Chorioamnionitis: review of the literature

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Abstract
Chorioamnionitis is a pathology typical of pregnancy, which evidences itself through different symptoms, both in the mother and in the fetus. It is the acute inflammation of the placental membranes (amnion and chorion). Chorioamnionitis continues to be a frequent and extremely dangerous pathology during pregnancy, so it is necessary to work promptly and efficiently.

Keywords: Pregnancy; Chorioamnionitis; Infection; Ovular membranes; Spontaneous rupture of membranes.

1. Introduction
Chorioamnionitis is a pathology typical of pregnancy, which evidences itself through different symptoms, both in the mother and in the fetus [1].

Is a polymicrobial infection, produced by the rise to the uterine cavity of pathogenic, aerobic, and anaerobic microorganisms, which affect the chorion, amnion, and fetus. This is an important cause of maternal and fetal morbidity, as it has been linked to premature rupture of membranes and preterm delivery [2].

We decided to review the literature regarding the frequency of this pathology and for its influence on maternal and fetal morbidity in many countries around the world.

2. Concept
According to Spanish Society of Obstetrics and Gynecology [3] and Plaza A [4], it is an acute inflammation of the placental membranes (amnion and chorion), generally of infectious origin, and it is accompanied by an infection of the amniotic content, fetus and cord, for which in clinical practice the terms are used interchangeably chorioamnionitis or intraamniotic infection.

Intra-amniotic infection (IAI) or microbial invasion of the amniotic cavity (MIAC) corresponds to the presence of germs in the amniotic cavity, identified by a positive culture [5].
3. Anatomy and physiology

3.1. Corion

It is the fetal membrane in direct contact with the endometrium of the uterus and that covers the chorionic sac. It is formed by the syncytiotrophoblast, the cytotrophoblast and the extraembryonic mesoderm. Chorionic villi are formed on its surface for the exchange between maternal blood and that of the embryo/fetus. It is formed during the second week of development, simultaneously with the implantation of the blastocyst in the uterine endometrium. Before this, the blastocyst had a hollow sphere shape where the covering of cells that make up its wall is called the trophoblast, and inside there is a bilaminar embryonic disc (hypoblast and epiblast) between two cavities: amniotic cavity primary or primitive and the exocoelomic cavity. Upon implantation, the trophoblast forms two layers: syncytiotrophoblast (the outermost) and cytotrophoblast (the innermost). Inside the latter, the amnion begins to form from the epiblast and the extra-embryonic endoderm from the hypoblast, which line the amniotic and exocoelomic cavities (this becomes the primary yolk sac). As development progresses, the cells from the extraembryonic endoderm separate, placing themselves between it and the trophoblast to form the extraembryonic mesoderm. At the end of the second week, the extraembryonic mesoderm is divided into two layers: somatic extra-embryonic mesoderm (adjacent to the trophoblast cells) and splanchnic extra-embryonic mesoderm (adjacent to the amniotic membrane and the yolk sac wall), and the cavity is formed between them chorionic when leaving a wide space. There is the embryonic disc, the amniotic cavity, the yolk sac, and the fixation pedicle inside the chorionic cavity. From this moment it is said that the chorion is formed [6].

3.2. Amnion

The innermost fetal membrane is responsible for the formation of a fluid-filled amniotic sac that surrounds the embryo. It is avascular and lacks nerves and lymphatic vessels. It comes from the fetal ectoderm of the embryonic disc (and not from the trophoblast as previously believed). This is an important consideration from a functional point of view since the gene expression of HLA class I is more closely related to that of embryonic cells than to that of trophoblasts.

As gestation progresses, the amnion grows, progressively obliterating the chorionic cavity and constituting the epithelial lining of the umbilical cord. Histologically, it is made up of a layer of amniogenic cells, precursors of the amniotic epithelium, and another of cells like fibroblasts. Between them occurs the deposit of interstitial collagen (mainly type I and III) which is the source of most of the tensile strength of the fetal membranes. The epithelial cells of the amnion are filled with highly developed microvilli, which is compatible with a major transfer site between amniotic fluid and amnion [3,7].

This membrane should be considered as a metabolically active site since it is involved in the transport of solutes and water to maintain the homeostasis of the amniotic fluid, and in the production of a wide variety of bioactive compounds such as cytokines, growth factors, prostaglandins and vasoactive peptides. The synthesis capacity of these last compounds (endothelin 1-vasoconstrictor, a protein related to parathyroid hormone, BNP, CRH) with vascular or muscular activity suggests that the amnion could be involved in the modulation of the tone of the chorionic vessels and blood flow. Finally, it is worth highlighting the current study of a family of molecular water channels, aquaporins, which seem to be involved in water homeostasis during fetal development [7].

