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Abstract

Since the beginning of the COVID-19 pandemic, discussions on social media and blogs have indicated that women have experienced menstrual changes, including altered menstrual duration, frequency, regularity, and volume (heavier bleeding and clotting), increased dysmenorrhea, and worsened premenstrual syndrome. There have been a small number of scientific studies of variable quality reporting on menstrual cycle features during the pandemic, but it is still unclear whether apparent changes are due to COVID-19 infection/illness itself, or other pandemic-related factors like increased psychological stress and changes in health behaviours. It is also unclear to what degree current findings are explained by reporting bias, recall bias, selection bias and confounding factors. Further research is urgently needed. We provide a list of outstanding research questions and potential approaches to address them. Findings can inform policies to mitigate against gender inequalities in health and society, allowing us to build back better post-COVID.

Menstrual cycles may have been disrupted by the COVID-19 pandemic

Features of the menstrual cycle are increasingly recognised as 'vital signs' – acting as both indicators, and possible determinants of broader health and wellbeing (1). For example: infrequent and absent menstruation can be an indicator of reduced fertility (2); irregular and long menstrual cycles have been associated with a greater risk of premature mortality (3); heavy menstrual bleeding can cause severe anaemia (4); dysmenorrhea can be associated with other symptoms such as vomiting, fatigue and dizziness and can affect wellbeing and work productivity (5); and premenstrual symptoms and disorders can affect mental health and quality of life (6). Since the beginning of the COVID-19 pandemic, there have been accumulating discussions on social media and blogs indicating that women have experienced menstrual changes, including altered menstrual duration, frequency, regularity, and volume (heavier bleeding and clotting), increased dysmenorrhea, and worsened premenstrual syndrome (PMS) (e.g. (7)). More recent anecdotal reports of menstrual changes after

vaccination for COVID-19 have fuelled vaccine hesitancy or refusal. There is an important public health imperative for accurate scientific investigation of these phenomena.

Unfortunately, questions about menstruation have been excluded from most largescale COVID-19 studies (including vaccine trials), so it is currently unclear how many women have experienced menstrual cycle changes, how long these changes persisted, and the extent of their impact. In this paper, we aimed to identify and evaluate the existing scientific literature and provide suggestions for future research. Using a pre-specified search protocol (available at: https://osf.io/xg3mw/), we identified seven small studies reporting on menstrual cycle features during the pandemic, either in relation to the COVID-19 pandemic period (Table 1;(8–11)) or COVID-19 infection/illness specifically (Table 2; (12–14)). Articles were included if they described features of the menstrual cycle (e.g., cycle length, regularity, heaviness, pain, PMS symptoms) before and during, or over the course of, the COVID-19 pandemic. The final search was performed on the 8th May 2021.

Table 1. A summary of studies comparing menstrual cycle features during and before the COVID-19 pandemic

