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Review Article

Challenges in the Diagnosis and Management of Intrauterine infection, Inflammation, or both (TRIPLE-I)

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Abstract

Objective: To review the diagnostic challenges and the management issues in women with chorioamnionitis.

Design: A narrative review.

Method: An online MEDLINE and Embase search was conducted on studies published in English between January 2000 and January 2022 on chorioamnionitis. 1204 studies were retrieved. Fifty-two quality studies published within the time zone reporting relevant data with good sample size and statistical analysis were included. Issues like diagnostic challenges in women with other causes of maternal pyrexia/tachycardia, challenges with CTG interpretations due to baseline tachycardia, safe mode of induction of labor to expedite delivery in women with poor BISHOP score, challenges in the management of refractory cases and criteria for NICU admission in suspected cases were addressed. The data focused on the challenges and management in chorioamnionitis was retrieved from the studies.

Results: The diagnosis of CA may perturb in situations with other causes of maternal pyrexia and after EA, however a good clinical history and examination may aid in excluding the differential diagnosis of CA. The use of Propess (vaginal delivery system) for IOL in these women should be preferred to reduce the induction-delivery interval and unnecessary vaginal examinations. Women with CA should have continuous fetal monitoring in labor, any abnormalities in CTG should be addressed in time to avoid neonatal complications. With isolated uncomplicated tachycardia, corresponding to maternal tachycardia, close observation is recommended but in cases with reduced variability and associated decelerations in CTG, delivery needs to be expedited. If pyrexia persists despite the treatment of CA, MDRO may be considered and placental culture results to be followed and antibiotics to be changed accordingly. Neonatal admission should be based on the clinical scenario and with the aid of Early Onset-Sepsis Calculator, unnecessary admissions can be minimized.

Conclusion: The diagnosis and management of chorioamnionitis may be challenging in different scenarios. To avoid delay in the diagnosis of chorioamnionitis and unnecessary neonatal admissions, meticulous patient history with assessment of clinical scenarios and excluding the differential diagnosis proves to be beneficial. Future studies on CA will be helpful in deriving recommendations for these controversial issues.

Keywords: ctg; nicu; maternal fever

Introduction

Intrauterine infection, inflammation, or both (Triple I), previously known as chorioamnionitis is defined as the infection of the chorion and amniotic sac including the membranes, the amniotic fluid and or placental decidua. It affects approximately 3-5% of infants at term deliveries. The prevalence is higher for those born preterm and was noted in 94% of extremely preterm babies delivered between 21-24 weeks [1,2]. The prevalence is more in the intrapartum period [85% vs 15%] as compared to that in pregnancy [3,4]. TRIPLE I is known to cause detrimental pregnancy outcomes [1,3,4]. Not only does TRIPLE I leads to an increase in feto-maternal morbidity and mortality but also increases the financial burden on the patient and the healthcare facilities due to prolong hospital stay and the use of antibiotics. On one hand delay in the diagnosis of TRIPLE I can potentially cause adverse pregnancy outcomes, on the other hand, over-diagnosis leads to inapt antibiotic use, prolonged neonatal intensive care unit (NICU) stay, disruption

of mother-infant bonding, delays in breastfeeding, economic burden and emotional stress from the prolonged hospital and NICU stay [4,5] In the literature, many studies and reviews have discussed TRIPLE I in detail. However, the following issues with diagnosis and management remain unclear:

1. Diagnostic challenges

2. Epidural analgesia and fever, when to consider TRIPLE I?

3. Challenges with cardiotocography (CTG) interpretation.

4. Mode of IOL in women with suspected Triple I and poor BISHOP score

5. How long is it safe to wait in absence of CTG abnormalities?

6. Diagnostic challenges with Triple I caused by multiple drugs resistant organism.

7. Criteria for NICU admission in suspected cases.

This review is mainly focused on these diagnostic challenges to clarify the management in these situations and the need for future research in this regard.

Objective

To study the current issues with diagnosis and management of Triple-I.

Methods

A narrative was conducted to clarify the current issues with diagnosis and management of Triple-I. This review is based on the search results of internet in the PubMed/MEDLINE, Scopus, Cochrane, and EMBASE databases. The studies conducted between 2000-2022 that were relevant to the study questions were evaluated. 51 quality studies were included n the review. Each study question was reviewed to assess the clarity in the diagnostic/management aspects.

