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The risk of miscarriage following COVID-19 vaccination: a systematic review and meta-analysis

Running title: Miscarriage risk following COVID-19 vaccination

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Abstract

Study question: What is the risk of miscarriage among pregnant women who received any of the COVID-19 vaccines?

Summary answer: There is no evidence that COVID-19 vaccines are associated with an increased risk of miscarriage.

What is known already: In response to the COVID-19 pandemic, the mass roll-out of vaccines helped to boost herd immunity and reduced hospital admissions, morbidity and mortality. Still, many were concerned about the safety of vaccinesfor pregnancy, which may have limited their uptake among pregnant women and those planning a pregnancy.

Study design, size, duration: For this systematic review and meta-analysis, we searched MEDLINE, EMBASE and Cochrane CENTRAL from inception until June 2022 using a combination of keywords and MeSH terms.

Participants/materials, setting, methods: We included observational and interventional studies that enrolled pregnant women and evaluated any of the available COVID-19 vaccines compared to placebo or no vaccination. We primarily reported on miscarriage in addition to ongoing pregnancy and/or live birth.

Main results and the role of chance: We included data from 21 studies (5 randomised trials and 16 observational studies) reporting on 149,685 women. The pooled rate of miscarriage among women who received a COVID-19 vaccine was 9% (n=147,49/123,185, 95%CI 0.05-0.14). Compared to those who received a placebo or no vaccination, women who received a COVID-19 vaccine did not have a higher risk of miscarriage (RR 1.07, 95%CI 0.89-1.28, I^2 35.8%) and had comparable rates for ongoing pregnancy or live birth (RR 1.00, 95%CI 0.97-1.03, I^2 10.72%).

Limitations, reasons for caution: Our analysis was limited to observational evidence with varied reporting, high heterogeneity and risk of bias across included studies, which may limit the generalisability and confidence in our findings.

Wider implications of the findings: COVID-19 vaccines are not associated with an increase in the risk of miscarriage or reduced rates of ongoing pregnancy or live birth among women of reproductive age. The current evidence remains limited and larger population studies are needed to further evaluate the effectiveness and safety of COVID-19 in pregnancy.

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Keywords: COVID-19 vaccination, vaccine safety, miscarriage, pregnancy loss, live birth.

Introduction

The last two years saw the mass rollout of multi-national vaccination campaigns for the SARS-CoV-2 (COVID-19) virus with the hope of attenuating its devastating effect on society and restoring normality (de Gier *et al.*, 2021; Lopez Bernal *et al.*, 2021). The rapid development and rollout of these vaccines raised concerns about their short and long-term health side effects leading to vaccine hesitancy among pregnant women and those planning a pregnancy (Egloff *et al.*, 2022; Kiefer *et al.*, 2022). However, to date, most studies and regulatory bodies support their safety and effectiveness (American College of Obstetricians and Gynecologists, 2022; Royal College of Obstetricians & Gynaecologists, 2022; UK Health Security Agency., 2022). Most early studies evaluating the efficacy of COVID-19 vaccines excluded pregnant women, which limited evidence synthesis on the safety of vaccines in pregnancy (Baden *et al.*, 2021; Madhi *et al.*, 2021; Polack *et al.*, 2020; Sadoff *et al.*, 2021). The majority of health authorities currently support the safety of COVID-19 vaccination in pregnant women (American College of Obstetricians and Gynecologists, 2022; Royal College of Obstetricians & Gynaecologists, 2022) to reduce the risk of poor pregnancy outcomes observed in unvaccinated women with COVID-19 infection (Stock *et al.*, 2022).

Some authors have raised concerns about the potential cross-reactivity of SARS-CoV-2 spike protein antibodies following mRNA vaccination with human syncytin-1 protein in trophoblastic tissue (Ciapponi *et al.*, 2021; Mattar *et al.*, 2021; Schaler *et al.*, 2021; Shanes *et al.*, 2021). Autoreactive antibodies against syncytin-1 were presumed to cause placental damage and early pregnancy loss due to the potential homology with the SARS-CoV-2 spike protein. However, further characterisation of the SARS-CoV-2 spike protein structure and amino acid sequencing showed low homology with syncytin-1, disproving claims of cross-

reactivity and potential damage to placental tissue (Gong *et al.*, 2005; Kloc *et al.*, 2021; Prasad *et al.*, 2021). Given the increased risk of morbidity and mortality among pregnant women with COVID-19, it is critical to maximise prevention efforts by encouraging vaccine uptake and promoting its safety during pregnancy (Royal College of Obstetricians & Gynaecologists, 2021). We performed a systematic review and meta-analysis of the available literature to evaluate the rates of miscarriage and live birth among women who received a COVID-19 vaccination.

Materials and methods

We performed a systematic review and meta-analysis using a prospectively registered protocol (CRD42021289098) and reported our findings as per PRISMA guidelines (Page *et al.*, 2021).

Search strategy

We searched MEDLINE, EMBASE and Cochrane CENTRAL until June 2022 using a combination of keyword and MeSH terms for studies of any design that compared the risk of miscarriage and other pregnancy outcomes between vaccinated and non-vaccinated pregnant women (Supplementary Data File S1).

Study selection and inclusion process

Relevant studies were screened in duplicate (MPR and JJT). Studies of any design that reported on miscarriage and other pregnancy outcomes in women who received any COVID-19 vaccine with or without a control cohort (placebo or no vaccine) were included. We excluded animal studies, those reporting on non-clinical outcomes in human participants, review articles and case reports. Data submitted to health regulators for evaluation of vaccine effectiveness and safety were also included if they were made publicly available ahead of peer review.

Data extraction

Data extraction was performed in triplicate (MPR, JJT and SCM) using a piloted electronic data collection tool with the following characteristics collected: study publication year and journal, inclusion-exclusion criteria, type of intervention and comparison evaluated, characteristics of the included study population and the evaluated COVID-19 vaccine, and all relevant clinical outcomes.

126

127 Outcome measures

128 We reported on the following pregnancy outcomes: miscarriage (defined as spontaneous loss
129 of a pregnancy before 24 weeks gestation), live birth (defined as the birth of a live child after
130 24 weeks gestation) and ongoing pregnancy (defined as a viable pregnancy after 12 weeks
131 gestation).

132

133 Risk of bias assessment

134 Two reviewers (MPR and JJT) assessed the risk of bias and applicability of included studies
135 independently using The Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-
136 I) tool (Sterne *et al.*, 2016). We evaluated the risk of bias in the included studies compared to
137 a target randomised trial that evaluated the risk of miscarriage, live birth and ongoing
138 pregnancy in women of reproductive age who received a COVID-19 vaccine compared to
139 placebo or no vaccine. As most of the included studies were cohorts or interrupted time
140 series that followed up on women who received a COVID-19 vaccine, we assessed the risk of
141 bias due to confounding, participant selection, classification of intervention, deviation from the
142 intended intervention, missing data, outcome measurement and selection of reported results.
143 We then generated an overall risk of bias assessment for each study. Studies were deemed to
144 be low risk of bias if they were assessed as low risk in all domains, moderate risk of bias if
145 they were assessed as low or moderate risk of bias in any domain, serious risk of bias if they
146 were assessed as serious risk of bias in at least one domain, but not at critical risk of bias in
147 any domain, or critical risk of bias if one or more domains was assessed as critical.

148

149 Statistical analysis

We pooled data to evaluate the overall rate of miscarriage and live birth/ongoing pregnancy across all women who received a COVID-19 vaccine and generated a pooled risk ratio compared to women who were not vaccinated. We reported on the pooled event rate using risk with 95% confidence intervals (CI). For our comparative meta-analysis, we reported on dichotomous outcomes using summary risk ratio (RR) with 95% CI and on continuous outcomes using weighted mean difference (WMD) with 95% CI. We used a random effect meta-analysis and applied a restricted maximum likelihood (REML) model. Study heterogeneity among included trials was assessed using the I^2 statistics. We also assessed the publication bias and small study effect using a funnel plot for each pairwise comparison and performed Egger's test to assess its statistical significance. We planned a sensitivity meta-regression and subgroup analyses to investigate potential effect modifiers where relevant. All statistical analyses were conducted in Stata V13 (StataCorp, TX, USA) and Open Meta-analyst software (Brown University; Providence, RI, USA).