Study (publication status)	Comparison	Design	Data collection and sample characteristics	Main findings
Yuksel & Ozgor, 2020 (8)	During the pandemic vs before	Longitudinal data collected prospectively before and during the pandemic via telephone	• Setting: Turkey • Data collection: 1st Feb 2018 – 30 Sep 2019; 11 Mar – 12 Apr 2020 • Selection: Participants originally enrolled in a previous study after admission to a urology and gynaecology outpatient clinic. Participants had to be married, >18 years, not menopausal, no history of urinary incontinence, gynaecological operation or pelvic surgery, no pelvic organ prolapse, malignancy, psychiatric or neurological disease, pelvic radiation, heart disease, renal impairment, hepatitis B or C, or HIV infections. Participants experiencing marital relationship problems were excluded, as were patients who had tested positive for COVID-19 or were living with someone who had tested positive, or were suspected to have COVID-19 • Sample: N=58, mean age=27, mean BMI=28, mostly middle socioeconomic status • Hormonal contraception status: not reported • COVID-19 status: suspected or confirmed cases were excluded	• More women reported having undefined "menstrual disorders" during the pandemic (28%) than prior (12%) [McNemar p=0.008]
Aolymat 2020 (9)	During the pandemic vs before	Cross-sectional online survey	• Setting: Jordan • Data collection: 1st – 8th Sep 2020 • Selection: invited via social media, married women, aged >=18 years • Sample: N=200, mostly aged 25-34 and university educated • Hormonal contraception status: 30% using hormonal contraception • COVID-19 status: unknown	• Fewer women reported having undefined "menstrual disorders" during the pandemic (11% during a very short strict national curfew [McNemar p=0.016], 13% after the curfew was relaxed [McNemar p=0.163]) than prior (18%)
Bruinvels et al., 2021 (10) *(preprint)*	During the pandemic vs before	Cross-sectional online survey	• Setting: Multinational (geographic breakdown not presented) • Data collection: 27th May – 17th Jun 2020 • Selection: aged >=18 years, exercising at any level, eumenorrheic pre-COVID-19 and having experienced a minimum of 9 menstrual cycles or withdrawal bleeds over the past 12 months prior to the pandemic • Sample: N=749, mostly aged 21-40, white and nulliparous, ranging from physically active to elite athletes • Hormonal contraception status: 25% using hormonal contraception • COVID-19 status: 3% diagnosed	• 25% had an increase in cycle length, 20% had a decrease • 36% had a change in bleeding time • Over 50% experienced increased psychosocial menstrual symptoms such as mood changes, lack of motivation, and reduced concentration • 17% said they were worried or stressed by their menstrual cycle changes • Decision tree analysis and Fisher tests suggested use of hormonal contraception was the main factor associated with cycle length change (Fisher p<0.001) and high levels of stress were associated with longer bleeding time (Fisher p<0.001)
Phelan et al., 2021 (11)	During the pandemic vs before	Cross-sectional online survey	• N=1031 • Setting: Multinational (98% based in Ireland or the UK) • Data collection: two weeks in late Sep 2020 • Selection: all women of reproductive age, invited via social media, menstrual data were excluded for women who became pregnant or delivered a baby during the pandemic, or were amenorrhoeic for any reason • Sample: N=1031, mean age=36, mean BMI=26, 97% white • Hormonal contraception status: 23% using hormonal contraception • COVID-19 status: 3% diagnosed	• No change in median cycle length or number of days of bleeding • 53% reported worsening PMS • Women reported new (i.e. did not occur prior to the pandemic) symptoms: 18% new heavy bleeding; 30% new pain; 9% new missed periods • 21% of those who occasionally missed periods pre-pandemic missed periods often during the pandemic • Women who reported low mood, anxiety or significant stress were more likely to report worse menstrual symptoms (p<0.0001)

Table 2. A summary of studies comparing menstrual cycle features in COVID-19 cases or controls, or before vs during illness

