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Short communication

Third trimester stillbirth during the first wave of the SARS-CoV-2 pandemic: Similar rates with increase in placental vasculopathic pathology

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ABSTRACT

Whether early SARS-CoV-2 definitively increases the risk of stillbirth is unknown, though studies have suggested possible trends of stillbirth increase during the pandemic. This study of third trimester stillbirth does not identify an increase in rates during the first wave of the pandemic period, however investigation of the placental pathology demonstrates trends towards more vascular placental abnormalities.

1. Introduction

Whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection increases the risk of stillbirth remains under investigation, with early contradictory data from global publications. Fetal death in the third trimester (28 weeks or greater) is a rare outcome affecting fewer than 1 in 340 deliveries in the United States (US), yet has been reported in women with symptomatic, laboratory-confirmed coronavirus disease 2019 (COVID-19) [1]. Infection is one potential fetal stressor, thus it is reasonable to consider that third trimester stillbirth rates may increase during a pandemic. The United Kingdom (UK) Obstetric Surveillance System reported 3 stillbirths among 247 deliveries in women with confirmed COVID-19 (12.1 per 1000 births vs national rate of 4–5 per 1000 births), although whether SARS-CoV-2 contributed to fetal death was unclear [2]. A study by Khalil et al. found a significantly increased rate of stillbirth during the coronavirus pandemic compared to the pre-pandemic period (9.31 per 1000 births vs 2.38 per 1000 births), however there were no cases of stillbirth among women with symptoms suggestive of COVID-19 or postmortem or placental pathology suggestive of SARS-CoV-2 [3]. Another UK study showed no evidence of any increase in stillbirths regionally or nationally during the COVID-19 pandemic [4]. A US study (Handley et al., 2020) noted a similar lack of increase at two major Philadelphia Hospitals [5].

None of these studies have looked specifically at fetal or placental factors that may have changed during the pandemic period. A thorough stillbirth evaluation can reveal evidence of placental insults that may have caused or contributed to fetal death. Some of the more commonly identified insults in stillbirth include maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM) [6,7]. Maternal vascular malperfusion refers to gross and microscopic findings of pathologic maternal perfusion of the placenta leading often to placental hypoplasia, officially defined as placental weight <10th percentile, a thin umbilical cord, and other findings (i.e. decidual ateriopathy, placental infarcts, increased perivillous fibrin, accelerated villous maturation, distal villous hypoplasia, and/or placental aburption). Fetal vascular malperfusion can include thrombosis and avascular villi, as well as other pathologies including vascular intramural fibrin deposition, stem vessel obliteration, or villous stromal-vascular karyorrhexis [8,9]. Multiple studies have shown COVID-19 affects the placenta, including increased rates of decidual arteriopathy and other features of MVM [10] and increased findings of FVM [14,15]. These vascular insults can occur at any point during pregnancy, or, in some cases, can occur due to an insult at the time of fetal death (e.g. in the setting of abruption). There is placental pathology that has been suggested to be relatively specific for SARS-CoV-2 placental infection assocaited with vertical transmission–histiocytic intervillositis, perivillous fibrin deposition, and trophoblast necrosis [16].

We sought to assess whether the first surge of early COVID-19 in the Northeast of the US was associated with an increased risk of stillbirth in three major Boston-area hospitals and to examine causes of fetal death to

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explore the potential role of COVID-19 on placental pathology.

2. Methods

We compared third trimester stillbirth rates (28 weeks or greater) during the first wave of the COVID-19 pandemic (February 2020 to July 2020) to those in equivalent time periods in 2019 and 2018. While there is no described seasonality to stillbirth at our institutions, we chose to use equivalent time periods in the two years prior to minimize potential unmeasured confounders between the compared groups. We included the 3 largest delivery volume hospitals within our hospital system, all with level 3/4 NICUs (2 large academic teaching hospitals and 1 community-based hospital). Known predictors of stillbirth, such as history of hypertension, autoimmune disease or thrombophilia were abstracted from the medical record (Table 1). Causes of fetal death were obtained from review of pathology reports (Table 2). Detailed placental pathology findings are also described in Table 2. A combination of chi-square and Fisher's exact were used for between group comparisons.

