COVID-19 Vaccines and Fertility

08/19/2021

Key Messages

- In human and animal-model studies, there is no evidence for increased risk to female fertility following vaccination against severe acute respiratory coronavirus 2 (SARS-CoV-2) using BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna) or AZD1222 (AstraZeneca) vaccines.

- Prior to the announcement of emergency use authorization for Coronavirus Disease 2019 (COVID-19) vaccines, there were claims on social media of a risk of placental damage due to the cross-reactivity of the human placenta protein syncytin-1 and the SARS-CoV-2 spike protein (vaccine-elicited). These claims are not supported by evidence, but are being cited as reasons for vaccine hesitancy.

- To date, there is no evidence of an association between COVID-19 vaccination and menstrual irregularities or fertility; however, research is limited, and evidence should continue to be monitored.

- There is no evidence to date to suggest that COVID-19 vaccination impacts male fertility. Studies evaluating male sperm parameters before and after receiving two doses of mRNA vaccine (Pfizer-BioNTech, Moderna) have not demonstrated differences.

- Unless otherwise contraindicated, couples or individuals planning to conceive should receive the COVID-19 vaccination.

Issue and Research Question

As vaccines against SARS-CoV-2 became widely available in early 2021, information began circulating indicating there were concerns by some individuals and groups about the potential impacts of COVID-19 vaccines on male and female fertility. Among these concerns are potential damage to reproductive organs/cells and the potential for adverse events following COVID-19 vaccination, including menstrual irregularities. For example, in a commentary on vaccine hesitancy among ethnic minority groups, a consistent concern raised was the longer-term effects of COVID-19 vaccination, such as fertility (Reid and Mabhala 2021).

To assess the evidentiary basis for these concerns, Public Health Ontario (PHO) examined the scientific evidence surrounding female and male reproductive health following COVID-19 vaccination. Out-of-scope for this Evidence Brief are studies on the potential impacts of COVID-19 vaccination after conception (e.g., fetal development, early pregnancy loss, newborn outcomes, breast-feeding).
Methods

On August 11, 2021, PHO Library Services conducted searches of primary and preprint literature using MEDLINE, Embase and National Institutes of Health COVID-19 Portfolio databases (search strategies available upon request). We searched PubMed and Google Scholar on August 12, 2021, for additional articles of interest. We included English-language, peer-reviewed and non-peer-reviewed (preprint) records that described COVID-19 vaccines and fertility.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in this document is only current as of the date of respective literature searches.

Fertility Concerns: Vaccine Claims and Hesitancy

Main findings: Prior to the announcement of emergency use authorization for COVID-19 vaccines (in particular the mRNA-based vaccines), claims were made on social media that there is a risk of placental damage due to the cross-reactivity of the human placenta protein syncytin-1 and the SARS-CoV-2 spike protein (vaccine-elicited). These claims are not currently supported by evidence but are being cited as reasons for vaccine hesitancy in some individuals.

Vaccine claims related to fertility

The sharing of disinformation on social media platforms has fuelled much of the concern regarding the fertility safety of COVID-19 vaccines. Claims about vaccination and infertility have emerged in relation to other diseases, in which campaigns have been launched during polio and human papillomavirus vaccination programs, despite scientific evidence to the contrary. In addition, claims on the COVID-19 vaccines has contributed to vaccine hesitancy even among healthcare workers.

- Claims were made concerning the similarities between the human placenta protein syncytin-1 and the SARS-CoV-2 spike protein, leading to cross reactivity and potential damage to the placenta; however, there is no evidence that antibodies produced against the SARS-CoV-2 spike protein cross-react with syncitin-1 (Male 2021). The source was a blog that falsely quoted a Pfizer official; the erroneous claim was that antibodies elicited from COVID-19 vaccines would attack the placenta. There is no significant similarity between the amino acid sequences of SARS-CoV-2 spike protein and syncytin-1 and convalescent serum from patients with COVID-19 does not react with syncytin-1.

