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RESEARCH ARTICLE

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Adherence to and early adverse events of COVID-19 vaccine in a cohort of 600 Italian breastfeeding and pregnant physicians

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ABSTRACT

Pregnant and breastfeeding women (PBW) have been excluded from COVID-19 vaccine registry and the majority of post-marketing trials, despite the recognized increased risk of severe infections and complications. The lack of efficacy and safety data prevented the formulation of specific indications/guidelines for vaccination and could have also contributed to increased vaccine hesitancy (VH) in PBW. The aim of this cross-sectional study is to assess the rate and predictors of VH, and early adverse events (AEFI) following COVID-19 vaccine in PBW with a cross-sectional study. In January 2021, a purposely designed questionnaire was administered to 600 PBW part of a Facebook group of physicians, immunized with two doses of Comirnaty®. Thirty-eight (29%) pregnant women and 13 (2.8%) breastfeeders were hesitant. The only statistically significant negative predictor of COVID-19 VH appeared to be having had the flu shot in 2020/2021 (OR: 0.35; 95% CI: 0.13–0.97; $p = .044$). Approximately 27% of PBW reported hesitancy toward the 2020/2021 season influenza vaccine. Among the vaccinated subjects, 51.6% of pregnant and 75.2% of breastfeeding women reported at least one symptom after the first, and 82.4% and 81.6%, respectively, after the second dose. Nausea/vomiting, fatigue, headache and arthralgia/myalgia were the most common symptoms; dizziness, shivering, syncope and limb paresthesia were rarely reported. Among infants of breastfeeding mothers, six experienced fever, five rash and four moderate and self-limiting diarrhea. Preliminary data on mRNA COVID-19 vaccine in PBW and in their infants are reassuring since AEFI, although frequent, are typically mild and similar to those occurring in the general population, and in PBW after other vaccines. Larger studies with longer follow-up after vaccination are strongly recommended to develop recommendations in these patients.

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Introduction

The ongoing COVID-19 pandemic keeps putting health systems and societies to the test. The most recent data from high vaccination coverage countries indicate vaccination campaigns as the main viable strategy to tangibly impac the pandemic course.[1] In this context, identifying and implementing vaccination coverage in more susceptible subjects represents a priority.

Pregnancy has been associated with a higher risk for severe COVID-19 infections requiring intensive care unit admission with invasive ventilation and death, especially in case of maternal age >35 years, black/Asian/Hispanic ethnicity, or cardiovascular and metabolic comorbidities.[2–7] Some studies have also reported an increased risk of preterm births and cesarean deliveries.[8] Nonetheless, because of safety concerns, pregnant and breastfeeding women, and women who intended to become pregnant during the study have been purposely excluded by the vast majority of pre- and post-marketing trials assessing the efficacy and safety of COVID-19 vaccines [9–12] without justification, especially after the removal of pregnant women from "vulnerable patients" in the CIOMS and WHO ethical guidelines on human research.[13]

Due to the lack of specific scientific or governmental directives/guidelines, in the majority of countries at the beginning of vaccination campaigns, pregnant and breastfeeding women had to choose autonomously about the opportunity to get vaccinated based on their subjective risk-benefit perception, while in others vaccination was temporarily withheld for lactating women. This was originally decided due to the absence of breastfeeding women among the vaccine approval trial subjects, and to the consequent lack of data on their risk from being vaccinated.[14]

This could have contributed to increased vaccine hesitancy (VH) [15] among pregnant and breastfeeding women, with detrimental health and socio-economic consequences associated with the persistence of COVID-19 pandemic.

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Based on these premises, our study aimed at assessing the rate of VH at the beginning of the Italian COVID-19 vaccination campaign, together with the type and relative incidence of Adverse Events Following Immunization (AEFI) in a large cohort of pregnant and breastfeeding physicians.

Materials and methods

Study design and data collection

A cross-sectional study was devised using data collected from an online survey using a purposely designed questionnaire (the English version can be found in the Supplementary Material section), delivered from January 1 to 28 2021, to female members of the Facebook group "Coronavirus, SARS-CoV-2 e COVID-19 gruppo per soli medici," that have been pregnant or breastfeeding for the entire duration of the survey. Only physicians could be part of this group, which counted 100,141 members; medical license was verified at admission.