Results

We screened 505 potentially relevant citations, assessed 28 in full and included 21 studies: 5 randomised control trials (RCTs) (Hillson *et al.*, 2021; United States Food and Drug Administration, 2020; United States Food and Drug Administration, 2020; United States Food and Drug Administration, 2021; United States Food and Drug Administration, 2021) and 16 observational studies (Aharon *et al.*, 2022; Avraham *et al.*, 2022; Bleicher *et al.*, 2021; Bookstein Peretz *et al.*, 2021; Citu *et al.*, 2022; Favre *et al.*, 2022; Huang *et al.*, 2022; Kachikis *et al.*, 2021; Kharbanda *et al.*, 2021; Magnus *et al.*, 2021; Moro *et al.*, 2022; Nabila Arfah *et al.*, 2021; Qiao *et al.*, 2021; Trostle *et al.*, 2021; Wang *et al.*, 2022; Zauche *et al.*, 2021). All together the studies reported on pregnancy outcomes in 149,685 women (Table 1 and Supplementary Table S1). Two studies reported on the same population (Aharon *et al.*, 2021; Aharon *et al.*, 2022) while an additional two studies reported on the same data registry (Moro *et al.*, 2022; Shimabukuro *et al.*, 2021) (Figure 1). All of the RCTs in this review excluded pregnant women at the time of recruitment but reported on those who became pregnant during the trial.

Six vaccines were used in included studies, including Pfizer-BioNTech BNT162b2 mRNA, Moderna mRNA-1273 SARS-CoV-2, Janssen Ad26.COV2.S, AstraZeneca ChAdOx1 nCoV-19, Sinopharm BBIBP-CorV and Sinovac-CoronaVac. Ten studies reported on pregnancy outcomes following at least one vaccine dose, eight studies reported pregnancy outcomes following two doses and one study reported outcomes after a third booster dose (Table 1).

Quality of included studies and risk of publication bias

Overall, the quality of the included studies was considered to have low to moderate risk of bias while four studies were considered to have a serious risk of bias (Supplementary Figure S1). All included studies were assessed as having missing information on adherence to the vaccine administration schedule, not allowing accurate assessment of the risk of bias for deviations from the intended intervention. Six of the included studies had an overall low risk of bias (6/21, 29%), half showed a moderate risk (11/21, 52%), and four showed a high risk of bias (4/21, 19%) mainly due to participant selection and measurement and outcomes reporting. Outcome reporting was poor overall with only two studies offering a clear outcome definitions for miscarriage and ongoing pregnancy (Aharon *et al.*, 2021; Hillson *et al.*, 2021). Our funnel plot suggested no major variation across included studies with a non-significant Egger's test at p=0.81 (Supplementary Figure S2).

Pregnancy outcomes

We pooled the overall miscarriage rate across all included studies among women who received any COVID-19 vaccine which was 9% (n= 18 studies, 147,49/123,185, 95%CI 0.05-0.14) (Figure 2). We then compared the risk of miscarriage among those who received any COVID-19 vaccine to those who did not, which suggested no significant difference between the two groups (RR 1.07, 95%CI 0.89-1.28, I^2 35.8%) (Figure 3).

The overall proportion of women with ongoing pregnancies or live birth among those who were vaccinated was consistent with the reported population levels at 77% (n= 14 studies, 103,240/117,766, 95%CI 0.65-0.89) (Figure 2). Compared to the unvaccinated group, women who received the COVID-19 vaccines had similar rates of ongoing pregnancies or live birth (RR 1.00, 95%CI 0.97-1.03, I^2 10.7%) (Figure 3).

Discussion

We identified 21 studies reporting miscarriage or live birth/ongoing pregnancy outcomes among 149,685 women. Our results demonstrate no apparent increase in the risk of miscarriage among pregnant women who received the COVID-19 vaccines, which was consistent with the rate of miscarriage in the general population before the pandemic (Quenby *et al.*, 2021). Compared to unvaccinated women, those who received the vaccine had a slightly higher risk of miscarriage, though this was not statistically significant. This trend could be explained by several confounders, such as population socio-economics, baseline risk factors (e.g. recurrent pregnancy loss), co-morbidities and access to health care services, which were observed in cohort studies evaluating third-trimester pregnancy outcomes among vaccinated women (Fell *et al.*, 2022; Magnus *et al.*, 2022). There was no significant difference in the relative risk (RR) of live birth or ongoing pregnancy among women who received COVID-19 vaccination compared to those who did not receive a vaccine.

Overall, the certainty in the pooled evidence was low (Figure 4) due to serious concerns about the consistency, precision and directness of our synthesised effect estimate. Given the high heterogeneity across included studies, our results should be interpreted with caution pending larger well-powered controlled studies.

Strengths and limitations

We present a systematic review that employed a prospectively registered protocol and reported as per established guidelines, therefore offering a comprehensive assessment of the literature on the safety of COVID-19 vaccines in pregnancy. Only about half of the included studies had appropriately matched controls which limited our ability to generate a risk ratio with accurate

239 confidence intervals. Still, we reported narratively on all included studies and generated a
240 weighted average to estimate the overall proportion of miscarriage and ongoing pregnancy or
241 live birth among vaccinated pregnant women.
242
243 We included studies from various countries including data from large regulatory randomised
244 trials that were used to licence the use of COVID-19 vaccine in the general population.
245 However, as pregnant women were excluded from these trials at the time of randomisation, the
246 evidence included in this review is mainly observational with high level of heterogeneity.
247 Several factors could explain this heterogeneity including variation in study design and patient
248 characteristics, and the high risk of bias across included studies. This limits the generalizability
249 of our meta-analysis and highlights the need for better quality primary studies involving
250 pregnant women.
251
252 The majority of the included studies practiced suboptimal and varied outcome reporting which
253 limited our ability to synthesise high-quality evidence, as reflected in our GRADE assessment
254 (Figure 4). This reduced the certainty of our pooled estimates, especially since other important
255 pregnancy outcomes, e.g. stillbirth and ectopic pregnancy, were not reported.
256
257 While we reported a relatively low miscarriage rate (9%) across a large cohort (n=123,184),
258 our pooled rate offers a limited snapshot assessment over a short period of time and therefore
259 should be interpreted with caution. Clearly, several factors could influence the overall
260 miscarriage rate during the pandemic such as ethnicity, mode of conception, and access to
261 maternity services during lockdown periods (García-Enguídanos *et al.*, 2002).
262

As most of these studies focused on short snapshot assessment of COVID-19 vaccine safety, the majority reported on the combined outcome of ongoing pregnancy or live birth. Clearly, this outcome does not offer an accurate assessment of the long-term reproductive outcome as not all ongoing pregnancies captured will yield a live birth. Still, we chose to report on this outcome to provide an accurate summary of the current available literature, assess the knowledge gap, and make recommendations to improve the quality of future research.

We planned to perform meta-regression and subgroup analysis to evaluate and adjust for important confounders such as patient characteristics, vaccine types (e.g. mRNA versus vector) and the number of vaccine boosters. However, we were unable to produce these additional analyses due to poor reporting across included studies (Table 1). Other important effect modifiers that were also poorly reported included patient age group, method of conception, multiples pregnancy, and the impact across first versus second-trimester miscarriage. Standardised outcome reporting is therefore essential to improve the quality of future evidence synthesis particularly to facilitate patient-level data analysies.

Implications for clinical practice

The COVID-19 pandemic introduced unprecedented challenges with enduring humanitarian and economic crises that are still unfolding (Spinelli *et al.*, 2020). In addition to its high virality, rapid mutations and lack of curative treatments, a key challenge in controlling the COVID-19 virus was the role of mass media misinformation that often undermined efforts to promote key prevention strategies like mask-wearing, social distancing and vaccination (Loomba *et al.*, 2021; Roozenbeek *et al.*, 2020).

Generally, concerns about the safety of vaccines in pregnancy could be attributed to the generic immunological and inflammatory response that could impact fetal implantation and embryogenesis (Arora *et al.*, 2021; Moodley *et al.*, 2021). However, in the case of COVID-19 mRNA vaccines, there were concerns disseminated on social media platforms claiming higher risk of miscarriage due to the formation of antibodies that could cross the placenta and bind to the spike protein called syncytin-1, a critical protein in the formation of the syncytiotrophoblast layer of the human placenta and embryogenesis (M. Blake Evans *et al.*, 2021). Several studies have came out since to disproof these claims with no evidence from immunological studies to support such interaction (Moodley *et al.*, 2021). Our findings further support the lack of harmful evidence pending larger, better-quality studies at a population level.

Considering the increased risk of miscarriage and other adverse pregnancy outcomes associated with COVID-19 infection in pregnancy (Stock *et al.*, 2022), vaccines play a vital role to minimise the impact of this disease on pregnant women and their offspring (Arora *et al.*, 2021; Moodley *et al.*, 2021). Ideally, the risks of vaccination should be evaluated considering the patient's current medical health, risk profile for COVID-19 morbidity, and past adverse reactions or febrile illnesses to previous vaccinations. Vaccinations in the firsttrimester could pose some risks of high immunogenicity and inflammation from a febrile illness to the fetus; especially in patients who have few or no risk factors for serious morbidity should they contract COVID-19. However, the merits of avoiding COVID-19 vaccination in the first trimester in favour of the pre-conception period or the second trimester remain unclear and further research is needed.

