

# Evaluation and Management of Women and Newborns With a Maternal Diagnosis of Chorioamnionitis

## Summary of a Workshop

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In January 2015, the Eunice Kennedy Shriver National Institute of Child Health and Human Development invited an expert panel to a workshop to address numerous knowledge gaps and to provide evidence-based guidelines for the diagnosis and management of pregnant women with what had been commonly called chorioamnionitis and the neonates born to these women. The panel noted that the term chorioamnionitis has been used to label a heterogeneous array of conditions characterized by infection and inflammation or both with a consequent great variation in clinical practice for mothers and their newborns. Therefore, the panel proposed to replace the term chorioamnionitis with a more general, descriptive term: “intrauterine inflammation or infection or both,” abbreviated as “Triple I.” The panel proposed a classification for Triple I and recommended approaches to evaluation and management of pregnant women and their newborns with a diagnosis of Triple I. It

is particularly important to recognize that an isolated maternal fever is not synonymous with chorioamnionitis. A research agenda was proposed to further refine the definition and management of this complex group of conditions. This article provides a summary of the workshop presentations and discussions.

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The term “chorioamnionitis” has been in existence for several decades.<sup>1</sup> In the strictest sense, the term implies that a pregnant woman has an “inflammatory or an infectious” disorder of the chorion, amnion, or both. This diagnosis often implies that the mother and her fetus may be at an increased risk for developing serious infectious consequences. Because of its connotation, the mere entry of chorioamnionitis in the patient’s record triggers a series of investigations and management decisions in the mother and in the neonate, irrespective of probable cause or clinical findings. As a result of the imprecise nature of

See related editorial on page 423.

\*For a list of names and affiliations of the workshop participants, see Appendix 1 online at <http://links.lww.com/AOG/A755>.

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the definitional elements and the heterogeneity of clinical manifestations, there is no unanimity in the approaches for diagnostic workup or for obstetric and neonatal management. To address these wide-ranging issues, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the Society for Maternal-Fetal Medicine, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics (AAP) invited a group of maternal and neonatal experts to a workshop on January 26–27, 2015. In this article, we provide a brief summary of the workshop discussions and the expert opinion concerning management and evaluation of what has heretofore been labeled chorioamnionitis. This is not a formal Consensus Development Conference recommendation by the National Institutes of Health.

## REVIEW OF THE CURRENT UNDERSTANDING OF CHORIOAMNIONITIS

The term chorioamnionitis has transitioned from its original autologic scope (to express what it describes) to a more heterologic term (not corresponding), essentially becoming an out-of-date misnomer. Although the term literally points to “inflammation limited to the chorion and amnion layers of the fetal membranes,” it is often used when other intrauterine components are involved such as amniotic fluid or the decidua. Adding to the confusion, the term is commonly used to denote clinical suspicion of intrauterine inflammation or infection even before any laboratory or pathologic evidence of infection or inflammation is uncovered. The findings on such an examination are often not conclusive, are not available until after the neonate is delivered, and are not always aligned with clinical features. The term chorioamnionitis does not consistently convey the degree and severity of maternal or fetal illness, which makes it difficult to assess the consequences of this diagnosis for the mother or neonate.

In its current use, the term chorioamnionitis refers to a heterogeneous group of conditions that includes inflammation as well as infections of varying degrees of severity and duration. Inflammation includes a reaction that results in tissue edema, swelling, and irritation. Infection includes inflammation with concurrent invasion of bacteria, virus, fungus, or other infectious agent. Often a designation of chorioamnionitis is made when any combination (or even one) of the following elements is noted: maternal fever, maternal or fetal tachycardia or both, elevated maternal white blood cell (WBC) count, uterine tenderness, and purulent fluid or purulent discharge from the cervical os. However, the presence of one (or even

more than one) of these signs and symptoms does not necessarily indicate intrauterine infection, or actual chorioamnionitis, is present.

