

MESTRADO INTEGRADO EM MEDICINA

Amniotic fluid sludge and risk of preterm labor: what's in the pipeline?

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Revisão Bibliográfica

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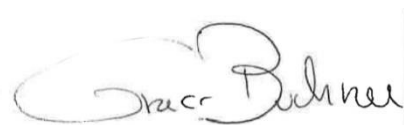
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Resumo

O termo *Sludge* do Líquido Amniótico tem atraído cada vez mais a atenção da comunidade obstétrica, devido à sua associação com parto pré-termo, uma das principais causas de morbidade e mortalidade neonatais. Tal achado pode ser detetado através de ecografia transvaginal e descrito como agregados hiperecogênicos adjacentes ao orifício interno do colo do útero em gestantes. No que toca à sua composição, esta ainda permanece controversa mas há fortes evidências que esteja associado a processos inflamatórios e/ou infecciosos intra-amnióticos.

Este artigo de revisão bibliográfica aborda as principais evidências descritas na literatura acerca da origem e desenvolvimento do *sludge*, bem como os métodos de diagnóstico mais utilizados e os tratamentos disponíveis, que se baseiam na utilização de antibióticos, havendo diferentes eficácias consoante a classe dos mesmos, juntamente com outras medidas como progesterona ou cerclagem cervical em circunstâncias específicas.

Dada a heterogeneidade de estudos acerca deste tema, esta revisão bibliográfica destaca a importância de abordagem diagnóstica e terapêutica, abordando o doente de forma holística de modo a reduzir o risco de parto pré-termo e garantir o melhor prognóstico possível quer para o recém-nascido como para a gestante.

Objetivos: Com esta revisão bibliográfica pretende-se apresentar uma visão sistemática e abrangente dos avanços científicos mais recentes sobre o *sludge* do líquido amniótico e a sua associação com o risco de parto pré-termo.

Metodologia: A revisão bibliográfica foi realizada com o recurso às plataformas Pubmed, ScienceDirect e UpToDate, com os seguintes filtros de pesquisa: linguagem (inglês e português) e data de publicação do artigo (últimos 15 anos). Os artigos filtrados, foram posteriormente selecionados consoante o seu resumo e pertinência para a presente dissertação.

PALAVRAS-CHAVE:

Líquido amniótico; sludge; parto pré-termo

Abstract

The term amniotic fluid sludge has attracted increasing attention from the obstetric community due to its association with preterm labor, one of the main causes of neonatal morbidity and mortality. This finding can be detected by transvaginal ultrasound and described as hyperechogenic aggregates adjacent to the internal orifice of the cervix in pregnant women. Its composition remains controversial, but there is strong evidence that it is associated with intraamniotic inflammatory and/or infectious processes.

This literature review article discusses the main evidence described in the literature about the origin and development of sludge, as well as the most commonly used diagnostic methods and available treatments, which are based on the use of antibiotics, with different efficacies depending on their class, along with other measures such as progesterone or cervical cerclage in specific circumstances. Given the heterogeneity of studies on this subject, this literature review highlights the importance of the diagnostic and therapeutic approach, treating the patient holistically in order to reduce the risk of preterm birth and ensure the best possible prognosis for both the newborn and the pregnant woman.

Objectives: In this review article, we aim to provide a systematic and comprehensive overview of the latest scientific advancements regarding amniotic fluid sludge and its association with the risk of preterm labor.

Methodology: The literature review was conducted using the PubMed, ScienceDirect and UptoDate platforms, with the following search filters: language (English and Portuguese) and article publication date (last 15 years). The resulting set of articles from this process were then filtered based on the abstract.

Keywords:

