Vaginal delivery in SARS-CoV-2 infected pregnant women in Northern Italy: a retrospective analysis.

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Summary

Objective: To report mode of delivery and immediate neonatal outcome in COVID-19 infected women.

Design: This is a retrospective study..

Setting: Twelve hospitals in northern Italy.

Participants: Pregnant women with COVID-19 confirmed infection who delivered.

Exposure: COVID 19 infection in pregnancy.

Methods:SARS-CoV-2 infected women who were admitted and delivered during the period 1-20 march 2020 were eligible. Data were collected from the clinical records using a standardized questionnaire on maternal general characteristics, any medical or obstetric co-morbidity, evolution of pregnancy, clinical signs and symptoms, treatment of COVID 19 infection, mode of delivery, neonatal data and breastfeeding

Main Outcome and Measure: Data on mode of delivery and neonatal outcome

Results: 42 women with COVID-19 delivered at the participating centres: 24(57,1%, 95% CI= 41,0-72,3) delivered vaginally. An elective cesarean section was performed in 18/42 (42,9%, 95%CI 27,7-59,0) cases: in 8 cases the indication was unrelated to COVID-19 infection. Pneumonia was diagnosed in 19/42(45,2%, 95%CI 29,8-61,3) cases: of these 7/19(36,8%,95CI 16,3-61,6) required oxygen support and 4/19(21,1%,95%CI=6,1-45,6) were admitted to a critical care unit. Two women with COVID-19 breastfed without a mask because infection was diagnosed in the post-partum period: their new-borns tested positive for SARS-Cov-2 infection. In one case a new-born had a positive test after a vaginal operative delivery.

Conclusions:. Although post-partum infection cannot be excluded with 100% certainty, these findings suggest that vaginal delivery is associated with a low risk of intrapartum SARS-Cov-2 transmission to the new-born.

Key words: delivery, COVID-19, transmission

Running title: Delivery in SARS-CoV-2 infected women

Tweetable abstract:
This study suggests that vaginal delivery may be associated with a low risk of intrapartum SARS-Cov-2 transmission to the new-born.

Funding: No funding

INTRODUCTION.

Most of the information on the effect of COVID-19 infection during pregnancy is based on data relating to other highly pathogenic coronaviruses (i.e., severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome(MERS) [1].

Recently Chen et al.[2] have reported nine cases of deliveries in women with COVID-19 pneumonia. In their study all nine patients had a caesarean section in the third trimester. The neonatal outcomes were favourable and all neonatal throat swabs performed tested negative for the virus.

Another clinical series of 11 women with COVID 19 infection who had successful deliveries (10 cesarean and 1 vaginal) has been reported: in all the new-borns the 2019-nCoV nucleic acid test was negative[3].

Chen et al concluded their paper by underlining that "there is currently no evidence for intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in late pregnancy" [2]. This finding is, however, based on very few reported cases, particularly for vaginally delivered newborns[3,4]. Accordingly, a recent consensus stated that there is no clear evidence regarding optimal delivery timing, the safety of vaginal delivery, or whether cesarean delivery prevents vertical transmission at the time of delivery; therefore, route of delivery and delivery timing should be individualized based on obstetrical indications and maternal-fetal status. [5]

Due to the recent outbreak of the infection in Italy, particularly in Lombardy, a number of infected women have already delivered. Regione Lombardia, Northern Italy, has established a network of six designated COVID-19 maternity hospitals in order to offer adequate assistance and epidemiological surveillance to symptomatic infected pregnant women.
The goal of this study was to report the mode of delivery and immediate neonatal outcome in SARS-CoV-2 infected women observed in the early phase of the epidemic in Lombardy

METHODS.

We performed a retrospective multicenter study of COVID-19 infected women who were admitted and delivered during the period 1-20 march 2020. Most deliveries of infected women occurred in the designated COVID-19 hubs, but some were delivered in spoke hospitals because they were in advanced active phase labour. Designated Hub-Maternity Hospitals were: Milan-Mangiagalli and Sacco, Bergamo-Pap Giovanni XXIII; Brescia-Spedali Civili; Monza-S. Gerardo Hospital/MBBM Foundation; Pavia-San Matteo. Spokes Maternity Hospitals were: Milan-Melloni and S. Giuseppe; Seriate-Bolognini; Treviglio-Civil Hospital. The Maternity Hospital of Padua and the Maternity Hospital of Modena were not hub hospitals of Lombardy Region, but also reported their cases for this study".

Criteria for entry to the study were:
-pregnant women who delivered during the study period with a confirmed diagnosis of COVID-19 infection prior to or within 36 hours after delivery.

