Article

COVID-19 disease and menstrual-related disturbances: a Spanish retrospective observational study in formerly menstruating women

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Abstract

After three years of the onset of the pandemic, there is scarce evidence about how COVID-19 disease affect the female reproductive system, and consequently, the menstrual cycle. Since the common causes of secondary amenorrhea are considered as exclusion criteria in the studies about menstrual changes following SARS-CoV-2 infection, the prevalence of this event and the influencing factors in formerly menstruating women remains unknown. A retrospective observational cross-sectional study was conducted on Spanish adult women (N= 17,512), using an online survey; a subpopulation of SARS-CoV-2-infected-formerly menstruating women was included in the present analysis (n= 72). Collected data included general characteristics, medical history, and specific information about COVID-19 disease. 38.9% of the respondents experienced menstrual-related disturbances after suffering from the COVID-19 disease, unexpected vaginal bleeding being the most common (20.8%). Other alterations related with the length – "shorter" by 12.5% – and the flow – "heavier than usual" 30.3% – of the menstrual bleeding were reported. The binary logistic regression showed that being a perimenopausal woman (AOR 4.608, CI 95%, 1.018 – 20.856, p = 0.047) and having heavy menstrual bleeding (AOR 4.857, CI 95%, 1.239 – 19.031, p=0.023) are influential factors. This evidence could help health professionals to provide scientifically up-to-date information to their patients, empowering them to actively manage their reproductive health, especially in those societies where menstrual health is still a taboo.

Keywords: SARS-CoV-2 infection, COVID-19 disease, women´s health, menstrual-related disturbances, formerly menstruating women, secondary amenorrhea, perimenopause, heavy menstrual bleeding.

1. Introduction

Undoubtedly, since the WHO declared the novel coronavirus SARS-CoV-2 outbreak as a global pandemic on March 2020, the life of billions of people worldwide has completely changed due to this unprecedent health crisis. To date, it is estimated that the infectious respiratory disease known as COVID-19 disease has affected 761.402.282 people, causing 6.887.000 deaths [1].

Focusing on the physiopathology, SARS-CoV-2 has been reported to trigger multisystem complications in addition to respiratory symptoms [2-4]. This is due to the ubiquitous expression of the membrane protein called angiotensin-converting enzyme 2 (ACE2), which is known to be the route of entry of SARS-CoV-2 virus into the host cells [5,6]; additionally, other enzymes such as the transmembrane protease serine subtype 2 (TMPRSS2) and the dipeptidyl peptidase-4 (DPP4) have been identified as co-receptors of this coronavirus during host cell entry [7]. Regarding the female reproductive system, this receptor complex is also expressed − predominantly in ovaries and regardless of the age and the ovarian reserve – [8]. As Reis et al. [9] point out, ACE2 plays a major role in the generation of angiotensin-(1-7), which stimulates ovarian follicle growth, oocyte maturation and ovulation; its precursor angiotensin II promotes vasoconstriction of the spiral arteries and consequently induces menstruation [10]. Thus, as a result of the COVID-19 disease, the altered functions of this molecular pathway and other neuroendocrine systems – e.g. hypothalamic-pituitary-gonadal (HPG) axis and hypothalamic-pituitary-adrenal (HPA) axis − may lead to menstrual cycle irregularities [7]. Additionally, the immune response resulting from the infection may also be implicated in this phenomenon, given its interaction with the endocrine system [11]. Therefore, it would be expected that SARS-CoV-2 can temporarily or even permanently impair female fertility. Unfortunately, our knowledge of the basic uterine and menstrual physiology is not enough to understand more complex processes of this kind.

Previous studies have linked viral infections with women´s reproductive health alterations [12-14]. Nevertheless, conflicting results have so far been achieved in relation to SARS-CoV-2 infection in menstruating women [15-17]. Additionally, the prevalence of menstrual-related disturbances (MRD) in formerly menstruating women (FMW) − that is, those who have secondary amenorrhea for different causes − remains unknown. Amenorrhea is defined as the absence or lack of menstrual period. Common causes of secondary amenorrhea include pregnancy, breastfeeding, menopause, contraceptives methods and gynecological conditions [18,19], most of them considered as exclusion criteria in the studies about MRD following SARS-CoV-2 infection. For this reason, the aims of this study were 1) to determine the occurrence of MRD in FMW after COVID-19 disease and 2) to analyze the factors that may be influencing this phenomenon.