Available COVID-19 vaccines seem to have high immunogenicity and reactogenicity (Gray *et al.*, 2021), often associated with a systemic inflammatory process manifesting with headache,

myalgia, chills and fever (Shimabukuro *et al.*, 2021). Pregnant women receiving COVID-19 vaccines reported a higher incidence of systemic fever after the second dose compared to non-pregnant women (Gray *et al.*, 2021). Fever in early pregnancy and during embryogenesis may be a teratogenic phenomenon and this may increase the risk of miscarriage especially in the first trimester or among those with more severe vaccine side effects (Dreier *et al.*, 2014; Graham *et al.*, 1998). We were unable to explore the optimal timing to provide COVID-19 vaccines in pregnancy and whether such side effects could have a differential impact on first versus second-trimester pregnancies.

As the rate of re-infection with new mutations of the COVID-19 virus is increasing progressively (Jain *et al.*, 2021), there is a need to evaluate the optimal timing to provide COVID-19 vaccines for both de-novo and booster immunity. This is particularly relevant to high-risk women planning for pregnancy such as those with chronic disease or those undergoing assisted conception (Han *et al.*, 2022).

Future research

There is a critical need to evaluate the short and long-term safety and effectiveness outcomes of the different COVID-19 vaccines on pregnant women and their offspring. As the experience with the different types of COVID-19 vaccines grows (mRNA versus vector vaccines), large prospective cohorts with appropriately matched controls are needed to evaluate the effectiveness and safety of the different COVID-19 vaccination programmes in reducing the reported risks of adverse maternal and neonatal outcomes (Wei *et al.*, 2021).

Several studies have identified binding and neutralising antibody titres for COVID-19 in infant cord blood and the breast milk of lactating vaccinated women. This could suggest long-lasting

protective immunity that might help to reduce the risk of re-infection or severe disease among this vulnerable cohort (Fell *et al.*, 2022; Goldshtein *et al.*, 2022; Magnus *et al.*, 2022). However, more epidemiological and translational studies are needed to evaluate the long-term health outcomes among both mothers and offspring post vaccine exposure.

We encountered a high degree of varied outcome reporting which significantly hindered effective evidence synthesis. Future studies should adopt standardised reporting of core outcomes as per published core sets for miscarriage, fertility and pregnancy to enable more efficient evidence synthesis and reduce research wastage (Duffy *et al.*, 2020; Duffy *et al.*, 2021; Smith *et al.*, 2017).

Conclusions

COVID-19 vaccines are not associated with an increased risk of miscarriage or decreased rates of ongoing pregnancy or live birth rates among women of reproductive age. The current evidence remains limited and larger population studies are needed to evaluate the effectiveness and safety of COVID-19 vaccines in pregnancy.

Data availability: All data generated or analysed during this study are included in this published article and its supplementary information files.

Authors' roles: MPR and JJT drafted the initial protocol and manuscript, and conducted the search, study selection and initial analysis. SCM contributed to the data extraction and visualisation. BHA conceived the idea, conducted the final analysis, and drafted the final manuscript. All authors approved the final version of the manuscript.

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Conflict of interest: All authors declare no conflict of interest.

Figure 1. Study screening and inclusion process for systematic review evaluating the risk of miscarriage and ongoing pregnancy live birth among pregnancy women who received COVID-19 vaccine.

Figure 2. Pooled event rate of miscarriage and ongoing pregnancy/live birth among pregnancy women who received the COVID-19 vaccinations. A) miscarriage. B) ongoing pregnancy/live birth.

Figure 3. Forest plot showing the risk ration of miscarriage and ongoing pregnancy/live birth among pregnancy women who received COVID-19 vaccination compared to unvaccinated women. A) miscarriage. B) ongoing pregnancy/live birth.

Figure 4. GRADE evidence assessment table for the risk of miscarriage and ongoing pregnancy/live birth among pregnancy women who received COVID-10 vaccine.

Supplementary Figure S1. ROBBINS1 assessment of the quality of included studies that evaluated the risk of miscarriage among pregnancy women who received COVID-19 vaccine.

Supplementary Figures S2. Funnel plot showing the variation in effect estimates by standard error across studies that evaluated the risk of miscarriage among pregnancy women who received COVID-19 vaccine.

References

Aharon D, Canon CM, Hanley WJ, Lee JA, Lederman MA, Stein DE,Copperman AB. mRNA covid-19 vaccines do not compromise implantation of euploid embryos. *Fertility and sterility* 2021; **116:**e77-e77.

Aharon D, Lederman M, Ghofranian A, Hernandez-Nieto C, Canon C, Hanley W, Gounko D, Lee JA, Stein D, Buyuk E et al. In Vitro Fertilization and Early Pregnancy Outcomes After Coronavirus Disease 2019 (COVID-19) Vaccination. *Obstetrics and gynecology* 2022; **139:**490-497.

American College of Obstetricians and Gynecologists. COVID-19 Vaccination Considerations for Obstetric–Gynecologic Care. 2022. American College of Obstetricians and Gynecologists.

Arora M,Lakshmi R. Vaccines - safety in pregnancy. *Best practice & research. Clinical obstetrics & gynaecology* 2021; **76:**23-40.

Avraham S, Kedem A, Zur H, Youngster M, Yaakov O, Yerushalmi GM, Gat I, Gidoni Y, Hochberg A, Baum M et al. Coronavirus disease 2019 vaccination;and infertility treatment outcomes. *Fertility and sterility* 2022; **117:**1291-1299.

Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *The New England journal of medicine* 2021; **384:**403-416.

Bleicher I, Kadour-Peero E, Sagi-Dain L,Sagi S. Early exploration of COVID-19 vaccination safety and effectiveness during pregnancy: interim descriptive data from a prospective observational study. *Vaccine* 2021; **39:**6535-6538.

Bookstein Peretz S, Regev N, Novick L, Nachshol M, Goffer E, Ben-David A, Asraf K, Doolman R, Levin EG, Regev Yochay G et al. Short-term outcome of pregnant women

vaccinated with BNT162b2 mRNA COVID-19 vaccine. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2021; **58:**450-456.

Ciapponi A, Bardach A, Mazzoni A, Alconada T, Anderson S, Argento FJ, Ballivian J, Bok K, Comandé D, Erbelding E et al. Safety of COVID-19 vaccines, their components or their platforms for pregnant women: A rapid review. *medRxiv : the preprint server for health sciences* 2021**:**2021.2006.2003.21258283.

Citu IM, Citu C, Gorun F, Sas I, Bratosin F, Motoc A, Burlea B, Rosca O, Malita D,Gorun OM. The Risk of Spontaneous Abortion Does Not Increase Following First Trimester mRNA COVID-19 Vaccination. *J Clin Med* 2022; **11**.

de Gier B, Andeweg S, Joosten R, Ter Schegget R, Smorenburg N, van de Kassteele J, Hahné SJ, van den Hof S, de Melker HE,Knol MJ. Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. *Euro Surveill* 2021; **26**.

Dreier JW, Andersen AM,Berg-Beckhoff G. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. *Pediatrics* 2014; **133:**e674-688.

Duffy J, Cairns A, Richards-Doran D, van 't Hooft J, Gale C, Brown M, Chappell L, Grobman W, Fitzpatrick R, Karumanchi S et al. A core outcome set for pre-eclampsia research: an international consensus development study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2020; **127:**1516-1526.

Duffy JMN, AlAhwany H, Bhattacharya S, Collura B, Curtis C, Evers JLH, Farquharson RG, Franik S, Giudice LC, Khalaf Y et al. Developing a core outcome set for future infertility research: an international consensus development study. *Human Reproduction* 2021.

Egloff C, Couffignal C, Cordier AG, Deruelle P, Sibiude J, Anselem O, Benachi A, Luton D, Mandelbrot L, Vauloup-Fellous C et al. Pregnant women's perceptions of the COVID-19 vaccine: A French survey. *PLoS ONE* 2022; **17:**e0263512.

Favre G, Maisonneuve E, Pomar L, Winterfeld U, Daire C, Martinez de Tejada B, Delecraz D, Campelo S, Moser M, Todesco-Bernasconi M et al. COVID-19 mRNA vaccine in pregnancy: Results of the Swiss COVI-PREG registry, an observational prospective cohort study. *The Lancet Regional Health – Europe* 2022; **18**.

Fell DB, Dhinsa T, Alton GD, Török E, Dimanlig-Cruz S, Regan AK, Sprague AE, Buchan SA, Kwong JC, Wilson SE et al. Association of COVID-19 Vaccination in Pregnancy With Adverse Peripartum Outcomes. *Jama* 2022; **327:**1478-1487.

