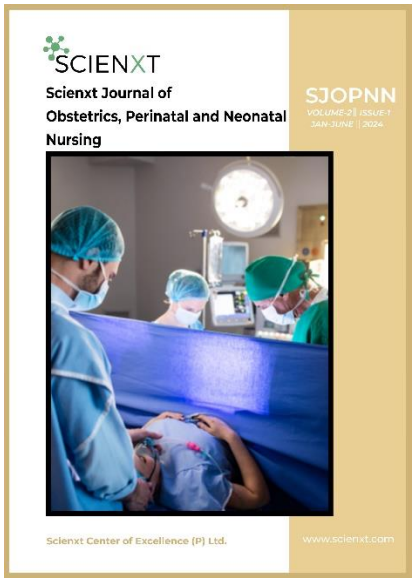

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Review of causes for late miscarriages due to COVID-19 infections

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Abstract:

This study aimed to describe the characteristics of fetal demise after SARS-CoV-2 infections and clarify whether it is associated with clinical severity, placental lesions, or malformations or due to actual fetal infections. Cohort, cross-sectional, and case-control studies and case series or case reports describing stillbirths or late miscarriages (ie, pregnancy loss occurring between 14 and 22 weeks of gestation, before and after the onset of labor) from mothers with SARS-CoV-2 infection during pregnancy (demonstrated by at least 1 positive real-time reverse transcription-polymerase chain reaction from nasopharyngeal swabs and/or SARS-CoV-2 placental infection). No language restriction was applied; cases with other causes possibly explaining the fetal demise were excluded. The synthesis of available data showed that fetal demise generally occurs a few days after the infection with histologic placental inflammatory lesions associated with transplacental SARS-CoV-2 transmission and eventually causing placental insufficiency.

Keywords:

COVID-19 fetal demise fetus loss malformation neonate placenta pregnancy transmission virus

1. Introduction:

In December 2019, the first cases of pneumonia caused by a novel coronavirus (SARS-CoV-2) were reported by the World Health Organization (WHO), and since then, approximately 552,000,000 confirmed cases of COVID-19 have occurred, causing more than 4,300,000 deaths. It is unknown whether fetal demise (miscarriage or stillbirth) is associated with clinical severity, placental lesions, or malformations and whether it is due to actual SARS-CoV-2 fetal infection.

Fetal demise generally occurred in the second and third trimesters of pregnancy (between 14 and 39 weeks of gestation), approximately 6 to 13 days after the diagnosis of infection or the onset of symptoms, without a link to maternal clinical severity and comorbidities or congenital fetal malformations. Most placentas were positive for SARS-CoV-2 or presented the histologic anomalies previously observed in transplacentally transmitted infections, which causes placental insufficiency. Moreover, 65% of the fetuses had a confirmed or possible in utero transmitted infection.This study synthesized the characteristics of fetal demise from women with SARS-CoV-2 infection and helps in understanding the role of SARS-CoV-2 infection in fetal demise.

Although several studies indicate SARS-CoV-2 infection during pregnancy as a risk factor for poor maternal outcomes, the results of large cohorts are discordant regarding the effect on fetal outcomes because of the rarity of negative fetal outcomes, leading to relatively a low power to detect any association. The association of preterm birth, miscarriage, and stillbirth with SARS-CoV-2 infection and COVID-19 remains unclear.Starting from 2020, some cases have suggested a link between SARS-CoV-2 infection and pregnancy loss, and the rate of stillbirth in women with SARS-CoV-2 infection is estimated to be between 1% and 3%. In some cases, SARS-CoV-2 has been isolated in fetal tissues and suspected to be responsible for pregnancy loss through fetal infection.

2. Methods:

2.1. Protocol:

Before commencing the project, a protocol was established, including the search modalities, eligibility criteria, and all methodological details. Several meetings among the authors were

organized. The work was performed using secured files; however, the original articles only provided deidentified data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed throughout the project.

