Standpunt COVID-19 en zwangerschap, bevalling en kraambed

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Disclaimer

Algemeen
De werkgroep heeft de grootst mogelijke zorg besteed aan de inhoud van dit standpunt. Desondanks accepteert zij geen aansprakelijkheid voor eventuele onjuistheden in dit document, voor enigerlei schade of voor andersoortige gevolgen die voortvloeien uit of samenhangen met het gebruik van dit standpunt.

Dit standpunt biedt concrete aandachtspunten en besluitvormingscriteria voor zwangere vrouwen met COVID-19. Omdat de literatuur voornamelijk Engelstalig is en om internationale afstemming te bevorderen, is een groot deel van de tekst in het Engels geschreven. De aanbevelingen zijn ook vertaald naar het Nederlands.

Looptijd
Dit standpunt is geldig vanaf 17 juni 2020. De hoofdstukken 2. miskraam en 3. verticale transmissie zijn toegevoegd op 6 augustus 2020. Er zijn op 12 januari 2021 aanpassingen doorgevoerd t.a.v. hoofdstuk 1, vraag 1 ‘Pregnancy in women with COVID-19: more complications of COVID-19 and/or more pregnancy complications?’. Dit n.a.v. nieuwe bewijsvoering vanuit de literatuur (Allotey et al. 2020) dat weergeeft dat COVID-19 schadelijker is voor zwangeren dan eerder bekend.

Dit standpunt kan worden bijgewerkt en/of gewijzigd op basis van nieuwe informatie.

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Aanbevelingen; recommendations

1. Zwangerschapscomplicaties - Pregnancy complications

Tot nu toe is er geen bewijs om aan te nemen dat infectie met SARS-CoV-2 tijdens de zwangerschap leidt tot meer pre-eclampsie, foetale groeivertraging en/of spontane vroeggeboorte.

Ernstige of kritische SARS-CoV-2 infectie bij zwangere vrouwen zou een effect kunnen hebben op de foetale groei. Daarom adviseren wij om de foetale groei in het derde trimester van de zwangerschap te bewaken met tenminste 2 echo's vanaf 28 weken zwangerschapsduur met een interval van 2 weken; indien de uitslag niet verontrustend is vervolgens met langere tussenpozen.

In overeenstemming met het recente advies om alle patiënten die zijn opgenomen vanwege COVID-19 te behandelen met LMWH, wordt dit ook voor zwangere vrouwen aangeraden.

Na een ernstige of kritische SARS-CoV-2 infectie bij een zwangere vrouw bevelen wij aan om de prenatale zorg in het ziekenhuis te laten plaatsvinden.

So far, there is no evidence to assume that SARS-CoV-2 infection during pregnancy leads to a higher prevalence of preeclampsia, fetal growth restriction and/or spontaneous preterm birth.

Based on the hypothesis that severe or critical cases of SARS-CoV-2 infection in pregnant women might have an effect on fetal growth, we recommend monitoring of fetal growth in the third trimester of pregnancy (at least two ultrasound scans starting at 28 weeks of gestation with a 2 weeks interval; if reassuring with a longer interval thereafter).

According to recent guidelines it is advisable to treat all patients admitted because of COVID-19 disease with LMWH, this is recommended for pregnant women as well.

We recommend for pregnant women after a severe or critical SARS-CoV-2 infection to continue prenatal care in hospital.

Hoewel een ernstig verloop van COVID-19 bij vrouwen in de vruchtbare leeftijdsfase weinig voorkomt, hebben zwangeren met COVID-19 meer risico opgenomen te worden op de intensive care en is er bij hen vaker noodzaak tot invasieve beademing. Dit geldt vooral in het tweede helft van de zwangerschap.

Zwangere vrouwen met milde COVID-19 moeten behandeld worden zoals gebruikelijk, en verwijzing vanuit de eerste naar de tweede of derde lijn is niet nodig.

In geval van ernstig respiratoir falen door COVID-19 bij een zwangere vrouw wordt behandeling en beleid door een multidisciplinair team (intensivist en/of anesthesioloog, obstetricus en neonatoloog) aanbevolen. Afhankelijk van de ernst van de ziekte en de zwangerschapsduur dient de vrouw naar een derdelijns centrum te worden verwezen.

Although severe illness is uncommon in women of reproductive age, intensive care admission and invasive ventilation is more common in pregnant women with COVID-19 compared to non-pregnant women of the same age.

This is mainly applicable to the second stage of pregnancy.

Pregnant women with mild COVID-19 should receive care as usual, and referral from primary to secondary or tertiary care is not necessary.

It is recommended that in cases of severe respiratory failure in pregnant women due to COVID-19, therapy and management should be undertaken in a multidisciplinary team (critical care physician and/or anesthesiologist, obstetrician and neonatologist). Depending on the severity and the gestational age the woman should be referred to a tertiary care center.

2. Complicaties bij de bevalling - delivery complications

De bevalling van een vrouw met milde COVID-19 onder leiding van een verloskundige (eerste lijn, thuis of poliklinisch) kan op de voorgenomen locatie plaatsvinden en wij adviseren om de ademhalingsfrequentie extra in de gaten te houden om de klinische conditie van de vrouw te bewaken. Hiertoe kan een MEOWS-score worden gebruikt; bij een score ≥3 wordt verwijzing naar het ziekenhuis geadviseerd.

Bij een ziekenhuisbevalling (tweede of derde lijn) is er bij milde COVID-19 geen reden voor intensievere bewaking, maar is de gebruikelijke zorg met regelmatige maternale en foetale bewaking voldoende.

Bied bij ernstige ademhalingsproblemen van de barende vrouw hetzelfde ondersteunende beleid als bij niet-zwangere patiënten (moeder op de eerste plaats).

In midwifery-led care (primary care) and at home we advise additional monitoring of respiratory rate during labour to assess the clinical condition of women with mild COVID-19. A MEOWS score could be used for this purpose, with a cut-off of ≥ 3 for referral to hospital-led care.

During hospital deliveries (secondary or tertiary care), there is no reason to monitor women with mild COVID-19 more closely during labour. Care as usual with regular maternal and fetal monitoring is advised.

In cases of severe respiratory distress, supportive management should be similar to that in non-pregnant patients (mother always comes first).

3. (P)PROM

De werkgroep adviseert bij (P)PROM de standaard protocollen te volgen. Er kan geen specifiek advies worden gegeven over de timing van de bevalling na (P)PROM bij vrouwen met COVID-19.

Het advies om het kind geboren te laten worden, wordt gegeven op basis van de klinische conditie van moeder en foetus.

Als er tekenen zijn van intra-uteriene infectie adviseren wij dringend om de baring op korte termijn na te streven.

The working group recommends to follow standard protocols in case of (P)PROM. No specific advice can be given on the timing of delivery after (P)PROM in women with COVID-19.

The advice to deliver should be made based on the clinical condition (maternal as well as fetal).

If there are any signs of intrauterine infection, we strongly advise prompt delivery.

4. Borstvoeding en verzorging van de pasgeborene - nursing of the neonate

Een pasgeborene van een symptomatische moeder met COVID-19 kan borstvoeding krijgen, mits er aanvullende beschermende maatregelen worden toegepast om het risico van besmetting te minimaliseren. Aan de moeder moet worden uitgelegd dat horizontale transmissie niet 100% kan worden voorkomen.

Een moeder met COVID-19 tijdens de bevalling in de thuissituatie dient instructies te krijgen over handhygiëne en hoe een chirurgisch masker te gebruiken tijdens contactmomenten zoals het voeden. Dat masker kan maximaal drie keer gebruikt worden (of 3 uur achtereen).

Dezelfde hygiënische maatregelen worden aanbevolen bij het geven van flesvoeding en bij andere contactmomenten zoals knuffelen. Deze aanbevelingen gelden evenzeer voor andere leden van het huishouden indien deze SARS-CoV-2 positief zijn.

Deze hygiënische maatregelen worden toegepast tot de ouder vrij is van COVID-19 (1. tenminste 72 uur na afname van de positieve test bij een asymptomatische infectie of 2. bij een patiënt tenminste 7 dagen na de start van de symptomen en die nu voor tenminste 24 uur geen symptomen meer heeft (koorts, diarree, spierpijn, keelpijn, benauwdheid of neusverkoudheid).

Neonates who are born to symptomatic mothers with COVID-19 can be breastfed, provided that additional protective measures are applied to minimize the risk of horizontal transmission. It should be explained that horizontal transmission cannot be prevented completely.

Women with COVID-19 during delivery, who are at home, should be instructed about proper hand hygiene and how to use a surgical mask during contact moments such as feeding of their neonate, and use a mask for a maximum of three times (or 3 hours consecutively).

Similar hygiene measures should be taken in case of formula feeding and other contact moments, such as cuddling. This recommendation not only applies to the mother, but also to the other parent if SARS-CoV-2 positive.

These hygiene measures need to be applied until the parent is free from COVID-19 (1. at least 72 hours after positive testing in case of an asymptomatic infection, or 2. in a patient at least 7 days after the start of the symptoms and not having symptoms for more than 24 hours (of fever, diarrhea, myalgia, sore throat, shortness of breath or nasal congestion).

5. Miskraam - miscarriage

Tot op heden is er geen bewijs dat een SARS-CoV-2 infectie tijdens de zwangerschap leidt tot een hoger miskraam risico.

SARS-CoV-2 infectie tijdens de zwangerschap is geen reden om iets te veranderen aan de gebruikelijke zwangerschapscontroles.

So far, there is no evidence to assume that SARS-CoV-2 infection during pregnancy leads to a higher prevalence of miscarriage.

There is no reason to change the usual antenatal care for women with SARS-CoV-2 infection during pregnancy.

6. Verticale transmissie - vertical transmission

Verticale transmissie en horizontale transmissie vroeg na de geboorte komen voor.

Op dit moment zijn er geen aanwijzingen dat een vaginale bevalling het risico op verticale transmissie verhoogt ten opzichte van een sectio caesarea. Informeer de zwangere hierover.

Laat de beslissing over de modus partus, het plaatsen van een caput elektrode en het doen van micro-bloedonderzoek niet beïnvloeden door een maternale SARS-CoV-2 besmetting.

It cannot be ruled out that vertical transmission or horizontal transmission early after birth occurs in some cases.

At this point in time there is no reason to assume that vaginal delivery increases the risk of vertical transmission compared to delivery by caesarean section. This information should be conveyed to the pregnant woman.

Decisions about the mode of delivery, application of an electrode on the presenting part and micro blood sampling should not be influenced by maternal SARS-CoV-2 infection.

Korte inleiding

Eind 2019 werd COVID-19, het ziektebeeld veroorzaakt door het SARS-CoV-2 virus voor het eerst gediagnosticeerd in Wuhan, China. Inmiddels heeft het virus zich wereldwijd verspreid. In Nederland is het aantal patiënten sinds eind februari 2020 en het aantal ziekenhuis opnamen sinds halverwege maart, sterk gestegen.

In dit document worden adviezen gegeven over:

- Antenatale controles bij vrouwen die COVID-19 hebben (doorgemaakt) tijdens de zwangerschap.
- Verloskundig beleid tijdens de bevalling bij vrouwen met COVID-19.
- Borstvoeding en verzorging bij COVID-19.

Voor het opstellen van dit document is gebruik gemaakt van beschikbare wetenschappelijke publicaties en de ervaringen binnen en buiten het ziekenhuis met de behandeling van SARS-CoV-2 besmette patiënten.

Het document is ter consultatie voorgelegd aan de volgende wetenschappelijke verenigingen en beroepsorganisaties: NVOG, KNOV, NVA, NVK, Patiëntenfederatie Nederland, Stichting Zelfbewust Zwanger, Stichting Kind en Ziekenhuis, RIVM, NVMM, BO Geboortezorg, NBVK, V&VN, NFU, NVZ, STU.

Definities
De werkgroep hanteert de volgende definities (*conform de Leidraad persoonlijke bescherming in de poliklinische setting vanwege SARS-CoV-2 Versie 1.0 - 290420*):

Asymptomatische COVID-patiënt: een persoon bij wie de SARS-CoV-2 RT-PCR positief is, maar die op geen enkel moment aantoonbare symptomen ontwikkelt.

Presymptomatische COVID-patiënt: een besmet persoon in de 1 tot 2 dagen direct voordat symptomen duidelijk worden, bij wie het virus reeds uitgescheiden wordt.

De asymptomatisch en presymptomatisch patiënten worden samengenomen als *subklinische COVID-patiënten*.

De meest voorkomende symptomen van COVID-19 zijn: koorts, vermoeidheid, droge hoest, spierpijn, neusverkoudheid (verstopte neus en loopneus), keelpijn en (minder vaak) diarree. Onder *patiënten met COVID-19* verstaat de werkgroep mensen die één of meer van deze symptomen hebben en een positieve SARS-CoV-2 RT-PCR test.

Voor de ernst van de ziekte wordt de volgende indeling aangehouden (Wu Z, 2020):

- Mild - ie. non-pneumonia and mild pneumonia.
- Severe - ie. dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or lung infiltrates > 50% within 24 to 48 hours.
- Critical - ie. septic shock, respiratory failure, and/or multiple organ failure.