2. Materials and Methods

2.1. Experimental design

A retrospective observational cross-sectional study was conducted on Spanish adult women using an online survey (Microsoft Forms®, Microsoft Corporation, Washington, USA).

2.2. Recruitment, data collection and participants

The online survey was released in December 2021 via social networks; the snowball method was applied. Thus, a total of 17,512 were recruited within 15 days; from this sample, the data pertaining to a subpopulation of FMW was selected for the present analysis (N= 72, Figure 1). The inclusion criteria were women: (i) over 18 years of age, (ii) having secondary amenorrhea for different causes, and (iii) having a diagnosis of COVID-19 disease (positive PCR test).

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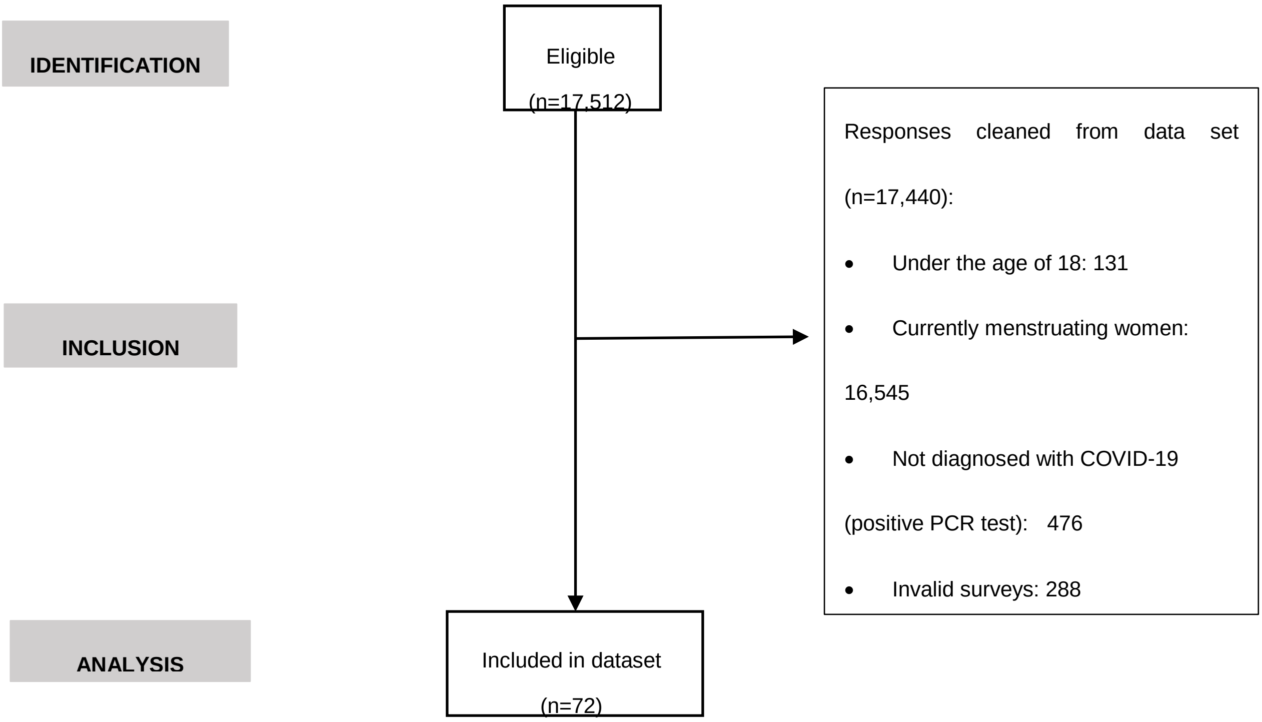

Figure 1. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flow diagram.

2.3. Survey information

A customized questionnaire based on the survey launched on April 2021 by Lee et al. [20] was designed. It was composed by 56 multiple-choice and text entry questions divided into 6 sections. Participants were asked about 1) the general characteristics of their menstrual cycles, 2) COVID-19 disease, 3) COVID-19 vaccine, 4) menstrual experiences both after the SARS-CoV-2 infection/COVID-19 vaccination in comparison with the expected period symptoms, 5) other MRD, 6) time between infection/vaccine and MRD, 7) duration of MRD, 8) side effects from each dose of the vaccine, 9) reproductive history, 10) medical history, and 11) demographics. The survey took approximately 10-15 min to complete. Variables related to COVID-19 vaccination and MRD have been excluded from the present analysis.

