationship. Future studies should concentrate on measuring the physiological aspects of the HPA axis, HPO axis, and the immune system in women with PMDs and menstrual abnormalities. This will allow for evidence-based knowledge to be provided, which in turn can be used to develop targeted treatments for PMDs. Additionally, a follow-up study is needed to assess the menstrual cycle characteristics of women with PMDD through prospective tracking. This is to test the hypothesis of whether menstrual abnormalities were a temporary response following the COVID-19 vaccines or if they are commonly experienced by women with PMDD when various inflammation triggers, such as chronic inflammatory diseases, and psychological stress are present.

V. CONCLUSION

This study examined the mediating effect of PMDs on the relationship between ACEs and menstrual abnormalities after COVID-19 vaccination among Korean women of reproductive age. The current study found that women who have experienced ACEs are more likely suffer from PMDD and experience menstrual abnormalities after COVID-19 vaccination. Among mechanisms involved in this indirect relationship, inflammation and stress sensitivity followed by hyperreactive immunity is plausible proposal with evidence from previous studies. However, there is a limited number of studies that demonstrate a relationship between them. Unlike transient menstrual abnormalities, which have been shown to be vaccination responses, long-term menstrual abnormalities are considered to be distinctive symptoms of gynecological disorders. As one of the gynecologic disorders related to the menstrual cycle, this study suggests that women with PMDD frequently demonstrate menstrual abnormalities in response to different stressors. Further studies are needed to explore this hypothesis.

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APPENDICES

스크리닝 설문조사

SQ1. 귀하의 성별은 어떻게 되십니까?

1) 남자 2) 여자

SQ2. 귀하의 연령은 어떻게 되십니까? 출생연도를 입력하여 주십시오.

[출생연도로 응답]

출생연도 ( )년 = 만 _____세

SQ2-1. 귀하의 생년월일을 입력하여 주십시오.

( )월 ( )일

SQ3. 귀하는 현재 월경 중이십니까?

1) 예 2) 아니오

SQ3-1. 지난 4 개월 동안 최소 3 번 이상 월경하였습니까?

1) 예 2) 아니오

SQ4. 귀하는 현재 임신 중입니까?

1) 예 2) 아니오

SQ5. 코로나 19 예방 접종을 하였습니까?

1) 예 2) 아니오

SQ6. 아래 있는 질환으로 진단받은 적이 있습니까?

1) 자궁내막증 2) 다낭성 난소 증후군

3) 자궁선근증 4) 자궁근종

5) 난소암 6) 갑상선 질환

7) 간 질환 8) 출혈장애 (혈우병, von Willebrand 병)

9) 해당 사항 없음

SQ7. 귀하께서는 본 연구 참여에 동의하십니까?

1) 동의 2) 동의하지 않음

SQ8. 민감정보 수집에 대하여 동의를 거부할 수 있으며, 동의를 거부하실 경우 조사 참여에 제약이 있습니다.

1) 동의 2) 동의하지 않음

1. <기본 인적 사항 조사>

1. 교육기간: 총 교육 기간 _____년

a) 고졸 (중퇴포함)

b) 전문대: ( ) 졸업, ( )학년 재학, ( )학년 휴학/중퇴

c) 4 년제대학: ( ) 졸업, ( )학년 재학, ( )학년 휴학/중퇴

d) 석사과정 :( ) 졸업, ( ) 재학, ( ) 휴학/중퇴

e) 박사과정 : ( ) 졸업, ( ) 재학, ( ) 휴학/중퇴

f) 기타 ( )

2. 결혼 상태: a. 미혼 b. 기혼 c. 이혼 d. 사별 e. 기타 ( )

3. 임신한 적이 있습니까? a.예 b.아니오

4. 임신한 적이 있는 경우 몇 번 입니까? _____

5. 자녀가 있습니까? a.예 b.아니오

6. 자녀가 있는 경우 몇 명 입니까? _____

7. 직업: a.정규직 b. 계약직 및 임시직 c. 학생 d. 주부
e. 무직 f. 기타 ( )