3.3. Amniotic fluid

Amniotic fluid is essential for development as it protects, maintains the temperature, encourages the development of the lungs, and allows symmetrical growth and free movement of the fetus. At the beginning of gestation, it is produced by the amniotic membrane and maternal tissues. During the first half of gestation, the fetus is responsible for most of the amniotic fluid from tissue fluid that is released through its skin. In the second half of gestation, there is a large contribution to amniotic fluid from fetal urine. The amount increases slowly, so that at 10 weeks there are approximately 30 ml, at 20 weeks it is around 350 ml and at 38 weeks it is between 500 and 1000 ml. Is mainly composed of water (99%), inorganic salts, organic salts, proteins of maternal and fetal origin, carbohydrates, fats, enzymes, hormones and desquamation of fetal epithelial cells, the pH is generally 7.4. During the second half of gestation, there will be fetal urine and during labour, meconium (intestinal contents of the fetus) may also be found.

Features

- Protects the fetus from external trauma.
- Allows symmetrical growth preventing compression of the fetus.
- Allows normal development of the lungs.
• Prevents adherence to the amnion of the embryo/fetus.
• Helps maintain fetal temperature.
• Allows the free movement of the fetus, which helps its muscle development.
• Participates in the regulation of homeostasis of fluids and electrolytes.
• Acts as a hydrostatic wedge over the lower segment of the uterus, helping to dilate the cervix during labour [6].

4. Pathophysiology
Classically, the etiology of intraamniotic infection is polymicrobial.

The most frequently identified germs are from the family of mycoplasmas and anaerobes.

• Genital mycoplasmas: Ureaplasma urealyticum, Mycoplasma hominis. They have been linked to preterm delivery.
• Gram-positive aerobes: Streptococcus agalactiae, Enterococcus faecalis, Gardnerella vaginalis, Streptococcus viridans, Listeria monocytogenes.
• Gram-negative aerobes: Escherichia coli, Proteus mirabilis
• Anaerobes: Bacteroides fragilis, Fusobacterium, Peptoestreptococcus, Propionobacterium.

Despite being frequently isolated, they are rarely associated with fetal infections and are not usually associated with maternal infections except in cases of caesarean section. Regardless of the role of different germs in the etiology of preterm birth, the germs most frequently isolated from maternal and neonatal cultures are Streptococcus agalactiae and Gram-negative germs, especially Escherichia coli [7].

4.1. Routes of entry of intraamniotic infection
Four main routes of entry for microorganisms in intraamniotic infection are described:

• Ascending route from the vagina and cervix (it is the most frequent route).
• Hematogenous route spreading through the placenta (e.g., listeriosis).
• The iatrogenic route is secondary to invasive procedures. Ortiz U and cols [8]
• Retrograde route from the peritoneal cavity through the fallopian tubes (as in the case of peritonitis). Proposed by Couto Núñez [2].

5. Fetal inflammatory response syndrome
Within the pathophysiological process of this entity, the inflammatory response produces the release of maternal and fetal cytokines that induce the migration of leukocytes and the release of prostaglandins from the myometrium and fetal membranes. This release of prostaglandins leads to the initiation of uterine contractions and rupture of membranes.

Zaga-Clavellina V et al [9] said that the increase in cytokine release as a result of infection of the amniotic fluid has been recognized for some time, in particular high levels of IL1, IL6, TNF alpha, IL8, colony-stimulating factor, platelet-activating factor, among others, which have been evidenced during intrauterine infections. The elevation of IL1 and TNF alpha in amniotic fluid before the third trimester has been considered responsible for preterm labour due to its effect on the induction of prostaglandin production. Elevation of IL1 in amniotic fluid has been reported to be the best predictor of vascular extension of chorioamnionitis, and high levels of TNF alpha are a predictor of neonatal sepsis. It has also been determined that intrauterine infection involves the T cell system. Cord samples from infected neonates reveal more CD3 + cells that produce interferon gamma. The inflammatory response also involves the presence of phagocytes, which are activated by lipopolysaccharides, especially those bound to proteins present in amniotic fluid. Neutrophils and monocytes have certain peculiarities responsible for the failure of normal expression of surface glycoproteins, especially L-selectin and CR3, leading to abnormal adherence and activation of neutrophil surface antigens. Interactions between cytokines and phagocytes can be verified by the production of free radicals and other products of phagocyte activation, which can be involved in tissue damage of various organs.