García-Enguídanos A, Calle ME, Valero J, Luna S,Domínguez-Rojas V. Risk factors in miscarriage: a review. *European journal of obstetrics, gynecology, and reproductive biology* 2002; **102:**111-119.

Goldshtein I, Steinberg DM, Kuint J, Chodick G, Segal Y, Shapiro Ben David S,Ben-Tov A. Association of BNT162b2 COVID-19 Vaccination During Pregnancy With Neonatal and Early Infant Outcomes. *JAMA Pediatr* 2022; **176:**470-477.

Gong R, Peng X, Kang S, Feng H, Huang J, Zhang W, Lin D, Tien P,Xiao G. Structural characterization of the fusion core in syncytin, envelope protein of human endogenous retrovirus family W. *Biochem Biophys Res Commun* 2005; **331:**1193-1200.

Graham JM, Jr., Edwards MJ,Edwards MJ. Teratogen update: gestational effects of maternal hyperthermia due to febrile illnesses and resultant patterns of defects in humans. *Teratology* 1998; **58:**209-221.

Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, Baez AM, Shook LL, Cvrk D, James K et al. Coronavirus disease 2019 vaccine response in pregnant and lactating

466 women: a cohort study. *American journal of obstetrics and gynecology* 2021; **225:**303.e301-
467 303.e317.
468 Han AR, Lee D, Kim SK, Choo CW, Park JC, Lee JR, Choi WJ, Jun JH, Rhee JH,Kim SH.
469 Effects and safety of COVID-19 vaccination on assisted reproductive technology and
470 pregnancy: A comprehensive review and joint statements of the KSRM, the KSRI, and the
471 KOSAR. *Clinical and Experimental Reproductive Medicine* 2022; **49:**2-8.
472 Hillson K, Clemens SC, Madhi SA, Voysey M, Pollard AJ, Minassian AM,Oxford CVTG.
473 Fertility rates and birth outcomes after ChAdOx1 nCoV-19 (AZD1222) vaccination. *Lancet*
474 *(London, England)* 2021; **398:**1683-1684.
475 Huang J, Xia L, Lin J, Liu B, Zhao Y, Xin C, Ai X, Cao W, Zhang X, Tian L et al. No Effect
476 of Inactivated SARS-CoV-2 Vaccination on in vitro Fertilization Outcomes: A Propensity
477 Score-Matched Study. *Journal of inflammation research* 2022; **15:**839-849.
478 Jain VK, Iyengar K, Garg R,Vaishya R. Elucidating reasons of COVID-19 re-infection and
479 its management strategies. *Diabetes Metab Syndr* 2021; **15:**1001-1006.
480 Kachikis A, Englund JA, Singleton M, Covelli I, Drake AL,Eckert LO. Short-term Reactions
481 Among Pregnant and Lactating Individuals in the First Wave of the COVID-19 Vaccine
482 Rollout. *JAMA Netw Open* 2021; **4:**e2121310.
483 Kharbanda EO, Haapala J, DeSilva M, Vazquez-Benitez G, Vesco KK, Naleway AL,Lipkind
484 HS. Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy. *Jama*
485 2021; **326:**1629-1631.
486 Kiefer MK, Mehl R, Costantine MM, Johnson A, Cohen J, Summerfield TL, Landon MB,
487 Rood KM,Venkatesh KK. Characteristics and perceptions associated with COVID-19
488 vaccination hesitancy among pregnant and postpartum individuals: A cross-sectional study.
489 *BJOG : an international journal of obstetrics and gynaecology* 2022.

Kloc M, Uosef A, Kubiak JZ,Ghobrial RM. Exaptation of Retroviral Syncytin for Development of Syncytialized Placenta, Its Limited Homology to the SARS-CoV-2 Spike Protein and Arguments against Disturbing Narrative in the Context of COVID-19 Vaccination. *Biology* 2021; **10**.

Loomba S, de Figueiredo A, Piatek SJ, de Graaf K,Larson HJ. Measuring the impact of COVID-19 vaccine misinformation on vaccination intent in the UK and USA. *Nature Human Behaviour* 2021; **5:**337-348.

Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, Simmons R, Cottrell S, Roberts R, O'Doherty M et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ (Clinical research ed.)* 2021; **373:**n1088.

M. Blake Evans, Carolyn Alexander, Emily Barnard, M. Max Ezzati, Micah J. Hill, Luis R. Hoyos, E H, S M,A P. COVID-19 vaccine and infertility: baseless claims and unfounded social media panic. 2021, https://www.fertstertdialog.com/posts/covid-19-vaccine-and-infertility-baseless-claims-and-unfounded-social-media-panic.

Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, Padayachee SD, Dheda K, Barnabas SL, Bhorat QE et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *The New England journal of medicine* 2021; **384:**1885-1898.

Magnus MC, Gjessing HK, Eide HN, Wilcox AJ, Fell DB,Håberg SE. Covid-19 Vaccination during Pregnancy and First-Trimester Miscarriage. *The New England journal of medicine* 2021; **385:**2008-2010.

Magnus MC, Örtqvist AK, Dahlqwist E, Ljung R, Skår F, Oakley L, Macsali F, Pasternak B, Gjessing HK, Håberg SE et al. Association of SARS-CoV-2 Vaccination During Pregnancy With Pregnancy Outcomes. *Jama* 2022; **327:**1469-1477.

Mattar CN, Koh W, Seow Y, Hoon S, Venkatesh A, Dashraath P, Lim LM, Ong J, Lee R, Johana N et al. Addressing anti-syncytin antibody levels, and fertility and breastfeeding concerns, following BNT162B2 COVID-19 mRNA vaccination. *medRxiv* 2021**:**2021.2005.2023.21257686.

Moodley J, Khaliq OP,Mkhize PZ. Misrepresentation about vaccines that are scaring women. *2021* 2021; **13**.

Moro PL, Olson CK, Clark E, Marquez P, Strid P, Ellington S, Zhang B, Mba-Jonas A, Alimchandani M, Cragan J et al. Post-authorization surveillance of adverse events following COVID-19 vaccines in pregnant persons in the vaccine adverse event reporting system (VAERS), December 2020 - October 2021. *Vaccine* 2022; **40:**3389-3394.

Nabila Arfah M,Murizah M. Preliminary findings on inadvertently exposed pregnancies to COVID-19 mRNA vaccine in Kedah Darul Aman. *Med J Malaysia* 2021; **73**.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical research ed.)* 2021; **372:**n71.

Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *The New England journal of medicine* 2020; **383:**2603-2615.

Prasad M, Lin JL, Gu Y, Gupta R, Macary P,Schwarz H. No crossreactivity of anti-SARS-CoV-2 spike protein antibodies with Syncytin-1. *Cellular & Molecular Immunology* 2021; **18:**2566-2568.

Qiao Y, Lopes de Abreu AdJ, Dias CZ, Meng X, Ferreira RV, Gonçalves Pereira R, Julian GS,Yin W. Safety profile of COVID-19 vaccines in pregnant and postpartum women in brazil. *medRxiv* 2021**:**2021.2012.2014.21267777.

539 Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, Brosens JJ,
540 Brewin J, Ramhorst R, Lucas ES et al. Miscarriage matters: the epidemiological, physical,
541 psychological, and economic costs of early pregnancy loss. *The Lancet* 2021; **397:**1658-
542 1667.
543 Roozenbeek J, Schneider CR, Dryhurst S, Kerr J, Freeman ALJ, Recchia G, van der Bles
544 AM,van der Linden S. Susceptibility to misinformation about COVID-19 around the world.
545 *Royal Society Open Science* 2020; **7:**201199.
546 Royal College of Obstetricians & Gynaecologists. RCOG supports calls from NHS to
547 pregnant women to get vaccinated against COVID-19. 2021.
548 Royal College of Obstetricians & Gynaecologists. Coronavirus (COVID-19) infection and
549 pregnancy 2022.
550 Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, Goepfert PA,
551 Truyers C, Fennema H, Spiessens B et al. Safety and Efficacy of Single-Dose Ad26.COV2.S
552 Vaccine against Covid-19. *The New England journal of medicine* 2021; **384:**2187-2201.
553 Schaler L,Wingfield M. COVID-19 vaccine - can it affect fertility? *Ir J Med Sci* 2021**:**1-3.
554 Shanes ED, Otero S, Mithal LB, Mupanomunda CA, Miller ES,Goldstein JA. Severe Acute
555 Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination in Pregnancy: Measures of
556 Immunity and Placental Histopathology. *Obstetrics & Gynecology* 2021; **138**.
557 Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, Marquez
558 PL, Olson CK, Liu R, Chang KT et al. Preliminary Findings of mRNA Covid-19 Vaccine
559 Safety in Pregnant Persons. *The New England journal of medicine* 2021; **384:**2273-2282.
560 Smith P, Cooper N, Dhillon-Smith R, O'Toole E, Clark TJ,Coomarasamy A. Core Outcome
561 Sets in Miscarriage Trials (COSMisT) study: a study protocol. *BMJ Open* 2017; **7:**e018535.
562 Spinelli A,Pellino G. COVID-19 pandemic: perspectives on an unfolding crisis. *The British*
563 *journal of surgery* 2020; **107:**785-787.