Hoofdstuk 1 - de eerste vijf vragen; the first five questions

Uitgangvragen

1. Leidt besmetting met SARS-CoV-2 in de zwangerschap tot meer zwangerschapscomplicaties zoals pre-eclampsie, intra-uteriene groeivertraging en vroeggeboorte?
2. Zijn er complicaties van COVID-19, met name pulmonale complicaties, die ernstiger zijn bij zwangere vrouwen dan bij niet-zwangere vrouwen (en bij mannen)?
3. Leidt COVID-19 tijdens de zwangerschap tot meer complicaties bij de bevalling?
4. Wanneer moet een vrouw met COVID-19 en (P)PROM bevallen?
5. Welke aanpassingen zijn nodig voor vrouwen met COVID-19 ten tijde van de bevalling om borstvoeding te geven en het risico op besmetting te voorkomen? Wat is het risico van besmetting tijdens de voeding en verzorging van de pasgeborene? Mogen zij huid op huid contact hebben?

Clinical questions

1. Do SARS-CoV-2 infections in pregnant women lead to more pregnancy complications like preeclampsia, fetal growth restriction and preterm birth?
2. Which complications are more prevalent among pregnant women with SARS-COV-2 infections than in non-pregnant women (and men)?
3. Do SARS-CoV-2 infections in pregnant women lead to more complications during delivery?
4. When should pregnant women with COVID-19 after (P)PROM be delivered?
5. What precautions do women with SARS-CoV-2 infections at the time of delivery need to take to breastfeed their newborn while minimizing the risk of transmission? What is the risk of transmission of the virus during nursing? Is skin to skin contact allowed?

Search and select

The databases PubMed and Embase (via Embase.com) were searched with relevant search terms until 20 April, 2020. The detailed search strategy is depicted below. The initial search also included MERS and SARS. However, based on the results of the rapid review by Mullins (2020), showing that the consequences of SARS-CoV-2 for pregnant women were not comparable to those of MERS and SARS, these papers were not considered further. The systematic literature search (limited to COVID-19) initially resulted in 126 hits. The search was updated on a weekly basis and further supplemented with 219 hits, resulting in a total of 345 hits. During the updating process, other information sources such as Google Scholar, the preprint source medRxiv, and the database of the World Health Organization were searched in addition to the conventional databases. Studies were selected based on the following criteria: any reports of original clinical data concerning pregnant women with COVID-19. Forty-five articles were selected, 14 of which were excluded. The reasons for exclusion are presented in the table 'Excluded papers with reasons' below. One additional paper was found by searching the references of the review articles. This resulted in the inclusion of 32 papers reporting original data.

Results

Thirty-two papers were included in the analysis of the literature. From the identified papers information was extracted regarding all five clinical questions, so no distinction was made between papers identified by the four initial search strategies. Important study characteristics are summarized in Table 1 and results are summarized in Tables 2 to 5.

Summary of the literature

Description of studies

Thirty-two papers were included, 22 from China, two from the USA, and one from Korea, Honduras, Turkey, Sweden, Italy, Peru, Australia and Iran each. Fifteen were case reports, and 17 were case series, the number of cases varying from 2 to 42, median 9. Assuming that there were no duplicate descriptions of patients in the included papers, these papers report the clinical data of 251 pregnant women and 156 neonates. The majority of the reported cases were admitted in the last trimester of pregnancy, and delivery was mostly by Caesarean section (CS). The indications for the CS were often not reported.

Results

The sparse information in the literature did not give any indication of an increased risk of pregnancy complications apart from the symptoms of the disease which may lead to fetal distress due to hypoxia, nor of an increased risk of pulmonary complications in pregnant women (Table 2).

The sparse information in the literature did not give any indication of an increased risk of complications during delivery, apart from the symptoms of the disease which may lead to fetal distress due to hypoxia (Table 3).

There was virtually no information in the literature about (P)PROM (Table 4).

In 12 women breast milk samples were tested for the presence of the virus, and in all cases the tests were negative (Table 5).

1. Pregnancy in women with COVID-19: more complications of COVID-19 and/or more pregnancy complications?

1. Do SARS-CoV-2 infections in pregnant women lead to more pregnancy complications like preeclampsia, fetal growth restriction and preterm birth?
2. Which complications are more prevalent among pregnant women with SARS-CoV-2 infections than in non-pregnant women (and men)?

Considerations

Pros and cons of the intervention and the quality of evidence

Of the 251 pregnant women currently described in the included literature, three women were diagnosed with preeclampsia, nine with gestational hypertension, nine with spontaneous preterm birth and 18 with gestational diabetes (Table 2).

Although not all studies made a clear distinction in spontaneous versus induced or iatrogenic preterm births, it seems that pregnant women with COVID-19 more frequently underwent a preterm CS (< 37 weeks) due to their worsening maternal condition, but this was rarely before 32 weeks.

One case of stillbirth at 34 weeks' gestational age was described in a patient with a severe ARDS and multi-organ disease caused by COVID-19 (Liu Y, 2020). Although there is a risk of underreporting due to the non-structural data collection and low level of evidence of the selected articles (only retrospective case-reports or case series with small numbers), there is no evidence that the pregnancy complications preeclampsia, fetal growth restriction and preterm birth are more frequent in women with COVID-19 compared to healthy pregnant women.

Furthermore, due to the short follow-up period of COVID-19 so far and the fact that most of the women presented in the third stage of pregnancy and delivered shortly after the diagnosis or were diagnosed postpartum, nothing can be concluded yet about the possible effects of SARS-CoV-2 infections during early pregnancy on the prevalence of preeclampsia and fetal growth restriction later in pregnancy.

From other respiratory viruses (Influenza, SARS Cov1, MERS) it is known that these infections may have a higher risk of respiratory failure during pregnancy (particularly in the third trimester). This may be caused by reduced lung volume and the changed cardiopulmonary status of pregnant women. Based on a recent living systematic review on COVID-19 during pregnancy the odds of admission to the intensive care unit and the need for invasive ventilation appears to be higher among (recently) pregnant women, compared with non-pregnant women with COVID-19. The following maternal risk factors are associated with severe COVID-19: increasing age, high body mass index, chronic hypertension and pre-existing diabetes. Furthermore, pre-existing maternal comorbidity is associated with intensive care unit admission and the need for invasive ventilation. (Allotey et al., August 2020)

Values and preferences of patients (and if applicable their caretakers)

Women experiencing possible symptoms of COVID-19 during pregnancy may be worried about the effects of the disease on themselves and their fetuses. For both midwifery-led care and hospital-led care it is important to take this into account and to inform them that based on the above mentioned (limited) data there is no evidence to assume that SARS-CoV-

2 infection during pregnancy leads to a higher prevalence of preeclampsia, fetal growth restriction and/or preterm birth. So far, women with only mild symptoms and no need for oxygen treatment (mild disease) can be reassured that it is safe to continue care as usual during their pregnancies. Attention has to be paid to the fact that the long-term effects on the fetus (especially from an infection in the 1st or 2nd trimester) are not known yet.

Costs
Not applicable to this item.

Acceptability, feasibility and implementation
Not applicable to this item.

Recommendations
Rationale of the recommendation: weighting of arguments for and against the intervention
No reliable answer can be given on the prevalence of preeclampsia, fetal growth restriction and preterm birth in SARS-CoV-2 infected pregnant women. Based on a low level of evidence, COVID-19 seems not to increase the risk of preeclampsia, fetal growth restriction and spontaneous preterm birth. More structural data and longer follow-up of COVID-19 patients with an ongoing pregnancy is needed to have a final answer on this question and also on the effects of an infection in the 1st or 2nd trimester.

For severe or critical cases it is not known whether a period of maternal hypoxemia with need for oxygen has an effect on the fetal growth. Because this is not known yet, we consider that in these cases (but not for the mild cases) fetal growth should be monitored in the 3rd trimester of pregnancy. Furthermore, for severe or critical cases follow-up of the ongoing pregnancy in the hospital is recommended.

Recent data show that thrombosis and pulmonary embolism plays an important role in severe and critical cases of SARS-CoV-2 infections (Tang, 2020; Klok, 2020; Cui, 2020). As pregnancy is characterized by a state of hypercoagulability, theoretically there might be an increased risk for venous thromboembolism (VTE) in pregnant women with SARS-CoV-2 infections. The Dutch guideline recommends to treat all hospitalized patients with COVID-19 with low molecular weight heparin (LMWH) (*Leidraad COVID-19 coagulopathie, 14 april 2020*).

So far, there is no evidence to assume that SARS-CoV-2 infection during pregnancy leads to a higher prevalence of preeclampsia, fetal growth restriction and/or spontaneous preterm birth.

Based on the hypothesis that severe or critical cases of SARS-CoV-2 infection in pregnant women might have an effect on fetal growth, we recommend monitoring of fetal growth in the third trimester of pregnancy (at least two ultrasound scans starting at 28 weeks of gestation with a 2 weeks interval; if reassuring with a longer interval thereafter).

According to recent guidelines it is advisable to treat all patients admitted because of COVID-19 disease with LMWH, this is recommended for pregnant women as well.

We recommend for pregnant women after a severe or critical SARS-CoV-2 infection to continue prenatal care in hospital.

Tot nu toe is er geen bewijs om aan te nemen dat infectie met SARS-CoV-2 tijdens de zwangerschap leidt tot meer pre-eclampsie, foetale groeivertraging en/of spontane vroeggeboorte.

Ernstige of kritische SARS-CoV-2 infectie bij zwangere vrouwen zou een effect kunnen hebben op de foetale groei. Daarom adviseren wij om de foetale groei in het derde trimester van de zwangerschap te bewaken met tenminste 2 echo's vanaf 28 weken zwangerschapsduur met een interval van 2 weken; indien de uitslag niet verontrustend is vervolgens met langere tussenpozen.

In overeenstemming met het recente advies om alle patiënten die zijn opgenomen vanwege COVID-19 te behandelen met LMWH, wordt dit ook voor zwangere vrouwen aangeraden.

Na een ernstige of kritische SARS-CoV-2 infectie bij een zwangere vrouw bevelen wij aan om de prenatale zorg in het ziekenhuis te laten plaatsvinden.

Although severe illness is uncommon in women of reproductive age, intensive care admission and invasive ventilation is more common in pregnant women with COVID-19 compared to non-pregnant women of the same age. This is mainly applicable to the second stage of pregnancy.

Pregnant women with mild COVID-19 should receive care as usual, and referral from primary to secondary or tertiary care is not necessary.

It is recommended that in cases of severe respiratory failure in pregnant women due to COVID-19, therapy and management should be undertaken in a multidisciplinary team (critical care physician and/or anesthesiologist, obstetrician and neonatologist). Depending on the severity and the gestational age the woman should be referred to a tertiary care center.

Hoewel een ernstig verloop van COVID-19 bij vrouwen in de vruchtbare leeftijdsfase weinig voorkomt, hebben zwangeren met COVID-19 meer risico opgenomen te worden op de intensive care en is er bij hen vaker noodzaak tot invasieve beademing. Dit geldt vooral in het tweede helft van de zwangerschap.

Zwangere vrouwen met milde COVID-19 moeten behandeld worden zoals gebruikelijk, en verwijzing vanuit de eerste naar de tweede of derde lijn is niet nodig.

In geval van ernstig respiratoir falen door COVID-19 bij een zwangere vrouw wordt behandeling en beleid door een multidisciplinair team (intensivist en/of anesthesioloog, obstetricus en neonatoloog) aanbevolen. Afhankelijk van de ernst van de ziekte en de zwangerschapsduur dient de vrouw naar een derdelijns centrum te worden verwezen.

2. Labour in women with COVID-19: more delivery complications?

3. Do SARS-CoV-2 infections in pregnant women lead to more complications during delivery?

Considerations

Pros and cons of the intervention and the quality of evidence

The vast majority of the SARS-CoV-2 infected women reported in the included literature who delivered, had a cesarean section (Table 3). The study with most of the vaginal deliveries was the only study from Italy (Ferrazzi, 2020). Twenty-four of the 42 COVID-19 patients delivered vaginally in this study. Most other studies were in Chinese patients with a high percentage of CS. Indications for CS were not always mentioned (Table 3). In mild cases of COVID-19 induction of labor or waiting for the spontaneous onset of labor are feasible options. Fetal distress caused by hypoxemia was described in 15 cases.

Values and preferences of patients (and if applicable their caretakers)

Women with (suspicion of) COVID-19 need information about the optimal place for delivery, whether their risk of labour complications is increased, and what may be different due to COVID-19 during labour.

Costs

Not applicable to this item.

Acceptability, feasibility and implementation

Not applicable to this item.

Recommendations

Rationale of the recommendation: weighting of arguments for and against the intervention

Based on the currently available data (mostly Chinese reports) most women delivered by a CS. However, taking into account that in general the percentage of CS is twice as high in China (41.3 %) and Italy (38%) compared to the Netherlands (17%) (Macfarlane 2014, Boerma 2018), the described high percentage of CS in COVID-19 patients is presumably not comparable to our setting. Only in severe COVID-19 cases during pregnancy (severe cases defined as: hospital admittance with oxygen therapy or artificial ventilation) it is likely that a woman has a higher chance for a CS on either maternal or fetal indication (fetal distress possibly caused by maternal hypoxemia seems to occur more frequently in severe cases of COVID-19). To detect a potential deteriorating clinical condition of the mother, the MEOWS-score (Modified Early Obstetric Warning Score) (Figure) might be of assistance during labour. This may be especially helpful for women with COVID-19 delivering in midwifery-led care and at home.

