A systematic catalog of studies on fetal heart rate pattern and neonatal outcome variables

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Abstract

Objectives: To study the methodology and results of studies assessing the relationship between fetal heart rate and specified neonatal outcomes including, heart rate, infection, necrotizing enterocolitis, intraventricular hemorrhage, hypoxic-ischemic encephalopathy, and seizure.

Methods: Embase, Medline ALL, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and CINAHL were searched from inception to October 5, 2023.

Results: Forty-two studies were included, encompassing 57,232 cases that underwent fetal monitoring and were evaluated for neonatal outcome. Heterogeneity was observed in the timing and duration of fetal heart rate assessment, classification guidelines used, number of assessors, and definition and timing of neonatal outcome assessment. Nonreassuring fetal heart rate was linked to lower neonatal heart rate variability. A significant increase in abnormal fetal heart rate patterns were reported in neonates with hypoxic-ischemic encephalopathy, but the predictive ability was found to be limited. Conflicting results were reported regarding sepsis, seizure and intraventricular hemorrhage. No association was found between necrotizing enterocolitis rate and fetal heart rate.

Conclusions: There is great heterogeneity in the methodology used in studies evaluating the association between fetal heart rate and aforementioned neonatal outcomes. Hypoxic-ischemic encephalopathy was associated with increased abnormal fetal heart rate patterns, although the predictive ability was low. Further research on developing and evaluating an automated early warning system that integrates computerized cardiotocography with a perinatal health parameter database to provide objective alerts for patients at-risk is recommended.

Keywords: hypoxic-ischemic encephalopathy; intraventricular hemorrhage; necrotizing enterocolitis; neonatal heart rate; neonatal infection; seizure

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Introduction

Cardiotocography (CTG) is used in pregnancy to assess fetal wellbeing, particularly oxygen homeostasis, with the aim of improving perinatal outcomes. The gold standard for fetal monitoring is visual interpretation of the fetal heart rate (FHR) in relation to uterine activity according to established guidelines. In addition to the various guidelines used worldwide, this method is subject to a high inter-observer and intra-observer variability, which may have contributed to the limited effectiveness of CTG in improving perinatal outcome [1]. In antepartum monitoring, CTG was not found to improve outcome compared to pregnancies in which CTG was not performed [2]. In intrapartum monitoring, CTG was found to be associated with lower neonatal seizure rates, but it did not improve other outcomes [3]. In addition, continuous CTG registration was associated with a higher rate of caesarean section and instrumental vaginal delivery [3].

New opportunities for assessment of fetal wellbeing have arisen from technological advances in FHR monitoring and signal processing. Conventionally, Doppler ultrasound technology is used. However, signal quality is affected by maternal adiposity, fetal movement, maternal-fetal heart rate confusion, and the averaging nature of the signal processing technique [4–6]. A promising alternative technology, non-invasive fetal electrocardiography, is not affected by maternal adiposity or fetal movement, and maternal-fetal

heart rate confusion is minimized [4, 5, 7]. In fetal electrocardiography, the FHR is determined from the R-R interval and the measured fetal electrocardiogram can provide insights into the cardiac cycle and how it relates to fetal wellbeing. The development of computerized CTG has objectified the assessment of the FHR and gives the opportunity to assess FHR variability not only in the time-domain, but also in the frequency-domain and nonlinear-domains, covering the more complex mechanisms involved in heart rate regulation. Computerized CTG can provide more comprehensive information about FHR variability and can aid to study the relationship between FHR variability and the functioning of the autonomic nervous system, and perinatal outcome [8]. Although still predominantly used in research settings, implementing computerized CTG and assessment of heart rate variability in multiple domains has the potential to improve diagnostic accuracy [8].

The objectives of this systematic catalog are (1) to summarize the methodology used in studies that examine the relationship between FHR and neonatal outcome, and (2) to demonstrate the relationship between FHR and neonatal outcome. Our catalog focuses on the following neonatal outcomes: neonatal heart rate (NHR), infection (sepsis-pneumonia), necrotizing enterocolitis, intraventricular hemorrhage, hypoxic-ischemic encephalopathy, and seizure.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [9].

Eligibility criteria

Studies that examined the relationship between the FHR, recorded by CTG, and one of the following neonatal outcomes: NHR, infection (sepsis/pneumonia), necrotizing enterocolitis, intraventricular hemorrhage, hypoxic-ischemic encephalopathy, and seizure, were included in this review. Gray literature, duplicates, abstracts, nonstatistical studies, and studies with fewer than 10 cases were excluded.

Information sources and search strategy

Five databases were searched from inception to July 1, 2021: Embase, Medline ALL, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and CINAHL. The reference list of publications included in the systematic review were searched to identify additional studies. The database search was updated on October 5, 2023. The search strategy was developed in consultation with the library of the Erasmus University Medical Center, Rotterdam, The Netherlands. Search terms for FHR and designated neonatal outcomes were combined in the search strategy. The full search strategy is provided in Supplementary Information 1. The search strategy was limited to studies in English language and human studies. Identified records were transferred into EndNote (version X9; Thomsen Reuters, New York, USA). Duplicate records were removed using the find duplicates tool in EndNote.

Study selection

Two reviewers (CE, CR) independently screened titles and abstracts and excluded clearly ineligible studies from further screening. The full text of potentially eligible articles was then assessed independently by two reviewers (CE, SW). Disagreements about inclusion during both title and abstract screening and full-text screening were resolved by consensus through discussion. Final reasons for exclusion were recorded. For the updated search, title and abstract screening, and full-text screening were performed by two reviewers (CE, SW).

Data extraction

A data collection form was designed using Excel (version 2016; Microsoft Corporation, Redmond, WA, USA). The form was used by one researcher (CE) to extract data from eligible studies. First, the study's general characteristics were extracted, which consisted of the first author's name, year of publication, study design, country, sample size, source of participants, participant characteristics, and study objective. Second, data on FHR assessment were extracted. This included time of assessment, duration of assessment, definition of patterns, classification guidelines used, number of assessors. Third, data on the neonatal outcome were extracted. This included definition of neonatal outcome and time of assessment. Fourth, the reported outcomes of interest were collected. This included associations and predictions between FHR patterns and adverse neonatal outcomes.

Assessment of risk of bias

The Newcastle-Ottawa Scale (NOS) was used to assess the quality and risk of bias. The NOS scale includes eight items

within the following three categories: selection, comparability and ascertainment of exposure or outcome. Each individual item may receive a star, with the exception of comparability, which can be awarded up to two stars. A maximum of nine stars may be awarded. The risk of bias was considered low if nine stars were awarded, median if eight or seven stars were awarded, and high if six or less stars were awarded [10]. Two reviewers (CE, SW) independently performed the NOS assessment. Disagreements were resolved by consensus through discussion.

