Received: 13 July 2022 | Accepted: 2 January 2023 | Published online: 5 February 2023

DOI: 10.1002/ijgo.14682

CLINICAL ARTICLE

Obstetrics

Preliminary results of COVID-19 vaccination among Taiwanese pregnant women: A single-center, prospective, case–control study

Kim Seng Law[1,2] | Yi-Ting Hsu[1] | Hsu-Peng Chen[1]

[1]Department of Obstetrics and Gynecology, Tung's Taichung MetroHarbour Hospital, Taichung City, Taiwan

[2]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung City, Taiwan

Correspondence
Kim Seng Law, Department of Obstetrics and Gynecology, Tung's Taichung MetroHarbour Hospital, 699 Taiwan Boulevard, Section 8, Wuchi, Taichung City 435, Taiwan.
Email: kimsenglaw@gmail.com

Abstract

Objective: To evaluate the impacts of messenger RNA coronavirus disease 2019 (COVID-19) vaccines in Taiwanese pregnant women in terms of obstetrical and neonatal outcomes.

Methods: The authors prospectively followed up 450 pregnant women receiving vaccination at a single center. Patients recorded prespecified adverse reactions via a mobile application up to 30 days after the first and second doses. Obstetrical and neonatal outcomes were compared with those of pregnant women, during the same period, who did not undergo vaccination.

Results: Among the 387 women who received the first dose and were followed up for 30 days, injection site pain, fatigue, injection site swelling, muscle ache, and headache were the most prevalent side effects. There were 4.7-, 5.7-, 7.1-, and 9.3-fold increases in fatigue, injection site swelling, muscle ache, and headache, respectively, among the 231 women who received the second dose. Most of the side effects resolved by 14 days and all resolved by 30 days after each doses. There were no significant differences ($P > 0.05$) in obstetrical and neonatal morbidity or mortality between the vaccinated and unvaccinated cohorts.

Conclusion: No serious adverse reactions were noted among pregnant women receiving messenger RNA vaccinations with comparable obstetrical and neonatal outcomes to unvaccinated pregnant women.

KEYWORDS
COVID-19, pregnancy, SARS-CoV-2, side effects, vaccine

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has profound adverse effects on pregnant women, increasing the incidences of preeclampsia, preterm birth, maternal admission to intensive care units, and even maternal death in addition to an increased risk of severe neonatal morbidity.[1–3] Acceptance of the COVID-19 vaccine was low at the beginning of the pandemic owing to the initial paucity of data in the pregnant population, with such hesitancy especially high in societies with a low prevalence of the disease.[4]

With the outbreak of COVID-19 at the beginning of June 2021 in Taiwan, the Taiwanese Centers for Disease Control (TCDC) encouraged pregnant women to be vaccinated after weighing the risks and benefits of the vaccines available at that time. However, at the time, there were no data on the safety profile of messenger RNA (mRNA) vaccines in the Asian population, especially among pregnant women.

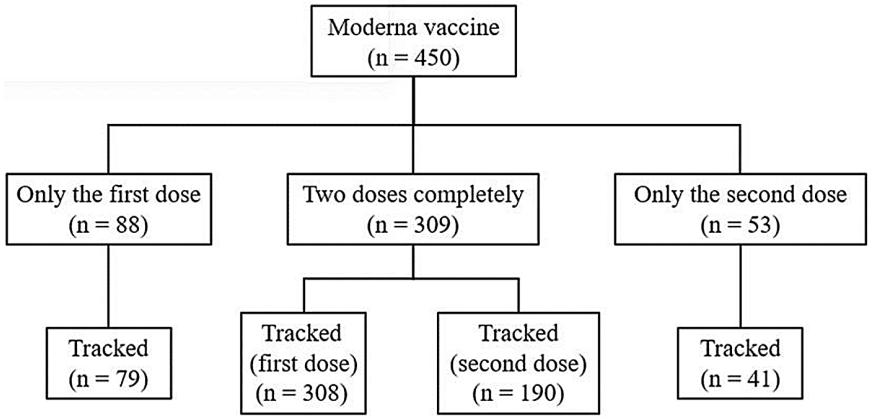

FIGURE 1 Flowchart of the study population.