Participants were interviewed about socio-demographic and clinical aspects, including history of vaccination, COVID-19-related experiences, perceived risk of infection and attitude toward COVID-19 vaccination. In patients receiving vaccine during pregnancy/breastfeeding, the type and severity of early adverse events following immunization (AEFIs) occurring after the first and/or the second dose were investigated in the mother and in the newborns in breastfeeding women.

All participants received two doses of Comirnaty®, as it was the only vaccine available at the time of data collection. Participants were asked to complete the survey 72 h after vaccination if they did not experience any side effects, or after the resolution of the AEFI.

This study was found to be exempt by Harvard Longwood Medical's Institutional Review Board as this was not found to be human subjects research. Participant informed consent was requested before answering the questionnaire.

Statistical analysis

All variables were reported as absolute and relative frequencies. Determinants of VH were assessed by uni- and multivariate analyses. A backward stepwise analysis with a significance level of entry and removal equal to 0.2 was run to define the variables to be included in the final multiple logistic regression model, according to the results of univariate models and to the principles of parsimony and biological plausibility. Results of multivariate analyses were reported as odds ratio (OR) and 95% Confidence Interval (CI) (95% CI). $\chi 2$ was adopted to compare the incidence of AEFIs between first-dose and second-dose.[16] All tests were performed in a two-sided manner, using a nominal significance threshold of $P < .05$. All statistical analyses were performed using Stata Statistical Software 15 (StataCorp, College Station, TX).

Systematic literature review

PubMed database (https://pubmed.ncbi.nlm.nih.gov) was searched to identify relevant studies written in English and published between 30 November 2020 and 15 May 2021, following PRISMA guidelines.[17] Search was performed using the purposely created string: "(covid or sars-cov-2 or ncov or covid19 or coronavirus) and (vaccine or vaccination or vaccin*) and (pregnancy or pregnant or breastfeeding)." To maximize the string sensitivity, a combination of keywords and indexed terms (e.g., PubMed Medical Subject Headings) was used. Reference lists of selected studies were also searched to find additional pertinent articles.

Results

Sample characteristics

The sample included 600 female physicians aged from 24 to 60 years old; 131 were pregnant and 469 breastfeeding. The main sample features are reported in Table 1. The great majority (n = 114, 87.0% of pregnant women; n = 367; 78.3% of breastfeeding ones) were aged 31–40 years old. Eleven (8.4%) pregnant and 26 (5.5%) breastfeeding women had diabetes mellitus. Nine (6.9%) pregnant and 29 (6.2%) breastfeeding women had had SARS-CoV-2 infection.

Vaccine hesitancy (VH)

Only 26.7% (n = 35) of pregnant women had received COVID-19 vaccine. Of the remaining, 20.6% (n = 27) reported to be prone to be vaccinated but were not allowed to by health authorities, while 23.7% (n = 31) presented health-related contraindications, and 29.0% (n = 38) were hesitant (Table 1).

Table 1. The main epidemiological and clinical sample features.

Feature (n, %)	Breastfeeding *N* = 469	Pregnancy *N* = 131
Age		
24–30 years	20 (4.3)	9 (6.9)
31–40 years	367 (78.3)	114 (87.0)
41–50 years	81 (17.3)	8 (6.1)
51–60 years	1 (0.2)	0 (0.0)
Italian region		
Northern	206 (42.9)	73 (53.4)
Central	150 (32.0)	38 (29.0)
Southern	113 (24.1)	20 (15.3)
Cohabitation with subject/s aged ≥65 years		
Yes	42 (9.0)	18 (13.7)
No	427 (91.0)	113 (86.3)
Diabetes mellitus		
Yes	26 (5.5)	11 (8.4)
No	443 (94.5)	120 (91.6)
Previous confirmed COVID-19 infection		
Yes	29 (6.2)	9 (6.9)
No	440 (93.8)	122 (93.1)
Vaccination for influenza (2020/21)		
Yes	340 (72.5)	99 (72.8)
No	129 (27.5)	35 (26.7)
COVID vaccination intentions		
Vaccinated during breastfeeding/pregnancy	382 (81.4)	35 (26.7)
Extremely/somewhat likely to get vaccinated but it was not permitted by the authorities	61 (13.0)	27 (20.6)
Unsure or unlikely	13 (2.8)	38 (29.0)
Unsure	1 (0.2)	8(6.1)
The vaccine might have dangerous side effects	*8 (1.7)*	*26 (19.8)*
Past SARS-CoV-2 infection	*2 (0.4)*	*2 (1.5)*
I have certified contraindications	11 (2.3)	31 (23.7)
No answer	2 (0.4)	0 (0.0)

