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What does the cardiotocography say about SARS-CoV-2 infection? Cardiotocograph monitoring during the pandemic era: a narrative short review

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ABSTRACT

Although emerging data indicate an increased risk of preeclampsia, intrauterine growth restriction, preterm birth, and stillbirth, several questions remain unsolved in the case of SARS-CoV-2 infection in pregnant women. Cardiotocography (CTG) is the main method for monitoring the foetal well-being during the intrapartum period and is now used worldwide for the early detection of foetal distress during labour and delivery. This literature review aims to assess different intrapartum CTG changes observed in SARS-CoV-2 positive mothers, to understand whether CTG should be specifically interpreted or correlated with the seropositivity of mother to improve their management.
We reviewed titles and abstracts of 44 records regarding CTG and SARS-CoV-2, in PubMed and SCOPUS, abstracting the full text for 10. Of these, 6 studies met the eligibility criteria and were included in this narrative short review. Maternal SARS-CoV-2 infection has been associated with changes observed in CTG, such as the increase in the baseline due to fever, inflammatory response and the "cytokine storm". Moreover, the impact that SARS-CoV-2 had on the placenta has noticed to be still accountable for most of the alterations in CTG.
Despite the lack of specificity of CTG alterations in SARS-CoV-2 positive patients, obstetricians are encouraged not to neglect foetal monitoring because of the isolation of positive woman, owing the virus's harmful effects on placentas and maternal health.

INTRODUCTION

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), known as the cause of the COVID-19 disease, was declared a pandemic by the World Health Organization in March 2020. It infected over 100 million individuals at an exponential accelerating rate, since its first identification in December 2019 [1]. Pregnant women and their foetuses are particularly exposed to adverse outcomes, such as maternal mortality and morbidity, and perinatal death, when infected by coronaviruses, basing on past epidemics experiences [2]. SARS-CoV-2 has been associated with a more severe clinical presentation of COVID-19 disease during pregnancy, since pregnancy is a time of increased susceptibility to infection [2-4]. The most important pregnancy-related complications, include a higher risk of stillbirth, intrauterine growth restriction (IUGR), preeclampsia and

preterm birth [4-6]. The potential role of the placenta in the infectious process has been postulated basing on the presence of the angiotensin-converting enzyme 2 (ACE2) receptor on the cell membrane [7]. As well as being a potential site of virus entry, the receptor is part of the renin-angiotensin-aldosterone system, which plays a pivotal role in maternal hemodynamic adaptation during pregnancy [7, 8].

Cardiotocograph (CTG) is a worldwide used method to assess foetal well-being monitoring foetal heart rate (FHR) and detecting signs of intrapartum hypoxia and acidaemia [9]. Qualitative and quantitative descriptions of several parameters, including the baseline foetal heart rate, variability, accelerations and decelerations, are part of the interpretation of a CTG trace [9, 10]. These parameters give us information about the oxygenation of the foetal brain and heart, reflecting the activity of foetal somatic and autonomic nervous systems [10]. In case of utero-placental insufficiency, foetal metabolism shifts from aerobic to anaerobic as a result of the hypoxia, causing a reduction in the cardiac workload of the foetus [11]. This complex mechanism is displayed in the CTG trace as deceleration [11]. Moreover, baseline tachycardia and decelerations in the CTG trace may be indicative of foetal distress caused by maternal pyrexia or other inflammatory diseases [12]. In 2008, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the American College of Obstetricians and Gynaecologists, and the Society for Maternal-Fatal Medicine, revisited the nomenclature, the interpretation, and the recommendations for intrapartum electronic foetal heart rate monitoring [13] simplifying its categorization and interpretation into a 3-tier system, as shown in **Table 1** [14].

That said, since SARS-CoV-2 infection and the consequent COVID-19 disease trigger an important inflammatory process, negative consequences and unfavourable obstetric outcomes on women and foetuses are possible risks.

