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Giuseppe Rizzo , Giuseppe Maria Maruotti

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Pregnant women perspectives on SARS-COV-2 vaccine.

Luigi Carbone,[1] Ilenia Mappa,[2] Angelo Sirico,[1] Raffaella Di Girolamo,[1,3] Gabriele Saccone,[1] Daniele Di Mascio,[4] Vera Donadono,[1] Lara Cuomo,[1] Olimpia Gabrielli,[1] Sonia Migliorini,[1] Maria Luviso,[2] Francesco D'antonio,[3] Giuseppe Rizzo[2,5*] and Giuseppe Maria Maruotti[1*]

[1] *Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, Federico II University of Naples, Naples, Italy*

[2] *Division of Maternal Fetal Medicine, Ospedale Cristo Re, University of Rome Tor Vergata, Rome, Italy*

[3] *Centre for Fetal Care and High-Risk Pregnancy, Department of Obstetrics and Gynecology, University of Chieti, Chieti, Italy.*

[4] *Department of Maternal and Child Health and Urological Sciences, La Sapienza University of Rome, Rome, Italy*

[5] *Department of Obstetrics and Gynecology, The First I. M. Sechenov Moscow State Medical University, Moscow, Russia.*

[*] These two authors share last authorship

Corresponding author:

Luigi Carbone, MD

Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

Via Sergio Pansini no. 5, 80131, Naples, Italy

Email: drcarboneluigi@gmail.com

ORCID ID: https://orcid.org/0000-0002-2127-1876

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Condensation

Most of Italian pregnant women would not agree to get the SARS-COV-2 vaccine, irrespective of having features of high risk themselves, or being high-risk pregnancies.

AJOG at a Glance:

A. Why was the study conducted?

To know the current perspectives of Italian pregnant women, during the first phase of SARS-COV-2 vaccine distribution, regarding its uptake.

B. What are the key findings?

Italian pregnant women are still largely suspicious towards the SARS-COV-2 vaccination program, independently from social, cultural and pregnancy-related features.

C. What does this study add to what is already known?

These results are the first report from a patient's point of view that reinforce the need for urgent data from vaccine trials, in which women should be included since now on, to avoid the current uncertainty and denial. Counseling without data lacks power.

Abstract

Background: Since COVID-19 vaccines have been distributed, a debate has raised on whether pregnant women should get the vaccine. No available data exist so far regarding safety, efficacy and toxicology of these vaccines when administered during pregnancy. Most of the Obstetrics and Gynecology societies suggested that pregnant could agree to be vaccinated, after a thorough counseling of risks and benefits with their gynecologists, thus leading to an autonomous decision. **Objective:** The aim of this study was to evaluate the attitude to COVID-19 vaccination in pregnant and breastfeeding women in Italy.

Study design: A survey was made at University of Naples Federico II and University of Rome Tor Vergata Ospedale Cristo Re on pregnant and breastfeeding women asking their perspectives on the available vaccines after reading the recommendations issued by our national Obstetrics, Gynecology and Neonatology societies. The questionnaire included 12 items finalized to evaluate general features of the women and 6 items specifically correlated to their attitudes towards the SARS-COV-2 vaccination. Chi square (χ^2) or Fisher exact tests were used to compare group differences of categorical variables and Wilcoxon signed rank or Mann Whitney U test for continuous variables. The study was approved by the Institutional Review Boards of the University of Naples Federico II (ref. no. 409/2020), and University of Rome Tor Vergata Ospedale Cristo Re (ref. #Ost4-2020).

Results: Most of the included women did not agree to eventually receive SARS-COV-2 vaccine during pregnancy (40, 28.2% vs 102, 71.8%). Being pregnant was considered a determinant factor to refuse the vaccine prophylaxis (99, 69.7% vs 43, 30.3%; χ^2= 24.187, p<0.001), even if a very large percentage declared to be generally in favor of vaccines (128, 90.1% vs 14, 9.9%; χ^2= 6.091, p=0.014) and most of them confirmed they received or would receive other recommended vaccines during pregnancy (75, 52.8% vs 67, 47.2%; χ^2= 10.996, p=0.001).

