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ASSISTED REPRODUCTION TECHNOLOGIES

Vaccine hesitancy, distress, and medical mistrust in women considering or undergoing fertility treatment during the COVID-19 pandemic

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Abstract

Objective To evaluate perceptions of COVID-19 vaccination and psychological distress during the COVID-19 pandemic in women considering or undergoing fertility treatment.

Materials and methods Cross-sectional anonymous survey (n= 3558) from a single academic fertility center. A total of 1103 patients completed the survey (response rate = 31% of those emailed, 97.6% of those who opened the email). Participants were randomized 1:1 to a one-page educational graphic providing facts and benefits regarding COVID-19 vaccination. Assessment of vaccine hesitancy was conducted via the Medical Mistrust Index (MMI). Mental health was assessed via the Patient Health Questionnaire Depression Scale (PHQ-8) and the Generalized Anxiety Disorder-7 (GAD-7).

Results The majority of participants were married, nulliparous, white women with > 1 year of infertility and moderate to severe distress. As compared to the non-intervention group, participants in the intervention group believed that COVID-19 vaccination does not cause genetic abnormalities in a fetus (98.0% v. 94.2%) and infertility (99% v. 96.2%) and that severe infection has been associated with pregnancy (81.3% v. 74.6%) (P <0.05). Higher MMI scores were associated with vaccine hesitancy ($P = 0.01$), higher GAD-7 scores ($P = 0.01$), and greater concerns about side effects of the vaccine ($P < 0.05$). GAD-7 and PHQ-8 scores were not associated with vaccine hesitancy. Nearly a quarter of participants initiated psychiatric treatment after March 2020.

Conclusion Vaccine hesitancy was associated with mistrust of the medical system. Psychological distress was highly prevalent in this study. Efforts should be made to improve patient trust and provide psychological support for fertility patients.

Keywords COVID-19 · Coronavirus · Pregnancy · Fertility · Vaccine hesitancy

Introduction

The rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to a global pandemic beginning in the early 2020. The USA continues to be one of the nations with the highest burden of 2019 coronavirus disease (COVID-19) deaths and infections. Since 2020, nearly 50 million cases of COVID-19 have been reported in the USA alone, with close to 800,000 deaths. By early 2021, the Food and Drug Administration (FDA) authorized the emergent use of three SARS-CoV-2 vaccines in the USA (Pfizer-BioNTech COVID-19, Moderna, and Johnson & Johnson). None of these vaccines have been shown to have adverse pregnancy-related outcomes or infant adverse outcomes in vaccination trials and thus pregnant and postpartum women, as well as women attempting to conceive, were encouraged to receive the vaccine [1, 2].

Since the onset of the pandemic, multiple studies have demonstrated that pregnant women who are COVID-19 positive have an increased risk of severe infection [1–3]. Pregnant women with COVID-19 have been shown to be 3 times more likely to be admitted to an intensive care unit (ICU) and require respiratory support compared to non-pregnant women with COVID-19. Symptomatic pregnant women with COVID-19 have also been reported to have a 70% increased risk of death compared to non-pregnant women with COVID-19 with pregnant women of color having a

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greater risk of death from COVID-19 than pregnant white women [3, 4]. There have also been reports of increased stillbirth and preterm delivery associated with COVID-19 infections in pregnancy [5].

As a result of the significant risks of the COVID-19 virus in pregnant women and the safety of the vaccines (which was supported by limited research at the time of vaccine availability), the American College of Obstetricians and Gynecologists (ACOG), the American Society for Reproductive Medicine (ASRM), and the Society of Maternal Fetal Medicine (SMFM) issued a joint statement in February 2021 and recommended COVID-19 vaccination for women who were trying to conceive or who were pregnant [6]. However, despite these recommendations, anecdotal stories of women and men who feared that vaccination could directly harm their chances of conceiving or cause negative pregnancy outcomes began to be shared through social media [7]. To date, no study has identified an association between COVID-19 vaccination and infertility in either men or women and COVID-19 vaccination has not been shown to increase the risk of miscarriage or other pregnancy risks and is therefore considered safe in pregnancy [3–5, 8–10].

In addition to unfounded concerns related to the effects of the COVID-19 vaccines on reproduction, distrust of information about the vaccines from healthcare systems and organizations has also resulted in vaccine hesitancy [11, 12]. Medical mistrust is defined as the extent to which an individual or a community demonstrates a lack of trust in the healthcare system, medical scientists, and government health agencies, as well as doctors or other healthcare professionals [11]. Medical mistrust has previously been shown to affect vaccine hesitancy (e.g., influenza vaccine hesitancy) and shown to be higher among racial and ethnic minority groups, especially among Black individuals [12]. Cultural mistrust of medical systems is another factor that is likely contributing to the disproportionate impact of COVID-19 within the Black community [13]. Cultural medical mistrust has been attributed to the tendency to mistrust traditional medical institutions, which is deeply rooted in inequalities in medical treatment and unethical/abusive historical medical research (e.g., the Tuskegee Syphilis Experiment) and has been linked to COVID-19 vaccination hesitancy among the Black community [13].