Results

Study selection

The literature search resulted in 10,499 records. Eight papers were additionally identified from the reference lists. After removal of duplicates, 5,891 records remained for title and abstract screening. Full-text was reviewed of 190 articles. Finally, 42 papers were included. The PRISMA flow diagram is presented in Figure 1. The reasons for full-text exclusions are presented in Supplementary Table S1.

General characteristics of the studies

A general overview of the study characteristics is provided in Tables 1 and 2. The included studies consisted of 19 cohort studies and 23 case-control studies. The studies were published between 1975 and 2023. The studies were conducted in Africa, Asia, Europe, North America, and South America, all in hospital settings. The populations studied included preterm, term, post-term, or (extremely) low birth weight deliveries. FHR monitoring was performed antepartum in nine studies and intrapartum in 37 studies. Four studies examined the NHR, three studies necrotizing enterocolitis, nine studies neonatal infection, seven studies neonatal seizures, 11 studies intraventricular hemorrhage, and 16 studies hypoxic-ischemic encephalopathy. The NOS quality assessment indicated a low risk of bias for five studies, a medium risk of bias for 27 studies and a high risk of bias for 10 studies. A summary of the awarded stars per sub-question is provided in Supplementary Table S2. The data retrieved from the included studies are presented as a narrative synthesis, in Figure 2, and in Supplementary Table S3–S8, grouped by neonatal outcome.

Heart rate

A total of 561 term delivered neonates were included in four studies, where heart rate monitoring was performed during both fetal and neonatal periods (Figure 2 and Table S3) [11–14]. The FHR was assessed visually [11–13] or by computer [14]. The studies used different guidelines for FHR assessment and did not specify who rated the FHR. Three studies examined the FHR intrapartum [11, 12, 14]. Time-domain [11–14], frequency-domain [12, 13], and nonlinear-domain [13] metrics of the NHR were examined, which were based on international guidelines and other relevant heart rate variability research. The moment of assessment varied from the first 60 min of life [14], the first 90 min of life [11], the first day of life [13], and 5 min on the third day of life [12].

A postnatal increase in heart rate was found [11, 14]. Also, nonreassuring FHR patterns were associated with lower NHR variability [12]. And abnormal CTG classification was significantly associated with NHR variability [13].

Necrotizing enterocolitis

The relationship between FHR patterns and necrotizing enterocolitis was examined in three studies involving 18,458 preterm deliveries (Figure 2, Table S4) [15–17]. FHR was assessed visually, either antepartum [15] or intrapartum [16, 17]. Reported guidelines for FHR classification were: ACOG (2010) and NICHD (2009) [15]. In two studies, one grader performed the FHR evaluation [15, 16]. The definition of necrotizing enterocolitis was not reported.

No statistically significant associations were found in the three studies between necrotizing enterocolitis, and FHR decelerations [15], reactivity [15], and nonreassuring classification [16, 17].

Infection

Nine studies examined FHR patterns in relation to neonatal sepsis [16–22], or neonatal pneumonia-sepsis (Figure 2, Table S5) [23, 24]. A total of 27,238 neonates were included. FHR patterns were assessed visually antepartum [18, 19, 21] or intrapartum [16, 17, 20–24]. Different FHR classification guidelines were used. The FHR was evaluated by one [16, 20, 22] or three assessors [21]. Two studies focused on early onset neonatal sepsis [20, 21]. Neonatal sepsis was determined by positive cultures and clinical symptoms. Neonatal pneumonia was determined by leukocyte count and X-ray findings.

Conflicting results were reported. Five studies found no significant association between FHR patterns and neonatal sepsis [16, 18, 20, 22] or neonatal pneumonia-sepsis [23]. While four studies found statistically significant associations

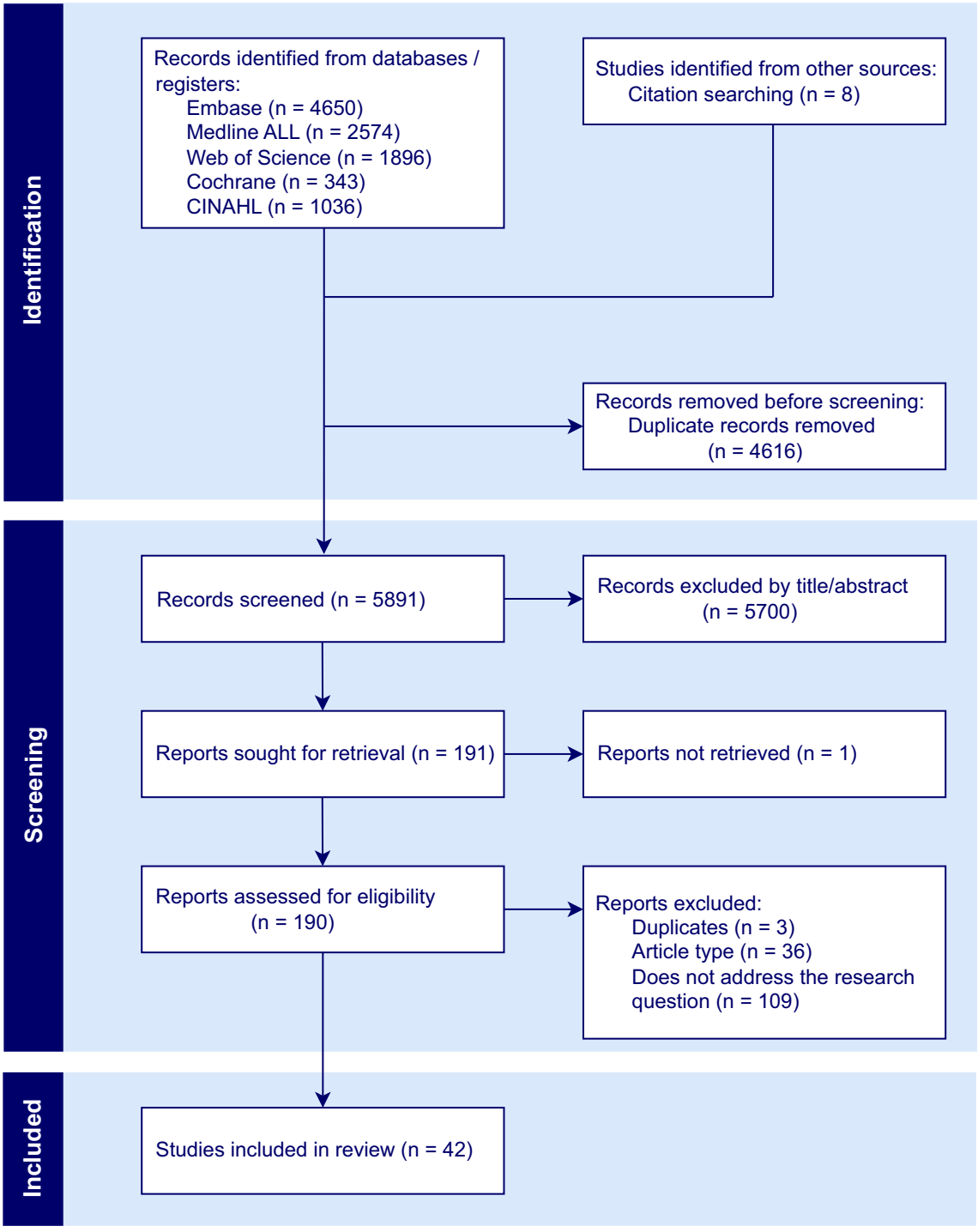

Figure 1: PRISMA flow diagram.

