



A Comprehensive Analysis of Maternal and Newborn Disease and Related Control for COVID-19

Nevio Cimolai^{1,2}

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Abstract

The maternal-fetal/newborn unit is established at risk for COVID-19 infection. This narrative review summarizes the contemporary and cumulative publications which detail maternal infection, antenatal and newborn infections, and maternal/fetal/newborn management and prevention. There is a wide spectrum of maternal disease, but the potential for severe disease albeit in a minority is confirmed. COVID-19 carries risk for preterm delivery. Pregnant females can suffer multisystem disease, and co-morbidities play a significant role in risk. Congenital infection has been supported by several anecdotal reports, but strong confirmatory data are few. No typical congenital dysmorphisms are evident. Nevertheless, placental vascular compromise must be considered a risk for the fetus during advanced maternal infections. Clinical manifestations of newborn infection have been mild to moderate and relatively uncommon. Proven antiviral therapy is of yet lacking. The mode of delivery is a medical decision that must include patient risk assessment and patient directives. Both presymptomatic and asymptomatic mothers and offspring can complicate infection control management with the potential for spread to others in several regards. In the interim, infections of the maternal-fetal-newborn unit must be taken seriously both for the disease so caused and the potential for further dissemination of disease.

Keywords COVID-19, · Coronavirus, · Maternal, · Fetus, · Newborn, · Pregnancy

Introduction

The maternal-fetal/newborn unit has not been spared from pandemic COVID-19 infection [1, 2]. What was debatable very early on was the possibility that maternal-fetal transmission could occur and the magnitude of disease among both mother and infant [3]. Considerable experience has emerged and has provided sufficient data that may be used to better understand the epidemiology, disease course, and prevention for maternal-newborn care.

There are four key considerations that set the foundation for this review. These are based on the understanding of both the basic science and the clinical parameters of SARS-CoV-2 infections. The first of these is that maternal infection does

occur as would be anticipated, but the clinical presentation is considerably variable. Secondly, newborns do acquire infection early and late postnatally, and the fetus can be impacted by maternal illness regardless of whether antenatal infection does or does not occur. Third, prevention and control management strategies for the pregnant female are therefore required. Lastly, prevention and control management strategies are also needed for the fetus and newborn. It is these four broad topics of review which set the stage for other aspects of supportive treatment, prevention, and necessary follow-up.

This narrative review was accumulated after thorough review of related publications as abstracted in PubMed, EMBASE, CINAHL Plus, and the Cochrane Library. The compendium of material was current to the end of December, 2020.

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✉ Nevio Cimolai
ncimolai@mail.ubc.ca

¹ Faculty of Medicine, The University of British Columbia, Vancouver, Canada

² Children's and Women's Health Centre of British Columbia, 4480 Oak Street, Vancouver, B.C. V6H3V4, Canada

Maternal Infection with SARS-CoV-2

Nature of Disease

Clinical characteristics and associated morbidity and mortality from SARS-CoV-2 infections generally have been aptly

characterized in many reports to this point [4, 5]. The presenting illness is mainly one of the upper and/or lower respiratory tracts. Patients may less commonly progress to an advanced pulmonary crisis which requires intensive care and oxygenation. Most systemic facets of disease are largely ascribed to severe complications arising from a cascade of pathological and immunological events in the lung [6]. Age and comorbidities factor as risks for accentuated illnesses. Demographic variables otherwise may also predict risk for infections in pregnancy specifically [7].

COVID-19 infection does not seem to be acquired among pregnant patients any more than the general population [8]. Infection however does not spare any trimester of gestation [9–14]. Some reports suggested that COVID-19 in pregnancy is analogous to the disease experienced in the general population [1, 4, 15–17]. From Denmark, a cohort study did not find ultrasound evidence of fetal compromise during first trimester infections nor increased pregnancy loss [18]. The latter was supported by comparative studies in which infected pregnant patients were compared to either non-infected pregnancies, non-pregnant infected females in the community, or patients with alternative virus infections [19–24]. In this context, the study of Wei et al. stands out in that both pregnant and non-pregnant controls equally had a high rate of influenza virus co-detection [17]. Nayak et al. did not find a difference for maternal complications between infected and non-infected pregnancies [21]. The latter was also found in an Iranian population, but more COVID-19-infected pregnancies required intensive care [25]. In the study of Cheng et al., pregnancies with COVID-19 were said to have less severe disease than non-pregnant patients, but the control group was significantly older for age [19]. Evidently, the pre-selection of the patient population for testing influences the likelihood of severe disease [26]. In the latter study, all incoming pregnancies in a California setting were offered screening despite being asymptomatic, and the SARS-CoV-2 positive frequency was 0.43% during April–May, 2020. Collin et al. thereafter provided data which suggested that infected women, either pregnant or postpartum, were more likely to have a complicated course compared to non-pregnant females of equivalent age [27]. The diversity of infection in pregnancy and the magnitude of potential complications have now become more apparent [2, 9–11, 14, 28–44]. It is of interest to see how COVID-19 disease in pregnancy parallels that which was formerly experienced in the SARS era [45]. Symptoms may last for up to 1–2 months in the extremes of resolution [9].

Concerns over disease potential for mother and fetus led some to consider pregnancy termination in the first and second trimesters when the knowledge base for COVID-19 was rudimentary [22, 23, 43, 46]. Gastrointestinal illness occurs in a minority of pregnancies [3, 47]. The latter is common however in other COVID-19-infected populations [48]. Although causation may be multifactorial and complex, pre-eclampsia and eclampsia

were complicated by COVID-19 infection [38, 49–59]. In contrast, Gulersen et al. found a near equal frequency of pre-eclampsia between infected and controls, and Adhikari et al. did not find that pre-eclampsia was associated with infection [60, 61]. Another similar citation distinguished the putative presentation of pre-eclampsia and HELLP syndrome [62]. Coagulopathy has been highlighted as a complication of special concern in COVID-19 generally and as in pregnancy otherwise [63]. Blood dyscrasias from COVID-19 must be differentiated nonetheless from chronic illness that occurs in pregnancy for other reasons [64]. Healthcare workers are among those with infected pregnancies [65]. In one study, up to 13% of infections occurred for mothers with gestations <13 weeks [43]. In the US, ~5–9% of women with COVID-19 were identified to be pregnant [33, 44]. Tug et al. found more severe illness among pregnancies after 20 weeks gestational age [42].