In addition to individuals in the Black community, the emergent approval of the COVID-19 vaccines was met by vaccine hesitancy among several groups of individuals. For example, vaccination rates were shown to be lower among individuals under the age of 50, in women, Black individuals, and among people without a college degree [14]. In addition to anxiety related to the pandemic and vaccines, high levels of psychological distress were also found among people of color and other minority communities due to ongoing experiences of racism and discrimination [11].

High levels of distress were also seen among patients trying to conceive during the pandemic because of the effect of the pandemic on their lives in general, but also specifically related to their chances of conceiving. Fertility treatments were paused for several months in the early 2020 and delays in restarting treatment were also reported. It is generally accepted that fertility patients often report high levels of distress related to infertility and delays in fertility care due to the pandemic appear to have intensified that distress [15, 16]. Patients undergoing fertility treatment have also been reported to alter their behaviors (e.g., lifestyle habits) in order to maximize their chances of conceiving [17]. Concerns related to the COVID-19 vaccine and negative reproductive-related side effects could therefore lead to reduced acceptance of the vaccine and increased health risks during pregnancy. Indeed, a study published prior to the availability of the COVID-19 vaccines in fertility patients showed that few women were open to future receipt of a COVID-19 vaccine [18].

This study aimed to assess the perception of COVID-19 vaccination in a large population of women undergoing or planning on undergoing fertility treatments at a time when COVID-19 vaccines were available for use. A secondary goal of the study was to assess if providing a one page educational graphic would affect COVID-19 vaccination beliefs.

Materials and methods

Study design

This was a cross-sectional study performed at a single center, in the Division of Reproductive Endocrinology and Infertility at Northwestern Medicine in Chicago, Illinois. All patients with an email address on file in the electronic medical record and seen for follow-up or treatments between February 1st 2021 and April 19th 2021 were contacted electronically via Survey Monkey to participate in an anonymous survey. There were no exclusion criteria for study participation. Responses were collected over 5 days, from April 19th 2021 to April 23rd 2021, after which, the survey was closed. The survey was initially emailed to 3558 patients of which 1130 opened the survey invitation, and 1103 completed the survey (response rate = 31.0%, with a 97.6% participation rate among those who completed the survey); 2 participants skipped the online consent form, 25 participants declined to participate in the survey (2.2%). Follow-up reminder messages were sent via email to patients, 2 and 5 days after the initial survey invitation in order to optimize and encourage participation. No personal identifying information was obtained for participants. Institutional Review Board (IRB) approval was obtained.

Measures

Multiple demographic characteristics were collected including age, race/ethnicity, marital status, education level, and household annual income. Obstetrical history, fertility treatments, and delays (if applicable) were also included in this study. Participants' emotional wellbeing and distrust of the medical system were assessed via empirically validated measures. The first section of the questionnaire was on demographics characteristics, followed by previous and/or current fertility treatment history. Once these were completed, the next section of the questionnaire was focused on mental health before and after the onset of the COVID-19 pandemic as well as medical mistrust. Vaccine hesitance was asked via the question about whether or not the participant planned to get the COVID-19 vaccine. The randomization with the educational handout was found in the last section of the survey, where participants were randomized to either receive the supplemental education handout or a basic summary of ASRM COVID-19 Task Force which encouraged pregnant women or women who are trying to conceive to get vaccinated against COVID-19. After the randomization with the educational handout section, participants answered a set of questions about vaccine receipt and beliefs that were created by the study authors (see Table 1). As summarized in Table 1, questions included (1) the impact of the COVID-19 pandemic on the participant's employment, (2) previous or current COVID-19 infection, (3) previous hospitalization due to COVID-19 or if a loved one died from COVID-19, (4) concerns that the COVID-19 vaccine has potential risks on future pregnancy (e.g., leading to a miscarriage or genetically abnormal fetus, (5) concerns that COVID-19 vaccination can negatively impact fertility and/or the ability to get pregnant, and (6) concerns that COVID-19 vaccination would cause genetically abnormalities in vaccine recipients or (7) in a fetus if administered to a pregnant woman. Additionally, questions assessed participants' knowledge regarding (8) clinically proven more severe COVID-19 infection in pregnant women compared to non-pregnant women as well as (9) in women of color, specifically Black or Latina women.

Patient Health Questionnaire (PHQ-8)

The PHQ-8 is an 8-item measure that assesses for signs and symptoms of major depressive disorder (MDD). Scores greater or equal to 10 are concerning for clinical evidence of MDD; scores of 0–4 indicate no depression, 5–9 indicate mild depression, 10–14 indicates moderate depression, 5–19 indicates moderately severe depression, and 20 or higher indicates severe depression [19].

Generalized Anxiety Disorder-7 (GAD-7)

The GAD-7 scale is a commonly used and validated 7-item measure assessing for symptoms of generalized anxiety disorder and has been validated in the assessment of general anxiety symptoms [20, 21]. Higher scores indicate more anxiety; scores indicate minimal (0–4), mild (5–9), moderate (10–14), and severe anxiety (15–21).