Table 2. Variables associated with vaccine hesitancy in pregnant physicians (n = 100) in multiple logistic regression analysis.

	Multivariable model		
	OR	95% C.I.	*p*-value
Age			
24-30	5.03	0.47–53.6	.180
31-40	1.00		
41-50	0.69	0.07–6.82	.750
Italian Region			
Northern	1.00		
Central	0.96	0.34–2.67	.938
Southern	0.57	0.16–1.99	.382
Cohabitation with subject/s aged ≥65 years	0.31	0.58–1.62	.164
Diabetes mellitus			
Previous confirmed COVID-19	3.20	0.66–15.47	.148
infection	1.89	0.27–13.08	.520
Vaccination for influenza (2020/21)	0.35	0.13–0.97	**.044**

Table 3. Variables associated with vaccine hesitancy among breastfeeding physicians (n = 453) in multiple logistic regression analysis.

	Multivariable model		
	OR	95% C.I.	*p*-value
Age	1.46	0.17–12.5	.728
24-30	1.00		
31-40	0.51	0.63–4.08	.525
41-50			
Italian Region	1.00		
Northern	2.01	0.54–7.44	.295
Central	1.43	0.31–6.69	.647
Southern			
Cohabitation with subject/s aged ≥65 years*	1.00		
Diabetes mellitus	4.25	0.81–22.30	.087
Previous confirmed COVID-19 infection*	1.00		
Vaccination for influenza (2020/21)	0.27	0.09–0.86	**.026**

*Variable predicts failure perfectly.

Among breastfeeding women, 81.4% (n = 382) had been vaccinated; 13% (n = 61) were denied vaccination by health authorities despite their willingness; only 2.8% (n = 13) were hesitant (Table 1).

About one-third (26.7% of pregnant and 27.5% of breastfeeding) of respondents reported hesitancy toward the influenza vaccine in the 2020/2021 season (Table 1).

We compared hesitant and confident respondents on sociodemographic characteristics, having Diabetes Mellitus (DM) as a comorbidity, COVID-19 related experiences and being vaccinated for influenza during 2020/2021. Results indicate that both pregnant and breastfeeding physicians who had been vaccinated against the flu in 2020/2021 were more likely to accept COVID-19 vaccination in a statistically significant way (OR: 0.35; 95% CI: 0.13–0.97; $p = .044$) (Tables 2, 3).

Reported Adverse Events Following Immunization (AEFI)

Overall, 336 participants (31 pregnant and 315 breastfeeding) who had received COVID-19 vaccine filled the questionnaire section on AEFI occurred after the first dose, and 191 (17 pregnant and 174 breastfeeding) after the second dose. The list of reported AEFI is summarized in Table 4.

Of the 31 immunized pregnant women, 16 (51.6%) reported at least one symptom after the first, and 14 (82.4%) of those who responded regarding the second vaccine dose. After the first dose, 64.5% (n = 20) experienced nausea/vomiting, 25.8% (n = 8) fatigue, and 12.9% (n = 4) headache and arthralgia/myalgia; flushing and low back pain were more rare. After the second dose, 76.5% (n = 13) of respondents reported nausea/vomiting, 70.6% (n = 12) fatigue and 41.2% (*n*=) arthralgia/myalgia.