Severe respiratory disease requiring extra-ordinary treatment or monitoring is consistently described [2, 10, 13, 14, 19, 28, 30–33, 39–41, 43, 44, 46, 47, 59, 61, 66–91]. Cardiac disease may accompany the latter [92]. The frequencies of severe illness have been variably inclusive of 3–25% of the infected mothers, but these numbers are influenced by the variation that is inherent for admitting patients to hospitals or in the classification of disease severity at presentation or thereafter. A study from Spain found that nearly 50% of patients with pneumonia subsequently suffered what would have been classified as severe disease [86]. Regardless, however, COVID-19 can be directly implicated as a cause of maternal demise [4, 12, 21, 30, 32–34, 39–41, 44, 47, 68, 72, 76, 80, 88, 93–98]. In Brazil, most such maternal deaths were occurring in the postpartum period [96]. Others have found similar timing [3]. Rios-Silva et al. did not find a difference for maternal demise among COVID-19 infections and controls [4]. Despite the latter, asymptomatic presenting infections are common [2, 41, 43]. Cosma et al. found that disease in very early pregnancy is likely to be relatively mild [11]. Disease progression and duration of symptoms did not apparently depend on the trimester of infection [14]. Generalizing, more severe illness tends to be found among maternal populations of lower socioeconomic status, but there is nevertheless great variation.

Obstetrical complications associate with infection generally [99]. Some complications may depend on the nature of the symptomatic and asymptomatic state [56]. Preterm delivery is relatively common, but the frequency has been considerably influenced by concerns for the pregnancy and hence by iatrogenic intervention [2, 13, 23, 29–31, 34, 35, 37, 39–42, 46, 55, 56, 59–61, 66, 68, 77, 83, 90, 94, 95, 101–110]. Overall, the preterm delivery rate generally approaches 14–37%, but the frequency is as high as 75% when the maternal illness is severe. The study of Andrikopoulou et al. posed an exception to this with a preterm rate of just over 1% [28]. Others have not found an association of preterm birth and infection [61]. Gulersen and colleagues determined that the preterm birth rate during hospital stay was lower among those pregnancies

where mothers were first diagnosed with COVID-19 during earlier preterm periods [101]. They also found that the majority of early preterm infections fared well and were eventually able to return to their homes. The latter findings were also duplicated by Cosma et al. [11]. Barbero et al. found no difference in preterm delivery whether patients were admitted to hospital or not [29]. As well, some have recorded a high rate of preterm labour [3]. Although premature rupture of membranes has been cited for some, it is not clear at this time that SARS-CoV-2 infection is a cause [110–114]. Co-morbidities among pregnant patients with COVID-19 infection are common [115]. Co-morbidities are very common, however, in those with more aggressive illnesses, and these have especially included obesity and diabetes [1, 2, 12, 14, 19, 28, 30, 31, 33, 34, 38–40, 42, 68, 79–81, 88, 89, 94, 96, 105, 110, 116]. The anticipation of potential complications or the advanced nature of disease has led to a high rate of Caesarean section [1–3, 10, 21–23, 25, 29–32, 35, 38–42, 51, 55, 56, 59, 60, 68, 74–77, 82, 87, 94, 101, 105, 107, 109–115, 117–129]. The frequencies of the latter have ranged 20–100%. These frequencies are very much geographically influenced by the pattern of medical practice, and the rates have proportionately decreased over time as familiarity with disease potential in pregnant women has emerged. Not all such surgical deliveries however were directly attributable to COVID-19. Some Caesarean sections were prompted by various maternal complications. Barbero and colleagues found a higher rate among patients admitted to hospital initially [29]. They also found increased rates of Caesarean sections and preterm birth compared to uninfected pregnancies. One large study of neonatal outcomes did not find a difference in section rates for infected and non-infected pregnancies [61]. The latter is a reminder that outcomes can be population specific, have multiple covariates, and may be affected by the time course over the duration of the pandemic.

We are reminded that routine vaginal deliveries are nevertheless often successful [130]. The burden of evidence however must be taken to impress the medical and lay communities that disease in pregnancy is sufficiently severe for some such that prevention is clearly desirable. This is especially true when it has been realized that antiviral therapies of variable choice have not been associated with improvements in outcome in this context [1]. The potential for an effective antiviral nevertheless has promise and continues to be studied widely. Apart from tissue pathology, several have also alerted the medical community to the psychological consequences of infection in pregnancy [70, 131–134].

Diagnostic Dilemmata

Diagnosis of maternal infection has depended largely on genetic amplification technologies which identify the presence of viral RNA in a clinical sample. Although technologically

reproducible and widely available, detection of viral RNA does not necessarily equate to the presence of infectious virus, perhaps as would the detection of virus by culture. As disease progresses, it is much easier to detect viral RNA even if the virus presence is non-infectious. Some have proposed a correlation of viral quantitation with measured viral RNA load, but diagnostic assays may have variable determinations for positive tests depending on the details of assay performance [135]. Thresholds for the determination of positive genetic amplifications are also variably applied. The result of a molecular diagnostic test is only as good as the quality of the specimen submitted. Variation may also occur depending on the site of acquisition, and such variations may be seen when the samples are from different respiratory tract sites. From a confirmatory perspective, research studies can utilize sequencing of amplified products or secondary confirmatory amplification tests to validate initial findings. Another such approach is to re-perform genetic amplification with a different set of virus targets. Commercial diagnostic assays for viral RNA are usually supported by studies which produce validation data using common samples such as those of the respiratory tract. Although liberally used to assess for viral RNA in many other body fluids or swabs, standardization for non-respiratory sampling is often lacking. Bertino et al. illustrate the use of control genome template in the context of testing breast milk samples [136]. Thus, although positive results may have secondary confirmatory tests to garner credibility, the specificity of negative results may be less certain if the samples are non-respiratory ones. Further research is yet required to resolve this issue definitively. One must also consider that some patient series have included both laboratory-confirmed and clinically suspect patients [3, 117].

Given the potential for diagnostic respiratory or other specimens to be collected either overly early or late, there is also the potential to miss a positive diagnosis based on viral RNA amplification or culture [137]. There is thus a potential role for serodiagnostic assays to provide support for viral infections retrospectively [117, 138–141]. Serodiagnosis can be complementary to other methods or can be used alone as the circumstances require. For the determination of fetal infection, a time-honored approach could be the determination of IgM-virus specific antibody in newborn immediately in the post-natal period [52]. IgG-based serology for the newborn may be difficult to use since maternal IgG is capable of nonspecifically crossing the placenta for much of late pregnancy [73, 117, 142–145]. Confirmatory or immunoblotting techniques would be useful to validate the likelihood of positive serodiagnoses in the research context at least. Zeng et al. found two newborns with anti-SARS-CoV-2 IgM and raised concern for vertical transmission [140]. There were no confirmatory tests, and the offspring were not reportedly ill. Dong et al. also found a newborn with serum IgM reactivity, but no illness arose and again there were no confirmatory assays [138].

Wu et al. found two newborns with reactive IgM and IgG; one had serology taken on day 1 post-birth when an active infection was evident, but the other had serology taken late on day 28 and was ill much earlier [116]. Correia and colleagues showed that IgG and IgM in a newborn followed shortly (15 days) after the onset of a late term congenital infection [52]. Similar findings were also noted after another putative vertical transmission [146]. During the first trimester infections, maternal SARS-CoV-2 antibody was found among some women but not consistently so [18]. Edlow et al. provided findings of cord bloods harboring IgG antibodies to both the viral receptor binding domain and nucleocapsid for a small majority [73]. As for other virus infections, a one-size fits all laboratory approach to maternal-fetal diagnosis is not always possible [147].