Medical Mistrust Index

The Medical Mistrust Index (MMI) assesses for participants' trust in the healthcare system, and we used to this measure to predict vaccine hesitancy in our study. The MMI is a reliable and validated 17-item questionnaire with Likert-type responses [22]. Higher scores indicate more severe mistrust.

Vaccine hesitancy

The items assessing vaccine hesitancy were created by the study authors and include asking if the participant was planning or was already vaccinated with the following options: (1) I received one dose, (2) I received both doses, (3) I am scheduled to receive it, (4) I plan to receive it once available to me, (5) I am not planning on receiving it.

Education intervention

Participants were randomized 1:1 to view a supplemental electronic educational graphic explaining the reasons why vaccination was important for women who were considering conceiving. The one-page graphic described "5 things you need to know about the COVID-19 vaccines" based on updated ASRM COVID-19 taskforce recommendations from January 2020, as well as other societies (ACOG and the Society of Maternal Fetal Medicine) [6]. The graphics included a lay description of information regarding (1) how the COVID-19 vaccines were created, (2) what is messenger RNA (mRNA), (3) what is the use of mRNAs, (4) the effect of the vaccines in women actively trying to conceive, and (5) the risks of COVID-19 infection in pregnancy (see supplemental appendix).

Data analysis

Statistical analyses were performed with the use of SPSS (Version 26.0) (IBM) using parametric tests for normally distributed data and nonparametric tests for non-normally distributed data, unequal sample variances, categorical data, and/or comparisons with small sample sizes. Chi-square analyses with pairwise Bonferroni adjusted Z-tests and ANOVA were used to compare responses between the intervention and the non-intervention groups, as well to examine the MMI, GAD-7, and PHQ-8 scores among

Table 1 COVID-19 experiences and beliefs

Variable	Intervention *N* (%)	No intervention *N* (%)
You or a partner lost your job as a result of the COVID-19 pandemic or at risk of losing your job?		
Yes	56 (14.1)	49 (12.3)
No	335 (84.6)	348 (87.2)
Unknown	5 (1.3)	2 (0.5)
Yes	56 (14.1)	49 (12.3)
You or a loved one been diagnosed with COVID-19?		
Yes, myself	26 (6.6)	34 (8.5)
Yes, a loved one	111 (28.0)	129 (32.3)
No	256 (64.6)	236 (59.1)
Unknown	3 (0.8)	2 (0.2)
Personally know anyone who was hospitalized or died from COVID-19?		
Yes, myself	4 (1.0)	3 (0.8)
Yes, a loved one	196 (49.5)	191 (47.9)
No	193 (48.7)	205 (51.4)
Unknown	3 (0.8)	0 (0)
Concerned about the potential risks that the COVID19 vaccine can have on your future pregnancy (such as having a miscarriage or a fetus with genetic abnormalities)?		
Strongly disagree	134 (34.2)	106 (26.6)
Disagree	107 (27.3)	106 (26.6)
Neutral	67 (17.1)	62 (15.5)
Agree	56 (14.3)	86 (21.6)
Strongly agree	38 (7.1)	39 (9.8)
You are concerned about the side effect of the COVID19 vaccine on your fertility and/or your ability to get pregnant.		
Strongly disagree	136 (34.7)	116 (29.1)
Disagree	111 (28.3)	102 (25.6)
Neutral	69 (17.6)	69 (17.3)
Agree	52 (13.3)	75 (18.8)
Strongly agree	24 (6.1)	37 (9.3)
The COVID-19 vaccine can cause genetic abnormalities in your body.		
True	3 (0.8)	11 (2.8)
False	389 (99.2)	385 (97.2)
The COVID-19 vaccine given to a pregnant woman can cause genetic abnormalities in a fetus.		
True	8 (2.0)	23 (5.8)
False	383 (98.0)	371 (94.2)
COVID-19 infection is more severe and dangerous in a pregnant woman compared to a non-pregnant woman.		
True	318 (81.3)	297 (74.6)
False	73 (18.7)	101 (25.4)
The COVID-19 vaccines have been shown to cause infertility in both men and women.		
True	4 (1.0)	15 (3.8)
False	385 (99.0)	378 (96.2)
Women of color, specifically Black or Latina women, are disproportionally affected by severe illness from COVID-19.		
True	353 (89.8)	339 (85.6)
False	40 (10.2)	57 (14.4)

participants. $P < 0.05$ was considered to be significant. Only data from individuals who identified as female were included in analyses due to the small sample size of male respondents.