The investigators reported all women consecutively observed who met the inclusion criteria.
All centers carefully revised all delivery charts of the study period and all cases who had a confirmed throat swab by RT-PCR positive test for SARS-CoV-2 infection were included. The clinical triage was performed according to WHO guidelines[6]. Diagnosis of COVID 19 infection was based on the results of maternal and child throat swab samples according to Italian National Procedures[7]. All women were treated according to the National Guidelines for COVID-19 in pregnancy and treatment was then tailored according to the individual evolution of signs, symptoms, laboratory data and radiologic findings. There were no additional obstetric diagnostic procedures or monitoring in addition to normal clinical practice, apart from a confirmative chest x-ray, and 48 hours monitoring of white blood cell count and CRP.

Fetal growth and well-being were assessed at admission and the fetal heart rate was monitored continuously during labour and delivery.

Surgical mask for the labouring woman, her accompanying person and the midwife and/or doctor were worn during labours. More strict personal protective equipment (PPE) were worn during delivery ,as bearing down expulsive efforts risk may cause the woman to emit infected droplets.

When the positive infected status of the mother was known at delivery, breast feeding was allowed according to international guidelines[8] if the mother was asymptomatic or had only minor symptoms. Women were instructed how to wear and dispose of surgical masks, in combination with frequent hand-cleaning with alcohol-based hand rub or soap and water.

Data were collected from the clinical records using a standardised questionnaire on maternal general characteristics, any medical or obstetric co-morbidity, course of pregnancy, clinical signs and symptoms, treatment of COVID 19 infection, mode of delivery, neonatal data and breastfeeding. In relation to the neonatal outcome, we recorded only whether there was a positive or negative test for COVID-19. Women and new-borns were followed up until discharge from hospital or till March 25th, whatever came first.

For the recorded variables, averages, range or proportion and corresponding 95%confidence intervals (CI) were computed, as appropriate. Statistically significant differences among groups was tested using the common chi square test for heterogeneity. Patients were not involved in the development of the research. No core outcome set was used in the research.

The study protocol was approved by the Institutional Review Boards.
No funding supports this study

RESULTS.

A total of 42 women eligible for the study delivered in the participating centres.A total of 32 women delivered at hub hospitals and 10 in the spoke ones.

Diagnosis of COVID-19 infection was known before admission to hospital in 10 cases, in the delivery room in 27 cases and in 5 cases the diagnosis was made within 36 hours following delivery, while the women were still in hospital.

A total of 24/42 (57,1%, 95% CI= 41,0-72,3) women delivered vaginally, with three cases undergoing induction of labour for obstetric reasons.

An elective cesarean section was performed in 18/42 (42,9%, 95%CI 27,7-59,0) cases: in 8 cases the indication was unrelated to COVID-19 infection, but in 10 cases the indications were worsening dyspnoea or other COVID-19 related symptoms. In women who attempted vaginal delivery, no emergency cesarean section occurred

The characteristics, signs, symptoms and treatment of COVID-19 infection of this cohort are presented in table 1 according to the mode of delivery. Mean maternal age was 32.9 (range 21-44). Fever was the most common symptom. Pneumonia was diagnosed in 19/42 (45,2%, 95%CI 29,8-61,3) cases. 7 of these 19 (36,8%,95CI 16,3-61,6) required oxygen support and 4 of the 19 (21,1%,95%CI=6,1-45,6) were admitted to a critical care unit. Pneumonia was more common in women who delivered by caesarean section due to COVID-19 related infection (chi-square=7.45, p-value= 0,024).

Table 2 presents the course of pregnancy and the neonatal outcome. Gestational diabetes was reported in 6/42 cases (14%) without any significant difference between the three groups. 30/42 (71,4%, 95%CI=55,4-84,3) women delivered at term. Spontaneous preterm birth occurred in 5 cases and in 6 cases elective cesarean section was performed.

Two very preterm new-borns had a 5min Apgar score <7; all the rest had 5 min Apgar scores of 7 or more.

Newborn outcomes and breastfeeding.

In 10 cases breastfeeding was allowed, with the women using a surgical mask. Two women had a new diagnosis of COVID-19 infection in the post-partum period and breastfed without a surgical mask; both the newborns had a positive test for COVID-19 infection at day one and three, respectively.
In another case after vaginal delivery the new-born of an infected woman had a positive test. This case deserves additional details. One newborn from a COVID-19 mother delivered vaginally at term in good condition was immediately separated because of a severe maternal postpartum haemorrhage. Within a few hours he developed gastrointestinal symptoms, and after three days he developed respiratory symptoms and was transferred to the neonatal intensive care unit where he recovered after one day of mechanical ventilation. The first test for SARS-CoV-2 was equivocal a few hours after delivery, but positive three days later. The mother did not breastfeed. No associated health care providers had a confirmed diagnosis of COVID-19 infection. No other positive test was found among the newborns.