Results of the Review

Definition and diagnostic challenges

Intrauterine infection, inflammation, or both (Triple I) is essentially a clinical diagnosis. TRIPLE I is diagnosed if a pregnant woman is febrile (Temperature ≥37.8°C or ≥38.0°C) with at least two or more of the following:

1. Maternal tachycardia (heart rate >100 beats/min)

2. Fetal tachycardia (heart rate >160 beats/ min)

3. Purulent or foul-smelling amniotic fluid or vaginal discharge

4. Uterine tenderness on palpation

5. Maternal leukocytosis (white blood cell count >15,000/mm3) [6,7,8]

Maternal fever may be caused by numerous causes. Specifically, in the last 3 years with the Sars-COV-2 pandemic, fever is frequently noted on admission. Irrespective of the cause of fever, feto-maternal tachycardia will be evident. Not only this, but in labor due to maternal anxiety and labor pains, maternal tachycardia is usual. In women with anemia, thyroid disorders, dehydration etc. tachycardia maybe even more significant [9,10,11,12]. Green et al., reported in their study that in more than ten per cent of women, a baseline heart rate of more than 100 bpm at >18 weeks and 105 bpm at >28 weeks was observed [12]. In these cases, the diagnosis of TRIPLE I is usually challenging and often leads to overdiagnosis of Triple I due to the triad of maternal fever with feta-maternal tachycardia]. In cases of new onset of fever in labor, TRIPLE I should be suspected. However, in women who present with fever and associated feto-maternal tachycardia, a thorough history and clinical examination should be carried out to exclude other causes of fever and associated maternal risk factors that can accelerate maternal tachycardia. TRIPLE I should be considered as a diagnosis of exclusion in these cases, rather than as the preliminary diagnosis.

Epidural analgesia and fever

One of the very effective and widely practiced method of pain relief during labor is Epidural Analgesia (EA). Different studies have been reported the use of epidural analgesia varies between 20-70% of all deliveries [13,14]. The aim of good pain control is achieved by instillation of local anesthetic drug and the opioid analgesic in the epidural space (lumbar region) and it is efficacious in achieving analgesia during labor [15]. In many studies a positive association between EA and maternal intrapartum pyrexia is noted [16,17,18]. Maternal fever with EA is suggested to be caused by multiple causes, common ones are oxidative stress, inflammatory response, subclinical Triple I and alteration in sympathetic stimulation [19,20, 21]. With controlling various confounding factors for maternal fever, the adjusted odds ratios for epidural analgesia-related maternal fever were between 2.9 and 14.5 [21]. Mothers who receive epidural analgesia have a higher likelihood of clinical suspicion of TRIPLE-I as fever may mimic the symptoms of TRIPLE-I. In a study, neonatal admission due to suspected maternal Triple I was substantially higher in the women who received epidural in labor (Odds Ratio 4.30, 95% CI 2.44 to 7.58) [19]. Wang et al., reported a comparable association between epidural analgesia and Triple I (OR 8.3, 95% CI 2.63-26.40) [20]. In a study with 37,786 parturient women, higher association of maternal intrapartum fever [Risk Ratio 4.12; 95%CI, 3.78 to 4.50] and histologic Triple I (Risk Ratio 4.08; 95%CI, 3.59 to 4.64) was noted with EA [22]. Other studies found a higher rate of histologic Triple I in epidural analgesia and maternal fever [22,23]. These studies indicate that in women with epidural analgesia, diagnosis of TRIPLE-I should be done with caution. If fever is noted immediately after epidural, it is likely due to EA. However, if the patient has other risks for TRIPLE-I and fever is noted hours of taking EA, TRIPLE-I and other causes of fever should be considered. While considering the diagnosis of TRIPLE-I, other possible causes of pyrexia should be excluded.

Challenges with Cardiotocography (CTG) Interpretations

In cases of TRIPLE-I, CTG interpretation may be challenging. Usually, baseline tachycardia is noted. However, cases of prolonged tachycardia or associated CTG abnormalities like reduced variability and the presence of decelerations may categorize the CTG as pathological (based on the classification criteria). This may lead to unnecessary interventions like fetal blood sampling (FBS), instrumental delivery and emergency cesarean section. A dilemma in interpretation leads to inappropriate management. There is a need to understand the CTG interpretations in TRIPLE-I to improve neonatal outcomes and reduce interventions. Uncomplicated baseline tachycardia usually is not associated with adverse outcomes, however, decreased baseline variability or late decelerations or both are associated with poor neonatal outcomes [24,25]. Miyake et-al noted that the intensity of maternal fever on fetal heart rate [FHR] abnormalities was not significant [26] and Wendel et al., did not detect any correlation between arterial PH at birth <7.20 and FHR patterns in TRIPLE-I if babies were delivered within 12 hours of the diagnosis [27]. While Pereira et al., observed the absence of cycling pattern and poor outcomes with maternal tachycardia [28]. This reveals that uncomplicated tachycardia [absence of any other pathological feature] and the presence of a cyclical pattern in FHR in TRIPLE-I does not affect neonatal outcomes. Reduced variability in presence of decelerations with baseline tachycardia should be considered pathological and interventions may be needed for FBS/delivery.

