Listeriosis in pregnancy

An umbrella review of maternal exposure, treatment and neonatal complications

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Listeriosis in pregnancy: An Umbrella Review of Maternal Exposure, Treatment, and Neonatal Complications

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Running title:

Listeriosis in pregnancy: An Umbrella Review.

ABSTRACT

Background:

Listeria monocytogenes is a commonly found organism in processed and prepared food and the disease of listeriosis is associated with a high morbidity and mortality. Compared to the general population, the risk of being diagnosed with listeriosis increased during pregnancy. Listeriosis can lead to miscarriage, spontaneous preterm labour and preterm birth, stillbirth, and congenital neonatal infections.

Objectives:

We conducted a universal review of listeriosis in pregnancy and in the newborn.

Search Strategy:

The EMBASE, PubMed, Cinahl, and Web of Science databases were searched for Systematic Reviews (SRs) indexed before 1st December 2020.

Selection criteria:

Any SR evaluating the prevalence, treatment, diagnosis, and effects of listeriosis during pregnancy and up to 4-weeks postnatally were included.

Data collection and analysis:

Eligibility assessment, data extraction, and quality assessment by the Methodological Quality Assessment of Systematic Reviews (AMSTAR-2) were performed in duplicate.

Main Results:

We identified 397 citations of which nine Systematic Reviews comprising 330 studies and 487 patients' reviews were included. Most SRs (7 of 9) were of moderate to high quality. Prevention in pregnant women was based on adherence to strict dietary recommendations, such as reheating leftovers until steamed and avoiding unpasteurized dairy products. Listeriosis infections were likely to occur in the third trimester (66%) rather than in the first trimester (3%) of pregnancy. Symptoms are mostly fever and other flu-like, such as fatigue. Diagnosis was primarily made by culture of the pathogen. Intravenous amoxicillin or ampicillin were first line treatment.

Conclusions:

Listeriosis, a rare but serious infectious disease in pregnancy, can cause devastating consequences for the fetus and new-borns. Appropriate preventative treatment should be initiated during early pregnancy to avoid complications.

Funding:

This research received no external funding.

Keywords: Diagnosis, Listeriosis, Neonate, New-born, Pregnancy, Prevention, Treatment.

Tweetable abstract: Listeria is commonly found in processed and prepared food. Prevention is the best way to avoid listeriosis during pregnancy.

INTRODUCTION

Pregnant women appear to be 10 to 20 times more likely to be diagnosed with listeriosis compared with the general population, possibly due to a down-regulation of cellular immunity [1-4]. The intracellular Gram-positive bacterium *Listeria monocytogenes* is the causative agent of listeriosis, a serious food-borne infection [5, 6]. *Listeria monocytogenes* is a small, anaerobic, Gram positive, flagellated, non-spore forming, linear motile rod that can affect pregnant women and neonates [7]. It can also be transmitted vertically to the fetus [8-10]. Exposure to and transient colonization of the gastrointestinal tract by listeria is common, but invasive disease is rare [11]. During pregnancy, the typical clinical presentation of listeriosis is with mild flu-like symptoms [8-12]. The bacterium is capable of crossing three host barriers: i) the intestinal mucosa; ii) the placenta and iii) the blood-brain barrier [13]. Neonatal infection can occur because of maternal chorioamnionitis, which is the cause of early-onset sepsis, or by passage through a listeria-colonized birth canal from the gastrointestinal tract resulting in late-onset meningitis [14]. The incidence of neonatal listeriosis is 8 in 100,000 live births with a fatality rate of 20% [7, 15, 16]. The consequences can be sepsis or meningitis, permanent neurological deficits, or death [7].

Listeriosis in pregnancy presents with complications such as spontaneous abortion, spontaneous preterm labour (SPTL) leading to preterm birth (PTB) and stillbirth [17]. *L.*

monocytogenes infection in neonates is a serious concern and can cause neurobehavioral abnormalities, and respiratory distress [7, 15, 18].

To control listeriosis, it is necessary to have precise information about the magnitude of the disease, the preventative measures, the diagnostic process, and treatment. The current clinical guidelines on the management of listeriosis in pregnancy are based on systematic reviews (SR) published more than seven years ago [12, 19]. Our hypothesis is that the epidemiology of listeriosis in pregnancy varies geographically, but the diagnostic and treatment procedures, although they seem consensual, are not evidence based. The objective of this Umbrella Review (UR) was to collect current evidence-based knowledge with respect to the prevalence, diagnosis, and effects or complications of listeriosis during pregnancy.

MATERIAL AND METHODS

This UR was prospectively registered with PROSPERO CRD 42020222318. The population studied was pregnant women or neonates. Outcomes were prevention, diagnosis, treatment, and complications of listeriosis in pregnancy and in the neonate.