amniotic fluid; sludge; preterm birth

List of Abbreviations

PTB - Preterm birth

WHO - World Health Organization

RDS - Respiratory distress syndrome

NICU - Neonatal Intensive Care Unit

AFS - Amniotic fluid sludge

IL – Interleukins

TNF- α - Tumor necrosis factor-alpha

MIAC - Microbial invasion of the amniotic cavity

PPROM - Preterm prelabor rupture of membranes

PCR - Polymerase Chain Reaction

BPD - Bronchopulmonary dysplasia

DNA - Deoxyribonucleic acid

MMP-8 - Matrix Metalloproteinase-8

RNA - Ribonucleic acid

CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats

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1. Introduction

Prematurity continues to represent a major challenge within obstetric care, being the leading cause of neonatal mortality and morbidity, accounting for approximately 75% of cases. It is also implicated in the majority of cases involving adverse long-term outcomes, such as cerebral palsy and delayed neurological development. Since 1961, the World Health Organization (WHO) has defined Preterm birth (PTB) as delivery occurring before 37 completed weeks (or 259 days) of gestation, regardless of fetal weight.⁽¹⁾ Among preterm newborns, the incidence of severe neonatal complications—such as respiratory distress syndrome (RDS) and necrotizing enterocolitis, which frequently require admission to the Neonatal Intensive Care Unit (NICU), is ten times higher than in those delivered after 37 weeks of gestation. The primary cause of pre-term labor remains idiopathic, accounting for approximately 50% of cases. Among the known causes, maternal infections, cervical insufficiency, and short cervix are the most significant.

Cervical insufficiency is defined as an inability of the uterus cervix to stay closed during gestation. Although the precise pathophysiologic mechanisms behind it are not fully understood, it is believed to be linked to a structural defect in the cervical-isthmic junction, which may be exacerbated by inflammation-induced cervical shortening. This weakening of the cervical sphincter leads to painless cervical dilation, often resulting in late miscarriage or spontaneous preterm birth. Notably, cervical length measurements below 20–25 mm have been strongly associated with an increased risk of preterm labor.⁽²⁾

Similar to cervical shortening, which is a well-established risk factor for preterm birth, the presence of amniotic fluid sludge (AFS) has been proposed as another potential predictor of preterm labor. AFS refers to “the presence of dense aggregates of particulate matter near the internal cervical os”⁽³⁾ typically observed during transvaginal ultrasonography. Although the precise composition is still debated, it has been linked to elements such as blood clots, meconium, caseous vernix, or microbial biofilm within the amniotic cavity.⁽³⁾ The most widely accepted theory suggests that when observed in the first half of pregnancy, AFS is associated with an inflammatory process, whereas in the second half, it represents a maturational process attributed to the presence of vernix caseosa and/or meconium.⁽⁴⁾ It is present in 4% of ultrasounds performed between the first and second trimesters. Transvaginal ultrasound offers higher diagnostic accuracy during this period, as the increased presence of meconium and

caseous vernix in the third trimester may lead to false-positive findings and create diagnostic confusion for the clinician. ⁽⁵⁾

AFS is thought to indicate intra-amniotic infection and the most common microorganisms isolated are *Ureoplasma urealyticum*, *Fusobacterium sp.* and *Mycoplasma hominis*. ⁽⁴⁾ The subsequent development of inflammation that leads to the accumulation of cytokines, such as interleukins IL-1, IL-6, tumor necrosis factor-alpha (TNF- α), chemokines and metalloproteinases in the membranes, the umbilical cord and the placenta are thought to contribute to the stimulation of contractions, cervical ripening and rupture of membranes. The impact of antibiotics on the pregnancy course of women presenting AFS has been a topic of research in the last few years. ⁽⁶⁻⁸⁾

AFS has emerged as an independent risk factor for imminent preterm labor, the presence of histological chorioamnionitis, and microbial invasion of the amniotic cavity (MIAC), especially in patients with spontaneous PTB without ruptured membranes, and independent risk factor for preterm prelabor rupture of membranes (PPROM). ⁽⁹⁾ Several other indices have been suggested as adjunct biomarkers that might contribute in forecasting PTB, including the width of the uterocervical angle, the evaluation of cervical consistency (using elastography), and the assessment of fetal fibronectin which may be useful in multivariate predictive models that target spontaneous PTB. ⁽¹⁰⁾

A deeper understanding of these factors could help refine risk assessment and improve management strategies for pregnancies at risk of preterm delivery, ultimately enhancing neonatal outcomes. Given the importance of this subject, this bibliographic review looks at the relationship between AFS and the risk of PTB, focusing on its underlying mechanisms, diagnostic methods, pertinent biomarkers, and potential therapeutic interventions. It will also go over possible methods for treating and preventing PTB, as well as recent advancements in AFS research.

To conduct this literature review, a bibliographic search was performed using the PubMed/Medline, ScienceDirect, and UpToDate databases, employing the keywords "**amniotic fluid**," "**sludge**," and "**preterm birth**" in combination and 31 references published within the last 15 years were selected. This dissertation includes: 11 references to observational studies (cohort and case-control), 6 clinical case series, 5 clinical trials or interventional studies involving antibiotics or cerclage, 3 systematic reviews or meta-analyses, 4 narrative reviews and 1 article presenting a clinical or conceptual hypothesis.