- On December 1, 2020, two physicians petitioned the European Medicines Agency (EMA) to withhold emergency use authorization of the Pfizer-BioNTech vaccine due to concerns for female infertility (but acknowledged the lack of evidence). Sajjadi et al. (2021) used Google Trends to analyze results for the search terms "infertility," "infertility AND vaccine," and "infertility AND COVID vaccine" in the United States (US) (February 4, 2020 to February 3, 2021). At peak interest (100), the forecasted relative search volumes interest for "infertility" was 45.5 (95% confidence interval [CI]: 33.27–57.66; p<0.001); for "infertility AND vaccine" was 0.88 (95% CI: 2.87–4.63; p<0.001); and for "infertility AND COVID vaccine" was 0.29 (95% CI: 2.25–2.82; p<0.001). The actual relative search volumes at peak searching represented 120%, 11,251%, and 34,900% relative increases, respectively, when compared with forecasted values. Claims correlated with increased internet searches related to infertility in the US.
Vaccine hesitancy and fertility concerns

We examined eight studies (7 primary studies and 1 systematic review) that evaluated vaccine hesitancy and fertility concerns among vaccine hesitant individuals.

- In a systematic review of 12 studies (with sample sizes of 85 to 20,852,692 individuals), Galanis et al. (2021) (preprint) reported on factors contributing to vaccine hesitancy. Some of the factors associated with having higher vaccination uptake included white race, male sex, higher education level, and higher income. Reasons for declining COVID-19 vaccination included, but were not limited to, concerns with fertility, pregnancy and breastfeeding; however, proportions for each concern were not reported.

- In a survey of 16,292 healthcare workers in Pennsylvania, United States (US) (December 2020), Meyer et al. (2021) reported that 16.3% would not get the vaccine and 28.4% were undecided. The proportion of vaccine hesitant respondents who were concerned that the “vaccine could impair fertility” was not reported. The mean age of the survey respondents was 43 years and 73% of respondents were female.

- In a survey of 1,367 community individuals in Ontario, Canada (January 15 to February 15, 2021), Syan et al. (2021) (preprint) reported that 17.2% were unwilling to get a COVID-19 vaccine. Seven percent of those unwilling to be vaccinated reported their reason as concerns with “pregnancy or lactation”, but do not report specific concerns with fertility. Survey participants had a mean (standard deviation [SD]) age of 38.6 years (±14), 60.3% were female, 65.5% had a Bachelor’s degree or higher education, and 80.5% were white. Those more likely to decline vaccination were female (p=0.002) or have less than a Bachelor’s degree for education (p<0.001).

- In an April 2021 survey of 1,033 parents of children less than 18 years old in California, US, Naso et al. (2021) (preprint) reported that 8% of parents (vaccinated and unvaccinated) were hesitant when considering vaccination of their children, and 19% of vaccine hesitant individuals indicated they were concerned with future infertility of their child after they have received vaccination. Fifty-six percent of respondents were female, and the median age of respondents was 41 years (interquartile range [IQR]: 35–46). Eighty-five percent completed the survey immediately after vaccination and 15% prior to vaccination. Seventy-six percent of respondents identified as Latino. In a multivariate analysis, vaccine hesitancy in parents was associated with having younger children (e.g., child aged 0–4 years: adjusted odds ratio [aOR]: 3.43; 95% CI: 1.46–8.09; relative to having a child aged 16–17 years).

- Tulloch et al. (2021) (preprint) used a survey to identify the factors contributing to healthcare workers declining COVID-19 vaccination rates in Liverpool, United Kingdom (UK) (January 2021). Among unvaccinated staff (n=1,009), the proportion that declined vaccination due to “staff member was pregnant, planning a family, or concerned about long term fertility impact of vaccine” was 5.6% (95% CI: 4.3–7.2), much lower compared to the number one reason of “staff member believes that not enough research has been performed into vaccine safety” (37.0%; 95% CI: 34.0–40.0).