Search and selection of reviews

From the databases used (EMBASE, PubMed, Cinahl, and Web of Science) we selected SRs or meta-analyses (MAs) indexed before December 1, 2020 (Appendix S1). The following queries and search terms were used: ((listeria OR listeriosis) AND (mothers OR newborn*) AND transmission AND review) OR (listeriosis AND pregnancy AND literature review) OR ((listeria OR listeriosis) AND (pregnant* OR newborn OR neonate* OR birth OR fetal) AND (vertical transmission OR disease transmission) AND (systematic review OR meta-analysis)) OR ((Maternal Listeriosis OR neonatal listeriosis) AND (systematic review OR meta-analysis OR review)). SRs related to prevention, prevalence, diagnosis or treatment and effects of listeriosis during pregnancy and in the newborn, including those that carried out a search in at least one international database, and were focused on pregnancy and neonatal outcomes were included.

Data extraction and review quality assessment

Data extraction was performed independently by two reviewers (AMA & IFK). Disagreements were discussed and resolved by consensus or arbitration with a third reviewer (CAP). The quality of the SR was assessed by two independent reviewers, using the tool A Measurement Tool to Assess Systematic Reviews (AMSTAR-2)[20]. AMSTAR-2 is usually used to evaluate critically the quality of SRs. This consists of 16 questions with detailed assessment of SRs that included randomized and non-randomized studies.

Data synthesis

A tabulation and narrative description of the included reviews was made addressing the epidemiology of listeriosis in pregnancy, prevention measures, diagnosis, treatment, and complications in pregnancy and in the neonatal stage.

RESULTS

Our UR search yielded 397 citations indexed before 1st December 2020. Fifty-eight duplicates were excluded. After reading the titles and abstracts, 283 references were excluded, and 56 full-text studies remained. Of these, 47 were excluded due to lack of relevant results, unavailability of the full text, or because they were animal studies. Finally, nine reviews comprising (330 studies, 487 patients) were selected for data extraction (Figure 1). Table S1 provides a summary of the main characteristics of the selected reviews.

Review quality

Table 1 shows the quality of the SRs and MAs using AMSTAR-2. Of nine articles, only six of the SRs did not explain their selection of study designs for inclusion. Seven of the studies did not use appropriate methods for statistical combination of results [7, 8, 11, 15, 18, 21, 22].

Epidemiology of listeriosis and listeriosis in pregnancy

In the USA, listeriosis has a prevalence of 3-4 cases per million of the population, and

in Europe this is between 0.1 and 11.3 per million. It is 13 to 20 times more common during pregnancy [5-7]. Between 2008 and 2015 the number of cases of listeriosis in Europe increased, such that in 2015, 28 European countries reported 2206 cases and 270 deaths. The prevalence of listeriosis was 8.8% in Austria, 17.7% in France, 6.5% in Germany, 11% in Italy, and 16.9% in the U.K. In the USA, 116 cases were reported, 111 cases were hospitalized, and 15 died [8]. Some reviews have found that in ethnic minorities such as Hispanic women and women of African origin in France have a higher incidence of listeriosis in pregnancy [7, 8]. A study that focused on neighbourhood deprivation found that listeriosis was higher in the most deprived areas of England, when compared to less deprived districts. Those who were affected were more likely to purchase food from local bakeries and butchers and the author's hypothesis was that these small businesses may not have had the same level of food safety as the larger retail outlets[5].

Prevention of Listeriosis

Measures like education on food preparation, hygiene, and the avoidance of high-risk foods are mandatory during pregnancy and effective in preventing listeriosis. For prevention, it is crucial to educate pregnant women and raise their awareness as it is important to avoid certain types of foods such as soft cheeses, hot-dogs, and refrigerated smoked seafood. The potential sources of contamination are caused by ready-to-eat meals such as hot-dogs (unless reheated to an internal temperature of 74ºC or steaming hot), unpasteurised milk, dairy products, soft cheese such as feta, brie, camembert [15], refrigerated smoked seafood or Mexican style cheese, unless made with pasteurized milk. Unwashed raw fruits and vegetable-skins should be washed thoroughly prior to eating, even if peeled or cut. Listeria can grow and multiply when the refrigerator is between 4-10ºC [5, 7, 15].

Diagnosis of listeriosis in pregnancy

To diagnose maternal listeriosis, cultures from blood, placenta, cerebrospinal fluid (CSF), stool, vagina, or amniotic fluid by amniocentesis for targeted cell cultures with subsequent Gram staining, enzyme immunoassay (EIA), enzyme-linked immunosorbent assays (ELISA), and/or polymerase chain reaction test (PCR) are recommended. The standard diagnostic procedure is placental cultures [7]. Even though an ELISA assay can detect listeriolysin-O (LL-O) antibodies, it cannot be used to exclude completely a prior

infection [8] , but it could represent a useful screening tool for monitoring of suspected or exposed patients. With a presentation of flu-like or gastrointestinal symptoms in an afebrile pregnant woman, a presumption of exposure to listeria should be considered and blood cultures performed. If a symptomatic patient presents with a fever >38.1ºC, blood culture should be performed for confirmation [12, 15, 19, 23]. To diagnose neonatal listeriosis, blood and CSF cultures should be performed. Alternatively, ear and umbilical swabs, DNA hybridization and/or monoclonal antibodies should be performed [5, 11].