Score	3	2	1	0	1	2	3
Temperature		<35 °c	35-35.9 °c	36-37.4 °c	37.5-37.9 °c	38.0-38.9 °c	≥39 °c
Systolic BP	≤69	70-79	80-89	90-139	140-149	150-159	≥160
Diastolic BP			≤49	50-89	90-99	100-109	≥110
Pulse		<40	40-49	50-99	100-109	110-129	≥130
Respiratory Rate	≤10			11-19	20-24	25-29	≥30
AVPU				Alert	Responds to Voice	Responds to Pain	Unconscious
Urine output mLs/hr	<10	<30		Not Measured			

In midwifery-led care (primary care) and at home we advise additional monitoring of respiratory rate during labour to assess the clinical condition of women with mild COVID-19. A MEOWS score could be used for this purpose, with a cut-off of ≥ 3 for referral to hospital-led care.

During hospital deliveries (secondary or tertiary care), there is no reason to monitor women with mild COVID-19 more closely during labour. Care as usual with regular maternal and fetal monitoring is advised.

In cases of severe respiratory distress, supportive management should be similar to that in non-pregnant patients (mother always comes first).

De bevalling van een vrouw met milde COVID-19 onder leiding van een verloskundige (eerste lijn, thuis of poliklinisch) kan op de voorgenomen locatie plaatsvinden en wij adviseren om de ademhalingsfrequentie extra in de gaten te houden om de klinische conditie van de vrouw te bewaken. Hiertoe kan een MEOWS score worden gebruikt; bij een score ≥ 3 wordt verwijzing naar het ziekenhuis geadviseerd.

Bij een ziekenhuisbevalling (tweede of derde lijn) is er bij milde COVID-19 geen reden voor intensievere bewaking, maar is de gebruikelijke zorg met regelmatige maternale en foetale bewaking voldoende.

Bied bij ernstige ademhalingsproblemen van de barende vrouw hetzelfde ondersteunende beleid als bij niet-zwangere patiënten (moeder op de eerste plaats).

3. (P)PROM in pregnant women with COVID-19

4. When should pregnant women with COVID-19 after (P)PROM be delivered?

Considerations

Pros and cons of the intervention and the quality of evidence

There is no valuable literature regarding the clinical course of (P)PROM during SARS-CoV-2 infection (only 9 cases have been described in literature). Since this is too little information to formulate specific recommendations, the working group has the opinion to follow the identical protocol as for women without COVID-19 in case of (P)PROM. It is well known that (P)PROM increases the risk of intrauterine infection, and this should therefore be monitored. Furthermore, maternal deterioration can be a reason to terminate pregnancy.

Values and preferences of patients (and if applicable their caretakers)

If SARS-CoV-2 positive women with (P)PROM would be immediately induced instead of watchful waiting, this would have consequences for mother and child after birth. Depending on the gestational age at (P)PROM, there is a chance that the child will be admitted to the neonatal ward because of prematurity. Since SARS-CoV-2 positive parents are not allowed on the neonatal ward, this would mean in some hospitals that parents and child will be separated after birth.

Costs

Not applicable to this item.

Acceptability, feasibility and implementation

Since the advice is to follow standard protocol, acceptability, feasibility and implementation are not applicable.

Recommendations

The working group recommends to follow standard protocols in case of (P)PROM. No specific advice can be given on the timing of delivery after (P)PROM in women with COVID-19.

The advice to deliver should be made based on the clinical condition (maternal as well as fetal).

If there are any signs of intrauterine infection, we strongly advise prompt delivery.

De werkgroep adviseert bij (P)PROM de standaard protocollen te volgen. Er kan geen specifiek advies worden gegeven over de timing van de bevalling na (P)PROM bij vrouwen met COVID-19.

Het advies om het kind geboren te laten worden, wordt gegeven op basis van de klinische conditie van moeder en foetus.

Als er tekenen zijn van intra-uteriene infectie adviseren wij dringend om de baring op korte termijn na te streven.

4. Nursing of the neonate[1]

5. What precautions do women with SARS-CoV-2 infections need to take to breastfeed their newborn while minimizing the risk of transmission? What is the risk of transmission of the virus during nursing? Is skin to skin contact allowed?

Considerations

Pros and cons of the intervention and the quality of evidence

Literature regarding breastfeeding during maternal SARS-CoV-2 infection is sparse and therefore the evidence grade is low. Breastmilk samples of 12 SARS-CoV-2 positive mothers have been tested for the presence of the virus, all samples were negative. Therefore, so far, there is no reason to assume that the virus is transmitted from mother to child through breastmilk. Furthermore, breastfeeding has beneficial effects, such as the transmission of maternal antibodies and stimulates bonding between mother and baby. However, since there is an increased risk of horizontal transmission during direct contact between a symptomatic SARS-CoV-2 positive mother and her child, it is essential to apply additional hygiene measures during breastfeeding. However, these hygiene measures apply for all contact moments with the child, and thus also for formula feeding. It could be considered to pump breastmilk and leave the feeding of the baby to a SARS-CoV-2 negative person. However, this also reduces the (skin-to-skin) contact between mother and baby, which is beneficial for bonding. According to the World Health Organization, asymptomatic patients (definition according to 'Leidraad persoonlijke bescherming in de poliklinische setting vanwege SARS-CoV-2 Versie 1.0 - 290420': a person with a positive SARS-CoV-2 RT-PCR test, who does not develop demonstrable symptoms at any moment) are much less infectious than symptomatic patients, and do not contribute to the spread of the disease. Therefore, extra protective measures do not seem necessary: 1) at least 72 hours after positive testing in case of an asymptomatic infection, or 2) in a patient at least 7 days after the start of the symptoms and not having symptoms for more than 24 hours (fever, diarrhea, muscle soreness, sore throat, shortness of breath or nasal congestion).

It is important, especially for care-givers and parents, to realize that a neonate may develop COVID-19 up to 14 days after the mother has become free of symptoms (see NVK guideline: Beleid bij neonaat en zwangere bij verdenking COVID-19, 17 april 2020). This means that care professionals visiting families at home should use protective equipment in case of close contact with the neonate and/or the mother:

- until the mother is disease-free (defined as minimal 7 days since start of symptoms and at least free of symptoms for 24 hours);
- and during the entire quarantaine period of the neonate (until 14 days from the moment the mother is disease-free)(LCI bijlage Uitgangspunten PBM buiten het ziekenhuis).

General guidance on prevention of horizontal transmission in households can be found on the following sites:

- https://lci.rivm.nl/informatiepatientthuis
- https://lci.rivm.nl/informatiebriefhuisgenootthuis

[1] These considerations and recommendations pertain to the situation of a mother who is tested SARS-CoV-2 positive at the time of delivery.

Values and preferences of patients (and if applicable their caretakers)
It is understandable that women who are keen to breastfeed their child want to do this also in case of a SARS-CoV-2 infection. These women should be well informed about the possible risks of transmission and how to minimize these risks. The possibility of horizontal transmission cannot be fully prevented, but proper hygiene measures lower this risk. Furthermore, similar risks and advices apply to formula feeding and other contact moments (for example cuddling, diaper changes), and to the partner. In case of a partner with COVID-19, similar measures apply to nursing of the baby by the partner. The infection could be transmitted both to his/her partner and the neonate.

Costs
The advice to wear a surgical mask during feeding increases the costs. However, the same advice applies to formula feeding.

Acceptability, feasibility and implementation
It should be considered whether it is feasible to supply surgical masks to symptomatic mothers with COVID-19 for all contact moments with their child, since these masks are sparse.

Recommendations

Neonates who are born to symptomatic mothers with COVID-19 can be breastfed, provided that additional protective measures are applied to minimize the risk of horizontal transmission. It should be explained that horizontal transmission cannot be prevented completely.

Women with COVID-19 during delivery, who are at home, should be instructed about proper hand hygiene and how to use a surgical mask during contact moments such as feeding of their neonate, and use a mask for a maximum of three times (or 3 hours consecutively).

Similar hygiene measures should be taken in case of formula feeding and other contact moments, such as cuddling. This recommendation not only applies to the mother, but also to the other parent if SARS-CoV-2 positive.

These hygiene measures need to be applied until the parent is free from COVID-19 (1. at least 72 hours after positive testing in case of an asymptomatic infection, or 2. in a patient at least 7 days after the start of the symptoms and not having symptoms for more than 24 hours (of fever, diarrhea, myalgia, sore throat, shortness of breath or nasal congestion).

Een pasgeborene van een symptomatische moeder met COVID-19 kan borstvoeding krijgen, mits er aanvullende beschermende maatregelen worden toegepast om het risico van besmetting te minimaliseren. Aan de moeder moet worden uitgelegd dat horizontale transmissie niet 100% kan worden voorkomen.

Een moeder met COVID-19 tijdens de bevalling in de thuissituatie dient instructies te krijgen over handhygiëne en hoe een chirurgisch masker te gebruiken tijdens contactmomenten zoals het voeden. Dat masker kan maximaal drie keer gebruikt worden (of 3 uur achtereen).

Dezelfde hygiënische maatregelen worden aanbevolen bij het geven van flesvoeding en bij andere contactmomenten zoals knuffelen. Deze aanbevelingen gelden evenzeer voor andere leden van het huishouden indien deze SARS-CoV-2 positief zijn.

Deze hygiënische maatregelen worden toegepast tot de ouder vrij is van COVID-19 (1. tenminste 72 uur na afname van de positieve test bij een asymptomatische infectie of 2. bij een patiënt tenminste 7 dagen na de start van de symptomen en die nu voor tenminste 24 uur geen symptomen meer heeft (koorts, diarree, spierpijn, keelpijn, benauwdheid of neusverkoudheid).

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Tables first five questions

Table 1. Papers reporting on cases of pregnant women with COVID-19 - search date 20 April 2020

first author, year (journal)	place	time	number of women / neonates	consecutive patients?	gestational age at entry	gestational age at delivery	information about (1 or more of the following) 1. pregnancy complications 2. complications of labour 3.(P)PROM 4. breastfeeding
Alzamora (Am J Perinatol)	British American Hospital, Lima, Peru	March 29, 2020	1/1	NA	33	33	1, 2
Breslin (Am J Obstet Gynecol MFM)	Columbia University Irving Medical Center and Allen Hospital (New York, NY)	March 13 to 27, 2020	31 of 43 women who tested positive were symptomatic	yes; all pregnant women who tested positive in this period were included	not extractable for symptomatic women separately	not extractable for symptomatic women separately	1, 3
Chen H (Lancet)	Zhongnan Hospital of Wuhan University, Wuhan, China,	from Jan 20 to Jan 31, 2020	9 /9	not clear	36 – 39 weeks	not reported	1, 2, 4
Chen R (Canadian Journal of Anesthesia)	Renmin hospital of Wuhan University, China	30 Jan – 23 Feb 2020	17	Not clear	Not reported	3 < 37 weeks, 14 > 37 weeks	1, 2
Chen S (Zhonghua Bing Li Xue Za Zhi)	Union Hospital, Tongji Medical College, Huazhong University, Wuhan, China	Placental tissue received on 4 Feb 2020	3/3	Not reported	35-39 weeks	35-39 weeks	1, 2
Chen S, Liao E and Shao Y	Maternal and Child Hospital of Hubei	between January 20 and	5/5	'all 5 cases of pregnant women with COVID-19'	38 – 41 weeks	38 – 41 weeks	1, 2

(Journal of Medical Virology)	Province, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China	February 10, 2020					
Chen Y (Front Pediatr)	Tongji Hospital, Wuhan, China	Not reported	4/4	Not clear (only live born neonates included)	Not reported	>37	1,2
Fan (Clin Infect Dis)	Renmin Hospital, Wuhan, China	Jan 2020	2/2	no	36-37	36+5-39	1,2,4
Ferrazzi E (Pre Print SSRN)	12 northern Italian centres	1-20 March 2020	42/42	Yes ('few might have slipped through this network and not reported')	Not reported	term: n =30 34-37 wk: n =7 <34 wk: n = 4 Missing: n =1	1,2, 4
Gidlöf (Acta Obstet Gynecol Scand)	Stockholm South General Hospital, Sweden	Not reported	1 / 2	NA	36+2	36+2	1,2,4
Iqbal (NEJM)	Washington DC, USA	Not reported	1/1	NA	39	39+	2,4
Kalafat (UOG)	Ankara, Turkey	March 2020	1/1	NA	35+3	36+	1,2,4
Khan (Infection Control & Hospital Epidemiology)	Renmin Hospital, Wuhan China	Jan 28 – Mar 1 2020	3/3	Not clear	34+6-39+1	34+6-39+1	2
Lee (Korean J of Anesthesiol)	Daegu Fatima Hospital, South Korea	Feb 2020	1/1	NA	36+2	37+6	1,2
Li N (Clin Infect Dis)	Hubei Provincial Maternal and Child Health Center, Wuhan	Jan 24 – Feb 29, 2020	16/17 (confirmed cases only)	yes	33+6-40+4	Mean 38	1,2,3