- Sutton et al. (2021) surveyed patients, healthcare workers and staff at a single facility in New York, US (January 2021) to evaluate acceptance of COVID-19 vaccines. Of the 656 participants in the non-pregnant participant group, 22.6% of them either declined vaccination, or were still unsure. In people who declined vaccination or were hesitant, respondents were moderately
concerned that the vaccine might make them infertile (scored on a scale from 0 “low or no concern” to 5 “highly concerned”). The mean (SD) age of respondents was 37.0 years (±16.0).

- In a survey of 514 healthcare workers in London, UK (December 1–21, 2020), Abuown et al. (2021) reported that 24% of respondents were likely to decline vaccination, and 17% were unsure if they would get vaccinated. Among the 169 respondents to ‘If you would say no to having the COVID-19 vaccine, what other information or factors might influence you to have the vaccine?’, less than five said “effect on fertility”. Female respondents were more likely to reject vaccination (OR: 1.26; 95% CI: 1.12–1.42).

- Using Google Trends, Diaz et al. (2021) investigated Google queries related to COVID-19 vaccines and fertility between October 24, 2020 and January 27, 2021. The most queried term was ‘COVID Vaccine Fertility CDC’ (+2,944%), followed by ‘COVID Vaccine Fertility’ (increase of 711%), ‘COVID 19 Vaccine Infertility’ (+529%), ‘COVID Vaccine Infertility’ (+264%), and ‘COVID Vaccine and Infertility’ (+208%) (all p<0.001). Overall, the search volume index (SVI) increased by 485%. The increase in search terms related to fertility coincided with the Centers for Disease Control and Prevention (CDC) announcement of the emergency use authorization for the Pfizer-BioNTech vaccine made on December 11, 2020. SVI was highest in US, Canada, UK, and Ireland.

Female Fertility

Main findings: In human clinical and animal-model studies, there has been no evidence for an increased risk to female fertility following vaccination against SARS-CoV-2 using Pfizer-BioNTech, Moderna or AstraZeneca vaccines. There is also no evidence that the antibodies to the SARS-CoV-2 spike protein (derived from infection, vaccination, or convalescent plasma) and syncytin-1 cross-react. As such, there is currently no evidence to support the claim that COVID-19 vaccines contribute to female infertility. To date, there has been no evidence for a link between COVID-19 vaccination and menstrual irregularities or infertility; however, evidence should continue to be monitored. We should note that most of the studies reviewed reported on surrogate outcomes of ovarian function and cellular development, not on pregnancy, live birth and miscarriage rates.

On August 12, 2021, the Society of Obstetricians and Gynaecologists of Canada (SOGC) released the following statement via social media: “The SOGC recommends that all individuals who are pregnant or those trying to become pregnant should receive the #COVID19 vaccination; there is no evidence to suggest that COVID-19 vaccines will affect fertility.”

Human clinical studies

We examined five studies looking at the potential impacts of COVID-19 vaccination on female fertility.

- Male (2021) reported on data collected in the UK during trials of the Pfizer-BioNTech, Moderna and AstraZeneca vaccines, in which females were advised not to become pregnant during the trial. The rate of pregnancy in vaccinated and unvaccinated females did not differ, indicating vaccination did not impact their ability to become pregnant. For the Pfizer-BioNTech vaccine, pregnancy occurred in 0.058% (11/18,860) of vaccinated subjects (includes males and females), compared to 0.064% (12/18,846) of unvaccinated subjects. Similar results were reported for the Moderna vaccine (0.040%, 6/15,181 vs. 0.046%, 7/15,170) and the AstraZeneca vaccine (0.21%, 12/5,807 vs. 0.15%, 9/5,829).