2. Amniotic fluid and its function

Amniotic fluid envelops the embryo and fetus throughout their development, serving an essential function by creating a protective environment that aids in their growth and maturation. It physically protects the fetus in instances of maternal abdominal injuries. Moreover, it cushions the umbilical cord, preventing it from being compressed against the uterine wall.

This fluid also acts as a barrier against infectious agents due to its natural antibacterial qualities. In addition, it provides a supply of nutrients and fluids for the fetus, containing a mixture of proteins, electrolytes, immunoglobulins, and vitamins sourced from the mother. Its composition and volume evolve throughout pregnancy, mirroring fetal development and the interactions between mother and fetus.

It offers the essential environment of space, hydration, and growth factors necessary for the proper development of fetal organs, such as the musculoskeletal, gastrointestinal, and respiratory systems. The equilibrium between the creation and absorption of fluid, fetal swallowing, and fluid exchange through membranes sustains an optimal intrauterine environment. ⁽¹¹⁾

Changes in amniotic fluid characteristics, for example, AFS reflect underlying conditions, such as intra-amniotic inflammation and infection. The existence of these factors usually implies an elevated risk of preterm labor. An observation of such changes is a necessary stage in identifying the threatened conditions of a pregnancy and selecting medical interventions suited to it.

3. Pathophysiology of Amniotic Fluid Sludge

3.1. Composition and Formation Mechanisms of AFS

AFS is defined as a freely floating, hyperechogenic, dense, and homogeneous material within the amniotic cavity, located near the internal os. The best imaging method for diagnosis is transvaginal ultrasound, which allows for a detailed evaluation of the lower uterine segment and cervix.

AFS can be found in approximately 4% of pregnancies during transvaginal ultrasound in the first and second trimesters, and its prevalence increases as pregnancy progresses, reaching 88% by 35 weeks. During the second trimester, the presence of particulate matter has been linked to inflammation or infection within the amniotic fluid, bleeding, and desquamated material, as noted in conditions such as the acrania-anencephaly sequence or congenital ichthyosis. In fact, AFS has been studied as an ultrasound marker of infection/inflammation in the amniotic cavity during preterm pregnancy. ⁽¹⁻³⁾

The ultrasound differential diagnosis of AFS incorporates intra-amniotic hematoma and subchorionic hemorrhage, which are also associated with an increased likelihood of preterm labor and intra-amniotic bleeding. Earlier research indicated that dense particles found within the amniotic fluid might also be related to meconium and vernix caseosa, particularly in the final trimester. ⁽¹²⁾

3.2. Role of Inflammation and Infection in AFS Development

There is some evidence in the literature suggesting that AFS may be linked to intra-amniotic infections caused by certain bacteria or fungi, including *Fusobacterium sp.*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Candida albicans*, and *Streptococcus mutans*. These infectious agents have been found in women experiencing conditions such as cervical insufficiency, premature birth with membranes still intact, rupture of membranes before term, chorioamnionitis, spontaneous labor at term with undamaged membranes, and idiopathic vaginal bleeding.

However, in 2018, Yoneda *et al.* carried out a retrospective study—the first to use a Polymerase Chain Reaction (PCR)-based method to identify bacteria inside the amniotic cavity in pregnant women with AFS. Their results highlighted that AFS is associated with inflammation inside the amniotic cavity rather than intra-amniotic infection, indicating the possibility of sterile inflammation. ⁽²⁾

3.3. Impact of AFS on Pregnancy Outcomes

The association between intra-amniotic inflammation/infection and the onset of PTB, along with its subsequent impact on neonatal health, is largely mediated by elevated levels of pro-inflammatory cytokines. These include tumor necrosis factor-alpha (TNF- α) and various interleukins (ILs), including IL-1, IL-2, IL-3, IL-4, IL-6, IL-7, IL-8, and IL-10. These cytokines facilitate the release of various enzymes and uterotonins - such as prostaglandins and matrix metalloproteinases – that contribute to the beginning of uterine contractions, compromise the integrity of fetal membranes, and lead to their premature rupture. ^(13,14)

These findings highlight the importance of developing point-of-care rapid tests to recognize inflammatory processes, alongside molecular testing to detect the existence of bacteria, including specific genus and type. Such approaches could complement traditional methods, such as assessing amniotic fluid white blood cell count and glucose concentration, for detecting intra-amniotic inflammation.