The purpose of this short review is to summarize the evidence related to the association between SARS-CoV-2 infection and detectable changes in the CTG trace. In addition, we reported possible patterns identified in relation to the severity of the disease, with the specific purpose of gaining knowledge in this area, to ensure better management of these cases under emergency conditions.

Table 1. *3-Tier foetal heart rate interpretation system [14].*

Category	Tracing	Description
I	Normal	• Baseline rate: 110-160 beats/min • Moderate variability • Absence of any late or variable decelerations • Early decelerations may or may not be present • Accelerations may or may not be present

II	Indeterminate	• Baseline rate
		  • Tachycardia
		  • Bradycardia not accompanied by absent baseline variability
		• Baseline Foetal Heart Rate variability
		  • Minimal baseline variability
		  • Absent baseline variability not accompanied by recurrent decelerations
		  • Marked baseline variability
		• Absence of induced accelerations after foetal stimulation (*e.g.*, scalp stimulation, vibroacoustic stimulation, direct foetal scalp sampling, transabdominal halogen light)
		• Periodic or episodic decelerations
		  • Recurrent variable decelerations accompanied by minimal or moderate baseline variability
		  • Prolonged deceleration ≥ 2 min but < 10 min
		  • Recurrent late decelerations with moderate baseline variability
		  • Variable decelerations with other characteristics, such as slow return to baseline, "overshoots", or "shoulders"

III	Abnormal	• Absent baseline Foetal Heart Rate variability along with any of the following:
		  • Recurrent late decelerations
		  • Recurrent variable decelerations
		  • Bradycardia
		• Sinusoidal pattern

METHODS

An initial systematic search was conducted using the Medline, PubMed, and Scopus databases. Publications without a limit in the timeframe were selected. The following set of search terms were included: Cardiotocography OR Cardiotocograph OR CTG AND SARS-CoV-2 OR COVID-19 (Title/Abstract). Forty-four articles resulted from the initial search. A preliminary screening of titles and abstracts according to the scope of the review, was carried out by the authors after eliminating duplicates (**Figure 1**). If it was not clear from the abstract whether the article might contain relevant data or not, the full article was assessed. Non-English articles were excluded. The first and the third