Foci of Virus Excretion

Excretion of infectious virus from the respiratory tract is well-established in SARS-CoV-2 infections. The pattern is similar to that previously known for SARS-CoV and MERS-CoV and represents an obvious route to infect the newborn from an ill mother whether from aerosols or direct contact contamination. What is not as well understood is the potential for other routes of infection. SARS-CoV-2 RNA has been found in blood, urine, stool, and vagina, but it was not consistently clear if these routes could carry infectious virus that could be an infectious risk [41, 148–158]. Anecdotes of live virus isolation from stool have been cited, and thus enteric contamination of the vagina and newborn is plausible [154, 159, 160]. Some have found a correlation of viral RNA quantitation in blood with the severity of clinical disease, and hence the potential for bloodborne direction to the placental interface must be accepted [150].

Precedence for coronavirus presence in the vagina was published by Gagneur et al. [161]. In the context of assessing pregnancies for coronaviruses generally, endemic respiratory human coronavirus 229E was found in vaginal samples with genetic amplification. Some of these mothers were also found to have 229E in respiratory samples. SARS-CoV-2 had not been found among serum, urine, or vaginal samples from pregnant women with genetic amplification from some reports albeit the numbers assessed were small [41, 52, 90, 95, 162–169]. Edlow et al. however did not find maternal viremia in a larger infected cohort [73]. That the virus could possibly exist in these sites would not be surprising among some infected females knowing that live virus can be present in the bowel and rarely in urine and given the experience had with other coronaviruses and enteric excretion [48, 152, 170]. Furthermore, the finding of coronaviruses in the female genital tract might also be ascribed to direct contamination from skin and hands. Thus, there is ample opportunity for infection to be spread to a newborn from a maternal source. Of note,

however, Qiu et al. did not find SARS-CoV-2 in vaginal samples from infected postmenopausal women despite the presence of severe illness [171]. Carosso et al. provided evidence that a newborn could transiently acquire the virus (viral RNA) at the time of birth via the maternal intestinal source [142]. Spread from healthcare workers and the immediate patient environment must also be considered [172, 173]. The finding of viral RNA in vagina, placenta, and fetal and newborn surfaces must also be guarded as an indication of infection if actively infected mothers maintain such viral RNA in their blood which could contaminate the latter specimens. Tainting of a newborn with maternal blood would not be uncommon. Likewise, viral RNA in maternal urine could also complicate the validity of samples that could be tainted from that source.

Epidemiological Parameters

The epidemiology of spread for coronaviruses has been studied considerably [172]. In addition, SARS-CoV-2-specific epidemiology is rapidly becoming exposed. For pregnancies as in the general population, sentinel points of SARS-CoV-2 contact are often unknown [1, 26]. The development of asymptomatic infections in pregnancy is now appreciated [1, 2, 15, 26, 30, 32, 37, 39, 41, 56, 61, 71, 73, 75, 77, 81, 104, 114, 118, 119, 123, 127, 173–178]. Screening for temperature on admission to healthcare settings far from guarantees that an infected mother will be detected [26, 175, 177]. The latter provides unknown risk for spread to newborns, family, healthcare workers, and others. The latter also provides concerns for extending environmental burdens of the virus in healthcare facilities. Presymptomatic transmission is inevitable therefore for those that eventually do develop symptoms or signs of infection [172]. For patients generally, Jing et al. have suggested that presymptomatic patients may be responsible for secondary infectivity equal to or more than symptomatic patients [179]. What is not clear is whether pregnancy allows virus to be shed for longer periods of time compared to the general previously-well population when they become infected. Molina et al. offer one example where viral RNA shedding from the respiratory tract could be found for over 100 days from an initial positive test [180]. Although live virus shedding typically occurs for less than one week for most infections, outliers to the latter are likely to extend to over 2 weeks albeit uncommon [181]. There is little reason to believe that the latter should be any different for pregnant patients. Among patients with SARS, urinary and enteric excretion of virus past two weeks were established [182–184]. From yet another perspective, viral genome can be found in the blood of patients especially with correlates to severe disease and outcome [185]. Conceivably if any such represents the corporal dissemination of live virus, it would be credible that infectious virus should reach the placenta on the maternal side and place itself

to position for transplacental crossing as a breach in the physical barrier would allow. SARS-CoV-2 specific data, to include studies that observe infectivity and measure live virus, continue to be desirable for pregnant and infected patients [181, 186].

Antenatal or Neonatal Infection with SARS-CoV-2

The Search for Intrauterine Infection

The potential for small viruses to penetrate the placental barrier from the maternal bloodstream poses some initial theoretical concern for SARS-CoV-2 antenatal infection. Studies which have searched for such infections are now emerging although relatively few have been highly detailed in their diagnostic assessments. Some studies have found no viral RNA in amniotic fluid, cord blood, newborn blood or cerebrospinal fluid, meconium, and placental tissue [3, 41, 59, 73, 79, 82, 90, 111, 112, 121, 126, 142, 149, 162–166, 176, 180, 187–197]. Fetal samples taken at autopsy also proved negative in a few assessments [79, 187]. There is no consistent teratogenic effect observable among offspring of infected mothers [198]. Antenatal infections of major consequence in other virus systems would typically occur well before birth and are generally more worrisome for the first and second trimesters. Stillbirth could not be directly attributed to fetal COVID-19 infection for most studies [2, 13, 50, 55, 76, 79, 125]. Others have found fetal demise for seven citations ranging from 20 to 37 weeks gestational age, but fetal sampling did not have evidence of viral RNA [37]. One large American cohort study found a frequency of 2.2% for infection-related pregnancy loss [71]. Another American cohort study found that infected mothers had three times the incidence of stillbirth compared to controls [81]. Some fetal deaths are likely to be directly attributable to the consequences of severe maternal infection [12, 31]. A large multinational prospective cohort review found that neonatal deaths were prematurity-related rather than infection-related [13]. Pique-Regi et al. provide a theoretical argument against the likelihood of frequent transplacental spread by the finding that, throughout the pregnancy, the placenta is relatively deplete of the *ACE2* receptor binding domain for SARS-CoV-2 [199]. As well, they found that the placenta is relatively deplete of *TMPRSS2* which is the serine protease associated with virus cell entry. Hecht et al. place a somewhat different view of the latter [125]. They found *ACE2* expression polarized to membranous stromal regions of syncytiotrophoblasts as well as cytotrophoblasts and extravillous trophoblasts. They also determined that *TMPRSS2* was weakly present in the villous endometrium and syncytiotrophoblast. Other publications support the latter [73, 200, 201]. Lü et al. found that both trophoblast and fetal

lung alveolar cells are very low in *ACE2* expression, but high levels of expression were found in multiple other fetal tissues [202]. Jing and colleagues provide an alternate model for vertical transmission [203].

