CHORIOAMNIONITIS OR TRIPLE I

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1. DEFINITION

Chorioamnionitis is defined as an acute inflammation of the placental membranes (amnion and chorion) of infectious origin, accompanied by infection of the amniotic content: the foetus, cord, and amniotic fluid. Its prevalence is estimated at 1-2% of full-term deliveries and 5-10% of preterm deliveries (1).

It is an important cause of maternal and foetal morbidity. At the maternal level it has been described as an increased risk of endometritis, sepsis, adult respiratory distress, postpartum haemorrhage, hysterectomy, need for ICU admission, as well as maternal mortality (2). At the foetal level, there is a greater risk of a worse Apgar score, early sepsis, grade III-IV intracranial haemorrhage, and neurodevelopmental disorders (3, 4).

Traditionally, the diagnosis of chorioamnionitis was based on the clinical criteria reported by Gibbs et al. in 1982 (5). Some of these criteria are very non-specific since they may be signs of other processes (infectious or not), which is why it is currently proposed to replace the term clinical chorioamnionitis with that of "Intrauterine Inflammation and/or Infection", better known as "Triple I" (6).

We will suspect chorioamnionitis or triple I in the presence of:

- Maternal fever (≥ 38.0ºC) and the presence of at least 1 of the following criteria:
  - Foetal tachycardia (> 160 bpm for ≥ 10 min)
  - Leukocytosis > 15000/mm3 (without corticosteroids)
  - Purulent cervical discharge.

In this classification, neither maternal tachycardia, uterine irritability or contractions, nor other infectious markers such as elevated C- Reactive Protein (CRP) are considered diagnostic criteria for chorioamnionitis or triple I, although their presence reinforces the diagnosis.

2. DIFFERENTIAL DIAGNOSIS

Fever is always present in chorioamnionitis or triple I. We define fever as the presence of an isolated febrile peak of ≥ 38ºC.

In case of fever, we must differentiate:

- Isolated fever of unknown origin (mainly intrapartum): related to non-infectious causes such as epidural anaesthesia, high room temperature, the use of prostaglandins for labour induction, etc. It is usually not accompanied by laboratory abnormalities.
- Fever of non-uterine infectious causes: pyelonephritis, respiratory infections (bacterial or viral), etc.
- Fever secondary to chorioamnionitis or triple I.

3. ASSESSMENT OF FEVER IN PREGNANCY

In the event of one fever spike (≥ 38ºC) the following complementary tests should be carried out:

- **Blood test**: complete blood count, CPR and coagulation. In case of suspicion of sepsis (SBP < 90 mmHg, HR > 120 bpm, RR > 24 rpm, basal oxygen saturation < 95%, oliguria, maternal confusion or agitation), we will add lactate, liver and kidney function tests (go to specific protocol).
- Foetal monitoring (nonstress test - **NST**).
- **Urine culture**
- **Blood culture** (obtained during fever peak). If possible, two determinations (no need to wait between them). In each determination, perform a vein puncture on each arm (left/right).
- If fever occurs in pregnant women with preterm labour or preterm prelabour rupture of membranes, a **Streptococcus agalactiae** (GBS) culture should be performed if this has not been done in the last 5 weeks.
- In the event of a specific focus of fever, appropriate **imaging tests** or cultures should be performed (chest X-ray for instance).
- If the suspicion is chorioamnionitis or triple I, diagnostic **amniocentesis** will be performed for confirmation.

4. DIAGNOSIS OF CHORIOAMNIONITIS OR TRIPLE I

To confirm chorioamnionitis or triple I, an **amniocentesis** will be performed, including:

- **Biochemical markers**: glucose, Interleukin (IL)-6 in amniotic fluid.
- **Microbiological study**: a Gram stain and aerobic/anaerobic/genital mycoplasma culture. In the event that Gram-negative bacteria such as Klebsiella or Escherichia coli are isolated, test whether they are extended-spectrum beta-lactamases (ESBL) germs, with the aim of adjusting the antibiotic treatment.

The diagnostic confirmation of chorioamnionitis or triple I is based on the presence of **maternal fever** ≥ 38ºC and at least one of the following: **foetal tachycardia >160 bpm**, **leukocytosis > 15,000/mm3** (without corticosteroids), **purulent cervical discharge**, and the presence of **one of** the following:

- Visualization of germs in amniotic fluid in **Gram stain** and/or
- **Glucose** in amniotic fluid ≤ 5 mg/dL and/or
- Positive amniotic fluid **culture**.