How long is it safe to wait?

Women who are diagnosed with TRIPLE-I in early labor, usually have labor dystocia. In these women's labor progress is slow despite augmentation of labor. Cheng et al., noted a higher risk of Triple I in women with the prolonged first stage of labor (>30 hours) (OR-1.58) [29]. Most of these women had histological evidence of Triple I and were associated with poor neonatal outcomes. In another study by Wendel et al., it was observed that in absence of any CTG abnormalities babies born within 12 hours of diagnosis of TRIPLE-I, did not have any neonatal complications or sepsis [27]. Though women with a duration of labor more than 30 hours after rupture of membranes had a higher incidence of TRIPLE-I [12.5% compared with 23.5%; adjusted OR, 1.58; 95% CI, 1.25-1.98] [30]. In a systematic review in 2018, planned early birth in women with ROM was associated with reduced incidence of TRIPLE-I, neonatal sepsis and use of antibiotics for

neonates [31]. In another retrospective cohort study on 101,170 term infants with TRIPLE-I [32], it was noted that infants of mothers with TRIPLE-I had higher morbidity including the risk of meconium aspiration syndrome, pneumonia. And need for intubation at birth. Length of labor was regarded as a confounding factor as it was correlated to the neonatal outcomes [32]. This signifies that the duration of labor after TRIPLE-I is diagnosed is relevant in assessing neonatal outcomes. Venkatesh et al., noted that neonatal outcomes in women with TRIPLE-I were dependent on gestational age. They reported that in preterm neonates with gestational age less than 34 weeks, 62% had adverse outcomes [OR 1.78; 95% CI: 1.54-2.06] in comparison to 9.2% with the gestational age of more than thirty-four weeks when compared to those without TRIPLE-I [3]. They observed that the duration of antibiotic [<9h versus>9 hours] use did not alter the neonatal outcomes in both groups [3]. This gives us an insight that management and delivery should be expedited in women with TRIPLE-I to improve neonatal morbidity and mortality. Delivery within twelve hours of the diagnosis may be a safe cut-off. Research in this regard would aid in drawing any consensus.

Mode of IOL in women with PROM and poor BISHOP score

TRIPLE-I is known to be associated with labor dystocia [33,34]. In women with pre-labor rupture of membranes >37 weeks of gestation, conservative management for 24 hours is considered safe but in cases with suspected TRIPLE-I, induction of labor may be considered to expedite labor progress [30]. Whether to induce women with TRIPLE-I with prostaglandins [PGs] or augment labor with oxytocin remains debatable. Reviewing the literature, it is difficult to find consensus in this regard. Gulerson et al., noted reduced TRIPLE-I incidence [p<0.001], neonatal ICU admissions, and shorter ROM to the delivery interval in women induced with oxytocin as compared to those induced with prostaglandin E2(PGE2) [35]. Women with ROM [rupture of membranes] induced with PGE2 may have higher TRIPLE-I rates due to prolonged ROM to the delivery time and the need for digital examination in the placement of PGE2 [35]. ACOG (2021) has advised the use of PGE2 with caution in women with ROM due to the higher reported risk of TRIPLE-I [36]. In another study, by Longley et al., no difference was noted in labor induction with Misoprostol and oxytocin and risk of TRIPLE-I [37]. The use of PGE2 for IOL necessitates multiple vaginal examinations and hence the risk of TRIPLE-I. In an RCT, by Unthanan et al., the use of sublingual Misoprostol to induce labor in patients with PROM at term was associated with shorter induction time and similar complication rates in comparison to oxytocin [38]. Ting et al., demonstrated that the use of Propess [vaginal delivery system] for IOL was associated with a reduced need for vaginal examinations and a shorter induction to delivery interval [39]. The newer studies have demonstrated that in women with PROM, with poor BISOP scores, the prostaglandin vaginal delivery system seems a better option. Sublingual Misoprostol may yet be another option; however, future studies are required in this regard.