Therefore, with this study, we aimed to prospectively evaluate the impacts of COVID-19 mRNA vaccination on maternal and neonatal outcomes, to provide data for future decision-making in Taiwan.

2 | MATERIALS AND METHODS

From July 1, 2021, to October 31, 2021, 450 women at various stages of pregnancy were offered mRNA vaccination (BioNTech vaccine was not available at that time in Taiwan) through the National Health System network. All pregnant women were attended by obstetricians in our department and evaluated by a family doctor on the date of appointment for the vaccine. For all eligible women, a bedside obstetrical ultrasound was performed by our senior residents to monitor their basic obstetrical conditions, including fetal heartbeat, estimated fetal weight, amniotic fluid index, placentation, and uterine contraction status, before they received their first dose. Any questions they had were answered during that same visit.

All women were followed up at 72 h and at 7, 14, and 30 days after the first and second doses by study nurses via a mobile application developed by the Taiwanese Central Epidermic Command Center (TCECC), named *Taiwan V-Watch*. Patients used the application to record prespecified reactions, which was evaluated by our study nurses during the follow-up time points. Appointments were made in the case of serious adverse events or any discomforts that the patients felt needed attention.

Obstetrical and neonatal results were documented in these vaccinated pregnant women and compared with those of a comparable cohort of unvaccinated pregnant women at the same period (controls).

Descriptive statistics were used to describe the demographic variables. Continuous variables are expressed as means and ranges, and categorical variables are expressed as frequencies and percentages. With the outcome of transferring units for the baby as the response variable, a multivariate logistic regression model was constructed for each variable. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A P value <0.05 was considered statistically significant. All statistical analyses were performed using R (R Foundation for Statistical Computing). The study was approved by the appropriate institutional review board, and the requirement for written informed consent was waived by the institutional review board.

TABLE 1 Demographics of vaccinated pregnant women.

Parameter	Moderna (n = 450)
Age, years	31.66 (18–44)
Weight, kg	65.37 (39.9–114.3)
Height, cm	159.86 (145–174)
BMI, kg/m^2	25.56 (18.81–49.03)
Gestational age at first dose, weeks	25^{+1} (10^{+6}–39^{+4})
Gestational age at second dose, weeks	27^{+2} (11^{+5}–40^{+3})
Delivery	233 (51.78)

Note: Data are presented as mean (range) or frequency (percentage).
Abbreviation: BMI, body mass index.

3 | RESULTS

In total, 450 pregnant women received the Moderna (Spikevax) vaccination, with 88 receiving only the first dose, 53 only the second dose, and 309 completing both scheduled doses (Figure 1). The overall mean gestational age was 25^{+1} weeks and 27^{+2} weeks at the time of receiving the first and second dose, respectively, with most of the study population being vaccinated during the second and third trimesters (Table 1; Figure 2).

Among the 387 patients who received the first dose and were followed up for 30 days, injection site pain was the most prevalent side effect experienced 72 h after the first injection, in 213 (55.0%) women, followed by fatigue (33, 8.5%), injection site swelling (26, 6.7%), muscle ache (17, 4.4%), headache (13, 3.4%), and injection site redness (11, 2.8%). Most of the side effects disappeared by 14 days after the first injection; 19 (4.9%), 32 (8.3%), 26 (6.7%), one (0.3%), one (0.3%), and one (0.3%) women had injection site swelling, injection site redness, injection site itching, rashes, nausea, and arm

weakness at that time (Table 2). All of the prespecified side effects disappeared by 30 days after the first dose.