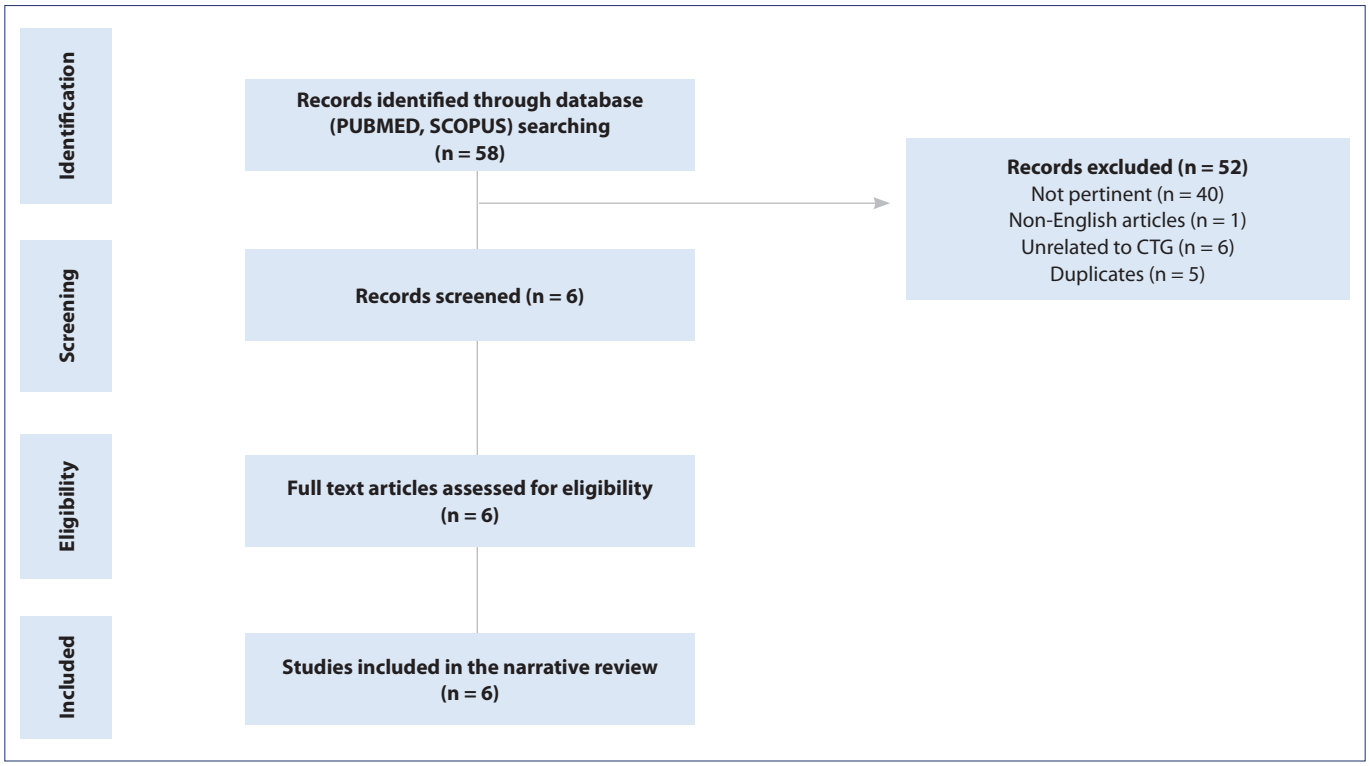

Figure 1. *Flowchart of included studies.*

Table 2. *Included articles with main findings in the cardiotocographic pattern.*

Author/ Date	Participants	Type of article	Gestational age (weeks)	Primary Objective(s)	Cardiotocographic patterns
Sinaci *et al.*, 2022	224 COVID-19 positive women	Prospective cohort study	37 (32-41)	Relation between CTG traces and the severity of COVID-19	○ 25.0% minimal or absence of variability; ○ 4.0% ZigZag pattern; ○ 13.4% absence of acceleration; ○ 25.0% presence of decelerations; ○ 5.4% tachycardia; ○ 1.3% bradycardia; ○ 66.5% uterine contractility.
Farhan *et al.*, 2022	30 COVID-19 positive women; 60 Controls	Case–control study	36.73 ± 2.47 (cases) 38.38 ± 1.6 (Controls)	Verify intrapartum CTG changes and their impact on delivery mode and neonatal outcome	○ 60% of COVID-19 cases exhibited abnormal CTG changes *versus* 19.4 % in controls; ○ CS for abnormal foetal heart tracing occurred in 33.3 % *versus* 15.6 % (P-value = 0.015) for cases *versus* healthy controls.
Gracia-Perez-Bonfils *et al.*, 2020	12 COVID-19 positive women	Retrospective analysis	38+1 (28-40+6)	Determine the CTG changes in COVID-19 positive patients	○ Increased baseline FHR > 10% compared to the initial recording in all foetuses; ○ Gross foetal tachycardia (>210 bpm) in one case; ○ Absence of acceleration in all fetuses; ○ 83.3% Late or prolonged decelerations; ○ 58.3 % absence of cycling; ○ 33% ZigZag pattern. None sinusoidal pattern; ○ 83.3% evidence of excessive uterine activity.
Ivert *et al.*, 2023	5 COVID-19 positive women	Case series	28+5 (24-33+5)	SARS-CoV-2 effect on the placenta	○ CTG was interpreted as pathological.
Dumont *et al.*, 2021	1 COVID-19 positive women	Case-report	29+1	SARS-CoV-2 Alpha variant effects on the placenta	○ Abnormal pattern with greatly reduced variability.
Suresh *et al.*, 2020	1 COVID-19 positive women	Case-report	34+1	Highlights the challenges of modifying ante-partum testing strategies during the COVID-19 pandemic	○ CTG was interpreted as pathological.

