
Maternal Coronavirus Infections and Pregnancy Outcomes

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The emergence of a novel coronavirus, termed SARS-CoV-2, and the potentially life-threatening respiratory disease that it can produce, COVID-19, has rapidly spread across the globe, creating a massive public health problem. Previous epidemics of many emerging viral infections have typically resulted in poor obstetric outcomes including maternal morbidity and mortality, maternal-fetal transmission of the virus, and perinatal infections and death. This article reviews the effects of 2 previous coronavirus infections—severe acute respiratory syndrome (SARS) caused by SARS-CoV and Middle East respiratory syndrome (MERS) caused by MERS-CoV—on pregnancy outcomes. In addition, it analyzes literature describing 38 pregnant women with COVID-19 and their newborns in China to assess the effects of SARS-CoV-2 on the mothers and infants, including clinical, laboratory, and virologic data, and the transmissibility of the virus from mother to fetus. This analysis reveals that unlike coronavirus infections of pregnant women caused by SARS and MERS, in these 38 pregnant women COVID-19 did not lead to maternal deaths. Importantly, and similar to pregnancies with SARS and MERS, there were no confirmed cases of intrauterine transmission of SARS-CoV-2 from mothers with COVID-19 to their fetuses. All neonatal specimens tested, including placentas in some cases, were negative by RT-PCR for SARS-CoV-2. At this point in the global pandemic of COVID-19 infection there is no evidence that SARS-CoV-2 undergoes intrauterine or transplacental transmission from infected pregnant women to their fetuses. Analysis of additional cases is necessary to determine if this remains true.

infections. Changes in the maternal cardiovascular and respiratory systems, including increased heart rate, stroke volume, oxygen consumption, and decreased lung capacity, as well as the development of immunologic adaptations that allow a mother to tolerate an antigenically distinctive fetus, increase the risk for pregnant women to develop severe respiratory disease.22 Outcomes data from multiple studies of influenza have demonstrated an increased risk of maternal morbidity and mortality when compared with nonpregnant women.22,23 This association has also been previously demonstrated to occur when pregnant women develop either of 2 pathogenic coronavirus infections: severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).9

Severe Acute Respiratory Syndrome

The SARS epidemic occurred from November 2002 to July 2003, affecting greater than 8000 persons in 26 countries and resulting in 774 fatalities.24 The causative agent, a coronavirus termed SARS-CoV, was transmitted through close person-to-person contact, respiratory droplets, environmental contamination, and potentially sewage.9,25 There were 12 reports of pregnant women who developed SARS during the epidemic, of whom 3 died during pregnancy (case fatality rate of 25%).9 Miscarriages during the first trimester occurred in 4 of 7 women. Two of 5 women in the second and third trimester had a neonate with intrauterine growth restriction. In addition, 4 of 5 pregnancies resulted in preterm birth: 1 spontaneous and 3 induction deliveries that were performed for maternal conditions.26 Vertical transmission of the SARS-CoV virus did not occur in any of the infants, however, the clinical outcomes of pregnant women with SARS were worse than those of infected women who were not pregnant.13,26,29

Middle East Respiratory Syndrome

MERS is another coronavirus infection that causes potentially severe respiratory disease. It was first reported from Saudi Arabia in 2012, after which it spread to more than 27 countries both within and outside of the Arabian Peninsula.9,20 MERS-CoV has been identified in camels, which have been suggested as the primary source of human infections, as well as in bats, but more research is needed to understand the role that these and other animals may play in transmission. MERS-CoV is characterized by sporadic zoonotic transmission events as well as spread between infected patients and close contacts (ie, intrafamilial transmission). Outbreaks of MERS in health care settings are characteristic and result from poor infection control and preventative measures.30,31

MERS-CoV infection has been reported from 11 pregnant women, where it has been associated with a variety of adverse clinical outcomes among 10 (91%) of them. These outcomes have included maternal deaths, premature delivery, intensive care treatment for newborns, and perinatal death. There have been no confirmed cases of vertical transmission of MERS-CoV.9