Intrauterine infection may lead to serious maternal complications such as sepsis, prolonged labor, wound infection, need for hysterectomy, postpartum endometritis, postpartum hemorrhage, adult respiratory distress syndrome, intensive care unit admission, and, in rare instances, maternal mortality. However, by erring on the side of treatment for any suspected chorioamnionitis, health care providers may not be fully considering the adverse effects of unnecessary treatment. Treatment with antimicrobial agents for fever during labor is generally safe for the mother with relatively few side effects. However, rare instances of anaphylaxis<sup>2,3</sup> have been reported with serious implications for the fetus when uteroplacental blood flow and oxygenation are adversely affected. The prevalence of anaphylaxis was found to be 2.7 cases per 100,000 deliveries.<sup>2</sup> In addition, a diagnosis of maternal chorioamnionitis has significant implications for the evaluation and management of the newborn. It often leads to additional laboratory evaluation, unnecessary treatment, and hospitalization in higher acuity units.<sup>4–6</sup> For all these reasons, the workshop participants agreed that there is a need to change the prevailing and unsubstantiated perceptions associated with the term chorioamnionitis.

Maternal fever can occur as a result of intrauterine or extrauterine causes. Infectious causes can include pyelonephritis, upper and lower respiratory tract infections such as influenza as well as infections in other organ systems. Noninfectious causes of fever include use of epidural analgesia during labor,<sup>7,8</sup> hyperthyroidism, dehydration, elevated ambient temperature, and the use of pyrogens such as prostaglandin E2 for the induction of labor. It may not always be possible to differentiate between intra- and extrauterine causes of fever or to categorically exclude chorioamnionitis, particularly early in its presentation. For these reasons, a plan to “rule out chorioamnionitis” or to treat “presumptive chorioamnionitis” is sometimes made and entered into the medical records, which often triggers an unnecessary workup for “sepsis” and antimicrobial treatment for the newborn. Because not every intrapartum fever is of infectious origin, treating all fevers with antimicrobial agents will result in overtreatment of mothers.

The neonatal team might interpret maternal antimicrobial treatment itself as evidence of potential maternal and fetal infection, leading to additional neonatal laboratory testing and treatment of the neonate with antimicrobial agents for varying duration. Thus, a diagnosis of chorioamnionitis has serious



implications for the management of the newborn. The guidelines developed by the Centers for Disease Control and Prevention (CDC),<sup>9</sup> the AAP,<sup>10</sup> and the National Institute for Health and Care Excellence<sup>11</sup> differ in some of their specifics, but all three guidelines recommend treatment of well-appearing neonates born to women with suspected or proven chorioamnionitis. For example, for well-appearing neonates born to women with suspected chorioamnionitis, both the CDC<sup>9</sup> and the Committee on Fetus and Newborn of the AAP<sup>10</sup> recommend a blood culture at birth followed by treatment and subsequent laboratory tests (eg, WBC and differential count, C-reactive protein, or platelet count). The National Institute for Health and Care Excellence guideline from the United Kingdom<sup>11</sup> recommends blood culture and C-reactive protein determination followed by initiation of antimicrobial agents for any neonate whose mother received antimicrobial agents for confirmed or suspected bacterial infection including chorioamnionitis.

The consequences of the three sets of guidelines outlined include a significant increase in the number of neonates exposed to antimicrobial agents in an attempt to treat rare cases of early-onset sepsis as well as an increase in the workload for health care providers and cost.<sup>4-6</sup> In addition, many newborns are treated with antimicrobial agents for prolonged periods despite negative blood culture results.<sup>5,6</sup> Because administration of antimicrobial agents oftentimes is accompanied by admission to a neonatal intensive care unit (NICU), a large number of newborns are additionally exposed to the NICU environment where there is increased risk of acquiring infections with multidrug-resistant bacteria. Children in NICUs are also separated from their families, which may have consequences for mother-neonate attachment and successful breastfeeding. Antimicrobial agents also alter the gut microbiota.<sup>12,13</sup> The overall implications are even more concerning considering the likelihood of an infectious etiology is small. Since the early 1970s, neonatal care providers have been rightly concerned about early-onset sepsis, especially group B streptococci (GBS) disease because of its high morbidity and mortality. Much of this concern began in an era before routine maternal screening for GBS and intrapartum antimicrobial prophylaxis. However, after publication of GBS management guidelines by several professional societies and organizations, the incidence of early-onset GBS sepsis has dropped significantly.<sup>14</sup> The authors found no concomitant increase in *Escherichia coli* sepsis during the study period from 2006 to 2009.<sup>14</sup>

Although confirmed maternal infection needs to be treated with appropriate antimicrobial agents

(which also treat the fetus), they are frequently given for febrile episodes with a low likelihood of intrauterine infection. Therefore, giving antimicrobial agents to a newborn simply based on an isolated maternal fever will likely treat many neonates with a very low likelihood of infection. Because such circumstances are relatively common, some consensus around the management of well-appearing neonates exposed to antimicrobial agents in utero and how to target investigation and treatment of neonates at highest risk for early-onset sepsis is needed.