Despite the above, there are yet other citations that raise some concern about the potential for congenital infections albeit overall reports are conflicting [204]. Zamaniyan et al. found viral RNA in an amniotic fluid during Caesarean section in a pregnancy of 32 weeks gestational age whose newborn was also positive for viral RNA but asymptomatic [98]. Viral RNA on placental membranes and in placental tissue within 30 min of birth has been found [152, 205]. Viral RNA has also been found in one episode on the fetal side of the placenta in combination with inflammation of the umbilical cord substance [152, 187]. In the context of two newborns with positive assays for respiratory SARS-CoV-2, virus was found on the fetal side of the placenta with in situ hybridization [206]. Despite the latter, however, both newborns did not develop symptomatic disease. No serological assays were performed, and the findings were made for two of 22 births from mothers with COVID-19. One case report, for an ill female of 28 weeks gestation who was delivered by Caesarean section, found evidence of virus in the placenta through electron microscopy [207]. There was also decidual vasculopathy, but confirmatory assays for the virus were lacking. In this context, one must be cautious about the interpretation of virus morphology alone given past difficulty with the same [48]. Mulvey et al. did not find viral RNA or spike protein in the placenta with special stains, but reported evidence of fetal vascular perfusion defects [208]. Shanes et al. also placed a different perspective on placental pathology and found that placental changes during COVID-19 are more likely to reflect features of generalized maternal vascular compromise [209]. Such a thesis is credible given the vascular events including coagulopathy that occur for many patients, let alone pregnant ones, during severe infections [210, 211]. The publication of Shanes et al. did not however detail viral studies [209]. Other investigators also found some placental pathology mainly consistent with vascular compromise [3, 212, 213]. In the small series reviewed by Menter et al., evidence of both fetal and maternal malperfusion in placental tissues was suggested [214]. Inflammation in the latter study included villitis and intervillitis. Hsu et al. cite hypertrophic arteriopathy, subchorionic laminar necrosis, and chronic villitis in a placenta of an infected term mother whose offspring did not develop disease [215]. Immunohistochemistry of the placenta for SARS-CoV-2 nucleocapsid antigen revealed diffuse placental presence including trophoblasts. Others found placental macrophage infiltration in the absence of vasculopathy despite placental abruption, but SARS-CoV-2-specific antibody staining gave evidence of localization predominantly to the syncytiotrophoblast cells [54]. Ferraiolo et al. indicated that several placental swabs were positive for the same

asymptomatic pregnancy, but placental pathology included only some fibrin deposition and intervillous hemorrhages [216]. The newborn was not infected. Nevertheless, regardless of whether fetal or newborn infections have occurred, it is prudent to routinely assess the placenta for pathology when maternal infection has been documented [217]. Blauvelt et al. found evidence of acute chorioamnionitis in one citation [69]. For a single suspected vertical transmission in a large observational cohort, massive chronic intervillitis was found [61]. Others did not find placental pathology among several infections [67, 111, 112, 121]. Liu et al. did not find differences in the frequency of chorioamnionitis among infected and control patients albeit the comparison groups were small [126]. In the context of a maternal death, placental pathology was also not found by others [97]. Of particular note, Gulersen et al. did not measure statistically significant differences in placental pathology for those patients who were infected versus historical controls [60].

In a prospective study from New York, fetal vascular malperfusion and fetal vessel thrombi were found in up to ~50% of infected mothers which was much different from ~11% in controls [37]. Meconium staining, suggestive of fetal/newborn stressors, was also much more common on the placentae of infected mothers. Remarkably, however, there was no significant difference between infected and non-infected mothers for evidence of histological chorioamnionitis or chronic villitis. In their assessment overall, the lack of finding viral RNA among newborns was more supportive of vascular compromise rather than direct fetal or placental infection. The findings of Hecht et al. are also supportive of the latter in that there was no characteristic pathology in placentae from infected mothers [125]. The majority of placentae did not have evidence of viral RNA or viral protein. Only 2/19 placentae were found to have viral RNA and with localization to both syncytiotrophoblasts and cytotrophoblasts.

A more suggestive anecdote of possible intrauterine transmission was that reported by Sisman et al. [218]. A newborn was delivered vaginally at 34 weeks and developed fever and respiratory illness on day 2. A nasal sample yielded a positive RT-PCR assay at 24 hrs. of life. Although one could speculate that the virus may have been acquired at birth through a contaminated vagina, histopathology of the placenta was very suggestive of localized infection, and there was also evidence of meconium staining. Immunohistochemistry gave evidence of virus presence in syncytiotrophoblast cells, and virus was found by electron microscopy within the same cells. Therefore, if transmission occurred antenatally and to cause symptomatic infection shortly after birth, the virus would likely have been transmitted very near the vaginal delivery. Schwartz et al. cite an example of virus detection in amniotic fluid [219].

Kirtsman et al. also provide strong evidence for late intrauterine transmission [152]. A newborn of 35 weeks

gestational age was born to a symptomatic mother by Caesarean section in the context of presumed intact membranes. The newborn had viral RNA detected at the time of surgical delivery, and multiple samples of the placental tissues, both fetal and maternal aspects, yielded positive samplings. Placental pathology was also very suggestive of active inflammation by the finding of chronic histiocytic intervillitis.

Another convincing report of late vertical transmission was described by Vivanti et al. [89]. An infected newborn was delivered from a symptomatic mother at 35 weeks gestational age by Caesarean section on account of presumed fetal compromise. Despite intact membranes, viral RNA was detected in the amniotic fluid, neonatal throat and rectum, neonatal blood, and placenta. The placenta had evidence of diffuse fibrin deposition, infarction, and acute and chronic intervillitis. The inflammation was comprised of CD68+ histiocytes, and viral presence in perivillous trophoblasts was identified by immunohistochemical analyses. Late vertical transmission was also likely in the report of Correia et al. where a symptomatic mother delivered a newborn whose blood and respiratory samples were positive for SARS-CoV-2 [52]. The offspring was acutely symptomatic with moderately severe respiratory disease and acidosis. Live virus was cultured from the respiratory tract shortly after birth, and the newborn developed seropositivity (both IgG and IgM) within two weeks of the illness.

Gupta and colleagues found evidence of virus acquisition vertically from a mother who was symptomatic for a considerable period prior to birth [146]. The newborn delivered at 29 weeks gestational age and was already symptomatic with advanced respiratory disease and acidosis at delivery during caesarean section. The newborn also seroconverted after 2 weeks with both IgM and IgG antibody. Placental pathology revealed acute and chronic villitis, intervillitis, and placenta hemorrhage and fibrin deposition. Hinojosa-Velasco et al. found virus in respiratory secretions and stool of a newborn at delivery from Caesarean section, and the infant suffered respiratory distress at the same time [165].

Shende et al. showed proof for vertical transmission during the first trimester of one pregnancy where the mother had been asymptomatic [220]. There was fetal demise found approximately five weeks after maternal infection, and the fetus clinically showed hydrops. Amniotic fluid tested positive by RNA amplification. The placenta showed considerable pathology, and immunohistochemistry localized virus proteins to syncytiotrophoblast and villous stroma.