Injection site pain (123, 53.2%), fatigue (93, 40.3%), injection site swelling (88, 38.1%), headache (72, 31.2%), and muscle ache (72, 31.2%) were the most prevalent side effects 72 h after the second dose among the 231 pregnant women and were followed-up for 30 days (Table 3). A comparison of side effects between the first and second doses is provided in Table 4, with 4.7-, 5.7-, 7.1-, and 9.3-fold increases in fatigue, injection site swelling, muscle ache, and headache, respectively. By 14 days after the second dose, the only documented side effects were two (0.9%), two (0.9%), two (0.9%), five (2.2%), one (0.43), and two (0.9%) cases of injection site pain,

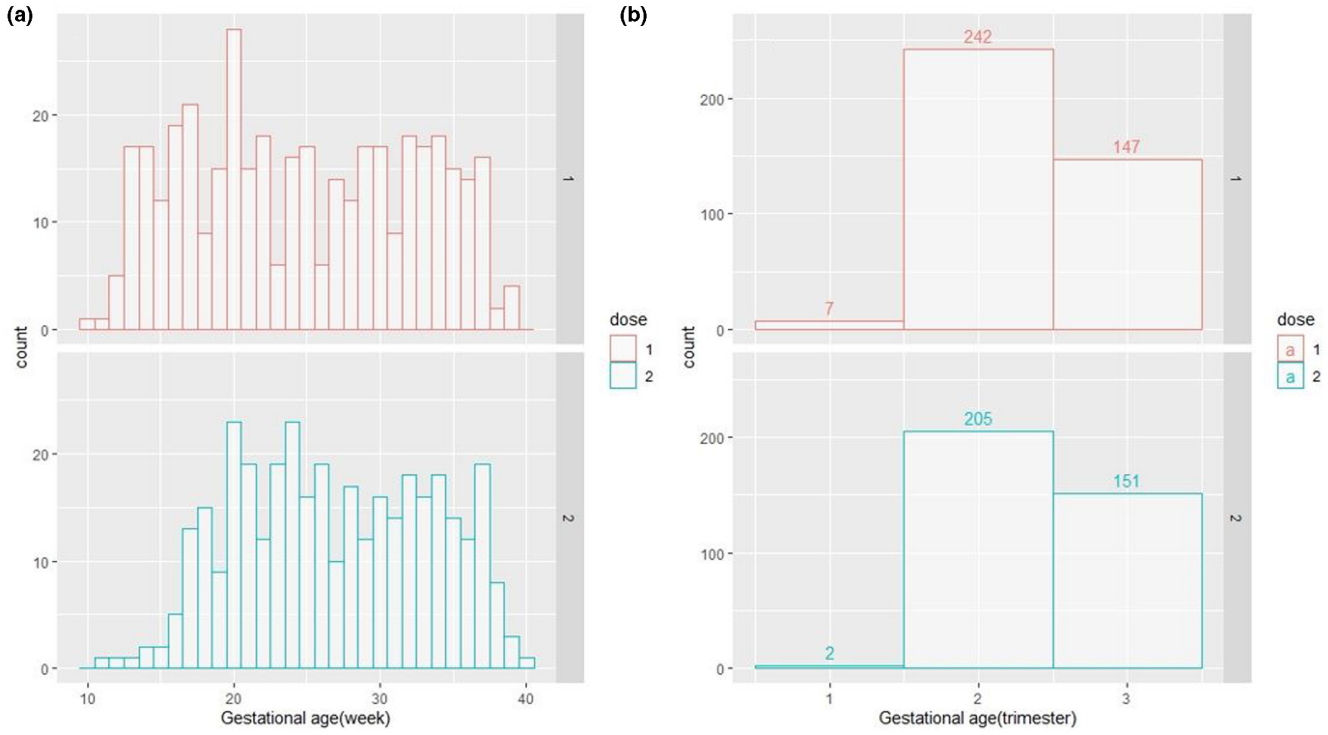

FIGURE 2 Gestational age for each dose. (a) unit: weeks. (b) unit: trimester.

TABLE 2 Side effects of the first dose ($n = 387$).