Another important consequence of intra-amniotic infection and the inflammatory response is the induction of metalloproteinases, enzymes that destroy the extracellular matrix. These belong to a family of zinc-dependent enzymes capable of degrading components of the extracellular matrix. They have been related to the remodeling of it under pathological conditions. Some, such as MMP-7 and MMP-9, have been identified in the uterus, amnion, and chorion, along with their inhibitors. Elevated concentrations of MMP-7 (produced by macrophages in response to lipopolysaccharides and cytokines) and MMP-9 have been observed during the microbial invasion of the amniotic cavity.
in preterm gestations. MMP-8, also known as collagenase II, has been found in amniotic fluid during the microbial invasion and is considered a potent predictor of intra-amniotic infection and preterm delivery. It is also an indicator of neonatal condition since its high levels have been associated with poor perinatal outcomes [9].

6. Risk factor's

Hurtado Sánchez FM et al [10], found many risk factors like:

- Preterm delivery
- Prolonged rupture of membranes
- Age
- Numerous vaginal examinations (more than six)
- Prolonged labour
- Nulliparity
- Internal monitoring (fetal electrodes on scalp)
- Urogenital infections (particularly cervical or vaginal, including sexually transmitted diseases)
- Chronic maternal diseases, malnutrition, and alterations of the immune system.
- Low socio-economic situation
- First son
- History of bacterial infection (e.g., group B streptococci [GBS], bacterial vaginosis)
- Premature rupture of membranes (the bursa breaks before going into active labour)
- Prolonged labour

7. Predisposing factors

- Deficiency of the antimicrobial activity of the amniotic fluid. It appears at the beginning of the second trimester and increases progressively until the end of the pregnancy. The antimicrobial factor is a peptide bound to zinc. Therefore, low levels of zinc in the diet predispose to infection.
- Increase in vaginal pH: Acidic vaginal pH inhibits the growth of many microorganisms.
- Absence of cervical mucus. This has an antimicrobial action.
- Intercourse especially near term. The seminal fluid would help the penetration of the germs due to its proteolytic action on the cervical mucus and the spermatozoa would help the transport of the bacteria towards the uterine cavity. The bactericidal power of the seminal fluid would in some cases be insufficient to counteract the facilitating actions of the infection mentioned above.
- Polyhydramnios
- Cervical incompetence
- Premature rupture of membranes
- Other factors like Anemia, immunosuppression, low socio-economic status, etc., according to Ferrer Montoya R [1]

8. Acute chorioamnionitis clinical picture

According to Baffoe P [11], Machado J [12] and Faneite P [13], sudden appearance of high fever over 38ºC, during gestation, especially with PROM, during labour, in those tedious deliveries with more than 6 hours of ruptured bags or the immediate puerperium, before 48 hours (this limit defines the beginning of puerperal sepsis and the end of Acute Chorioamnionitis (ACA).

- Armpit temperature greater than 37.8ºC in two feedings separated by one hour
- Fetal tachycardia with a heart rate greater than 160 beats per minute
- Maternal tachycardia greater than 100 beats per minute
- Tenderness on uterine palpation
- Increased uterine contractility.
- Purulent amniotic fluid with a bad smell. All these symptoms can occur with ruptured and intact membranes, both in term and preterm gestations.
- It is considered that if a patient has a fever or more than one of these clinical criteria, a diagnosis of clinical chorioamnionitis can already be made.
9. Asymptomatic chorioamnionitis clinical picture

9.1. Bacterial
It is based exclusively on the study of amniotic fluid in the absence of clinical signs and is characterized by the following biochemical criteria:

- Amniotic fluid glucose <5 mg/dl and/or
- Gram with visualization of germs and/or
- Leukocytosis in amniotic fluid (> 50 cells/mm3) [14].

9.2. Histological
García-de la Torre [15] is defined from a histological point of view as the infiltration of the chorion and/or amnion by polymorphonuclear cells of maternal origin. Diagnosis based on histological criteria requires neutrophil infiltration of at least 50% of the membranes in the sample section studied.

Histological chorioamnionitis cases are classified into two groups: (1) the inflammatory response is confined exclusively to the placenta (maternal response) and (2) the inflammation affects the membranes, the fetal vessels and/or the umbilical vessels (maternal and fetal response). Aseptic and asymptomatic.