8. 당신을 포함한 전가구원의 경제 구준: a. 상 b. 중 c. 하 c

9. 흡연 여부: a.평생 비흡연자 b. 현재 흡연 중
c. 과거 흡연자 (금연기간 12 개월 미만 시)

10. 음주 여부: a.전혀 안 마신다 b. 약간 마신다 c. 즐겨 마신다
d. 과거에 마시다 끊었다 (금주기간 12 개월 미만 시)

<월경에 대해 조사>

11.1. 초경 시작 연령:_____세 (만으로)

11.2. 월경의 규칙성: a. 규칙적이다 b. 불규칙적이다

11.3. 월경 주기 평균: a. 21 일 이하 b. 21 – 24 일 c. 26 – 30 일
d. 31 – 34 일 e. 35 일 이상

11.4. 월경 기간: _____일

11.5. 생리 달력 앱을 사용합니까? a.예 b.아니오

8.5.1 생리 달력 앱을 사용한 경우 지난 3 번의 월경을 입력하였습니까?
a.예 b.아니오

12. 피임약 복용 여부:

a.현재 복용 하고 있다

b. 18 개월 전에 복용하다 끊었다

c. 지난 18 개월 동안 잠깐 복용하다 끊었다

d. 복용한 적이 없다

12.1 현재 피임약 복용 한 경우 언제부터 복용하고 있습니까? _____

12.2 처방 받은 피임약을 복용합니까? a.예 b.아니오

<복용 약 조사>

1. 지난 18 개월 안에 복용한 약이 있습니까? a.예 b.아니오

2.1 있는 경우 어떤 약을 복용하였습니까? _____

2. <월경 전기 증상 평가 설문지>

월경 전에 나타나서 월경 시작 수 일 내에 사라지는 월경전기 증상들 입니다. 각 증상들의 유무와 정도를 표시하여 주십시오.

증상	전혀 없다	약하다	심하다
1.화가 나거나 짜증이 난다			
2.불안하거나 긴장이 된다			
3.감정기복이 있다 (쉽게 슬퍼지거나/ 눈물이 나거나/ 또는 쉽게 민감해진다)			
4.우울해지고 쉽게 절망감이 느껴진다			
5.일에 흥미가 떨어진다			
6.집안일에 흥미가 떨어진다			
7.사회활동에 흥미가 떨어진다			
8.주의집중이 안된다			
9.피로하고 기운이 없다			
10.과식을 하거나 식탐이 많아진다			
11.불면증 생긴다			
12.잠을 더 많이 잔다			
13.무언가에 압도당하거나 자신을 조절할 수 없다고 느껴진다			
14.신체 증상들 (유방통, 두통, 근육통, 관절통, 복부 불쾌감, 몸이 붓거나 체중 증가 등)			

위의 증상들이 있다면, 다음 영역에서 어느 정도로 지장이 있습니까?

영역 분류	전혀 없다	약간 있다	심하게 있다
A. 학업 또는 일의 효율 및 생산성			
B. 동료들과의 관계			
C. 가족들과의 관계			
D. 사회 활동			
E. 가정에서의 책임 또는 의무			

- PMDD :
o #1, #2, #3, #4 중 하나 이상이 중증
o #1-#14 중 최소 5개가 중증
o A, B, C, D, E 중 하나 이상이 중증

- 중등도~중증 PMS :
o #1-#14 중 하나 이상이 중증
o A, B, C, D, E 중 하나 이상이 중증

- PMS가 없거나 경증 :
o 전혀 없거나 A,B,C,D,E 중 경증

3.<성장기 부정적 경험에 대한 상세 설문지> 장문형

I. 당신이 살아오는 동안 부모님이나 다른 사람들로부터 다양한 형태로 상처를 받거나 제대로 돌봄을 받지 못하는 일들을 경험한 적이 있을 수 있습니다. 18 세 이전에 다음 문항과 같은 일이 얼마나 자주 있었는지 아래의 칸에 O 표 해 주십시오. 기억이 나지 않는다면 모른다고 표시하여 주십시오.