CURRENT CLINICAL FEATURES AND OBSTETRIC OUTCOMES OF PREGNANT WOMEN WITH COVID-19

Reports have been published on a total of 38 pregnant women with COVID-19 originating from the epicenter of the pandemic in China.13–17 All women were in the third trimester of pregnancy and included 37 women whose SARS-CoV-2 positivity was confirmed by reverse transcription–polymerase chain reaction (RT-PCR). These pregnancies resulted in 39 infants (1 set of twins); detailed clinical information, obstetric outcomes, and SARS-CoV-2 status were available for 29 neonates.

Zhongnan Hospital of Wuhan University, Wuhan, China

The condition of 9 pregnant women with COVID-19 has been described in a retrospective review of medical records by Chen et al13 (Table 1). The women were tested for SARS-CoV-2 with RT-PCR kits recommended by the Chinese Center for Disease Control and Prevention (BioGerm, Shanghai, China). Samples were tested simultaneously using RT-PCR at the Clinical Laboratory of Zhongnan Hospital and State Key Laboratory of Virology/Institute of Medical Virology, School of Basic Medical Sciences, Wuhan University. Positive confirmatory cases of SARS-CoV-2 infection were reported when a positive test result from either laboratory was obtained. The mothers’ ages varied between 26 and 40 years of age; they had documented exposure to the novel coronavirus and were in the third trimester of pregnancy when they developed COVID-19 infection. Although none of the women had a preexisting chronic condition such as diabetes, cardiovascular disease,
or hypertension, 3 women had comorbid conditions that developed during their pregnancy: influenza (case 1), gestational hypertension occurring since 27 weeks’ gestation (case 3), and preeclampsia developing at 31 weeks’ gestation (case 4). Seven women were febrile upon admission; additional findings included cough (4 of 9), myalgia (3 of 9), sore throat (2 of 9), malaise (2 of 9), gastrointestinal symptoms (1 of 9), and shortness of breath (1 of 9). Laboratory findings included elevated C-reactive protein (6 of 9), lymphopenia (5 of 9), and increased alanine aminotransferase and aspartate aminotransferase (3 of 9).

Chest computed tomography (CT) scans showed abnormalities for 8 of the 9 women, demonstrating lungs with linear fibrosis in the left lung and enlarged mediastinal lymph nodes. An RT-PCR test finding for SARS-CoV-2 by CT scans showed abnormal findings in all 9 women, demonstrating lungs with patchy ground-glass shadows. Four women had preterm labor, but none occurring before 36 weeks’ gestation. Cases 5 and 8 had fetal distress, and cases 7 and 9 had premature rupture of membranes. None of the women developed severe pneumonia, and there were no maternal deaths.

All 9 women underwent cesarean deliveries. Two of the 4 preterm infants were delivered at 36 weeks 2 days and weighed less than 2500 g (cases 4 and 7)—one of the newborn infants (case 4) had a birth weight of 1880 g and weighed less than 2500 g (cases 4 and 7)—one of the newborn infants (case 4) had a birth weight of 1880 g and was delivered to a mother with preeclampsia. All of the infants had good Apgar scores.

The presence of SARS-CoV-2 was evaluated in 6 of the 9 cases from amniotic fluid, breastmilk, umbilical cord blood, and neonatal throat swabs; all test results were negative. The specific cases tested were not specified. All of the 6 neonatal samples tested were negative for SARS-CoV-2.

Tongji Hospital of Tongji Medical College, Huazhong University, Wuhan, China

Liu et al.14 reported on 3 pregnant women from the Tongji Hospital who became infected with SARS-CoV-2 during the third trimester. These 3 women were among a total of 17 pregnant women admitted to the obstetrics ward during the study period—a COVID-19 prevalence of approximately 18%. The women’s ages ranged from 30 to 34 years (Table 2). COVID-19 testing was performed by using the RT-PCR assay with a SARS-CoV-2 ORF1ab/N gene detection kit (Shanghai Huirui Biotechnology Co, Ltd, Shanghai, China), a product based on the recommendation of the National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention.