564 Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D,
565 Altman DG, Ansari MT, Boutron I et al. ROBINS-I: a tool for assessing risk of bias in non-
566 randomised studies of interventions. *BMJ (Clinical research ed.)* 2016; **355:**i4919.
567 Stock SJ, Carruthers J, Calvert C, Denny C, Donaghy J, Goulding A, Hopcroft LEM,
568 Hopkins L, McLaughlin T, Pan J et al. SARS-CoV-2 infection and COVID-19 vaccination
569 rates in pregnant women in Scotland. *Nature medicine* 2022; **28:**504-512.
570 Trostle ME, Limaye MA, Avtushka V, Lighter JL, Penfield CA,Roman AS. COVID-19
571 vaccination in pregnancy: early experience from a single institution. *Am J Obstet Gynecol*
572 *MFM* 2021; **3:**100464.
573 UK Health Security Agency. COVID-19 vaccination: a guide on pregnancy and
574 breastfeeding. 2022, Gov.uk.
575 United States Food and Drug Administration. Pfizer- BioNTech COVID-19 vaccine
576 (BNT162, PF-07302048). Vaccines and related biological products advisory committee
577 briefing document. FDA. 2020.
578 United States Food and Drug Administration. Vaccines and Related Biological Products
579 Advisory Committee December 17, 2020 Meeting Presentation - FDA Review of Efficacy
580 and Safety of Moderna COVID-19 Vaccine Emergency Use Authorization Request. 2020.
581 United States Food and Drug Administration. Vaccines and Related Biological Products
582 Advisory Committee Meeting FDA Briefing Document October 14, 2021 EUA amendment
583 request for a booster dose of the Moderna COVID-19 Vaccine. 2021.
584 United States Food and Drug Administration. Vaccines and Related Biological Products
585 Advisory Committee Meeting February 26, 2021 FDA Briefing Document Janssen
586 Ad26.COV2.S Vaccine for the Prevention of COVID-19. 2021.

587 Wang Y, Ren X, Wang Z, Feng X, Li M,Liu P. Receipt of inactivated COVID-19 vaccine
588 had no adverse influence on embryo implantation, clinical pregnancy and miscarriage in early
589 pregnancy. *Science China Life Sciences* 2022.
590 Wei SQ, Bilodeau-Bertrand M, Liu S,Auger N. The impact of COVID-19 on pregnancy
591 outcomes: a systematic review and meta-analysis. *Cmaj* 2021; **193:**E540-e548.
592 Zauche LH, Wallace B, Smoots AN, Olson CK, Oduyebo T, Kim SY, Petersen EE, Ju J,
593 Beauregard J, Wilcox AJ et al. Receipt of mRNA Covid-19 Vaccines and Risk of
594 Spontaneous Abortion. *The New England journal of medicine* 2021; **385:**1533-1535.
595

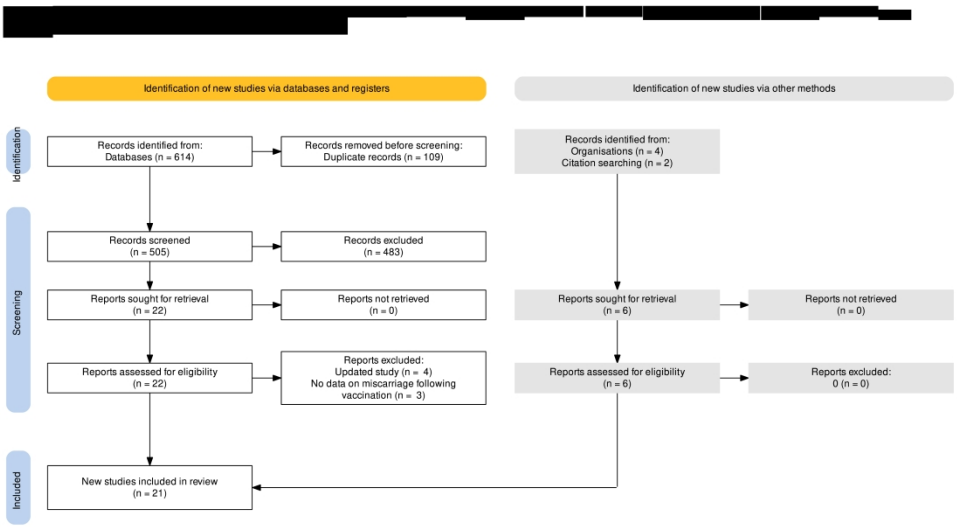

Fig. 1

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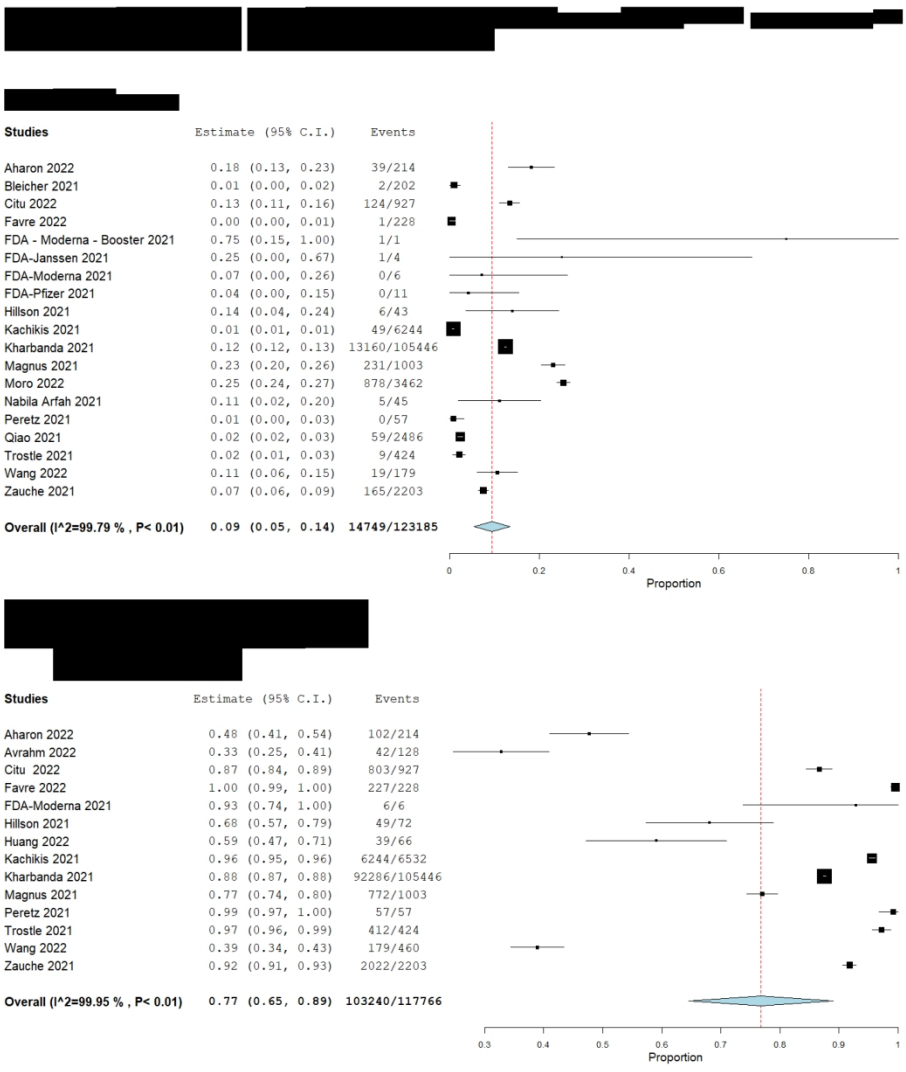