FHR: foetal heart rate; CTG: cardiotocography, CS: caesarean section.

author, assessed independently, and subsequently discussed the quality of all eligible studies. The analytic process was then completed by reading and categorizing all articles and summarizing the findings. Six articles were included in this narrative review, responding to the author's purpose (**Table 2**). A narrative synthesis of the studies was conducted, integrating the material with theoretical notions selected from book chapters or other articles referenced in included studies.

EVIDENCE SYNTHESIS

A prospective cohort study [15], evaluated the CTG traces of 224 women, infected with SARS-CoV-2 (**Table 2**). The authors included 224 pregnant women of 32 weeks or more (mean 36.4 ± 3.44), including only singleton pregnancies. All women resulted positive for SARS-CoV-2 using quantitative RT-PCR (qRT-PCR) on samples from the respiratory tract. CTG traces were observed comparing the one performed during hospital admission with the one performed the third day of positivity. The rationale was that the SARS-CoV-2's viral replication reaches its higher replication rate on day 3 [16]. 84% of patients had a mild COVID-19 symptomatology. 96% didn't report a worsening in the disease during the observation, and 83.9% didn't require any medical treatment at all. The CTG category was I in 63% (163/224) of patients. The CTG classification didn't change in 82.1% of the cases (184/224) during the observation. On the other hand, twenty-five % (56/224) of patients had minimal or absence of variability, while 4.0% (9/224) had a ZigZag pattern (exaggerated variability). 13% (30/224) hadn't acceleration, and 25.0% (56/224) showed decelerations. 5% (12/224) of the patients had tachycardia, while 1.3% (3/224) had bradycardia. 66% (149/224) of patients showed uterine contraction at the trace, and a caesarean section (CS) was performed in 44.6% (100/224) of the cases. Along these observations, authors concluded that there was no statistically significant relationship between the COVID-19 severity and the CTG category.

A case-control study [17] analysed 90 pregnant women at term. Patients were categorized into two groups: COVID-19 positive (30/90), confirmed by real-time RT-PCR test, and healthy controls (60/90) who tested negative (**Table 2**). COVID-19 patients showed significantly higher maternal pulse rate, temperature, and leukocyte counts. The CS rate was higher in the group of positive *versus* controls (70% *vs* 53.3%; p = 0.45). The CS indication was "abnormal foetal heart tracing" for 33.3% of patients in the COVID-19 positive group, while 15.6 % (p = 0.015) in the group of negative. 60% of cases in the group of positive patients had foetal tachycardia and reduced variabilities at the CTG trace. These features were registered in 19.4% of cases in the control group. In 23% of the positive patients, there variability was reduced and 3% had a foetal demise.

A retrospective analysis [18] evaluated 12 CTG traces in symptomatic COVID-19 infected pregnant women, over the 37th week of gestation (**Table 2**). The aim was to understand if there were correlation between the CTG trace, the maternal severity of COVID-19 infection and the perinatal outcomes. These latter were defined by APGAR Score < 7 at five minutes, umbilical cord arterial pH < 7.0 or admission to the neonatal unit that was not expected. According to the authors, all CTG where uterine contractions were registered (10 out of 12) showed excessive uterine activity. Moreover, late, or prolonged decelerations were recorded in 10 out of 12 traces (83.3%). Just a single case presented a gross foetal tachycardia (> 210 bpm). 58% of cases showed no cycling. An exaggerated or augmented variability > 25 bpm was recorded in 33% of the cases, confirming a ZigZag pattern.