Study (publication status)	Comparison	Design	Data collection and sample characteristics	Main findings
Li et al., 2021 (12)	COVID-19 patients vs controls AND COVID-19 patients during disease vs before	Cross-sectional hospital-based study, with a nested case-control study and follow-up 1-2 months after discharge	• Setting: Hospital in Wuhan, China • Data collection: 19th Jan – 1st Apr 2020 (cases); Jun 2019 – Mar 2020 (controls) • Selection: Hospitalised confirmed COVID-19 patients plus hospitalised controls with non-ovarian infertility who received fertility tests in the early follicular phase. Cases and controls were eligible if aged 18-45 years without a history of ovarian dysfunction (in the 6 months before recruitment or COVID-19 onset), not pregnant or lactating, and with no previous hysterectomy or oophorectomy • Sample: N cases=177 (119 non-severe cases, 58 severe); N controls=91; average age=36 • Hormonal contraception status: unknown • COVID-19 status: all cases confirmed with PCR tests	• 20% of COVID-19 cases showed a decrease in menstrual volume and 5% showed an increase. These proportions were greater than in controls (5% of controls showed any change) and they persisted in most COVID-19 cases at follow-up • 18% had cycles >=7 days longer than normal during COVID-19 and 3% had cycles <=7 days shorter. These proportions were greater in COVID-19 cases than controls (6% of controls showed any change) but changes did not persist at follow-up • Women with severe COVID-19 were more likely (34%) than women with mild COVID-19 (19%) to have cycles over 37 days long [univariable logistic regression p=0.001]
Ding et al., 2021 (14)	Severe vs non-severe COVID-19 cases	Cross-sectional hospital-based study	• Setting: Hospital in Wuhan, China • Data collection: 28th Jan – 8th Mar 2020 • Selection: Female patients with COVID-19 who were of reproductive age and younger than 50, excluding any patients with ovarian diseases or ovarian surgery history and those who refused a request for blood collection • Sample: N=78 (61 non-severe cases, 17 severe), median age=43, median BMI=22.7, all had at least one child, 48% had a recent mental disorder, 12% had a history or benign gynaecological disease, 36% had undergone gynaecological surgery • Hormonal contraception status: none had taken oral or transdermal estrogen-containing products (including hormonal contraceptives) • COVID-19 status: all cases confirmed with PCR tests	• Severe COVID-19 cases had higher levels of menstrual pain, irregular periods, amenorrhea and increases in menstrual volume compared to non-severe cases, but none of these changes were significant at P<0.05
Davis et al., 2020 (13) *(preprint)*	During Long Covid* vs before infection	Cross-sectional online survey	• Setting: Multinational (76% based in the USA or UK) • Data collection: 6th Sep – 25th Nov 2020 • Long Covid sufferers (illness lasting over 28 days) • Selection: Advertised on social media and online Long Covid patient support groups. Participants must have had a COVID-19 or suspected COVID-19 infection for longer than 1 week and be >=18 years. Analysis was limited to respondents with illness lasting longer than 28 days and symptom onset between Dec 2019 and May 2020 • Sample: N=1752, mostly white, aged 30-49 • Hormonal contraception status: unknown • COVID-19 status: all had suspected or confirmed COVID-19 infection	• 36% experienced at least one menstrual issue • 26% had abnormally irregular periods; 20% had abnormally heavy periods or clotting and 3% (2-4%) experienced early menopause among women in their 40s • 5% of women over 49 had post-menopausal bleeding/spotting • 35% experienced relapses in COVID-19 symptoms during or before menstruation

**Long Covid incorporates both what the UK's NICE guidelines describe as Ongoing Symptomatic COVID-19 (symptoms continuing 4-12 weeks after initial infection) and Post-COVID-19 Syndrome (symptoms continuing for more than 12 weeks) (https://www.nice.org.uk/guidance/ng188), whereas the clinical term that is emerging in the United States is Post-Acute Sequelae of COVID-19 (PASC) (https://directorsblog.nih.gov/tag/post-acute-sequelae-of-covid-19/). The condition has also been referred to as Post-COVID Syndrome or, colloquially, as 'long haul' COVID. At the time of writing, the WHO has not yet released an internationally standardised clinical definition.*

Possible causal explanations

Figure 1 illustrates potential causal pathways linking the COVID-19 pandemic to menstrual cycle changes.

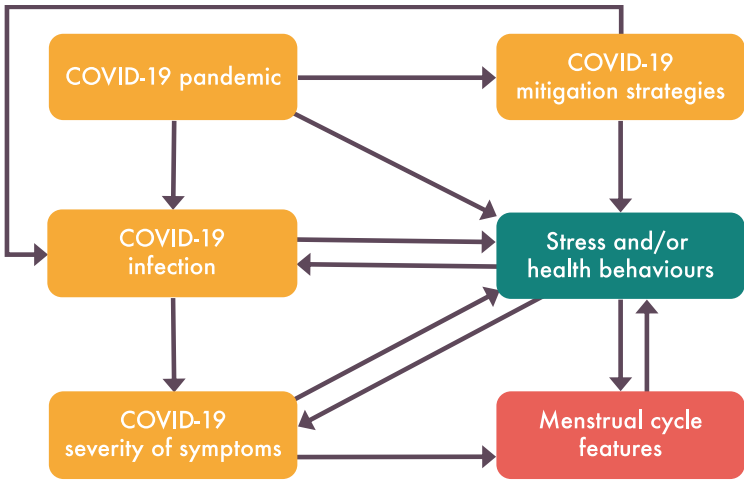

Figure 1. Potential causal pathways from the COVID-19 pandemic to changes in menstrual cycle features

The menstrual cycle is regulated by a complex interplay of hormones that interact with the immune, vascular and coagulation systems, and these interactions can influence menstrual bleeding and severity of (pre) menstrual symptoms (15). These changes will occur following effects on hypothalamic-pituitary-ovarian-endometrial function (Figure 2).