between antepartum [19, 21] or intrapartum [17, 24] measured FHR patterns and neonatal infection. An increase in neonatal sepsis rate was associated with tachycardia [24], nonreassuring [17, 21], and nonreactive FHR patterns [19]. Moreover, a nonreassuring/nonreactive FHR was found to be a specific but not a sensitive predictor of early onset neonatal sepsis in preterm deliveries [19, 21]. Although, one study reported that a nonreactive FHR had a high sensitivity and specificity for predicting neonatal (suspected) sepsis in preterm deliveries [18].

Table 1: Study characteristics.

First author, year	Study design	Country	Sample size	Source of participants	Participant characteristics	Fetal heart rate monitoring period	Neonatal outcome	NOS Score
Barrois, (2019)	Case-control	France	179	Hospital	Deliveries from 35 weeks of gestation	Intrapartum	Hypoxic-ischemic encephalopathy	6
Buhimschi, (2008)	Cohort	United States of America of America	86	Hospital	Preterm labor (<35 weeks), singleton	At admission, intrapartum	Early onset neonatal sepsis	8
Bustos, (1975)	Cohort	Uruguay	23	Hospital	Term labor, singleton, vertex, vigorous and mildly depressed neonates	Intrapartum	Neonatal heart rate	6
Casey, (1997)	Cohort	United States of America	84	Hospital	Singleton, very low birth weight (700–1,500 g)	Intrapartum	Periventricular-intraventricular hemorrhage	7
Day, (1992)	Case-control	United States of America	36	Hospital	Singleton	Intrapartum	Early onset neonatal sepsis	7
di Pasquo, (2022)	Cohort	Italy	431	Hospital	Deliveries from 36 weeks of gestation, singleton, acidemia	Intrapartum	Moderate-to-severe hypoxic-ischemic encephalopathy, neonatal seizure	6
Elliot, (2010)	Cohort	Not specified	2,472	Hospital	Deliveries greater than 35 weeks of gestation.	Intrapartum	Hypoxic-ischemic encephalopathy	7
Eventov-Friedman, (2012)	Cohort	Israel	96	Hospital	Preterm labor (≤30 weeks) Extremely low birth weight (420–1,000 g)	In last 24 h prior to birth	Intraventricular hemorrhage	7
Geva, (2023)	Case-control	Israel	185	Hospital	Deliveries greater than 34 weeks of gestation, low risk, singleton, vertex	Intrapartum	Hypoxic-ischemic encephalopathy	8
Glantz, (2011)	Cohort	United States of America	488	Hospital	Preterm labor (<34 weeks), singleton	Antepartum	Necrotizing enterocolitis, intraventricular hemorrhage	9
Gonen, (1991)	Case-control	Canada	26	Hospital	Preterm labor, prolonged premature rupture of membranes	Within 24 h of delivery	Neonatal sepsis	8
Graham, (2014)	Case-control	United States of America	117	Hospital	Delivers from 35 weeks of gestation	Intrapartum	Hypoxic-ischemic encephalopathy	8
Hameed, (1986)	Cohort	United States of America	76	Hospital	Low birth weight (≤2,000 g)	Intrapartum	Periventricular-intraventricular hemorrhage	7
Hannaford, (2016)	Case-control	United States of America	79	Hospital	Preterm labor (≤30 weeks), singleton	Intrapartum	Intraventricular hemorrhage	5
Hayes, (2013)	Case-control	Ireland	654	Hospital	Deliveries greater than 36 weeks of gestation.	Intrapartum	Hypoxic-ischemic encephalopathy	5
Herbst, (1997)	Case-control	Sweden	212	Hospital	Deliveries greater than 36 weeks of gestation, singleton, maternal fever	Intrapartum	Neonatal infection (neonatal sepsis, neonatal pneumonia)	8
Keegan, (1985)	Cohort	United States of America	132	Hospital	Preterm and term labor	Intrapartum	Seizure activity	7
Kumari, (2022)	Cohort	India	250	Hospital	Preterm, term and post-term labor	Intrapartum	Neonatal seizure	5
Larma, (2007)	Case-control	United States of America	107	Hospital	Preterm and term pregnancies with metabolic acidosis	Intrapartum	Hypoxic-ischemic encephalopathy	8
Locatelli, (2010)	Case-control	Italy	127	Hospital	Term labor	At admission Intrapartum	Hypoxic-ischemic encephalopathy	5
Martinez-Biarge, (2013)	Case-control	England	561	Hospital	Delivers from 35 weeks of gestation	Intrapartum	Hypoxic-ischemic encephalopathy	6

Table 1: (continued)