2.4. Statistical analysis

Participants were categorized according to the occurrence or not of MRD after COVID-19 disease. Values were expressed as mean±standard deviation for quantitative variables and number of participants and frequency (%) for qualitative ones. Chi-square and Mann-Whitney U tests were performed for qualitative and quantitative variables, respectively. Subsequently, a bivariate logistic regression analysis was performed to investigate possible associations between the occurrence of MRD following SARS-CoV-2 infection (dependent variable) and the independent variables that were significant ($p<0.05$) in the previous analyses. Thus, the results were presented as adjusted odds ratios (ORAs) with 95% confidence intervals (CI). The aforementioned analyses were performed using the Statistical Package for Social Sciences (SPSS v.25, IBM, New York, USA) for Windows. Statistical significance was set at $p<0.05$.

3. Results

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3.1. Anthropometric characteristics and medical history

56.9% of the study participants (N=72, mean age 41.4 ± 11.4 years) had normal weight (mean BMI value= 27.8 ± 4.6), 19.4% had autoimmune diseases, and 27.1% had other clinical conditions. Among the causes of amenorrhea, the use of contraceptives (31.9%) and postmenopause (22.2%) were mainly reported, followed by other causes such as polycystic ovary syndrome (19.4%,), perimenopause (15.3%), and breastfeeding (11.1%). Furthermore, 31.9% of women surveyed used hormonal contraceptives for less than 10 years, 61.1% had been pregnant, and 52.8% reported having been diagnosed with a gynecological disease, being the most common polycystic ovary syndrome (18.1%), followed by heavy menstrual bleeding (18.1%), and endometriosis (11.1%) (Table 1).

Table 1. Anthropometric characteristics and medical history of the study population (formerly menstruating women, N=72).

Variable		Category	Total (N=27)
Age (years) [a]		-	41.4±11.4
Weight (kg) [a]		-	66.5±13.2
Height (cm) [a]		-	163.7±6.0
BMI [a, b]		-	27.8±4.6
		Underweight	5 (6.9)
		Normal weight	41 (56.9)
		Pre-obesity/overweight	13 (18.1)
		Obesity I	12 (16.7)
		Obesity II	0 (0.0)
		Obesity III	1 (1.4)
Medical history [b]			
Autoimmune diseases	Diagnosis	Yes	14 (19.4)
		No	58 (19.4)
	Comorbidity	Yes	1 (7.1)
		No	13 (92.9)
	Types	Thyroid	6 (8.3)
		Gastrointestinal	3 (4.2)
		Other	3 (4.2)
		Dermatological	2 (2.8)
		Rheumatic/articular	2 (2.8)
Other clinical conditions	Diagnosis	Yes	19 (27.1)
		No	51 (72.9)
	Comorbidity	Yes	5 (23.8)
		No	16 (76.2)
	Types	Other	6 (8.3)
		Gynecological	4 (5.6)
		Cancer	3 (4.2)
		HPV	3 (4.2)
		Cardiovascular	2 (2.8)
		Gastrointestinal	2 (2.8)
		Neurological/mental	1 (1.4)
		Respiratory	1 (1.4)
		Rheumatic/articular	1 (1.4)

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		Thyroid	1 (1.4)
		Dermatological	0 (0.0)
Allergies	Diagnosis	Yes	26 (36.1)
		No	46 (63.9)
Gynecological history [a, b]			
Age 1st menstruation		-	12.8±1.4
Amenorrhea	Causes	Contraceptives	23 (31.9)
		Postmenopause	16 (22.2)
		Other	14 (19.4)
		Perimenopause	16 (22.2)
		Breastfeeding	8 (11.1)
Current/ past use of contraceptives	Time of use	<10 years	23 (31.9)
	Types	>10 years	6 (8.3)
		None	43 (59.7)
		Hormonal	23 (31.9)
		IUD (nonhormonal)	6 (8.3)
Reproduction	Have you ever been pregnant?	Yes	44 (61.1)
	Nº pregnancies	No	28 (38.9)
		0-2	60 (83.3)
		>2	16 (16.7)
	Nº children	0-2	68 (94.4)
		>2	4 (5.6)
Diseases	Diagnosis	Yes	38 (52.8)
		No	34 (47.2)
	Comorbidity	Yes	7 (18.4)
		No	34 (47.2)
	Types	PCOS	13 (18.1)
		Endometriosis	8 (11.1)
		Heavy menstrual bleeding	13(18.1)
		Other	8 (11.1)
		Fibroids	4 (5.6)
		Menorrhagia	1 (1.4)
		Adenomyosis	0 (0.0)
		Uterine bleeding	0 (0.0)