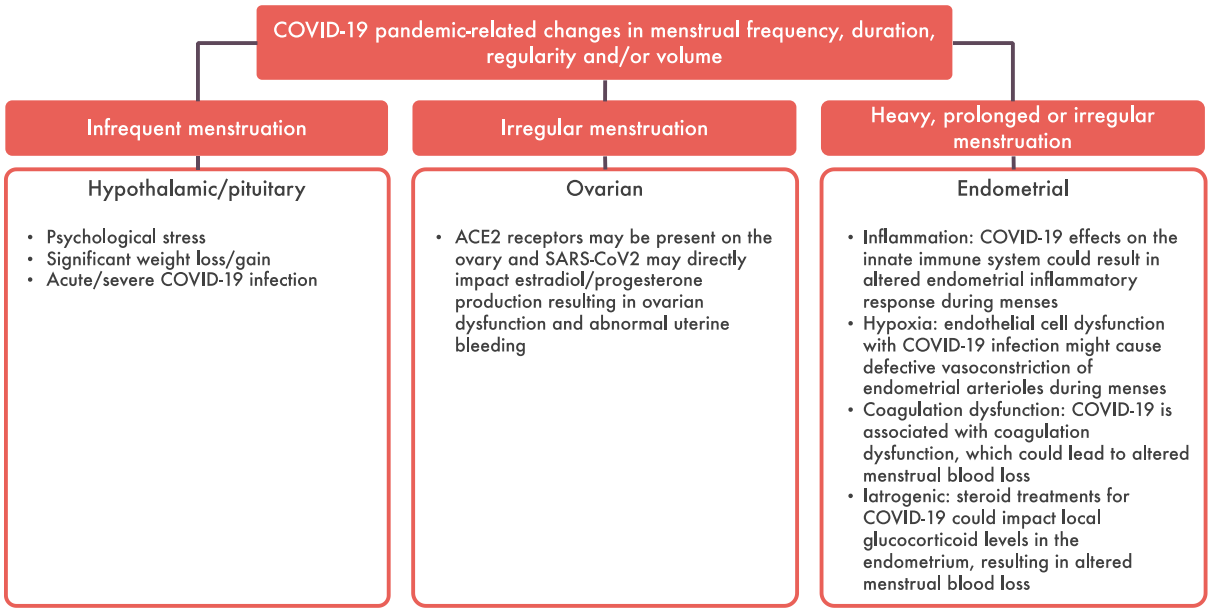

Figure 2. How the pandemic and COVID-19 may impact the hypothalamic-pituitary-ovarian-endometrial axis to alter menstrual frequency, duration, regularity and/or volume (16–19)

Psychological stress is a known risk factor for hypothalamic hypogonadism, resulting in infrequent or absent menstruation (20). The COVID-19 pandemic and mitigation and control strategies like lockdowns and social distancing have led to increases in psychological stress, depression and anxiety, and reductions in general wellbeing, particularly in young adults and women (21). There is also a well-known link between ***changes in weight*** and the menstrual cycle and some (inconclusive) evidence that the menstrual cycle can be altered by ***health behaviours***, such as changes in alcohol consumption, diet and physical activity (22). Studies have identified associations between the pandemic and weight gain and changes in health behaviours (23).

COVID-19 infection and illness could impact hypothalamic-pituitary-ovarian-endometrial function. It is proposed that ACE2 receptors are present on ovarian and endometrial tissue, hence COVID-19 may exert a direct impact on the female reproductive system (24,25). The reproductive hormone progesterone has been described as a predominantly anti-inflammatory hormone (26). Progesterone levels fall dramatically prior to menstruation and there is an influx of inflammatory cells to the local endometrial environment, culminating in shedding of the functional endometrium at menstruation (27) and a heightened inflammatory state. Altered number/phenotype of these leukocytes during or following COVID-19 infection may significantly alter menstrual blood loss. Previous research has shown that viral infection-induced immune disruption can exacerbate menstrual cycle features like premenstrual symptoms (28). Long term symptoms of Ebola infection (Post Ebola Syndrome; possibly analogous to Long Covid) include menstrual cessation or irregularity (29). COVID-19 has also been associated with endothelial cell dysfunction and alterations in the coagulation system, both critical components of endometrial function at menstruation (27,30).