Among breastfeeders, 75.2% (n = 237) reported at least one symptom occurring after the first dose, and 81.6% (n = 142) after the second. The most common AEFI occurring after the first dose were nausea/vomiting (60%; n = 189), fatigue (28.3%; n = 89), and headache (26.3%; n = 83). Rarer events (overall listed as "Others" in Table 4) included dizziness, shivering and limb paresthesia. After the second dose, 51.1% (n = 89) of them reported nausea/vomiting, 48.9% (n = 85) fatigue, and 49.4% (n = 86) arthralgia/myalgia. Two episodes of syncope were recorded after both the first and the second dose (for details, see Table S2 in Supplementary Material section).

Significant differences ($p < 0.05$) of incidence for the various symptoms after the first and the second dose are highlighted in Table 4.

Overall, 18 breastfeeders reported fever (33.3%, n = 6), rash (27.8%, n = 5) and diarrhea (22.2%, n = 4) in their infants, after the first or second vaccine dose (see Table S3 of the Supplementary Material).

Rapid systematic literature review

Literature review identified only one article [18] presenting original data on AEFI in PBW; the remaining were opinion pieces and comments expressly stating the exclusion of pregnant women from pre-marketing clinical trials, and the primary need for post-marketing studies on this topic. The study by Gray et al.,[18] including 84 pregnant and 31 breastfeeding women vaccinated with mRNA vaccines (58 with Moderna and 57 with Pfizer-BionTech), was kept. The flow chart of the study selection process is reported in Fig S1 of the Supplementary Material.

The main reported AEFI after the first dose were injection site soreness (88%), fatigue (14%) and headache (8%) in pregnant women; injection site soreness (67%), headache (30%), muscle aches (13%) and fatigue (13%) in breastfeeders. As for the second dose, the most frequently experienced AEFI were injection site soreness (57%), fatigue (53%) and muscle ache (48%) in pregnant women; injection site soreness (61%), muscle ache (57%) and fatigue (50%) in breastfeeders. The results of our and the other studies are reported in Table S4.

Discussion

Principal findings

Our study, performed in January 2021, at the beginning of the Italian COVID-19 vaccination campaign, revealed a VH rate of 29% in pregnant, and of 2.8% in breastfeeding women.

AEFI were very common, especially after the second vaccine dose (51.6% in pregnant and 75.2% in breastfeeding women after the first, and 82.4% and 81.6%, respectively, after the second dose), although typically mild (i.e. nausea, fatigue, headache, myalgia and arthralgia). The patient cohort presented similar baseline features and showed comparable

Table 4. Adverse Events Following Immunization (AEFI) reported by vaccinated pregnant (a) and breastfeeding (b) women.

a)	Pregnancy		
	First dose (n = 31)	Second dose (n = 17)	*p*
b)	Breastfeeding		
	First dose (n = 315)	Second dose (n = 174)	*p*
Symptoms (n, median)	1 [0;1]	2 [1;4]	
Patients with at least one symptom (n, %)	16 (51.6)	14 (82.4)	**.043**
Local reactions (i.e. pain, itching or paresthesia) in the vaccination site	2 (6.5)	1 (5.9)	.900
Fever	2 (6.5)	2 (11.8)	.530
<38°C	*2 (6.5)*	*2 (11.8)*	*.530*
>38°C	*0*	*0*	*0*
Fatigue	8 (25.8)	12 (70.6)	**.004**
Myalgia/arthralgia	4 (12.9)	7 (41.2)	**.033**
Headache	4 (12.9)	4 (23.5)	.351
Tachycardia/tachyarrhythmia	3 (9.7)	1 (5.9)	.650
Diarrhea	1 (3.2)	0 (0.0)	.744
Nausea/vomiting	20 (64.5)	13 (76.5)	.396
Other	1* (3.2)	1** (5.9)	.664
Symptoms (n, median)	1 [0;2]	2 [1;4]	
Patients with at least one symptom (n, %)	237 (75.2)	142 (81.6)	.107
Local reactions (i.e. pain, itching or paresthesia) in the vaccination site	13 (4.1)	6 (3.4)	.710
Fever	12 (3.8)	58 (33.3)	**<.001**
<38°C	*7 (2.2)*	*38 (21.8)*	*<.001*
>38°C	*5 (1.6)*	*17 (9.8)*	*<.001*
Fatigue	89 (28.3)	85 (48.9)	**<.001**
Myalgia/Arthralgia	54 (17.1)	86 (49.4)	**<.001**
Headache	83 (26.3)	68 (39.1)	**<.001**
Urticaria	5 (1.6)	2 (1.1)	.698
Tachycardia/Tachyarrhythmia	15 (4.8)	6 (3.4)	.495
Lymphadenopathy	11 (3.5)	12 (6.9)	.095
Diarrhoea	7 (2.2)	6 (3.4)	.423
Nausea/Vomiting	189 (60.0)	89 (51.1)	.059
Flushing	15 (4.8)	14 (8.0)	.145
Syncope	2 (0.6)	2 (1.1)	.551
Other	10* (3.5)	11** (6.3)	.107

