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Meta-analysis on COVID-19-pregnancy-related placental pathologies shows no specific pattern

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ABSTRACT

Coronavirus disease 2019 (COVID-19) pneumonia rarely occurs in pregnant women. Case reports indicate that fibrin and lymphohistiocytic lesions in placentas may be typical. However, a meta-analysis to clarify whether there is a COVID-19-associated pattern of placental lesions has not yet been conducted.

Systematic literature search with meta-analysis of publications on 10 or more cases of pregnancy with SARS-CoV-2 infection and placenta examination (30 publications from 2019 to 2021; 1452 placenta cases) was performed.

The meta-analysis did not reveal any COVID-19-specific placenta changes. The incidence of both vascular and inflammatory lesions was mainly comparable to that of non-COVID-19 pregnancies.

Transplacental viral transmission is very rare and there are no typical placental changes. The most important prognostic factor seems to be maternal-fetal hypoxia in the context of pneumonia.

1. Introduction

During pregnancy, viral pneumonia is generally a rare comorbidity. However, since 2019, there has been an increase in infection rate with “severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) which may lead to pneumonia, designated coronavirus disease 2019 (COVID-19) [1].

Aerosolic transmission and infection can be asymptomatic or variable symptoms manifest, including acute respiratory distress syndrome (ARDS) and death. Approximately 5% of all infections result in COVID-19, with respiratory failure occurring in ~20% of hospitalized patients and ~75% of these patients requiring oxygen therapy [1]. Among pregnant women, the rate of hospitalization is ~30% [2]. In symptomatic courses, fever, dry cough, and dyspnea manifest typically 5–12 days after infection and lymphopenia as well as elevated lactate dehydrogenase levels are often found [1]. There are no specific radiologic changes that distinguish COVID-19 pneumonia from other pneumonias [3]. The definite diagnosis requires integration of all clinical, laboratory and radiologic findings and a positive SARS-CoV-2 test [1].

Therapy includes conventional oxygen administration, extracorporeal membrane oxygenation (ECMO), as well as dexamethasone therapy, anticoagulation and, possibly, remdesivir administration [1]. Secondary bacterial pneumonias significantly increase the morbidity and mortality of COVID-19 [4]. Post-infection symptoms may occur and are designated as “long COVID” syndrome [5].

1.1. COVID-19 during pregnancy: rarely vertical transmission

Pregnancy per se is no risk factor for maternal infection and SARS-CoV-2 does not appear to have an increased risk to transplacentally infect the fetus [6]. However, this does not completely exclude vertical transmission. The presence of prominent viremia appears to favor vertical transmission [7]. In general, vertical transmission occurs in 3–6% of pregnancies and seems to occur predominantly in the third trimester and rarely earlier [8,9]. However, these data also include newborns who were tested positive up to 48 h after birth and this may bias the frequency due to inclusion of peripartum infection cases [10].

The first case in which the virus from a COVID-19-affected mother infected the fetus via the placenta was described by Vivanti et al. [11]. The child was born in the third trimester and SARS-CoV-2 was detectable in the placenta, in a broncho-alveolar lavage and in a stool sample of the child. A diffuse perivillous fibrin position with infarcts and an intervillositis was found in the placenta [11]. This seems striking at first and considering other case reports of placenta pathologies, this