Results

Demographics

Of the respondents who elected to answer, "sex assigned as birth", $n = 848$ self-identified as female, $n = 72$ as male, and $n = 210$ did not provide a response. Of the female participants, $n = 658$ (77.8%) self-identified as White; $n = 79$ (9.3%) as Asian or Pacific Islander; $n = 37$ (4.4%) as Black or African American; $n = 37$ (4.4%) as Hispanic, Spanish, or Latino; $n = 34$ (4.0%) as multiple ethnicity/other; $n = 1$ (0.1%) as American Indian or Alaskan Native; and $n = 257$ chose to not answer. Women in the intervention v. the non-intervention group were 35.87 ($SD = 4.0$) and 35.86 ($SD = 4.148$) years old, married (90.2% v. 90.0%), nulliparous (67.8% v. 70.7%), had at least a graduate degree (61.7% v. 56.1%), and a household income greater than $100,000 per year (85.8% v. 86.1). Except for age ($P < 0.05$), both the intervention and non-intervention groups were demographically similar (see Table 2). The majority of participants in the study had been actively undergoing fertility treatment or evaluation for at least 6 months to 1 year (71.5%) were not currently pregnant (71.7%), had received fertility treatments in order to have previous children (60.2%), and had previously lost a pregnancy by abortion, miscarriage, or stillbirth (53.2%) (see Table 2); the two groups were similar in fertility histories.

Vaccination perception

Among the participants who reported their vaccination status ($n = 790$), 25.3% received one dose ($n = 200$), 61.4% had received both doses ($n = 485$), 2.3% were scheduled to receive a vaccine ($n = 18$), 3.7% planned to receive a vaccine once available to them ($n = 29$), and 7.3% did not plan on getting vaccinated ($n = 58$) (Fig. 1).

Regarding COVID-19 exposures, 30.3% reported that a loved one or themselves (7.5%) had previously tested positive for COVID-19 and 46.7% knew someone who had been hospitalized or who died of COVID-19. Most participants (54.8%) strongly disagreed or disagreed that the vaccine could affect future fertility (Table 1).

Compared to women who did not plan to get vaccinated, women who had received or planned to receive the vaccine (92.7% v. 7.3%) were more likely to believe that the COVID-19 vaccine given during pregnancy would not cause genetic abnormalities in a fetus (97.9% v. 70.4%) and would not cause infertility (98.8% v. 81.5%). Those who had received or planned to receive the vaccine also believe that a more severe infection has been associated with pregnancy (81.3% v. 74.6%) and strongly disagreed (32.7% v. 1.7%) or disagreed (29.0% v. 1.7%) about having concerns on the impact of the vaccine on future pregnancies ($P < 0.05$) (Table 1).

When analyzing groups by intervention, participants in the intervention group were more likely to believe that COVID-19 vaccination does not cause genetic abnormalities in a fetus (98.0% v. 94.2%) and does not cause infertility (99% v. 96.2%) and that a more severe infection has been associated with pregnancy (81.3% v. 74.6%) (all $P < 0.05$) (Table 1). Higher scores on the MMI but not the intervention were associated with vaccine hesitancy ($P < 0.001$) (Table 3).

Chi-square analysis showed that vaccine hesitancy was not associated with household income, marital status, race, parity, pregnancy status, time trying to conceive, history of pregnancy loss, duration of fertility treatment, or use of fertility treatment to conceive a prior child. Education was recoded into three groups (less than a 4-year college degree, bachelor's degree, and graduate degree; having less than a 4-year college education was associated with greater hesitancy ($\chi 2$ ($n = 788$) = 25.04; $df = 2$, $P < 0.001$). *T*-test analyses were run to examine the role of age and medical mistrust on vaccine hesitancy; greater medical mistrust was associated with being vaccine hesitant ($P < 0.001$).

Emotional distress

Over a third (36.2%) of participants reported a history of medical treatment for depression or anxiety. Additionally, 50.3% of respondents were currently receiving or had received psychotherapy in the past and 23.1% reported initiating psychotherapy and/or medical treatment after March 2020. When assessing for mild, moderate, and severe symptoms of depression based on PHQ-8 scores, participants from the intervention group as compared to those who did not receive the intervention reported at least mild (34.3% v. 31.3%), moderate (46.8% v. 52.4%), moderately severe (14.6% v. 13.2%), or severe (4.3% v. 3.1%) symptoms of depression (*ns*). Similarly with the GAD-7 scale, participants from the intervention group compared to those who did not receive the intervention reported mild (43.7% v. 49.6%), moderate (41.4% v. 37.5%), and severe (14.8% v. 12.9%) anxiety symptoms (*ns*). The MMI scale, with a maximum score of 56 points, indicates severe mistrust in the healthcare system and in this case, vaccine hesitancy. The mean MMI score for the intervention group was higher ($M = 37.31$, $SD = 5.85$) compared to the non-intervention group ($M = 37.24$, $SD = 5.9$). Results showed that higher scores on the MMI were associated with higher GAD-7 scores ($P = 0.01$), greater concerns about vaccine side effects on fertility and/or ability to get pregnant and belief that the vaccine could cause abnormalities in a fetus or one's body ($P < 0.05$) (Table 3).