First author, year	Study design	Country	Sample size	Source of participants	Participant characteristics	Fetal heart rate monitoring period	Neonatal outcome	NOS Score
Mendez-Figueroa, (2015)	Cohort	United States of America	1,291	Hospital	Preterm labor (<37 weeks), singleton, cesarean delivery	Intrapartum	Necrotizing enterocolitis, neonatal sepsis, intraventricular hemorrhage, neonatal seizure	9
Mendez-Figueroa, (2022)	Cohort	United States of America	16,679	Hospital	Preterm labor (<37 weeks), singleton, cesarean delivery	Intrapartum	Neonatal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, neonatal seizure	9
Michaeli, (2021)	Case-control	Israel	133	Hospital	Deliveries greater than 36 weeks of gestation	Intrapartum	Hypoxic-ischemic encephalopathy	7
Milsom, (2002)	Case-control	Sweden	82	Hospital	Term labor, asphyxiated newborns	Intrapartum	Hypoxic-ischemic encephalopathy	7
Minchom, (1987)	Case-control	Wales	103	Hospital	Term labor, neonatal acidosis hypoxic-ischemic encephalopathy	Intrapartum	Seizure activity	7
Munyaw, (2023)	Cohort	Tanzania	305	Hospital	Term labor, singleton, vaginal delivery, normal neonatal outcomes	Intrapartum	Neonatal heart rate	7
Murray, (2009)	Cohort	Ireland	35	Hospital	Term labor, hypoxic-ischemic encephalopathy	At admission, intrapartum	Hypoxic-ischemic encephalopathy	7
Oliveira, (2019)	Cohort	England	150	Hospital	Term labor, healthy infants	Not specified	Neonatal heart rate	9
Polnaszek, (2020)	Cohort	United States of America	8,580	Hospital	Term labor, singleton, non-anomalous	Intrapartum	Suspected neonatal sepsis	9
Rayburn, (1987)	Case-control	United States of America	76	Hospital	Preterm labor (26–34 weeks), low birth weight (600–2,000 g), singleton	Intrapartum	Intraventricular hemorrhage	8
Reynolds, (2022)	Case-control	Ireland	170	Hospital	Deliveries from 35 weeks of gestation	Intrapartum	Hypoxic-ischemic encephalopathy	5
Schiano, (1984)	Case-control	United States of America	207	Hospital	Vaginal delivery, no persistent fetal heart rate abnormalities during first stage of labor	Intrapartum	Neonatal infection (neonatal sepsis, neonatal pneumonia)	5
Sheen, (2014)	Cohort	Taiwan	83	Hospital	Term labor, singleton, cesarean delivery	Intrapartum	Neonatal heart rate	7
Soncini, (2014)	Cohort	Italy	314	Hospital	Term labor, singleton, cephalic,	Intrapartum	Hypoxic-ischemic encephalopathy	7
Strauss, (1984)	Case-control	United States of America	117	Hospital	Preterm deliveries (≤34 weeks), very low birth weight (<1,500 g)	Intrapartum	Intraventricular-subependymal hemorrhage	7
Tejani, (1984)	Cohort	United States of America	76	Hospital	Low birth weight (≤2,000 g)	Intrapartum	Periventricular-intraventricular hemorrhage	7
Torbenson, (2017)	Case-control	England	126	Hospital	Deliveries from 35 weeks of gestation, singleton	Intrapartum	Hypoxic-ischemic encephalopathy	7
Vargas-Calixto, (2021)	Cohort	United States of America	22,016	Hospital	Deliveries from 35 weeks of gestation, singleton	Intrapartum	Hypoxic-ischemic encephalopathy	7
Vintzileos, (1986)	Cohort	United States of America	121	Hospital	Deliveries from 25 weeks of gestation, singleton, premature rupture of membranes	At admission, every 24–48 h until delivery	Neonatal infection (possible neonatal sepsis, neonatal sepsis)	7
Vlastos, (2007)	Cohort	United States of America	97	Hospital	Preterm labor, very low birth weight (≤1,200 g)	Antepartum Intrapartum	Intraventricular hemorrhage	7
Williams, (2004)	Case-control	United States of America	50	Hospital	Term labor, singleton	Intrapartum	Neonatal seizure	8

Table 2: Study objective.

First author, year	Objective
Barrois, (2019)	Our objective was to identify factors associated with hypoxic-ischemic encephalopathy among newborns with an umbilical pH<7.00.
Buhimschi, (2008)	The purpose of this study was to examine the relationships between fetal heart rate monitoring patterns abnormalities, intra-amniotic inflammation, histological chorioamnionitis and early-onset neonatal sepsis in pregnancies complicated by preterm birth. Additionally, the ability of various fetal heart rate monitoring patterns to predict early-onset neonatal sepsis at birth was investigated.
Bustos, (1975)	To present the results obtained in vigorous and mildly depressed newborns by the continuous recording of fetal heart rate during labor and of neonatal heart rate during 90 min after birth.
Casey, (1997)	To investigate the association of fetal heart rate patterns with periventricular-intraventricular hemorrhage in infants with birth weights less than 1,500 g.
Day, (1992)	To evaluate the utility of conventional electronic fetal monitoring in detection of established perinatal sepsis.
di Pasquo, (2022)	To compare the type of hypoxia on the intrapartum cardiotocography traces among the acidaemic neonates with and without composite adverse neonatal outcome.
Elliot, (2010)	The objective of this study was to measure the performance of a 5 level classification system of electronic fetal monitoring in 3 groups of term babies, defined by functional and biochemical markers of perinatal abnormality.
Eventov-Friedman, (2012)	To investigate the correlation between fetal heart rate patterns with the incidence of severe (grade 3+) intraventricular hemorrhage and periventricular echogenicity, which may later result in periventricular leukomalacia, in extremely low birth weight infants within 4 days of birth.
Geva, (2023)	To investigate whether an association exists between deceleration and acceleration areas on continuous fetal cardiotocography and neonatal encephalopathy.
Glantz, (2011)	The primary purpose was to determine whether preterm nonstress tests are associated with perinatal outcome and whether using the 10×10 criterion is equivalent to the 15×15 criterion. The secondary purpose was to determine the effect of decelerations and the pattern of sequential nonstress tests on perinatal outcome.
Gonen, (1991)	To investigate further the role of the nonstress test in predicting congenital sepsis in pregnancies complicated by preterm premature rupture of the membranes.
Graham, (2014)	To estimate the diagnostic accuracy of human assessment of electronic fetal heart rate tracings during the hour prior to delivery to identify abnormalities associated hypoxic ischemic encephalopathy qualifying for whole-body hypothermia treatment.
Hameed, (1986)	To evaluate the role of intrapartum fetal heart rate characteristics and fetal acid-base status in the production of periventricular-intraventricular pathology seen in low birthweight neonates within the first 24 h of life.
Hannaford, (2016)	To evaluate electronic fetal monitoring characteristics among very preterm infants to determine whether specific patterns can predict the development of intraventricular hemorrhage.
Hayes, (2013)	The purpose of this study was to determine risk factors that are associated with hypoxic ischemic encephalopathy.
Herbst, (1997)	To determine 1. whether maternal fever during term labor is associated with acidemia at birth and neonatal infection and 2. whether fetal tachycardia precedes maternal fever and is associated with neonatal infection.
Keegan, (1985)	To examine fetal heart rate patterns of infants who had seizure activity in the newborn period.
Kumari, (2022)	The aim of the study is to identify the intrapartum fetal heart rate patterns associated with increased risk of neonatal depression using cardiotocography.
Larma, (2007)	The purpose of this study was to determine whether electronic fetal monitoring can identify fetuses with metabolic acidosis and hypoxic-ischemic encephalopathy.
Locatelli, (2010)	To evaluate perinatal factors potentially involved in the genesis of neonatal encephalopathy, we have performed a case controlled study in which we included information on fetal heart rate tracing.
Martinez-Biarge, (2013)	To determine whether antepartum factors alone, intrapartum factors alone, or both in combination, are associated with term neonatal hypoxic-ischemic encephalopathy.
Mendez-Figueroa, (2015)	To compare the rates of neonatal morbidity and cerebral palsy among preterm neonates (less than 37 weeks of gestation) delivered by cesarean for a nonreassuring fetal heart rate tracing compared with those who did not.
Mendez-Figueroa, (2022)	To compare adverse outcomes among preterm births that underwent cesarean delivery for nonreassuring fetal heart rate tracing vs. those that did not.
Michaeli, (2021)	To identify fetal heart rate characteristic patterns and perinatal factors associated with neonatal hypoxic–ischemic encephalopathy treated by therapeutic hypothermia.
Milsom, (2002)	To investigate the incidence and importance of potential maternal, obstetrical and fetal risk factors, as well as fetal heart rate changes in term-asphyxiated newborns from an urban Swedish population.
Minchom, (1987)	To determine which intrapartum fetal heart rate parameters in the presence of severe neonatal acidosis (pH<7.0) appropriately predicts the development of neonatal seizures in the context of hypoxic ischemic encephalopathy.