DISCUSSION.

Main findings.

This paper reports the obstetric outcome of a cohort of COVID-19 affected pregnant women and the rate of SARS-CoV-2 positivity in new-borns according to the mode of delivery and breastfeeding status
The general results show that vaginal delivery occurred in about the 60% of women A low risk of intrapartum SARS-Cov-2 transmission to the new-born cannot be excluded. Further, the majority of pregnant women affected by the COVID-19 respiratory syndromes suffered mild or moderate symptoms. Fever, cough and mild dyspnoea were the most common symptoms, (80%), but pneumonia was diagnosed in about the 40% of women.

Strengths and limitations.

Among the strengths of this analysis we have to consider the fact that we have included in our study all consecutive positive women delivered in, or admitted to the post-partum COVID-19 ward, in all maternity units of the COVID-network in Lombardy and Units of Padua and Modena, so as to be sure to include all symptomatic cases who tested positive on the nasopharyngeal sampling. The reported cases represent approximately 0.6% of the total deliveries occurring in the same area during the 20 days of the study.
Among the limitations we should underline that due to the limited follow up, the not immediate maternal and new-born outcome was not considered.

Interpretation.

In our study, the maternal conditions were generally mild to moderate. Radiologically confirmed pneumonia was diagnosed in 42% of cases and four of these 19 cases required admission to a critical care unit. As suggested by others[9], the findings of our cohort support the hypothesis that COVID-19 respiratory syndrome may be less severe for maternal prognosis than SARS and MERS.
Lymphopaenia and high CRP values were part of the clinical scenario that induced clinicians to deliver patients by cesarean section.

Of note, two cases were delivered < 34 weeks of gestation because of worsening respiratory function. Five women delivered spontaneously before term (one before 34 weeks of gestation). These observations are compatible with no increase in the risk of preterm birth, consistent with the findings of a previously published series reporting no cases of preterm birth before 33 weeks of gestation[4].

Vertical and intrapartum transmission are among the most serious complications of viral diseases during pregnancy. In the previously quoted published series of a total of 30 women[2,3], delivery in all but one cases was by cesarean section. No new-born infection was reported. Vertical transmission does not seem to occur after infection with other pathogenic coronaviruses such SARS-CoV and MERS-CoV- infection, although it has been suggested that coronaviruses may cause early pregnancy loss[10,11].

Previous data on virus transmission are based substantially on women delivered by cesarean section. Vertical transmission of viral infection generally occurs during intrauterine life by transfer across the placenta, or during delivery by ingestion or aspiration of cervicovaginal secretions, and in the postpartum period via breastfeeding[1.] The risk of

ingestion or aspiration of cervical secretion or with contact with perineal infected tissue is of course higher in case of vaginal delivery. Among the 24 women who delivered vaginally, one new-born was infected probably due to post-partum contamination (see below). In a second cases after vaginal delivery a potential intrapartum infection may have occurred, but it was not possible to exclude infection immediately post-partum.

It should be emphasized that we can only consider the risk of transmission among women who were infected during the third trimester or at term and the risk of intrapartum transmission, because the infections in Northern Italy are all recent, and women infected in early pregnancy are still pregnant.

We report five cases who were diagnosed to be COVID-19 positive because of fever in the post-partum period. In two cases in which skin to skin contact after birth and breastfeeding was allowed without a mask because infection was not known, the COVID-19 test of the new-born was positive at days 1 and 3 after birth. Although no viral load has been detected in breast milk by Chan et al. [2], close maternal contact may represent a potential route of transmission. In these two cases, because viral testing was not carried out immediately after birth, vertical transmission cannot be excluded.
To our knowledge, other two cases of SARS-CoV-2 infected new-borns have been reported in which the diagnosis was made 36 hours following delivery and at 17 days of life. In both cases a postpartum neonatal infection acquired through an infected contact was suggested [4]. In all these cases, because viral testing was not performed immediately after birth, the route of transmission cannot be definitely established.

Elevated IGM antibodies against Coronavirus have been also reported in a case after caesarean section by Dong et al [13]. Three additional newborns with elevated IGM antibodies to SARS-COv-2 virus, but a throat swab by RT-PCR negative test, have been also reported [14]. Caution in interpreting these findings has been suggested, including the possibility that IGM positivity could represent a laboratory artifact[15].

Conclusion.