The link between the immune system and the menstrual cycle also provides a biological mechanism for a potential effect in the reverse direction; i.e. of variation in severity of symptoms of COVID-19 (or vaccine side-effects) across different stages of the menstrual cycle (31). This has been documented in the case of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a chronic condition often triggered by infection which has been compared to Long Covid. Female ME/CFS patients often notice flare-ups of their symptoms during the premenstrual phase of their cycles or at the onset of menopause (32).

Potential research bias

In addition to true causal effects, it is also possible that observed associations between the COVID-19 pandemic and menstrual cycles could be explained by various types of bias. These include ***reporting bias*** introduced by heightened health awareness, stemming from people monitoring their own health more closely during the pandemic/illness and consequently being more likely to notice menstrual cycle features and report (apparent) changes compared to pre-pandemic/illness. This type of bias is possible even in hospital-based studies for some menstrual cycle features, like pain and PMS, which are measured subjectively. Many of the studies in Table 1 relied on self-reported, often retrospective or cross-sectional data, which could introduce ***recall bias***. Studies have also relied on small, selected samples, meaning their findings are highly susceptible to ***selection bias***. For example, online surveys select for internet users and are more likely to be completed by and shared among people affected by the condition being studied. This may result in biased estimates as well as limit the generalisability of findings to larger populations. Furthermore, because of ***confounding*** (Figure 1), some studies are unable to distinguish between an effect of COVID-19 infection/illness and other pandemic-related factors, such as stress and changes to health behaviours. Another source of confounding (or mediation, depending on the research question and study sample) is hormonal contraceptive use, which is highly prevalent

among women of reproductive age and can be prescribed for menstrual disorders. Depending on the type of contraceptive, hormonal contraceptive use alters hormonal cyclicity, which can influence immune cyclicity and COVID-19 symptom severity. There is some evidence that estradiol, a component of the combined hormonal contraceptive pill, offers a protective effect against COVID-19 severity and mortality (33), and a study using data from the COVID Symptom Tracker App reported that women aged 18-45 taking the combined oral contraceptive pill had lower rates of predicted COVID-19 and lower hospital attendance than women taking no form of hormone therapy (34). Thus, the relationship between COVID-19 severity and features of the menstrual cycle is expected to differ between hormonal contraceptive users and non-users, as well as between users taking progesterone only and combined hormonal contraceptives. Only four of the seven studies in Table 1 and Table 2 reported data on hormonal contraceptive use for their samples.

The need for further research

While new research is continuously being published on COVID-19, the lack of high-quality research focusing on COVID-19 and the menstrual cycle mirrors the broader focus of medical research, which does not prioritise women's health, particularly outside the context of pregnancy. The finding that menstrual cycles appear to have been affected by the COVID-19 pandemic could have important implications for society, gender-based inequalities and the post-COVID economic recovery. Women are more likely than men to have significant childcare responsibilities and insecure employment and finances (35), and therefore are disproportionately affected by the COVID-19 pandemic (35). Twenty-six percent of the global population are women of reproductive age and the vast majority menstruate. This population is also of working age and/or in education. In addition to affecting women's physical health, mental wellbeing and quality of life (1), menstruation-related symptoms are an important source of economic burden, through decreased productivity and increased absence from the workplace (36) and school (37). Exacerbation of menstrual symptoms during the pandemic may be further compounded by pandemic-related issues with living arrangements and privacy, access to and affordability of menstrual products and reduced availability and accessibility of sexual and reproductive healthcare services (38). Therefore, as the world continues to cope with and begins to recover from the COVID-19 pandemic, there is a need for further research to help understand and mitigate the impacts of the pandemic on menstrual health, which could help to minimise gender-based health and social inequalities. The pandemic has also highlighted the need for more research to inform a broader understanding of how external, environmental factors can influence the menstrual cycle, and how the menstrual cycle can interact with other aspects of health in a bidirectional manner.