Conclusion: Urgent data are needed on safety, efficacy and toxicology of SARS-COV-2 vaccines during pregnancy to modify this trend and to help obstetricians during the counselling. Furthermore, pregnant women should be included in future vaccine development trials to not incur again in such uncertainty.

INTRODUCTION

COVID-19 pandemic has determined an incredible burden on national healthcare systems worldwide. In Obstetrics and Gynecology practice, all non-urgent clinical and surgical activities have been postponed during the most critical phases, also raising the debate on which conditions should be considered as urgent and how to reorganize obstetrical, gynecological and reproductive medicine units [1-8].

Large multicenter cohort studies have found that SARS-COV-2 infection during pregnancy was associated with a 0.8% rate of maternal mortality and 11.1% rate of intensive care unit admissions, with increased rates of preterm deliveries (both spontaneous and iatrogenic) and cesarean section deliveries [9,10]. The earlier is the infection the more the increase of the risk for adverse fetal outcomes [11], even though the risk of vertical transmission seems to be negligible [9,10]. Actually, no general consensus exists on the optimal management for pregnant women with SARS-COV-2 infection [12-15]; moreover, there is a huge heterogeneity among hospitals and, regarding therapy, combinations of azithromycin or other antibiotics, hydroxychloroquine, low-molecular-weight heparin and a large variety of antivirals have been used, without any significant difference between therapeutic regimes [9,16].

Less than a year after the recognition of this new infection, vaccines against SARS-COV-2 virus have been developed and open to worldwide distribution, in order to counteract the pandemic. It has been widely proposed to include pregnant women into COVID-19 vaccine trials [17,18], since they could be considered at higher risk, and the International Federation of Gynecology and Obstetrics (FIGO) endorsed this recommendation [19].

On the 27th of December 2020 the vaccine against SARS-COV-2 infection started to be administered in Italy and across Europe. Thereafter, the most important Italian Obstetrics and Gynecology societies released a position paper ad interim on COVID-19 vaccine and pregnancy, stating that it is not recommended but neither contraindicated to receive SARS-COV-2 vaccine during pregnancy and breastfeeding, as well as in women with reproductive desire, and that each woman should evaluate with her gynecologist risks and benefits of its administration [20].

Therefore, the aim of the present survey is to understand which are the perspectives of pregnant and breastfeeding women regarding the possibility to receive COVID-19 vaccine during pregnancy.

MATERIALS AND METHODS

Study design and participants

This was a multicenter cross-sectional cohort study involving 2 centers in Italy (University of Naples Federico II and University of Rome Tor Vergata, Ospedale Cristo Re), conducted in January 2021.

Our study included pregnant women attending the two centers for outpatient visits, and early post-partum inpatient women who were asked to participate to a survey on the possible uptake of the SARS-COV-2 vaccine during pregnancy and puerperium. Exclusion criteria were inability to comprehend the text and to sign the informed consent.

After signing an informed consent and reading the position paper ad interim on "Pregnancy and COVID-19 vaccine" [20], participants were given a questionnaire to fill. An anonymous online semi-structured questionnaire was developed using google forms (https://docs.google.com/forms. Google Mountain View, CA, US).

Outcome measures

The questionnaire was structured in 2 sections: Part A was finalized to acquire data on maternal characteristics (socio-cultural and demographic variables, past and current obstetrical history, maternal age and gestational age at the receipt of the questionnaire); Part B was structured to test women's knowledge and concerns about vaccines (Supplementary Material 1).

We defined education as of a medium-low level in case of primary school or early secondary school, and of a medium-high level in case of late secondary school or degree and more. Any work was considered to fill in the worker subgroup, compared to women who were housewives or unemployed.

Women were specifically asked if they were in favor or against the SARS-COV-2 vaccine during pregnancy. Furthermore, questions were asked regarding general acceptance of vaccines, whether the acceptance of SARS-COV-2 vaccine was dependent on the pregnant/breastfeeding status and if they would receive other

vaccine recommended during pregnancy (referring to the trivalent DTPa – Diphtheria, Tetanus, acellular Pertussis – and the influenza vaccines).

Patients were then grouped according to their response to the survey (acceptance or decline of the SARS-COV-2 vaccine during pregnancy or breastfeeding).

