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March 15, 2022

Our request of January 11, 2022 concerning Safety of Covid-19 vaccines around conception and during pregnancy by European members of the Coalition Advocating for Adequately Licensed Medicines

Your e-mail response to ASK-104599 - Regulatory information about safety of covid-19 vaccines of February 15, 2022

Dear Drs. Burgos, Cavaleri, Sweeney, and Genov,

We appreciate your statement that "EMA fully recognises the need for safety data in pregnant women." However, EMA's COVID-19 task force (ETF) recent review [1] provides no answers to the issues we raised. In general, these studies only looked at highly selected outcomes, mainly miscarriage, preterm delivery or small for gestational age at birth. There is not much information on other important outcomes such as fetal death, stillbirth, congenital malformations, ectopic pregnancy, neonatal/infant death, morbidity and other serious adverse events (SAE) related to maternal exposure to mRNA vaccines during pregnancy and breast-feeding.

Of the 12 studies recently posted on the EMA website [1] that aim to provide reassurances regarding the use of mRNA vaccines in pregnancy, only three specifically addressed vaccination during the first trimester. An early pregnancy registry in Norway [2] compared women reporting a miscarriage before the 14th week of gestation (cases) to controls with ongoing pregnancy, looking at Covid-19 vaccination status at 3 and 5 weeks, respectively, prior to the adverse event. Among 13,184 ongoing pregnancies, 772 women were vaccinated while out of 4,290 women experiencing a miscarriage, 231 were exposed to Covid-19 vaccines within the last 3 weeks (adjusted OR 0.92, 95% CI [0.75-1.10]).

There are several possibilities for bias in this study. Firstly, the registry comprises only 40% of all early pregnancies in Norway (selection bias). Secondly, vaccination during the first trimester is not recommended in Norway except for women with underlying risk conditions (collider bias). Thirdly, the registry lacks information on gestational age at the time of early pregnancy registration which did not allow for matching vaccinated to unvaccinated women according to gestational age. If vaccination of women occurred, for example because of their underlying health conditions mostly after week 10 when risk of spontaneous miscarriage usually decreases, the comparison to non-vaccinated women experiencing a miscarriage during the higher risk period between weeks 6-10 of gestation could mask an elevated risk of covid-19 vaccines (misclassification bias).

A study by Kharbanda et al. [3] found that among 105,446 unique pregnancies, 13,160 spontaneous abortions occurred during weeks 6-8, 9-13, and 14-19 of gestation. The total number of women who received 1 or more doses of Pfizer-BioNTech, Moderna or Janssen

vaccines is not disclosed. Instead, the study reports 1128 spontaneous abortions among 20,139 vaccinated compared to 12,032 abortions among 250,944 non-vaccinated pregnancy periods and concluded that vaccination during early pregnancy is not associated with an elevated risk of abortion. (Person-time-based risk estimates were calculated from seven distinct 4-week surveillance periods between December 15, 2020 and June 28, 2021, where each woman could contribute data to 1 or more surveillance periods, yielding a total number of 250,944 ongoing pregnancy periods of which 20,139 (8%) were attributed to Covid-19 vaccine pregnancy periods.) The authors discuss that "rollout of Covid-19 vaccines has been complex and some vaccines may have been missed, potentially biasing findings to the null". Even more so, the chosen exposure-time categories may add to this dilution effect by over-representing non-vaccinated women with ongoing pregnancies. Of note, throughout the 4-week surveillance periods, in the unvaccinated time periods, there is a stable low abortion risk of around 5%, while among the vaccinated time periods, risk of miscarriage is increasing from 3% (Dec 15, 2020 – January 11, 2021) to more than 7% in the last two surveillance periods (derived from stratification by surveillance period, Table 1). Calculating crude odds ratios from the stratified data provided in Table 1, an elevated risk of abortions after Covid-19 vaccination in early pregnancy cannot be excluded at young maternal age (16-24 years) (crude OR 1.37), and during gestational weeks 9-13 (OR 1,18), and between weeks 14-19 (OR 1.11). These findings need further thorough exploration.

A very recent analysis guided also by the CDC of January 7, 2022 made far reaching conclusions that Covid-19 vaccination was safe throughout pregnancy, but this study of more than 40,000 pregnant women did not have sufficient data for estimating risks of vaccination during the first trimester [4].