- Safrai et al. (2021a) (preprint) reported on a retrospective single-center study in Israel that assessed women’s in vitro fertilization (IVF) treatment parameters and pregnancies before and
after their vaccination with 2 doses of the Pfizer-BioNTech vaccine (February to May 2021).\textsuperscript{19} In 47 women, the mean (SD) period between intracytoplasmic sperm injection (ICSI) was 362 days (±368) between the two ovum pick-ups (OPUs). The characteristics of ICSI cycles before and after the vaccination were similar (p$$\geq$$0.01) for all the parameters (e.g., number oocytes picked up, number of fertilized oocytes). The mean (SD) age of patients was 37.4 years (±7.5).

- In an observational study at a tertiary medical center in Israel (date not reported), Orvieto et al. (2021) examined couples undergoing consecutive ovarian stimulation cycles for IVF before and after receiving two doses of the Pfizer-BioNTech vaccine, and reached the OPU stage.\textsuperscript{20} Thirty-six couples had IVF treatment 7–85 days after vaccination. No in-between cycles differences were observed in ovarian stimulation and embryological variables (e.g., mean number of oocytes per OPU, mean number of mature oocytes, peak estradiol and progesterone levels; p>0.05) before and after vaccination. The mean (SD) age of female participants was 37.3 years (±4.6) and the mean (SD) time from second dose of vaccine to OPU cycle was 32.6 days (±17.5).

- In a cohort study of female patients undergoing oocyte retrieval at a single IVF center in Israel (February to March 2021), Bentov et al. (2021) (preprint) reported on potential impacts of COVID-19 infection and vaccination (Pfizer-BioNTech, 2 doses) on ovarian function (vaccinated, n=9; COVID-19 infection, n=9; non-exposed to virus or vaccine, n=14).\textsuperscript{21} There were no differences in the three groups with respect to ovarian follicle quality reporting parameters (e.g., steroidogenesis, oocyte yield). Natural and vaccine-elicited anti-COVID IgG antibodies were detected in the follicular fluid in levels proportional to the IgG serum concentration. The mean (SD) age of all participants was 33.8 years (±4.8).

- In an observational study from Singapore of frontline workers (n=15) with no evidence of COVID-19 exposure (February to April 2021), Mattar et al. (2021) (preprint) examined cross-reactivity to syncytin-1 on the developing trophoblast following vaccination with Pfizer-BioNTech.\textsuperscript{22} None of the patients had placental anti-syncytin-1-binding antibodies following vaccination (0–4 days, or 4–7 weeks post vaccination). The Pfizer-BioNTech vaccine did not produce a humoral response to syncytin-1, indicating that cross-reactivity is unlikely. The mean (SD) age of participants was 40.4 years (±12.2).

**Animal-model studies**

We examined two studies that investigated potential impacts of COVID-19 vaccination on female rodent fertility.

- In a developmental and reproductive toxicity (DART) study in rats vaccinated with two human doses of the Pfizer-BioNTech vaccine prior to mating (n=44; control, n=44), vaccination did not have any impact on female mating performance, fertility, or any ovarian or uterine parameters (e.g., number of corpora lutea, number of implantations) (Bowman et al. 2021).\textsuperscript{23}

- In a DART study in CD-1 mice vaccinated with the AstraZeneca vaccine, Stebbings et al. (2021) reported that there was no difference between vaccinated (n=25) and control (n=25) female rats in terms of mating performance, fertility, or other uterine and ovarian parameters.\textsuperscript{24}

**Menstrual irregularities**

Much of the currently available information about menstrual irregularities in women following COVID-19 vaccination has been anecdotal, with few sources offering details about the prevalence and type of menstrual irregularity. Menstrual irregularities have included heavy menstrual bleeding and
intermenstrual bleeding.\textsuperscript{25,26} Media have reported varying numbers of post-vaccination females experiencing menstrual irregularities (e.g., Canada: 27.8\% of vaccinated women; US: 140,000 reports).\textsuperscript{27,28} To date, there has been no evidence for a link between COVID-19 vaccination and menstrual irregularities; however, more research is needed to better assess a possible association (e.g., Kurdoğlu 2021).\textsuperscript{29}