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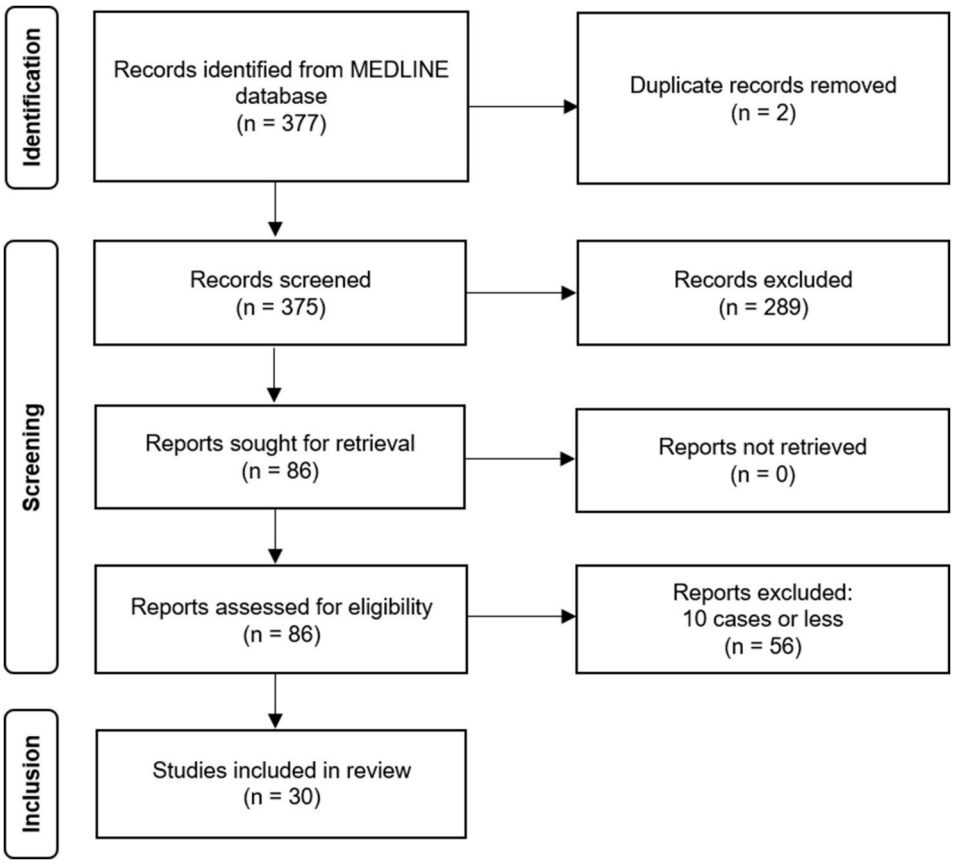

Fig. 1. PRISMA flow diagram of database search.

prompted us to conduct a systematic meta-analysis. The aim was to clarify whether there is a particular COVID-19-associated pattern of placenta pathologies.

1.2. Meta-analysis

Inclusion criteria for the meta-analysis were publications with more than 10 COVID-19-associated pregnancies, histologic evaluation of placentas and an arbitrary time interval from December 2019 to August 2021. In order to avoid a bias by inclusion of cases reported only because of pathologic findings and small case numbers, single case reports and series of 10 cases or less were excluded from the analysis.

MEDLINE database (PubMed®) was searched for the following key words: "covid-19 placenta*", "sars-cov-2 placenta*" and "covid placenta*". Two authors (JTS and NS) screened all search results independently and consensus was found in case of different assessment (Fig. 1).

The following parameters were collected and analysed: number of placenta cases, maternal age, gestational age, sex of child, preterm births, stillbirths, and SARS-CoV-2 positive/negative placenta samples detected by *in situ* hybridisation and/or polymerase chain reaction. Placenta pathologies were classified as follows: placenta being too small (<10. percentile) or too large (>90. percentile) for gestational age, maturation disorders, chorangiosis, malperfusion, infarction, fetal thrombotic vasculopathy (FTV), acute inflammation, villitis of unknown etiology (VUE), plasma cell-rich villitis with or without iron-laden macrophages such as typical for cytomegalovirus- or Epstein-Barr-virus-associated placentitis, chronic histiocytic intervillositis (CHI), massive fibrin deposition (MFD), chronic deciduitis (CD), giant cell reaction, eosinophilia, the presence of amnial, meconium-laden macrophages or umbilical cord pathologies.

2. Results

2.1. Cohort of COVID-19-associated placenta cases

We identified a total of 1452 cases from 30 publications [12–41] (Table 1). It should be taken into consideration that histological changes were not graded in all publications and even minor changes could have been summarized as "pathology". Thus, some of these findings might not even be considered significant without knowledge of COVID-19 disease. For example, decidual vasculopathy and Tenney-Parker changes (syncytial nuclear buds) may occur, but such lesions are regarded as non-specific [11].

2.2. Mostly non-specific placental changes in COVID-19

While normal size and maturation of the placenta without any signs of inflammation or significant circulatory disturbance was found in a subfraction of COVID-19-associated pregnancies, almost the full spectrum of other placental pathologies has also been reported.