Fig.2

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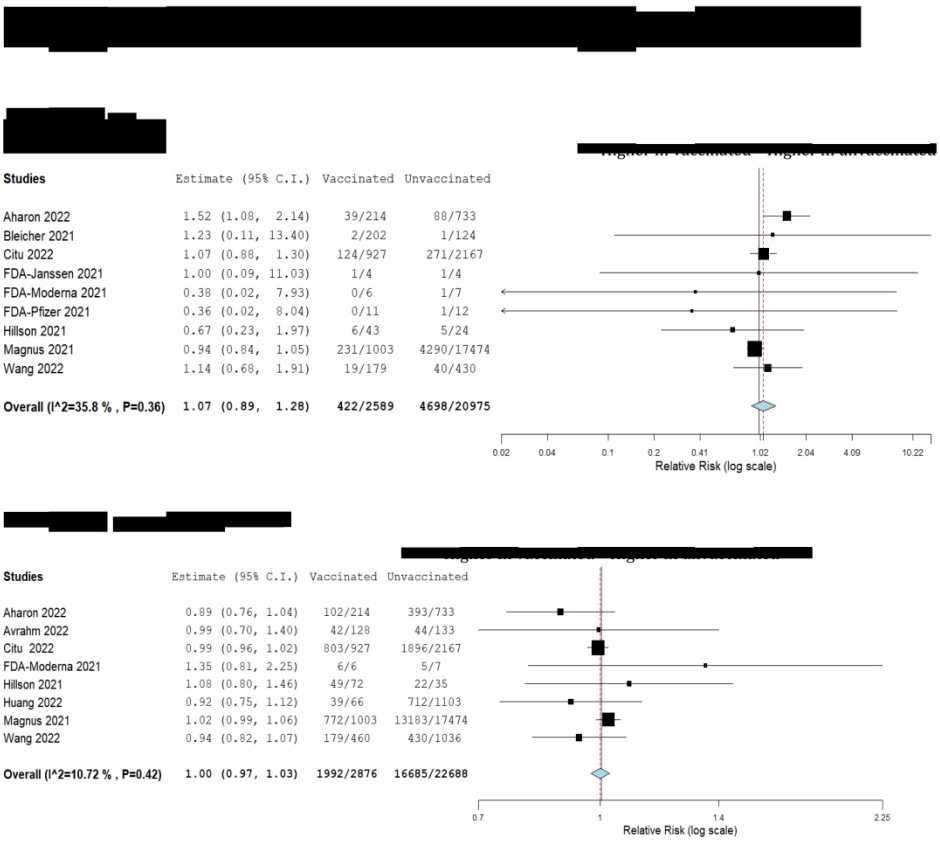

Fig. 3

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		
Miscarriage												
9	observational studies	serious	serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	422/2589 (16.3%)	4698/20975 (22.4%)	**RR 1.07** (0.89 to 1.28)	**16 more per 1,000** (from 25 fewer to 63 more)	⨁⨁◯◯ Low	CRITICAL
Ongoing pregnancy/Live birth												
8	observational studies	serious	serious	serious	serious	all plausible residual confounding would reduce the demonstrated effect	1992/2876 (69.3%)	16685/22688 (73.5%)	**RR 1.00** (0.97 to 1.03)	**0 fewer per 1,000** (from 22 fewer to 22 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Fig. 4

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Table 1: Characteristics of included studies that evaluated the risk of miscarriage and rates of ongoing pregnancy/live birth among pregnant women who received a COVID-19 vaccine.

Study	Design	Countries	Funding source	Covid-19 vaccine	Vaccine doses	Inclusion Criteria	Numbers analysed (n=)	Risk of Bias
Aharon (2022)	Cohort	USA	Not stated	Pfizer, Moderna	2	Women undergoing fertility treatment who were vaccinated at least 14 days prior to starting medication for ovarian stimulation or a frozen-thawed embryo transfer cycle	2153	Moderate
Avraham (2022)	Cohort	Israel	No external funding	Pfizer	2	Women 20-42 years old undergoing IVF treatment cycles at a single centre	400	Moderate
Bleicher (2021)	Cohort	USA	Not stated	Pfizer	≥1	Being pregnant at enrolment and valid questionnaire	326	Serious
Bookstein Peretz (2021)	Case-control	Israel	Not stated	Pfizer	2	Pregnant women between 2-40 weeks' gestation who completed two doses of vaccine	57	Serious
Citu (2022)	Cohort	Romania	No external funding	Pfizer, Moderna	≥1	Women aged >18 years who were vaccinated during the first trimester of pregnancy	3094	Moderate
Favre (2022)	Cohort	Switzerland	Swiss Federal Office of Public Health and the CHUV Foundation	Pfizer, Moderna	≥1	Pregnant women with at least one injection between one week before last menstrual period to end of pregnancy	228	Moderate
FDA - Janssen (2021)	RCT	Brazil, Chile, Argentine, Colombia, Peru, Mexica, USA, South Africa	Janssen Research and Development	Janssen	1	Adults 18 to 59 years of age and 60 years of age or older, respectively, who were in good or stable health and did not have coexisting conditions that have been associated with an increased risk of severe COVID--19	8	Low

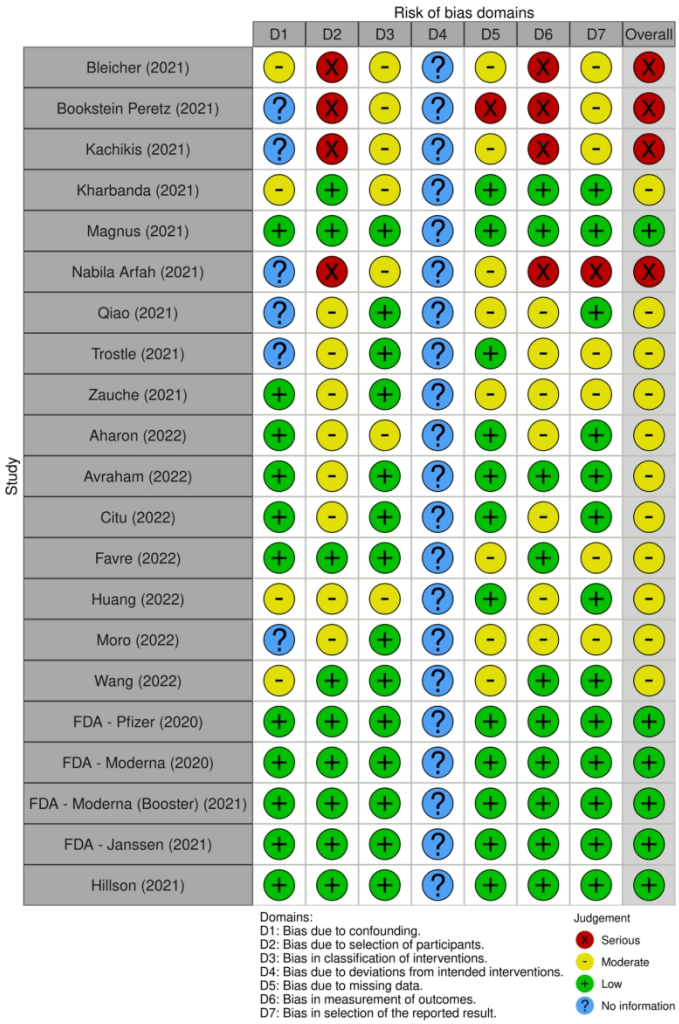
FDA - Moderna (2020)	RCT	USA	Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases	Moderna	2	18 years old and had no known history of SARS-CoV-2 infection and whose locations or circumstances put them at appreciable risk of acquiring SARS-CoV-2 infection or who were at high risk for severe disease (or both)	13	Low
FDA - Moderna (Booster) (2021)	RCT	USA	Not stated	Moderna booster	2 + 1	Individuals 65 years of age and older, individuals 18 through 64 years of age at high risk of severe COVID-19, and individuals 18 through 64 years of age whose recent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19	1	Low
FDA - Pfizer (2020)	RCT	USA, Brazil, Argentina, Turkey South Africa, Germany	BioNTech and Pfizer	Pfizer	2	Adults 16 years of age or older who were healthy or had stable chronic medical conditions, including but not limited to human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus infection	23	Low
Hillson (2021)	RCT	UK, Brazil, South Africa	UK Research and Innovation, National Institutes of Health Research (NIHR), The Coalition for Epidemic Preparedness Innovations, the Bill & Melinda Gates Foundation, the Lemann Foundation, Rede D'Or, the Brava and Telles Foundation, NIHR Oxford Biomedical Research Centre, Thames Valley and South Midland's NIHR Clinical Research Network, and AstraZeneca.	AstraZeneca	2	Women enrolled on a RCT, who were thought not to be pregnant but found to be pregnant, and this occurred in four ongoing phase 1, phase 2 and phase 3 clinical trials	67	Low
Huang (2022)	Cohort	China	National Natural Science Foundation of China, Key Research and Development Program of Jiangxi Province	Sinopharm, Sinovac	2	Women undergoing a fresh IVF cycle who had received at least two vaccine doses at least 3 weeks apart	2185	Moderate
Kachikis (2021)	Cohort	USA	National Institute of Child Health and Human Development	Pfizer, Moderna, Janssen	2	Women who were pregnant, lactating, or planning pregnancy at the time of COVID-19 vaccination	6244	Serious