문항	전혀없음/절대아님	거의없음/거의아님	때때로 혹은 가끔있음	종종 또는 자주있음
1. 모욕적인 이야기나 심한 말 등을 해서 마음이 상한 적이 있다.	0	1	2	3
2. 나에게 소리를 지르거나 고함을 쳤다.	0	1	2	3
3. 어디로 보내버리거나 내쫓겠다고 말했다.	0	1	2	3
4. 나를 때리겠다고 위협했지만 실제로	0	1	2	3

때리지는 않았다.				
5. 때리거나 물건을 집어던지겠다고 위협했다	0	1	2	3
6. 회초리나 자로 손바닥이나 종아리, 엉덩이 등을 맞았다.	0	1	2	3
7. 나에게 물건을 집어 던졌다.	0	1	2	3
8. 세게 밀침을 당했다.	0	1	2	3
9. 손바닥으로 뺨을 맞았다.	0	1	2	3
10. 발로 차이거나 주먹으로 맞았다.	0	1	2	3
11. 회초리 이외의 물건(혁대, 몽둥이 등)으로 맞은 적이 있다.	0	1	2	3
12. 사정없이 마구 맞았다.	0	1	2	3
13. 목을 졸린 적이 있다.	0	1	2	3
14. 칼(가위) 등의 흉기로 위협을 당하거나 상해를 입은 적이 있다.	0	1	2	3
15. 내가 씻지 않는 것을 내버려 두었다.	0	1	2	3
16. 내가 철 지난 옷을 입게 내버려 두었다.	0	1	2	3
17. 나에게 제때 밥을 챙겨주지 않았다.	0	1	2	3
18. 나에게 음식제공이나 영양관리가 부족했다.	0	1	2	3
19. 초등학교 들어가기 전에 내가 어른 역할을 도맡아 했다.	0	1	2	3
20. 초등학교 들어가기 전에 내가 밤늦도록 집밖에서 놀아도 내버려 두었다.	0	1	2	3
21. 나의 준비물(혹은 도시락 등)을 챙겨주지 않았다.	0	1	2	3

22. 나의 학교생활에 관심이 없었다.	0	1	2	3
23. 필요할 때 나를 병원에 데려가지 못했다.	0	1	2	3
24. 나에게 필요한 보조장치(안경 등)를 해주지 않았다.	0	1	2	3

Ⅱ. 당신이 살아오는 동안 당신은 매우 부끄럽거나 민감할 수도 있는 일들을 경험한 적이 있을 수 있습니다. 18 세 이전에 원치 않게 다음과 같은 일을 경험한 적이 있는지, 있다면 얼마나 자주 경험했는지 아래의 칸에 O 표 해 주십시오. 기억이 나지 않는다면 모른다고 표시하여 주십시오.

문항	전혀없음/절대아님	거의없음/거의아님	때때로 혹은 가끔있음	종종 또는 자주있음
1. 음란한 말(혹은 행동)로 나를 희롱했다.	0	1	2	3
2. 고의로 신체 일부에 접촉을 했다. (예: 손, 머리, 어깨, 허리, 다리, 엉덩이 등)	0	1	2	3
3. 나에게 강제로 키스를 하거나 애무를 했다.	0	1	2	3
4. 나에게 자신의 성기를 보여주었다.	0	1	2	3
5. 내 옷을 벗기거나 나의 벗은 몸을 바라보았다.	0	1	2	3
6. 나에게 상대의 몸이나 성기를 만지게 했다.	0	1	2	3
7. 나의 옷을 벗겨 가슴이나 성기를 만졌다.	0	1	2	3