In 13–15% of cases, the placenta was too small or too large, 10–14% showed maturation defects and/or chorangiosis, and in 14–20% signs of malperfusion, infarcts, and/or thrombangiitis obliterans were found (Table 2).

Acute chorioamnionitis was relatively common and detectable in 26% of placentas (Table 3).

T-cell-rich and plasma cell-free lymphohistiocytic villitis, indicating a VUE-type pattern, manifested in 16% of placentas (Table 3). CD manifested in 14% of placentas while CHI and MFD were found in ≤5% of cases (Table 3). Plasma cell-rich villitis, iron-laden macrophages within villitis or other unusual inflammation types (e.g. histiocytic giant cells, eosinophilia, necrosis/calcification of umbilical cord) were not reported.

Table 1
Clinical characteristics of COVID-19 pregnancies.

Source	COVID-19-associated pregnancies (n)	SARS-CoV-19-positive placenta (n)	Age of the mother (years)	Sex of the child	Live births (n), thereof premature births (n)	Intrauterine death (gestational age in weeks)
Total (n/N, %)	1452	50/580, 9%	mean ca. 31	~1:1	1040/1066, 98% (95/636, 15%)	25/1227, 2%
[22]	16	n.a.	mean 32	n.a.	15 (1)	1 (16th week)
[23]	20	n.a.	mean 31	n.a.	20 (4)	0
[24]	29	n.a.	n.a.	n.a.	29 (n.a.)	0
[25]	51	0	10 > 37 years, 41 ≤ 37 years	n.a.	51 (n.a.)	0
[26]	20	[unclear#]	mean 31	n.a.	19 (9)	1 (22nd week)
[27]	74	2	n.a.	n.a.	71 (n.a.)	n.a.
[28]	50	n.a.	mean 30	n.a.	50 (2)	0
[29]	15	[15##]	mean 32	6 male, 9 female	15 (n.a.)	n.a
[30]	21	n.a.	mean 28	n.a.	21 (3)	0
[31]	77	n.a.	mean 30	n.a.	77 (7)	0
[41]	187	n.a.	n.a.	n.a.	n.a.	0
[32]	75	1	n.a.	n.a.	75 (n.a.)	0
[33]	11	[11##]	mean 33	4 male, 3 female, 5 unknown	6 (4)	5 (22-40th week)
[34]	50	n.a.	mean 29	n.a.	n.a.	n.a.
[35]	34	n.a.	mean 26	16 male, 18 female	34 (4)	0
[36]	27	n.a.	mean 27	16 male, 11 female	23 (n.a.)	4 (n.a.)
[37]	101	n.a.	n.a.	n.a.	101 (n.a.)	0
[38]	65	0	[median 30]	n.a.	65 (12)	2 (2nd trimester)
[39]	21	n.a.	[median 33]	n.a.	21 (2)	0
[40]	32	n.a.	mean 32	n.a.	32 (4)	0
[21]	71	[unclear#]	mean 31	n.a.	71 (7)	0
[20]	27	2	[median 32]	14 male, 15 female	27 (n.a.)	n.a.
[19]	64	7	mean 32	n.a.	64 (3)	0
[18]	19	1	mean 32	n.a.	18 (7)	1 (29th week)
[17]	31	5	mean 31	15 male, 16 female	30 (n.a.)	1 (n.a.)
[16]	59	2	n.a.	n.a.	n.a.	n.a.
[15]	54	22	mean 32	n.a.	52 (9)	2 (30th and 37th week)
[14]	90	n.a.	mean 34	n.a.	n.a.	0
[13]	22	4	mean 31	n.a.	14 (6)	8 (22-40th week)
[12]	39	4	mean 34	n.a.	39 (11)	0

Abbreviation: not specified (n.a.); result of virus detection is not clear from the publication (#); inclusion criterion in this publication was a positive virus detection in the placenta and therefore these numbers were not included for the meta-analysis (##).

A quarter of COVID-19 placentas had increased meconium-laden macrophages in the amnion membrane, indicative of a non-specific epiphenomenon of fetal stress (Table 3).