Ideally, antimicrobial treatment of the newborn at high risk of early-onset sepsis should be initiated immediately after birth but restricted only to newborns who might benefit from treatment (ie, those likely to be infected). Unfortunately at this time, diagnostic tests with the ability to identify newborns likely to be infected are not clinically available. One approach to limiting the unnecessary use of antimicrobials is to use the “sepsis calculator” developed by Puopolo et al<sup>15</sup> to estimate the probability of early-onset sepsis using maternal risk factors in neonates born at 34 weeks of gestation or greater. The model uses three categorical variables: GBS status (positive, negative, uncertain), maternal intrapartum antimicrobial treatment (GBS-specific or broad spectrum), and intrapartum prophylaxis or treatment given 4 hours or greater before delivery (yes, no) in addition to the following continuous variables: highest maternal intrapartum temperature (centigrade or Fahrenheit), gestational age (weeks and days), and duration of rupture of membranes (hours). A predicted probability per 1,000 live births can be estimated using the calculator (<http://www.dor.kaiser.org/external/DORExternal/research/InfectionProbabilityCalculator.aspx>). In a retrospective study, Shakib et al<sup>16</sup> demonstrated that the use of the sepsis calculator in a population of well-appearing neonates (34 weeks of gestation or greater) with a clinical diagnosis of chorioamnionitis would have reduced the proportion of neonates having laboratory tests and antimicrobial agents to 12% of the total and would not have missed any cases of culture-positive early-onset sepsis.<sup>16</sup>

Escobar et al<sup>17</sup> recently refined the sepsis calculator developed by Puopolo<sup>15</sup> by combining the same risk factors for sepsis described (pretest probability) and the neonate’s clinical presentation (clinically ill, equivocal presentation, or well-appearing) during the first 6–12 hours of life (posttest probability) to estimate the probability of sepsis in neonates born at 34 weeks of gestation or greater. Escobar demonstrated that in well-appearing neonates with risk factors for sepsis, the incidence of early-onset sepsis is extremely low (sepsis rate of 0.11/1,000 [0.08–0.13]), but not



quite zero. Both algorithms will need further modification as new data are generated.

There is a general consensus that neonates who have persistent signs associated with sepsis, whether or not born to mothers with a diagnosis of chorioamnionitis (suspected or proven), should receive broad-spectrum antimicrobials after appropriate cultures are taken. However, some newborns will initially be symptomatic immediately after birth and will become asymptomatic over the ensuing 4–6 hours. Those neonates should be managed as if they were healthy-appearing. The management of the well-appearing asymptomatic neonate born to a mother with a chorioamnionitis diagnosis remains controversial. As noted, the CDC,<sup>9</sup> the AAP,<sup>10</sup> and the National Institute for Health and Care Excellence<sup>11</sup> recommend a diagnostic evaluation and antimicrobial coverage. Given that clinicians may have a low threshold for labeling the patient as having chorioamnionitis, and this decision does not take into consideration the resulting neonatal interventions, it is important to reevaluate the approach to this group of women and neonates.

### INTRAUTERINE INFLAMMATION, INFECTION, OR BOTH (TRIPLE I)

The workshop participants noted that use of the term chorioamnionitis conveys a definitive infectious etiology when this may not always be the case. Health care providers often use this term even when the only sign is a maternal fever. The panel of experts agreed that maternal fever alone should not automatically lead to a diagnosis of infection (or chorioamnionitis) and to antimicrobial therapy. They also sought to develop new terminology to better describe various scenarios associated with fever or infection during the intrapartum period.