Kharbanda (2021)	Cohort	USA	Centre for Disease Control and Prevention	Pfizer, Moderna, Janssen	≥1	Women with ongoing pregnancies between 6- and 19-weeks' gestation	105446	Moderate
Magnus (2021)	Case-control	Norway	Research Council of Norway	Pfizer, Moderna, AstraZeneca	≥1	Women who had miscarriage before 14 weeks of gestation or primary care–based confirmation of ongoing pregnancy in the first trimester	18477	Low
Moro (2022)	Cohort	USA	No funding received	Pfizer, Moderna, Janssen	≥1	Pregnant women who received COVID-19 vaccine and reported an adverse events to VAERS by using a pregnancy-status question in the form	3462	Moderate
Nabila Arfah (2021)	Cohort	Malaysia	Not stated	mRNA COVID-19 vaccine	≥1	Pregnant women after receiving a mRNA COVID-19 vaccine	45	Serious
Qiao (2021)	Cohort	Brazil	Sinovac Life Sciences	Sinovac, Janssen, AstraZeneca,Pfizer	≥1	Pregnant or postpartum women who reported vaccine-related adverse effects to adverse events following immunisation surveillance information system.	3333	Moderate
Trostle (2021)	Cohort	USA	Not stated	Pfizer, Moderna	≥1	Pregnant women who received at least one dose of an mRNA COVID-19 vaccination during pregnancy	424	Moderate
Wang (2022)	Cohort	China	National Natural Science Foundation of China	Inactivated COVID-19 vaccine	2	Participants who had completed gamete retrieval and embryo cryopreservation prior to vaccination with two doses of inactivated COVID-19 vaccine followed by a frozen-thaw embryo transfer cycle.	1496	Moderate
Zauche (2021)	Cohort	USA	Not stated	Pfizer, Moderna	≥1	Singleton pregnancy who had received at least one dose of an mRNA Covid-19 vaccine either before conception or before 20 weeks of gestation and who did not have a pregnancy loss before 6 weeks of gestation	2203	Moderate

Supplementary Data File S1: Search strategy to identify primary studies that evaluated the risk of miscarriage among pregnant women who received COVID-19 vaccine.

1	exp COVID-19 Vaccines/
2	(Pfizer-BioNTech or Comirnaty or Moderna or Spikevax or (Johnson adj2 Johnson) or Janssen or AstraZeneca or AZD1222 or Vaxzevria or Covishield or ChAdOx1 or BBIBP-CorV or BIBP or Sinopharm or Sputnik* or Gam- COVID-Vac-8 or Sputnik light or CoronaVac or Sinovac or Dream vaccin*).mp.
3	1 or 2
4	exp SARS-CoV-2/
5	exp COVID-19/
6	(COVID 19 or Corona* or 2019-n* or novel CoV or sarscov2 or 2019nCoV or nCOV or COVID-19 or SARS-CoV-2 or txid2697049).mp.
7	4 or 5 or 6
8	exp Immunization/
9	exp Vaccines/
10	(Vaccin* or Immuni* or injection* or Inoculat* or boost*).mp.
11	8 or 9 or 10
12	7 and 11
13	3 or 12
14	exp Pregnancy Outcome/
15	Pregnancy Complications/
16	exp Pregnancy, High-Risk/
17	exp abortion, spontaneous/
18	((f?etal or f?etus*) adj3 (death* or die* or dead or decease*)) or ((recur* or habitual or spontaneous or tubal) adj2 (abort*)) or miscarr* or (pregnan* adj3 outcome) or (pregnan* adj3 los*)
19	14 or 15 or 16 or 17 or 18
24	13 and 19

Supplementary Figure S1: ROBBINS I assessment of the quality of included studies that evaluated the risk of miscarriage among pregnant women who received COVID-19 vaccine.



S1

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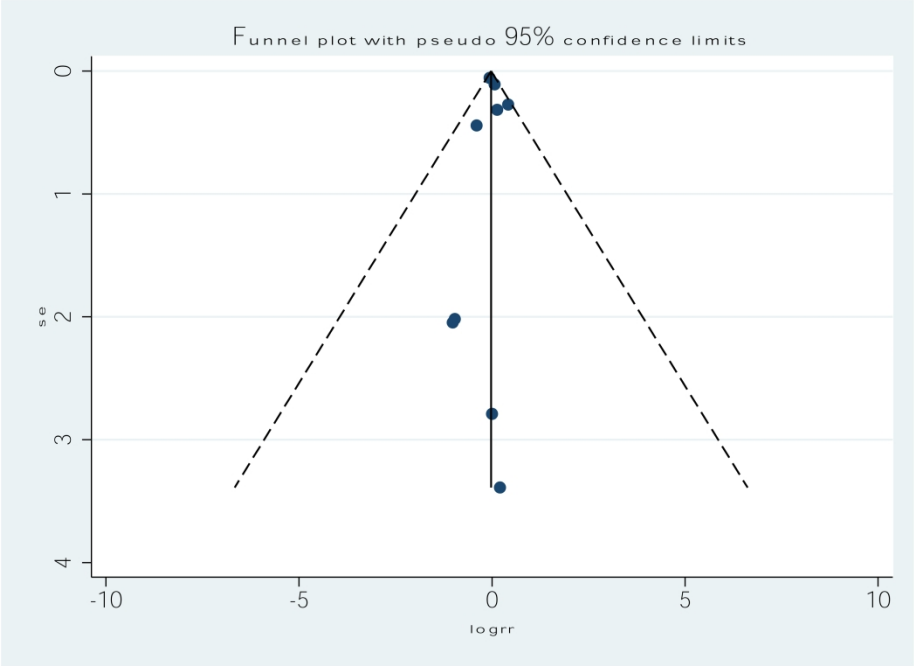
Supplementary Figure S2: Funnel plot showing the variation in effect estimates by standard error across included studies that evaluated the risk of miscarriage among pregnant women who received COVID-19 vaccine



S2

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Supplementary Table SI: Summary of the characteristics and findings of included studies that evaluated the risk of miscarriage and ongoing pregnancy/live birth among pregnant women who received COVID-19 vaccine.

STUDY	SETTINGS	PARTICIPANTS	OUTCOMES
AHARON (2022)	Single-centre retrospective observational study of women who underwent controlled ovarian hyperstimulation for IVF or single euploid frozen-thawed embryo transfer.	Women who received two doses of Pfizer or Moderna COVID-19 vaccination at least 14 days prior to starting medication for controlled ovarian hyperstimulation or frozen-thawed embryo transfer cycle were included. A control group consisted of unvaccinated women undergoing controlled ovarian hyperstimulation or frozen-thawed embryo transfer cycles.	Higher parity, lower use of antagonist protocol and higher use of the flare protocol was observed in the control group. No associations were observed between vaccinated and control groups with regard to fertilization rate (primary outcome), clinical pregnancy rate or rate of miscarriage.
AVRAHAM (2022)	Retrospective observational study with data from two centres of women undergoing IVF treatment.	200 women who had received at least two doses of Pfizer COVID-19 vaccination were compared to 200 age-matched non-vaccinated controls.	The main outcome measures were the mean number of oocytes retrieved and clinical pregnancy rate. The mean number of oocytes retrieved and clinical pregnancy rate were similar among vaccinated women and non-vaccinated controls. Additionally, no difference was observed in fertilisation rate, embryo quality or mean number of cryopreserved embryos between vaccinated and non-vaccinated controls.
BLEICHER (2021)	Prospective observational cohort study where short-term pregnancy outcomes were assessed among vaccinated (Pfizer) and unvaccinated pregnant women through online questionnaires.	An initial questionnaire was shared via social media with responders being invited to complete a follow-up questionnaire after one month. Data collected included vaccination intentions, vaccination status, aspects of personal medical and obstetric history, and complications of their current pregnancy. The method by which pregnancy and	432 women responded to the initial questionnaire, with the follow up questionnaire receiving 326 responses. No significant differences in composite pregnancy complications, first trimester miscarriage or other adverse obstetric outcomes were observed between vaccinated and unvaccinated groups.

		miscarriage were confirmed was not defined.	
BOOKSTEIN PERETZ (2021)	Observational case-control study of pregnant women vaccinated with a two-dose Pfizer regimen aiming to assess the vaccines' immunogenicity, reactogenicity and impact on obstetric outcomes.	Outcomes among vaccinated pregnant participants were compared to a control group comprising age-matched non-pregnant vaccinated women. Pregnant participants were recruited via social media, and data was collected via serial questionnaires and blood sampling.	390 women returned the questionnaire and were included in the study alongside 260 control women. The method by which pregnancy and miscarriage were confirmed was not defined. Adverse obstetric outcomes were rare, and comparable to the general population. The Pfizer vaccine induced humoral immunity in all vaccinated pregnant participants, however levels of SARS-CoV-2 IgG were lower in pregnant women compared to non-pregnant controls.
CITU (2022)	Single-centre retrospective observational study of pregnant women in the first trimester who were either vaccinated or unvaccinated.	The method by which pregnancy and miscarriage were confirmed was not defined.	The risk of miscarriage after mRNA COVID-19 immunization iis commensurate with the predicted risk in non-vaccinated pregnant women.
FAVRE (2022)	Swiss nationwide multicentre prospective cohort study	Pregnant women who received at least one dose of mRNA vaccine using the COVI-PREG registry.	Early and late spontaneous abortion was reported in 1/107 patient and 1/228 patient respectively. No stillbirth was reported among 530 patients exposed with covid-19 vaccines in pregnancy.