3. Discussion

3.1. Possible complications of a COVID-19-associated pregnancy

To date there is no known typical pattern of fetal COVID-19 disease [9]. The risk of cesarean section or preterm delivery is increased in a COVID-19 pregnancy, most likely due to hypoxia-associated complications [8]. It must be assumed that COVID-19-related respiratory insufficiency of the mother is the major adverse prognostic factor [42]. Growth retardation, premature birth and miscarriage may occur due to oxygen deficiency [42,43]. The fetal brain seems to be most vulnerable to the COVID-19-related decline of maternal and consequently feto-placental oxygen saturation. An indirect inflammatory reaction may be another possible pathomechanism for cerebral damage in the fetus. In adults, severe COVID-19 may result in a cytokine storm of interleukin 2 (IL-2), IL-6, IL-7, IL-10, interferon-gamma and tumor necrosis factor-alpha [7]. Viremia may be a possible trigger for increased cytokine production, while placental ischemia resulting from maternal hypoxia during pregnancy could constitute another trigger [7]. This maternal-derived cytokine storm can lead to an inflammatory response in the fetus, which could lead to impairment of brain development and increased risk of neuropsychological disorders later in life [7]. The cytokine storm could also lead to placental damage with consecutive fetal maturation retardation, preterm birth or abortion [7]. For example, Vivanti et al. [11] reported that the aforementioned child with vertical viral transmission had virus-negative cerebrospinal fluid but manifested transient neurologic symptoms and bilateral periventricular and subcortical gliosis [11]. It is possible that these brain changes are complications of transient hypoxia and/or cytokine-associated.

3.2. Placenta pathologies in COVID-19-associated pregnancies

In adults, the possible binding and internalization of SARS-CoV-2 via the angiotensin-converting enzyme 2 receptor on endothelial cells may lead to the development of endothelial dysfunction and thus microthrombi [7]. It appears unlikely that this is a major pathomechanism in the placenta. Signs of placental malperfusion are mainly non-specific phenomena and may not be directly related to viral infection. Moreover, “malperfusion” is a vaguely defined diagnosis, and minor perivillous fibrin depositions and small infarcts were probably also included in some of the studies.

Acute chorioamnionitis was relatively common in COVID-19 cases (26%). In non-COVID-19 placentas a frequency of 10–20% is to be expected [44,45]. Maternal hypoxia and systemic inflammation may possibly be factors that make the placental-amniotic fluid barrier more vulnerable for bacterial amnion fluid infection during COVID-19 disease.

Table 2
Noninflammatory placental changes in COVID-19.

Source	Too small placenta (n)	Too large placenta (n)	Maturation disorder (n)	Chorangiosis (n)	Malperfusion (n)	Infarction (n)	FTV (n)
Total (n/N, %)	87/585, 15%	61/495, 12%	94/674, 14%	84/878, 10%	208/1045, 20%	101/708, 14%	47/343, 14%
[22]	5	1	5	4	12	4	0
[23]	n.a.	n.a.	3	1	9	2	1
[24]	n.a.	n.a.	n.a.	0	14	n.a.	n.a.
[25]	n.a.	n.a.	10	8	n.a.	7	4
[26]	4	2	0	1	4	3	0
[27]	n.a.	n.a.	0	0	n.a.	7	36
[28]	7	3	10	3	4	4	n.a.
[29]	n.a.	n.a.	0	0	n.a.	5	1
[30]	14	0	3	6	10	1	n.a.
[31]	7	1	n.a.	0	25	20	n.a.
[41]	31	30	n.a.	n.a.	37	n.a.	n.a.
[32]	n.a.	n.a.	3	5	6	5	5
[33]	n.a.	n.a.	0	0	1	3	0
[34]	n.a.	n.a.	n.a.	7	n.a.	n.a.	n.a.
[35]	n.a.	n.a.	1	4	0	5	0
[36]	n.a.	n.a.	13	13	n.a.	15	0
[37]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
[38]	0	18	n.a.	5	6	8	n.a.
[39]	n.a.	n.a.	1	2	2	1	n.a.
[40]	0	1	17	19	1	n.a.	n.a.
[21]	n.a.	n.a.	n.a.	n.a.	15	n.a.	n.a.
[20]	6	5	n.a.	0	3	2	n.a.
[19]	n.a.	n.a.	9	n.a.	5	n.a.	n.a.
[18]	n.a.	n.a.	6	3	n.a.	2	n.a.
[17]	n.a.	n.a.	2	n.a.	n.a.	6	n.a.
[16]	n.a.	n.a.	n.a.	n.a.	8	n.a.	n.a.
[15]	n.a.	n.a.	1	1	18	1	n.a.
[14]	13	n.a.	n.a.	2	26	n.a.	n.a.
[13]	n.a.	n.a.	n.a.	n.a.	2	n.a.	n.a.
[12]	n.a.	n.a.	10	n.a.	n.a.	n.a.	n.a.