In selected cases in which it is technically difficult to perform an amniocentesis (as in anhydramnios), the diagnosis of chorioamnionitis will be based on the clinical-analytical criteria, having ruled out other sources of infection.
Although it is not considered a diagnostic criterion so far, the levels of IL-6 in amniotic fluid in chorioamnionitis are generally high (> 3000 pg/mL).

5. TREATMENT OF CHORIOAMNIONITIS OR TRIPLE I

1. Antipyretics

Maternal fever (especially intrapartum) is related to adverse neonatal outcomes due to foetal hyperthermia, which can lead to tissue hypoxia, increasing the risk of neurological depression (Apgar <7, hypotonia, seizures, and even neonatal encephalopathy) (7,8).

In the event of a fever spike ≥ 38ºC, antipyretics should be administered to avoid hyperthermia in the mother and foetus: **paracetamol 1 g/8 h** intravenous (IV)/oral.

2. Antibiotics:

While waiting to confirm the diagnosis, given a clinical or analytical suspicion of chorioamnionitis or triple I, **piperacillin-tazobactam 4 g/6 h IV + clarithromycin 500 mg/12 h oral** (9) should be started.

Some women are at higher risk of being carriers of extended-spectrum beta-lactamases (ESBL):

1. Previous infection or colonisation in the last 6 months by ESBL (major criterion)
   OR
2. 2 or more of the following factors (minor criteria):
   - Comorbidity (Chronic renal failure, pre-pregnancy diabetes mellitus, Cardiopathy, Chronic Obstructive Pulmonary Disease) / Immunosuppression (neutropenia, transplant, corticosteroids (> 20 mg/day of prednisone or equivalent for more than 2 weeks), immunosuppressants or cytostatics, HIV with < 200 CD4+, primary immunodeficiencies).
   - Urinary catheter carrier.
   - Hospital admission for more than 72 h in the previous 3 months.
   - Use of systemic antibiotic (oral or IV) for ≥ 5 days in the previous 3 months (frequent in patients with recurrent urinary tract infections).
   - Coming from endemic areas (Latin America, Caribbean, Asia, non-EU Mediterranean Region) living outside of those areas for less than 6 months.

When these risk factors exist (1 major or 2 minor) or the laboratory reports the presence of ESBL germ, ampicillin 2 g/6 h IV + ertapenem 1 g/24 h IV + clarithromycin 250 mg/12 h oral should be administered. In these selected cases, a rectal smear should be taken for ESBL screening upon admission, since its information may be important for the obstetrician and neonatologist.

In case of allergy to penicillin or beta-lactams, the treatment of choice will be: teicoplanin 600 mg loading dose, 12 h later 400 mg/12 h during 24 h at and then 400 mg/24 h IV + aztreonam 1 g/8 h IV + clarithromycin 500 mg/12 h oral.

3. Corticosteroids for lung maturation:

The administration of antenatal corticosteroids in women with chorioamnionitis has been associated with a reduction in respiratory distress syndrome, grade III-IV intraventricular haemorrhage, and periventricular leukomalacia (10) without increasing the risk of maternal and foetal sepsis. Therefore, there is no contraindication to the administration of antenatal corticosteroids in suspected or confirmed chorioamnionitis. Lung maturation with corticosteroids should not be a reason for delaying delivery in case of confirmation of chorioamnionitis or triple I (see below).

4. Magnesium sulphate for neuroprotection:

If chorioamnionitis is suspected or confirmed, neuroprophylaxis with magnesium sulphate should be started if < 32 weeks, since an imminent delivery is expected in the following hours (11).

5. Tocolysis:

It is CONTRAINDICATED both in suspected and in confirmed chorioamnionitis.

6. Delivery:

Upon confirmation of chorioamnionitis or triple I, delivery will be indicated regardless of gestational age.

Exceptionally, at very extreme gestational ages (< 26 weeks) in which uterine contractions and fever subside after initiation of antibiotics and antipyretics, and provided lactate levels are ≤2 mmol or ≤18 mg/dL, it can be considered to complete lung maturation before active labour induction.

- The diagnosis of chorioamnionitis is NOT an indication for an emergency caesarean section. Mode of delivery will be decided according to obstetrical indications.
- Delivery will be **under broad-spectrum antibiotic coverage** (see above). According to the literature, the results improve when intrapartum antibiotic has been administered for **at least 4 hours**. After 12 hours of induction of labour, there is an increased risk of uterine atony and a low neonatal Apgar score, but no increased incidence of other maternal or neonatal complications has been observed.
- **Continuous foetal monitoring** should be performed during vaginal delivery.