Values are expressed as: [a] mean±standard deviation; [b] n (%).

Abbreviations: IDU, Intrauterine Device; BMI, Body Mass Index; PCOS, Polycystic Ovary Syndrome; HPV, Human Papillomavirus.

3.2. Impact of COVID-19 disease on the menstrual health

As shown in table 2, most of the women with amenorrhea were diagnosed with COVID-19 in the first wave (29.2%), followed by the second (23.6%) and the fifth (20.8%); only 2.8% required hospitalization. 38.9% of the respondents experienced MRD after suffering from the COVID-19 disease, unexpected vaginal bleeding being the most common (20.8%). Other alterations related with

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the length – "shorter" by 12.5% − and the flow − "heavier than usual" 30.3% − of the menstrual bleeding were reported. When asked about the time between the SARS-CoV-2 infection and the occurrence of menstrual bleeding, a 20.8% of the FMW answered "more than 14 days" (20.8%); in 53.3% of cases, this event was unexpected in comparison with the probable period date. With regard to premenstrual syndrome, 56.0% of women suffered from 2 or more symptoms, including fluid retention (8.0%) and pain (4.0%). The majority of participants experiencing MRD after the infection reported that these last "until today" (27.8%).

Table 2. COVID-19 disease and the occurrence of MRD in the study population (formerly menstruating women, N=72).

Variable	Category	Total (N=72
Date of COVID-19 diagnosis (pandemic waves)	1st wave	21 (29.2)
	2nd wave	17 (23.6)
	3rd wave	12 (16.7)
	4th wave	7 (9.7)
	5th wave	15 (20.8)
Hospitalization	Yes	2 (2.8)
	No	70 (97.2)
MRD occurrence	Yes	28 (38.9)
	No	44 (61.1)
Types	Spotting	8 (11.1)
	Shorter menstrual cycle	3 (4.2)
	Unexpected vaginal bleeding	15 (20.8)
	Longer menstrual cycle	1 (1.4)
Length of menstrual bleeding	None	45 (62.5)
	Shorter	9 (12.5)
	Unchanged	16 (22.2)
	Longer	8 (11.1)
Flow of menstrual bleeding	Not applicable	39 (54.2)
	Lighter	7 (21.2)
	Unchanged	16 (48.5)
	Heavier	10 (30.3)
Time between SARS-CoV-2 infection and period/abnormal bleeding	I was menstruating when I got infected	1 (1.4)
	After 1-3 days	3 (4.2)
	After 4-7 days	6 (8.3)
	After 8-14 days	5 (6.9)
	After more than 14 days	15 (20.8)
Coincidence with period date	Not applicable	42 (58.3)
	Yes	9 (30.0)
	No	16 (53.3)
	Not applicable	5 (16.7)
Premenstrual syndrome		
Nº symptoms	2 symptoms	7 (28.0)
	≥3 symptoms	7 (28.0)

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Types	None	6 (24.0)
	Fluid retention	2 (8.0)
	Pain	1 (4.0)
	Swelling	0 (0.0)
	Thirst	0 (0.0)
	Appetite	0 (0.0)
	Other	2 (2.8)
Duration of MRD	1 cycle	4 (5.6)
	<3 months	3 (4.2)
	3-6 months	4 (5.6)
	6-12 months	3 (4.2)
	Until today	20 (27.8)
	Not applicable	38 (52.8)

Values are expressed as: n (%).

Abbreviations: BMI, Body Mass Index; IUD, Intrauterine Device; MRD, menstrual-related disturbances.