Abbreviation: fetal thrombotic vasculopathy/thrombangiitis obliterans (FTV); not specified (n.d.).

Table 3
Inflammatory placental lesions in COVID-19.

Source	Acute inflammation	VUE	CHI	MFD	CD	Meconium-laden macrophages
Total (n/N, %)	376/1430, 26%	187/1177, 16%	57/1096, 5%	13/924, 1%	152/1061, 14%	249/1011, 25%
[22]	1	2	0	0	2	0
[23]	2	3	0	0	0	7
[24]	3	5	0	0	0	0
[25]	26	2	0	0	0	0
[26]	8	1	1	2	1	4
[27]	48	17	0	2	0	24
[28]	27	2	0	0	0	9
[29]	2	1	0	0	0	8
[30]	2	5	0	0	4	0
[31]	19	19	3	0	0	16
[41]	69	34.	12	2	40	72
[32]	15	3	3	0	6	n.a.
[33]	0	0	11	1	0	0
[34]	3	n.a.	n.a.	n.a.	n.a.	3
[35]	9	0	0	0	3	n.a.
[36]	8	0	0	0	0	4
[37]	47	22	0	6	40	30
[38]	16	19	0	0	18	11
[39]	2	4	4	n.a.	n.a.	0
[40]	7	6	8	0	2	2
[21]	5	n.a.	n.a.	n.a.	23	n.a.
[20]	5	5	0	n.a.	7	n.a.
[19]	2	n.a.	n.a.	n.a.	n.a.	n.a.
[18]	7	1	4	0	0	n.a.
[17]	7	n.a.	3	n.a.	n.a.	n.a.
[16]	12	n.a.	n.a.	n.a.	n.a.	n.a.
[15]	4	6	2	n.a.	n.a.	16
[14]	10	19	n.a.	n.a.	n.a.	43
[13]	n.a.	1	[22##]	n.a.	n.a.	n.a.
[12]	10	10	6	n.a.	6	n.a.

Acute inflammatory lesions include acute chorioamnionitis and/or omphalovasculitis. Abbreviation: chronic deciduitis (CD); chronic histiocytic intervillositis (CHI); massive fibrous deposition (MFD); not specified (n.d.); villitis of unknown etiology (VUE); inclusion criterion in this publication was presence of CHI in the placenta and therefore this data was not included for the meta-analysis (##).

In general, adult lymphocyte and macrophage function may be altered in COVID-19 [1]. This could also constitute an immunological trigger during pregnancy that, in turn, may result in non-granulocytic inflammatory lesions in the placenta. VUE is not believed to be viral placentitis (which would typically involve plasma cell-rich villitis) but instead an immunologic response of the maternal immune system to the semi-allogeneic placenta, and expected to occur in ≤10% of placentas in non-COVID-19 cases [46,47]. In non-COVID-19 placentas, CHI, MFD and CD can be found in <10% of cases [46]. Therefore, the frequency of these lesions are mainly comparable between non-COVID-19 and COVID-19 pregnancies. The relatively frequent COVID-19-associated CD may correspond to local antibody production by decidual plasma cells. Co-infections of SARS-CoV-2 with other pathogens may occur, but this does not always result in increased mortality, and co-infections do not appear to be more common in pregnant women [48]. In general, CD is considered to be unspecific and not related to viral or bacterial inflammation [47] and in most COVID-19 cases CD does not manifest, indicating that is unlikely to be a typical anti-SARS-CoV-2 inflammation pattern.

In conclusion, there is no evidence of a typical COVID-19-associated pattern of placenta pathology; the placenta may show no gross pathology or inflammatory lesions, which occur with similar histopathologic features and frequencies in non-COVID-19 pregnancies. Symptomatic COVID-19 disease with maternal hypoxia during pregnancy is the major risk factor for miscarriage.

Declaration of competing interest

The authors declare no conflict of interest.

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