Table 2 Demographic characteristics of participants who received ($n = 271$) or did not receive ($n = 285$) the supplemental education

Variable	Intervention *N* (%)	No intervention *N* (%)
Age (mean, SD)		
Participant age	35.87 (4.0)	35.86 (4.148)
Partner's age	37.44 (6.227)	36.88 (5.328)
Race		
American Indian/Alaskan Native	0 (0)	1 (0.3)
Hispanic/Spanish/Latino	20 (5.1)	15 (3.8)
Black	17 (4.3)	19 (4.8)
Asian/Pacific Islander	36 (9.1)	41 (10.3)
White/Caucasian	305 (77.0)	306 (76.7)
Multiple ethnicities/other	16 (4.0)	17 (4.3)
Partner's sex		
Female	19 (4.8)	15 (3.8)
Male	358 (90.4)	361 (90.5)
Unknown	19 (4.8)	23 (5.8)
Marital status		
Single (never married)	33 (8.3)	35 (8.8)
Married/partnered	357 (90.2)	359 (90.0)
Divorced	5 (1.3)	4 (1.0)
Separated	1 (0.3)	1 (0.3)
Education		
High school degree	6 (1.5)	6 (1.5)
Associate's degree	6 (1.5)	12 (3.0)
Bachelor's degree	139 (35.1)	156 (39.1)
Master's degree	158 (39.9)	150 (37.6)
Doctorate/professional degree	85 (21.5)	74 (18.5)
Unknown	2 (0.5)	1 (0.3)
Household income		
<$50,000	6 (1.5)	3 (0.8)
$50,000–$100,000	49 (12.4)	52 (13.0)
$100,000–$200,000	(134 (33.8)	157 (39.3)
>$200,000	199 (50.3)	185 (46.4)
Unknown	8 (2.0)	2 (0.5)
Desired number of children		
0	1 (0.3)	1 (0.3)
1	44 (11.1)	40 (10.0)
2	216 (54.5)	239 (59.9)
3	112 (28.3)	87 (21.8)
4+	22 (5.7)	30 (7.6)
Unknown	1 (0.3)	2 (0.5)
Fertility care duration		
0–6 months	93 (23.5)	77 (19.3)
6 months–1 year	63 (15.9)	65 (16.3)
1–2 years	112 (28.3)	123 (30.8)
2 + years	124 (31.3)	125 (31.3)
Unknown	4 (1.0)	9 (2.3)
Pregnancy loss		
No	106 (26.8)	113 (28.3)
Yes	131 (33.1)	121 (30.3)
Unknown	159 (40.2)	165 (41.4)
Number of children		
0 (never pregnant)	265 (66.9)	277 (69.4)

Table 2 (continued)

Variable	Intervention *N* (%)	No intervention *N* (%)
1	96 (24.2)	100 (25.1)
2	29 (7.3)	16 (4.0
3+	1 (0.3)	3 (0.8)
Unknown	5 (1.3)	3 (0.8)
Prior birth with fertility treatment		
No	81 (20.5)	84 (21.1)
Yes	127 (32.1)	129 (32.3)
No prior births/unk	188 (47.5)	186 (46.6)
Partner's children		
0	244 (61.6)	254 (63.7)
>1	98 (24.8)	88 (22.1)

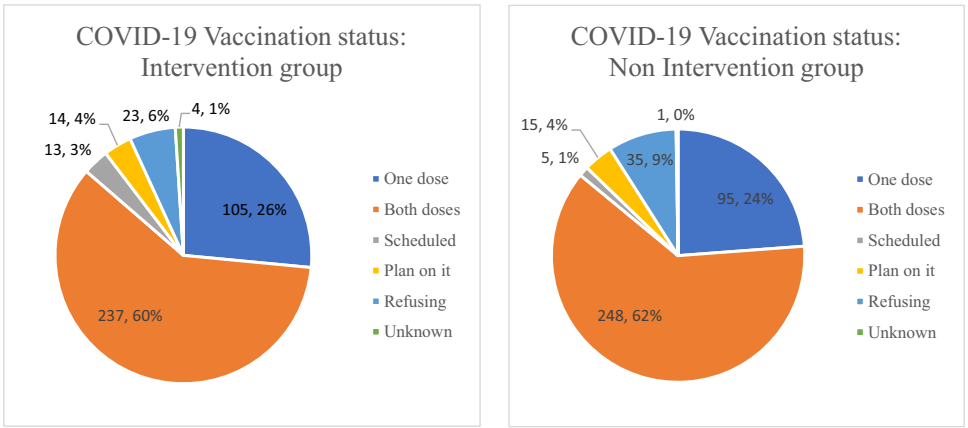

Fig. 1 COVID-19 vaccination status based on participants who received and who did not receive the intervention (educational handout) (*N*,%)

Table 3 Patient Health Questionnaire Depression (PHQ-8) and Generalized Anxiety Disorder-7 (GAD-7) Scales when comparing the intervention and non-intervention groups

Variable	Intervention *N* (%)	No intervention *N* (%)
GAD-7		
0–4 (minimal)	0 (0)	0 (0)
5–9 (mild)	171 (43.2)	196 (49.1)
10–14 (moderate)	162 (40.9)	148 (37.1)
15–21 (severe)	58 (14.6)	51 (12.8)
Unknown	5 (1.3)	4 (1.0)
PHQ-8		
0–4 (minimal)	0 (0)	0 (0)
5–9 (mild)	134 (33.8)	123 (30.8)
10–14 (moderate)	183 (46.2)	206 (51.6)
15–19 (moderately severe)	57 (14.4)	52 (13.0)
20–27 (severe)	17 (4.3)	12 (3.0)
Unknown	5 (1.3)	6 (1.5)