- As of August 4, 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK has received 30,304 reports of menstrual irregularities after female vaccination with Pfizer-BioNTech, Moderna, AstraZeneca vaccines.\textsuperscript{30} Irregularities included heavier than usual periods, delayed periods, and unexpected vaginal bleeding. The Commission on Human Medicines’ COVID-19 Vaccines Benefit Risk Expert Working Group and the Medicines for Women’s Health Expert Advisory Group, after reviewing the data, concluded that there is no link between changes to menstrual periods following COVID-19 vaccines. Approximately 44,800,000 doses of vaccine have been administered to women in the UK, suggesting that these reports of menstrual irregularities are relatively uncommon. The MHRA reports that most of the reported menstrual problems were transient, and that these irregularities have been reported in women with acute or long COVID-19.

- Duncan (2021), using data from the ZOE COVID Study application in the UK (as of July 2, 2021), reported there were approximately 3,000 cases of women having menstrual changes after vaccination.\textsuperscript{31} Menstrual changes included unexpected bleeding, missed/late periods, and particularly heavy bleeding. By the end of April 2021, the number of women of reproductive age who received the vaccine was over 657,000, with less than 0.1\% (0.5\% by end of June 2021) reporting a menstrual irregularity or change. The author stated that it is difficult to link vaccination with these menstrual changes, as changes could be due to numerous factors, including: 1) irregular periods in pre-menopausal women; 2) impacts of stress on hormones regulating the menstrual cycle; 3) that immunization impacts uterine cytokines; and/or 4) use of non-steroidal anti-inflammatories after vaccination to help with injection pain or fever may have impacted menstrual flow.

- Merchant (2021) reported that, as of April 5, 2021, using data from the MHRA in the UK, there were approximately 958 reports of menstrual irregularities in women following COVID-19 vaccination.\textsuperscript{25} Six hundred and forty-three of these cases were reported following the AstraZeneca vaccine, the remainder following the Pfizer-BioNTech vaccine. The author posits that vaccine-induced thrombocytopenia may be the cause for heavy menstrual bleeding, which could possibly lead to anemia. However, platelet counts or platelet function were not assessed therein.

### Male Fertility

**Main findings:** There is no evidence to date to suggest that COVID-19 vaccination impacts male fertility. We examined three studies that investigated sperm parameters before and after vaccination with two doses of an mRNA vaccine (Pfizer-BioNTech, Moderna), and no differences were demonstrated.

- In a single-center prospective study in Florida, US (December 2020 to January 2021), Gonzalez et al. (2021) reported there were no significant decreases in sperm parameters before and after vaccination with the Pfizer-BioNTech (n=21) and Moderna (n=24) vaccines.\textsuperscript{32} Medians for sperm concentration, semen volume, total mobile sperm count (TMC), and total motility significantly increased following two doses of vaccine (\textit{p}<0.02). Increases in sperm parameters were within normal individual variation. Prior to receiving the first vaccine dose, participants provided a
semen sample after a median abstinence period of 2.8 days (IQR: 2–3) and at a median of approximately 75 days (IQR: 70–86) after the second dose. The median age of 45 healthy participants was 28 years (IQR: 25–31).

- In an observational study of 36 couples undergoing IVF treatment in Israel (date not reported), Orvieto et al. (2021) reported that there were no differences in mean sperm parameters (i.e., semen volume, sperm concentration, sperm percent motility, pre-wash TMC; p>0.05) before and after receiving two doses of the Pfizer-BioNTech vaccine in male participants.20 The mean (SD) period from second vaccine dose to sample collection was 33.3 days (±14.9) (range: 7–85). The mean (SD) age of male patients was 40.1 years (±4.8).