Side effects	72 h	7 days	14 days	30 days
Injection site pain	213 (55.04)	9 (2.33)	0 (0)	0 (0)
Injection site swelling	26 (6.72)	34 (8.79)	19 (4.91)	0 (0)
Injection site redness	11 (2.84)	43 (11.11)	32 (8.27)	0 (0)
Injection site itching	8 (2.07)	34 (8.79)	26 (6.72)	0 (0)
Chills	2 (0.52)	0 (0)	0 (0)	0 (0)
Pyrexia	6 (1.55)	0 (0)	0 (0)	0 (0)
Fever	4 (1.03)	0 (0)	0 (0)	0 (0)
Headache	13 (3.36)	2 (0.52)	0 (0)	0 (0)
Myalgia	17 (4.39)	1 (0.26)	0 (0)	0 (0)
Arthralgia	1 (0.26)	1 (0.26)	0 (0)	0 (0)
Abdominal pain	2 (0.52)	1 (0.26)	0 (0)	0 (0)
Diarrhea	1 (0.26)	0 (0)	0 (0)	0 (0)
Erythema	1 (0.26)	4 (1.03)	1 (0.26)	0 (0)
Fatigue	33 (8.53)	2 (0.52)	0 (0)	0 (0)
Nausea	7 (1.81)	0 (0)	1 (0.26)	0 (0)
Vomiting	4 (1.03)	0 (0)	0 (0)	0 (0)
Others	12 (3.11)	2 (0.52)	1 (0.26)	0 (0)

Note: Data are presented as frequency (percentage).

TABLE 3 Side effects of the second dose ($n = 231$).

Side effects	72 h	7 days	14 days	30 days
Injection site pain	123 (53.25)	3 (1.3)	2 (0.87)	0 (0)
Injection site swelling	88 (38.1)	3 (1.3)	2 (0.87)	0 (0)
Injection site redness	65 (28.14)	6 (2.6)	2 (0.87)	0 (0)
Injection site itching	61 (26.41)	9 (3.9)	5 (2.16)	0 (0)
Chills	32 (13.85)	0 (0)	0 (0)	0 (0)
Pyrexia	64 (27.71)	0 (0)	1 (0.43)	0 (0)
Fever	51 (22.08)	0 (0)	0 (0)	0 (0)
Headache	72 (31.17)	1 (0.43)	0 (0)	0 (0)
Myalgia	72 (31.17)	3 (1.3)	0 (0)	0 (0)
Arthralgia	31 (13.42)	0 (0)	0 (0)	0 (0)
Abdominal pain	8 (3.46)	0 (0)	0 (0)	0 (0)
Diarrhea	6 (2.6)	1 (0.43)	0 (0)	0 (0)
Erythema	9 (3.9)	0 (0)	0 (0)	0 (0)
Fatigue	93 (40.26)	4 (1.73)	2 (0.87)	0 (0)
Nausea	25 (10.82)	0 (0)	0 (0)	0 (0)
Vomiting	18 (7.79)	0 (0)	0 (0)	0 (0)
Others	10 (4.31)	0 (0)	0 (0)	0 (0)

Note: Data are presented as frequency (percentage).

TABLE 4 Comparison of side effects between the first and second doses after 72 h.

Side effects	First dose ($n = 387$)	Second dose ($n = 231$)	Change
Injection site pain	213 (55.04)	123 (53.25)	▼1.79%
Fatigue	33 (8.53)	93 (40.26)	▲31.73%
Injection site swelling	26 (6.72)	88 (38.1)	▲31.38%
Headache	13 (3.36)	72 (31.17)	▲27.81%
Pyrexia	6 (1.55)	64 (27.71)	▲26.16%
Injection site redness	11 (2.84)	65 (28.14)	▲25.3%
Injection site itching	8 (2.07)	61 (26.41)	▲24.34%
Fever	4 (1.03)	51 (22.08)	▲21.05%
Chills	2 (0.52)	32 (13.85)	▲13.33%
Arthralgia	1 (0.26)	31 (13.42)	▲13.16%
Nausea	7 (1.81)	25 (10.82)	▲9.01%
Vomiting	4 (1.03)	18 (7.79)	▲6.76%
Erythema	1 (0.26)	9 (3.9)	▲3.64%
Abdominal pain	2 (0.52)	8 (3.46)	▲2.94%
Diarrhea	1 (0.26)	6 (2.6)	▲2.34%

Note: Data are presented as frequency (percentage).

injection site swelling, injection site redness, injection site itching, pyrexia, and malaise, respectively. By 30 days after the second dose, no side effects remained.