2.2. Eligibility and exclusion criteria:

We searched for cohort, cross-sectional, and case-control studies and case series or case reports published between December 1, 2019, and April 30, 2022, describing stillborn fetuses or late miscarriages (ie, pregnancy loss occurred between 14 and 22 weeks of gestation, before and after the onset of labor; after 22 weeks of gestation, only intrauterine fetal deaths have been considered) from mothers with SARS-CoV-2 infection during pregnancy, as demonstrated by (1) at least 1 positive real-time reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal swabs and/or (2) placental infection with SARS-CoV-2 (ie, a positive placental RT-PCR, immunostaining, in situ hybridization, or electron microscopy). All these tests had to be performed according to the WHO or national guidelines.

No language restriction was applied: non-English publications were examined using Google Translator. We excluded conference abstracts, meta-analysis, and cases of women exposed to SARS-CoV-2 but not fulfilling at least one of the two aforementioned eligibility criteria. In addition, we excluded "gray" literature and cases with other causes possibly explaining stillbirth and late miscarriage.

Duplicate reports were identified and eventually excluded.

2.3. Information sources and search strategy:

We searched PubMed and Web of Science databases with the following key words or Medical Subject Headings terms: "fetal demise," "stillbirth," "miscarriage," "SARS-CoV-2," and "COVID-19." Furthermore, we hand-searched references cited in the eligible manuscripts or review articles on the subject and the authors' archives. Following Boolean strings were used: (Fetal demise AND Covid) OR (Fetal demise AND SARS-CoV-2) OR (stillbirth AND Covid)) OR (stillbirth AND SARS-CoV-2) OR (Miscarriage AND Covid)) OR (Miscarriage AND SARS-CoV-2)) OR (Intrauterine death AND Covid)) OR (Intrauterine death AND SARS-CoV-2).

2.4. Study selection:

Abstracts and, where necessary, full texts of each article were assessed by 2 independent researchers (N.A. and G.R.), following the Meta-analysis Of Observational Studies in Epidemiology guidelines.

The Consensus-based Clinical Case Reporting Guideline Development (CARE) recommendations, specifically dedicated to case reports and case series, were considered for the evaluation of these types of manuscripts.

If an article was eligible but reported data on both stillbirths and late miscarriages and living neonates, only data about the former were considered and directly extracted when available. In case of unavailability, or when additional information was needed anyway, the authors were contacted, and at least 2 e-mails were sent 2 weeks apart to the corresponding author. If discrepancies or uncertainties persisted, they were resolved by discussion between the 2 independent researchers, and if no agreement was reached, a third researcher was consulted (A.V.). All articles finally deemed eligible were included in an electronic database (Zotero; version 5.0.65; Roy Rosenzweig Center for History and New Media, Fairfax, VI).

2.5. Data collection and extraction:

We customized an online data extraction sheet, pilot-tested it on 3 randomly selected manuscripts, and refined it accordingly. Data from included records were extracted independently by 2 investigators (N.A. and G.R.) and cross-verified. If data were missing, they were requested from the corresponding authors as described above. Data were considered lacking if the authors did not provide them after 2 e-mail requests; lacking data were considered as such and not estimated. If discrepancies or uncertainties about data interpretation persisted, they were resolved by discussion between the 2 independent researchers, and if no agreement was reached, a third researcher was consulted (A.V.).

2.6. Data synthesis:

Data collected included article type; country; number of fetuses; date; maternal characteristics, such as age, number of pregnancies, parity, or singleton or twin pregnancy; gestational age (GA) at SARS-CoV-2 infection; medical history; obesity (defined as a body mass index of ≥30 kg/m^2); and any obstetrical complication. Moreover, data about SARS-CoV-2 infection features, vaccination status, hospitalization for COVID-19, and COVID-19 severity were collected. The clinical severity was classified according to the WHO criteria based on clinical data accumulated before the occurrence of fetal demise. The criteria were not influenced by pregnancy characteristics, and severity was not upgraded on the basis of the clinical evolution occurring after fetal demise.