Discussion

Since the beginning of the pandemic and the emergency approval of the COVID-19 vaccines (Pfizer-BioNTech, Moderna, Johnson & Johnson), vaccine hesitancy in the USA has been contributing to the propagation of COVID-19 disease [23]. Vaccine hesitancy may also hinder the potential to achieve herd immunity, which occurs when a large enough percentage of a population becomes immune to a disease via prior infection or vaccination, in order to indirectly protect the rest of the nonimmune population [4]. Although research conducted prior to introduction of the COVID-19 vaccines indicated that the majority of fertility patients would not get the vaccine, results of our study showed that the majority of respondents did receive the vaccine. However, this study also found that medical mistrust was negatively related to vaccination status and both psychological distress and having less than a 4-year college degree.

Though data from our study were collected in April 2021, multiple studies continue to demonstrate that vaccine hesitancy rates have remained steady since the onset of the pandemic with approximately 10.2% of American reporting that they will probably not get a vaccine and approximately 8.2% stating they will definitely not get vaccinated [24]. Our study demonstrated a slightly lower but overall consistent rate of vaccine hesitancy, with 7.3% of participants refusing COVID-19 vaccination. It is

important to recognize that our study had a much higher rate of vaccination than expected (61.4% fully vaccinated and an additional 25.3% of participants received one vaccine dose) compared to an earlier study of women in a fertility clinic [18]. Given that research on unvaccinated individuals shows that increased information and research about the vaccines could positively influence vaccination, it is likely that new information and research during the months preceding our study influenced the uptake in vaccinations [25]. Additionally, the high level of education in our population could explain such a trend as it may be that this group of women have greater access to accurate, evidence-based information and sources related to COVID-19.

Although new data about vaccine safety likely influenced the increased acceptance of the vaccine for some, that new data may not change the beliefs of those who distrust the scientific bodies generating that new information. By June 2021, it was reported that up to 65% of Americans over the age of 18 received at least one vaccine dose [25]. However, vaccination rates among pregnant people have been lower, with population data from the CDC showing that as of January 1st 2022, only approximately 40% of pregnant women between the age of 18 and 49 had been fully vaccinated either prior to pregnancy or antenatally. For Black pregnant patients, the number was even lower, at 25% which may suggest the greater presence of medical mistrust and thus vaccine hesitancy among these patients [26].

Among the risk factors related to medical mistrust and vaccine hesitancy, race and ethnicity, especially within the Black/African American community, have been reported to be strongly associated with general vaccine hesitancy (e.g., influenza vaccine hesitancy) in the USA [23, 27, 28]. Historically, medical mistrust in the Black, Indigenous, and People of Color (BIPOC) population is triggered by factual historical root causes, particularly unethical practices during clinical trials [13]. Vaccine hesitancy among specific populations such as Latina/Hispanic and Black individuals during the COVID-19 pandemic continued to negatively affect these populations, with these groups experiencing more severe COVID-19 illness in pregnancy, including higher intensive care unit admissions and even death [3, 4, 13, 23]. These disparate beliefs about vaccines could also potentially propagate long-term racial health inequalities with patients who do not receive the vaccine having greater risks to morbidity and mortality when exposed to the COVD-19 virus.

Despite prior research finding a relationship between race and vaccine hesitancy, our study did not show any significantly statistical differences in vaccine hesitancy based on race or other demographic or fertility treatment-related variables except for education. However, our findings may be limited by the demographically homogenous sample in our study, with a highly educated group of primarily married White women (77.1%) and only 4.4% of respondents being Hispanic/Latina and Black/African American participants. Additionally, even though we found that the educational intervention was not associated with vaccine hesitancy, which may be due to the majority of respondents being vaccine receptive, it was associated with a small but significant increase in knowledge related to the vaccine. Because we did not conduct a pre-intervention assessment of vaccine receptivity, we do not know if this difference in knowledge was related to the intervention or some other factor. However, given that there were no significant demographic differences between the intervention and no-intervention groups, it is reasonable to hypothesize that group differences in knowledge were influenced by the intervention; this remains to be further explored in the future. With this limitation in mind, it may be that education about the safety of the vaccines may aid in improving vaccine knowledge for those who trust the source of the scientific data but not for those exhibiting distrust of the medical/scientific systems conducting or promoting the research-driven data.

Interestingly, we also found that higher scores on the Medical Mistrust Index were associated with both vaccine hesitancy and psychological distress. In our study, participants were found to be distressed since the beginning of the pandemic, with almost a quarter of women reporting an initiation of mental health treatment due to anxiety and/or depression. Higher levels of anxiety were associated with greater mistrust in the medical system though the direction of the relationship is unclear. Our study supports the idea that reducing psychological distress but also mistrust in the healthcare system could potentially have a positive impact on COVID-19 vaccination.