3. Results & discussion

The rates of stillbirth in our cohort of approximately 6000 births each year per 5-month period between February 1 to July 1 were similar across the three time periods (0.188%, 0.187, 0.150 in 2020, 2019, 2018 respectively) (Table 1). This rate was stable and similar to prior reports [1].

None of the early pandemic stillbirths were documented to have vertical transmission of SARS-CoV-2. Two-thirds (8/12) of the late term 2020 stillbirths had maternal testing for COVID 19. Two patients were either proven to be or presumed to be COVID-19 positive and neither showed the pathologic findings reported by Schwartz et al to be the pathological footprint of SARS-CoV-2 placentits, however they both showed vasculopathic findings of MVM. The first patient was a 19 year-old gravida 1 who presented to triage with vaginal bleeding and loss of fluid at 35 weeks gestational age and tested positive for COVID-19 on admission. She was diagnosed with an intrauterine fetal demise (IUFD) and developed disseminated intravascular coagulation. The fetus was normal appearing by external examination. Her placenta was noted to be small (less than the 10% percentile for gestational age) with pathologic findings characteristic of MVM. SARS-CoV-2 immunohistochemistry for the Nucleocapsid protein was negative in the placental parenchyma in this case [17]. The second patient was a 24 year-old gravida 1 diagnosed with an IUFD at 37 weeks gestational age in the setting of pre-eclampsia with severe features by blood pressure and known intrauterine growth restriction to the 3rd percentile. COVID PCR testing had revealed a positive result by nasal PCR 6 weeks prior to the stillbirth diagnosis with admission PCR test negative. The fetus was normal appearing by external examination. The placenta was notable for being less than the 10th percentile by weight, having marginal cord insertion and with placental findings consistent with an acute abruption, a feature of MVM. SARS-CoV-2 immunohistochemistry for the Nucleocapsid protein was also negative in the placental parenchyma and membranes in this case. (Schaefer et al., 2020).

We found no difference in the proportions of stillbirths across the majority of the maternal demographic characteristics that we examined. There was a significant difference in gestational age between groups with stillbirths in 2018 being diagnosed at the latest gestational age with similar gestational ages at diagnosis between 2019 and 2020 (Table 2).

Table 1
BASIC DEMOGRAPHICS
Data are n (%) unless otherwise specified. P
-value from Fischer's exact (continuous) or chi-square (categorical).

	2020	2019	2018	p-value
Stillbirths >28wk/Total births	12/6406 (0.187)	12 (0.188)	9 (0.148)	.84
Maternal				
Maternal age, range (mean)	20-40 (30.5)	26-40 (35.4)	23-38 (32.7)	.13
Race				.62
White	8 (72)	8 (67)	7 (78)	
Black/African-American	2	1	2	
Asian	1	2	0	
Other	0	1	0	
Non-Hispanic ethnicity	7	11	7	.33
Multiparity	7 (64)	7 (58)	6 (67)	
Stillbirth/preterm history	0	0	0	
Hypertensive history	0	1	1	
Hypertension at delivery	6 (50)	2 (17)	3 (33)	
BMI (pre-preg) range (mean)	24-36 (30.1)	20-56 (31.7)	17-39 (28.1)	.60
Gestational diabetes	1 (9)	1 (8)	2 (22)	
Known IUGR	2	3	3	
Confirmed COVID positive (nasal PCR)	2	n/a	n/a	
GA at stillbirth, range (mean)	28.0–39.4 (32.4)	28.4–39.0 (33.4)	30.4–41.0 (37.4)	0.01
Fetal				
Aneuploidy screening	9 (82)	9 (82)	9 (100)	
Chromosomal anomaly	1	1 (8)	1 (11)	
Nuchal translucency (mm)	0.7–4.5	1.1–2.4	2.0–3.1	
Birth weight (g)	852–4170	415–2778	1410–4240	
Small for gestational age				
Sex (male)	8 (67)	5 (42)	6 (67)	

Tabel 2
Cause of death & placental pathology.