3.3. Factors associated with the occurrence or not of MRD after COVID-19 disease

Focusing on gynecological history, the comparative analysis (Table 3) revealed a significantly higher percentage of perimenopausal women in the subgroup who experienced alterations (MRD subgroup) compared to the subgroup of those who did not (n-MRD subgroup); among gynecological diseases, heavy menstrual bleeding was more frequent in the MRD subgroup. Similarly, statistically significant differences were found between subgroups in relation to the fourth pandemic wave. Furthermore, the FMW who required hospitalization belong to the MRD subgroup, being the difference between subgroups of marginal significance.

Subsequently, binary logistic regression was performed (Table 4). The analysis showed that being a perimenopausal woman (AOR 4.608, CI 95%, 1.018 – 20.856, p = 0.047) and having heavy menstrual bleeding (AOR 4.857, CI 95%, 1.239 – 19.031, p=0.023) are influential factors in the occurrence of MRD after COVID-19 infection in women with amenorrhea.

Table 3. Differences in the study variables according the occurrence or not of MRD after suffering from COVID-19 disease in the study population (formerly menstruating women, N=72).

		Subgroup			
Variable	Category	n-MRD (n=44)	MRD (n=28)	X^2	p-value
Age (years)[a]		41.4±12.3	41.5±9.9	-	0.954
Weight (kg)[a]	-	66.1±13.8	67.0±12.5	-	0.785
Height (cm)[a]	-	163.6±6.5	163.8±5.3	-	0.889
BMI [a,b]	-	24.7±5.0	24.9±4.1	-	0.768
	Underweight	3 (6.8)	2 (7.1)		0.683
	Normal weight	27 (61.4)	14 (50.0)		
	Pre-obesity/ overweight	6 (13.6)	7 (25.0)		
	Obesity I	7 (15.9)	5 (17.9)		

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		Obesity II	0 (0.0)	0 (0.0)		
		Obesity III	1 (2.3)	0 (0.0)		
Medical history [b]						
Autoimmune diseases	Types	Dermatological	1 (2.3)	1 (3.6)	0.107	0.744
		Gastrointestinal	1 (2.3)	2 (7.1)	1.016	0.313
		Rheumatics/ articular	1 (2.3)	1 (3.6)	0.107	0.744
		Other	3 (6.8)	0 (0.0)	1.992	0.158
		Thyroid	3 (6.8)	3 (10.7)	0.340	0.560
Other clinical conditions	Types	Cardiovascular	1 (2.3)	1 (3.6)	0.107	0.744
		Cancer	2 (4.5)	1 (3.6)	0.041	0.840
		Dermatological	0 (0.0)	0 (0.0)		
		Gastrointestinal	2 (4.5)	0 (0.0)	1.309	0.253
		Gynecological	3 (6.8)	1 (3.6)	0.344	0.558
		Neurological/ mental	1 (2.3)	0 (0.0)	0.645	0.422
		Other	4 (9.1)	2 (7.1)	0.085	0.711
		Respiratory	0 (0.0)	1 (3.6)	1.594	0.207
		Rheumatic/ articular	0 (0.0)	1 (3.6)	1.594	0.207
		Thyroid	1 (2.3)	0 (0.0)	0.645	0.422
		HPV	1 (2.3)	2 (7.1)	1.016	0.313
Allergies		-	31 (70.5)	13 (29.5)	2.114	0.146
Gynecological history [a,b]						
Age 1st menstruation		-	12.7±14	12.8±1.4		0.921
Contraceptives	Time of use	<10 years	12 (27.3)	11 (39.3)	1.810	0.405
		>10 years	3 (6.8)	3 (10.7)		
	Types	None	29 (65.9)	14 (50.0)	2.511	0.285
		Hormonal	11 (25.0)	12 (42.9)		
		IUD (nonhormonal)	4 (9.1)	2 (7.1)		
Reproduction	Have you ever been pregnant?	Yes	27 (61.4)	17 (60.7)	0.003	0.956
		No	17 (38.6)	11 (39.3)		
	Nº pregnancies	0-2	37 (84.1)	23 (82.1)	0.047	0.29
		> 2	7 (15.9)	5 (17.9)		
	Nº children	0-2	40 (90.9)	28 (100.0)	2.695	0.101
		> 2	4 (9.1)	0 (0.0)		
Amenorrhea	Types	Perimenopause	3 (6.8)	8 (28.6) *	6.809	0.033
		Postmenopause	12 (27.3)	4 (14.3)		
		Other	29 (65.9)	16 (57.1)		
Diseases	Types	Adenomyosis	0 (0.0)	0 (0.0)		
		Endometriosis	3 (6.8)	5 (17.9)	2.111	0.146