Facchetti et al. reviewed fifteen placentas from infected pregnancies [221]. The placental pathology, if any, was variable and included vascular thrombi, placental infarction, chorioamnionitis, hematoma, fibrin deposition, and/or funisitis. Mononuclear cell infiltrates stained commonly for CD68+CD14+CD163+. One particular pregnancy of 37

weeks gestation was delivered vaginally due to maternal complications. The newborn developed respiratory disease in the first 24 hrs. of birth but did not have confirmation of viral RNA excretion until 2 days later. Placental examination for the latter showed viral presence on both maternal and fetal aspects by a variety of methods. Inflammatory infiltrate was evident. The authors posed these findings as being indicative of vertical transmission. From this and other reports, it appears that many of the proposed vertical transmissions so published have occurred late in pregnancy.

Debelenko et al. compared the pathology of 75 placentas from infected mothers to 75 control placentas [222]. There was meagre evidence of significant differences between groups, and there was no confirmation of vertical transmission. It must be emphasized however that the infected cohort had existing or pre-existing very mild disease. Subtle differences among groups often did not reach statistical significance. One placenta had evidence of placental viral invasion despite no evidence of disease in the newborn. Virus was identified by immunohistochemistry in the syncytiotrophoblast where there was also evidence of cellular injury, intervillous inflammation, and infiltration by CD68+ cells. Of note, 74 of 75 placentas from infected mothers with such mild illness did not have evidence of viral infiltration of the placenta. A similar lack of placental infection was also found by Edlow et al. [73]. The latter investigators did not find any characteristic placental pathology for COVID-19 but did see evidence of placental malperfusion which correlated somewhat with increasing disease severity.

Schwartz and Morotti have collated a review of placental pathology and its association with infection [219]. Adhikari et al. examined a large series of placentas from COVID-19 infections and could not find an association of increased pathology with various stages of maternal disease severity [61]. They also found, however, that pregnancy loss was associated with severe disease in early (<37 weeks) gestations even though no stillbirths per se were seen in their large cohort.

Garcia-Manau and colleagues detail of two fetuses that developed transient skin edema during maternal COVID-19 infections at 20 and 22 weeks gestation [223]. These clinical manifestations resolved as did the maternal respiratory illness. In each case, amniotic fluid and peripheral blood did not have evidence of viral RNA. Majachani et al. portray an episode of late congenital infection in an offspring born to an HIV-positive mother [58]. Of a mother with severe compromise from COVID-19, a newborn was found positive for viral RNA and developed pneumonia and acidosis [224]. The latter newborn however did not convert with IgG reactivity over 21 days. Early infection occurred in a newborn from a vaginal delivery where maternal-newborn contiguity was abrogated [225].

The detection of viral IgM in the newborn at birth would be suggestive of intrauterine infection [188, 226]. Despite the latter, early neonatal manifestations of infection were not detailed nor

was there description of complicated maternal illnesses. Wu et al. found neonatal IgM and IgG in a newborn shortly after birth who was symptomatic; the latter was re-reported from Dong et al. [116, 138]. He et al. make similar findings in a small cohort [188]. Marzollo et al. detail very early newborn deterioration with respiratory acidosis and likely pneumonia that required ventilator support [227]. The latter infant was born to a mother near term who suffered a febrile illness some 9 days prior to vaginal delivery in the context of presumed intact membranes. At best, the latter would represent very late in utero transmission. In a large review, Cavicchiolo and colleagues did not find evidence of significant serological responses among newborns of infected mothers [228]. Similar findings were made for a newborn reported by Toner et al. whose mother was infected at 27 weeks gestational age; delivered at 33 weeks, both intrauterine and newborn cord blood did not yield anti-coronavirus antibody even though antibody to rubella and varicella-zoster virus could be detected [229]. Blauvelt et al. did not find either IgG or IgM in the blood of the preterm newborn [69]. In contrast, others have found newborn IgG but not IgM in an infant born at 38 weeks gestational age whose mother was infected at 29 weeks [143]. In utero transplacental passage of IgG in any regard occurs more readily as the placenta matures.

It must be concluded that intrauterine infections are not common, but further data in this regard continues to be welcome. For congenital malformations arising as a consequence of early infections, no such association has been found [13].

Neonatal Infections

Coronavirus infections as generically defined by electron microscopic findings were believed to have occurred in neonatal intensive care and in outbreak fashion causing neonatal necrotizing enterocolitis [230–232]. Culture-confirmation of such outbreaks was then lacking. In this regard, it is of interest that Wu et al. have described three near-term newborns who developed necrotizing enterocolitis in the context of maternal COVID-19 [116]. Cooke and colleagues detail a premature newborn who developed a bowel perforation and required a bowel resection, although it was likely that the complications were connected to prematurity [70]. Human respiratory coronavirus OC43 was found to have caused an infection in an infant in the first 3 weeks of life, but there was no discussion of the mechanism of acquisition [233]. In the latter study, prolonged viral RNA shedding was found for OC43 and NL63 in other children less than one year of age. Gerna et al. cited infections with OC43, NL63, and 229E among infants ranging from 12 days to 2 months of age [234]. Gagneur et al. diagnosed infections in neonatal intensive care, but given the delayed onset, nosocomial acquisition seemed likely [235]. Sizun et al. also found newborn infections, but sources of infection were indeterminate [236].

In a large American cohort, perinatal COVID-19 infection was estimated at 2.6% [108]. Most studies, however, report an infrequency of neonatal SARS-CoV-2 infection at birth or thereafter despite maternal infection of varying severity [1–3, 13, 16, 19, 20, 22–25, 29, 30, 35, 38, 41, 42, 46, 47, 51, 55, 59–61, 66, 68, 72, 82, 90, 100, 104–107, 109, 110, 112, 113, 117–120, 123, 126, 128, 129, 139, 162, 168, 185, 188, 191, 193, 196, 197, 213, 222, 228, 237–244]. The latter has also been evident despite some newborn exposure to maternal breastfeeding [82, 118, 127, 136, 241]. In a small series, Cojocar et al. did not find newborn infection regardless of whether infants were bonded with mothers after birth [244]. Apart from respiratory specimens, these newborns have at times been sampled for meconium, gastric aspirates, cord blood, urine, and feces. Newborn deaths in this context were not directly attributable to COVID-19 infections [34, 55, 77, 78, 94, 149, 245]. Some have been admitted to newborn intensive care, but disease has often not been definitively attributed to viral infection [38, 55, 94, 124, 239, 245–249]. Newborn infection may be asymptomatic [32, 58, 118, 136, 250, 251]. Among a large collection of pediatric data throughout China, the infection of newborns under the age of 29 days constituted 0.7% of all infections [252]. Complications among these newborns commonly occur, but it is more often attributable to non-viral mechanisms [128]. Schwartz et al. mentioned two newborn deaths among those of a retrospective cohort study in Iran, but there are no details to confirm that the infection was the direct or indirect cause of death [95]. Another report from Iran found that 28% of newborns acquired SARS-CoV-2 from their infected mothers [40]. Liu et al. examined the immunological profiles of uninfected newborns from infected mothers and did not find significant aberrations [240]. One must however keep in mind the potential for in utero compromise to arise out of placental dysfunction. Severe maternal infection may be associated with newborn complications or earlier birth [253]. Nayak et al. did not find differences in Apgar scores for newborns from infected or non-infected mothers [21]. In a collation of forty-six children with COVID-19 under one year of age in Wuhan, China, five newborns within 0–7 days of birth were said to have been affected, but details of these were not reported [254]. As for older children and adults, asymptomatic infections of newborns do occur [255]. Zamaniyan et al. cite a possible vertical transmission in the context of a well newborn [98].