	2020 (12)	2019 (12)	2018 (9)
Autopsy performed	6	7	7
Cause of Death[a]			
FVM[b]	3	2	0
MVM[c]	2	0	0
TTTS (pair)[d]	2	0	0
Cytomegalovirus infection	0	1	0
Acute chorioamnionitis	0	1	1
Meconium aspiration	0	1	1
Cord obstruction	0	0	1
Cord rupture	0	0	1
Acute abruption	1	0	1
Chronic abruption	1	1	0
Gastroschisis	0	0	1
Autosomal trisomies	0	1	1
Chronic vilitis	1	1	0
Unknown/Undetermined	2	4	2
Placental Pathology (performed in all cases)			
MVM[c]	5	2	5
FVM[b]	5	5	0
VUE (HG)[e]	1	1	0
Cytomegalovirus placentitits	0	2	0
Meconium aspiration	0	0	0
Acute chorioamnionitis	0	1	0
Hypo-coiled cord	0	0	2
Umbilical cord rupture	0	0	1
Histiocytic intervillositis	0	0	0
Massive perivillous fibrin deposition	0	0	0
Trophoblast necrosis	0	0	0
Normal	0	0	1

[a] Cause of death determined by gross pathologic exam and/or autopsy.
[b] FVM: Fetal vascular malperfusion, any grade.
[c] MVM: Maternal vascular malperfusion, defined as 2 or more features from: placental hypoplasia, accelerated villous maturation, distal villous hypoplasia, decidual arteriopathy, placental infarcts, or increased perivillous fibrin.
[d] TTTS: Twin-twin transfusion syndrome.
[e] VUE-HG: Villitis of unknown etiology- high grade.

On review of placental pathology, we identified a trend toward an increase in vasculopathic pathology with 11 of 12 placentas affected by either MVM or FVM in 2020, 9 of 12 in 2019 and 5 of 9 in 2018 (Table 2).

COVID-19 is known to result in hypoxic events with described vascular insults to the placenta, though whether these insults are correlative versus causative cannot be proven with the limited data currently available . Furthermore, the vascular insults that are described to occur in the setting of COVID-19 infection, are insults that may not lead directly to fetal death, but could cause micro insults to the placenta throughout fetal development leading to an increased risk of stillbirth and adverse pregnancy outcome in later gestation. For this reason, and others related to the potential severity of COVID-19 infection in pregnancy, some are recommending increased antenatal surveillance [10].

This study includes an examination of over 18,000 pregnancies across three years at three hospitals, demonstrating no change in the rates of third trimester stillbirth during the first five months of the COVID-19 pandemic. Our study results are similar to those published by Handley et al. (2020), showing no change in stillbirth rates or phenotypes in an urban US hospital system during the early pandemic period [5]. We add an examination of primary placental pathology during this time, which shows that rates of fetal and maternal vascular malperfusion trended toward an increase during the early pandemic period. These increased rates of abnormal placental perfusion suggest that the effects of COVID-19 on the rates of stillbirth may go unrecognized without placental pathologic examination. Small vascular insults occurring throughout pregnancy may not accumulate until later in gestation [11].

Our study limitations include a narrow population within a single health system in a large urban environment with small numbers of late term stillbirth. We are also unable to identify an association between stillbirth, placental pathology, and COVID-19 illness as the majority of our late term stillbirths were not known to be associated with maternal SARS-CoV-2 infection. The first two months of data were collected at a time when COVID-19 testing was not readily available and was restricted to patients with symptomatic COVID-19 illness.

Universal testing of asymptomatic patients on labor and delivery was initiated in mid-April. Given the limited availability of PCR testing, the relatively short time course of PCR positivity during and after infection, and the lack of routine use of COVID-19 serologies, we are unable to know if any of the women who experienced stillbirth during the pandemic were infected with SARS CoV-2 at some earlier point in their pregnancy. However given the high rate of community spread during this time period and the high prevalence of asymptomatic disease, COVID-19 may have been a contributor to the observed pathology [12, 13].

Further research is needed to establish a causative link between COVID-19 and the observed placental pathologies, as well as to understand the effect of COVID-19 and these placental insults on stillbirth and other adverse pregnancy outcomes.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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