To clarify this issue, the panel recommended new terminology that differentiates the mere presence of fever from infection or inflammation or both and clarifies that inflammation can occur without infection. Therefore, given the historical inconsistency in use, the panel proposed to altogether discontinue the intrapartum use of the term chorioamnionitis and instead use “intrauterine inflammation or infection or both” or “Triple I” as shown in Table 1. Under the new proposal, Triple I is diagnosed when fever is present with one or more of the following:

1. Fetal tachycardia (greater than 160 beats per minute for 10 minutes or longer)<sup>18</sup>
2. Maternal WBC count greater than 15,000 in the absence of corticosteroids
3. Purulent fluid from the cervical os (cloudy or yellowish thick discharge confirmed visually on

**Table 1. Features of Isolated Maternal Fever and Triple I With Classification\***

Terminology	Features and Comments
Isolated maternal fever (“documented” fever)	Maternal oral temperature 39.0°C or greater (102.2°F) on any one occasion is documented fever. If the oral temperature is between 38.0°C (100.4°F) and 39.0°C (102.2°F), repeat the measurement in 30 minutes; if the repeat value remains at least 38.0°C (100.4°F), it is documented fever
Suspected Triple I	Fever without a clear source plus any of the following: 1) baseline fetal tachycardia (greater than 160 beats per min for 10 min or longer, excluding accelerations, decelerations, and periods of marked variability) 2) maternal white blood cell count greater than 15,000 per mm <sup>3</sup> in the absence of corticosteroids 3) definite purulent fluid from the cervical os
Confirmed Triple I	All of the above plus: 1) amniocentesis-proven infection through a positive Gram stain 2) low glucose or positive amniotic fluid culture 3) placental pathology revealing diagnostic features of infection

\* Discontinue the use of the term “Chorioamnionitis.” See the text for discussion.

speculum examination to be coming from the cervical canal)

4. Biochemical or microbiologic amniotic fluid results consistent with microbial invasion of the amniotic cavity (see subsequently).

Fever in the absence of any of these criteria should be categorized as “isolated maternal fever.” Isolated maternal fever can include but is not limited to fever secondary to epidural anesthesia, prostaglandin use, dehydration, hyperthyroidism, and excess ambient heat. In the clinical situation of labor with fever and unknown GBS status at 37 weeks of gestation or greater, intrapartum prophylaxis should be initiated as per CDC guidelines.<sup>9</sup>

The panel also recommended that the diagnosis of fever be standardized as follows: maternal temperature 39.0°C or greater or 102.2°F on one reading constitutes a fever. If the temperature is 38.0°C or greater or 100.4°F but less than 39.0°C or 102.2°F, the temperature should be retaken in 30 minutes for



confirmation. A repeat temperature 38.0°C or greater or 100.4°F constitutes a documented fever.<sup>19,20</sup> For the diagnosis of fever, temperature should be measured orally.<sup>21</sup>

The panel suggests that Triple I be categorized as suspected or confirmed. Without confirmation, Triple I should be qualified with the term “suspected.” To be confirmed, Triple I should be accompanied by objective laboratory findings of infection in amniotic fluid (AF) (eg, positive Gram stain for bacteria, low AF glucose, high WBC count in the absence of a bloody tap, or positive AF culture results), or histopathologic evidence of infection or inflammation or both in the placenta, fetal membranes, or the umbilical cord vessels (funisitis).<sup>19,22,23</sup> Obviously, the histopathologic evidence would be applied in retrospect.

Cases can thus be categorized as follows (Table 1):

1. Isolated maternal fever (not Triple I)
2. Suspected Triple I
3. Confirmed Triple I.

## BIOMARKERS

Members of the panel agreed on the critical need for discovery, validation, and implementation in clinical workflow of biomarkers that could objectively assess the level of risk for early-onset sepsis. Biomarkers with potential to guide neonatal management can either be antenatal or postnatal.

Antenatal markers should be aimed at diagnosing Triple I and assessing its severity. In combination with gestational age and clinical manifestations, such biomarkers have potential to play an active role in the management as noted subsequently:

- Consideration for admission or transfer to a health care facility with maternal–fetal medicine service and level 3 or 4 NICU if warranted by the clinical assessment
- Decision for expectant management compared with delivery
- Decision to perform a cervical cerclage or to withhold such a procedure
- Timing for steroid administration
- Decision whether to initiate tocolytic treatment
- Decision whether antimicrobial treatment of the mother is needed.