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		Fibroids	2 (4.5)	2 (7.1)	0.220	0.639
		Menorrhagia	0 (0.0)	1 (3.6)	1.594	0.207
		Other	5 (11.4)	3 (10.7)	0.007	0.932
		Heavy menstrual bleeding	4 (9.1)	9 (32.1)*	6.146	0.013
		Uterine bleeding	0(0.0)	0(0.0)		
		PCOS	8 (18.2)	5 (17.9)	0.001	0.972
COVID-19						
Date of COVID-19 diagnosis (pandemic waves)	1st wave		15 (34.1)	6 (21.4)	10.378	0.035
	2nd wave		9 (20.5)	8 (28.6)		
	3rd wave		10 (22.7)	2 (7.1)		
	4th wave		1 (2.3)	6 (21.4)*		
	5th wave		9 (20.5)	6 (21.4)		
Hospitalization	Yes		0 (0.0)	2 (7.1)	3.233	0.072
	No		44 (100.0)	26 (92.9)		

Values are expressed as: a mean ± standard deviation; b n (%). *p<0.05 vs. subgroup n-MRD.

Abbreviations: BMI, Body Mass Index; IDU, Intrauterine Device; MRD: menstrual-related disturbances subgroup; n-MRD: non-menstrual-related disturbances subgroup; PCOS, Polycystic Ovary Syndrome; HPV, Human Papillomavirus.

Table 4. Factors associated with the occurrence of MRD after suffering from COVID-19 disease (formerly menstruating women, N=72): binary logistic regression.

		Subgroup MRD (n=28)	
Variable	**Category**	**AOR(CI95%)**	**p-value**
Amenorrhea	Perimenopause	4.608(1.018-20.856)	0.047
	Postmenopause	0.541(0.139-2.103)	0.375
	Other	1	
Gynecological history			
Heavy menstrual bleeding	Yes	4.857(1.239-19.031)	0.023
	No	1	

Note: Reference group: Do not experience changes COVID-19 disease-related.

AOR: adjusted odd ratio; CI 95%: confidence interval.

4. Discussion

COVID-19 pandemic makes it clear once again that the influence of sex and gender on human health and diseases continues nowadays to be underestimated [21]. Although it is now well established that COVID-19 exhibits gender disparities due to several biological factors, very few studies have analyzed the impact of this disease on women´s health, particularly on the female reproductive system. Based on this scarce scientific evidence available, MRD may affect 16-25% of women of childbearing age infected with SARS-CoV-2 [15,22,23]. In this subpopulation, most commonly reported disturbances were worsened premenstrual syndrome, irregular and infrequent menstruations [23], and decreased menstrual volume – regardless of the severity of the disease [15,22]. For severe hospitalized patients, prolonged menstrual cycles have been also recorded. 15 Furthermore, in a global multinational survey conducted by Davis et al. [24], approximately 30-40% of 2969 women surveyed – most 30 to 60 years old− reported post-COVID-19 menstrual/period issues, including abnormally irregular menstrual cycles (26%) and abnormally heavy periods or clotting (20%); moreover, a 3% of women in their 40s experienced early menopause. Barabás et al. [25] also observed this level of menstrual changes prevalence among infected women of the same age range. Compared with our results in FMW, these findings suggest the existence of differences in the prevalence and characteristics of the MRD between young and middle-aged women, which needs to be confirmed by further research. Moreover, although this kind of alterations seems to be of a transient nature for the majority of the study participants, the possibility that some women may also experience long-term menstrual changes cannot be excluded [22,24]. In this sense, Li et al. [15] observed that while 99% of the patients returned to their normal cycle within 1-2 months after discharge from the hospital, a 44-year-old women reported the absence of menstruation for 4 months after COVID-19 onset. In fact, the binary logistic regression performed in this study revealed that being a perimenopausal woman is influencing factor in experiencing MRD. Therefore, this also confirms that the impact of SARS-CoV-2 infection may differ throughout the different stages of a woman´s life.