A fever greater than 38°C occurred in four (1.0%) and 51 (22.1%) of women 72 h after the first and second doses, respectively, with all of them exhibiting normal body temperatures within 1 week of the doses.

A total of 233 women gave birth during the study period, with a mean gestational age of 38^{+3} (23^{+3}–40) weeks and a mean birthweight of 3036 g (576–4128 g). Among them, 113 (48.5%) births

TABLE 5 Demographics of women who delivered during the study period.

Parameter	Delivered ($n = 233$)
Maternal age, years	31.9 (19–43)
Maternal weight, kg	70.95 (48–106)
Maternal height, cm	159.81 (145–173.8)
Maternal BMI, kg/m^2	27.75 (19.83–43.56)
Gestational age at delivery, weeks	38^{+3} (23^{+3}–40^{+0})
Birthweight, g	3035.67 (576–4128)
Gravidity	2.04 (1–8)
Parity	
Multiparous	134 (57.51)
Nulliparous	99 (42.49)
Mode of delivery	
CS	113 (48.5)
NSD	95 (40.77)
VED	25 (10.73)
Gestational morbidities	
GD	35 (15.02)
Placenta previa	3 (1.29)
PPH	4 (1.72)
Preeclampsia	7 (3)
Multiple birth	
Singleton	229 (99.13)
Twin	2 (0.87)
Newborn transfer units	
BR	202 (86.7)
NICU	8 (3.43)
SNU	22 (9.44)
Stillbirth	1 (0.43)

Note: Data are presented as mean (range) or frequency (percentage).
Abbreviations: BMI, body mass index; BR, baby room; CS, cesarean section; GD, gestational diabetes; NICU neonatal intensive care unit; NSD, natural spontaneous delivery; PPH, postpartum hemorrhage; SNU, sick neonatal unit; VED, vacuum-assisted delivery.

TABLE 6 Comparison between vaccinated and unvaccinated parturients.

Parameter	Total ($N = 462$)	Unvaccinated ($n = 229$)	Moderna ($n = 233$)	*P* value
Maternal age, years	31.58 (18–43)	31.26 (18–43)	31.9 (19–43)	0.164[a]
Maternal weight, kg	70.65 (43–111.8)	70.35 (43–111.8)	70.95 (48–106)	0.593[a]
Maternal height, cm	159.39 (145–179)	158.95 (147.2–179)	159.81 (145–173.8)	0.091[a]
Maternal BMI, kg/m^2	27.77 (18.81–49.03)	27.8 (18.81–49.03)	27.75 (19.83–43.56)	0.902[a]
Gestational age at delivery, weeks	38^{+2} (21^{+1}–40^{+0})	38^{+1} (21^{+1}–40^{+0})	38^{+3} (23^{+3}–40^{+0})	0.11[a]
Birthweight, g	3000.69 (424–4246)	2965.1 (424–4246)	3035.67 (576–4128)	0.156[a]
Gravidity	2.06 (1–9)	2.08 (1–9)	2.04 (1–8)	0.705[a]
Parity	0.69 (0–6)	0.7 (0–6)	0.67 (0–2)	0.695[a]
Multiparous	245 (53.03)	111 (48.47)	134 (57.51)	0.064[b]
Nulliparous	217 (46.97)	118 (51.53)	99 (42.49)	
Mode of delivery				0.353[c]
CS	226 (48.92)	113 (49.34)	113 (48.5)	
NSD	173 (37.45)	79 (34.5)	94 (40.34)	
VED	60 (12.99)	35 (15.28)	25 (10.73)	
Vaginal	3 (0.65)	2 (0.87)	1 (0.43)	
GD	71 (15.37)	36 (15.72)	35 (15.02)	0.937[b]
Heart disease	2 (0.43)	2 (0.87)	0 (0)	0.245[c]
Placenta abruption	2 (0.43)	2 (0.87)	0 (0)	0.245[c]
Placenta previa	5 (1.08)	2 (0.87)	3 (1.29)	>0.99[c]
Postpartum hemorrhage	11 (2.38)	7 (3.06)	4 (1.72)	0.378[c]
Preeclampsia	24 (5.19)	17 (7.42)	7 (3)	0.054[b]
Neonate transfer units				0.389[c]
BR	389 (84.2)	187 (81.66)	202 (86.7)	
NI	16 (3.46)	8 (3.49)	8 (3.43)	
SN	53 (11.47)	31 (13.54)	22 (9.44)	
Stillbirth	4 (0.87)	3 (1.31)	1 (0.43)	