Triple-I with multiple drugs resistant organism.

The diagnosis of TRIPLE-I remains a challenge due to the presence of multiple factors that may contribute to maternal and fetal tachycardia. Though rare, TRIPLE-I by multiple drug-resistant organisms [MDRO] may be more challenging. The maternal and neonatal outcomes in these cases are worse. The diagnosis in these cases is usually delayed as cultures results may take 48 hours or more. That is why poor outcomes are noted in TRIPLE-I with MDRO [40,41]. In a cross-sectional review by Ballot et al., on neonates admitted to a tertiary neonatal unit, an increase in the admissions due to MRDO sepsis in neonates was observed. The mortality rate in these neonates was 33.3%. Klebsiella pneumoniae was identified as the most common MDRO (66.2%). These neonates had higher rates of resuscitation at birth, mechanical ventilation, necrotizing enterocolitis and need for oxygen supplementation till 4 weeks of birth in comparison to neonates with sepsis with non MDRO [40]. Out of these babies, TRIPLE-I was diagnosed in 2.9% of labor. Preterm and low birth weight babies had higher prevalence and poorer outcomes as compared to term neonates [40]. Shittu et al., reported MDRO TRIPLE-I with extended-spectrum beta-lactamase-producing Escherichia coli that caused poor neonatal outcomes and the patient developed septicemia and surgical site infection with the same organism. In these cases, early diagnosis and management play a pivotal role in improving the outcomes. However, as this diagnosis is based on the placental culture results, it may be delayed or missed. In cases of TRIPLE-I that are non-responsive to broad-spectrum antibiotics, MDRO infection may be a possibility. Placental cultures should be followed up to avoid any delays in the treatment. In women with TRIPLE-I who remain febrile after 24 hours of commencement of antibiotics or develop signs of sepsis, changing antibiotics should be considered.

Criteria for NICU Admission in Suspected Cases

Management of newborn babies exposed to maternal TRIPLE-I is rigorous. Increased fetal morbidity and mortality due to early-onset sepsis (EOS) among babies exposed to maternal TRIPLE-I is reported. In view of poor neonatal outcome, evaluation and empirical antibiotics in all Triple I-exposed infants is recommended [42,43]. The use of intrapartum antibiotic prophylaxis in women Group B Streptococcus (GBS) colonization in labor has significantly reduced the risk of early onset sepsis [EOS] in neonates. In all cases with suspected TRIPLE-I, due to risks of EOS among newborn babies, antibiotics are and leads to frequently used. Antibiotics use among late preterm and term infants about 5-7% [44,45]. This usual empirical antibiotic approach in Triple I exposed babies leads to excessive antibiotic exposure among well appearing uninfected infants 44, 45. This also leads to hospitalization and unnecessary investigation in well-looking low-risk infants. Also, maternal separation leads to a low exclusive breastfeeding rate [46]. The data from studies are suggesting harmful effect of excessive antibiotic use on microbiota of neonates and also increases maternal infant separation which have negative effect on bonding and rate of breast feeding, so there was increasing need to balance risk of EOS and unnecessary excessive antibiotic use [46,47]. So, the aim was to reduce unnecessary antibiotic use without compromising the safety of fragile neonates.

To reduce unnecessary antibiotic use among Triple I exposed neonates, a risk-based approach to focus on clinical monitoring and meticulous examination to determine the need for antibiotics and laboratory testing has been developed. A special calculator was developed by Kaiser Permanente Division of Research[https://neonatalsepsiscalculator.kaiserpermanente.org] to estimate risk of early onset sepsis [Neonatal Early-Onset Sepsis Calculator]. This Kaiser Permanente neonatal early-onset sepsis calculator has been developed to screen the neonates, who were suspected with early-onset sepsis. This calculation is based on based on different risk factors and would aid to decide the need for the empiric antibiotic therapy.

This calculator uses multivariate approach based on various risk factors and uses objective data as gestation age, the duration of rupture of membranes, maternal GBS colonization status, the highest maternal intrapartum temperature and the type and duration of intrapartum antibiotic uses. The calculator also uses the ongoing clinical condition of neonates during first two to hour of life.

Neonatal Sepsis Calculator (NSC), is a prediction calculator for EOS and the model is based on clinical examination of newborn and five perinatal risk factors for sepsis [gestation age, duration of rupture of membranes, highest maternal temperature, GBS status, and the type and duration of intrapartum antibiotic uses], to guide the need for antibiotics and blood investigation. This risk-based calculator was developed using data from over 600000 newborn babies [48,49,50].