In addition, we extracted fetal and placental data: the interval between SARS-CoV-2 infection and stillbirth or late miscarriage diagnosis, fetal sex and growth, and fetal (any tissue) and

placental SARS-CoV-2 positivities. Fetal or placental SARS-CoV-2 positivity was interpreted according to the WHO criteria for vertical SARS-CoV-2 transmission: in detail, fetal or placental tissue was considered positive if there was a positive RT-PCR, immunostaining, in situ hybridization, or electron microscopy.

Clinical chorioamnionitis was considered according to the US National Institute of Child Health and Human Development consensus criteria, and where data were available, the diagnosis of histologic chorioamnionitis was also considered. Fetal growth was evaluated using Association des Utilisateurs de Dossiers Informatisés en Pédiatrie, Obstétrique et Gynécologie curves.

The likelihood (confirmed, possible, or unlikely) of fetal infection was evaluated using the specific WHO criteria.

Maternal and fetal characteristics were considered as the main outcomes.

2.7. Assessment of risk of bias:

As we expected most articles to be case reports or case series, we decided to evaluate their methodological quality according to 4 domains (selection, ascertainment, causality, and reporting) using the Mayo Clinic Evidence-Based Practice Center tool, which is specifically dedicated to the evaluation of case report or case series quality. Of note, 2 investigators (N.A. and G.R.) independently summarized the results of this evaluation by aggregating the eight binary responses into a 0 to 8 score (the higher the score, the better the quality), and the results were also qualitatively summarized, as previously done.

If discrepancies or uncertainties persisted, they were resolved by discussion between the 2 researchers (N.A. and G.R.), and if no agreement was reached, a third researcher was consulted (A.V.).

2.8. Summary measures:

Cumulative estimates of event rates (frequency) were reported as a percentage. The percentage refers to the total number of fetuses, unless otherwise indicated. Continuous data were described as mean (standard deviation); minimum and maximum values were also reported. Excel 2016 online (Microsoft Corporation, Redmond, WA) was used.

3. Results:

3.1. Study selection:

Abstracts and full texts of each article were assessed by 2 independent researchers after duplicate removal, with discrepancies resolved by a third researcher.

3.2. Study characteristics:

Fig. 1 illustrates the project flowchart with included and excluded records (and the reasons for their exclusions). Finally, 54 articles were considered, consisting of 19 case series, 30 case reports, 1 case-control study, and 4 cohort studies, accounting for a total of 184 mothers and 190 fetuses, that is, 166 stillbirths and 24 late miscarriages. Most of the articles were already peer-reviewed.