FDA - JANSSEN (2021)	A large Phase 3 randomised, double-blinded placebo-controlled trial of a single dose of Ad26.COV2.S in approximately 40, 000 participants in the United States for assessment of safety, immunogenicity, and efficacy endpoints.	Participants who were pregnant or planned to conceive within 3 months of vaccine administration were excluded.	Subgroup analyses of adverse events identified 8 reported pregnancies (4 vaccine, 4 placebo). 1 miscarriage was reported in each arm respectively. The method by which pregnancy and miscarriage were confirmed was not defined.
FDA - MODERNA (2020)	A large Phase 3 randomised, double-blinded placebo-controlled trial of two 100µg doses of mRNA-1273	30,400 participants in the United States for assessment of safety and efficacy endpoints. A negative pregnancy test was required prior to receiving study intervention.	There were no miscarriages in the vaccinated group and 1 miscarriage in the placebo group. The method by which pregnancy and miscarriage were confirmed was not defined. Subgroup analyses of adverse events identified 13 reported pregnancies (6 vaccine, 7 placebo).
FDA - MODERNA (BOOSTER) (2020)	An open-label intervention study where participants who had previously received two 50µg or 100µg doses of mRNA-1273 received a 50 µg booster dose of mRNA-1273.	343 participants in the United States were enrolled to assess the safety and immunogenicity of the booster dose.	Subgroup analyses of adverse events reported 1 miscarriage 52 days after receiving booster dose, and subsequently conceived 115 days after the booster dose.
FDA - PFIZER (2020)	A large global Phase 1/2/3 randomised, double-blinded placebo-controlled pivotal registration study of two 30µg doses of BNT162b2 vaccine	44,000 participants for assessment of safety, immunogenicity, and efficacy endpoints. A negative pregnancy test was required prior to receiving study intervention. With approximately 18,800 participants in both control and vaccinated groups, a comparable number of pregnancies were observed (11 vaccine, 12 placebo).	There were no miscarriages in the vaccinated group and 1 miscarraige in the placebo group. A cumulative analysis of post-authorisation adverse event reported 270 pregnancies, of which there were 23 miscarriages reported. The method by which pregnancy and miscarriage were confirmed was not defined.
HILLSON (2021)	4 Phase 1/2/3 randomised, double-blinded placebo-controlled trials of	23848 participants between April and November 2020 across UK, Brazil and South Africa. A negative pregnancy test was required prior to	Miscarriage was defined as pregnancy loss before 23 weeks of gestation. The method by which pregnancy was confirmed

	two 0.5ml doses of ChAdOx1 nCoV-19.	receiving study intervention. Pregnancy outcome analysis set included 107 out of 9755 women of childbearing age who reported a pregnancy (72 vaccine, 35 control).	was not defined. There were no evidence of an association between reduced fertility and vaccination, Excluding Brazilian data, 11 miscarriages were reported (6 vaccine, 5 control),
HUANG (2022)	Single-centre retrospective matched case-control study of women undergoing fresh IVF cycles.	Women vaccinated with two doses of Sinopharm or Sinovac comprised a case group and unvaccinated women comprised a control group. Cases and controls were matched using propensity scoring based on 14 covariates.	Similar outcomes including number of oocytes retrieved, good quality embryo-rate, clinical pregnancy rate and biochemical pregnancy rate were observed between case and control groups.
KACHIKIS (2021)	Large online prospective cohort study of adults who were pregnant, lactating, or planning pregnancy at the time of COVID-19 vaccination. Participants were recruited online to the University of Washington COVID-19 Vaccine in Pregnancy and Lactation Registry via chain-referral and snowball sampling.	Data including participant demographics, vaccine side-effects and outcome data were collected via questionnaires. The method by which pregnancy and miscarriage were confirmed was not defined. 17 525 participants were included, including 7809 participants who were pregnant at the time of their first vaccine (Pfizer, Moderna or Janssen) dose and 6586 pregnant participants who had received a second vaccine dose at the time of data analysis.	6244 individuals remained pregnant, and 49 individuals reported miscarriage.
KHARBANDA (2021)	Observational case-control study of COVID-19 vaccination during pregnancy and spontaneous abortion using the Vaccine Safety Datalink.	A database collaboration between the Centres for Disease Control and Prevention and nine US health systems. The likelihood of receiving a COVID-19 vaccine in the 28 days prior to a spontaneous abortion were compared with the likelihood of receiving a COVID-19 vaccine in the 28 days prior to index dates for ongoing pregnancies. The method by which pregnancy and miscarriage were confirmed was not defined.	Spontaneous abortions did not have an increased odds of exposure to COVID-19 vaccination compared to ongoing pregnancies.

MAGNUS (2021)	Observational case-control study from Norwegian health registries using data on first trimester pregnancies and COVID-19 vaccination.	Odds ratios for COVID-19 vaccination in a period prior to miscarriage or ongoing pregnancy were estimated, adjusted for potential confounders and stratified according to number of vaccinations. The method by which pregnancy and miscarriage were confirmed was not defined.	No evidence of increased risk of miscarriage after COVID-19 vaccination among the study group.
MORO (2022)	Observational study of COVID-19 vaccination	Pregnant individuals using data from the Vaccine Adverse Event Reporting System (VAERS) across 3 different vaccines. The method by which pregnancy and miscarriage were confirmed was not defined.	Among 3462 reports involving pregnant women, there were 878 (25.4%) cases of miscarriage, 76 (2.2%) cases of preterm delivery, 62 (1.8%) cases of stillbirth and 8 (0.2%) maternal deaths.
NABILA ARFAH (2021)	Small prospective observational study of COVID-19 vaccination during pregnancy in	45 healthcare workers in Kedah, Malaysia who were found to be pregnant after vaccination. The method by which pregnancy and miscarriage were confirmed was not defined.	5 miscarriages were reported among this group, however due to limited data present the authors are unable to comment on the safety of COVID-19 vaccination safety during pregnancy.
QIAO (2021)	Observational study of COVID-19 vaccination	Pregnant individuals using data from the Brazilian surveillance information system for adverse events (SI-EAPV) across 4 different vaccines. The method by which pregnancy and miscarriage were confirmed was not defined.	Among 2486 reports involving pregnant and postpartum women, there were 59 (2.4%(reported cases of miscarriage, 13 (0.52%) cases of neonatal death, 7 (0.28%) cases of preterm delivery
TROSTLE (2021)	Descriptive observational study	424 pregnant women who received at least one dose of mRNA COVID-19 vaccine in New York University Langone Health. The method by which pregnancy and miscarriage were confirmed was not defined.	9 miscarriages, 3 terminations and 327 ongoing pregnancies were reported. No concerning trends were observed regarding birth outcomes among 85 women.
WANG (2022)	Retrospective observational study of cryopreserved embryo transfer cycles at a single	Participants who had received two doses of inactivated COVID-19 vaccine were compared with unvaccinated controls.	Subgroups comprising those transferred cleavage-stage embryos and blastocysts were analysed, finding no differences in embryo implantation,

	tertiary centre in China.		clinical pregnancy or miscarriage rates between vaccinated and unvaccinated groups.
ZUACHE (2021)	Observational study of COVID-19 vaccination in pregnant individuals who received at least one dose of an mRNA COVID-19 vaccine either before conception or before 20 weeks gestation.	2456 pregnant women between 6 and 20 weeks gestation were identified from Centres for Disease Control and Prevention V-safe COVID-19 Pregnancy registry. The method by which pregnancy and miscarriage were confirmed was not defined. Life table methods were used to calculate the cumulative risk of miscarriage according to gestational week, with appropriate left truncation.	Sensitivity analysis after age standardisation demonstrated the cumulative risk of miscarriage from 6 to less than 20 weeks gestation was 18.5% (95% CI, 16.1 to 20.8), which was within the expected risk range.