Table 2: (continued)

First author, year	Objective
Munyaw, (2023)	To describe the fetal to neonatal heart rate transition from 1 h before to 1 h after normal vaginal deliveries.
Murray, (2009)	To examine fetal heart rate patterns during labor in infants with clinical and electroencephalographic evidence of hypoxic-ischemic encephalopathy and to relate these findings to neurodevelopmental outcome.
Oliveira, (2019)	Our primary aim was to describe standard reference values for HRV trends over the first 24 h of postnatal life in healthy term infants. As a secondary aim, we investigated which (if any) clinical characteristics or risk-factors exert higher impact on heart rate variability (including cardiotocography findings).
Polnaszek, (2020)	To investigate the incidence of marked variability fetal heart rate patterns before delivery and its association with neonatal morbidity and abnormal arterial cord gases.
Rayburn, (1987)	To determine whether the frequency and type of intrapartum fetal heart rate abnormalities were more common in infants with intraventricular hemorrhage.
Reynolds, (2022)	To describe the accuracy of intrapartum fetal heart rate abnormalities as defined by National Institute of Health and Care Excellence guidelines to predict moderate-severe neonatal encephalopathy of apparent hypoxic-ischemic etiology.
Schiano, (1984)	To report the association between fetal tachycardia during the second stage of labor and rate of neonatal infection in the absence of other signs of chorioamnionitis.
Sheen, (2014)	To explore the influence of nonreassuring fetal status, as depicted by electronic fetal monitoring, on the heart rate variability of newborn infants.
Soncini, (2014)	To assess the ability of the intrapartum fetal heart rate interpretation system developed in 2008 by the National Institute of Child health and human Development to predict fetal metabolic acidosis at delivery and neonatal neurological morbidity (such as the development of neonatal hypoxic-ischemic encephalopathy).
Strauss, (1984)	A prospective study was undertaken to see whether intrapartum fetal distress with or without acidosis, as judged by objective measurements of fetal heart rate and umbilical arterial blood pH, plays a role in the etiopathogenesis of intraventricular-subependymal hemorrhage in very low-birth infants.
Tejani, (1984)	To correlate the occurrence of sonographically demonstrated periventricular and intraventricular hemorrhage and variants in the first 24 h of neonatal life with possible causative obstretic factors in inborn low birth weight neonates.
Torbenson, (2017)	Our objective was to identify antepartum and intrapartum factors associated with the development of neonatal hypoxic-ischemic encephalopathy.
Vargas-Calixto, (2021)	We examined the temporal evolution of fetal heart rate features as labor progressed in normal fetuses and fetuses that were diagnosed with hypoxic-ischemic encephalopathy.
Vintzileos, (1986)	To determine the value of the nonstress test in evaluating patients who presented with premature rupture of the membranes and no clinical signs of infection or labor. Measures of pregnancy outcome included the presence of clinical amnionitis, possible neonatal sepsis, and neonatal sepsis.
Vlastos, (2007)	We tested the hypothesis that the presence of intracranial lesions and abnormal neurodevelopmental outcome in preterm neonates with birthweight 1,200 g is associated with nonreactive fetal heart rate tracing prior to delivery.
Williams, (2004)	To identify which specific fetal heart rate parameters might predict the development of early onset neonatal seizures.

Seizure

Seven studies performed intrapartum FHR monitoring and assessed neonates for seizure activity, involving 18,936 neonates (Figure 2, Table S6) [16, 17, 25–29]. The FHR was evaluated visually by one [26, 27], two [25], or three assessors [28]. Different FHR classification guidelines were used (Figure 2). Seizure activity was assessed within the first 24–48 h [27], first 48 h of life [26], or first seven days of life [17].

One study reported no association between nonreassuring FHR patterns and seizure rate [16]. One study reported that the incidence of neonatal seizures was statistically significant higher in fetuses classified with chronic hypoxia compared to intrapartum hypoxia, and in subacute hypoxia compared to gradually evolving hypoxia, as defined by the physiological interpretation of CTG FHR parameters [28]. Five studies found statistically significant associations between an abnormal or nonreassuring FHR and seizures [17, 25–29]. One study additionally reported a statistically significant loss of FHR variability in the preterm seizure group [25].

Intraventricular hemorrhage

A total of 19,159 neonates were included in the 11 studies where FHR monitoring was performed antepartum [15, 30, 31] or intrapartum [16, 17, 31–37] and were reviewed for intraventricular hemorrhage [15–17, 30, 31, 34, 35], intraventricular-periventricular hemorrhage [32, 33, 37], intraventricular-subependymal hemorrhage [36], or intraventricular hemorrhage-periventricular leukomalacia [31]. The details of the studies are described in Figure 2 and Table S7. The FHR was visually evaluated by one [15, 16, 30,