Statistical analysis

Descriptive statistics were calculated for the variables considered and data were expressed as *n* and % for categorical variables and median and interquartile range (IQR) for continuous variables. Chi square (χ^2) or Fisher exact tests were used to compare group differences of categorical variables and Wilcoxon signed rank or Mann Whitney U test for continuous variables. Pearson correlation analysis was used to calculate the univariate associations variables. All hypotheses were tested at a significance level of 0.05. Statistical analysis was performed using SPSS Statistic 21.0 (IBM SPSS Statistics, New York, United States).

Ethical approval

The study was approved by the Institutional Review Boards of the University of Naples Federico II (ref. no. 409/2020), and University of Rome Tor Vergata Ospedale Cristo Re (ref. #Ost4-2020).

RESULTS

168 women were asked to participate in the study, 26 of which (15.5%) refused the invitation; therefore, 142 (84.5%) women were enrolled in the survey.

Out of 142 women, 119 (83.8%) were pregnant and 23 (16.2%) were in the early post-partum period. Maternal and obstetric characteristics of included women are described in Table 1.

The median age of the women was 34 years [31-37.25]. For pregnant women, the median gestational age at survey was 29 weeks [19 – 35]. Most of the included patients were Italian (96.5%), 1 (0.7%) was from a European country and 4 (2.8%) were non-European. In our cohort, 58 (40.8%) pregnant women were >35 years old, and 31 (21.8%) suffered from pathologic conditions during pregnancy (pregnancy induced hypertension, gestational diabetes, threatened miscarriage and threatened preterm birth) (Table 1).

Most of the included women did not express their agreement to eventually receive SARS-COV-2 vaccine during pregnancy (40, 28.2% vs 102, 71.8%). Interestingly, no patient affirmed to be totally sure about the safety of SARS-COV-2 vaccine, only 39 (27.5%) patients where quite secure, 69 (48.6%) patients were quite insecure and 34 (23.9%) were totally insecure about vaccine safety (Table 2). Furthermore, they affirmed that being pregnant was a determinant factor guiding the eventual choice to accept the vaccine prophylaxis (99, 69.7% vs 43, 30.3%; χ^2= 24.187, p<0.001), even if a very large percentage declared to be generally in favor of vaccines (128, 90.1% vs 14, 9.9%; χ^2= 6.091, p=0.014) and most of them confirmed they received or would receive other recommended vaccines during pregnancy (75, 52.8% vs 67, 47.2%; $\chi2$= 10.996, p=0.001) (Table 3). When we compared maternal characteristics and survey answers according to women's agreement to receive SARS-COV-2 vaccine in pregnancy, no statistically significant differences were found in relation to nationality, marital status, education, employment, smoke, pre-existing diseases, type of conception, pregnancy trimester at survey and pregnancy complications during current pregnancy, between women who would undergo SARS-COV-2 vaccine in pregnancy and women who would not (Table 3). Indeed, women who had a previous pregnancy (irrespectively from defining it as a livebirth or a miscarriage) (91, 64.1% vs 51, 35.9%; $\chi2$= 4.354, p=0.037) and women who were still pregnant at survey time (119, 83.8% vs 23, 16.2%; $\chi2$= 10.904, p=0.001) would preferably decline the SARS-COV-2 vaccine in a statistically significant manner (Table 3).

Performing a subgroup analysis, we evaluated women > 35 years old who were suffering from previous diseases or had complications during pregnancy and were still pregnant at survey, but there were no statistically significant differences in the eventual SARS-COV-2 vaccine uptake for these subgroups (Table 3).

Last, we asked to women who did not want to receive the SARS-COV-2 vaccine during pregnancy, which were the reasons for such refusal, and the two most frequent answers were "fear of baby's health consequences" in 61 (59.8%) of cases and "too short time from development to commercialization" in 41 (40.2%) of cases (Figure 1).