Case 1 involved a 34-year-old woman with hypothyroidism who was febrile before her hospital admission. Her chest CT showed progressively worsening bilateral pulmonary infiltrates. The mother had positive RT-PCR test results for SARS-CoV-2 from an oropharyngeal swab and feces; testing of breast milk, vaginal mucus, and placenta was negative. Her 3250-g infant was delivered at 40 weeks’ gestational age by cesarean birth with chronic fetal distress, chorioamnionitis, meconium-stained membranes, but with good Apgar scores. Specimens from the infant including whole blood, plasma serum, umbilical cord blood, and an oropharyngeal swab were negative for SARS-CoV-2 by RT-PCR.

Case 2 involved a 34-year-old woman with no significant obstetric history or comorbid conditions. She developed a fever at 37 weeks of gestation, and a CT scan of the chest revealed bilateral ground-glass opacities and pulmonary consolidation, nodules in the left lower lobe, and patchy consolidation in the right middle lobe. An oropharyngeal swab taken 1 day before delivery was positive for SARS-CoV-2 by RT-PCR. A 3250-g infant was delivered by cesarean birth at 38 weeks 4 days’ gestation on good Apgar scores. The newborn had slightly decreased muscle tone and responsiveness that had improved the day after delivery. Testing for SARS-CoV-2 from whole blood, serum, oropharyngeal swabs, urine, and feces by RT-PCR yielded all negative results for the novel coronavirus.

Case 3 involved a 30-year-old woman who had developed gestational hypertension during her first pregnancy. She developed cough at 37 weeks’ gestation, and upon admission to the hospital had a chest CT scan that demonstrated ground-glass opacities, subsolid patch, and linear fibrosis in the left lung and enlarged mediastinal lymph nodes. An RT-PCR test finding for SARS-CoV-2 performed on an oropharyngeal swab was positive; follow-up testing of an anal swab, vaginal mucus, and breast milk yielded all negative results. She delivered a 3670-g infant by vaginal delivery at 39 weeks 5 days’ gestation with good Apgar scores. Two RT-PCR tests for SARS-CoV-2 were performed on successive days with whole blood, plasma, oropharyngeal swabs, urine, and feces, and all yielded negative results.

The mothers in this report all presented with either fever or cough accompanied by CT abnormalities during the

| Table 2. Characteristics of Additional 7 Pregnant Women With COVID-19 and Their Infants (after Chen et al.13 Liu et al.14 and Zhu et al.15) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **First Author and Case** | **Chen13** | **Liu14** | **Zhu15** |
| Maternal age, y | 28 | 34 | 34 | 34 | 25 | 35 |
| Gestational age at delivery | 38 wk | 39 wk 4 d | 40 wk | 38 wk 4 d | 39 wk 5 d | 38 wk 4 d |
| Comorbid events | Fetal distress | PROM | Hypothyroid | Placenta acr eta | Gestational diabetes | Fetal distress, oligo |
| Maternal RT-PCR for SARS-CoV-2 | Positive | Positive | Positive | Positive | Positive | Positive |
| Symptom-to-delivery interval | 2 d | 7 d | ~1 d | ~7 d | ~13 d | <1 d |
| C- or vaginal | C-s | C-s | C-s | C-s | C- | C-s |
| Birth weight, g | 2800 | 3530 | 3250 | 3250 | 3670 | 2450 |
| Apgar scores at 1 and 5 min | 9, 10 | 8, 10 | 8, 9 | 8, 9 | 9, 10 | 9, 10 |
| Neonatal outcome | Normal | Normal | Normal | Normal | SGA | SOB |
| Neonatal RT-PCR for SARS-CoV-2 | See Table 1 | See Table 1 | See Table 1 | See Table 1 | See Table 1 | See Table 1 |

Abbreviations: C-s, C-section; oligo, oligohydramnios; PROM, premature rupture of membranes; RT-PCR, reverse transcription–polymerase chain reaction; SARS, severe acute respiratory syndrome; SGA, small for gestational age; SOB, shortness of breath.