Several studies comparing the frequency of positive amniotic cultures and histological chorioamnionitis in patients with and without AFS have demonstrated a higher prevalence in the AFS group. Additionally, neonates born to mothers with AFS have shown increased rates of admission to the NICU, along with a higher incidence of RDS and bronchopulmonary dysplasia (BPD).

3.4. Relationship Between AFS and Cervical Insufficiency

Acute cervical insufficiency is generally defined as the inability of the uterine cervix to retain a pregnancy in the absence of contractions. Clinically, it is characterized by cervical dilation, which, in severe cases, may progress to membrane bulging through the cervical opening and subsequent membrane rupture. The primary treatment for this condition is the placement of a cerclage. Without intervention, cervical insufficiency can result in spontaneous abortion in the mid-trimester or the early onset of preterm labor.

This condition is considered as multifactorial and may be caused by several factors, including:

1. In utero exposure to estrogens (for instance, due to diethylstilbestrol exposure)
2. Loss of cervical tissue from surgical procedures (such as loop electrosurgical excision procedure or conization)

3. Decreased progesterone activity
4. Intra-amniotic infection ^(15,16)

AFS and intra-amniotic infection/inflammation are both associated with cervical insufficiency. This condition is typically defined as a cervical length of < 25 mm before 24 weeks in women with a history of pregnancy loss or preterm birth between 14 and 36 weeks, or as cervical changes detected on physical examination before 24 weeks of gestation. Intra-amniotic infection may serve as a primary cause of cervical insufficiency by activating mechanisms responsible for cervical ripening. However, it can also act as a secondary cause when microorganisms from the lower genital tract area penetrate intact membranes, resulting in an infection within the amniotic cavity. ⁽¹⁷⁾

4. Diagnostic Methods and Biomarkers

The accurate identification of AFS is crucial for guiding clinical management and predicting the risk of adverse pregnancy outcomes. Currently, available diagnostic methods range from conventional ultrasound to emerging biomarker-based approaches.

4.1. Ultrasound Identification of AFS

The ultrasound evaluation is the main modality for detecting AFS through non-invasive means. Transvaginal ultrasound is widely used to detect echogenic material in the amniotic fluid, which are usually found near the internal cervical os, that can correspond to vernix, meconium, blood, and inflammatory material associated with intraamniotic infection or inflammation, as well as desquamated skin cells related to congenital ichthyosis. However, a question that often emerges is whether the ultrasound features of these particles can shed light on the nature of the material reflected in sonographic image. ⁽¹⁸⁾

4.2 Amniotic Fluid Analysis: Biomarkers and Microbiological Testing

Amniocentesis provides critical diagnostic information through transvaginal needle amniotomy with aspiration of sonographic particulate matter under direct visualization. The macroscopic appearance of AFS has been described as pus-like material.

These samples allow for the assessment of white blood cell count, glucose concentration, and Gram staining, aiding in the distinction between sterile and infectious AFS. Elevated white blood cell counts and low glucose levels suggest a possible infection. In addition to Gram staining for microorganism identification, PCR testing can detect bacterial DNA, offering a more sensitive and rapid method for diagnosing microbial infections. ^(2,18)

Advanced microbiological tools, such as scanning electron microscopy, enable the detection of bacterial communities embedded in amorphous material and inflammatory cells – structures commonly known as biofilms. ⁽¹⁸⁾ Recognizing that bacteria can form biofilms within the amniotic cavity is crucial for both diagnosis and treatment.

From a diagnostic perspective, biofilms are difficult to detect using conventional culture methods, leading to an underestimation of intra-amniotic infection prevalence. In terms of treatment, biofilms protect bacteria from host immune responses and antibiotics, posing a challenge in determining optimal therapeutic strategies. ^(19,20) Additionally, the presence of multiple microorganisms—most notably *Ureaplasma* species and *Mycoplasma hominis*—has implications for selecting appropriate antimicrobial agents.