DISCUSSION

Main Findings

This survey analyzed the grade of acceptance of women during pregnancy and breastfeeding to eventually receive SARS-COV-2 vaccine during pregnancy after being informed on the basis of actual evidence and recommendations from the main Italian Obstetrics, Gynecology and Neonatology societies. Our data show that most of women were not in favor to receive SARS-COV-2 vaccine in pregnancy, being overall insecure about the safety of this vaccine, even if most of them were usually in favor to receive vaccines and almost half of them received or would receive other vaccines recommended during pregnancy. Indeed, the state of pregnancy itself has been largely considered as a determinant factor to refuse the SARS-COV-2 vaccine, combined with the current lack of certainty.

Results in the context of what is known

Although the absolute risk for SARS-COV-2 severe infection is low, the Centers for Disease Control and Prevention (CDC) has included pregnancy as a risk factor for severe COVID-19 illness [21]. Unfortunately, clinical trials for the available vaccines excluded pregnant and lactating women. Therefore, since the safety and efficacy of the vaccines for pregnant women, the fetus and the newborn remain unknown, there is no general consensus on whether pregnant women should be vaccinated against SARS-COV-2. UK Royal College of Obstetricians and Gynecologists (RCOG) last recommendations on SARS-COV-2 vaccine in pregnancy stated that despite the available data do not indicate any safety concern or harm to pregnancy, there is insufficient evidence to recommend routine use of COVID-19 vaccines during it, and pregnant women should undergo an individualized and autonomous evaluation with their obstetrician on whether they should receive the vaccine [22].

Clinical and research implications

US Centers for Disease Control and Prevention (CDC) last recommendations on SARS-COV-2 vaccine in pregnancy, issued on 12th February 2021, stated that SARS-COV-2 vaccine is an mRNA-based vaccine that firstly, does not contain the live virus that causes COVID-19 and, therefore, cannot transmit COVID-19 to someone and secondly, mRNA vaccines do not interact with a person's DNA because the mRNA does not

enter the nucleus of the cell [23]. Nevertheless, the CDC stated that getting vaccinated is a personal choice for people who are pregnant [23]. In January 2021, the European Medicine Agency (EMA) authorized the use of COVID-19 vaccines and issued a report [24] stating that no harmful effects, with respect to pregnancy and lactation were observed during animal studies. However, it also declared that the decision to receive the vaccine during pregnancy and lactation should be based upon a discussion with the healthcare provider and on a case-by-case basis, taking into consideration benefits and possible risks. Since currently there are no available data on the safety or possible established risks for SARS-COV-2 vaccination in pregnancy, it appears to be difficult for women and for their doctors to perform and individualized counselling on the possible benefits and risks of the vaccination. The lack of strong recommendations based on evidence for clear safety seems to explain the results of our survey, where 71.8% of women felt unsure on whether eventually undergo SARS-COV-2 vaccination, 59.8% of women who did not agree for SARS-COV-2 vaccine were afraid of possible baby's health consequences and 40.2% of women were afraid of vaccine safety considering the short time from development to commercialization compared to other vaccines.

Authors have pointed out how pregnancy is considered an emotional phase in women life and how it can impact women's mental health even in uneventful pregnancies. Recently, the concept of maternal anxiety has been described, distinct from general anxiety or depression [25]. Maternal anxiety is characterized by the fear of real or anticipated threat to pregnancy or its outcomes and low perceived control. de Jesus Silva et al. found that 26.8% women with low-risk pregnancies scored a high grade of anxiety, with a greater incidence in the third trimester (42.9%) [26]. These results are in line with findings from Giardinelli et al., who found that 21.9% of pregnant women in the study group had a high score at Edinburgh Postnatal Depression Scale (EPDS) [27].

SARS-COV-2 pandemic, national lockdown, severe restrictions and safety measures into hospitals and labor wards caused a great impact in pregnant women emotional balance. Moyer et al. analyzed 2740 pregnant women and found that 93% of them reported increased stress about getting infected with COVID-19 [28], as well as Saccone et al. [29] reported that 68% of pregnant women included in a survey performed a high score of State-Trait Anxiety Inventory scale during the first months of the COVID-19 pandemic; Mappa et al. [30] observed that 47% had fear of structural anomalies and 51% of preterm birth. These data are consistent with

our findings of increased perception of risk for pregnancy or baby outcomes associated with SARS-COV-2 vaccine in pregnancy, mostly because of the lack of adequate safety data and of strong clear recommendations from the main scientific societies and agencies. In this view, it is of outmost importance the evidence that, even if most women in the survey would not get vaccinated against SARS-COV-2, 90.1% of them are generally in favor of vaccines and 52.8% of them received or would receive other vaccines strongly and clearly recommended in pregnancy (dTPa or influenza vaccine). Klein et al. [31] affirmed that it is not ethical to ask to pregnant women or their providers to decide if to get or not the COVID-19 vaccine, given the such limited evidence so far; in addition, they acknowledge the need to include them in phase III trials, especially if preclinical data on safety and toxicology seem encouraging.