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Pharyngeal swab specimens were collected from 9 of the hospitalized at the time of submission of the report. One premature infant developed shortness of breath and fluctuations of oxygenation with a decrease in platelets treated with transfusions. There was 1 neonatal death among the cohort (case 4)—a premature newborn and died on the ninth day of life. Four neonates remained on respiratory support and died on the ninth day of life. None of the neonates had a rapid heart rate.

The initial symptoms among these women were fever and cough. Prenatal conditions included fetal distress in 6 cases, premature rupture of membranes in 3 cases (5 to 7 hours before the onset of labor), oligohydramnios and polyhydramnios in 1 case each, umbilical cord abnormalities in 2 cases, and placenta previa in 1 case. Third-trimester obstetrical ultrasound findings were all normal. Seven of the mothers underwent cesarean deliveries and 2 had vaginal deliveries. There were no cases of severe organ failure, and disseminated intravascular coagulation developed among the cohort.

Maternal age ranged from 25 to 35 years, and they had deliveries at 5 hospitals in Hubei Province (Tables 2 and 3). The women's ages ranged from 25 to 35 years, and they had deliveries at 5 hospitals in Hubei Province. Seven of the 9 women were full-term and 6 were premature. Two newborns were small for gestational age and 1 was large for gestational age. Two newborns had a PCIS of less than 90—6 infants had shortness of breath, 2 were febrile, and 1 had a rapid heart rate. Gastrointestinal cytopenia associated with liver dysfunction. One premature infant developed shortness of breath and fluctuations of oxygenation with a decrease in platelets treated with transfusions. There was 1 neonatal death among the cohort (case 4)—a premature newborn and died on the ninth day of life. Four neonates remained on respiratory support and died on the ninth day of life. None of the neonates had a rapid heart rate.

Maternal Coronavirus Infections and Pregnancy Outcomes—Schwartz

### Table 3. Characteristics of Additional 7 Pregnant Women With COVID-19 and Their Infants Including 1 Set of Twins (after Zhu et al15)