We have searched https://www.adrreports.eu/en/ for reports on neonates and infants 0-2 years of age, and spontaneous reports on pregnancy events for Comirnaty in 2021 and 2022. There was a total of 2718 pregnancy reports for Comirnaty, 2117 in 2021, and already 601 in 2022. The table summarizes the main outcomes:

Main outcomes	**Year of 2021**	**Year of 2022**	**Total (n)**
Abortions	1368	373	1741
Malformations	15	15	30
Foetal deaths/stillbirths	95	29	124
Ectopic pregnancies	39	17	56
Premature baby	10	3	13
Non-fatal fetal growth restriction	27	6	33
Fatal fetal growth restrictions	10		10

For comparison: Adverse event reports of split-virion inactivated influenza vaccines

All pregnancy outcomes :	Years	total (n)
	2022:	3
	2021	7
	2020	4
	2019	13
	2018	13

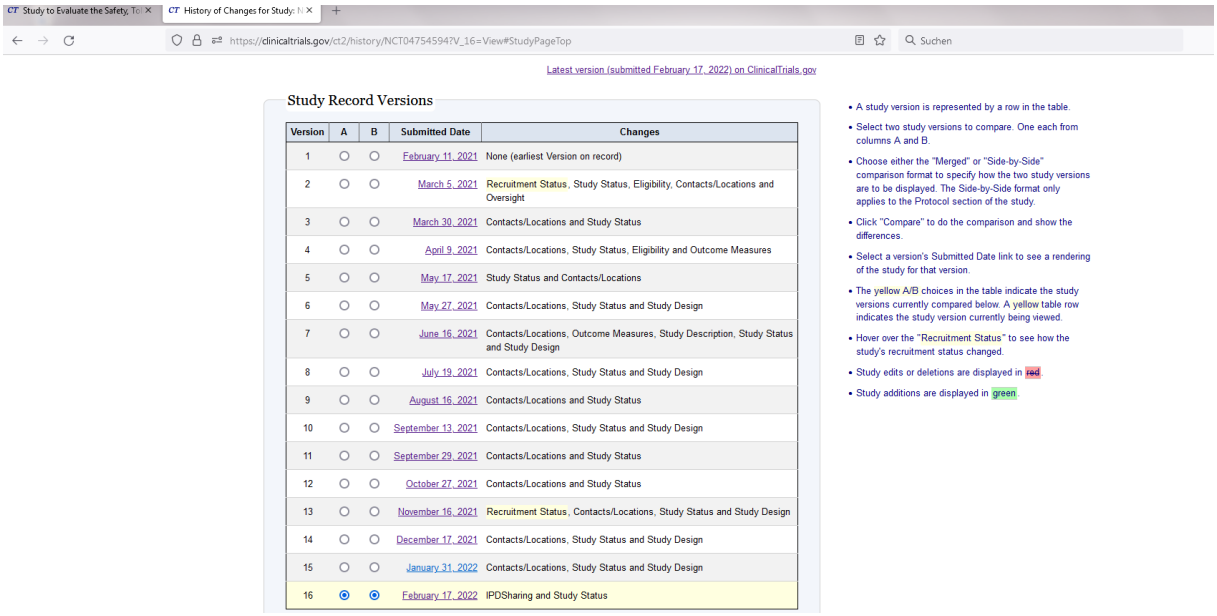
Combining these findings with the reports from neonates and small children up to 2 years of age, we retrieved 138 reports of fetal or infant deaths associated with Comirnaty vaccination of mothers during pregnancy and breast feeding (last access February 20, 2022).

SAE reports submitted to the FDA by Pfizer

From the first release of post-authorization SAE data obtained by Public Health and Medical Professionals for Transparency [5] we found further details on pregnancy. Table 6, page 12, shows 413 SAE cases reported from vaccinated pregnant or lactating women, among them 205 from the U.S., 31 from Canada, 64 from the UK, 86 (+10?) from EU countries. Besides, on page 15, footnote a. mentions that 4 women were reported to have been vaccinated in the pivotal trial with Comirnaty during pregnancy “off label” and hence were simply excluded from the post-authorization SAE data analysis. According to the cumulative analysis of reports until 28 February 2021, there were 274 pregnancy cases (270 cases in mothers, plus 4 fetal cases). Of those 270 maternal cases, 238 pregnancy outcomes including specific SAEs remain unknown. There are 23 reports of spontaneous abortion; intrauterine death or neonatal death after premature birth occurred in 4 cases and there was one additional case of spontaneous abortion with neonatal death. First trimester exposure was only reported in 22/270 cases. Pfizer merely comments that “there were no safety signals that emerged from the review of these cases of use in pregnancy”. Then, among 133 reported breastfeeding cases 116 specific SAE remain unknown, 17/133 SAE are reported, with 3 classified as "serious", and 14 as "non-serious": The list includes pyrexia 5 cases, rash 4, infant irritability 3, vomiting 2, diarrhea 2, insomnia 2, illness 2, allergy to vaccine 1, increased appetite 1, anxiety 1, crying 1, poor sleep 1, eructation 1, agitation 1, pain1, urticaria 1.