*See Supplementary Material, Table S3; **Flushing; ***Low back pain.

incidences for common AEFI if compared to the study by Gray et al.[18] Headache, myalgia and fatigue are the most frequently reported, especially after the second dose in breastfeeders.

Results in the context of what is known

Our study responds to numerous calls for research on the efficacy and safety of COVID-19 vaccine in PBW.[19–21] Indeed, the exclusion of pregnant and breastfeeding women from the registration and the majority of post-marketing studies for safety concerns prevented the assessment of risk-benefit, and, thus, the definition of guidelines by scientific societies to be followed by health authorities. Altogether, these elements are significantly contributing to increase the apprehension and VH related to the new COVID-vaccines.[22]

Notably, the gap found between pregnant and breastfeeding women VH was also noted by another study conducted in Germany on COVID-19 vaccinations and which emphasized that pregnant women, having a higher perceived risk, stated that additional reliable scientific studies showing the safety of the vaccination in pregnancy, as well as more information on risks of a COVID-19 infection and benefits of the vaccination were needed.[23] Another recent study conducted in Italy found how having received influenza vaccination during past seasons (at least one in the past 5 years) was significantly associated with taking other vaccinations during pregnancy, confirming our findings. In addition, the implementation of vaccination education interventions on maternal immunization during antenatal classes significantly improved adherence to vaccinations during pregnancy.[24]

At the same time, some general considerations on COVID-19 mRNA vaccine safety are worth mentioning. First, mRNA vaccines, although with different platforms, have been used since 2006, even in PBW, with reassuring data on safety and efficacy. In particular, immune response against the viral mRNA – encapsulated in a lipid nanoparticle and delivered into the host cells – should mainly occur in regional lymph nodes, like in the nonpregnant persons,[25] with an expected similar efficacy. Second, the claims of possible cross-reactions between syncytin 1 and the spike protein have been disproved by several observations. It is in fact unlikely that antibodies recognizing the SARS-CoV-2 spike protein can cross-react with the human placental protein syncytin 1 and damage the placenta since no significant increase in miscarriage rates has been reported in women infected shortly before conceiving or in early pregnancy; moreover, the amino acid sequence of SARS-CoV-2 spike protein and syncytin 1 are not so similar, and the convalescent serum from patients with COVID-19 does not react with syncytin. Vaccines did not prevent female rodents from becoming pregnant nor harmed the pups if given

during pregnancy.[11] Finally, 57 women become pregnant across the trials, despite being asked to avoid it, with a miscarriage rate comparable to non-vaccinated women.[26]

Our data, in line with those of Gray et al.[18] demonstrated the overall safety of Comirnaty® in PBW at early follow-up, since the great majority of AEFIs were minor, short-lasting, self-limiting or curable with acetaminophen (paracetamol, that is acceptable in pregnancy); moreover, the type and severity were similar to those experienced by pregnant/breastfeeding women after other commonly administered vaccines against other pathogens, such as influenza o.[27] Incidence of fever, fatigue, headache, muscle and joint pain was in line with the general population immunized with Comirnaty®, with the exception of less frequent diarrhea.[28]