Other authors urged to include pregnant and lactating women in future clinical trials on SARS-COV-2 vaccines in the development and deployment of COVID-19 vaccines and early investment in this field [32]. The inclusion of these women will ensure that pregnant women and their infants could benefit from vaccine candidates that prove successful and help ensure that they will ultimately be protected against COVID-19 [33]. Furthermore, as soon as rigorously designed studies with proactive data collection, recording both vaccine-related symptoms and obstetric outcomes, will provide evidence-based recommendations regarding mRNA vaccination to reduce harms from COVID-19, expert opinion will be replaced [34]. As Heath et al. [32] stated, to enable the inclusion of pregnant and lactating women in the development of COVID-19 vaccines it is important to understand whether pregnant women wish to be vaccinated against COVID-19 and also participate in trials for vaccines development.

Strength and limitations

As far as we know, this is the first survey reporting women's attitudes towards the vaccination against COVID-19, in the context of lack of definitive data regarding its safety during pregnancy, demonstrating with its results that counseling is fundamental, but data are a very strong added value to reinforce it. A limitation of our analysis depends on the small sample size, which in part is due to the short time we decided to apply for the distribution of the survey. Another limitation is given by the survey method itself, since we gave the questionnaire after the administration of the abovementioned document produced by our national

societies [20], which could eventually be considered too technical by some women, resulting in a higher rate of negative answers.

Conclusions

This survey describes current perspectives in pregnant and breastfeeding women about SARS-COV-2 vaccine, of which the majority would opt to not get the vaccine, highlighting the need of evidence-based recommendations to guide pregnant women decision to get vaccinated. According to us, first safety reports on pregnant and lactating women who got vaccinated during these months as well as more clear indications on SARS-COV-2 vaccine in pregnancy from scientific societies will increase women adherence rate to the vaccine during pregnancy and lactation, hence reducing maternal morbidity due to SARS-COV-2 infection.

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TABLES

Table 1. General characteristics of the participants to the survey (Questionnaire Part A).

Features	Options	
Age		34 [31 – 37.25]
Nationality	Italian	137 (96.5)
	European	1 (0.7)
	Non-European	4 (2.8)
Marital status	Unmarried	11 (7.7)
	Married	71 (50)
	Divorced	2 (1.4)
	No answer	58 (40.8)
Education	Medium low	121 (85.2)
	Medium high	21 (14.8)
Employment	Worker	90 (63.4)

	Housewife/unemployed	52 (36.6)
Smoke	Yes	12 (8.5)
	No	130 (81.5)
Pre-existing diseases	Yes	108 (76.1)
	No	34 (23.9)
Previous pregnancy	Yes	91 (64.1)
	No	51 (35.9)
Previous children	Yes	58 (40.8)
	No	65 (45.8)
	No answer	19 (13.4)
Previous miscarriage	Yes	30 (21.1)
	No	93 (65.5)
	No answer	19 (13.4)
Conception	Spontaneous	120 (84.5)
	IVF	22 (15.5)
Gestational age at survey		29 [19 – 35]
Trimester at survey	1	18 (12.7)
	2	33 (23.2)
	3	68 (47.9)
	Post-partum	23 (16.2)
Still pregnant at survey	Yes	119 (83.8)
	No	23 (16.2)
Disease during pregnancy	Yes	31 (21.8)
	No	111 (78.2)

Data are presented as median [IQR] or number (percentage); IVF, *In-vitro* fertilization.

Table 2. Perspectives on SARS-COV-2 vaccine of the included women (Questionnaire Part B).