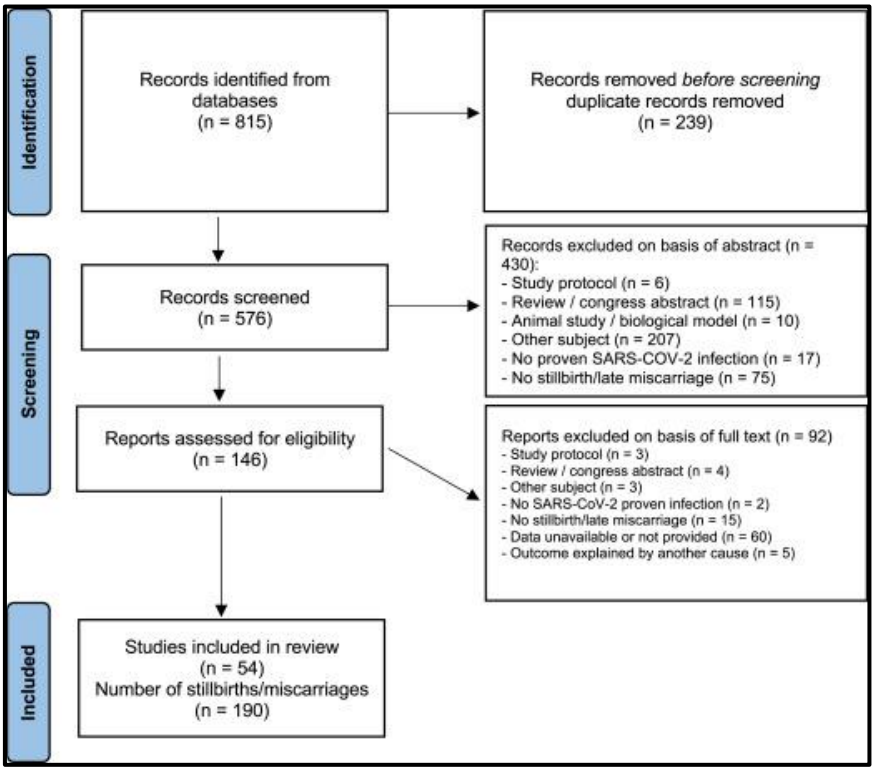

Figure. 1: PRISMA flowchart for the systematic review

3.3. Risk of bias of included studies:

According to the CARE recommendations, the methodological quality of case reports and case series was estimated as intermediate to good (Table. 1).

Table. 1: Characteristics of articles included in the systematic review

Author	*Article type*	*Country*	*Quality score*	*Overall quality*	*Publication status*	*Number of fetuses*
Popescu et al, 2021	Case report	Romania	6	Good	Reviewed	1

Author	***Article type***	***Country***	***Quality score***	***Overall quality***	***Publication status***	***Number of fetuses***
Aminimoghaddam et al,	Case report	Iran	4	Intermediate	Reviewed	1
Marinho et al,	Case report	Brazil	6	Good	Reviewed	1
Remaeus et al, 2020	Case series	Sweden	4	Intermediate	Reviewed	2
Schwartz et al,	Case series	United States	6	Good	Reviewed	2
Lokken et al	Case series	United States	6	Good	Reviewed	1
Shmakov et al	Cohort	Russia	NA	NA	Reviewed	2
Lesieur et al	Case report	France	6	Good	Reviewed	1
Futterman et al,	Case report	United States	5	Intermediate	Reviewed	1
Watkins et al,	Case series	United States	5	Intermediate	Reviewed	1
Michel et al,	Case report	France	6	Good	Reviewed	1
Valk et al	Case report	United States	5	Intermediate	Reviewed	1
Garrido-Pontnou et al,	Case series	Spain	4	Intermediate	Reviewed	5
Richtmann et al,	Case series	Brazil	6	Good	Reviewed	5
Stonoga et al,	Case report	Brazil	6	Good	Reviewed	1
Halici-Ozturk et al,	Case series	Turkey	4	Intermediate	Reviewed	5
Hachem et al,	Case report	France	4	Intermediate	Reviewed	1
Marton et al,	Case report	United Kingdom	5	Intermediate	Reviewed	1
Sadiq et al,	Case series	Pakistan	4	Intermediate	Reviewed	1
Hcini et al,	Cohort	French Guiana	NA	NA	Reviewed	7
Verma et al,	Case report	United States	4	Intermediate	Reviewed	3
Bouachba et al,	Case report	France	6	Good	Reviewed	3
Shanes et al,	Case-control study	United States	5	Intermediate	Reviewed	1
Mattar et al,	Case series	Singapore	4	Intermediate	Reviewed	1
Hodžić et al,	Cohort	Bosnia	5	Intermediate	Reviewed	2
Argueta et al,	Case report	United States	5	Intermediate	Preprint	2