Clinical implications

The currently available data on the risk of severe COVID-19 disease in pregnancy and of vertical transmission during pregnancy and lactation, on the one hand,[2–7] and on vaccine tolerability and safety for both the mother and the newborn, here including our data, on the other, support the indication of vaccination in PBW.[29,30]

Moreover, PBW should be informed on the frequent occurrence and most common type of AEFIs, although generally not severe and similar to those occurring after other types of vaccines, as well as about the opportunity of consuming acetaminophen to control them.[2,7]

Research implications

Since AEFI have been evaluated only in a limited cohort of cases and within a short-term follow-up, research on efficacy and safety of COVID-19 vaccination in PBW, including patients with conditions/comorbidities considered at higher risk,[2–6] is strongly suggested, to define the real vaccine impact on disease incidence and severity.[7,19,31]

As per the other vaccines that are currently routinely administered during pregnancy, because of the peculiarities of the profile and functioning of the immune response during pregnancy itself, and the potential implications for the newborn, COVID-19 vaccines deserve dedicated, well-structured trials, in which PBW should be enrolled after signing specific consent.[32] This is especially important for the prospect of rapidly achieving herd immunity through mass vaccination.[33] For newborns from vaccinated mothers, not only side effects but also the presence and efficacy of maternal antibodies crossing the placenta should be monitored.[7,32]

Study strengths and limitations

Main strengths of the study are the large and homogeneous cohort – especially considering that pregnant and breastfeeding women are a minority of the population and that all had received both doses of the same time of vaccine – the voluntary participation to the study and the enrollment of physicians, associated, at least in theory, with higher propensity and reliability in reporting and describing AEFIs, respectively.

On the other hand, a survey performed in a Facebook group restricted to physicians might not be representative of the entire female population: among other differences, willingness to vaccinate might be significantly higher than in the general population. Social media use requires some degree of digital literacy and a specific interest in the topics discussed in the group. A recall bias regarding self-reporting of AEFIs has also to be taken into account, as the survey was administered nearly 1 month after the start of the Italian anti-COVID vaccination campaign. The effect of social desirability bias, especially at such a sensitive time in the course of the COVID pandemic and in a population that might have felt under a strong social pressure to vaccinate, has also to be taken into account. Making the survey anonymous was aimed at tackling such bias. Moreover, as is to be expected with any single-country study, vaccine acceptance might be influenced by cultural factors. At the same time, the most important demographic characteristics of our sample and the rate of adherence to vaccination are similar to those registered in the Italian general population, supporting the representativeness of the study sample.

Conclusions

The currently available data support an advantageous safety-risk profile of mRNA COVID-19 vaccine in PBW. These reassuring data could help in contrasting VH while promoting the inclusion of these specific patients in future studies. Indeed, trials on larger cohorts and with longer follow-ups are strongly advised for the various types of available COVID-19 vaccines on mothers and their newborns, to univocally define the attitude of health authorities in terms of recommendation/opposition to immunization in pregnant and breastfeeding women. In particular, future studies could help in stratifying the risk profile according to gestational age and/or associated comorbidities (i.e. gestational diabetes or hypertension). This would play a pivotal role in the definition of targeted vaccination campaigns, thus implementing adherence to vaccination.

All the authors approved the final version of this manuscript. DG, MM (Matteo Monami) and MM (Marco Montalti) had full access to all data presented in the study and take responsibility for the integrity and the accuracy of the data analysis.

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Contribution to authorship

Conceptualization: all authors contributed equally; Data curation and formal analysis: M.M. (Marco Montalti), M.M. (Matteo Monami) and D. G.; Methodology: M.M. (Marco Montalti), F.G., Z.D.V. and D.G.; Supervision: D.T., E.M. and D.G.; Writing – original draft: M.M. (Marco Montalti), F.G. and Z.D.V; Writing – review & editing: E.M., M.M. (Matteo Monami) and D.G.

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