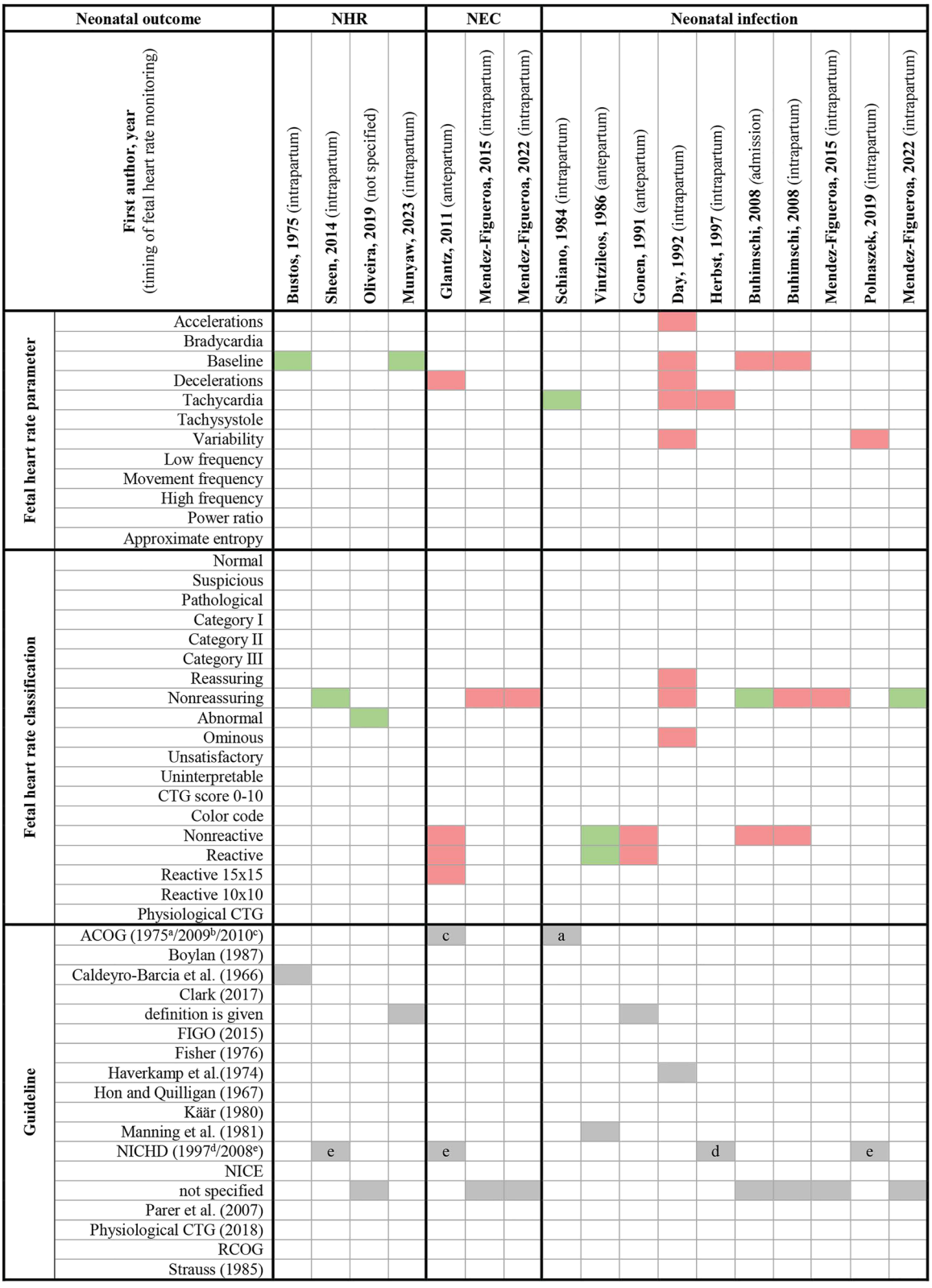

Figure 2: Reported associations between fetal heart rate and neonatal outcome. Green indicates that an association was found between the fetal heart rate and neonatal outcome, while red indicates that no association was found. The gray boxes indicate the which guideline is used. ACOG, American College of Obstetricians and Gynecologists; CTG, cardiotocography; FIGO, The International Federation of Gynecology and Obstetrics; NEC, necrotizing enterocolitis; NHR, neonatal heart rate; NICE, the National Institute for Health and Care Excellence; NICHD, National Institute of Child Health and Human Development; nl, nonlinear; RCOG, Royal College of Obstetricians and Gynecologists.

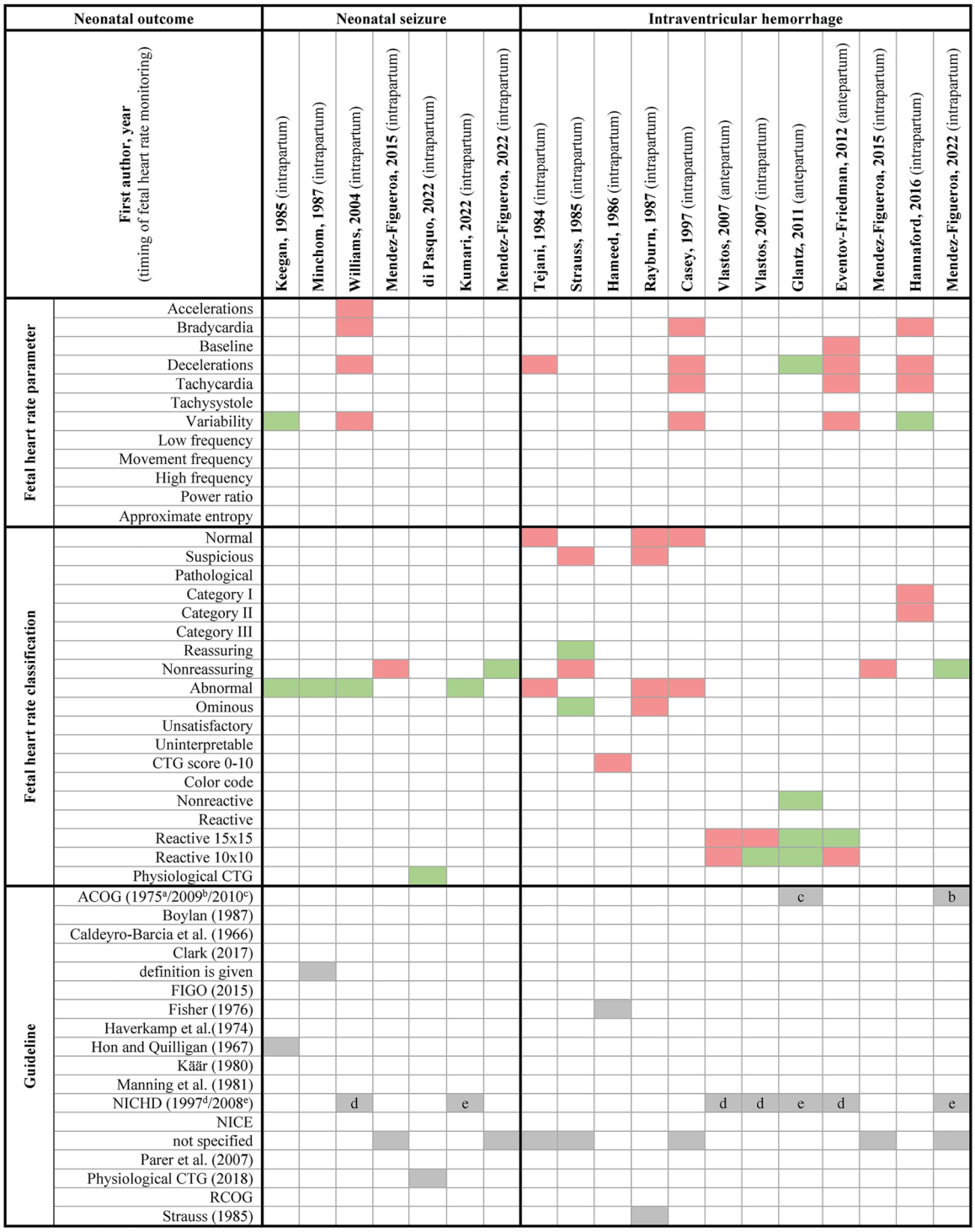

Figure 2: Continued.