Biofilms also pose a risk for fetal systemic inflammatory response, as fetal breathing or swallowing can disrupt the biofilm structure, releasing planktonic bacteria into the amniotic fluid.⁽²¹⁾

4.3 Point-of-Care Testing for Inflammatory Markers

Enzyme immunoassays can accurately measure levels of IL-6 and Matrix Metalloproteinase-8 (MMP-8), which serve as reliable biomarkers for gauging the intensity of the intraamniotic inflammatory response. Elevated concentration levels are strongly correlated with intra-amniotic inflammation and an increased risk of preterm labor, supporting clinical decision-making, regarding early intervention in threatened pregnancies.^(13,14)

4.4 Emerging Diagnostic Tools

In addition to the detection of intra-amniotic inflammation, the identification of bacteria taxa is crucial for customizing antibiotic treatment. Fast advancements in molecular microbiologic techniques and point-of-care tests make possible the identification of the 16S RNA gene in under an hour. Novel molecular diagnostics such as CRISPR-based techniques, e.g., SHERLOCK, promises to transform pathogen detection, enabling swift identification of bacterial species and facilitating targeted antimicrobial therapy, surpassing the traditional Gram staining in sensitivity and speed.⁽²²⁾

5. Therapeutic Approaches and Management Strategies

5.1. Antibiotic Therapy: Efficacy and Limitations

Considering the PTB risk as well as maternal and neonatal outcomes in patients with AFS, it is important to understand how AFS and infection/inflammation should be treated. According to the studies currently available, its treatment consists of oral antibiotics. The major difficulty is to know which class of antibiotics has a better outcome, and related to this, there are some studies that show some incongruity in the outcomes of the oral or intravenous antibiotics. In numerous studies, Azithromycin and Moxifloxacin were the most frequently used; however, findings showed that employing specific antibiotics did not treat or enhance the negative obstetric and neonatal outcomes that followed.⁽¹³⁾ Moreover, there are still many conflicting studies regarding the benefit of using or not using antibiotic therapy.

According to Cuff *et al.*'s study, antibiotic treatment, specifically Azithromycin and Moxifloxacin, was not correlated with a decrease in premature birth when comparing women who received treatment to those who did not.⁽¹³⁾ Additionally, the research indicates there were no variations in the rates of premature membrane rupture. In terms of the resolution of amniotic fluid "sludge", this condition was primarily observed in the group not receiving treatment (43%), suggesting that antibiotic therapy did not affect the persistence of "sludge". Furthermore, the average gestational age at the time of delivery was also unaffected by the antibiotic intervention.

However, later, Wan Wu Jin *et al.* conducted a retrospective study in 2021. The antibiotics utilized for treatment included Ceftriaxone, Clarithromycin, and Metronidazole. As a result, they noted a decreased incidence of preterm birth and neonatal complications.⁽²³⁾

Regarding Azithromycin, the findings reviewed in 2023 by Giles *et al.* did not endorse its use in women who have a short cervix, including in those with identifiable AFS.⁽²⁴⁾ To evaluate whether the use of Azithromycin in cases of a shortened cervix leads to extended pregnancy and better neonatal outcomes, a retrospective cohort study was conducted across three advanced maternity facilities in Melbourne, Australia, revealing no significant variations in premature rupture of membranes, chorioamnionitis, or neonatal health issues.

Hatanaka *et al.* carried out an observational study, evaluating the following antibiotic therapy regimen:

1. Women at low risk: Clindamycin 300 mg OA every 6 h + Cephalexin 500 mg OA every 6 h for a duration of 7 days;

2. Women at high risk: Clindamycin 600 mg IV every 8 h + Cefazolin 1 g IV every 8 h for 5 days + 5 days oral treatment.

They presented the advantages of antibiotics in lowering the rates of preterm delivery among women at high risk and those with AFS. In addition, the research highlighted the influence of antibiotic treatment on the birth weight of newborns. The discrepancy in birth weight was significant between the study groups, with the group receiving antibiotics showing higher weights.
(25)

In 2020, Pustotina *et al.* conducted a prospective study aiming to assess the association between oral and intravenous antibiotic therapies alongside vaginal antibiotics in expectant mothers between 15 and 24 weeks of gestation who had AFS detected via transvaginal ultrasound. Those with a cervical length of less than 25mm also received vaginal progesterone and indomethacin. Following the first and second weeks of treatment, all participants underwent a follow-up ultrasound to check for the resolution of the AFS and to re-evaluate the length of the cervix. The research confirmed the positive outcomes of antibiotic treatment, with all the patients experiencing the elimination of AFS. Additionally, it revealed a histological relationship between sludge and both chorioamnionitis and funisitis, proposing that the presence of AFS may indicate intra-amniotic infection. (26,27)

It can be concluded that there are substantial contradictions in the literature regarding the use of antibiotics, though azithromycin appears to not yield any benefit in treatment. Cephalosporins and clindamycin treatment, however, seems to create positive results. The most promising observed outcome was an association of oral and vaginal antibiotics, precisely cephalosporins and clindamycin, along with the administration of probiotics to all pregnant women, not only for strengthening the vaginal microbiome but as an important factor against ascending infections that might cause AFS. Additionally, vaginal progesterone and indomethacin, a tocolytic agent, were prescribed to patients with a short cervix, which led to the disappearance of the sludge.
(26) However, this calls for further research in these areas to have clear conclusions.