Author	*Article type*	*Country*	*Quality score*	*Overall quality*	*Publication status*	*Number of fetuses*
Baud et al,	Case report	Switzerland	6	Good	Reviewed	1
Rodrigues et al,	Case report	Portugal	6	Good	Reviewed	1
Baral et al,	Case report	Nepal	5	Intermediate	Reviewed	1
Pulinx et al,	Case report	Belgium	6	Good	Reviewed	2
Fernandez et al,	Case report	Brazil	4	Intermediate	Reviewed	1
Ferreira et al,	Case series	Brazil	4	Intermediate	Reviewed	1
Zaigham et al,	Case series	Sweden	6	Good	Reviewed	5
Coté et al,	Case report	United States	5	Intermediate	Reviewed	1
Patanè et al,	Case report	Italy	5	Intermediate	Reviewed	2
Fitzgerald et al,	Case series	Ireland	5	Intermediate	Reviewed	6
Schwartz et al,	Case series	United States	5	Intermediate	Reviewed	2
Thomas et al,	Case series	United States	4	Intermediate	Reviewed	2
Babal et al,	Case report	Slovakia	5	Intermediate	Reviewed	1
Eich et al,	Case report	Germany	4	Intermediate	Reviewed	1
Guan et al,	Case report	United States	6	Good	Reviewed	1
Mithal et al,	Case report	United States	5	Intermediate	Reviewed	1
Sagara et al,	Case report	Japan	5	Intermediate	Reviewed	2
Wong et al,	Case report	United States	4	Intermediate	Reviewed	1
Bewley et al,	Case report	United States	4	Intermediate	Reviewed	1
Borges Charepe et al	Cohort	Portugal	NA	NA	Reviewed	9
Schwartz et al,	Case series	Several	4	Intermediate	Reviewed	31
Huynh et al,	Case series	United States	5	Intermediate	Reviewed	18
Shook et al,	Case report	United States	6	Good	Reviewed	2
Stenton et al,	Case series	United Kingdom	5	Intermediate	Reviewed	29
Dubucs et al,	Case series	France	6	Good	Reviewed	7
Di Gioia et al,	Case report	Italy	5	Intermediate	Reviewed	1

Author	***Article type***	***Country***	***Quality score***	***Overall quality***	***Publication status***	***Number of fetuses***
Konstantinidou et al,	Case series	Greece	6	Good	Reviewed	6
Zinserling et al,	Case report	Russia	5	Intermediate	Reviewed	1
Total			5 (0.8)			190

The methodological quality of case reports and case series was evaluated using the Mayo Clinic Evidence-Based Practice Center tool, specifically dedicated to evaluation of the quality of these types of articles and shown both as a 0-6 score and as overall qualitative evaluation. The score was applied exactly in the same way to peer reviewed and non-peer reviewed articles. The score was summarized as mean (standard deviation). This tool was not applied to the retrospective cohort studies included in the review.

NA, not applicable.

Alcover. Fetal demises following SARS-CoV-2 infection. Am J Obstet Gynecol 2023.

3.4. Synthesis of results:

Basic obstetrical data are reported in Table 2. Of note, 42 mothers were multiparous; moreover, obesity, diabetes mellitus, and chorioamnionitis were the most common comorbidities. The following COVID-19 treatments had been provided in a few women: steroids (n=6), remdesivir (n=3), tocilizumab (n=2), and anakinra (n=1).

Table. 2: Basic obstetrical data of reviewed stillbirth and early miscarriage cases

Variable	***Summary statistics***	***IQR***
Maternal age (y)	30.5 (6.5)	15–42
Gravidity	2.9 (2.6)	0–14
Nulliparous	33 (17.9%)	
Multiparous	42 (22.8%)	
Singleton	175 (95.1%)	
Hospitalization for COVID-19	10 (5.4%)	
Comorbidities		
Diabetes mellitus (any type)	15 (8.1%)	
Obesity (body mass index)	28 (15.2%)	
Antiphospholipid syndrome	1 (0.5%)	

Variable	*Summary statistics*	*IQR*
Chronic hypertension	13 (7.0%)	
Disseminated intravascular coagulopathy	4 (2.2%)	
Obstetrical cholestasis	0 (0%)	
Preeclampsia	8 (4.3%)	
Clinical chorioamnionitis	1 (0.5%)	
Histologic chorioamnionitis	14 (7.6%)	

Data are presented as mean (standard deviation), IQR, or number (percentage).

The percentage refers to the number of pregnant women (n=184). Comorbidities were considered absent if not detailed in the reviewed articles and not declared by authors during e-mail communications with investigators.