Because most intrauterine infections have a sub-clinical stage,<sup>24</sup> one should recognize the challenges of interpreting results of antenatal markers of Triple I. The first challenge results from the compartmentalization of the gestational sac from the maternal systemic circulation.<sup>25</sup> As a result, studies focusing on markers traditionally associated with inflammatory

or infectious processes have failed to show clinical utility when these markers are assessed in the maternal circulation. Although some authors have proposed using AF analysis to rule out Triple I in women with preterm premature rupture of membranes managed expectantly, a recent Cochrane review found that the quality of evidence is poor.<sup>26</sup> Although a meta-analysis was not possible as a result of the small number of studies, it is clear that high-quality evidence is needed to guide clinical practice related to the role of amniocentesis and AF analysis in management of preterm premature rupture of membranes. There is a similar paucity of data regarding the need for amniocentesis in women presenting with preterm labor and intact membranes or advanced cervical effacement. Recent studies recommend ruling out Triple I using AF analysis before surgical placement of a foreign body such as cervical cerclage.<sup>27–29</sup> For example, sub-clinical microbial invasion of AF was found in 9% of women with an ultrasonographically short cervix (less than 25 mm in the midtrimester).<sup>30</sup>

Even when analyzed in AF, there is controversy as to which biomarkers are most informative and whether they are markers of intraamniotic infection, intraamniotic inflammation, or both. In the few institutions where amniocentesis is performed to confirm Triple I, the laboratory tests that are used for clinical management are glucose concentration, lactate dehydrogenase activity, WBC and red blood cell counts, Gram stain, and bacterial cultures. Culture results are usually not available in time for decision-making. Therefore, clinicians must rely on the remaining analyses, which have turnaround times in hours. Unfortunately, the tests noted (glucose, lactate dehydrogenase, WBC count, and Gram stain) do not always concur in ruling out or confirming Triple I; therefore, the interpretation of the test results may not be straightforward.<sup>22</sup> Studies of biomarkers of Triple I are confounded by the lack of a gold standard for diagnosis. Bacterial cultures depend on the choice of media and do not routinely identify all species, some of which are known etiologic agents of Triple I<sup>31</sup> and of early-onset sepsis.<sup>32</sup> Moreover, AF inflammation has been linked to poor pregnancy and neonatal outcomes<sup>27</sup> even in the absence of infection. Biomarkers also have different diagnostic accuracy in various subgroups of women (preterm premature rupture of membranes compared with preterm labor intact membranes compared with a short cervix). This makes them less practical in the clinical setting because the patient’s condition may evolve from one to the other. Despite a plethora of hypothesis-driven and “omics” discovery studies (primarily proteomics



and metabolomics), only a few biomarkers have been validated or tested clinically.

To overcome the need for amniocentesis, many investigators have searched for markers informative of Triple I in biological fluids that can be sampled noninvasively (urine) or through minimally invasive approaches (maternal blood, cervicovaginal secretions, vaginal amniotic, or vaginal washings fluid in preterm premature rupture of membranes cases). Maternal blood has been the compartment most extensively explored, but so far none of the markers is sensitive enough to diagnose Triple I or to estimate its severity. The issue of specificity is more difficult to evaluate because the majority of published studies fail to include cases with other types of systemic inflammatory conditions with overlapping symptomatology (pyelonephritis, appendicitis, and other conditions).

Postnatal markers have the potential to affect the postnatal care of the newborn. Indeed, postnatal markers could be particularly useful because they:

- Remove some of the subjectivity from the interpretation of symptoms of sepsis, which are nonspecific in newborns or may not be apparent to an untrained health care provider
- Help with the decision to admit a newborn to an intensive care unit and to promptly initiate broad-spectrum antimicrobial therapy
- Guide the duration of antimicrobial therapy
- Facilitate counseling of the mother and family with respect to probable cause of preterm birth and future pregnancies.

Cord blood and neonatal blood, sampled within 72 hours of birth, are the biological fluids most often explored for markers indicative of early-onset sepsis. The chief advantage of cord blood is that it is available in relatively large quantities immediately on delivery; its sampling is technically easy to perform and does not pose a risk of infection or hemorrhage for the neonate. Its disadvantage is that some analytes of placental origin might be present in increased concentration in cord blood compared with neonatal blood (although this has not been systematically addressed). Cord blood levels of C-reactive protein, procalcitonin, interleukin-6, interleukin-8 and more recently of haptoglobin and haptoglobin-related protein have been studied alone, in combination, and as add-ons to hematologic indices.<sup>33-37</sup>