5.2. Preventive Strategies and Cervical Cerclage Considerations

The association between AFS and cervical insufficiency is crucial in reducing the unnecessary use of cervical cerclage in patients who have a short cervix. This technique seeks to close the cervix using suture with the intent of extending the duration of the pregnancy and enhance the chances of a positive fetal result. Identifying AFS at an early stage enables clinicians to more accurately evaluate the underlying causes of preterm labor and inflammation, potentially circumventing interventions that may not be clinically indicated, because emergency cerclage placement can pose risks, especially in the presence of an underlying infection of the amniotic fluid, being not advised in those cases due to the high likelihood of maternal sepsis and related complications (including death), along with adverse effects on the newborn's health. In many instances, addressing AFS through alternative therapeutic approaches, such as infection management or anti-inflammatory treatments, may improve maternal and fetal outcomes without resorting to cerclage. Timely diagnosis and individualized treatment strategies are therefore essential in optimizing patient care and minimizing the need for unnecessary surgical procedures.

(28-30)

6. Recent Advances and Future Perspectives

Recently, a research study investigated the association between AFS and the amniotic fluid proteome in women diagnosed with acute cervical insufficiency. The aim was to detect possible infections in the most sensitive way and avoid the contraindicated performance of cervical cerclage. Findings suggest that AFS may represent an indolent intrauterine infection, or an infection caused by organisms capable of forming biofilms, which attenuate the innate inflammatory response. This could explain why microorganisms are sometimes undetectable in AFS cases and why antibiotic treatment is often challenging. Patterns of protein expression in AFS cases demonstrated a predominance of functions related to keratinization, epidermis development, and wound healing, indicating a latent inflammatory response.⁽³¹⁾

In terms of clinical management, it is crucial to perform amniocentesis to rule out infection and inflammation by assessing white blood cell count, glucose concentration, Gram staining, IL-6 levels, PCR, or even amniotic fluid proteome analysis. However, amniocentesis carries inherent risks, including pregnancy loss, preterm birth, and iatrogenic infection. Future research should focus on improving diagnostic methods, particularly emphasizing non-invasive biomarkers and advanced imaging techniques to enable early detection of AFS without the need for invasive procedures.

Regarding treatment, there is still no consensus on the optimal approach. The heterogeneous nature of AFS—where some cases are associated with infection while others are not—complicates the establishment of clear treatment guidelines. Future research should focus on developing standardized protocols to determine when to initiate treatment, which therapies to use, and how to monitor AFS progression throughout pregnancy.

7. Conclusion

The presence of AFS during pregnancy indicates that there has been a microbial entry into the amniotic space and is often linked to infections within the amniotic fluid, emerging as a significant predisposal condition to preterm labor. AFS has increasingly been studied due to the critical need for early identification and proper clinical management to prevent both negative maternal and neonatal outcomes.

Through vaginal ultrasound and biomarker analysis, our ability to detect AFS has improved. However, there is a long way to go through investigation in order to turn the diagnosis faster and to be able to differentiate between sterile and infected cases, crucial in the treatment approach of these patients. Also, upcoming studies ought to focus on how AFS influences women without symptoms, as well as populations that are susceptible to early delivery. Research should be conducted to identify the subsets of patients who are most likely to benefit from the ultrasound detection of AFS and, as a result, from its management.

Furthermore, there is still much space for advancement when it comes to the treatment of AFS. For adoption in clinical practice, future research should try to find which antibiotics will reduce the rates of preterm delivery, define a proposed regimen, and how long the treatment should be used.

In conclusion, although appreciable progress has been made in terms of understanding AFS and its effects, further research is necessary to have standardized clinical protocols and quality care for patients. Identifying novel therapeutic targets and embracing personalized treatment strategies may play a role in improving the management as well as the prevention of preterm labor concerning those patients affected by AFS.

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