Overall results of our study showing that education and psychological distress are associated with mistrust and vaccine hesitancy as well as prior research on vaccine hesitancy [7, 11, 12, 22, 28, 9] suggest that a multi-pronged approach is needed to improve use of vaccines in the future including (1) data driven education about the risks and safety of the vaccine that is transparent and acknowledges the limits to these data, (2) efforts to decrease medical mistrust through avenues such as collaboration between medical teams and trusted community organizations, shared-decision making, racially diverse medical teams, and the development of strong patient-provider relationships all of which must be contextualized within the history of racism in the USA [28], and (3) assessment of patients for psychological distress and provision of emotional support to those experiencing distress in order to reduce distress and potentially improve vaccine acceptance.

Some of the strengths of our study is its large sample size and the inclusion of a randomized educational intervention as well as the utilization of validated questionnaires

to measure depression, anxiety, and medical mistrust. Our study also highlights the unique experiences of infertility patients related to vaccine perceptions and vaccine hesitancy over a discreet period of time when the COVID-19 vaccine was available. This study also uniquely highlighted the relationship between increased anxiety and higher medical mistrust, which clinically allows for potential ways to intervene on and identify at risk patients who might need more counseling and education regarding COVID-19 vaccination. Limitations of our study include the selection of patients from a single academic center with an overall demographically homogenous sample with a high vaccination rate. However, this study included a large sample size and is currently the only study to assess the effect of supplemental education on acceptance of vaccines and medical mistrust. Replication of this study at another institution with potentially a more diverse patient population and with lower rates of vaccination could, however, provide additional information about vaccine hesitancy among different racial and ethnic groups.

Given the unpredictable trend of the COVID-19 pandemic and the ongoing risk of emerging highly contagious and even more virulent variants as well as future unrelated pandemics, reducing mistrust and addressing emotional distress are essential to future acceptance of vaccination. Such care delivered in a team-based approach by both mental health providers and physicians is crucial in providing empathetic and exceptional care to this patient population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10815-022-02641-7.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Centers for Disease Control and Prevention (2021). COVID-19 vaccination for pregnant people to prevent serious illness, deaths, and adverse pregnancy outcomes from COVID-19. https://emergency.cdc.gov/han/2021/han00453.asp
2. Centers for Disease Control and Prevention (2022). *COVID-19 vaccines while pregnant or breastfeeding*. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html.
3. Zambrano, L. D., Ellington, S., Strid, P., Galang, R. R., Oduyebo, T., Tong, V. T., Woodworth, K. R., Nahabedian, J. F., Azziz-Baumgartner, E., Gilboa, S. M., & Meaney-Delman, D. (2020). Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-October 3, 2020. *MMWR. Morbidity and mortality weekly report*, *69*(44), 1641-1647. https://doi.org/10.15585/mmwr.mm6944e3
4. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, Nahabedian J, Anderson K, Gilboa SM. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-June 7, 2020. MMWR Morb Mortal Weekly Rep. 2020;69(25):769-775. https://doi.org/10.15585/mmwr.mm6925a1
5. Delahoy MJ, Whitaker M, O'Halloran A, Chai SJ, Kirley PD, Alden N, Kawasaki B, Meek J, Yousey-Hindes K, Anderson EJ, Openo KP, Monroe ML, Ryan PA, Fox K, Kim S, Lynfield R, Siebman S, Davis SS, Sosin DM, Garg S. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19-COVID-NET, 13 States, March 1-August 22, 2020. MMWR Morb Mortal Weekly Rep. 2020;69(38):1347-1354. https://doi.org/10.15585/mmwr.mm6938e1
6. American Society of Reproductive Medicine (2020). COVID-19 task force. https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate12.pdf
7. Hsu AL, Johnson T, Phillips L, Nelson TB. Sources of vaccine hesitancy: pregnancy, infertility, minority concerns, and general skepticism. Open Forum Infect Dis. 2022;9(3), ofab433-ofab433. https://doi.org/10.1093/ofid/ofab433
8. Magnus MC, Gjessing HK, Eide HN, Wilcox AJ, Fell DB, Håberg SE. Covid-19 vaccination during pregnancy and first-trimester miscarriage. New Engl J Med. 2021;385(21):2008–10. https://doi.org/10.1056/NEJMc2114466.
9. Zauche LH, Wallace B, Smoots AN, Olson CK, Oduyebo T, Kim SY, Petersen EE, Ju J, Beauregard J, Wilcox AJ, Rose CE, Meaney-Delman DM, Ellington SR. Receipt of mRNA Covid-19 vaccines and risk of spontaneous abortion. New Engl J Med. 2021;385(16):1533–5. https://doi.org/10.1056/NEJMc2113891.
10. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, Marquez PL, Olson CK, Liu R, Chang KT, Ellington SR, Burkel VK, Smoots AN, Green CJ, Licata C, Zhang BC, Alimchandani M, Mba-Jonas A, Martin SW, Meaney-Delman DM. Preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons. New Engl J Med. 2021;384(24):2273–82. https://doi.org/10.1056/NEJMoa2104983.
11. Sanford K, Clifton M. The Medical Mistrust Multiformat Scale: links with vaccine hesitancy, treatment adherence, and patient-physician relationships. Psychol Assess. 2022;34(1):10-20. https://doi.org/10.1037/pas0001097
12. Quinn SC, Jamison A, An J, Freimuth VS, Hancock GR, Musa D. Breaking down the monolith: understanding flu vaccine uptake among African Americans. SSM - population health. 2018;4:25–36. https://doi.org/10.1016/j.ssmph.2017.11.003.
13. Cokley K, Krueger N, Cunningham SR, Burlew K, Hall S, Harris K, Castelin S, Coleman C. The COVID-19/racial injustice syndemic and mental health among Black Americans: the roles of general and race-related COVID worry, cultural mistrust, and perceived discrimination. J Community Psychol. 2021. https://doi.org/10.1002/jcop.22747.
14. Szilagyi PG, Thomas K, Shah MD, Vizueta N, Cui Y, Vangala S, Kapteyn A. National trends in the US public's likelihood of getting a COVID-19 vaccine—April 1 to December 8, 2020. JAMA : J Am Med Assoc. 2021;325(4):396–8. https://doi.org/10.1001/jama.2020.26419.
15. Boots CE, Venkatesh A, Anderson J, Citro L, Lawson AK. Covid conception catastrophe? The experience of fertility IQ users. Fertil Steril. 2020;114(3):e550–e550. https://doi.org/10.1016/j.fertnstert.2020.09.085.
16. Lawson AK, McQueen DB, Swanson AC, Confino R, Feinberg EC, Pavone ME. Psychological distress and postponed fertility care during the COVID-19 pandemic. J Assist Reprod Genet. 2021;38(2):333–41. https://doi.org/10.1007/s10815-020-02023-x.
17. Joelsson LS, Berglund A, Rosenblad A, Tyden T. Preconception lifestyles and lifestyle modification among women seeking for infertility. Fertil Steril. 2015;104(3):e182–3. https://doi.org/10.1016/j.fertnstert.2015.07.566.
18. Turocy J, Robles Alex, Reshef Evan, D'Alton Mary, Forman Eric J, Williams Zev (2021). A survey of fertility patients' attitudes