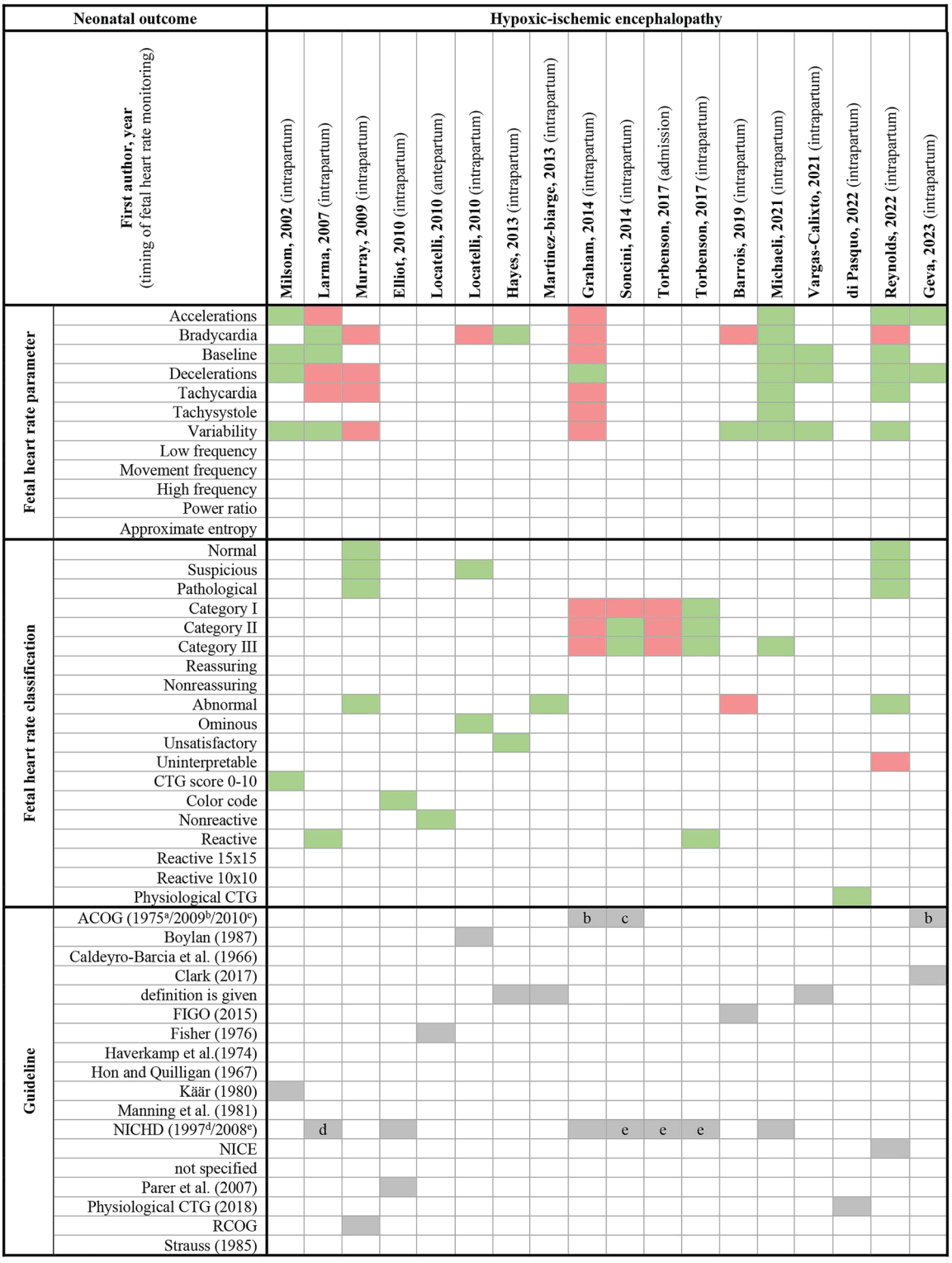

Figure 2: Continued.

32, 34, 36] or two assessors [31, 35], using different traditional FHR classification guidelines. Intraventricular hemorrhage was assessed between the first and fourth day of life. Two studies reported multiple assessment times [34, 35]. The guideline of Papile (1978) was most frequently used to define intraventricular hemorrhage [38].

Six studies did report significant associations [15, 17, 30, 31, 34, 36], while five studies found no statistically significant associations between FHR patterns and intraventricular hemorrhage [16, 32, 33, 35, 37]. An increase in intraventricular hemorrhage was associated with absence of reactivity [15, 30, 31], presence of decelerations [15], variability [34], ominous FHR patterns [36], nonreassuring tracing [17], and a lower incidence of reassuring [36]. However, it was found that FHR patterns were poorly predictive of intraventricular hemorrhage [34].

Hypoxic-ischemic encephalopathy

Sixteen studies were included where antepartum [39, 40] or intrapartum [28, 39–53] FHR monitoring was performed and neonates were reviewed for hypoxic-ischemic encephalopathy (Figure 2, Table S8). A total of 27,709 neonates were included. The FHR was visually assessed in 14 studies [28, 39–41, 43–52]. Either one [39, 41, 45, 51, 52], two [40, 48–50], or three assessors [28, 44, 46] evaluated the tracings. In three studies computerized algorithms were used to evaluate the FHR patterns [42, 53] or to provide an overall classification [51]. Twelve guidelines for interpreting FHR were reported. These include conventional guidelines, where the NICHD was most commonly used, and more recent developed guidelines, such as the physiological CTG interpretation. Most studies reported only traditional FHR parameters, such as baseline heart rate and number of accelerations or decelerations. The non-standard parameter "acceleration/deceleration area" was determined in three studies [43, 44, 48]. In addition, one study using computerized algorithms reported more advanced FHR parameters in the time-domain, frequency-domain, and nonlinear-domain [53]. The definition of hypoxic-ischemic encephalopathy was clearly stated in seven studies [40, 42–44, 47, 50, 53]. Eight studies only reported the guidelines used for the severity of the encephalopathy [28, 39, 41, 45, 46, 49, 51, 52]. The (modified) Sarnat and Sarnat criterion was most often used for grading hypoxic-ischemic encephalopathy [54]. All 16 studies found an association between FHR patterns and hypoxic-ischemic encephalopathy. Most commonly, a significant increase in the frequency of abnormal FHR patterns was reported in neonates with hypoxic-ischemic encephalopathy. Some of the observed FHR abnormalities include: decreased baseline heart rate, decreased variability, and decreased accelerations as well as increased decelerations, increased nonreactivity, and increased category II-III tracings, but there is no consensus among studies (Figure 2). Although associations have been reported, it has been demonstrated that the predictive ability of these abnormalities is low [44, 46, 51]. Reynolds et al. (2022) suggested that the predictive ability could be improved by assessing the total duration of the FHR abnormalities [51]. Elliot et al. (2010) also found a correlation between duration of FHR abnormality and hypoxic-ischemic encephalopathy [42]. However, four studies found no correlation between the duration of bradycardia [41], pathological CTG [50], or deceleration [43, 48] and hypoxic-ischemic encephalopathy.