10. Clinical diagnosis

For the diagnosis of clinical chorioamnionitis Gibbs RS [16] in 1991, proposed the following criteria:

- Fever: Axillary temperature equal to or greater than 38ºC, accompanied by two or more of the following signs:
  - Abnormal uterine sensitivity.
  - Amniotic fluid, a purulent or bad odor.
  - Maternal tachycardia is greater than 100 beats per minute.
  - Fetal tachycardia is greater than 160 beats per minute.
  - Leukocytosis > 15,000 / mm3.
  - Increased uterine contractility.
  - Pelvic pain in movement.

11. Diagnostic means

11.1. Laboratory
According to Espitia-De La Hoz [17] and Torrez Morales F [18], laboratory tests can help in the diagnosis of chorioamnionitis, we can use following:

- C Reactive Protein: Increased. It is the most widely used diagnostic medium. It usually increase 2 or 3 days before clinical symptoms, is the product of the acute phase hepatic reaction to infection, in response to the synthesis of IL-6 synthesized during infection.
- Leukogram: Leukocytosis and elevated sedimentation rate. In a normal pregnancy, the white blood cell count can be 10,000-15,000. Maternal leukocytosis > 15,000, perform it every 3 days.
- Erythrosedimentation: it rises in pregnancy due to the increase in Fibrinogen and Globulin
- Positive Hemoculture: it also has the disadvantage of a long time to obtain results, being of little clinical use, in addition to being a diagnosis of bacteremia as a possible late complication [10].
- Procalcitonin > 0.5 ng/ml in maternal serum.

11.2. Amniotic fluid

- Amniocentesis: Gram: the finding of bacteria is more important than that of leukocytes.
- Glucose concentration <5 mg/dL.
- Presence of leukocytes in amniotic fluid (> 50/ mm3) [14].
- Lactic dehydrogenase (LD) levels in the amniotic fluid have been elevated in the presence of chorioamnionitis and current concepts indicate it as a highly specific and early predictor of intra-amniotic infection. The predictive value of chorioamnionitis is 410 u/L in amniotic fluid.
• Leukocyte esterase: it is a product of polymorphonuclear. Leukocytes whose activity increases in the presence of amniotic infection. Its positivity in amniotic fluid has a sensitivity of 91%, a specificity of 84%, and a positive predictive value of 95% and a negative predictive value of 74%.

• Interleukin 6 cytokines in amniotic fluid, predicting chorioamnionitis with 100% sensitivity and 83% specificity. Some authors have concluded that interleukin 6 is the best marker of intraamniotic infection when IL-6 levels in the amniotic fluid are greater than 2.6 ng / mL [17].

• Metalloproteinase-8 and 9 (MMP-8 and MMP-9): is an enzyme of the collagenase family exclusively synthesized by neutrophils that are expressed in the amniotic fluid of women with preterm delivery, premature rupture of membranes and intra-amniotic infection. With a sensitivity of 95%, specificity of 78%, positive and negative predictive values of 52 and 98% respectively, it has been considered a marker of intra-amniotic infection [19].

• Proteomic study: the amniotic fluid allows detecting the presence of characteristic protein markers of intrauterine inflammation against microbial exposure. Proteins called neutrophil defensins-1 and 2 and calgranulins A, B and C. have been identified as protein biomarkers in the inflammatory phase of amniotic fluid. They have an S of 92.9% and E 91.8%.

• For fetal maturity studies: However, if the infection is frankly established, it is of no use [20,21,22].

• Procalcitonin: study between days 2 and 8 of rupture of membranes greater than 0.5 ng/ml, it is considered suggestive of infection [18].

11.3. Imaging

It is also important according to Williams [7] and Espitia-De Lá Hoz [14].

Biophysical profile: it has been reported that a score less than or equal to 7, which was performed in the 24 hours before the termination of pregnancy, is a good predictor of neonatal sepsis, and the more variables are compromised, the higher correlation with fetal infection is usually altered. Assess:

- Absence of respiratory movements
- Absence of fetal movements
- Absence of tone 11.4.

11.4. Other exams

• Electronic Fetal Monitoring: studies the behavior of the Fetal Heart Rate concerning fetal movements and uterine dynamics. A non-reactive pattern may appear with fetal tachycardia> 160 bpm and irritating uterine dynamics that does not respond to tocolytics before 20 minutes after delivery.