8. 내 앞에서 상대가 자위행위를 했다.	0	1	2	3
9. 나에게 구강성교를 요구하거나 구강성교를 했다.	0	1	2	3
10. 나에게 성교를 요구하거나 성교를 했다.	0	1	2	3

Ⅲ. 당신의 부모님이 서로 의견이 다를 수 있고, 서로의 행동으로 인해 화가 나거나 갈등이 생긴 상황을 당신이 옆에서 지켜본 경험이 있을 수 있습니다. 다음은 **부모님께서 서로 다툴 때** 보일 수 있는 몇 가지 행동들입니다. 당신은 **18 세 이전에** 다음과 같은 일을 경험한 적이 있는지 있다면 얼마나 자주 경험했는지 아래의 칸에 O 표 해 주십시오. 기억이 나지 않는다면 모른다고 표시해 주십시오.

문항	전혀없음/절대아님	거의없음/거의아님	때때로 혹은 가끔있음	종종 또는 자주있음
1. 모욕적인 이야기나 심한 말을 했다.	0	1	2	3
2. 물건을 부수거나 발로 걷어찼다.	0	1	2	3
3. 상대방에게 물건을 집어던졌다.	0	1	2	3
4. 세게 밀쳤다.	0	1	2	3
5. 손바닥으로 뺨을 때렸다.	0	1	2	3
6. 발로 차거나 주먹으로 때렸다.	0	1	2	3
7. 물건(혁대, 몽둥이, 골프채 등)으로 때렸다.	0	1	2	3
8. 사정없이 마구 때렸다.	0	1	2	3
9. 목을 졸랐다.	0	1	2	3

10. 칼이나 흉기로 위협하거나 다치게 했다.	0	1	2	3

Ⅳ. 당신은 학창시절이나 사회생활을 하는 동안 친구나 동료, 선후배 등으로부터 **집단따돌림**을 당한 경험이 있을 수 있습니다. **집단따돌림**이란 한 사람이 다른 사람들로부터 아래와 같은 괴롭힘을 당하는 것입니다.

* 다른 사람들이 상스럽고 불쾌한 말을 하거나, 놀리거나 욕하는 것
* 완전히 무시하거나 어떤 일을 할 때 고의로 끼워주지 않는 것
* 때리거나, 바로 차거나, 밀거나, 괴롭히거나, 위협하는 것
* 사실이 아닌 것을 소문내거나 나쁜 내용을 퍼드려서 다른 사람들이 싫어하게 만드는 것
* 한 사람을 부정적이고 상처 입히는 방식으로 여러 번 놀리는 것

그러나 친한 사이에서 재미로 놀리는 것은 **집단따돌림이 아닙니다**. 또 비슷한 수준의 두 사람이 힘을 겨루기 위해 싸우는 것도 **따돌림이 아닙니다.**

18세 이전에 위와 같은 **집단따돌림**을 경험한 적이 있는지, 있다면 얼마나 자주 있었는지 아래 칸에 O표 해 주십시오. 기억이 나지 않으면 모른다고 표시해 주십시오.

문항	전혀없음/절대아님	거의없음/거의아님	때때로 혹은 가끔있음	종종 또는 자주있음
1. 살아오는 동안 주위 사람들로부터 얼마나 자주 따돌림을 당했습니까?	0	1	2	3
2. 당신은 욕먹거나, 심하게 집적거리거나 놀림을 당한 경험이 있습니까?	0	1	2	3
3. 다른 사람들이 고의로 어떤 일에 끼워주지 않거나 사람들 사이에서 당신을 완전히 무시한 적이 있습니까?	0	1	2	3

4. 당신을 때리거나 발로 차거나 밀거나 괴롭히거나 위협하는 사람들이 있었습니까?	0	1	2	3
5. 당신에 대한 거짓 소문을 퍼뜨려서 사람들이 당신을 싫어하게 만드는 일을 경험했습니까?	0	1	2	3
6. 당신의 돈이나 물건을 뺏거나 망가뜨리는 일을 경험했습니까?	0	1	2	3
7. 당신의 신체특징이나 외모에 대하여 험한 욕을 듣거나 비난, 놀림을 당한 적이 있습니까?	0	1	2	3
8. 그 밖의 다른 방법으로 집단따돌림을 당한 적이 있습니까? (있다면 그 방법은 아래 칸에 적어주십시오.)	0	1	2	3
기타 따돌림:				