Li Y (Emerg Infect Dis)	Zhejiang University, Hangzhou, China	6 Feb 2020	1/1	NA	35 weeks	35 weeks	1, 2, 4
Liao (Balkan Medical Journal)	Chongqing University Three Gorges Hospital, Chongqing China	Feb 2020	1/1	NA	35+1	35+3	1,2
Liu D (AJR)	Union Hospital, Tongji Medical College, Huazhong University, Wuhan, China.	20 Jan – 10 Feb 2020	15/11	yes	12-38 weeks	Not reported	1, 2
Liu H (Journal of Infection)	Xinhua hospital and Maternal and Child Health hospital Hubei, China	Jan 27-feb 14 2020	41/? (no information about neonates)	No	22-40+5	Not reported	1
Liu W (Front Med)	Tongji Hospital, Huazhong University of science and technology, Wuhan, China	2 – 5 Feb 2020	3/3	yes	37-40 weeks	38-40 weeks	1, 2, 4
Liu Y (J Infect)	hospitals outside of Wuhan	From Dec 8, 2020 to Feb 25, 2020	13/9 (3 ongoing pregnancy, 1 stillbirth)	not clear	25-38+ weeks	not reported, 6 preterm, all >32 weeks	1,2,3
Lowe (Aust N Z J Obstet Gynaecol)	Gold Coast University Hospital (GCUH), Southport, Australia	not reported	1/1	NA	40+0	40+3	2, 4
Wang S (Clin Infect Dis)	Tongji Hospital, Wuhan, China.	Feb 1, 2020	1/1	NA	40	40	1,2,4
Wang X (Clin Infect Dis)	The Affiliated Infectious Hospital of Soochow University, Suzhou, China.	Feb 2, 2020	1/1	NA	30	30+6	1,2,3,4
Wen	Qingdao, Shandong,	Jan 21 2020	1/0	NA	30	NA	1

(J Microbiol Immunol Infect)	China						
Xia (Pediatric Pulmonology)	Wuhan Red Cross Hospital, Wuhan, China	Jan 20, 2020	1/1	NA	36+5	37+2	1,2,3
Yu (Lancet Infect Dis)	Tongji Hospital, Wuhan, China	Jan 1 – Feb 8, 2020	7/7	yes	37-41+2	37-41	1,2
Zamaniyan (Prenat Diagn)	Imam Khomeini Hospital, Sari, Iran	March 7, 2020	1/1	NA	32	32	1, 2
Zambrano (Travel Medicine and Infectious Disease)	Hospital Escuela of Tegucigalpa, Honduras	March 2020	1/1	NA	31	32	1,2
Zhang (Zhonghua Fu Chan Ke Za Zhi)	Eastern Hospital Wuhan University People's Hospital	Jan 30 – feb 17, 2020	16/10 (6 ongoing pregnancy)	yes	not reported	35+5 -41	2,4
Zhang, B (Chest)	Xiaolan People's Hospital of Zhongshan, China	Feb 2020	1/1	NA	35+2		1,2
Zhu (Transl Pediatr)	5 hospitals in Hubei	Jan 20 – feb 5, 2020	9/10 (twins)	no	not reported	31-39	1,2,3

NA: not applicable

Table 2. Information about pregnancy complications in women with COVID-19

First author	number of women	number with pregnancy complications	types of pregnancy complications	Maternal comorbidity (not pregnancy-related)
Alzamora	1	1	need for mechanical ventilation because of COVID-19 pneumonia	
Breslin	43	4 (not clearly reported)	29 initially symptomatic patients: 20 presented with COVID-symptoms, 9 with obstetric complaints; 1 case of 34-week preterm labor, 1 case of term prelabor rupture of membranes 14 initially asymptomatic patiens: 2 (initial obstetrical indication for induction of labour) postpartum ICU admission to the ICU due to complications including respiratory distress	not reported
Chen H	9	6	1 pre-existent pre-eclampsia 1 pre-existent gestational hypertension 2 PROM 2 fetal distress Outcomes favourable in all mothers and neonates	1 influenza
Chen R	17	Unclear if complications are in different patients	5 anemia 1 hypertension 1 diabetes Outcomes favourable in all mothers and neonates	*5 anemia* *1 hypertension* *1 diabetes* Not reported if this was pregnancy-related
Chen S	3	3	2 placenta praevia 1 placental abruption Outcomes favourable in all mothers and neonates	Not reported
Chen S, Liao E and Shao Y	5	3	2 gestational diabetes 1 preeclampsia	none (‘all were physically fit and conceived naturally’)
Chen Y	4	1	Placenta praevia	1 cholecystitis
Fan	2	1	Vaginal bleeding third trimester	none

Ferrazzi E	42	Not clearly reported	6 preterm elective CS (2 <34 wk) 5 spontaneous preterm birth (1 <34 wk) 6 gestational diabetes	Not reported
Gidlöf	1	1	PE, gestational diabetes	Not reported
Kalafat	1	0		thalassemia
Lee	1	0	none	none
Li N	16	11	3 gestational diabetes 1 PE 1 PROM 3 gestational hypertension 1 sinus tachycardia 2 hypothyroidism 3 premature birth (2 (P)PROM, 1 placental bleeding) 2 fetal distress	N=2: Chronic hypertension, PCOS and Hep B (not clearly reported which were in the same patient)
Li Y	1	1	Fetal distress	Not reported
Liao	1	1	Fetal distress	Not reported
Liu D	15	2	1 placenta previa 1 gestational diabetes Outcomes favourable in all mothers and neonates (4 still pregnant)	1 thalassemia 1 history of mitral and tricuspid valve replacement
Liu H	41	8	4 gestational diabetes 3 gestational hypertension	1 hepatitis B
Liu W	3	3	1 Fetal distress 1 scar uterus + placenta accrete 1 gestational diabetes Outcomes favourable in all mothers and neonates	1 hypothyroidism and epiglottic cysts
Liu Y	13	6	6 preterm labour (between 32 and 36 weeks) 1 stillbirth at 34 weeks GA (in patient with severe ARDS and MODS) 1 PROM 3 fetal distress Favourable outcome mothers and neonates, except for 1 severe case	None of the patients had underlying medical disease

			(see above)	
Wang S	1	1	1 vaginal blood loss, abdominal pain and fever Favourable outcome mother and neonate	hypothyroidism
Wang X	1	1	1 fetal distress Favourable outcome mother and neonate	no
Wen	1	0		
Xia	1	1	1 fetal distress Favourable outcome mother and neonate	not reported
Yu	7	0		3 scar uterus, 1 hypothyroidism, 1 PCOS
Zamaniyan	1	1	very ill during pregnancy, but no mention of mechanical ventilation	history of controlled hypothyroidism
Zambrano	1	1	Gestational hypertension, fetus with a multicystic kidney	hypothyroidism
Zhang, B	1	1	Fetal endouterine asphyxia	Not reported
Zhu	9	7	6 fetal distress 3 PROM 1 placenta praevia 1 oligohydramnios 1 polyhydramnios 1 vaginal bleeding third trimester	no

Table 3. Information about labour complications in women with COVID-19

First author	number of women / neonates	mode of delivery (Caesarean section (CS) or vaginal delivery (VD))	labour complications
Alzamora	1/1	CS	Maternal indication (respiratory distress)
Breslin	2/2	Both CS	Indications: failed induction and arrest of descent. 1 woman had extensive blood loss during CS. No neonatal complications or signs of vertical transmission. Postpartum both mothers admitted to ICU, 1 b/o need for endotracheal intubation and 1 b/o uncontrollable hypertension.
Chen H	9 / 9	All CS	indications for CS: 1 elevated liver enzymes, 1 history of CS, 1 preeclampsia, 2 fetal distress, 2 PROM, 1 history of stillbirth and 1 mature pneumonia
Chen R	17 / 17	All CS (3 emergency, 14 scheduled)	indications for CS not reported.

			3 premature births, no neonatal complications.
Chen S	3 / 3	All CS	Indications for CS: 1 complete placenta praevia, 1 placenta praevia and scar uterus, 1 placental abruption. 1 infant had low birth weight (but born at 35w)
Chen S, Liao E and Shao Y	5	3 vaginal, 2 CS	1 emergency CS due to fetal tachycardia, 1 elective CS due to gestational diabetes
Chen Y	4/4	3 CS, 1 VD	Indication for CS not clearly reported
Fan	2/2	Both CS	CS because of maternal illness (persistent fever and pneumonia) 1 neonate did develop mild pneumonia (but SARS-CoV-2 neg). Both mothers and neonates had good outcomes.
Ferrazzi E	42/42	24 VD 18 CS	10 CS because of worsening dyspnea or COVID related symptoms 8 indication unrelated tot COVID
Gidlöf	1/2	CS (uncomplicated)	Indication for CS: severe preeclampsia
Iqbal	1/1	Uncomplicated VD	
Kalafat	1/1	CS	Indication for CS: to relieve pressure of maternal lungs
Khan	3/3	All uncomplicated VD	
Lee	1/1	CS	Indication for CS: obstructed labor (cephalopelvic disproportion
Li N	16/17	14 CS, 2 VD	Indication for CS: COVID pneumonia. There were 3 preterm births, and 3 babies with low birth weight. This study compared outcomes with a matched non-COVID group: increased incidence of preterm birth and low birth weight. No differences in gestational age, APGAR and fetal distress. There were no cases of neonatal asphyxia and/or death. 3 neonates were tested: all negative.
Li Y	1 / 1	Emergency CS	Indicaton fetal distress. No other complications
Liao	1/1	CS	Indication for CS: fetal distress
Liu D	15 /11	10 CS, 1 VD, 4 still pregnant	Indications for CS not reported, no neonatal complications.
Liu W	3 / 3	2 CS, 1 VD	1 meconium stained fluids
Liu Y	13 / 10	10 CS (3 patients ongoing pregnancy)	1 stillbirth (preterm CS, severe maternal ARDS and MODS) 1 (P)PROM (preterm CS) 3 fetal distress (of which 1 preterm CS) 3 preterm CS (reason not mentioned) 2 term CS (reason not mentioned) All preterm deliveries >32 weeks
Lowe	1/1	rotational vacuum delivery for	none

		non-reassuring fetal CTG	
Wang S	1 / 1	CS	Emergency CS because of vaginal blood loss, abdominal pain and maternal fever. Meconium-stained amniotic fluid
Wang X	1 / 1	CS	CS because of severe maternal pneumonia and fetal distress
Xia	1 / 1	CS	CS because of severe maternal pneumonia and fetal distress
Yu	7/7	All CS	Indications not clearly reported
Zamaniyan	1/1	CS	Maternal indication (respiratory distress)
Zambrano	1/1	Spontaneous preterm VD	
Zhang	16 /10	10 CS (6 patients ongoing pregnancy)	Indications for CS not clearly reported
Zhang, B	1/1	CS	Indication for CS: severe maternal ARDS and multiple organ dysfunction syndrome. Newborn died of endouterine asphyxia. Mother recovered.
Zhu	9 /10 (twin)	7 CS, 2 VD	6 fetal distress 3 PROM

Table 4. Information about (P)PROM in women with COVID-19

First author	number of women	number with (P)PROM	information about clinical course
Breslin	29 initially symptomatic patients	1 term PROM	Not reported
Chen H	9	2	PROM at 36+2 and 39+4 days, both had CS, healthy neonate
Li N	16	2-3 (not clearly stated)	Not reported
Liu Y	13	1	Illness onset at 34 weeks. (P)PROM with CS. Healthy neonate transmission.
Wang X	1	0	
Xia	1	0	
Zhu	9	3	Not clearly reported

Table 5. Information about COVID-19 and breast feeding

First author	number of women	number of women with information about breast feeding	information about breast feeding
Chen H	9	6	all 6 breast milk samples were negative
Fan	2	1	Breast milk samples were negative
Ferrazzi E	42	11	11 neonates received breastfeeding if mother was asymptomatic/pauci-symptomatic. With a mask and frequent hand cleaning. Two neonates were breastfed without mask (maternal cases with post partum diagnosis) and had positive tests for COVID-19 infection at day one and three.
Gidlöf	1	1	Both babies were breast fed, milk samples were negative
Iqbal	1	1	Neonate received breast milk, not tested for SARS-CoV-2
Kalafat	1	1	Neonate is breast fed, milk sample negative
Li Y	1	1	Breast milk samples were negative
Liu W	3	2	Breast milk samples were negative
Lowe	1	1	breast feeding with surgical mask; neonate healthy
Wang S	1	1	no breast feeding was started
Wang X	1	1	no breast feeding was started
Zhang	16	16	'breast feeding could be started at least 14 days after isolation'

Excluded papers with reasons

First author	reason for exclusion
Chen D	Opinion-based recommendations for practice; no data
Mullins	rapid review, no original data
Rasmussen	educational paper, no original data
Chen L	retrospective report of 118 pregnant women with COVID-19 identified in 50 hospitals in Wuhan city between December 8, 2019 and March 20, 2020; not possible to idenitify possible duplicate reports
Di Mascio	SR of CoV infections including MERS and SARS in pregnancy; no original data
Gajbhiye	SR; no original data
Li L	update on 4 of 15 earlier reported cases (Liu D); no relevant additional information
Liu W	case series of 19 neonates admitted to Tongji Hospital from January 31 to February 29, 2020, born to SARS-CoV-2 infected mothers; not possible to idenitify possible duplicate reports
Sutton	screening study in pregnant women; no information about course of disease in symptomatic pregnant women
Wei	retrospective report of 17 pregnant and 32 non-pregnant women admitted to Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, China between January 19 and March 2, 2020; not possible to idenitify possible duplicate reports
Yang H	retrospective report of 55 suspected pregnant patients who were admitted to Maternal and Child Health Hospital of Hubei Province, Tongji Medical College, Huazhong University of Science and Technology, from January 20th to March 23th, 2020; not possible to idenitify possible duplicate reports
Yang J	retrospective report of 18 patients with COVID-19 in the 3rd trimester admitted to Renmin Hospital of Wuhan University between January 30 and March 1, 2020; not possible to idenitify possible duplicate reports
Yang P	case series of 7 newborns delivered by SARS-CoV-2 infected pregnant women in Zhongnan Hospital of Wuhan University between January 20 and January 29, 2020; not possible to idenitify possible duplicate reports
Yin	retrospective comparison of 31 pregnant and 35 non-pregnant women admitted to Wuhan Union and Tongji hospitals of Huazhong University of Science and Technology between January 28 and February 28, 2020; not possible to idenitify possible duplicate reports

Literature search strategy first five questions

Background:
The NVOG formulated several questions regarding COVID-19. Five of these were labeled as urgent/high priority. Since literature about COVID-19 was limited, every initial COVID-19 search was supplemented with a broader search including SARS and MERS. These results were collected separately and could be consulted if desirable.