The frequency of COVID-19 symptoms and positive laboratory and radiologic findings observed in this cohort is in line with the fact that this syndrome is generally mild or moderate in pregnancy and very likely many infected pregnant women are totally asymptomatic or develop symptoms only after delivery. Vaginal delivery is appropriate in mild cases and caesarean section should be reserved for women with severe respiratory embarrassment where delivering the baby will allow improved ventilation. Although post-partum infection cannot be excluded, our study also suggests that vaginal delivery may be associated with a low risk of intrapartum SARS-Cov-2 transmission to the new-born. This finding needs further data.
The observed occurrence of COVID-19 symptoms only after delivery suggests that, in areas characterized by a high prevalence of infection, safe procedures for midwives and doctors are to be recommended in any labour and to adopt mask and safe procedures in all breastfeeding women.

Contributors

FP, EF, IC and LF each led aspects of the contact investigation and provided overall leadership and guidance to the investigation.
FM, GZ and GM were the pediatricians in charge of treatment of the newborn babies in the main collaborating centres.
LF, VS, SB, FF, MTG, EI, AK, BM, LP, FeP, DS, AS, GT, PV, MV, AV completed the investigation of cases and7or collected epidemiological data, and provided clinical care to the patients and assisted with clinical descriptions.
FP and EF drafted the manuscript
IC revised the manuscript.
All authors reviewed and approved the final manuscript.

Conflict of interests

We declare no competing interests.

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Data sharing

With the permission of the corresponding authors, we can provide data without names and identifiers. The corresponding authors have the right to decide whether to share the data or not based on the research objectives and plan provided.

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy

Fabio Parazzini affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

The study was approved by the Institutional Review Boards (15408/2020 IRB Milan Area 1).

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Table 1. Maternal characteristics and symptoms.

	Elective Cesarean section for conditions determined by COVID-19 respiratory syndrome (No.= 10)	Elective Cesarean section for obstetric reasons unrelated with COVID-19 respiratory syndrome (No.=8)	Vaginal delivery° (No.=24)
Maternal characteristics			
Maternal age (mean, range)	30.9 (21-40)	30.5 (27-44)	34.6 (29-43)
Nulliparous women	4(40%)	2(25%)	9 (38%)
Sign and symptoms of SARS-Cov-2-infection			
Fever before delivery	7(70%)	4(40%)	9(38%)
Fever only in the post partum	-	1(13%)	5(21%)
Myalgia/malaise	5(50%)	-	2(8%)
Cough	8(80%)	2(25%)	8(33%)
Dyspnoea	7(70%)	-	1(4%)
Diarrhoea	-	1(13%)	1(4%)
Pneumonia	8(80%)	4(50%)	7(29%)
Treatment			
Oxygen support (nasal cannula, CPAP)	4(40%)	1(13%)	2(8%)
Admission to critical care unit (yes)	2(20%)	1(13%)	1(4%)
Laboratory findings			
High leukocyte count (>9.5 × 10^9 cells per L)°°	3(30%)	2(25%)	11(46%)
Lymphopenia (<10^9 cells per L)°°	3(30%)	1(13%)	2(8%)
Elevated C-reactive protein (>10 mg/L)°°	7(70%)	4(50%)	6(25%)
Elevated ALT (>45 U/L) or AST (>35 U/L)°°	2(20%)	-	3(13%)

° In 3 cases labour was induced for obstetric indication unrelated with COVID 19 respiratory syndrome. °°6 cases missing

443 Table 2. Pregnancy, delivery and neonatal outcome.

	Elective Cesarean section for conditions determined by COVID-19 respiratory syndrome (No.= 10)	Elective Cesarean section for obstetric reasons unrelated with COVID-19 respiratory syndrome (No.=8)	Vaginal delivery (No.=24)
Pregnancy and delivery			
Gestational diabetes (yes)	2(20%)	-	4 (17%)
Weeks of gestation at delivery			
>37	5 (50%)	7(88%)	18(78%)°
>34-37	3 (30%)	-	4 (17%)
<=34	2 (20%)	1 (13%)	1 (4%)
New-born			
Birth weight (grams; mean, range)°°	2730(840-4040)	3100(2770-3430)	3226(2450-3740)
Apgar score (5min)>7	8(80%)	8(100%)	24(100%)
NICU admission (Yes)	-	1 (13%)°°°	2(8%)°°°
Positivity to SARS-Cov-2 (Yes)	0	1(13%)	2(8%)
Breastfeeding (Yes)	0	1(12%)	10(42%)

444 NICU: Neonatal Intensive Care Unit.

445 °1 case missing

446 °°5 cases missing

447 °°° for preterm birth/respiratory distress

448