Despite the abnormalities recorded, such as absence of accelerations, increased baseline of the foetal heart, and the presence of late or prolonged decelerations, there were no adverse perinatal outcome.

In a case series [19], five pregnant women with a mild SARS-CoV-2 infection, were admitted for reduced foetal movements between 24+0 and 33+5 weeks of gestation. None of the women received a vaccination for COVID-19 (**Table 2**). At the time of admission, an ultrasound scan showed reduced foetal movements and CTG category was recorded as III. A few hours later, four out of the five women underwent a CS. Even if none of the new-borns was positive for SARS-CoV-2, all placentas tested positive. The histopathologic analysis of these latter, showed a massive peri-villous fibrin deposition and histiocytic inter-villosities, related to the placental insufficiency and the hypoxia.

In a case report [20], a 37-year-old woman who resulted positive for SARS-CoV-2 Alpha variant, was admitted to a tertiary care hospital at 29+1 weeks of

gestation because of oligohydramnios and reduced foetal movements for 10 days (**Table 2**). At the time of admittance, CTG demonstrated a normal pattern while the following day, CTG demonstrated abnormal pattern with greatly reduced variability. With the purpose of the foetal neuroprotection, intravenous magnesium sulphate was administered. An urgent caesarean section was therefore performed. Due to its prematurity, the neonate was admitted to the NICU. Two nasopharyngeal swabs were obtained from the neonate on two occasions: both were negative for SARS-CoV-2. Moreover, the umbilical cord and neonatal blood analysis, showed no SARS-CoV-2 RNA.

In another case report [21], a 28-year-old gravida at 34 weeks of gestation was found positive for SARS-CoV-2 after reporting rhinorrhoea, anosmia, and mild cough (**Table 2**). She reported normal perception of the foetal movement and denied any contractions, vaginal bleeding, or leakage of amniotic fluid. Findings from the CTG showed baseline rate 140 beats/min, moderate variability, periodic decelerations, and irregular uterine contractions. The CTG was recorded as Category II. Since the category II tracing persisted, the clinicians decided to perform an urgent repeated caesarean section.

DISCUSSION

SARS-CoV-2 infection seems to cause an excessive release of pro inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α) and chemokines such as monocyte chemoattractant protein-1 (MCP-1/CCL2) [6, 22, 23]. Moreover, the infection leads to an hyperactivation of immune cells especially in the lungs, and an hypercytokinemia with an abnormal innate immune response in the mother [6, 22, 23]. The severity of COVID-19 depends on this event, known as "cytokine storm", that could lead to an acute respiratory distress syndrome and in the worst of the cases to a multiorgan failure [24, 25]. On the other hand, the placental intervillous thrombosis is associated with the maternal hypoxia, the cytokine storm, and the hypercoagulability status [6, 26].

The changes in the CTG trace, in particular the FHR, is the result of a reactive response, more likely secondary to the maternal inflammatory status and the fever [27]. Plus, the foetal tachycardia (>210 bpm) is likely connected to the "cytokine storm" [27]. This result in an augmented foetal sympathetic reactivity with a cardiac arrythmia secondary to the incremented inflammatory response [27]. The ZigZag pattern is probably secondary to the autonomic instability [27] due, once again, to the maternal cytokine storm and pyrexia. The foetal bradycardia could be linked to the placental insufficiency and the thrombosis of the umbilical vein [27]. In addition, severe hypoxia of the mother can result as a sinusoidal pattern [27]. Absence of accelerations, late, or prolonged decelerations are most likely related to the depression of the foetal somatic nervous system [27]. The hypoxia status of the mother could lead to an increased placental oxygen consumption with the purpose of saving the foetal somatic muscle activity [15]. Plus, a depressive effect on the foetal brain for the loss of the normal active and quiet sleep phases, is recorded as an absence of cycling in the CTG trace [15].