Blood obtained from the neonate after birth is the biological fluid most often used to test for sepsis biomarkers (including hematologic indices), which are used in some centers to guide initiation and duration of antimicrobial therapy. Postnatal blood samples are also used for bacterial cultures. The problem with

blood sampling after birth is that it poses a small risk for the neonate and the amount of blood that can be safely obtained is severely limited, especially in very-low-birth-weight neonates. Most importantly, the interpretation of some biomarkers such as C-reactive protein and interleukin-6 is confounded by physiologic changes that occur in the immediate postnatal period, which affect their specificity.<sup>38,39</sup> Other soluble or cell-adhesion molecules have been suggested as markers for identifying newborns with early-onset sepsis, but none is accurate, widely available, or both enough for current clinical use.<sup>40</sup>

Commercial development of a diagnostic test for sepsis generally requires reporting of sensitivity and specificity, which is not possible for early-onset sepsis because an accurate gold standard does not exist and there is no established consensus on the definition for neonatal sepsis.<sup>41</sup> Despite claims that the neonatal blood cultures are “the gold standard for early-onset sepsis,” their use is severely limited by both false-negative and false-positive results.<sup>41</sup> Therefore, any new biomarker that is technically superior at identification of true disease will appear inferior when compared with blood culture results. Accordingly, novel biomarkers should be assessed against clinically important neonatal outcomes.

## MATERNAL MANAGEMENT

Isolated fever and suspected or confirmed Triple I are not, by themselves, indications for cesarean delivery. The approach to antimicrobial treatment in the mother is similar to the one for the neonate. In the presence of isolated fever, particularly in the late preterm and term patient after epidural analgesia, it may be appropriate to avoid antimicrobial agents and monitor the patient for additional signs or symptoms of infection.

The choice of antimicrobial agents in the case of suspected Triple I should be guided by the prevalent microorganisms causing intrauterine infection. In general, a combination of ampicillin and gentamicin should cover most relevant pathogens. If a cesarean delivery is performed, the addition of anaerobic coverage after delivery may be considered (clindamycin or metronidazole) to decrease the risk of endometritis.

In women treated intrapartum with antimicrobial agents for suspected or confirmed Triple I, continuation of antimicrobial agents postpartum should not be automatic, but rather based on risk factors for postpartum endometritis. Women who have a vaginal delivery are less likely to have postpartum endometritis and therefore are candidates for discontinuing



antimicrobial agents after delivery. Even in women undergoing cesarean delivery, one more dose of antimicrobial agents after delivery has the same efficacy as continuing for a longer duration.<sup>42-44</sup> The presence of other maternal factors in the postpartum period such as bacteremia, sepsis, and persistent fever may be used to guide duration of antimicrobial therapy.

Controlling the maternal temperature with antipyretics and judicious hydration may be required. Because antipyretics may prevent or mask further fever, a decision regarding the likelihood of infection should be made before they are given.

## NEONATAL MANAGEMENT

We recommend that neonatal management be guided by the maternal category of isolated fever, suspected Triple I or confirmed Triple I, gestational age at delivery, and clinical evaluation of the neonate. Clearly, for the appropriate neonatal treatment to be applied, communication of the diagnosis between obstetric and neonatal teams is essential. A proposed algorithm for neonatal management is provided in Figure 1. Typically, management is different for late preterm and term neonates compared with neonates born at less than 34 weeks of gestation.

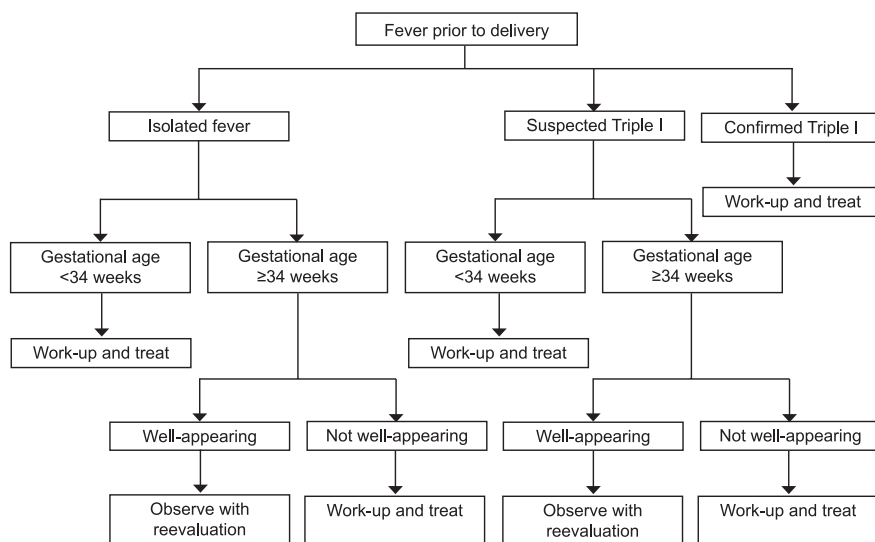
### Late Preterm and Term Neonates

In cases of isolated maternal fever not attributable to Triple I, current evidence suggests that treatment is not beneficial for well-appearing late preterm and term neonates, regardless of whether the mother was given antimicrobial agents. Conversely, when there is confirmed Triple I, these neonates should be