Questions:

1. Do COVID-19 infections in pregnant women lead to more pregnancy complications like preeclampsia, fetal growth restriction and preterm birth?
2. Which complications are more prevalent among pregnant women with COVID-19 infections than in non-pregnant women and men?
3. Do COVID-19 infections in pregnant women lead to more complications during delivery?
4. When should pregnant women with COVID-19 infections after (P)PROM be delivered?
5. Is it safe by women with COVID-19 infections to give their newborns breast feeding?

Initial database(s): Embase, PubMed Later complemented with: Medrxiv, Google Scholar and WHO	Initial search date: 25-3-2020 Last updated: 20-4-2020

Information specialist: Miriam van der Maten

Further remarks:

- Questions 1 and 2 are covered using: (pregnancy OR pregnancy complications) **AND** (COVID19 OR COVID19/MERS/SARS/SARI)
- Question 3 is covered using: (labor/delivery OR labor complications) **AND** (COVID19 OR COVID19/MERS/SARS/SARI)
- Question 4 is covered using: (P)PROM **AND** (COVID19 OR COVID19/MERS/SARS/SARI)
- Question 5 is covered using: (breastfeeding) **AND** (COVID19 OR COVID19/MERS/SARS/SARI)

When the combination of a question-specific search block and the COVID19/MERS/SARS/SARI block resulted in a large number of hits, the set of results was divided into different study designs (SR, RCT, observational studies or other). Standardized filters were applied as normally used by the knowledge institute.

E-mail alerts were created for every question to monitor new literature on a daily basis.

The most recent information (preprints, non peer-reviewed sources e.g.) regarding this topic did not always appear in the conventional databases. Hence, other information sources were consulted along the way.

Initial search results

	COVID 19	**COVID19/MERS/SARS/SARI**
Question 1 and 2 (pregnancy complications)	61	305
Question 3 (labor)	93	559
Question 4 ((P)PROM)	0	6
Question 5 (breastfeeding)	2	20
Total	**126**	

Results since last update (20 april 2020)

	COVID 19
Topics combined	345

Search justification

Database	Searched terms
Embase	**COVID19:** (2019ncov:ti,ab,kw OR '2019 ncov':ti,ab,kw OR 'novel coronavirus*':ti,ab,kw OR 'novel corona virus*':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw) AND (outbreak:ti,ab,kw OR wuhan:ti,ab,kw)) OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw) AND 2019:ti,ab,kw) OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR 'new coronavirus*':ti,ab,kw OR 'new corona virus*':ti,ab,kw OR 'ncov 2019':ti,ab,kw OR 'sars coronavirus 2':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome cov2':ti,ab,kw) AND [2019-2020]/py **MERS/SARS/COVID19/SARI** 2019ncov:ti,ab,kw OR '2019 ncov':ti,ab,kw OR 'novel coronavirus*':ti,ab,kw OR 'novel corona virus*':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw) AND (outbreak:ti,ab,kw OR wuhan:ti,ab,kw)) OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw) AND 2019:ti,ab,kw) OR sars*:ti,ab,kw OR 'new coronavirus*':ti,ab,kw OR 'new corona virus*':ti,ab,kw OR 'ncov 2019':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome':ti,ab,kw OR 'severe acute respiratory syndrome'/exp OR 'sars-related coronavirus'/exp OR 'sars-like cov':ti,ab,kw OR 'sars-like coronavirus':ti,ab,kw OR 'sars-related cov':ti,ab,kw OR 'sars-related coronavirus':ti,ab,kw OR 'sarsr-cov':ti,ab,kw OR 'severe acute respiratory syndrome-like coronavirus':ti,ab,kw OR 'severe acute respiratory syndrome-related coronavirus':ti,ab,kw OR 'sars coronavirus'/exp OR 'hcov-sars':ti,ab,kw OR 'human sars coronavirus':ti,ab,kw OR 'sars cov':ti,ab,kw OR 'sars associated coronavirus':ti,ab,kw OR 'sars coronavirus':ti,ab,kw OR 'sars virus':ti,ab OR 'sars-cov':ti,ab,kw OR 'sars-associated coronavirus':ti,ab,kw OR 'severe acute respiratory syndrome coronavirus':ti,ab,kw OR 'severe acute respiratory syndrome virus':ti,ab,kw OR 'middle east respiratory syndrome coronavirus'/exp OR 'mers coronavir*':ti,ab,kw OR 'mers vir*':ti,ab,kw OR 'mers-cov':ti,ab,kw OR 'middle east respiratory syndrome coronavir*':ti,ab,kw OR ‘severe acute respiratory infection*’:ti,ab,kw **Pregnancy and pregnancy complications:** 'pregnancy'/exp OR 'pregnant woman'/exp OR 'prepregnancy care'/exp OR pregnan*:ti,ab,kw OR gravidit*:ti,ab,kw OR gestation*:ti,ab,kw OR placentat*:ti,ab,kw OR prepregnan*:ti,ab,kw OR conception*:ti,ab,kw OR preconception*:ti,ab,kw **OR** 'pregnancy disorder'/exp OR (pregnan* NEAR/3 (complicat* OR disorder* OR disease*)):ti,ab,kw **OR** 'premature labor'/exp OR (((labo*r OR delivery OR parturition OR birth OR childbirth) NEAR/3 (premature OR preterm OR 'pre term' OR early OR prior)):ti,ab,kw) **OR** 'abortion'/exp or abort*:ti,ab,kw **OR** 'eclampsia and preeclampsia'/exp OR 'hellp syndrome'/exp OR eclamp*:ti,ab,kw OR preeclamp*:ti,ab,kw OR 'pre-eclamp*':ti,ab,kw OR preclamp*:ti,ab,kw OR hellp:ti,ab,kw OR 'h$emolysis elevated liver enzymes and low platelet*':ti,ab,kw **OR** 'intrauterine growth retardation'/exp OR iugr:ti,ab,kw OR ((restrict* OR retard* OR disorder) NEAR/2 growth NEAR/2 (fetal OR foetal OR fetus OR foetus OR intrauterine OR 'intra uterine' OR 'in utero' OR prenatal)):ti,ab,kw **OR** 'fetus disease'/exp OR ((fetal OR foetal OR fetus OR foetus) NEAR/3 (abnormalit* OR anomal* OR disease* OR disorder* OR complicat*)):ti,ab,kw OR fetopath*:ti,ab,kw OR foetopath*:ti,ab,kw **Labor:** 'obstetric delivery'/exp OR 'labor complication'/exp OR (labo*r OR delivery OR parturition* OR birth*

	OR childbirth*):ti,ab,kw **(P)PROM:** 'premature fetus membrane rupture'/exp OR prom:ti,ab,kw OR pprom:ti,ab,kw OR ((premature OR preterm OR prelabo*r) NEAR/3 ('rupture of membrane*')):ti,ab,kw **Breast feeding:** 'breast feeding'/exp OR (breastfeeding OR 'breast* feeding'):ti,ab,kw
Pubmed	**COVID19** ((coronavirus*[tiab] OR corona virus*[tiab] OR pneumonia virus*[tiab] OR cov[tiab] OR ncov[tiab]) AND (outbreak[tiab] OR wuhan[tiab])) OR covid19[tiab] OR "covid 19"[tiab] OR ((coronavirus*[tiab] OR corona virus*[tiab]) AND 2019[tiab]) OR "sars cov 2"[tiab] OR sars2[tiab] OR new coronavirus*[tiab] OR new corona virus*[tiab] OR "ncov 2019"[tiab] OR "sars coronavirus 2"[tiab] OR "sars corona virus 2"[tiab] OR "severe acute respiratory syndrome cov 2"[tiab] OR "severe acute respiratory syndrome cov2"[tiab] Filters: Publication date from 2019/11/01 **MERS/SARS/COVID19/SARI** "Severe Acute Respiratory Syndrome"[Mesh] OR "SARS Virus"[Mesh] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR 2019ncov[tiab] OR 2019 ncov[tiab] OR novel coronavirus*[tiab] OR novel corona virus*[tiab] OR ((coronavirus*[tiab] OR corona virus*[tiab] OR pneumonia virus*[tiab] OR cov[tiab] OR ncov[tiab]) AND (outbreak[tiab] OR wuhan[tiab])) OR covid19[tiab] OR covid 19[tiab] OR ((coronavirus*[tiab] OR corona virus*[tiab]) AND 2019[tiab]) OR sars*[tiab] OR new coronavirus*[tiab] OR new corona virus*[tiab] OR ncov 2019[tiab] OR “sars corona virus”[tiab] OR “sars-like cov”[tiab] OR “sars-like coronavirus”[tiab] OR sars-related cov[tiab] OR sars-related coronavirus[tiab] OR sarsr-cov[tiab] OR “severe acute respiratory syndrome-like coronavirus”[tiab] OR “severe acute respiratory syndrome-related coronavirus[tiab] OR hcov-sars[tiab] OR human sars coronavirus[tiab] OR sars cov[tiab] OR sars associated coronavirus”[tiab] OR sars coronavirus[tiab] OR sars virus[tiab] OR sars-cov[tiab] OR sars-associated coronavirus[tiab] OR severe acute respiratory syndrome coronavirus[tiab] OR severe acute respiratory syndrome virus[tiab] OR mers coronavir*[tiab] OR mers vir*[tiab] OR mers-cov[tiab] OR middle east respiratory syndrome coronavir*[tiab] OR severe acute respiratory infection*[tiab] **Pregnancy and pregnancy complications:** ((((((“Pregnancy”[Mesh] OR “Pregnant Women”[Mesh] OR “Preconception Care”[Mesh] OR pregnan*[tiab] OR gravidit*[tiab] OR gestation*[tiab] OR placentat*[tiab] OR prepregnan*[tiab] OR conception*[tiab] OR preconception*[tiab]) OR (“Pregnancy Complications”[Mesh] OR (pregnan* AND (complicat* OR disorder* OR disease*))[tiab])) OR (“Obstetric Labor, Premature”[Mesh] OR ((labor OR labour OR delivery OR parturition OR birth OR childbirth) AND (premature OR preterm OR 'pre term' OR early OR prior))[tiab])) OR (“Abortion, Spontaneous”[Mesh] OR abort*[tiab])) OR (“Hypertension, Pregnancy-Induced”[Mesh] OR eclamp*[tiab] OR preeclamp*[tiab] OR 'pre-eclamp*'[tiab] OR preclamp*[tiab] OR hellp[tiab] OR 'hemolysis elevated liver enzymes and low platelet*'[tiab] OR 'haemolysis elevated liver enzymes and low platelet*'[tiab])) OR (“Fetal Growth Retardation”[Mesh] OR iugr[tiab] OR ((restrict* OR retard* OR disorder) AND growth AND (fetal OR foetal OR fetus OR foetus OR intrauterine OR 'intra uterine' OR 'in utero' OR prenatal))[tiab])) OR (“Fetal Diseases”[Mesh] OR ((fetal OR foetal OR fetus OR foetus) AND (abnormalit* OR anomal* OR disease* OR disorder* OR complicat*))[tiab] OR fetopath*[tiab] OR foetopath*[tiab]) **Labor:** “Labor, Obstetric”[Mesh] OR “Obstetric Labor Complications”[Mesh] OR (labor OR labour OR delivery OR parturition* OR birth* OR childbirth*)[tiab] **(P)PROM:** “Fetal Membranes, Premature Rupture”[Mesh] OR prom[tiab] OR pprom[tiab] OR ((premature OR preterm OR prelabor OR prelabour) AND ('rupture of membrane*'))[tiab **Breast feeding:** “Breast Feeding”[Mesh] OR (breastfeeding OR 'breast* feeding')[tiab]
Filters	**EMBASE** *Sytematische reviews* ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) *RCT’s* 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind

	procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti *Observational research* 'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) **PubMed** *Systematic reviews* ((review[tiab] OR "Review"[Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR meta-analysis[tiab] OR "Meta-Analysis "[Publication Type]) NOT ("Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Comment"[Publication Type])) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) *RCT* ((random*[tiab] AND (controlled[tiab] OR control[tiab] OR placebo[tiab] OR versus[tiab] OR vs[tiab] OR group[tiab] OR groups[tiab] OR comparison[tiab] OR compared[tiab] OR arm[tiab] OR arms[tiab] OR crossover[tiab] OR cross-over[tiab]) AND (trial[tiab] OR study[tiab])) OR ((single[tiab] OR double[tiab] OR triple[tiab]) AND (masked[tiab] OR blind*[tiab]))) *Observational research* "Epidemiologic Studies"[Mesh] OR cohort[tiab] OR (case[tiab] AND (control[tiab] OR controll*[tiab] OR comparison[tiab] OR referent[tiab])) OR risk[tiab] OR causation[tiab] OR causal[tiab] OR "odds ratio"[tiab] OR etiol*[tiab] OR aetiol*[tiab] OR "natural history"[tiab] OR predict*[tiab] OR prognos*[tiab] OR outcome[tiab] OR course[tiab] OR retrospect*[tiab]

Hoofdstuk 2 - Miskraam; miscarriage

Clinical question

Do COVID-19 infections in pregnant women lead to more miscarriages?