Citations of newborn infection have emerged on the basis of positive findings of viral RNA [21, 32, 34, 40, 52, 76, 94, 95, 127, 136, 152, 218, 227, 245, 256–260]. As for maternal infections, viral RNA may be detected for a considerable period of time after infection onset [260]. Some of the positive samples were obtained from the newborn in the first 12 h of life. Occasional newborns have been ill immediately after birth [2, 95]. The positive diagnostic assay was established among some 2.3–7% of those born to infected mothers.

Savasi et al. found four of 57 newborns positive for viral RNA, but none of them developed obvious disease [87]. Nayak et al. found three of 131 newborns positive on initial screening, but none of the three were again positive on post-natal day five [21]. No disease among the latter newborns was evident. In India, newborn infections were mild and self-limited [258]. The latter studies are contrasted to the report from Farghaly et al. who found that newborns of COVID-19 infected mothers were more likely to have desaturations, have poor feeding, and be symptomatic during the first 2 weeks of post-natal follow-up [237]. Virus can be potentially found in both respiratory secretions and stool [260].

Symptomatic infections have occurred, but it must be understood that some suspect infections are not confirmed by diagnostic studies [102]. Disease may affect the respiratory tract, the digestive tract, or both [260]. After separation from a mother post-vaginal delivery, newborns have developed an episode of respiratory disease [75, 95, 152, 227, 245, 256, 261, 262]. Gale and colleagues report a varying spectrum of neonatal COVID-19 in a large prospective national surveillance in the UK [245]. Fernández Colomer et al. confirm a variable but relatively mild spectrum of disease including upper respiratory symptoms, apnea, fever, respiratory distress, and gastrointestinal symptoms [250]. Regardless of where the infection was acquired, a sizable proportion of these patients required new or continued hospital admission and the provision of supplemental oxygen. Length of hospital stays for community-acquired infections ranged 2–6 days. The report of Kirtsman et al. is highly suggestive of late vertical transmission, and the newborn had evidence of viremia in a plasma sample despite having a relatively mild clinical illness [152]. One newborn had a positive assay on postnatal day two but was not ill thereafter [83]. Some infants developed symptomatic respiratory infection by days 4–15 [76, 260, 262–267]. Four other newborn infections appeared to have occurred despite maternal Caesarean section and physical separation [261, 268]. The risk of nosocomial acquisition is real although suggested to be low [245, 260]. Respiratory infections occurred within 2 days of birth. A neonate developed presumed COVID-19 respiratory illness, but the infant had considerable pulmonary complications arising from prematurity (26 weeks) as well [269]. A near similar complicated lung disease and infection were detailed by Gordon et al. [270]. Alzamora et al. describe a pre-term birth from Caesarean section in which the newborn was immediately separated from the mother but where the infant developed an illness in the first 16 h of life [271]. They postulated a potential vertical transmission to account for the acute illness after delivery. It was not clear whether respiratory distress was solely attributable to COVID-19 in the latter report given the degree of prematurity. Hopwood et al. found a term newborn to be seemingly infected in the first 25 h of life and decompensation included severe respiratory failure [257]. The mother may have had ruptured membranes for several days prior to vaginal delivery. Demirjian et al. had a

laboratory diagnosis for a newborn at day 3 who became ill by day 5 [149]. They speculated on a vertical transmission given that the baby had been delivered by Caesarean section and had been segregated from mother fastidiously at birth. Two newborns screened negative for viral RNA at birth proved to have positive respiratory samples on day 2 after birth [19]. One of the latter developed what was called a ‘viral pneumonia’. A possible newborn infection was also reported by Yu et al. [272]. There are few convincing reports of fulminant respiratory illness nor severe systemic complications after newborn infection. Regardless, severe disease in older pediatric populations has been cited, and therefore it is justified to closely follow the newborn age group as well [273]. Anecdotal reports of COVID-19 late-onset newborn infections between days 4 and 90 have been published, and the patients have fared well in resolution [29, 245, 250, 256, 259, 265, 266, 274–278]. The need for intensive respiratory care in such late-onset infections is uncommon [259, 265]. A report from Spain provided a broad experience in which post-natal infections occurred for newborns with ages 7–43 days [250]. The latter included considerable numbers of both community-acquired infections and nosocomial infections. Two reports provided evidence for a newborn febrile neurological presentation [262, 274]. Whether asymptomatic or symptomatic, it is not known if a small proportion of newborns, whether with co-morbidities or not, will prove to be sources for prolonged or chronic shedding of the virus.

Viral co-infections seem to be uncommon for newborn patients with COVID-19 [250].

Maternal Management and Prevention

The Burden of Presenting Infection

The pattern for managing maternal patients before, during, and after births can be expectedly variable given the different health care contexts. It is much easier to garner consistency when the maternal healthcare unit is larger and where policies are more widely repeated. The first understanding of disease potential begins at intake. For those with planned interventions and deliveries, a pre-presentation screening process will have some benefit. The latter can include screening history prior to site visitation for fever, illness, or contacts. The patient may also be screened for potential infection at the time of ad hoc presentation to a care facility. The intensity of the latter should depend on the prevalence of COVID-19 in the given geography [26, 242]. Those presenting with asymptomatic infection will pose difficulty, and it should be widely taught that some patients will first raise concern for infection after entry into the healthcare setting. Furthermore, it is well understood that laboratory results are returned over a variable window of time which then places more burden on those admitting the patient.

For those mothers who are known SARS-CoV-2-positive or highly suspect, immediate triage to isolation is imperative, and staff will require personal protective equipment. Confinement to a negative pressure room is desirable. In absence of the latter, single room occupancy is essential in the least. Apart from infection control measures taken by staff, the mother can be encouraged to wear a mask during the time of personnel or visitor entry. Mask use is also prudent during patient transport.

Regular entry viral screening has its merits, but such a routine will again depend on the prevalence of disease in the community [2, 15, 26, 32, 139, 173, 175, 279–281]. In one of the latter studies, the frequency of finding viral RNA in a respiratory specimen from presenting asymptomatic patients in Spain was only 0.5%, but yet overall, including known and symptomatic presentations, 8% of pregnant mothers were infected [175]. In New York, routine screening identified considerable asymptomatic infections [242, 279]. The latter frequencies were occurring during peak pandemic. There is no established rule for determining where the threshold for universal screening should be. Given the timing for laboratory results to return, caution must be applied on an individual basis taking into account the patient’s status and the community burden. There is also the possibility that disease may occur later in the patient’s admission. Attendees with the mother for a delivery should be minimized and should be clinically screened as well. The patient should be encouraged to wear a mask during delivery. Although viral antigen detection systems have been widely adopted in other contexts, they are reknowned for lacking sensitivity when viral loads are low.