It is astounding that important safety signals from numerous spontaneous reports to EMA as well as those from the early post-authorization reports to FDA were not mentioned at all at the very recent IMCRA meeting in February (https://www.icmra.info/drupal/covid-19/9february2021) nor were they addressed in the harmonised guideline “General Considerations for Clinical Studies E8(R1)”.

In light of these many signals, it is unacceptable that EMA refuses to provide any information on the reasons why the only randomized controlled trial in pregnant women conducted by Pfizer-BioNTech (NCT04754594) [6] stopped enrolling patients at a recruitment rate of less than 10 percent of the planned number of participants (343 out of 4000 women) since November 16. Looking at the documented history of changes to the trial’s protocol, the last change occurred by February 17, 2022 as shown in the figure below:



CT Study to Evaluate the Safety, To | CT History of Changes for Study: N

https://clinicaltrials.gov/ct2/history/NCT04754594?V_16=View#StudyPageTop

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Latest version (submitted February 17, 2022) on ClinicalTrials.gov

Study Record Versions

Version	A	B	Submitted Date	Changes
1	○	○	February 11, 2021	None (earliest Version on record)
2	○	○	March 5, 2021	Recruitment Status, Study Status, Eligibility, Contacts/Locations and Oversight
3	○	○	March 30, 2021	Contacts/Locations and Study Status
4	○	○	April 9, 2021	Contacts/Locations, Study Status, Eligibility and Outcome Measures
5	○	○	May 17, 2021	Study Status and Contacts/Locations
6	○	○	May 27, 2021	Contacts/Locations, Study Status and Study Design
7	○	○	June 16, 2021	Contacts/Locations, Outcome Measures, Study Description, Study Status and Study Design
8	○	○	July 19, 2021	Contacts/Locations, Study Status and Study Design
9	○	○	August 16, 2021	Contacts/Locations and Study Status
10	○	○	September 13, 2021	Contacts/Locations, Study Status and Study Design
11	○	○	September 29, 2021	Contacts/Locations and Study Status
12	○	○	October 27, 2021	Contacts/Locations and Study Status
13	○	○	November 16, 2021	Recruitment Status, Contacts/Locations, Study Status and Study Design
14	○	○	December 17, 2021	Contacts/Locations, Study Status and Study Design
15	○	○	January 31, 2022	Contacts/Locations, Study Status and Study Design
16	◉	◉	February 17, 2022	IPDSharing and Study Status

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in red.
- Study additions are displayed in green.

We therefore renew our request to you, as EMA representatives:

1. To find out about and publicly disclose the reasons of the protocol changes/violations in the randomized controlled Pfizer pregnancy trial (NCT04754594). Was enrollment stopped due to serious adverse events occurring after vaccination in the intervention arm? Did EMA request individual patient data (IPD) from the trial? Did the data show serious adverse events in trial participants or their offspring?

2. What actions will you take with respect to the many alarming pregnancy/infant safety signals? What mechanisms does EMA apply to analyse severe cases such as fetal/infant deaths, malformations, ectopic pregnancies and severe side effects in neonates and small infants after maternal exposure to mRNA vaccination during pregnancy or during breast-feeding?

It is completely unacceptable, that mandates for the general population or for specific groups such as health care workers are even considered under these alarming safety signals on Covid-19 vaccination during pregnancy and breast-feeding.

Angela Spelsberg MD, SM., Aachen, Germany

Ulrich Keil MD, PhD, FRCP London, Prof. emeritus, Muenster, Germany

References:

[1] https://www.ema.europa.eu/en/news/covid-19-latest-safety-data-provide-reassurance-about-use-mrna-vaccines-during-pregnancy

[2] Magnus M, Gjessing H et al. Letter: Covid-19 Vaccination during Pregnancy and First-Trimester Miscarriage. NEJM 2022;385:21https://www.nejm.org/doi/10.1056/NEJMc2114466

[3] Kharbanda EO, Haapala J, et al. Spontaneous Abortion Following COVID.19 Vaccination During Pregnancy. JAMA 2021:326:1629-1631 doi:10.1001/jama.2021.15494

[4] Lipkind HS, Vazquez-Benitez G, et al. Receipt of COVID-19 vaccine during Pregnacy and Preterm or Small-for Gestational-Age at Birth – Eight Integrated Health Care Organizations, United States, December 15, 2020-July 22, 2021. MMWR Morb Mortal Wkly rep.2022, Jan7;71(1):26-30

[5] https://phmpt.org/pfizers-documents/

[6] https://clinicaltrials.gov/ct2/show/NCT04754594?term=NCT04754594&draw=2&rank=1