Increased uterine contractility recorded on CTGs could depends on maternal fever or the maternal inflammatory status [28]. This result in a reduction of the utero-placental oxygen transfer and could lead to an irritation of the myometrium [28]. The remarkable involvement of placenta during SARS-CoV-2 infection is confirmed by a higher rate of decidual arteriopathy and other maternal impaired perfusion features, when SARS-CoV-2 positive placentas are compared to normal placenta [29]. The same phenomenon was confirmed in other studies, where placental deposition of fibrin has been retained responsible for the maternal-foetal gas exchange, increasing foetal distress and risk of emergency caesarean section [20, 30].

Demise of foetuses in the case of positivity of the mothers, can be related to the pregnancy-induced maternal hypercoagulability status, which is increased by the viral pro-thrombotic effect [17]. At the same time, the fever and inflammatory mediators of the mother, are retained responsible for the thrombosis of the placenta and the umbilical veins according to other authors [31, 33].

The authors of a study included in this review [18] suggested, before considering any intervention based on abnormal CTGs, to correct the maternal hypoxia, pyrexia and inflammatory response.

The studies included in this review are not devoid of limitations. These limitations could be extended to most of the studies facing with the COVID-19. The most important issue encountered, is related to the patients' selection: most of the studies

reviewed, described CTG patterns of SARS-CoV-2-infected women without comparing them with an uninfected group. Another concern is that not all studies describe the SARS-CoV-2 variants involved, and we cannot determine whether different variants – for example, Omicron *versus* Delta – induce different CTG alterations [34, 35]. Furthermore, not in all the studies, the COVID-19 symptomatology was sufficiently described, determined nor specified [36].
Nevertheless, numerous factors or circumstances may have influence on the characteristics of the CTG trace, including the time of the day, the position and activity of the mother, her use of medications and even the foetal movements.
Despite the analysed CTGs showed a high percentage of abnormalities such as decelerations, excessive uterine activity, or the absence of accelerations, it is not possible to state that correcting the maternal environment, the CTGs traces change. Another imposing limitation is that women included in the studies had different gestational ages, and probably different severity of COVID-19 symptomatology. Other limitations are the lack of information on the newborns umbilical cord pH and APGAR score.
Finally, not all the analysed studies report histopathological exams of the placentas: we cannot therefore establish whether an infected placenta itself or specific histologic alteration related to the infection of the mothers, can further modify the CTG patterns.

CONCLUSIONS

Abnormal patterns in CTGs traces have been reported in studies on mothers infected by SARS-CoV-2. These include an increase in the baseline due to the maternal pyrexia, maternal inflammatory response and the "cytokine storm". Alternatively, the SARS-CoV-2 effect on the placentas is retained responsible for most of the changes in the CTG. CTG changes in SARS-CoV-2 positive patients seems to be non-specific but considering the negative effects of the virus on the placentas and on the maternal wellbeing, it is relevant to highlight the importance for obstetricians to implement foetal surveillance in these patients.
Further research is needed to understand the effect of SARS-CoV-2 on pregnancy and neonatal outcomes and in this regard, considering the lack of knowledge on placentas and COVID-19, histological examination should always be considered for SARS-CoV-2 positive patients, to increase the knowledge on the virus's effects on the placenta and the consequent effects on the foetus.
The authors self-evaluated the narrative review according to the Scale for the Assessment of Narrative Review Articles - SANRA [37] (justification of the article's importance for the readership, statement of concrete aims or formulation of questions, description of the literature search, referencing, scientific reasoning, appropriate presentation of data) totalizing a score of 12/12.
The authors followed the EQUATOR Guidelines for reporting health research [38].

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

A.L.: Conceptualization. A.L., A.N., L.T.: Data curation, formal analysis. A.L., A.N., L.T., V.R.: Investigation, project administration, visualization. A.L., L.T.: Methodology. V.R.: Supervision, validation. A.L., A.N.: Writing – original draft. A.L., L.T., V.R.: Writing – review & editing.

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Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

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