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Letter to the Editor

Stillbirths due to placental COVID infection associated with chronic histiocytic intervillositis do not recur in subsequent pregnancies

During the COVID-19 pandemic, when the SARS-CoV-2 B1.617.2 (Delta) variant was dominant, infected pregnant women had a 4-fold increased risk of stillbirth compared with non-infected women (2.70% vs. 0.63%).[1] The placenta in these stillbirths showed COVID placentitis, a combination of SARS-CoV-2 within the syncytiotrophoblast and a triad of histological features: chronic histiocytic intervillositis, trophoblast necrosis, and massive perivillous fibrin deposition. COVID placentitis only occurred in a minority of women who tested positive for SARS-CoV-2 in pregnancy (~1.5%).[2] Fetal deaths during the Delta wave usually occurred within days of a mild maternal infection, and the stillborn fetuses were appropriately-grown for gestational age (AGA).[3]

Chronic histiocytic intervillositis (CHI) has also been reported alongside other placental infections, including malaria, cytomegalovirus and listeriosis.[4] In these cases, massive infiltration of maternal CD68+ histiocytes leads to obliteration of the intervillous space, preventing the maternal-fetal exchange that is vital for fetal growth and survival. SARS-CoV-2 has emerged as the latest pathogen capable of causing CHI. Its global scale has thrown the importance of this histological finding and its potential catastrophic consequences into sharp relief.

CHI that occurs in the absence of SARS-CoV-2 resembles COVID placentitis histologically, but is a distinct and devastating disorder associated with recurrent pregnancy loss.[5] This form of CHI affects 1 in 2000 pregnancies and is diagnosed when > 5% of the intervillous space is occupied by maternal histiocytes, in the absence of infection.[6] It causes miscarriage, stillbirth and severe fetal growth restriction, and carries a high risk of recurrence (100% in severe cases). The etiology of non-infectious CHI is poorly understood, but its histological similarity to rejected solid organ allografts suggests an immunological mechanism.[7]

On this basis, over the last 30 years, women with CHI have been treated in subsequent pregnancies with a variety of immunosuppressive regimens. These have tempered recurrent inflammatory intervillositis and may improve pregnancy outcomes.[7,8]

It is uncertain whether CHI associated with SARS-CoV-2 (or other infections) recurs in the same way as the non-infectious form (immune-CHI). This is an important knowledge gap, as it is unclear whether women with a previous stillbirth due to COVID placentitis should be considered for immunosuppression in a future pregnancy. The aim of this study was to investigate the hypothesis that SARS-CoV-2-associated CHI (COVID-CHI) does not recur.

We identified women from our maternity services who had: (1) a stillbirth or late miscarriage due to histologically proven COVID-CHI; and (2) a completed subsequent pregnancy with placental histology available (primary cohort). Demographic, medical, obstetric and histological outcome data were collected. We then approached a larger group of women (validation cohort) by designing an online survey, which was disseminated in a social media support forum. Only women with a previous pregnancy loss due to COVID-CHI and a completed subsequent pregnancy (whatever the outcome) were eligible. The survey was completed anonymously, and no patient-identifiable data were collected. This work was approved by relevant research ethics committees (London: 19/LO/0105; Leiden: B21.034; Paris: CEROG 2021-OBST-0503). All participants in the primary cohort provided written informed consent for publication.

Five women with a previous stillbirth due to COVID-CHI underwent a subsequent pregnancy at our institutions. All five ended in live birth of an appropriately-grown infant with no recurrence of CHI. Comparative placental histology is shown in Fig. 1.

A further 14 women completed the survey, resulting in an overall cohort of 19 women. These 19 women had a total of 21 subsequent pregnancies, of which 19/21 (90%) ended in live birth and 16/21 (76%) had placental histology available. Table 1 compares outcomes of the index and subsequent pregnancies.

These results show that despite its histological similarities to immune-CHI, women who had a pregnancy loss due to COVID-CHI are not at risk of recurrent placental inflammation. The live birth rate was 90% in their subsequent pregnancies overall, and 100% in those that progressed beyond 16 weeks' gestation. Immunosuppression appears to be unnecessary following COVID-CHI, as most women went on to have a live birth and normal placental histology without immunomodulatory treatment.

We confirm an earlier observation that the stillborn fetus affected by COVID-CHI is AGA (median 35th centile in our cohort).[3] Although the COVID-CHI stillborn fetuses were smaller than their future unaffected siblings, an AGA stillborn suggests an acute pathology, as opposed to the severe fetal growth restriction associated with (recurrent) immune-CHI.[4]

It is interesting to speculate why the Delta variant proved more pathogenic to the placenta compared with the Alpha and Omicron variants. Possible mechanisms include higher levels of maternal viremia and enhanced cleavage of its S protein by furin, a serine protease that is highly expressed on the syncytiotrophoblast. Furin-mediated cleavage of the S protein facilitates viral entry into host cells via binding to the angiotensin-converting enzyme-2 (ACE2) receptor.[9]

Since the Delta variant was superseded by Omicron, there have been no known cases of placental infection. However, SARS-CoV-2 continues to circulate and future variants could also lead to CHI.