Questions	Answers	N (%)
Agreement to be vaccinated against SARS-COV-2	Yes	40 (28.2)
	No	102 (71.8)
Feeling safe about SARS-COV-2 vaccine	Totally insecure	34 (23.9)
	Rather insecure	69 (48.6)
	Safe enough	39 (27.5)
	Totally safe	0
Being pregnant influence the choice	Yes	99 (69.7)
	No	43 (30.3)
Usually in favor of vaccines	Yes	128 (90.1)
	No	14 (9.9)
Received or would receive other vaccine during pregnancy (DTPa and/or influenza)	Yes	75 (52.8)
	No	67 (47.2)

Data are presented as number (percentage); DTPa (Diphtheria, Tetanus, acellular Pertussis).

Table 3. Comparison of women characteristics according to their attitude to COVID 19 vaccine.

Items	Would get the SARS-COV-2 vaccine		Chi square	P Value
	Yes = 40	**No = 102**		
Nationality			189.347	0.51
- Italian	38 (95)	99 (97.2)		
- European				
- Non-European	0	1 (0.9)		
	2 (5)	2 (1.9)		
Marital status			1.562	0.81
- Unmarried	2 (5)	9 (8.9)		
- Married				
- Divorced	20 (50)	51 (50)		
- Separed				
- No answer	0	1 (0.9)		
	0	1 (0.9)		
	18 (45)	40 (39.3)		

Education			2.348	0.125
- Medium low	37 (92.5)	84 (82.3)		
- Medium high	3 (7.5)	18 (17.7)		
Employment			1.995	0.158
- Worker	29 (72.5)	61 (59.8)		
- Housewife/unemployed	11 (27.5)	41 (40.2)		
Smoke			0.857	0.355
- Yes	2 (5)	10 (9.8)		
- No	38 (95)	92 (90.2)		
Pre-existing diseases			0.064	0.801
- Yes	9 (22.5)	25 (24.5)		
- No	31 (77.5)	77 (75.5)		
Previous pregnancy			4.354	0.037*
- Yes	31 (77.5)	60 (58.8)		
- No	9 (22.5)	42 (41.2)		
Previous children			3.215	0.073
- Yes	22 (55)	36 (35.3)		
- No	15 (37.5)	50 (49)		
- No answer	3 (7.5)	16 (15.7)		
Previous miscarriage			0.2	0.655
- Yes	10 (25)	20 (19.6)		
- No	27 (67.5)	66 (64.7)		
- No answer	3 (7.5)	16 (15.7)		
Conception			0.01	0.919
- Spontaneous	34 (85)	86 (84.3)		
- IVF	6 (15)	16 (15.7)		
Trimester at survey			4.732	0.094
- 1	7 (17.5)	11 (10.8)		
- 2	9 (22.5)	24 (23.5)		
- 3	11 (27.5)	57 (55.9)		
- Post-partum				

18

	13 (32.5)	10 (9.8)		
Still pregnant at survey			10.904	0.001*
- Yes	27 (67.5)	92 (90.2)		
- No	13 (32.5)	10 (9.8)		
Disease during pregnancy			1.523	0.217
- Yes	6 (15)	25 (24.5)		
- No	34 (85)	77 (75.5)		
Age > 35 years old			0.278	0.598
- Yes	20 (50)	46 (45)		
- No	20 (50)	56 (55)		
Pre-existing diseases in age > 35 years old			0.2812	0.59
- Yes	4 (10)	12 (11.7)		
- No	16 (40)	34 (33.3)		
Pre-existing diseases in still pregnant > 35 years old			0.3626	0.547
- Yes	3 (7.5)	12 (11.7)		
- No	12 (30)	31 (30.4)		
Disease during pregnancy in age > 35 years old still pregnant at survey			1.2899	0.256
- Yes	2 (5)	12 (11.7)		
- No	13 (32.5)	31 (30.4)		
Being pregnant influence the choice			24.187	0.000*
- Yes	40 (100)	59 (57.8)		
- No	0	43 (42.1)		
Usually in favor of vaccines			6.091	0.014*
- Yes	40 (100)	88 (86.3)		
- No	0	14 (13.7)		
Received or would receive other vaccine during pregnancy (DTPa and/or influenza)			10.996	0.001*
- Yes	30 (75)	45 (44.1)		
- No				

19

	10 (25)	57 (55.9)		

Data are presented as number (%). * Statistically significant for p < 0.05. IVF, *in vitro* fertilization; DTPa (Diphtheria, Tetanus, acellular Pertussis).