Discussion

Main findings

This review reported the methodology used and associations found in 42 studies that evaluated the relationship between FHR patterns and designated neonatal outcomes. The risk of bias was scored low to medium for the majority of the studies (32/42). Methodology among studies differed in timing and duration of FHR assessment, classification guidelines used, number of assessors, and definition and timing of neonatal outcome assessment. Nonreassuring FHR patterns were associated with lower NHR variability. An increase in abnormal FHR patterns was observed in neonates with hypoxic-ischemic encephalopathy, although the predictive ability was found to be limited. Conflicting associations were reported for sepsis, seizure and intraventricular hemorrhage, while no association was found for necrotizing enterocolitis. FHR monitoring aims to detect acute hypoxic events. Since necrotizing enterocolitis is not linked to acute hypoxia, no associations are expected, aligning with the observed results. The association between FHR monitoring and sepsis, intraventricular hemorrhage, or seizures is indirect, as FHR patterns may reflect fetal distress caused by conditions like hypoxia or infection that could increase the risk of aforementioned outcomes. Hypoxic-ischemic encephalopathy, directly related to oxygen deprivation, is more likely to be associated with FHR, consistent with the findings. No clear correlation was identified between the timing of monitoring and the reported associations. However, antepartum studies mainly reported associations between overall FHR classification abnormalities and increased rates of infection, intraventricular hemorrhage, or hypoxic ischemic encephalopathy. The overall FHR classification, in which all four basic FHR

parameters (baseline, variability, accelerations and decelerations) were evaluated, seemed more frequently related to infection, seizure, intraventricular hemorrhage, or hypoxic-ischemic encephalopathy than individual FHR parameters alone. The visual evaluation and the wide variety of reported guidelines used in the reviewed studies to assess FHR patterns may have led to subjectivity in the interpretation and application of the guidelines. No relationship was identified between the FHR monitoring guidelines used and the reported associations. This lack of relationship is not surprising, given that the gold standard for visual assessment has remained consistently inconsistent over time, which likely contributes to the absence of the observed associations.

Comparison with existing literature

Previous systematic reviews on intrapartum FHR guidelines have highlighted agreement and differences in terminology [55, 56]. These reviews recommend standardizing FHR terminology and interpretation to establish consistency and reduce subjective variation. Another systematic review found considerable variation in reliability and agreement measures, with higher reliability for basic FHR parameters than for overall FHR classification [57].

Computerized analysis systems, such as the Sonicaid system 8000 developed by the Dawes and Redman group (1980s) or the SisPorto system developed by Bernardes' team (1990s), eliminate the subjectivity of visual analysis as the same rules are always applied [58, 59]. Previous systematic reviews have concluded that, compared with visual analysis, computerized analysis may reduce the time spent in hospital for a patient and may reduce onward investigations during the antepartum period [60]. However, computerized analysis did not reduce the rate of perinatal mortality, perinatal morbidity (acidosis, seizure, 5-min Apgar score<7, pH<7.2), obstetric intervention or NICU admission during both the antepartum or intrapartum period [60–62].

Our findings are in line with previous research that evaluated the relationship between FHR and adverse neonatal outcomes. Graham et al. (2006) reviewed the ability of intrapartum electronic fetal monitoring to prevent perinatal brain injury and death and reported no effect on their incidence [63]. Zullo et al. (2023) reviewed the association between rate of adverse neonatal outcomes and intrapartum FHR category I, II or III. An increase in incidence of 5-min Apgar score<7, pH<7.0, seizures, and hypoxic-ischemic encephalopathy with increasing FHR tracing category was reported. However, 98 % of the fetuses that had category II or III FHR tracings had no adverse neonatal outcomes [64]. These results highlight the short coming of CTG as screening tool in its current use.

Strengths and limitations

A key strength of this systematic review is its comprehensive overview of the methodology used and associations reported in studies examining FHR patterns and their potential correlation with adverse neonatal outcomes. Several limitations need to be addressed. First, the number of cases in some of the studies was small. Second, several studies lacked data on population description, timing of FHR assessment, guidelines used for FHR assessment, timing of neonatal outcome assessment, or definition of neonatal outcome. Third, the assessment of associations between FHR and neonatal outcome was not the primary aim of some of the studies, but was researched as sub-analysis. Fourth, the review included only English-language publications. Fifth, data extraction was performed by one reviewer. Sixth, no meta-analysis was conducted due to the significant heterogeneity among the studies and limited number of cases included, making it difficult to draw additional conclusions.

Implications

Early detection of clinical fetal deterioration is essential to provide clinicians with a window of opportunity to intervene and treat patients with the goal to improve maternal and perinatal outcomes. Conventional CTG monitoring is still used worldwide as a screening tool for fetal compromise, despite the lack of evidence-based studies confirming that its use improves perinatal outcomes. Moreover, its implementation increased caesarean section delivery rates [3]. In fact, the current gold standard for FHR monitoring and interpretation are still based on the same principles used when it was first introduced in the 1970s. All of this calls into question the viability of CTG as a screening tool for fetal compromise in its current form. A more objective, accurate and consistent screening tool can be developed by implementing technological innovations. Introducing computerized interpretation of CTG will not only objectify the evaluation, but also provide the opportunity for a more comprehensive analysis of the FHR in the time-domain, frequency-domain, and nonlinear-domain. Moreover, with computerized evaluation it is easier to assess the evolution of the FHR over time. Trends can provide valuable information on fetal health and may be used to predict possible clinical deterioration. Also, machine learning and deep learning approaches could be applied to assess fetal

wellbeing. In this way FHR data can be combined with clinical characteristics of the mother and fetus and an automated early warning system can be developed that provides an early warning signal when patients at risk are identified. And additive screening tools such as metabolic monitoring can be implemented in such a system. The development of an automated monitoring system starts with gathering CTG and patient data, which hospitals already save and store in the electronic patient record. A database of perinatal health parameters can be built by combining CTG data with relevant clinical data from the mother, fetus and neonate. Ideally data from different Medical Centers will be combined to create a diverse database to improve the generalizability of a system. Also, consensus needs to be reached on how data is gathered, processed, and evaluated. Studies are needed to evaluate the performance of such computerized-based monitoring systems.

Conclusions

Methodological heterogeneity was found among the studies we reviewed for association between FHR patterns and neonatal outcomes. FHR was mostly assessed intrapartum by visual interpretation, following a variety of guidelines. Nonreassuring FHR patterns were associated with decreased NHR variability. An increase in abnormal FHR patterns was noted in neonates with hypoxic-ischemic encephalopathy, although the predictive ability was found to be limited. Conflicting associations were reported for sepsis, seizure and intraventricular hemorrhage, while no association was found for necrotizing enterocolitis. It is recommended to further study the introduction of technological innovations in CTG monitoring. Such as the development and evaluation of automated early warning system that combines computerized CTG with a perinatal health parameter database and provides an objective early warning signal when patients at risk are identified.

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