<table>
<thead>
<tr>
<th>First Author and Case</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
<th>Case 9</th>
<th>Case 10</th>
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<tbody>
<tr>
<td>Maternal age, y</td>
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<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>34</td>
<td>39</td>
<td>34</td>
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<tr>
<td>Gestational age at delivery</td>
<td>34 w 2 d</td>
<td>34 wk 5 d</td>
<td>39 w</td>
<td>37 w</td>
<td>34 w 6 d</td>
<td>31 w</td>
<td>None</td>
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<tr>
<td>Comorbid events</td>
<td>Fetal distress</td>
<td>Vaginal bleeding, fetal distress</td>
<td>Cholecystitis</td>
<td>Placenta previa, fetal distress poly</td>
<td>Fetal distress</td>
<td>Twins, fetal distress, viral pneumonia c/w COVID-19</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Symptom-to-delivery interval</td>
<td>2 d after delivery</td>
<td>3 d after delivery</td>
<td>6 d before delivery</td>
<td>4 d before delivery</td>
<td>4 d before delivery</td>
<td>3 d before delivery</td>
<td>1 d after delivery</td>
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</tr>
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<td>C-s or vaginal</td>
<td>Vaginal</td>
<td>C-s</td>
<td>C-s</td>
<td>C-s</td>
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<td>C-s</td>
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</tr>
<tr>
<td>Birth weight, g</td>
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<td>2200</td>
<td>3030</td>
<td>3800</td>
<td>2300</td>
<td>1520</td>
<td>1720</td>
<td>2810</td>
</tr>
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<td>Apgar scores at 1 and 5 min</td>
<td>8, 9</td>
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<td>9, 10</td>
<td>9, 10</td>
<td>9, 10</td>
<td>10, 10</td>
</tr>
<tr>
<td>Neonatal outcome</td>
<td>SOB</td>
<td>Multiple organ failure, shock, gastric bleeding, DIC, death</td>
<td>Diffuse scattered rash, edema, facial skin lesions</td>
<td>LGA, in hospital</td>
<td>SOB, fever, GI bleeding DIC</td>
<td>SOB, in hospital</td>
<td>SOB, in hospital</td>
<td>SGA, SOB, cyanosis, in hospital</td>
</tr>
<tr>
<td>Neonatal RT-PCR for SARS-CoV-2</td>
<td>Negative</td>
<td>Negative</td>
<td>Not performed</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: C-s, C-section; c/w, consistent with; DIC, disseminated intravascular coagulation; GI, gastrointestinal; LGA, large for gestational age; poly, polyhydramnios; RT-PCR, reverse transcription–polymerase chain reaction; SARS, severe acute respiratory syndrome; SGA, small for gestational age; SOB, shortness of breath.
In a case report Wang et al\textsuperscript{16} described the condition of a 28-year-old pregnant woman who presented to the hospital with a fever of 1 week duration (Table 4). She was at 30 weeks' gestation at the time of her admission and 2 throat swabs tested negative for SARS-CoV-2 by RT-PCR. Chest CT examination 2 days later showed left-sided subpleural patchy consolidation and right-sided ground-glass opacities. A repeated RT-PCR examination of sputum performed 4 days after admission showed positivity for SARS-CoV-2. She was transferred to the intensive care unit where she was placed in isolation. Obstetric ultrasonography revealed a normal fetus of 30 weeks' gestation. On hospital day 3, decreased fetal movement was observed with absent variability of the fetal heart rate, and an emergency cesarean delivery was performed. A preterm male infant was delivered that weighed 1830 g and with Apgar scores of 9, 10 at 1 and 5 minutes, respectively. Samples were taken of placenta, amniotic fluid, umbilical cord blood, gastric juice, and throat swabs of the infant; all tests were negative for SARS-CoV-2 by RT-PCR. Three days following delivery RT-PCR test results of the neonatal throat swab and stool samples were negative. Seven and 9 days after birth throat swab and RT-PCR test findings from the mother and the infant remained negative for the novel coronavirus.

Renmin Hospital of Wuhan University, Wuhan and the Central Hospital of Qianjiang City, Qianjiang, China

Zhang and colleagues\textsuperscript{17} retrospectively examined medical records of 16 pregnant women with RT-PCR-confirmed COVID-19 and their newborn infants, and compared these results with a cohort of 45 pregnant women who were not infected (translated from Simplified Chinese by DAS); this constituted the first comparison study between women with and without SARS-CoV-2 infection during pregnancy. Among the 16 women with COVID-19 there were several mothers with comorbid obstetric conditions: 3 women had gestational diabetes, 3 had premature rupture of membranes, 3 had preterm deliveries, 2 had scarred uterus, and 2 required B-Lynch suture procedure (a form of compression suture used in obstetrics to mechanically compress an atonic uterus in the clinical setting of severe postpartum hemorrhage). There was 1 incident of severe preeclampsia, meconium-stained amniotic fluid, fetal distress, and fetal asphyxia. Three of 16 women with COVID-19 had cough, chest tightness, shortness of breath, and diarrhea that did not improve significantly with treatment. One of these mothers had COVID-19 pneumonia; she was 35 weeks' gestation with oxygen saturation of 93% accompanied by chest tightness and shortness of breath, and with decreased fetal movement and abnormal fetal heart monitoring. All of the women with COVID-19 underwent cesarean deliveries.

There were no significant differences between the groups of pregnant women with and without COVID-19 in occurrence of severe preeclampsia, gestational diabetes, premature rupture of membranes, fetal distress, meconium-
stained amniotic fluid, premature delivery, neonatal asphyxia, B-Lynch suture procedure or other compression sutures. The proportion of uterine scarring in the non–COVID-19 group was statistically higher than that in COVID-19 group ($P = .03$); this abnormality predated the development of COVID-19.