FIGURES

Figure 1. Main reason reported by the women to decline SARS-COV-2 vaccine.
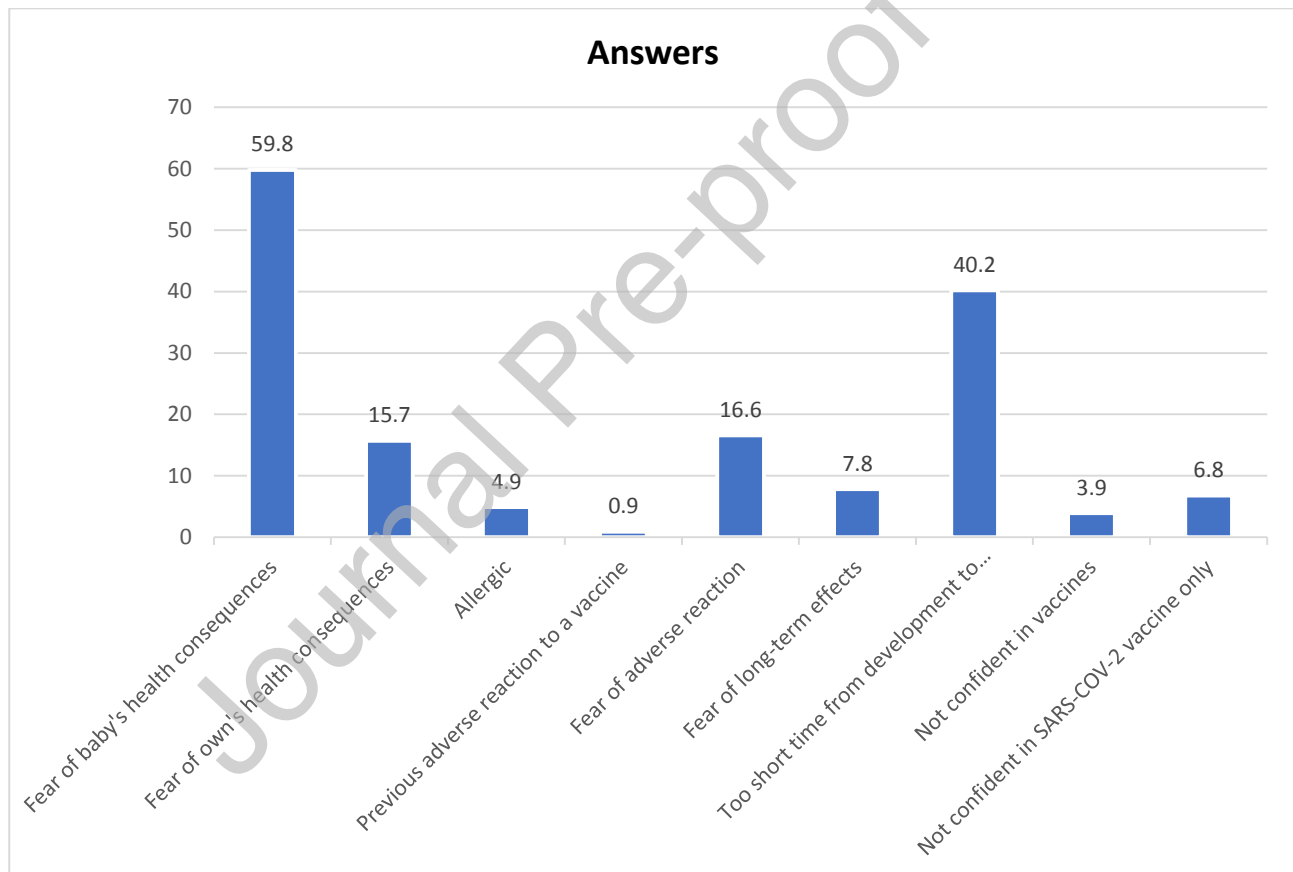
Participants could indicate more than one reason. Data are presented as percentage.