assessed and treated per current guidelines.<sup>9-11</sup> When Triple I is suspected, but not confirmed, care should be individualized, but the majority of well-appearing late preterm and term neonates can be observed without receiving antimicrobial agents provided they remain asymptomatic. The sepsis calculator of Puopolo et al<sup>15</sup> may help with the decision to treat or not to treat in cases with suspected Triple I. Using the original sepsis calculator, if the hypothetical risk of sepsis ranged from 0.65 to 1.54 per 1,000 live births (based solely on historical risk factors), 823 well-appearing neonates born to women with suspected Triple I would need treatment to capture the one truly infected neonate (the number needed to treat). Such newborns account for 11% of all live births. If the risk of sepsis at birth was less than 0.65 per 1,000, 9,370 newborns would need treatment to identify the one truly infected neonate. All neonates born to women with suspected or proven chorioamnionitis who are not treated need frequent close observations.

### Neonates Born at Less Than 34 0/7 Weeks of Gestation

There is currently no sepsis calculator for newborns born at less than 34 weeks of gestation. However, premature neonates born to women with risk factors for sepsis (including suspected or confirmed Triple I) are at a much higher risk for early-onset sepsis.<sup>45,46</sup> Therefore, the threshold for evaluation and treatment of these neonates should be significantly lower when compared with the late preterm and term neonates. There is a strong inverse relationship between gestational age at birth and the likelihood of an infectious



**Fig. 1.** Proposed algorithm for neonatal management.

Higgins. Chorioamnionitis Workshop Executive Summary. *Obstet Gynecol* 2016.



etiology, especially when Triple I is suspected or confirmed. Therefore, neonates born at less than 34 0/7 weeks of gestation to women with suspected or proven Triple I should be started on antimicrobial agents as soon as cultures are obtained. Healthy-appearing premature neonates born at less than 34 weeks of gestation to women with isolated maternal fever might be observed if laboratory testing is not suggestive of sepsis, but this recommendation is not evidence-based. Furthermore, as the degree of prematurity increases, most of these neonates will be symptomatic and not meet the designation of “healthy-appearing.”

### DURATION OF NEONATAL ANTIMICROBIAL THERAPY

Once antimicrobial therapy is started, evidence to guide the duration of treatment is limited. The National Institute for Health and Care Excellence guidelines<sup>11</sup> suggest 36 hours of antimicrobial agents for term newborns while awaiting negative blood culture results. Studies are warranted to guide clinical practice for duration of antimicrobial treatment when cultures are negative. In most well-appearing neonates, there is no compelling evidence that antimicrobial agents need to be continued beyond 48 hours, especially when blood cultures are negative and irrespective of how “abnormal” laboratory data are found in these newborns. Information regarding duration of antimicrobial therapy for “rule out sepsis” predates routine GBS screening and prophylaxis. Duration of antimicrobial agents was based on information from the 1970s assessing how long cultures generally needed to be evaluated to determine whether bacteria were present.<sup>47</sup> There is ongoing concern about the validity of blood cultures in neonates born to women who received broad-spectrum antimicrobial agents before delivery. More research is needed to address this concern, because it is a common reason for treating newborns with antimicrobial agents for 5 or more days.

### COST IMPLICATIONS

Depending on individual hospital practice, some well-appearing newborns who undergo evaluation or treatment for possible infection may be admitted to transitional care units, special care units, or NICUs. Costs vary widely depending where the evaluation and care are rendered in the hospital. The workshop participants agreed that evaluation of the well-appearing neonate can be performed in the regular nursery or in the mother–baby unit.