Search and select (Methods)

The databases Embase, PubMed, Google Scholar, WHO and MedRxiv were searched with relevant search terms until 13 May 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 43 hits. Studies were selected based on the following criteria: systematic reviews, (retrospective) cohort studies or case series/case studies on the risk of spontaneous abortion in pregnant women with COVID-19. Here we define miscarriage as pregnancy loss until 20 weeks' gestational age. Eighteen studies were initially selected based on title and abstract screening. After reading the full text, 14 studies were excluded (see the table with reasons for exclusion under the tab Methods) and four studies were included.

Results

Four studies were included in the analysis of the literature, one systematic review (Elshafeey, 2020), two case series (Buonsenso, 2020; Yan, 2020) and one case report (Baud, 2020). Important study characteristics and results are summarized in the information tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Elshafeey (2020) performed a systematic review to summarize the existing literature on COVID-19 infection during pregnancy and childbirth, particularly concerning clinical presentation and outcomes. The search was last updated on April 19, 2020 using the LitCovid, EBSCO MEDLINE, CENTRAL, CINAHL, Web of Science, and Scopus electronic databases. Thirty-three original studies were included reporting on 385 pregnant women: 1 case control study, 16 case reports, and 16 case series. Twenty-two studies were originated in China. Buonsenso (2020) presented a case series of seven pregnant women with documented COVID-19 infection from an Italian institution. Yan (2020) retrospectively reviewed the clinical records of 116 Chinese pregnant women with COVID-19 pneumonia (between January 20 and March 24, 2020) on maternal and neonatal outcomes. In this multicenter study 25 Chinese hospitals participated. Sixty-five cases were laboratory-confirmed and 51 cases were clinically diagnosed cases of COVID-19 pneumonia (all cases of clinically diagnosed COVID-19 pneumonia had abnormal chest CT findings). Baud (2020) presented a Swiss case of a second-trimester miscarriage in a 28-year old obese, primigravida woman with COVID-19 infection.

Results

Miscarriage

Elshafeey (2020) reported birth in 252/385 (65.5%) women, ongoing pregnancy in 124/385 (32.2%), induced abortion in 4/385 (1.0%), spontaneous abortion in 3/385 (0.8%), and 2/385 (0.5%) women with a tubal pregnancy. No definition of spontaneous abortion was given in this study. Of the seven pregnant women with documented COVID-19 infection described by Buonsenso (2020) one woman had a spontaneous abortion at 8 weeks of gestational age, four women recovered and were still in follow-up, and two women delivered. Eight of the 116 pregnant women with COVID-19 pneumonia reported by Yan were at < 24 weeks gestation. One of the eight patients (12.5%) had a spontaneous abortion at 5^{+2}weeks. Yan

and colleagues concluded that the risk of spontaneous abortion was not increased in pregnant women with COVID-19 infection compared to the background risk of the general population. Baud (2020) reported on a pregnant women presenting with clinical symptoms of COVID-19 at 19 weeks' gestation: a nasopharyngeal swab was positive for SARS-CoV-2. She was given oral paracetamol and discharged home. Two days later, she presented with severe uterine contractions and a stillborn infant was delivered vaginally after 10 hours of labor. The placenta was found negative for bacterial infection but positive for SARS-CoV-2

Considerations

Pros and cons of the intervention and the quality of evidence

Of the total 509 pregnant women currently described in the included literature, 125 had a pregnancy before 24 weeks of gestation. Of these 125 women, six (4,8%) had a pregnancy loss, four women a termination of pregnancy and two an ectopic pregnancy. The gestational age at which the miscarriage occurred was at 5 weeks, 8 weeks and 19 weeks of gestation. In the review the gestational age of the pregnancy loss was not mentioned.

The quality of evidence is low, evidence consists of case control, case series and case reports. Furthermore, due to the short follow-up period of COVID-19 so far and the fact that most of the women presented in the third stage of pregnancy evidence of early pregnancy is sparse.

In the general population approximately 20% of pregnancies result in a miscarriage. (NICE Guideline 126) According to the available evidence currently there are no signs of an increased risk of miscarriage in women with SARS-Cov-2 infection.

Values and preferences of patients (and if applicable their caretakers)

Women experiencing possible symptoms of COVID-19 during pregnancy may be worried about the effects of the disease on their fetuses. For both midwifery-led care and hospital-led care it is important to take this into account and to inform them that based on the above mentioned (limited) data there is no evidence to assume that SARS-CoV-2 infection during early pregnancy leads to a higher prevalence of miscarriage.

Costs

Not applicable for this item.

Acceptability, feasability and implementation

Not applicable for this item.

Recommendations

So far, there is no evidence to assume that SARS-CoV-2 infection during pregnancy leads to a higher prevalence of miscarriage.

There is no reason to change the usual antenatal care for women with SARS-CoV-2 infection during pregnancy.

Tot op heden is er geen bewijs dat een SARS-CoV-2 infectie tijdens de zwangerschap leidt tot een hoger miskraam risico.

SARS-CoV-2 infectie tijdens de zwangerschap is geen reden om iets te veranderen aan de gebruikelijke zwangerschapscontroles.

Literature miscarriage

1. Baud D, Greub G, Favre G, et al. Second-Trimester Miscarriage in a Pregnant Woman With SARS-CoV-2 Infection [published online ahead of print, 2020 Apr 30]. JAMA. 2020;e207233. doi:10.1001/jama.2020.7233.
2. Buonsenso D, Costa S, Sanguinetti M, et al. Neonatal Late Onset Infection with Severe Acute Respiratory Syndrome Coronavirus 2 [published online ahead of print, 2020 May 2]. Am J Perinatol. 2020;10.1055/s-0040-1710541. doi:10.1055/s-0040-1710541.
3. Elshafeey F, Magdi R, Hindi N, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth [published online ahead of print, 2020 Apr 24]. Int J Gynaecol Obstet. 2020;10.1002/ijgo.13182. doi:10.1002/ijgo.13182.
4. Nice Guideline, Ectopic pregnancy and miscarriage: diagnosis and initial management (NG126) Published: 17 April 2019.
5. Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases [published online ahead of print, 2020 Apr 23]. Am J Obstet Gynecol. 2020;S0002-9378(20)30462-2. doi:10.1016/j.ajog.2020.04.014.

Tables miscarriage

Table 1. Included studies - data

Study reference	Study characteristics	Patient characteristics	Exposure	Follow-up	Results	Comments
Elshafeey, 2020 [study characteristics and results are extracted from the SR (unless stated otherwise)]	SR of original case reports, case series, and case control studies. 33 studies were included. *The search was last updated on April 19, 2020.* Study design: 1 case control study, 16 case reports, and 16 case series. Setting and country: China (n=22), USA (n=3), one each from Australia, Honduras, Iran, South Korea, Sweden, Turkey, Italy, and The Netherlands Source of funding and conflicts of interest: Funding of the SR was not reported by the article. The authors of the SR declare no conflicts of interest. Funding and conflict of interest were	Inclusion criteria SR: • Any article reporting original research of COVID-19 during pregnancy, whether diagnosis was confirmed by reverse-transcription polymerase chain reaction (RT-PCR) or based on clinical, imaging, and laboratory criteria. • No language restrictions were imposed Exclusion criteria SR: Not reported Important patient characteristics at baseline: • 385 pregnant women • Laboratory confirmation (using RT-PCR): 346 (89.9%) women • Clinical and radiological features basis for diagnosis: 39 (10.1%) women • Chest imaging: 125 (32.5%) women • Maternal age: age ranged from 21–42 years	Exposure: COVID-19 during pregnancy	End-point of follow-up: Not reported but 252 of 385 (65.5%) women have delivered. Ongoing pregnancies in 124/385 (32.2%) women at time of data analysis. For how many participants were no complete outcome data available? Complete outcome data was not available for the ongoing	Spontaneous abortion The course of pregnancy included birth in 252/385 (65.5%), ongoing pregnancy in 124/385 (32.2%), induced abortion in 4/385 (1.0%), spontaneous abortion in 3/385 (0.8%), and 2/385 (0.5%) women with a tubal pregnancy.	Author's conclusion The currently available data suggest that COVID-19 infection during pregnancy has a similar clinical presentation and illness severity to non-pregnant adults and may not be associated with poor maternal or perinatal outcomes. Remarks • Infection was asymptomatic in 29 (7.5%) women • The authors did not perform a formal critical appraisal of primary studies for this scoping review • Some of the primary sources might overlap. The authors have traced the cases through careful data collection and contacted the papers' authors to minimize the possibility of double counting.

	not reported for the 33 included studies separately.	• Gestational age at time of diagnosis: ranged from 6–41 weeks of gestation, with 276 (71.7%) beyond 24 weeks of gestation and 109 (28.3%) in early pregnancy. • Course of pregnancy: birth in 252 (65.5%) women • Mode of delivery: among the 252 women who gave birth, 175 (69.4%) were delivered by cesarean and 77 (30.6%) had a vaginal birth.		pregnancies (32.3%)		

Study reference	**Study characteristics**	**Study population** (number, selection criteria, patient characteristics)	**Exposure**	**Follow-up**	**Results**	**Comments**
Baud, 2020	Type of study: Case-study Setting and country: Lausanne University Hospital, March 20, 2020, Sweden Source of funding and conflict of interests: Funding and conflict of interests were not reported by the article	N=1 • Primigravida obese women, 28 year old • Presented at 19 weeks' gestation with clinical symptoms of COVID-19: a nasopharyngeal swab was positive for SARS-CoV-2 • Patient was given oral acetaminophen and discharged home	COVID-19 during pregnancy	Length of follow-up: Two days	• Two days after the hospital visit, the patient presented with severe uterine contractions • A stillborn infant was delivered vaginally after 10 hours of labor • The placenta was found negative for bacterial infection but positive for SARS-CoV-2	Author's conclusion This case of miscarriage during the second trimester of pregnancy in a woman with COVID-19 appears related to placental infection with SARS-CoV-2, supported by virological finding in the placenta Remarks • This is a case study • Other causes of miscarriage, such as spontaneous preterm birth, cervical insufficiency, or undetected systemic or local bacterial infection, cannot be

						ruled out.
Buonsenso, 2020	Type of study: Case-series Setting and country: Italy Source of funding and conflict of interests: The authors declare no conflict of interests. Funding was not reported by the article.	N=7 Pregnant women with documented SARS-CoV-2 infection	COVID-19 during pregnancy	Length of follow-up: Not reported	One woman had a spontaneous abortion at 8 weeks of gestational age, four women recovered and were still in follow-up, and two women delivered.	Remarks This is a case series
Yan, 2020	Type of study: Retrospective study of clinical records Setting and country: 25 hospitals, between January 20 and March 24, 2020, China Source of funding and conflict of interests: The authors declare no conflict of interests. This study was supported by Science and Technology	N=116 • Pregnant women with COVID-19 pneumonia • In cases that had chest CT scans at the time of admission, 96.3% (104/108) revealed abnormal results. • Maternal age: mean age was 30.8 (range 24-41) years • Median gestational age on admission was 38^{+0} (IQR 36^{+0}-39^{+1}) weeks.	COVID-19 during pregnancy	Length of follow-up: Not reported	• Of the 116 pregnant women with COVID-19 pneumonia, eight cases were <24 weeks gestation • One of the eight patients (12.5%) had a missed spontaneous abortion at 5^{+2} weeks.	Author's conclusion The risk of spontaneous abortion was not increased in pregnant women with COVID-19 infection from the background risk of the general population. Remarks • This was an expanded series from four previous small case series. • Sixty-five cases were laboratory-confirmed and 51 cases were clinically diagnosed COVID-19 pneumonia (all cases of clinically diagnosed COVID-19 pneumonia had abnormal chest CT findings)

	Department of Hubei Province, New pneumonia emergency science and technology project, Perinatal management strategies and mother-to-child transmission of pregnant women infected with 2019-nCoV (grant number 2020FCA011).					