Among the cohort of 16 mothers with COVID-19 there were 10 infants for whom SARS-CoV-2 infection status was known; all findings were negative by RT-PCR analysis of throat swabs. Nine of these newborns were full-term and 1 was preterm (36 weeks 2 days). Three of the neonates had bacterial pneumonia as based on their symptoms, laboratory testing, sputum culture, and imaging results; all of them recovered after treatment. After discharge of the newborns from the hospital, follow-up examinations demonstrated no neonatal illness or deaths.

**DISCUSSION**

Intrauterine transmission is one of the most serious complications of viral diseases occurring during pregnancy. It can occur with maternal infection by congenitally transmitted TORCH agents (acronym for Toxoplasma, other, rubella, cytomegalovirus, herpes) that also include Zika virus and Ebola virus. Maternal-fetal transmission of viral diseases (with the exception of herpes virus) is usually through the hematogenous route in which the virus circulating in the maternal blood stream enters the placenta, reaches the chorionic villous tree and fetal blood vessels, and is transmitted to the fetus. Fortunately, this mechanism of transmission has been shown not to occur with infection of pregnant women with 2 other pathogenic coronaviruses—SARS-CoV and MERS-CoV—although the clinical infections caused by these coronaviruses has resulted in severe maternal pneumonia, maternal deaths, and early pregnancy losses.

In this analysis of the detailed published reports of 38 pregnant women with COVID-19, of whom 37 had RT-PCR–confirmed SARS-CoV-2 infection, there were no cases of either severe pneumonia or maternal deaths. Although there were comorbid conditions present in some of the women, some of which were obstetric in etiology, they did not result in life-threatening maternal SARS-CoV-2 disease. It is significant that these comorbid maternal conditions, which included pre eclampsia, pregnancy–induced hypertension, uterine scarring, gestational diabetes, and uterine atony, did not appear to be risk factors for intrauterine transmission of SARS-CoV-2 to the fetus.

Among the 29 neonates delivered to these women who underwent testing there were no cases of RT-PCR–confirmed SARS-CoV-2 infection, despite the existence of perinatal complications in some of the infants. An interesting observation is that in those cases where placentas were tested for SARS-CoV-2, the results were negative. This lack of maternal-fetal transmission of SARS-CoV-2 is consistent with past experiences with other coronavirus infections—SARS and MERS—occurring in pregnant women.

Early in the epidemic there were 2 reported cases of neonatal SARS-CoV-19 infection. One involved an infant diagnosed at 17 days of life with a history of close contact with 2 confirmed cases of SARS-CoV-2 infection (mother and nanny), and the other was a neonate who was found to be infected 36 hours following delivery. For both infants there was no direct evidence for vertical transmission, and because viral testing was delayed, a postpartum neonatal infection acquired through an infected contact could not be eliminated. A joint mission by the World Health Organization, consisting of 25 national and international experts, travelled to the affected regions of China between February 16 and 24, 2020. They investigated 147 pregnant women (64 confirmed, 82 suspected, and 1 asymptomatic with COVID-19). Among these women 8% had severe disease and 1% had critical conditions. The joint mission concluded that pregnant women were not at higher risk for developing severe disease due to COVID-19. This report did not examine vertical transmission or neonatal outcomes.

As this global epidemic continues to expand there will be additional information available on the effects of COVID-19 on pregnant women and their infants. In the unfortunate event of mortality resulting from SARS-CoV-2 infection among pregnant women or neonates, pathologic evaluation of tissues together with molecular characterization of the virus would be useful in determining the pathogenesis of the disease as it has in many cases of emerging infections.

There are currently updated recommendations available on the obstetric management of SARS-CoV-2 infection in pregnant women. In addition, it must be remembered that as vaccine development proceeds for COVID-19, pregnant women should be considered for inclusion in the clinical trials, as well as the eventual distribution of the vaccine, unless the risks outweigh the potential benefits.