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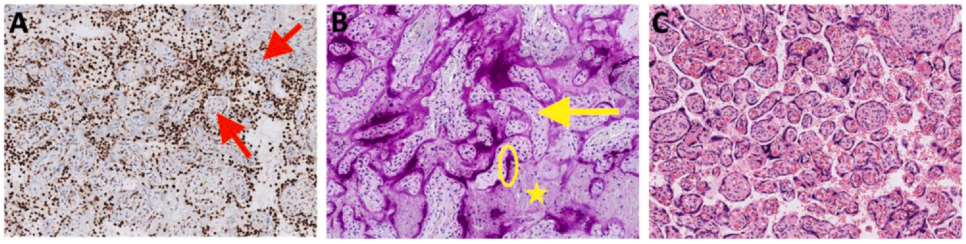

Fig. 1. Stillbirth due to COVID placentitis (Panels A and B), compared to subsequent healthy placenta (Panel C). *Panel A:* Placental chronic histiocytic intervillositis in a COVID-associated stillbirth. Red arrows indicate placental villi. Immunohistochemistry shows widespread infiltration of CD68+ maternal histiocytes (brown) in the intervillous space; X10. *Panel B:* Positive immunohistochemical staining for SARS-CoV-2 nucleocapsid protein (magenta; circled) on the syncytiotrophoblast of the same placenta as Panel A. Yellow star indicates chronic active infiltrate and necrosis in the intervillous space. Yellow arrow indicates villi with degenerative changes due to necrosis; X10. *Panel C*: Normal placental histology (hematoxylin & eosin) in the subsequent pregnancy, which ended in uncomplicated term live birth. Healthy maternal red blood cells are evident in the intervillous space; X10.

Table 1
Maternal demographics, medication use, obstetric and perinatal outcomes for 19 women who had an index pregnancy ending in fetal death due to COVID-CHI (n = 19), followed by one or more completed subsequent pregnancies (n = 21). Birthweight centiles were calculated using the INTERGROWTH-21st birthweight centile calculator. P-values were calculated with the Mann-Whitney U test (given non-normal distribution of pregnancy outcome data) using GraphPad Prism.

Maternal demographics			
Total		19	
Age (years); median (IQR)		31 (29-34)	
SARS-CoV-2 vaccination status prior to index COVID-CHI pregnancy			
Vaccinated (≥1 dose)		4 (21%)	
Unvaccinated		11 (58%)	
Unknown		4 (21%)	
Medication use			
	Index pregnancy affected by COVID-CHI (n=19)	**Subsequent pregnancy (n=21)**	
No medication	17 (89%)	6 (29%)	
Low-dose aspirin and/or prophylactic low-molecular weight heparin only*	2 (11%)	11 (52%)	
Hydroxychloroquine and/or prednisolone†	0	4 (19%)	
Obstetric outcomes			
Early miscarriage (<14 weeks)	0	1 (5%)	
Late miscarriage (14+0 to 23+6)	5 (26%)	1 (5%)	
Stillbirth (≥24 weeks)	14 (74%)	0	
Total live birth	0	19 (90%)	
Perinatal outcomes			P-value
Gestational age at death/delivery (weeks); median (IQR)	29.7 (24.3-31.4)	37.7 (36.6-39.0)	<0.0001
Birthweight (grams); median (IQR)	912 (561-1595)	3161 (2775-3658)	<0.0001
Birthweight centile; median (IQR)	34.6 (26.3-61.5)	67.4 (39.2-90.9)	0.030
Placental outcomes in subsequent pregnancy			
Recurrence of CHI	0		
Normal histology	14 (66.7%)		
Other pathology‡	2 (9.5%)		
Not performed	5 (23.8%)		

* Low-dose aspirin (LDA): 75-160 mg daily. Prophylactic low-molecular-weight heparin (LMWH): variable formulations, e.g. enoxaparin 40 mg once daily.
† All four patients who were treated with hydroxychloroquine and/or prednisolone in their subsequent pregnancy also received LDA and prophylactic LMWH.
‡ Two patients had another pathology (non-CHI) detected in their subsequent placenta. One showed focal ischemia due to mild maternal vascular malperfusion associated with preeclampsia; the other showed distal villous immaturity associated with a large-for-gestational-age placenta.

Vaccination reduces the risk of COVID-associated stillbirth and should therefore remain a strong recommendation for all pregnant women, especially those with a previous loss due to COVID-CHI.[10]

This study has several limitations: small numbers, self-reporting of outcomes in the validation cohort, and incomplete placental histology data for subsequent pregnancies. Quantifying recurrence of placental disorders is dependent on specimens from subsequent pregnancies being submitted for analysis (irrespective of outcome) and examined by an expert perinatal pathologist. Given the rarity of COVID-CHI, the patient cohort described here is a particularly hard-to-reach group. However, women who have experienced pregnancy loss due to COVID-CHI are themselves highly motivated to address the uncertainties about the implications of this diagnosis, as demonstrated by the dedicated online support group that has over 180 members.

Our study provides reassurance that women who have had a pregnancy loss due to COVID-CHI can expect a normal future pregnancy outcome. These observations are likely to also apply to other infections associated with CHI, but this remains to be confirmed. Unlike recurrent immune-CHI, women with previous COVID-CHI are not at risk of recurrent placental inflammation and immunosuppression is not required.

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Declaration of Competing Interest

None.

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