Table 2. Quality assessment

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Elshafeey, 2020	**Yes** The aim of this review was broad but fitted with the type of study i.e., scoping review. The review was guided by 4 questions: What is the clinical presentation of COVID-19 during pregnancy? What is the spectrum of COVID-19	**Yes** A systematic search was conducted using the LitCovid, EBSCO MEDLINE, CENTRAL, CINAHL, Web of Science, and Scopus electronic databases. The search was last updated on April 19, 2020. A detailed search strategy can be	**No** Studies excluded after reading the full text were not referenced with reasons.	**No** Relevant confounders not reported	**No** Descriptive data	**No** The authors did not perform a formal critical appraisal of the included studies.	**Unclear** Mainly case series and case reports were included.	**No** Some of the primary sources might overlap	**No** Only reported for he SR but not for each of the included studies

	disease severity during pregnancy? What are the maternal adverse outcomes in cases of COVID-19? What are the fetal and neonatal out-comes in cases of COVID-19?	found in the online supplementary materials							

Excluded papers with reasons

First author	Reason for exclusion
Bourne	Consensus statement on ultrasonography
Dashraath	Narrative review
Di Mascio	Composite outcomes on COVID, SARS, and MERS
Hussein	Editorial
Juan	SR, less comprehensive than Elshafeey
Karami	Case study on maternal death
Khan	Case series, included in the SR of Elshafeey
Kramer	Narrative review
Mullins	Composite outcomes on COVID, SARS, and MERS
Pérez-López	Communication
Rodriguez-Wallberg	Editorial
Shah	Editorial
Zaigham	SR, less recent and comprehensive than Elshafeey
Zhu	Case series, included in the SR of Elshafeey

Literature search strategy miscarriage

Questions: Do pregnant women with COVID-19 have a higher risk for miscarriages?	
Database(s): Embase, PubMed, Google Scholar, WHO, MedRxiv	Date: 13-5-2020
Informationspecialist: Miriam van der Maten	
Information: In addition to the conventional databases, other sources such as Google Scholar, WHO and preprint websites are searched. These sources can be searches less systematically and require a more hand-made approach.	

Results

	Embase	Pubmed	Other sources	Total
	16	20	14	43

Search justification

Database	Searched terms		
Embase	No.	Query	Results
	#3	#1 AND #2	16
	#2	'spontaneous abortion'/exp OR 'incomplete abortion'/exp OR miscarriage*:ti,ab,kw OR 'incomplete abortion*':ti,ab,kw OR 'pregnancy loss':ti,ab,kw OR 'fetus death'/exp OR 'fetus mortality'/exp OR (((fetus OR foetus OR fetal OR foetal OR intrauterine OR prenatal OR endouterine OR antepartum) NEAR/3 (abort* OR dead OR death OR mortality)):ti,ab,kw)	103658
	#1	(('coronavirinae'/exp OR 'coronavirus infection'/de OR coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw) AND (outbreak:ti,ab,kw OR wuhan:ti,ab,kw) OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw) AND 2019:ti,ab,kw) OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR 'coronavirus*':ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'ncov 2019':ti,ab,kw OR ncov:ti,ab,kw OR 'sars coronavirus 2':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome cov2':ti,ab,kw) AND [2019-2020]/py	9405
Pubmed	(("COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus		

	2"[Supplementary Concept] OR (("Coronavirus"[MeSH Terms] OR "Coronavirus Infections"[Mesh:NoExp] OR pneumonia virus*[tiab] OR cov[tiab]) AND (outbreak[tiab] OR wuhan[tiab] OR novel[all] OR 19[tiab] OR 2019[tiab] OR epidem*[tiab] OR epidemy[all] OR epidemic*[all] OR pandem*[all] OR new[tiab])) OR coronavirus*[tiab] OR corona virus*[tiab] OR ncov[tiab] OR 2019ncov[tiab] OR covid19[tiab] OR "covid 19"[tiab] OR "sars cov 2"[tiab] OR sars2[tiab] OR "ncov 2019"[tiab] OR "sars coronavirus 2"[tiab] OR "sars corona virus 2"[tiab] OR "severe acute respiratory syndrome cov 2"[tiab] OR "severe acute respiratory syndrome cov2"[tiab] OR severe acute respiratory syndrome cov*[tiab] OR cov2[tiab]) AND ("2019/12"[Date - Entrez] : "3000"[Date - Entrez])) (11278) **AND** ("Abortion, Spontaneous"[Mesh] OR miscarriage*[tiab] OR "Abortion, Incomplete"[Mesh] OR incomplete abortion*[tiab])))) OR "Fetal Death"[Mesh] OR "Fetal Mortality"[Mesh] OR ((fetus[tiab] OR foetus[tiab] OR fetal[tiab] OR foetal[tiab] OR intrauterine[tiab] OR prenatal[tiab] OR endouterine[tiab] OR antepartum[tiab]) AND (abort*[tiab] OR dead[tiab] OR death[tiab] OR mortality[tiab])) (109014)
Other sources	Variations of related search terms were applied.

Hoofdstuk 3 - Verticale transmissie; vertical transmission

Definities
Verticale transmissie: passage van een ziekteverwekker (pathogeen) van moeder naar baby in de periode onmiddellijk voor, tijdens en na de geboorte. Besmetting kan plaatsvinden via de placenta, in de moedermelk of door direct contact tijdens of kort na de geboorte.

Horizontale transmissie: de verspreiding van een besmettelijke ziekteverwekker van een individu naar een ander, gewoonlijk door contact met lichaamsvloeistoffen zoals sputum of bloed, die de ziekteverwekker bevatten.

Vertical transmission: Passage of a disease-causing agent (pathogen) from mother to baby during the period immediately before and after birth. Transmission might occur across the placenta, in the breast milk, or through direct contact during or after birth.

Horizontal transmission: The spread of an infectious agent from one individual to another, usually through contact with bodily excretions or fluids, such as sputum or blood, that contain the agent.

Uitgangsvraag
Kan een foetus/pasgeborene van een zwangere besmet met SARS-CoV-2 door verticale transmissie[2] besmet worden?

a. Kan een foetus tijdens de zwangerschap besmet worden (transplacentaire transmissie)?
b. Kan een foetus tijdens een vaginale baring besmet worden?
c. Kan een foetus besmet worden tijdens een sectio caesarea?

Clinical question
Is it possible that fetuses/newborns from pregnant women with SARS-CoV-2 infections may be infected by vertical transmission[3]?

a. Can a fetus be infected during pregnancy (transplacental transmission)?
b. Can a fetus be infected during vaginal delivery?
c. Can a fetus be infected during caesarean section?

Search and select (Methods)
The databases Embase, PubMed, Google Scholar, WHO and MedRxiv were searched with relevant search terms until 13 May 2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 135 hits. Studies were selected based on the following criteria: systematic reviews or prospective cohort studies providing information on pregnant women with COVID-19 and on testing and test results of their offspring. Twenty-five studies were initially selected based on title and abstract screening. After reading the full text, 23 studies were excluded (see the table with reasons for exclusion under the tab Methods), and two studies were included.

[2] Verticale transmissie via borstvoeding wordt hier buiten beschouwing gelaten; daarvoor wordt verwezen naar het Standpunt COVID-19 en zwangerschap, bevalling en kraambed (Link toevoegen)
[3] Here we exclude vertical transmission by breast feeding, which is addressed in a separate chapter (Link toevoegen)

Results
Two studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature
Description of studies
Two studies were included, one systematic review (Gajbhiye) and one prospective population-based cohort study from the UK (Knight). The systematic review (search date 3 May 2020) included all original studies reporting information on pregnant women with a diagnosis of SARS-CoV-2 infection. Fifty studies, mainly case reports and case series from 16 countries (30 from China, none from the UK) were included, with information about 441 pregnant women with COVID-19 and 313 neonates born to them. The study by Knight was a prospective national population-based cohort study using the UK Obstetric Surveillance System (UKOSS), comparing outcomes in 427 pregnant women with confirmed Sars-CoV-2 infection admitted to any of the 194 hospitals with obstetric units in the UK between 01/03/2020 and 14/04/2020 with 694 comparison women who gave birth between 01/11/2017 and 31/10/2018.

Results
Two hundred and sixty-one out of the 313 neonates that were reported in the 50 studies included in the review of Gajbhiye (84%) met both the following criteria: 1) confirmation of the diagnosis by RT-PCR or by presence of IgM antibodies only within the first 48 hours of life, and 2) a clearly mentioned source of sampling. Of these 261 neonates, 21 tested positive for SARS-CoV-2. The reviewers concluded that the vertical transmission rate could be 8%. However, no information was available about the possibility of horizontal transmission in these neonates, nor about the clinical symptoms in the neonates who tested positive.

In the cohort study reported by Knight information was available on 244 live-born neonates. According to Knight “Twelve (5%) infants of women hospitalized with infection tested positive for SARS-CoV-2 RNA, six of these infants within the first 12 hours after birth. Two of the six infants with early onset SARS-CoV-2 infection were unassisted vaginal births, four were born by caesarean, three of which were pre-labour. The six infants who developed later infection were born by pre-labour caesarean (n=4) and vaginal birth (n=2). Only one of the infants with an early positive test for SARS-CoV-2 RNA was admitted to a neonatal unit, compared to five infants with a later positive test.”

Considerations
Pros and cons of the intervention and the quality of evidence
Most reported cases (at least 92%) showed no signs of vertical transmission. However, there are a few cases of confirmed SARS-CoV-2 infections in neonates within the first 48 hours after birth. This could mean that transmission in these cases was vertical, however this cannot be confirmed, since there is no information regarding possible horizontal transmission.

The period of pregnancy when the vertical transmission occurred, cannot be deduced from these data.

There are a few reports of neonates with COVID-19 antibodies in their serum a few hours after birth, including IgM (Ambrosino, Fornari). It is generally thought that IgM antibodies do not cross the placental barrier, so that would indicate that the neonate has been infected in utero. However, no comparison was made with maternal IgM, therefore it cannot be stated with certainty. The accuracy of the tests showing IgM in neonates is not beyond doubt. Furthermore, there were no clinical signs of neonatal infection in these cases, questioning the clinical relevance of these findings. Most of the tested neonates (~80%) were delivered by caesarean section. The number of reported cases is too small to compare the risk of transmission at vaginal delivery versus caesarean section. Although case reports of neonatal infections are sparse, the course of the disease generally seems less severe than in adults.

Values and preferences of patients (and if applicable their caretakers)
Not applicable.

Costs
Not applicable.

Acceptability, feasibility and implementation
Not applicable.

Recommendation

It cannot be ruled out that vertical transmission or horizontal transmission early after birth occurs in some cases.

At this point in time there is no reason to assume that vaginal delivery increases the risk of vertical transmission compared to delivery by caesarean section. This information should be conveyed to the pregnant woman.

Decisions about the mode of delivery, application of an electrode on the presenting part and micro blood sampling should not be influenced by maternal SARS-CoV-2 infection.

Verticale transmissie en horizontale transmissie vroeg na de geboorte komen voor.

Op dit moment zijn er geen aanwijzingen dat een vaginale bevalling het risico op verticale transmissie verhoogt ten opzichte van een sectio caesarea. Informeer de zwangere hierover.

Laat de beslissing over de modus partus, het plaatsen van een caput elektrode en het doen van micro-bloedonderzoek niet beïnvloeden door een maternale SARS-CoV-2 besmetting.

Literature vertical transmission

1. Ambrosino, Pasquale, Antonio Storino, Roberta Lupoli, Ilenia Calcaterra, Antimo Papa, Giorgio Alfredo Spedicato, Mauro Maniscalco, and Matteo Nicola Dario Di Minno. "Pregnancy and Perinatal Outcomes in Women with SARS-CoV-2 Infection: A Meta-Analysis with Meta-Regressions." Available at SSRN 3582754 (2020).
2. Fornari, F. (2020). Vertical transmission of Covid-19-A systematic review. J Pediatr Perinatol Child Health, 4, 7-13.
3. Gajbhiye, R., Modi, D., & Mahale, S. (2020). Pregnancy outcomes, Newborn complications and Maternal-Fetal Transmission of SARS-CoV-2 in women with COVID-19: A systematic review. medRxiv.
4. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, O'Brien P, Quigley M, Brocklehurst P, Kurinczuk JJ. (2020). Characteristics and outcomes of pregnant women hospitalised with confirmed SARS-CoV-2 infection in the UK: a national cohort study using the UK Obstetric Surveillance System (UKOSS). medRxiv.

