COVID-19 and Gynecologic Health

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Gynecologic Health in the Pandemic

COVID-19 Infection

- Menstruation
- Fertility
- Health Inequity
- Miscarriage
- Sexual health
- Urinary Symptoms
- And many more.....

COVID-19 Vaccine
Gynecologic Health in the Pandemic

Menstrual symptoms often discounted by clinicians/researchers

Gynecologic health EXCLUDED from vaccine trials and COVID studies

Menstruation/fertility concerns can drive major health care decisions

Worldwide environment of amplified misinformation

Racism
Structural, Institutional, Interpersonal, Internalized
Can the COVID-19 vaccine affect your period?

PSST! THE ANSWER IS: WE'RE NOT SURE YET

Thousands reported
after COVID-19 vaccine

FACT: Being near someone who's received a COVID-19 vaccine can’t affect your menstrual cycle.

Does the COVID-19 vaccine cause infertility?

No. There is no evidence that the COVID-19 vaccine (or any vaccine) causes infertility.

Pandemic has affected periods

Vaccines and pandemic stress have all been linked to distributions to menstrual cycles.
SARS-CoV-2 Vaccines do not contain mRNA for Syncytin-1

Antibodies against Spike do not impact Syncytin-1

Vaccines do not cause female infertility

Spike Protein
SARS-CoV-2 mRNA vaccines create antibodies to Spike

Syncytin-1
Placenta protein involved in pregnancy growth

Lu-Culligan, et al, PLOS Biology, May 2022
Abbasi J, JAMA News, Feb 2022
Very low gene expression of SARS-CoV-2 receptors ACE-2 and proteases (TMPRSS2) in uterus, ovary, fallopian tubes

No SARS-CoV-2 found in endocervical or vaginal swabs or endometrial biopsies

Goad, et al, PLOS One, Dec 2020
Herarejos-Castillo, et al, Fertility and Sterility, Aug 2020
Soilen et al, Rev Chilena Infectol, Oct 2021
Takmaz et al, PLOS, Sept 2021
Miguel-Gomez, AJOG, March 2022
Immune Activity in Reproductive Tract

Vagina, Cervix, Uterus have immune activity

Endometrium produces prostaglandins and cytokines (eg IL-1, IL-6, TNFa)
Hypothalamic-Pituitary-Ovarian (HPO) messaging supports regular timed monthly menses but......

30% of females will have some type of abnormal uterine bleeding by age 50
What can cause changes to the menstrual cycle?

- Weight change
- Exercise
- Sleep
- Depression/Anxiety
- Acute and Chronic illness

Any stress can increase cortisol and disrupt GnRH secretion.
Several studies with online surveys report increase in menstrual changes during pandemic

Limitations
Cross-sectional (one point in time)
Bias in who answers surveys
Majority are white

Demir, et al, Triangle of COVID, anxiety, menstrual cycle, Jo of Ob and Gyn, 2021
Phelan et al, Impact of COVID-19 Pandemic on Women’s Reproductive Health, Front Endocrin, March 2021
Preethi et al, Pandemic induced stress and obesity leading to abnormal uterine bleeding, Health Science Reports, Feb 2022
Images from United Nations Population Fund
Menstrual Changes during Pandemic

- 18,000 menstrual app users
- Mean age 33 years, 80% >college
- 29% Great Britain, 23% USA
- 2019 PRE-pandemic vs March-Sept 2020

Nguyen et al, PLOS One, October 2021
Menstrual Changes during Pandemic

Nguyen et al, PLOS One, October 2021

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Cycle length</td>
<td>29.40 (29.34–29.46)</td>
<td>29.16 (29.10–29.22)</td>
</tr>
<tr>
<td>Menstrual duration</td>
<td>4.21 (4.19–4.23)</td>
<td>4.32 (4.30–4.34)</td>
</tr>
</tbody>
</table>

- No clinically significant differences in menstruation during pandemic
- High pandemic stress not associated with abnormal cycle
- Fewer anovulatory cycles DURING pandemic
Menses and COVID-19 Infection
Menses Volume change with COVID-19

- N=177, hospitalized in China with COVID
- 75% unchanged, 20% decreased, 5% increased
- No difference by disease severity

Li et al, Analysis of COVID-19 of sex hormones and menstruation in COVID-19 women of child-bearing age, RBMO, 2021
• 28% with menstrual cycle changes
• 99% returned to normal within 2 months
• More cycle changes than controls without COVID

Li et al, Analysis of COVID-19 of sex hormones and menstruation in COVID-19 women of child-bearing age, RBMO, 2021
Menstrual Changes after COVID

- N=158 in Indonesia, hospitalized with COVID
- Menses before infection by reported history and 3 months after

<table>
<thead>
<tr>
<th>Menstrual parameter</th>
<th>Before COVID-19 Infection (n = 158)</th>
<th>After COVID-19 Infection (n = 158)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cycle length (n [%])</td>
<td>17 (10.8%)</td>
<td>24 (15.2%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>• &lt; 24 days</td>
<td>125 (79.1%)</td>
<td>103 (75.1%)</td>
<td></td>
</tr>
<tr>
<td>• 24–32 days</td>
<td>16 (10.1%)</td>
<td>31 (19.6%)</td>
<td></td>
</tr>
<tr>
<td>• &gt; 32 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual irregularity (n [%])</td>
<td>28 (17.7%)</td>
<td>56 (35.4%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Heavy menstrual bleeding (n [%])</td>
<td>43 (27.2%)</td>
<td>53 (33.5%)</td>
<td>0.041*</td>
</tr>
</tbody>
</table>