Note: Data are presented as mean (range) or frequency (percentage).

Abbreviations: BMI, body mass index; BR, baby room; CS, cesarean section; GD, gestational diabetes; NICU, neonatal intensive care unit; NSD, natural spontaneous delivery; SNU, sick neonatal unit; VED, vacuum-assisted delivery.

[a]Student *t* test.

[b]χ^2 test.

[c]Fisher exact test.

occurred via cesarean section, 95 (40.8%) occurred vaginally, and 25 (10.7%) occurred via instrumental-assisted vaginal delivery (Table 5). Among the delivered babies, seven (3.0%) were admitted to the neonatal intensive care unit and 20 (8.6%) to the sick neonatal unit, and there was one stillbirth.

Compared with the unvaccinated cohort of women who delivered at the same period in our hospital, there was no significant difference in obstetrical and neonatal morbidity or mortality among the vaccinated cohort (Tables 6 and 7).

4 | DISCUSSION

No serious adverse events occurred among the 450 pregnant women receiving the mRNA vaccine (Moderna) during the study period, with most of the side effects resolving within 14 days in both the first and second dose groups in our preliminary study. Most of the side effects occurred at a higher rate after the second dose.

TABLE 7 Multivariate logistic regression for the association between neonates and mothers taking the Moderna vaccine.

Parameter	OR	(95% CI)	*P* value
Maternal age, years	1.023	(0.961–1.089)	0.48
Birthweight, g	0.999	(0.998–1)	0.005
Gestational age at delivery, days	0.926	(0.891–0.959)	<0.001
BMI (kg/m^2)			0.851
<30	Ref		
≥30	1.07	(0.515–2.142)	
Parity			0.799
Multiparous	Ref		
Nulliparous	1.084	(0.58–2.018)	
Diabetes	1.607	(0.719–3.43)	0.231
Moderna vaccine	0.808	(0.434–1.496)	0.497

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

As compared with the study by Shimabukuro et al.,[5] the overall injection site reaction (combined injection site pain and swelling) was comparable in both studies (91.3% vs 91.6%). There was a higher percentage of fatigue (68.5% vs 40.3%), muscle arche (59.6% vs 31.2%), headache (63% vs 31.2%), and chills (43% vs 13.8%), although they did not specifically mention what percentage of side effects occurred in different doses.

Obstetrical or neonatal morbidities did not differ between women who were vaccinated and those who were not during the study period, which was also verified in other studies.[5–8]

The strengths of this study are the detailed and real-time reporting of the side effects by patients and verification by our special nurses with a thorough 30-day follow-up via the mobile application developed by the TCECC. The thorough prevaccination evaluation by a family physician and obstetric residents to verify the well-being of mother and fetus not only provided peace of mind to the pregnant women but also allowed us to build relationships with them, simplifying follow-up.