### SYSTEMS ISSUES

The management of isolated maternal fever and Triple I requires important practical and logistic issues to be addressed. Communication regarding the maternal diagnosis among health care providers for optimal maternal and neonatal management is necessary. Improved communication also should occur during the postpartum period, because the maternal course, laboratory results, and histopathology results in the hours and days after delivery may be relevant to the management and treatment of the newborn. Communication at the time of patient handoff (shift change) also is key to ensuring continuity of care. Institution of a checklist that would convey information needed to assess and manage the neonates may be helpful. Box 1 provides items that could be potentially included on such a list. Furthermore, systems to communicate this postnatal information to the neonatal team should be established as well as neonatal information (ie, positive culture) to the obstetric team.

Education of obstetric and pediatric or neonatal staff is important for communication, identification, and appropriate treatment of mothers and neonates at risk for Triple I. Programs for recognition, evaluation, and intervention for Triple I should be introduced in labor and delivery, postpartum, and neonatal wards. Audit and feedback mechanisms can be utilized to determine whether guidelines are being followed and to identify opportunities for quality improvement.

### RESEARCH OPPORTUNITIES AND GAPS

Multiple areas in need of further investigation were identified during the workshop (Table 2). Key areas

#### Box 1. Checklist of Items to Include in Communication Between the Obstetric and Neonatal Teams

- Gestational age
- Maternal tachycardia
- Fetal tachycardia
- Maternal white blood cell count greater than 15,000
- Maternal group B streptococci status
- Duration of rupture of membranes
- Duration of labor
- Purulent fluid
- Amniotic fluid evaluation
- Highest maternal temperature
- Epidural anesthesia use
- Prostaglandin use
- Antimicrobial agent(s) used
- Antipyretic used
- Spontaneous preterm birth
- Prior spontaneous preterm birth





**Table 2. Research Gaps and Opportunities**

Area	Maternal Topics	Neonatal Topics
Prevention of infection	Yes	Yes
Prediction of infection	Yes, colonization vs infection	Yes
Scoring system for probability of sepsis; infection prediction models to guide clinical management	Yes, placental histology, microbiome	Yes, need to define by gestational age, microbiome
Isolated fever in labor	Management—antipyretics, nonsteroidal anti-inflammatory drugs, antimicrobial agents	Management evaluation and antimicrobial agents
Biomarkers	Prediction, consensus for design of biomarker validation studies, reporting of accuracy, or all of these	Prediction, guidance for management, consensus for design of biomarker validation studies or reporting of accuracy
Outcomes	In hospital; subsequent reproductive outcomes	In hospital, morbidities; longer term outcomes including neurodevelopment
Antimicrobial agents	Timing, duration, selection of antimicrobial agents used	Timing, duration, selection of antimicrobial agents used
Postpartum events	Fever, clinical course, and its relationship to newborn's care and management	
"Epidural fever" investigation	Management and treatment	Management and treatment
Maternal fever	Timing, duration, height, and effect on clinical care and course	Timing, duration, height, and effect on clinical care and course
Duration of antimicrobial therapy	Timing and selection of antimicrobial agents	Term neonate—well-appearing Term neonate—symptomatic Term neonate—resolved minor symptoms Preterm neonate
Link studies—mother and neonate cohorts		Effect of infection on neurodevelopment impairment or cerebral palsy
Observation vs treatment		Low-risk cohorts
Corticosteroids	Effects—short and long term	Effects prenatal and postnatal
Microbiome—maternal–fetal microbiome ecosystem	Perturbations, influence of gastrointestinal flora on genitourinary flora	Symbiosis vs pathology

for study include accurate identification of infection during labor and appropriate treatment of mothers to avoid poor maternal and neonatal outcomes. Much work is needed in the neonatal arena, particularly evidence-based studies for the management of the well-appearing late preterm and term neonate. Trials evaluating the effects of withholding antimicrobial agents as well as discontinuation of treatment after short periods of time (24–48 hours) could greatly reduce antimicrobial exposure of newborns and shorten hospital length of stay. Biomarkers and prediction models are likely to facilitate management of mothers and their newborns.

## DISCUSSION

Clinical use of the term chorioamnionitis is outdated and overused and implies the presence of infection. Use of the phrase maternal chorioamnionitis has significant implications for both mother and neonate. The expert panel recommended the use of new terminology, specifically Triple I, with the term

chorioamnionitis restricted to pathologic diagnosis. The participants identified many gaps in research and opportunities to advance knowledge to affect care for the health of mothers and newborns. Better evidence to guide appropriate provision of care is desperately needed.

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