As Khan et al. [23] point out, the menstrual cycle involves complex interactions between various tissues, hormones, and organ systems; thus, it can be influenced by a variety of endogenous and exogenous factors, including viral infections. In this regard, it is well established that viruses can affect the female reproductive endocrine system in different ways, as described elsewhere [26-29]. Therefore, potential direct and indirect effects of SARS-CoV-2 virus must be considered in the occurrence of menstrual changes. Systemically, the damage caused by the COVID-19 disease is suggested to be mediated by a direct viral role, pro-inflammatory immune responses, unbalanced physiological systems −e.g. renin-angiotensin-aldosterone system (RAAS) and ACE2/angiotensin-(1–7)/mitochondrial angiotensin axis, and HPG and HPA axes − and the downregulation of ACE2 expression [4,30]. This harmful context could be aggravated by local direct effects in the female reproductive system, as the tissue damage and the subsequent inflammation leading by the entry into the cell host via the receptor complex ACE2/TMPRSS2/DPP4, with undetermined consequences on menstrual physiology [16,31]. At this point, it should be remembered that estrogens are well known to act in a coordinated way with immune system and metabolism [4,21,31]. Particularly, estradiol has been suggested to play a protective role in COVID-19 through different pathways, including the RAAS system, the anti-inflammatory and anti-viral responses, the upregulation of endolysosomal degradation pathways and changes in the expression of several molecules involved in the virus entry, such as the components of the above-mentioned receptor complex and furin [31,32]. Therefore, the abnormal sex-hormone secretion derived from the SARS-CoV-2 infection, may also alter the immune-neuro-endocrine network. Nevertheless, evidence remains equivocal as conflicting results have been published. Whereas Li et al. [15] conclude that the average sex hormone concentrations and the ovarian reserve did not significantly change in those COVID-19 women of child-bearing age who experienced self-resolve menstrual changes, Ding et al. [16] point out that female COVID-19 patients probably have an ovarian injury, with a poor ovarian reserve of decreased anti-Müllerian hormone and reproductive endocrine disorder of aberrant sex hormone levels, especially high testosterone and prolactin. On the basis of the above, the question arises if the prevalence and the characteristics of menstrual disturbances could be subject to the fluctuation of the hormone levels in the different stages not only of the menstrual cycle, but also of a woman´s life – in other words, her age −. This assumption may also explain the reported differences for primary COVID-19 outcomes according to the menstrual status and the use of contraceptives [33,34]. In fact, our results from the binary logistic regression support these findings, pointing out perimenopause as an influencing factor in the occurrence of MRD in FMW. Taking into account that this transition phase is mainly characterized by lower circulating estradiol levels, it is supposed that the resulting dampened immune response – e.g. the increased levels of the pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α – and the downregulation of autophagy and the altered expression of ACE2, TMPRSS2, DPP4 and furin [31,32] could underly the increased risk of experience this unexpected event. Conversely, high estrogen levels and consequently the increased estrogen receptor (ER) signaling, may prevent further respiratory complications in SARS-CoV-2-infected pregnant women [34,35]. For this reason, estrogen supplementation has been proposed as a therapeutic approach to reduce the severity of the COVID-19 disease [35,36]. Furthermore, for authors such as Mateus et al. [37], not only estrogen but sex hormones all together might justify the differences between genders and age rates, which makes sense given the opposite effects of testosterone on immune response and virus clearance, in comparison with estradiol [31,32].