Outstanding research questions and considerations

In Table 3 we provide a list of outstanding questions with suggestions for how they might be addressed by future research. These and other questions could be applied to studies of any menstrual cycle feature. Given very recent interest related to COVID-19 vaccinations and menstrual cycle features, we have included questions about this in Table 3. At the time of our most recent literature search (8th May 2021), we did not identify any journal or pre-print research article on this. Previous research on HPV and flu vaccinations have shown these can be associated with short term changes in menstrual cycle features and progesterone levels , with no long term impact on fertility (39,40).

Table 3. Outstanding questions about the relationship between the COVID-19 pandemic and menstrual cycle features

Outstanding research questions	Potential approaches
Describing the relationship between the pandemic and menstrual changes in multiple and/or unselected populations What proportion of women have experienced changes to their menstrual cycle features? Which features were affected? To what extent? Does the association vary by demographic factors like age, parity, ethnicity and socioeconomic position? Is it influenced by any other factors, like hormonal contraceptive use?	Cross-sectional surveys with representative samples; collecting relevant menstrual cycle data in existing longitudinal cohort studies; using smartphone menstrual cycle tracker data collected longitudinally over multiple cycles before and during the pandemic.
The effect of pandemic-related stress and behaviour changes on menstrual cycle features Which pandemic-related stressors and behaviour changes are associated with changes to menstrual cycle features? What are the underlying biological mechanisms? How persistent are these effects; how long do menstrual cycle changes take to revert to normal? Can behaviour-related or stress-relieving interventions help to regulate menstrual changes?	Collecting relevant menstrual cycle data in existing longitudinal cohort studies; using smartphone menstrual cycle tracker data collected longitudinally before and during the pandemic linked with other digital tracker data on activity, diet, mood, etc.
The effect of COVID-19 infection on menstrual cycle features Is the severity of COVID-19 and the types of other symptoms experienced associated with variation in changes in menstrual cycle features? What biological mechanisms explain this effect?	Collecting relevant menstrual cycle data in existing longitudinal cohort studies; clinical studies recording data on menstrual cycle features in hospitalised COVID-19 patients over the course of their illness; using smartphone menstrual cycle tracker data linked with longitudinal COVID-19 symptom data (e.g. via a COVID-19 symptom tracker app); wet lab studies of hormonal, endocrine, vascular and coagulation systems to determine underlying biological mechanisms.
Management strategies during the pandemic How have affected people dealt with changes to their menstrual cycle features? Which self-care approaches have they used and how effective have these been? Have people experienced difficulties accessing support from healthcare providers? Have they had difficulty accessing menstrual products? (There have already been some studies on this, e.g. (38)). Which groups have been most affected? What are the most effective management strategies for healthcare providers to follow during a pandemic?	Cross-sectional surveys on representative samples from well-defined populations, collecting relevant data in existing longitudinal cohort studies; qualitative research using participants selected from cohort and survey participants.
Vaccine interactions How does the COVID-19 vaccine affect menstrual cycle features? Does menstrual cycle stage affect vaccine efficacy or side effects?	Collecting relevant menstrual cycle data in existing longitudinal cohort studies; clinical studies recording data on menstrual cycle stage at vaccination with longitudinal follow-up to collect data on side effects and COVID-19 infection/symptoms; using smartphone menstrual cycle tracker data linked with longitudinal COVID-19 symptom data (e.g. via a COVID-19 symptom tracker app), including dates of vaccination; collecting data on menstrual cycle stage and features at baseline and follow-up in COVID-19 vaccine trials.
The effect of menstrual cycle stage on COVID-19 and Long Covid symptoms Are women more susceptible to coronavirus infection, or at higher risk of experiencing severe symptoms, at certain stages of the menstrual cycle (e.g. during the peri-menstrual phase, when ovarian hormone levels are transiently but significantly decreased)? What are the underlying biological mechanisms? Does type and severity of acute COVID-19 or Long Covid symptoms show variation over the menstrual cycle? Does the menstrual cycle and/or female reproductive hormones explain the higher incidence of Long Covid in working-age women than in men? Does hormonal therapy or contraception affect symptoms? Does cycle stage influence the accuracy of COVID-19 tests? If Long Covid symptoms indeed fluctuate according to the menstrual cycle, what can this suggest about the pathophysiology of Long Covid itself?	Using smartphone menstrual cycle tracker data linked with longitudinal COVID-19 symptom data (e.g. via a COVID-19 symptom tracker app); collecting relevant menstrual cycle data in existing longitudinal cohort studies of Long Covid; wet lab studies of the underlying biological mechanisms.
Long term and latent effects of COVID-19 (and COVID-19 vaccines) on reproductive health Do COVID-19 and/or COVID-19 vaccines affect timing of menarche (if pre-pubertal children are infected) or the menopause? Are there effects on fertility (both achieving and maintaining a pregnancy)? How? What are the best strategies to mitigate any negative effects?	Longitudinal cohort studies with data on timing and severity of COVID-19 symptoms, timing and type of vaccine and long-term follow-up (directly or via linkage) for data on reproductive health outcomes; long-term follow-up of vaccine trial participants (directly or via linkage) for data on reproductive health outcomes; in future, retrospective cohort studies collecting/linking data on past exposure to COVID-19/COVID-19 vaccines with data on reproductive health.