Tables vertical transmission

Table 1. Included studies - data

Study reference	Study characteristics	Patient characteristics	Exposure	Follow-up	Results	Comments
Gajbhiye, 2020 [study characteristics and results are extracted from the SR (unless stated otherwise)]	SR of original case reports and case series. 50 studies were included. *Literature search up to 3rd May 2020* Study design: mainly case series and case reports Setting and country: China (n=30), USA (n=4), Iran (n=3), one each from Australia, Canada, Republic of Korea, Honduras in Central America, Jordan, Spain, Peru, Sweden, Turkey, Italy, Portugal, Switzerland and India. Source of funding and conflicts of interest: No specific funding was received for the SR and all authors report no conflict of interest. Funding and conflict of interest were not reported for the 50	Inclusion criteria SR: • original studies reporting information on pregnant women with a diagnosis of SARS-CoV-2 infection (in most studies confirmed by molecular detection of SARS-CoV-2 in at least the throat swabs) • the primary outcome measures were maternal clinical presentation, co-morbidities, adverse pregnancy outcomes, neonatal outcomes and SARS-CoV-2 infection in neonates. • no language restrictions were imposed (the articles were translated in English using google translator) Exclusion criteria SR:	Exposure: vertical transmission of SARS-CoV-2 from COVID-19 mothers to neonate	End-point of follow-up: Not reported but 387 of 441 women have delivered. Remaining were ongoing pregnancies. For how many participants were no complete outcome data available? Data of 261 of 313 neonates (84%) were used in the subgroup analysis to address the extent of maternal to fetal transmission of SARS-CoV-2.	Maternal-fetal (vertical) transmission of SARS CO-V-2 infection Data from the publications that explicitly reported the neonatal SARS-CoV-2 testing by the type of laboratory method used (RT-PCR or antibody or both), the neonatal samples tested and the time of testing. Neonatal SARS-CoV-2 should be confirmed by RT-PCR or by presence of IgM antibodies only within the first 48h of life and where the source of sampling was clearly mentioned. • 261/313 neonates (84%) met the above criteria and of these, 21 tested positive for SARS-CoV-2 resulting in a possible vertical	Author's conclusion The neonates even if RT-PCR negative but positive for IgM in first 48h of life are presumed to acquire the infection in utero. The analysis revealed the possibility of intrauterine mother to child transmission, of SARS-CoV-2 in 8% of cases. We must consider that there is a reasonable possibility of mother to child transmission of SARS-CoV-2 and this may have long term implications to fetal heath. Remarks • Nearly 50% of the pregnant women were asymptomatic on initial presentation and were diagnosed with COVID-19 after admission for induction of labor. • 7% of neonates (even those negative for SARS-CoV-2 by RT-PCR) developed pneumonia within first two days of life. This proportion is higher than the

	included studies separately.	Not reported <u>Important patient characteristics at baseline</u>: • 441 pregnant women and 391 neonates • <u>Source of infection:</u> Almost 50% had a history of residing either in the epicenter of COVID-19 epidemic or in direct contact with COVID-19 confirmed cases. • 387 women have delivered which include 4 sets of twins, 4 induced abortions, 6 still births and remaining are ongoing pregnancies • <u>Age:</u> age range 20-49 years • <u>Gestational age:</u> 95% 3rd trimester of pregnancy, 5% gestational age <28 weeks • <u>Mode of delivery:</u> 80% underwent cesarean section, rest vaginal			transmission rate of 8% • In one case amniotic fluid and in once case placenta and fetal membrane was also found to be positive for SARS-CoV-2 by RT-PCR	incidence of neonatal pneumonia in general population indicating the possibility of infection by the virus and perhaps the RT-PCR has more false negatives. • The authors could not strictly adhere to all the criteria for PRISMA and carry out a meta-analysis.

		delivery				

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Knight, 2020	Type of study: prospective national population-based cohort study using the UK Obstetric Surveillance System (UKOSS). Setting and country: 1 March to 14 April 2020, all 194 obstetric units in the UK Funding and conflicts of interest: The study was funded by the National Institute for Health Research HTA Programme (project number 11/46/12). The authors declare no conflict of interests.	Inclusion criteria: -Nominated reporting clinicians were asked to notify all pregnant women with confirmed SARS-CoV-2 admitted to their hospital (at the time covered by the study, that women were only tested if symptomatic for SARS-CoV-2 infection). -Following notification, clinicians were asked to complete an electronic data collection form containing details of each woman's characteristics, management and outcomes. Exclusion criteria: not reported	Describe intervention (treatment/procedure/test): 427 women in the exposed (hospitalised with SARS-CoV-2 infection) cohort	Describe control (treatment/procedure/test): 694 women in the comparison cohort Information about a comparison cohort of women was obtained from a previous study of seasonal influenza in pregnancy. Comparison cases were the two women giving birth immediately prior to any woman hospitalised with confirmed influenza between 01 November 2017 and 30 October 2018. A historical comparison cohort was used to ensure there was no possibility that comparison women had asymptomatic or minimally symptomatic SARS-CoV-2 infection.	Length of follow-up: Not reported but two hundred and forty-seven women (58%) hospitalised gave birth or had a pregnancy loss; the remaining 180 (42%) women had ongoing pregnancies at the time of this analysis. Loss-to-follow-up: 630 women were notified in the UK, data were returned for 579 women (92%). 15 were duplicate cases, 35 reported in error, 87 were diagnosed as outpatients and not admitted overnight, 9 had no positive PCR test and no evidence of pneumonitis on imaging, and 6 had	Vertical transmission Twelve infants (12/244; 5%) of women hospitalised with infection tested positive for SARS-CoV-2 RNA, six of these infants within the first 12 hours after birth. Two of the six infants with early onset SARSCoV-2 infection were unassisted vaginal births, four were born by caesarean, three of which were pre-labour. The six infants who developed later infection were born by pre-labour caesarean (n=4) and vaginal birth (n=2). Only one of	Author's conclusion: Transmission of SARS-CoV-2 to infants was uncommon. One in twenty of the babies of mothers admitted to hospital subsequently had a positive test for SARS-CoV-2; half had infection diagnosed on samples taken at less than 12 hours after birth. Remarks Outcomes for infants are largely reassuring when considering potential impacts of SARS-CoV-2 infection acquired before or during birth; the small number of early PCR positive

		N total at baseline: N=244 live born infants of women with SarsCoV-2 Important prognostic factors[2]: • Black and other minority ethnicity, the presence of pre-existing comorbidity, older maternal age and overweight or obesity were all associated with admission with SARS-CoV-2 infection in pregnancy • The majority of hospitalised women symptomatic in the third trimester of pregnancy or peripartum (n=342/424, 81%). • Fifty-nine percent of women (n=144) had a caesarean			no evidence of infection during pregnancy Incomplete outcome data: unclear	the infants with an early positive test for SARS-CoV-2 RNA was admitted to a neonatal unit, compared to five infants with a later positive test.	infants of mothers with infection did not have evidence of severe illness.

		birth, but the majority of caesarean births occurred for indications other than maternal compromise due to SARS-CoV-2 infection. *Groups comparable at baseline?* Variables that were significantly different between groups were included as confounders in the analyses comparing maternal and perinatal outcomes between groups.					

Table 2. Quality assessment

Study First author, year	Appropriate and clearly focused question? Yes/no/unclear	Comprehensive and systematic literature search? Yes/no/unclear	Description of included and excluded studies? Yes/no/unclear	Description of relevant characteristics of included studies? Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies? Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies? Yes/no/unclear	Enough similarities between studies to make combining them reasonable? Yes/no/unclear	Potential risk of publication bias taken into account? Yes/no/unclear	Potential conflicts of interest reported? Yes/no/unclear
Gajbhiye, 2020	**Yes**	**Yes** A systematic search in PUBMED, Medline, Google Scholar, preprint servers medRxiv, bioRxiv and arXiv databases utilizing combinations of word variants for "coronavirus", 2019 n-COV. or "COVID-19" and "pregnancy". The time line was restricted until 3rd May, 2020	**No** Studies excluded after reading the full text were not referenced with reasons.	**No** Relevant confounders not reported	**No**	**No**	**Unclear** Mainly case series and case reports were included.	**No**	**No** Only reported for he SR but not for each of the included studies

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?** (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?** (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?** (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?** (unlikely/likely/unclear)
Knight, 2020	**Unlikely** All pregnant women with confirmed SARS-CoV-2 admitted to all 194 obstetric units in the UK	**Unlikely** National population-based cohort study using the UK Obstetric Surveillance System (UKOSS).	**Unclear** Positive SARS-CoV-2 test of liveborn infant not further defined	**Unclear**

Excluded papers with reasons

First author	Reason for exclusion
Ambrosino	SR, less recent and comprehensive than Gajbhiye
Arabi	SR, less recent and comprehensive than Gajbhiye
Banaei	SR, less recent and comprehensive than Gajbhiye
Dashti	Protocol for SR
Sousa	SR, less recent and comprehensive than Gajbhiye
Della Gatta	SR, less recent and comprehensive than Gajbhiye
Di Mascio	SR, less recent and comprehensive than Gajbhiye
Duran	SR, less recent and comprehensive than Gajbhiye
Ferrazzi	retrospective case series
Fornari	SR, less recent and comprehensive than Gajbhiye
Hu	case series
Juan	SR, less recent and comprehensive than Gajbhiye
Ludvigsson	Narrative review
Muhidin	SR, less recent and comprehensive than Gajbhiye
Mustafa	SR, less recent and comprehensive than Gajbhiye
Panahi	narrative review'
Parazzini	SR, less recent and comprehensive than Gajbhiye
Pierce-William,	cohort study, no information about neonatal testing
Rodrigues	SR, less recent and comprehensive than Gajbhiye
Trad	no full text
Yan	retrospective case series
Yang	SR, less recent and comprehensive than Gajbhiye
Zaigham	SR, less recent and comprehensive than Gajbhiye

Literature search strategy vertical transmission

Questions: What is the risk of a fetus being infected by a pregnant woman with COVID-19 in utero, during labour or during a cesarean section? → What is the risk of vertical transmission?	
Database(s): Embase, PubMed, Google Scholar, WHO, Medrxiv	Date: 13-5-2020
Informationspecialist: Miriam van der Maten	
Information: In addition to the conventional databases, other sources such as Google Scholar, WHO and preprint websites are searched. These sources can be searches less systematically and require a more hand-made approach.	

Results

	Embase	Pubmed	Other sources	Total
	74	72	47	135

Search justification

Database	Searched terms		
Embase	No.	Query	Results
	#3	#1 AND #2	**74**
	#2	'vertical transmission'/exp OR (((vertical* OR intrapartum OR peripartum OR antepartum OR intrauterine OR transplacental*) NEAR/4 (transmission* OR transmit* OR infection)):ti,ab,kw) OR (('disease transmission'/exp	**44083**

	#1 OR transmission*:ti,ab,kw OR transmit*:ti,ab,kw) AND ('pregnant woman'/exp OR 'pregnant wom*n':ti,ab,kw OR mother*:ti,ab,kw OR maternal*:ti,ab,kw) AND (infan*:ti,ab,kw OR newborn*:ti,ab,kw OR 'new born*':ti,ab,kw OR perinat*:ti,ab,kw OR neonat*:ti,ab,kw OR 'baby'/exp OR baby*:ti,ab,kw OR babies:ti,ab,kw OR kid*:ti,ab,kw OR 'child'/exp OR child*:ti,ab,kw OR children*:ti,ab,kw OR foetal:ti,ab,kw OR fetal:ti,ab,kw OR foetus:ti,ab,kw OR fetus:ti,ab,kw OR embryo:ti,ab,kw)) (('coronavirinae'/exp OR 'coronavirus infection'/de OR coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw) AND (outbreak:ti,ab,kw OR wuhan:ti,ab,kw) OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw) AND 2019:ti,ab,kw) OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR 'coronavirus*':ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'ncov 2019':ti,ab,kw OR ncov:ti,ab,kw OR 'sars coronavirus 2':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome cov2':ti,ab,kw) AND [2019-2020]/py	**9372**
Pubmed	(("Infectious Disease Transmission, Vertical"[Mesh] OR (((perinatal OR vertical* OR intrapartum OR peripartum OR antepartum OR intrauterine OR transplacental*) AND (transmission*[tiab] OR transmit*[tiab] OR infection[tiab]))) OR (("transmission"[Subheading]) OR "Disease Transmission, Infectious"[Mesh] OR transmission*[tiab] OR transmit*[tiab]) AND ("Pregnant Women"[Mesh] OR 'pregnant wom*n'[tiab] OR mother*[tiab] OR maternal*[tiab]) AND (infan*[tiab] OR newborn*[tiab] OR 'new born*'[tiab] OR perinat*[tiab] OR neonat*[tiab] OR "Infant"[Mesh] OR "Infant, Newborn"[Mesh] OR baby*[tiab] OR babies[tiab] OR kid*[tiab] OR "Child"[Mesh] OR child*[tiab] OR children*[tiab] OR foetal[tiab] OR fetal[tiab] OR foetus[tiab] OR fetus[tiab] OR embryo[tiab]))) *(25717)* **AND** (("COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR (("Coronavirus"[MeSH Terms] OR "Coronavirus Infections"[Mesh:noexp] OR pneumonia virus*[tiab] OR cov[tiab]) AND (outbreak[tiab] OR wuhan[tiab] OR novel[all] OR 19[tiab] OR 2019[tiab] OR epidem*[tiab] OR epidemy[all] OR epidemic*[all] OR pandem*[all] OR new[tiab])) OR coronavirus*[tiab] OR corona virus*[tiab] OR ncov[tiab] OR 2019ncov[tiab] OR covid19[tiab] OR "covid 19"[tiab] OR "sars cov 2"[tiab] OR sars2[tiab] OR "ncov 2019"[tiab] OR "sars coronavirus 2"[tiab] OR "sars corona virus 2"[tiab] OR "severe acute respiratory syndrome cov 2"[tiab] OR "severe acute respiratory syndrome cov2"[tiab] OR severe acute respiratory syndrome cov*[tiab] OR cov2[tiab]) AND ("2019/12"[Date - Entrez] : "3000"[Date - Entrez])) *(11226)*	
Other sources	Variations of the search terms 'vertical transmission' and 'mother-to-child transmission' were applied.	