On the other hand, other concurrent factors must not be discarded in the prevalence of MRD following SARS-CoV-2 infection in FMW. Firstly, comorbidities may increase the risk of suffer from systemic complications, and hence menstrual changes. In this sense, Li et al. [15] reported that severely ill patients, which had more comorbidities – particularly diabetes, hepatic disease and malignant tumors – and complications than mildly ill ones, were more prone to experience menstrual cycle prolongation; on the contrary, Ding et al. [16] did not observe any differences according to the clinical and gynecological history of the participants. However, the low rate of hospitalization in our study and others [22,24,25] and the marginal significance found between subgroups makes it difficult to draw any conclusion about this issue. According to Suba [35], pre-existing chronic diseases associated with insulin resistant status – e.g. cardiovascular diseases, type-2 diabetes, chronic obstructive pulmonary disease, chronic kidney disease and cancer − aggravate the outcome of COVID-19 infection; insulin resistance, in turn, is associated with a deficient ER signaling and, therefore, with a dysregulated immune response. It should be remembered that HPG axis can be affected by different severe acute illness, leading to decreased levels of progesterone and estrogens [38]. In addition, different degree of ACE2 deficiency are related with some of the above-mentioned diseases [39]. Moreover, regarding gynecological disorders, our results showed that heavy menstrual bleeding may be an influencing factor in the occurrence of menstrual disturbances. In this case, the unbalance between estrogens and progesterone levels may be underlie this unexpected event [40,41], leading to the physiological dysfunctions previously described. Overall, it is worth considering whether the endocrine disorder observed in female COVID-19 patients are consequence of systemic effects rather than local ones. In this sense, Ding et al. [16] point out that the ovarian injury observed in their research must also be linked to nervous system injuries and pituitary dysfunction. However, there are conflicting results about the SARS-CoV-2 neuroinvasion [42]. Finally, stress-associated neuroendocrine-immune mechanisms should also be considered in the occurrence of menstrual disturbances during the pandemic [21,22,25]. In fact, hospitalization itself can be a stressful situation that can induce menstrual abnormalities [10]. Furthermore, as pointed by Barabás et al. [25] the great psychological burden caused by the COVID-19 pandemic on society, with the subsequent increasing levels of depression, may also underlie the menstrual irregularities. Epidemiology shows that women in reproductive age are nearly twice as likely as men to develop major depression [43]. In this condition, the increased levels of the main stress hormone cortisol inhibit the secretion of gonadotropin releasing hormone, which governs the menstrual cycle [25]. Nevertheless, the potential role of mental health in this phenomenon remains controversial and needs to be further investigated. Several other intrinsic and extrinsic factors such as genetics, sociodemographic, culture and lifestyle must also be taken into account [22,25,39,44].

This is one of the few studies conducted worldwide to focus on the impact of COVID-19 disease on the menstrual health of women with secondary amenorrhea, as well as on the potential influence of health-related factors. Although the sample was small and the different subgroups of secondary amenorrhea were not assessed independently, our findings offer a reasonable starting point for future studies. The experimental design could have influenced the detection of significant differences, and therefore causal relationships cannot be properly determined. The risk of recall bias or self-selection must also be considered. Nevertheless, this and other similar survey-based studies have provided insight into different aspects of the menstrual changes following COVID-19 infection/vaccination, when official reports did not yet reflect it. As in similar studies, our findings here might not be applicable to other countries than Spain, due to some of the above-mentioned reasons. Taking into account all of the above, we agree that a longitudinal and multinational study could help to establish the cause-effect relationship and to clarify the factors influencing the occurrence of menstrual alterations after COVID-19 disease.

5. Conclusions

Menstrual disturbances in formerly menstruating women following COVID-19 disease tend to appear more in perimenopause, probably due to the hypersensitivity of the gonadal hormonal axis around this stage of a woman´s life. The lack of scientific evidence on different aspects of women's health, as a consequence of the predominant androcentrism in modern medicine, continues to cause this type of phenomenon to be underestimated or directly ignored, in a so-called gender bias [45]. Therefore, increasing research efforts on this novel field would contribute directly to the achievement of the WHO´s Sustainable Development Goals 3 "Good Health and Well-being" and 5 "Gender equality" [46]. Furthermore, such evidence could help health professionals to provide scientifically up-to-date information to their patients, empowering them to choose the best option for their reproductive decisions, especially in those societies where menstrual health is still a taboo.

Author Contributions: MG and MA have contributed to this manuscript equally.
Conceptualization: CC, ABR, MA; Methodology: CC, ABR, MA; Investigation: MG, CC, ABR; Visualization: CC, ABR; Supervision: CC, ABR; Writing—original draft: MG, CC; Writing—review & editing: MG, CC, ABR, MA.

Funding: This work was supported by the Regional Government of Extremadura-ERDF funds under Grant BBB021- GR21042; Dermofarm S.A. under research agreement with the University of Extremadura (ref. 431/22). Neither the government agency nor the sponsoring company have played a role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of University of Extremadura (ref. 180/2021).

Informed Consent Statement: An informed consent was only obtained from those who agree to be contacted via email by the research group for additional data collection.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

Acknowledgments: The research team would like to thank all the participants who have collaborated in the study in an unselfish manner.

Conflicts of Interest: Authors declare that they have no competing interests.

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