The Burden of Institutional Virus

The environmental burden of virus in the patient vicinity is potentially considerable [282–286]. Rooms should be minimized for equipment and paraphernalia as feasible. Regular cleaning and disinfection of the patient environment is critical and should observe approaches used otherwise to prevent SARS-CoV-2 transmission between all patients [172]. The use of personal protective equipment should be commensurate with likelihood of aerosol generation during procedures. Operative care prevention should be no less than that used for other operative procedures. Herman et al. have crystallized the anaesthesia care concerns [287]. Visitor limitations should be enforced.

When patients present with known disease, the timing for quarantine should be a minimum of 10 to 14 days, and conservative estimates favor the latter [181, 288]. Some have proposed that consecutive negative diagnostic assays should be sufficient to de-isolate a known positive patient. For example, Shmakov et al. have used the double negative diagnostic assay approach to re-unite newborns and mothers after initial separation [41]. Krupp and colleagues, however, rightfully

raise concern about the use of qualitative versus quantitative diagnostic assays for the latter [289]. There is also remaining concern about live virus shedding past a two week period [48, 172, 181]. Infection of the healthcare worker has become a major institutional dilemma in the COVID-19 era and potentially a source for infection [173, 250]. The pointed use of telehealth mechanisms to follow pregnancies is just as relevant as it is for following other aspects of healthcare generally [290]. The role of antiviral treatment in diminishing viral excretion is yet to be realized in a significant manner, and indeed many clinical trials purposely exclude pregnant females [291].

Fetal and Newborn Management and Prevention

Does the Fetus or Newborn Benefit from Disease Prevention?

If it is true that antenatal infections are rare and that newborn disease is mild, one might not anticipate much of an impact for COVID-19 apart from maternal disease. The current findings detailed above in regard to placental pathology, however, suggest that severe disease may have a role to play in placental compromise. Any such pathology could have an effect on fetal blood supply and oxygenation that could go unmeasured at birth or thereafter with conventional techniques. Therefore, protection of the pregnant female is the first step to preventing disease for the fetus and newborn. There is also the prospect that disease prevention for the newborn thereafter contributes to curb further spread back to a post-partum maternal cohort, other newborns and their subsequent contacts, and equally important the healthcare worker. As has been experienced early, a general reduction of disease for any specific patient group may go a long way to sparing the needs for personal protective equipment and other resources. Narang et al. detail their experience with the management of fetal surgery during pandemic times [292]. Obstacles to maternal-neonatal care in the COVID-19 era amid a scenario with lesser resources can prove to be an extra-ordinary burden [293].

Nosocomial acquisition of the virus among newborns, especially those with pre-morbid conditions, has been cited [250, 260]. Although SARS-CoV-2 is generally mild for most newborns, the latter reports illustrate a significant consequential pattern for some. For nosocomial infections, both mother and healthcare worker can be vectors.

Mechanisms to Prevent Disease

Physical separation of infected mother and newborn can be effective [120, 122, 239]. Whereas the scenario of Caesarean section can be beneficial to assist in the latter, it is not an absolute indication in itself. The need for medical intervention

must take into consideration the entire maternal-fetal unit, and discretion is afforded to clinical decision-making as it is also for the method of surgical intervention if needed [100]. A vaginal birth theoretically carries greater risk for contamination of the newborn, and thus, even if separated, late-onset potential for newborn infection, symptomatic or asymptomatic, must be assumed. If possible, physical separation of newborns born to infected mothers from those born to non-infected mothers would be prudent as feasible. In the context of the newborn that may be screened for infection early on, a negative diagnostic assay should be repeated should the infant remain in the healthcare setting. Newborns of known infected mothers or those highly suspect should be screened. A respiratory sampling should be the minimum focus. Given that newborns can be infected, symptomatic maternal illness should lead to newborn isolation until the clinical and laboratory conclusions are otherwise. Concern should most be given to newborns that are premature, compromised, or carry potentially relevant risk factors. De Rose et al. provide their account of necessary changes made to newborn care in a neonatal intensive care unit, whereas others have outlined a proposal for newborn emergency transport in this context [294, 295]. Universal screening of newborns, parents, and healthcare workers in a neonatal intensive care unit has been assessed and has placed the burden of prevalent coronaviral infections on the associated adults [228]. Simon et al. provide a paradigm for the management of neonates from infected mothers [296]. Apart from infection risks, the maternal-fetal unit must also be considered for the various risks of pharmacotherapy including intended anti-SARS-CoV-2 treatments [297]. There is nevertheless some controversy with any one particular approach being mandated for all settings. For example, despite rooming-in and direct breastfeeding, some have found the outcome of newborn infection to be relatively negligible [35, 136, 253].

If the consensus for whatever approach is that the infected mother and newborn should remain together, preventative hygiene for the mother should be encouraged for the potential value that it may have [136, 241]. The totality of methods for potential spread are continuing to be better understood [298]. Maternal masking while breastfeeding and distancing within the room should be observed albeit the prevention potential in that context is far from well-known. Enhanced hand hygiene will likely have some role for prevention. It could be argued that skin-to-skin contact from breastfeeding may augment risk, but the overall clinical context should be taken into consideration by patient and medical decision-makers. Attention to maternal mental health may also be warranted especially given its potential impact on adherence to prevention strategies as they may be implemented [243, 299, 300]. Relative isolation of these patients also brings psychosocial problems to the forefront [301]. Maternal emphases of prevention may be variable [302].

Controversies with Breast Milk

One of the matters often raised in either separating mother from newborn or for rooming-in is breastfeeding [127]. The value of breastfeeding for bonding and nutrition is widely accepted. The interruption of the same for prevention measures, although undesirable, requires observation for the resolution of maternal disease and shedding [120]. Whereas the definition of a suitable quarantine time for mother may be a matter for debate, the 14-day rule post-exposure appears to be widely held and is a reasonable minimum. The effect of the pandemic on breastfeeding practices has been variable [8, 303]. Perrine et al. illustrate the heterogeneity in the conduct of breastfeeding alone [304]. Ronchi and colleagues found minimal transmission for mother-newborn pairs where breastfeeding was largely allowed [127]. Many of the mothers in the latter study however had been ill for a considerable period of time prior to delivery and may have had a low potential for infectivity.