This calculator had subsequently been validated in several studies throughout the world and found significantly reduces the use of antibiotics in well appearing more than 35 weeks infants exposed to maternal Triple I [51,52].

A meta-analysis done by Deshmukh M et al., of six good quality non-randomized controlled studies and involved 172385 newborn babies, evaluated this risk-based sepsis calculator verses the standard care recommended based on the CDC guidelines for the diagnosis and treatment of early onset sepsis [53]. This meta-analysis revealed a statistically eloquent decrement in the need of antibiotic therapy in babies who were managed using the risk-based sepsis calculator in comparison with the standard management [3.3%/ 6%, OR- 0.22; 95% CI, 0.14 to 0.36; P < .00001]. To avoid the use of antibiotics in one baby the number needed to treat NNT was

37. Data on laboratory testing for early onset sepsis was reported in five studies and included 168432 babies. Pooled data from these studies revealed a significant reduction in the requirement of laboratory tests in babies who were managed by the risk-based sepsis calculator in comparison with those managed with standard therapy (2.5% /15.5%, OR- 0.14, 95% CI- 0.08 to 0.27; P < .00001]), and number need to treat to prevent use of laboratory testing in one baby was eight [53]. Four studies reported the data regarding NICU admission and included 16628 babies, of which three reported a significant reduction in NICU admissions. Meta-analysis of four studies involving 16628 neonates found reduced number of NICU admission [5.4% vs. 19%, OR - 0.24; 95% CI-0.11 to 0.51, P < .0001] and NNT of 7 to decrease one NICU admission [53]. Meta-analysis regarding readmission to NICU from the three studies that included 156394 neonates found no difference in readmission rates (OR = 0.87; 95% CI, 0.57 - 1.33; P = 0.53). Pooled data of all studies, involving 172385 neonates, revealed no difference in the sepsis (culture-positive) rate between neonates treated using the NSC and standard therapy (OR- 0.94, 95% CI- 0.51 to 1.74, P = 0.85) [53]. In a study done by Bridges et al., the exclusive breastfeeding rate was improved from <10% to >50% after implementation of risk-based sepsis calculator among newborns exposed to Triple I [54]. This use of risk-based Early Onset-Sepsis Calculator decreases unnecessary NICU admissions and improve exclusive breastfeeding rate. It should be used in case of asymptomatic infants with suspected diagnosis of TRIPLE-I.

Conclusions

The diagnosis of TRIPLE-I may perturb in situations with other causes of maternal pyrexia and after EA, however a good clinical history and examination may aid in excluding the differential diagnosis of TRIPLE-I. The use of Propess (vaginal delivery system) for IOL in these women should be preferred to reduce the induction-delivery interval and unnecessary vaginal examinations. Women with TRIPLE-I should have continuous fetal monitoring in labor, any abnormalities in CTG should be addressed in time to avoid neonatal complications. With isolated uncomplicated tachycardia, corresponding to maternal tachycardia, close observation is recommended but in cases with reduced variability and associated decelerations in CTG, delivery needs to be expedited. If pyrexia persists despite the treatment of TRIPLE-I, MDRO may be considered and placental culture results to be followed and antibiotics to be changed accordingly. Neonatal admission should be based on the clinical scenario and with the aid of Early Onset-Sepsis Calculator, unnecessary admissions can be minimized. Future studies on Triple-I will be helpful in deriving recommendations for these controversial issues.

Conflict of Interest

The authors do not have any conflict if interest

Authors contribution

SA contributed to the concept, review of literature and drafting the manuscript. SAb contributed to the neonatal aspects in review of literature. Both authors approved the final manuscript.

Appendices

Abbreviations:

Triple I- intrauterine infection, inflammation, or both /chorioamnionitis, NICU- neonatal intensive care unit, CTG- , FBS- fetal blood sampling, FHR- fetal heart rate, IOL- , MRDO- multiple resistant drug organism, ESBL- extended spectrum Beta lactamase , PROM- premature rupture of membrane , ROM- rupture of membrane , , EA- epidural analgesia, OR- odds ratio, RR- risk ratio, CI- confidence interval, GBS- group B streptococci , EOS- early onset sepsis , IAP- intrapartum antibiotic prophylaxis , NNT- number needed to treat, NSC- Neonatal Sepsis Calculator.

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