- In a single-center prospective study of 43 men undergoing IVF treatment in Israel (February to May 2021), Safrai et al. (2021b) (preprint) reported that sperm parameters (i.e., sperm volume, sperm concentration, TMC; p>0.3) did not differ before and after two doses of the Pfizer-BioNTech vaccine.33 The mean (SD) age of participants was 37.1 years (±6.6) and the mean (SD) time from first vaccine dose to sample collection was 33.6 days (±20.2); the number of days from second dose to sample collection was not reported. The authors reported similar results in sub-set analyses of normosperm patients and those with male infertility.

Conclusions

To date, there is no evidence that COVID-19 vaccines have a negative impact on female or male fertility. In addition, concerns about fertility and vaccination may be the result of claims made on social media platforms. Overwhelmingly, medical science experts agree that currently there is no evidence of an increased risk of infertility after COVID-19 vaccination (also see Additional Resources).2,8,26,34,35 In addition, the risks of severe COVID-19 and adverse outcomes in pregnant women outweigh any perceived negative impacts of vaccination.8,36

While initial studies show no concern for fertility in vaccine recipients, final reports and studies on vaccine safety during pregnancy are underway.34 Further research is needed to confirm results from short-term follow-up clinical studies to those from long-term follow-up studies. In addition, study results need to be confirmed using all vaccines authorized for use or emergency use. The majority of the evidence comes from single arm cohorts, retrospective studies and historical controls; however, high-quality prospective cohorts that provide results adjusted for confounding factors and compared to a proper control group are needed.

While there are no completed clinical studies on COVID-19 vaccination and abnormalities in menstrual cycles, several studies are in progress.26,28,31

Practice Implications

Individuals looking to become pregnant should consult with their healthcare provider when receiving any vaccine.

- For the COVID-19 vaccines approved for use in Canada, the World Health Organization (WHO), CDC and EMA do not recommend that individuals seeking to become pregnant delay vaccination until after conception.34

- Unless otherwise contraindicated, couples or individuals wishing to conceive should be vaccinated as soon as possible.2,37 In healthy people planning to become pregnant, or who are
pregnant, the only contraindication for vaccination is hypersensitivity reactions to vaccine ingredients (e.g., polyethylene glycol) or to a previous COVID-19 vaccine.\textsuperscript{38-40}

### Additional Resources

**Ontario Ministry of Health**

- COVID-19 vaccination: special populations vaccination in pregnancy & breastfeeding patient decision-making (version 2.0) tool\textsuperscript{41}

**Society of Obstetricians and Gynaecologists of Canada (SOGC)**

- SOGC COVID-19 vaccination in pregnancy FAQ for health care providers\textsuperscript{39}
- SOGC COVID-19 vaccination in pregnancy FAQ for patients\textsuperscript{38}
- SOGC statement on COVID-19 vaccination in pregnancy\textsuperscript{40}

**Canadian Fertility and Andrology Society (CFAS)**

- Fertility care during the COVID-19 pandemic: guiding principles for COVID-19 vaccination in the fertility patient\textsuperscript{42}

**National Advisory Committee on Immunization’s (NACI)**

- An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI) recommendations on the use of COVID-19 vaccines\textsuperscript{43}

**American Society for Reproductive Medicine (ASRM)**

- ASRM, ACOG and SMFM issue joint statement: medical experts continue to assert that COVID vaccines do not impact fertility\textsuperscript{44}
- UPDATE No. 11 – COVID-19 vaccination\textsuperscript{45}

**Association of Reproductive and Clinical Scientists (ARCS) and British Fertility Society (BFS)**

- COVID-19 vaccines and fertility\textsuperscript{46}
References


18. Society of Obstetricians and Gynaecologists of Canada (SOGC). The SOGC recommends that all individuals who are pregnant or those trying to become pregnant should receive the #COVID19 vaccination; there is no evidence to suggest that COVID-19 vaccines will affect fertility via @SOGCorg [Twitter]. 2021 Aug 12 [cited 2021 Aug 13]. Available from: https://twitter.com/SOGCorg/status/1425876801688162310