towards the COVID-19 vaccine. Fertility and sterility. https://www.fertstertdialog.com/posts/a-survey-of-fertility-patients-attitudes-towards-the-covid-19-vaccine
19. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.
20. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med (1960). 2006;166(10), 1092-1097. https://doi.org/10.1001/archinte.166.10.1092
21. Johnson SU, Ulvenes PG, Øktedalen T, Hoffart A. Psychometric Properties of the General Anxiety Disorder 7-Item (GAD-7) Scale in a heterogeneous psychiatric sample. Front Psychol. 2019;10:1713–1713. https://doi.org/10.3389/fpsyg.2019.01713.
22. LaVeist TA, Isaac LA, Williams KP. Mistrust of health care organizations is associated with underutilization of health services. Health Serv Res. 2009;44(6):2093–105. https://doi.org/10.1111/j.1475-6773.2009.01017.x.
23. Willis DE, Andersen JA, Bryant-Moore K, Selig JP, Long CR, Felix HC, Curran GM, McElfish PA. COVID-19 vaccine hesitancy: race/ethnicity, trust, and fear. Clin transl Sci. 2021;14(6):2200–7. https://doi.org/10.1111/cts.13077.
24. Tram KH, Saeed S, Bradley C, Fox B, Eshun-Wilson I, Mody A, Geng E. Deliberation, dissent, and distrust: understanding distinct drivers of coronavirus disease 2019 vaccine hesitancy in the United States. Clin Infect Dis. 2021. https://doi.org/10.1093/cid/ciab633.
25. Diaz, P., Zizzo, J., Balaji, N. C., Reddy, R., Khodamoradi, K., Ory, J., & Ramasamy, R. (2021). Fear about adverse effect on fertility is a major cause of COVID-19 vaccine hesitancy in the United States. *Andrologia (Berlin, West)*, e14361-e14361. https://doi.org/10.1111/and.14361
26. Centers for Disease Control and Prevention (2022). COVID-19 vaccination among pregnant people aged 18-49 years overall, by race/ethnicity, and date reported to CDC - Vaccine Safety Datalink,* United States. https://covid.cdc.gov/covid-data-tracker/#vaccinations-pregnant-women
27. Groom HC, Zhang F, Fisher AK, Wortley PM. Differences in adult influenza vaccine-seeking behavior: the roles of race and attitudes. J Public Health Manag Pract. 2014;20(2):246–50. https://doi.org/10.1097/PHH.0b013e318298bd88.
28. Quinn SC, Jamison AM, An J, Hancock GR, Freimuth VS. Measuring vaccine hesitancy, confidence, trust and flu vaccine uptake: results of a national survey of White and African American adults. Vaccine. 2019;37(9):1168–73. https://doi.org/10.1016/j.vaccine.2019.01.033.