4.<성장기 부정적 경험 선별검사지> 단문형

※ 이 검사는 생애초기 스트레스에 대한 선별 검사입니다. 당신이 <u>18세가 되기 전</u>까지의 기억 중에 아래와 같은 일들을 경험한 적이 있는지 생각해 보십시오. 그 경험의 빈도를 해당되는 칸에 O로 표시하고, 있다면 간단하게 그 내용을 적어 주십시오.

항 목	전혀 없었음/ 절대 아님	거의 없었음/ 거의 아님	때때로 혹은 가끔 있었음	종종 또는 자주 있었음	내 용
	0	1	2	3	

1. 신체적인 폭력을 경험한 적이 있다. (예: 구타, 폭행, 매 맞음 등)	전혀	거의	가끔	자주	
2. 정서적인 폭력을 경험한 적이 있다.(예: 심한 욕, 모욕, 비난, 저주 등)	전혀	거의	가끔	자주	
3. 성적인 폭력을 경험한 적이 있다. (예: 성추행(성적 모욕), 성폭행(강간) 등)	없음		있음		
4. 가족 내에서 심하게 싸우는 것을 봤다. (예: 부모님의 부부싸움, 친척 간 싸움 등)	전혀	거의	가끔	자주	
5. 무관심하게 방치된 적이 있다. (예: 배고픈데도 먹지 못함, 깨끗한 옷을 입지 못함 등)	전혀	거의	가끔	자주	
6. 친밀한 사람의 죽은 모습을 직접 봤다. (예: 부모, 형제, 가까운 사람 등)	없음		있음		
7. 부모님과의 이별 (예: 이혼, 장기간 이별)	없음		있음		
8. 따돌림 (예: 친구, 선후배들로부터의 따돌림)	전혀	거의	가끔	자주	
9. 자연재해 혹은 사고 (예: 홍수, 교통사고, 화재사고 등)	없음		있음		
10. 기타 심한 스트레스를 주는 사건 (예: 전쟁, 유괴, 납치	없음		있음		

등)			

위의 10개의 항목 중 한 가지에서라도 경험한 적이 있다고 답한 경우, 그 사건을 경험할 당시를 생각해서 아래의 두 가지 질문에 답하여 주십시오.

	0	1
11. 그 당시 심한 불안, 공포, 두려움, 무력감을 경험했다.	아니요	네
12. 그 당시 꿈을 꾸거나 현실이 아닌 것처럼, 혹은 내 자신이 내가 아닌 것처럼 느껴졌다.	아니요	네

5. <코로나 19 예방 접종 부작용 설문지 >

1. 코로나 19 예방 접종을 몇 차까지 맞았습니까?

   a. 1 차 b. 2 차 c. 3 차 d. 4 차

2. 백신 이후 부작용(열, 주사 통증, 몸살, 도통, 피곤함,구역 등)이 어느 정도였습니까?

   a. 없음 b. 가벼운 증상 c. 중등도의 증상 d.심한 증상

3. 어떤 백신을 맞았습니까?