In particular, future studies that minimise selection and recall bias are needed, for example, prospective cohort studies and studies that use routinely collected clinical data. Care should be taken to control for key confounding factors, selected depending on the exposure and outcome of interest. In most cases, it will be important to stratify by hormonal contraceptive use.

To be most informative, future research should use harmonised or standardised definitions of menstrual cycle features, which will enable comparison across studies. For example, for menstrual bleeding disorders, studies should use the definitions of normal and abnormal menstrual bleeding produced by the global Menstrual Disorders Committee and endorsed by the International Federation of Gynaecology and Obstetrics (FIGO) (41). As has been highlighted in the COVID-19 research more widely, there is also a need to use common definitions of COVID-19 and Long Covid (42). Adherence to such recommendations during study design will increase consistency and facilitate the interpretation of results to drive clinical and societal impact.

Finally, as with COVID-19, menstrual health is a global issue, so future research should focus on populations from a variety of countries and settings. Four of the seven studies in Table 1 were conducted on populations from low- or middle-income countries (China, Jordan and Turkey) and two were open to people from any country (although we note that high income countries were over-represented in these). Future research should further expand the target populations and seek to include a representative sample. For their target populations, all future studies should consider and adequately describe the situation with the pandemic (for example, which restrictions were in place, for how long, how they were enforced, general compliance, etc), and social attitudes to menstruation, awareness of menstrual health and availability and accessibility of menstrual products and health services. These factors provide much needed social context to enable findings to be interpreted and compared across populations.

Feasibility to conduct future research following these recommendations will vary by research question. Even for individual research questions, it is likely that no single approach will be sufficient to address the question conclusively, but combining evidence from different studies is likely to make a step-change in comparison to existing evidence. For example, data from smartphone menstrual cycle tracker apps are collected frequently and longitudinally on large numbers of women, but the data are self-reported, affected by a high degree of missingness, and collected on a select group of smartphone users. Conversely, collecting relevant data on menstrual cycle changes within existing cohort studies enables longitudinal collection of data and missingness may be lower (and potential selection bias can be investigated with existing data), but frequency of repeat data collection and sample sizes are likely to be smaller than datasets collected from smartphone apps. Cautious interpretations from individual studies will be necessary. More conclusive inferences about the direction of any causal effect may be possible by triangulating evidence garnered using several different approaches with different and unrelated key sources of bias (43).

Conclusion

Anecdotal evidence discussed online, and a small number of scientific studies of variable quality, suggest that many women have experienced changes to features of their menstrual cycle during the COVID-19 pandemic, either due to pandemic-related factors like stress and behaviour changes and/or due to COVID-19 illness itself. Further research into the effects of COVID-19 and other health related exposures on women's menstrual health is urgently needed. Findings can inform policies to mitigate against gender inequalities in health and society, allowing us to "build back better" post-COVID.

Contribution to authorship

GCS: conceptualisation, manuscript writing. GS, GK, KE, ZO, GF, JM, AA, LDH, AF, DAL: manuscript review and edit. JM and DAL: clinical expertise.

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