• Culture or Placenta Smear: to reach the postpartum diagnosis of amniotic infection is the identification of polymorphonuclear cells (basophils, neutrophils, eosinophils) in the placenta studies of the umbilical cord section. It is also particularly important according to Martínez-Navarro J [23].

• Culture and Cytology of External Auditory Chanel of Newborn

• Gastric Aspirate Cytology

12. Management

The management is still a controversial matter, depend of the gestational age but also depend of the clinical picture. Hadavand S [24], Ballarta L [25] and Castrillo AL [26]. In the event of clinical chorioamnionitis, pregnancy will be terminated regardless of gestational age under antibiotic coverage with:

- Piperacillin-Tazobactam 4g / 6 EV + Clarithromycin 500 mg / 12h vo.

- In the case of allergies to penicillin or beta-lactams: the treatment of choice will be the combination of TTeicoplanin 600 mg / 12 hrs. + Aztreonam 1g / 8hrs + Clarithromycin 500 mg / 12 hrs.

- After delivery (regardless of whether it is via vaginal or cesarean section), an extra dose of Piperacillin-Tazobactam 4g IV and Clarithromycin 500 mg PO will be administered and later both antibiotics will be suspended.

In those cases, the type and duration of antibiotics will be individualized based on the results of the cultures and in collaboration with the infectious and microbiology services.

The route of delivery will depend on the fetal statics and the evolution of the delivery in the case of the option of vaginal delivery since the diagnosis of chorioamnionitis is not per se an indication for urgent cesarean section [4].

Considering gestational age, obstetric management is indicated although this point continues to be controversial.
In term pregnancies (more than 37 weeks): induce labour within the first 6 hours after making the diagnosis. Try to perform as few vaginal examinations as possible. In all situations and if the obstetric situation allows it, it will be ensured that the termination of pregnancy is vaginal, to minimize the risk of abdominal infection.

Between 34 and 36.6 weeks: proceed as if at term, since the risk of neonatal morbidity and mortality due to lung immaturity, after 34 weeks of gestation, is extremely low.

From 30 to 33.6 weeks: stimulate fetal lung maturity: 12 mg intramuscular Betamethasone every 24 hours for two occasions, until completing 48 hours of the first dose or 24 hours of the second, start antibiotic therapy immediately after the diagnosis is made. Discontinuation can be done immediately if the presence of a mature lung is confirmed.

Pregnancy could be managed expectantly, under antibiotic treatment and strict maternal and fetal supervision since clinical management requires a high degree of individualization since there is not enough information to manage these patients in a “standard” way.

In pregnancies of 25 weeks and less than 30 weeks: each day that passes increases survival and reduces neonatal morbidity by 1-5%, so that the gain in one or two days is much more significant; being relevant is the gains of more days. In the prognosis, the volume of the amniotic fluid plays an important role, severe oligohydramnios results in fetal pulmonary hypoplasia or severe musculoskeletal defects.

In pregnancies less than 24 weeks: if the diagnosis is made before 24 weeks, immediate delivery is the most efficient plan in terms of the morbidity-mortality and cost-benefit ratio. Once delivery has occurred, maintain antibiotic therapy for at least 7 days during the puerperium [27].

13. Complications

At the fetal level, it is associated with:

- Neonatal sepsis
- Pneumonia
- Intraventricular hemorrhage of the cerebral white matter with possible sequelae
- Short and long-term like cerebral palsy
- Perinatal death (25% vs 6%, in premature vs at term)
- Neonatal sepsis (28% vs 6%)
- Pneumonia (20% vs 3%)
- Grades 3 or 4 intraventricular hemorrhages (24% vs 8%)
- Respiratory distress (62% vs 35%)
- Neurodevelopmental disorders [10]

At the maternal level, it is associated with:

- Preterm delivery
- Caesarean section
- Uterine atony or postpartum hemorrhage
- Infection
- Pelvic abscess
- Thromboembolism
- Endometritis [10]

14. Conclusion

Chorioamnionitis continues to be a frequent and dangerous pathology during pregnancy. When it presents with all its clinical symptoms, it is easily diagnosed and treated, but in subacute or subclinical cases it is often overlooked and continues to influence maternal and fetal morbidity. Whenever it is suspected, it should be investigated early to make a certain diagnosis and be able to act more effectively.
Compliance with ethical standards

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Disclosure of conflict of interest
The authors declare that they have no conflict of interest.

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