The limitation of this study is its small size and single-center nature, limiting its generalizability in terms of recommendations regarding the safety of the vaccine for pregnant women in Taiwan. Studies of other mRNA vaccines (BNT162b2 mRNA COVID-19 vaccine) and ChAdOx1 nCoV-19 vaccines (AZD1222) in pregnant women were not available because of a lack of the BNT/Pfizer stock and hesitancy of AZ usage in pregnant women during the study period. However, as this was, to our knowledge, the first article describing COVID-19 vaccination in a Taiwanese pregnant population, the study laid the groundwork for further research in the field, and exploration of other available vaccines in pregnant women need to be elucidated.

None of the women in the vaccinated or control cohorts tested positive for COVID-19 during the study period; hence, we could not add information on the effectiveness of the vaccine. However, there have been several reports on the decrease of maternal and neonatal complications among infected individuals who had received a full vaccine dose.

Although the majority of our study cohort received their vaccination during their second or third trimester with few receiving preconceptionally or early in their pregnancy, the safety of the vaccination on the infertility and early spontaneous abortion rate has been verified by other studies.[9,10]

A high rate of acceptance of vaccination (52%) has been reported when the vaccine effectiveness is >90%.[11] As the rate of minor side effects in this study was acceptable, with most resolving within 14 days of the dose, and the proven effectiveness of vertical transmission of the protective antibody to the fetus from mothers who received full doses of vaccination in other studies,[8,11,12] our data may reassure pregnant women regarding vaccination and as a reference in policy-making in the future.

AUTHOR CONTRIBUTIONS

Kim Seng Law conceptualized the idea, analyzed the collected data, and drafted/wrote the manuscript. Yi-Ting Hsu and Hsu-Peng Chen performed the bedside obstetrical sonar and answered any questions for the study participants before receiving their first vaccination.

ACKNOWLEDGMENTS

The authors acknowledge the work performed by our residents and study nurses in documenting the well-being of the fetuses before vaccination and verifying the side effects after vaccination, respectively.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ORCID

Kim Seng Law https://orcid.org/0000-0002-2484-3761

REFERENCES

1. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370:m3320.
2. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. *CMAJ*. 2021;193:E540-E548.
3. Villar J, Ariff S, Gunier RB, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID multinational cohort study. *JAMA Pediatr*. 2021;175:817-826.
4. Kharbanda EO, Vazquez-Benitez G. COVID-19 mRNA vaccines during pregnancy: new evidence to help address vaccine hesitancy. *JAMA*. 2022;327:1451-1453.
5. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons. *N Engl J Med*. 2021;384:2273-2282.
6. Dagan N, Barda N, Biron-Shental T, et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. *Nat Med*. 2021;27:1693-1695.
7. Fu W, Sivajohan B, McClymont E, et al. Systematic review of the safety, immunogenicity, and effectiveness of COVID-19 vaccines in pregnant and lactating individuals and their infants. *Int J Gynaecol Obstet*. 2022;156:406-417.
8. Ciapponi A, Bardach A, Mazzoni A, et al. Safety of components and platforms of COVID-19 vaccines considered for use in pregnancy: a rapid review. *Vaccine*. 2021;39:5891-5908.
9. Zauche LH, Wallace B, Smoots AN, et al. Receipt of mRNA Covid-19 vaccines and risk of spontaneous abortion. *N Engl J Med*. 2021;385:1533-1535.
10. Hillson K, Clemens SC, Madhi SA, et al. Fertility rates and birth outcomes after ChAdOx1 nCoV-19 (AZD1222) vaccination. *Lancet*. 2021;398:1683-1684.
11. Skjefte M, Ngirbabul M, Akeju O, et al. COVID-19 vaccine acceptance among pregnant women and mothers of young children: results of a survey in 16 countries. *Eur J Epidemiol*. 2021;36:197-211.
12. Nana M, Hodson K, Lucas N, et al. Diagnosis and management of Covid-19 in pregnancy. *BMJ*. 2022;377:e069739.

How to cite this article: Law KS, Hsu Y-T, Chen H-P. Preliminary results of COVID-19 vaccination among Taiwanese pregnant women: A single-center, prospective, case–control study. *Int J Gynecol Obstet*. 2023;162:133-138. doi:10.1002/ijgo.14682