□아스트라제네카 코로나 19 백신 □얀센 코로나 19 백신

□화이자 코로나 19 백신 □모더나 코로나 19 백신

□ 노바백스 코로나 19 백신

□ 해외에서 다른 백신 접종하였다:……

4. 백신 이후 월경에 변화가 있었습니까?

   a. 월경이 불규칙해졌다　　b. 월경과다 나타났다

   c. 생리불순이 생겼다　　d. 월경량이 적어졌다

   e. 월경증후군 증상이 나타났다.　　f. 기타: ……

5. 월경전에 신체 증상(체중 증가, 유방통, 월경통, 두통)과 정동 증상 (우울감, 불안감,민감함, 불면증, 과다수면, 식욕 변화, 일상 생활에 흥미가 떨어짐, 주의집중 떨어짐 등) 이 있었던 경우 백신 이후 어떤 변화가 생겼습니까?

   a. 증상들이 나아졌다　　b. 증상들이 악화됐다

   c. 없었던 증상들이 나타났다　　d. 기타: ……

6. 백신 이후에 변화가 있었던 경우 몇 번째 월경부터 나타났습니까?

   a. 첫번째　　b. 두번째　　c. 세번째　　d. 네번째

7. 백신 후 생겼던 변화가 얼마 동안 있었습니까?

   a. 한 번의 월경에만　　b. 두 번의 월경　　c. 세 번의 월경　　d. 세 번의 이상 월경

8. 백신 이후에 변화가 있었던 경우 몇 차 이후 생겼습니까?

   a. 1 차 이후　　b. 2 차 이후　　c. 3 차 이후　　d. 4 차 이후

   e. 백신 접종 시 매 번

9. 월경에 변화가 있는 것을 알고 어떻게 대처하였습니까?

   a. 병원에 가서 진단을 받았다

   b. 아무것도 하지 않았다

   c. 집에서 치료 했다

   d. 기타:……

ABSTRACT(IN KOREAN)

코로나 19 예방접종 후 월경 이상과 부정적 아동기 경험의 관계 및 이 관계에 미친 월경전장애의 매개효과

<지도교수 석정호 >

연세대학교 대학원 의학과

Khishigbayar Uranbileg

전 세계 상당수의 여성들이 코로나19 백신 접종 후 흔한 부작용부터 월경 이상까지 다양한 부작용을 보고했다. 선행 연구에서 월경 이상과 코로나19 백신 접종 관계의 연관성이 밝혀졌지만 예측 요인과 기저 메커니즘은 여전히 불분명하다. 부정적 아동기 경험(ACE)은 월경전 장애(PMD)에 기여하는 요인인 것으로 밝혀졌다. PMD가 월경주기와 관련되어 산부인과 질환으로 간주됨에도 불구하고, 코로나19 백신 접종 후 월경 이상과의 관계는 조사되지 않았다. 이 단면조사연구는 ACE와 PMD 및 월경 이상 사이의 관계를 조사하는 것을 목표로 하였다. SPSS 버전 27을 사용하여 기술 통계 및 로지스틱 회귀를 수행하는 데 사용되었다. 매개 효과 분석은 SAS 버전 9.4를 사용하여 수행되었다.온라인 플랫폼을 통해 참여한 250명이 5개의 설문지를 작성했다. 본 연구에서는 3개 이상의 ACE는 PMDD 발병 확률을 5.7배 증가시켰다. 월경 이상을 경험한 여성의 경우 PMD 유형 간에 통계적 유의한 차이가 나타났다(p<0.01). PMDD가 있는 여성은 백신 접종 후 월경 이상을 경험할 확률이 2.3배 더 높았으며(p<0.05), PMDD는 코로나19 백신 접종 후 월경 이상과 ACE의 관계에 매개 효과를 보였다(p<0.02). 이 관계에 관한 메커니즘은 어린 시절 학대를 받은 PMDD 여성의 과잉 면역 반응성을 설명할 수 있다. 정확한 생리적 메커니즘을 발견하려면 추가 연구가 필요하다. 또한 후속 연구에서는 전향

적 추적 방법을 사용하여 PMDD가 있는 여성의 월경 주기 특성을 탐색하고 그들이 일반적으로 월경 이상을 경험하는지 여부를 확인할 필요가 있다.

핵심되는 말: 부정적 아동기 경험(ACE), 월경전당애(PMDs), 취약-보호 요인 도구(PROVE-ACE), 월경 전 증상 선별 도구(PSST), COVID-19 예방접종