Alcover. Fetal demises following SARS-CoV-2 infection. Am J Obstet Gynecol 2023.

Data regarding SARS-CoV-2 infection are presented in Table 3. No woman was vaccinated against SARS-CoV-2; GA at the diagnosis of SARS-CoV-2 infection spanned from a minimum of 14.0 weeks to a maximum of 39.2 weeks. Less than 5% of women suffered from severe COVID-19, whereas most women had mild-to-moderate disease. Of note, 4 women had a negative nasopharyngeal RT-PCR, but their infection was confirmed by a positive placental RT-PCR.

Table. 3: Main data about SARS-CoV-2 infection in reviewed cases of stillbirth and early miscarriage

Variable	*Summary statistics*
GA at the diagnosis of SARS-CoV-2 infection (wk)	27.4 (6.9)
GA classes at the diagnosis of SARS-CoV-2 infection	
14–22 wk	26 (13.7%)
22–32 wk	52 (27.4%)
32–42 wk	32 (16.8%)
Unknown	80 (42.1%)
Maternal COVID-19 severity	
Asymptomatic	49 (26.6%)
Mild	36 (19.6%)

Variable	***Summary statistics***
Moderate	25 (13.6%)
Severe	8 (4.3%)
Unknown	66 (35.9%)
Viral strain	
α	10 (5.4%)
β	3 (1.6%)
γ	1 (0.6%)
δ	5 (2.7%)
Unknown	165 (89.7%)

Data are presented as mean (standard deviation) or number (percentage). The percentage refers to the total number of fetuses (N=190), except that for maternal COVID-19 severity and viral strains where the percentage refers to the number of pregnant women (n=184). GA classes were defined using trimester thresholds.

Fetal and placental data are reported in Table. 4. Stillbirths and late miscarriages occurred approximately 6 to 13 days after the confirmation of SARS-CoV-2 infection or the onset of symptoms (only 9 cases (4.7%) were outliers; ie, they had fetal demise occurring more than 15 days from maternal infection). Most stillbirths and late miscarriages occurred during the second trimester of pregnancy. Fetal weight was appropriate for the GA: only 7 fetuses (4%) had a weight *z* score of <−2. Of note, 23 fetuses (12.1%) were positive for SARS-CoV-2 in at least 1 tissue, and positivity was detected with RT-PCR, immunostaining, and in situ hybridization in 10, 10, and 5 cases, respectively; 132 (69.5%) placentas were positive for SARS-CoV-2 as indicated by RT-PCR, immunostaining, and in situ hybridization in 54, 101, and 35 cases, respectively. Placental histology was examined in 150 cases (79%), and most placentas presented the histologic features previously observed in transplacentally transmitted infections (Table. 4). Of note, 3 cases presented with nonlethal congenital anomalies: 1 with hand malformation (shortening of 2 fingers and suspected absence of 2 metacarpal bones), 1 with isolated agenesis of the corpus callosum, and 1 with unilateral kidney agenesis.

Table. 4: Fetal and placental data of reviewed cases of stillbirth and early miscarriage

Variable	***Summary statistics***	***IQR***
Time between COVID-19 symptoms and stillbirth or miscarriage (d)	9.5 (6.0–9.5)	2–77

Variable	*Summary statistics*	*IQR*
Time between SARS-CoV-2 infection and stillbirth or miscarriage (d)	2.5 (0.0–9.3)	0–70
GA at stillbirth or miscarriage (wk)	28.37 (22.6–33.6)	14–41
GA classes at stillbirth or miscarriage		
14–22 wk	40 (21.1%)	
22–32 wk	85 (44.7%)	
32–42 wk	64 (33.7%)	
Unknown	1 (0.5%)	
Fetal characteristics		
Male	36 (19.0%)	
Female	39 (20.5%)	
Unknown sex	115 (60.5%)	
Fetal weight (g)	1416 (948)	120–4250
Fetal weight *z* score	−0.52 (3.17)	−22.10 to 4.77
Fetal SARS-CoV-2 positivity	23 (12.1%)	
Placental characteristics		
Fibrin deposition	136 (90.7%)	
Chronic intervillositis	128 (85.3%)	
Trophoblast necrosis	96 (64.0%)	
Villitis	19 (12.7%)	
Placental SARS-CoV-2 positivity	132 (88.0%)	

Data are presented as median (IQR), mean (standard deviation), IQR, or number (percentage). The percentage refers to the total number of fetuses, except that for placental histology where the percentage refers to the total number of placental histologic examinations (N=150). The *z* score is a dimensionless variable. GA classes were defined using trimester thresholds.