Persistent abnormalities in cycle length 3 months after COVID
Worse mental health associated with menstrual changes

Muharam, et al, PLOS One, June 2022
Menstrual Changes after COVID

- N=127 in Arizona (CoVHORT study)
- 16% reported change in menses after COVID (cycle length, duration, flow)
- More COVID symptoms=more likely to have abnormal menses

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>COVID-19 positive participants</th>
<th>SARS-CoV-2-positive participants who did not report a change in their menstrual cycle after infectiona,b (n=107; 84.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in premenstrual syndrome symptoms (e.g., greater than usual mood swings, feelings of anxiety or depression, tiredness, trouble sleeping, bloating or stomach pain, breast tenderness, changes in appetite or sex drive)</td>
<td>9 (45.0)</td>
<td>—</td>
</tr>
<tr>
<td>Most common COVID-19 symptoms, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (79.0)</td>
<td>29 (27.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (57.9)</td>
<td>21 (19.6)</td>
</tr>
<tr>
<td>Body aches and pains</td>
<td>10 (52.6)</td>
<td>17 (15.9)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>10 (52.6)</td>
<td>17 (15.9)</td>
</tr>
</tbody>
</table>

Khan, et al, AJOG, Feb 2022
Menses and COVID-19 Infection

There may be transient changes to menses but...
Data is very limited: More research needed!

Small sample sizes
Often hospitalized patients
Short-term or no follow-up
Recall bias vs. Prospective follow-up
Menstrual Changes after Vaccination

- Survey studies have reported changes in cycle length, duration, volume
- July 15, 2022: Online survey of 39,129 vaccinated people, 18-80 years

56%: Change in menstrual flow
42%: Heavier bleeding
No difference by use of hormonal contraception

High rates of breakthrough bleeding in people who do not menstruate
Gender-affirming hormones (39%), LARC (71%), postmenopausal (66%)

LIMITATIONS: Sample of app users,
84% white, no pre-vaccine data,
no comparison group of unvaccinated

Menstrual Changes after Vaccination

- 3,959 people with menstrual cycles tracked on app “Natural Cycles”
- Age 18-45 years, US residents, vaccinated vs unvaccinated
- Prospectively collected data, 3 months prior vs 3 months after vaccine

**Menstrual Changes after Vaccination**

Edelman, et al, Obstet Gynecol, Jan 2022

<table>
<thead>
<tr>
<th></th>
<th>Cycle Length</th>
<th>Menses Length</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Change in Length (d)</td>
</tr>
<tr>
<td><strong>1st dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>1,556</td>
<td>0.07 (−0.22 to 0.35)</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>2,403</td>
<td>0.71 (0.47–0.94)</td>
</tr>
<tr>
<td><strong>2nd dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>1,556</td>
<td>0.12 (−0.15 to 0.39)</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>1,919</td>
<td>0.91 (0.63–1.19)</td>
</tr>
</tbody>
</table>

Data are mean (98.75% CI) unless otherwise specified.

* Differences are from mixed-effects models with random intercepts and random slopes at the individual level, an interaction between vaccination status and prevaccination–postvaccination timing, and adjusted for age, race, body mass index, educational attainment, parity, and relationship status.

<1 day difference in cycle length between vaccinated and unvaccinated

If both doses within one menstrual cycle, cycle 2.32 days longer
Menstrual Changes after Vaccination

- 19,622 people with menstrual cycles tracked on app “Natural Cycles”
- Age 18-45 years, global population (Europe/Canada/US)
- Vaccinated vs unvaccinated (all vaccines)
- Prospectively collected data, 3 months prior vs 3 months after vaccine

<1 day difference in cycle length between vaccinated and unvaccinated

If both doses within one menstrual cycle,
3.91 (CI 2.5-5.3) days longer

Edelman, et al, BMJ Medicine, August 2022
Menstrual Changes after Vaccination

Small, temporary changes in cycle length of <1 day
No change in menstruation duration

Limitations of these studies:
Sample is app users
Missing demographic data
Restricted to normal cycles pre-COVID

Edelman, et al, BMJ Medicine, August 2022
Multiple studies have found no increased risk of miscarriage with COVID-19 infection

PRIORITY Study
Prospective nationwide cohort (N=1330)

- 139 enrolled <14 weeks gestation
- 6% loss <20 weeks in both COVID+ (n=94) and COVID- (n=15)
- Upper CI for loss 13.4% vs 10% in clinically recognized pregnancies

Jacoby et al, AJOG, Oct 2021
Most studies show...

• No change in AMH, FSH, Estradiol with infection
• No impact on ability to get pregnant without assistance
• No impact on IVF outcomes

## COVID-19 and Gynecology

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>COVID-19 Infection</th>
</tr>
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<tbody>
<tr>
<td>Menstruation</td>
<td>Small, transient change in cycle length</td>
<td>Possible changes, more data needed</td>
</tr>
<tr>
<td>Female fertility</td>
<td>No impact</td>
<td>No impact</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>No impact</td>
<td>No impact</td>
</tr>
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</table>
RECOVER and Gynecologic Health

RECOVER participants answer questions about... menstruation, sexual function, menopause, urinary symptoms, fertility

Strengths of RECOVER
Large sample (10,000 females), Diverse US population, Longitudinal follow-up