After delivery, cultures will be taken (from the maternal and foetal sides) of the placenta, since their information can help neonatal management. As one of the diagnostic criteria for chorioamnionitis is histological, placenta in formalin will be sent to Pathology.

7. Postpartum management:

After delivery (regardless of whether it was vaginal or caesarean section), **antibiotic therapy will be continued up to 48 h even in the absence of fever**. De-escalate or suspend the empirical antibiotic regimen based on clinical evolution and microbiological results.

- **Satisfactory clinical or analytical evolution:**
  - If the clinical evolution is correct and the patient remains afebrile, it is not necessary to perform serial postpartum blood tests. In case of significant intrapartum laboratory abnormalities (leukocytosis > 20,000 or leukopenia, marked left shift, CPR > 10 mg/dL (or > 100 mg/L), coagulation alteration), it is recommended to perform a postpartum analytical control even in the case of good clinical evolution to confirm analytical improvement.
  - Check the results of cultures:
    - Placental cultures: a positive placenta culture does not imply prolongation of antibiotic treatment if there is a correct clinical-analytical evolution.
    - Positive blood culture: adjust the treatment based on the clinical status and antibiogram. Maintain antibiotic treatment for at least 7 days. After 48 hours on intravenous treatment, if the patient is afebrile, it can be changed to oral antibiotic if the antibiogram allows it. It is recommended to discuss the case with the infectologists/microbiologists.
    - Positive urine culture: possible acute pyelonephritis (go to specific protocol).

- **Persistence of fever:**
  - If the clinical evolution is unfavourable, the type and duration of antibiotics should be individualised based on the results of the cultures and in collaboration with infectologists and microbiologists.

6. EPIDURAL AND INTRADURAL ANAESTHESIA IN PATIENTS WITH CHORIOAMNIONITIS

The following recommendations refer to neuroaxial blocks for both analgesic and anaesthetic purposes:

- Epidural catheterisation in patients with a systemic or local infection remains highly controversial. However, in obstetric patients, and for a short period of time, several

retrospective studies suggest this technique is probably safe. The decision to perform a regional anaesthetic or analgesic technique (epidural or intradural) in a febrile (bacteraemic) or infected patient must be assessed on an individual basis, considering other anaesthetic and analgesic alternatives, the benefits of regional anaesthesia and the risk of central nervous system infection (which theoretically exists in any patient with bacteraemia or who is immunocompromised). In any event, it should be performed under antibiotic coverage.

- A dural puncture can be performed safely, provided that appropriate antibiotic treatment has been started before the puncture and the patient has demonstrated a response to such therapy (for instance, with a decrease in fever).

6. CONDITIONS FOR PERFORMING AN AMNIOCENTESIS

- Prior to the procedure, the RhD blood type and the HIV and type B hepatitis serological status must be known. They should be requested urgently from the laboratory if they are unknown.
- The type C hepatitis serological status should be requested only in pregnant women at risk:
  - History of drug use, transfusion or transplantation
  - HIV or type B hepatitis infection
  - Type C hepatitis infected partner
  - Chronic hypertransaminasaemia
  - Tattoos
  - Piercings made with non-sterile or single-use material.
- In general, it is preferable to avoid a transplacental puncture as long as non-transplacental access is feasible. It should be avoided in pregnancies with positive serological status for HIV, type B hepatitis, type C hepatitis and in isoimmunisation.

- In case of maternal infection by HIV, type B hepatitis or type C hepatitis:
  - Assess the risk-benefit of performing a diagnostic amniocentesis to assess intra-amniotic infection, limiting it to cases with clinical suspicion of intra-amniotic infection. If indicated, transplacental puncture should be avoided.
  - HIV: perform the procedure under HAART and, ideally, with an undetectable viral load. In case of an untreated HIV infection or detectable viral load, try to delay the procedure and reassess together with the infectologists. If it is not possible to delay it, start the IV zidovudine protocol and consider urgent initiation of combined antiretroviral treatment.
  - Type B hepatitis: in case of HBeAg positive, positive viral load, an unavoidable transplacental puncture or third-trimester amniocentesis, specific immunoglobulin will be administered post-procedure (single dose if 600 IU IM within 24 hours).
  - Type C hepatitis: the risk of vertical transmission through an amniocentesis has been very poorly evaluated. If feasible, have an RNA determination available before the procedure.

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