According to the WHO criteria, 11 fetuses (5.8%) had a confirmed in utero transmitted SARS-CoV-2 infection, and 114 fetuses (60.0%) had a possible in utero transmitted SARS-CoV-2 infection; in 18 fetuses (9.5%), the transmission was considered unlikely; lack of data prevented

classification in approximately one-quarter of cases. The distribution of the likelihood of SARS-CoV-2 transplacental transmission in the reviewed cases is depicted in Fig. 2.

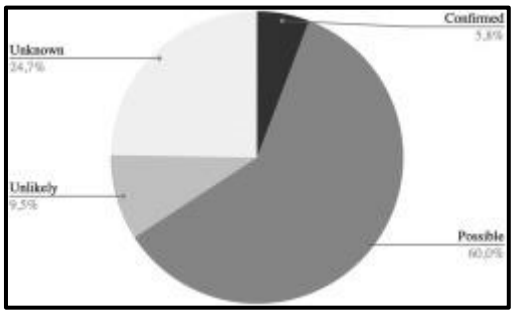

Figure. 2: Likelihood of in utero transplacental SARS-CoV-2 transmission in reviewed cases of stillbirth and early miscarriage

4. Conclusion:

The higher occurrence of fetal demise cases in the second trimester of pregnancy might have been biased by the testing policies that varied between centers and settings; moreover, the active management offered to women in the third trimester of pregnancy may have had an influence. The lack of a link between the clinical severity of COVID-19 and fetal demise might be surprising, although it indicates that several factors can interact and influence fetal outcomes. Stillbirth and transplacental SARS-CoV-2 transmission are both uncommon events (whose rates are between 1% and 3% of pregnancies). Therefore, the relatively small population of available cases (with <5% of severe cases) means that the link with maternal clinical severity may go undetected as much larger populations may be needed to capture its effects on such a rare outcome. Conversely, if a bias regarding clinical severity would exist, it would be visible because of more tests being performed in more symptomatic women. At the time of the publication of reviewed cases, no woman was vaccinated. With the current large diffusion of vaccination in the Western world, observation of a larger population of fetal demise cases after SARS-CoV-2 infections may be unlikely, as vaccines are efficacious in preventing maternal infections.

Unfortunately, vaccine hesitancy has been observed among pregnant women. As fetal demise cases occurred close to SARS-CoV-2 infection, an important role of this infection should be suspected. Previous biological or observational data seemed to support this role. Our work must be considered as an additional piece of information obtained with a different technique, that is, the meta-analysis and synthesis of clinical data (eg, maternal and fetal characteristics), to clarify the link between the infection and outcomes as commonly done during outbreaks.

Vertically transmittable infections may result in fetal demise either by placental damage or by direct fetopathy.

These placental histologic features may eventually impair fetal vascular perfusion, cause placental insufficiency, and, as recently demonstrated, lead to fetal hypoxia. These abnormalities (mainly constituted by massive perivillous fibrin deposition and chronic histiocytic intervillositis constitute the so-called SARS-CoV-2 placentitis and have been associated with both vertically transmittable infections and pregnancy loss.

The synthesis of available data about stillbirths and late miscarriages in mothers with SARS-CoV-2 infection showed that fetal demise occurs mostly in the third trimester of pregnancy and a few days after infection. Most stillbirths and late miscarriages presented with histologic placental abnormalities associated with transplacental SARS-CoV-2 transmission, causing placental insufficiency and eventually fetal hypoxia.

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