Apart from nutrition, breast milk is an important source of immunity for the newborn in many regards. Although IgG is transferred to the fetus in utero, secretory IgA (sIgA) and IgG in colostrum and milk provide first lines of mucosal protection for the newborn. The common mucosal immune system facilitates the production of sIgA in the breast milk that is common to the respiratory tract. Therefore, mothers who have been infected for more than 10 days will likely have some anti-SARS-CoV-2 antibody transferred to the fetus during the prebirth or will have anti-SARS-CoV-2 sIgA and IgG in milk; quantities of the latter will be considerably variable [143]. The amount of such acquisition by the fetus or newborn is time-accrued. As for other viruses, passive IgG acquired in utero declines in the newborn blood gradually over a 4–8-month period, whereas breast milk sIgA is likely to be secreted over a long period during the breastfeeding course. SARS-CoV-2-specific data would be welcome, and preliminary information on newborn antibody presence has recently emerged [163, 226, 305]. One such study did not find differences in neonatal outcome after maternal infections with the presence or absence of acquired IgG antibody [305].

There is some science that supports the role for breast milk in coronavirus prevention. In the bovine model, milk is virucidal for bovine coronavirus in the absence of vaccination [306]. Heating of the milk, including pasteurization, loses some of this virucidal activity, but the loss is not all-or-none. The changes in heated milk may include a partial loss of virus-neutralizing activity [307]. In the porcine model, infection results in the production of neutralizing IgA in milk for coronaviruses [308]. Several other experimental approaches have shown the value of coronavirus neutralizing antibodies in breast milk or IgY preparations [309–311]. Taking these observations a step further into the human realm, the classic studies on coronavirus 229E among volunteers from the

Common Cold Research Unit (Salisbury, Wiltshire, UK) should be rekindled [312, 313]. Pre-infection neutralizing antibody gave protection to homologous strains on rechallenge, but susceptibility remained in part to heterologous strains [312]. Both circulating and local mucosal IgA were associated with protection along with other mucosal factors [313]. These data are not only consistent with a post-infection protection at the mucosal site of viral entry, but also provide the potential to help define protective mucosal antibodies for the population as a whole [314, 315]. With the definition of a reproducible animal model, passive transfer of protective antibody to offspring can now be assessed [316]. Indeed passive immunotherapy has promise for both mother and newborn as may be required [317]. There has been considerable progress in the understanding of protective and passive immunity for COVID-19, and there is considerable potential in the field of maternal immunity from COVID-19 for translational research and potentially practical implementation [318, 319]. Pace et al. have begun such assessments with finding of SARS-CoV-2-specific antibody in breast milk; they also have found that virus-directed antibody has neutralizing capacity [320].

Risks from Breast Milk

Several studies have looked for viral RNA in breast milk, but these assessments lack observation for live virus [3, 38, 46, 53, 90, 138, 142, 143, 166–168, 180, 195, 240, 260, 266, 269, 320, 321]. Testing milk well after maternal disease onset may contribute to underestimation. Some of the reports have identified positive samples, although confirmatory tests have been lacking [38, 41, 136, 152, 165, 167, 168, 322]. The review from Bertino et al. details an infant whose breast milk supply was found to have viral RNA twice over a month but where the testing was negative with an interim specimen [136]. There is no evidence yet which confirms that such presence represents excretion through breast milk [323]. More likely, virus entry into milk could be connected to skin contamination and subsequent seeding of milk through breast expression, suction, pumping, and/or hand exposure. In the latter regard, Pace et al. found viral RNA on breast skin samples but not directly in breast milk [320]. If decisions are made for mother and newborn to room-in, the cohort may remain together, but the newborn will risk infection in a context of maternal risk reduction however mild the consequences may be. Regardless, Salvatore and colleagues have presented a scenario where such risk appears to be small given certain precautions [241]. If the mother and newborn are separated, the timing is relatively short for the infant to receive other sources of milk before they are re-united and breastfeeding resumes. There is yet however the opportunity for an infected mother to harvest milk and for it to be fed to the isolated newborn. This approach assumes that collection minimizes milk

contamination and that vessels for milk are disinfected as they are mobilized to the newborn's venue or beyond.

In respect of the above, heat sensitivity of SARS-CoV, MERS-CoV, and SARS-CoV-2 is known [172]. It is quite likely that several approaches to heat treatment of potentially infected maternal milk will inactivate infectious virus, including pasteurization [324–327]. The study of Chin et al. assessed heat inactivation in the context of the protein load of tissue culture medium [327]. Unger et al. have recently shown that Holder pasteurization (62.5°C, 30 min) reasonably inactivates SARS-CoV-2 [328]. Heat treatment of milk has otherwise been considerably analyzed [329–339]. At pasteurization temperatures, there is some loss variably of endogenous lysozyme, lactoferrin, lactoperoxidase, and IgA, but the reductions are only partial. Thus, an effective approach for heat-treating infected mothers' milk and eradication of viable virus along with the retention of many nutritious and protective factors is in reach. This would allow an infected mother to donate milk to her newborn after heat treatment if all precautions otherwise are maintained.

A Model for Care?

There is no approach to the management of COVID-19 for obstetrical care that will be perfect given the variations on clinical presentation, healthcare availability, and associated pressures of dealing with potentially large numbers of contacts and infections. Such variation is evident from the many care and prevention guidelines thus far posted [340–342]. Sharma and colleagues detail key considerations in a setting where maternal infection numbers are considerable [343]. All of these authorities are wary of the changing and cumulative information that is quickly arising and with which alterations to such guidelines will be incrementally made. We must certainly consider that SARS-CoV-2 could become the fifth common endemic respiratory coronavirus that will persist despite vaccination and/or widespread infection [344]. The concept of herd immunity does not necessarily impart absolute protection if the virus becomes established, but an associated mitigation for subsequent secondary illnesses is possible.

There are many similarities to guidelines previously had for prevention of other obstetrical and perinatal infections especially from respiratory viruses. We can generally accept that maternal infection can be sufficiently severe and frequent that prevention is imperative. As it is essential to contain the COVID-19 pandemic, secondary spread is a focus that must also be especially considered. Until either effective prevention or treatment chemotherapy is available or until effective vaccines arise and considerably mitigate and prevent disease, we need to provide an environment of safety for mother, fetus, newborn, contacts, and healthcare workers with the best of science and experience that exists.

Key Concluding Themes

In summary, the following statements summarize the current state of knowledge:

- Maternal COVID-19 infections commonly occur.
- The spectrum of maternal infection is considerably variable and includes both asymptomatic infection and advanced multisystem disease with potential for maternal demise.
- The propensity to severe maternal disease is often associated with co-morbidities.
- COVID-19 in pregnancy is associated with preterm delivery and a higher incidence of Caesarean section delivery.
- Maternal infections have risk for placental vascular abnormalities with potential adverse outcome for the fetus.
- Congenital infection is likely but occurs in very much a minority of infected pregnancies and more so near term.
- Most maternal infections do not result in subsequent newborn infection.
- Newborn infections occur both early and late, and disease manifestations are generally mild if they occur.
- Both infected pregnancies and infected newborns can serve as vectors for further SARS-CoV-2 transmission.
- Prevention in the maternal-newborn context must consider the specific healthcare context, depend on the prevalence of infection in that population, and should be sensitive to both caregiver and patient priorities.

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