Listeriosis treatment in pregnancy

Internationally, recommended treatment regimens differ substantially. If the pregnant woman is asymptomatic or has consumed a product that was been recalled or implicated after discovering listeriosis, the results of our UR suggest that no medical treatment is necessary but monitoring for symptoms should be continued for up to 2 - months. However, if the woman is symptomatic, the first-choice antibiotics are intravenous (IV) ampicillin or amoxicillin. As an alternative in women with penicillin allergy, a combination of IV trimethoprim and sulfamethoxazole is recommended [5, 10, 12, 14].

In Ireland, the USA and Canada, counselling of pregnant women with respect to symptomatology is recommended. Conversely, in Australia, as a precaution, starting antibiotic therapy with oral amoxicillin or ampicillin 2-3 g/day for 7-days beyond the first trimester of pregnancy was recommended. Pregnant women who consumed products that have been recalled, and who are afebrile with minor gastrointestinal or flu-like symptoms, should be treated in the same way as asymptomatic pregnant women. In Ireland and the USA, in case of severe infection, where the pregnant woman is febrile, the same approach is recommended, with simultaneous testing with blood cultures and commencement of antibiotic therapy (unspecified) and placental cultures post-delivery. If blood culture is negative, continuation of antibiotic therapy versus discontinuation is a consideration [5, 7, 8, 10, 12, 14, 24].

In Australia, antibiotic therapy with IV amoxicillin or IV ampicillin 4-6 g/day for 14 days is recommended. In Canada, high doses of IV ampicillin 6-12 g/day or amoxicillin orally 100mg/kg/day is given for 14 days or until delivery [1, 8]. This can be administered alone or in combination with gentamicin. If the patient is allergic to betalactams and is given trimethoprim in the first trimester as an alternative, it is recommended that

additional folic acid should be provided [1]. In France, IV amoxicillin is given for 2-weeks or until delivery in combination with IV gentamicin for 3-5 days [5, 24].

In general, in our UR, IV ampicillin or IV amoxicillin were first line treatments [1, 7, 8, 11, 15, 21, 23]. In Iran, herbal medicines that contain bioactive phytochemicals such as antioxidants monoterpenes, sesquiterpene, coumarin, flavonoids, tannins, saponins, alkaloids, and terpenoids are used as a treatment for listeriosis [24]. Despite promising results, the therapeutic mechanisms of these phytochemicals remain unknown.

Some experts suggest discontinuation of antibiotic therapy unless the blood culture demonstrates listeriosis. Others suggest antibiotic treatment, even when the culture results are still pending [8].

Listeriosis treatment in neonates

The most common complications of listeriosis in neonates are generalized sepsis and meningitis. Neonatal listeriosis can be divided into two forms: early-onset and late-onset disease. Early-onset disease takes place within the first week after delivery and late-onset occurs after 2 - weeks or more. Early-onset is usually caused by intrauterine infection and is associated with PTB [12]. Late-onset probably occurs during the passage through the birth canal and vertical, or nosocomial transmission [15]. In cases with early onset, the recommended treatment is IV ampicillin or IV amoxicillin 100-300 mg/kg/day in 4-6 doses with IV gentamicin or IV penicillin G (benzylpenicillin) for 2-weeks with IV gentamicin. In the case of late-onset, treatment with IV ampicillin or amoxicillin 100-300 mg/kg/day in 4-6 doses of IV penicillin G for 3 - weeks with IV gentamicin is recommended [5].

DISCUSSION

This UR of other SRs and MAs has considered the epidemiology, prevention, treatment, diagnosis of listeriosis and complications for the mother and the neonate within 4-weeks postnatally. Listeriosis is 16-20 times more common during pregnancy than in the non-pregnant population [8]. According to calculations done using disability-adjusted life years (DALY), the incidence of listeriosis has increased during pregnancy worldwide by 14.7% since 2010 [18]. The Center for Disease Control and Prevention (CDC) estimated a decline of about 42% in the USA but an increase in Europe between 2008 and 2012[15]. For correct diagnosis and confirmation of listeriosis in the mother, ~~positive~~

blood cultures from the placenta, maternal blood and PCR after antibiotic treatment should be performed.

Maternal listeriosis infection treatment with IV ampicillin, for 14 days, or IV amoxicillin with IV gentamicin, for 2-5 days, provides the best outcome for the mother [5-9]. In cases of allergic reaction to penicillin, the alternative is IV trimethoprim with IV sulfamethoxazole, for 14 days or until delivery [5, 6, 9]. To treat neonatal infection, IV ampicillin or IV amoxicillin with IV gentamicin, for at least 14 days, gives the best outcome [8-10].

Listeriosis maternal complications include miscarriage, spontaneous preterm birth and stillbirth whereas neonatal complications are sepsis, meningitis with the risk of neurobehavioral problems or even death [7, 8, 11, 15, 18, 23].

Strengths of the umbrella review

To our knowledge, this is the first UR of listeriosis in pregnant women and neonates in relation to its epidemiology, prevention, diagnosis, treatment, and complication. We have conducted the UR based on PRISMA and AMSTAR-2 guidelines selecting the SRs indexed before 1st December 2020. We have also included one meta-analysis, which makes the results more precise. The selected reviews were of moderate to high quality. Another strength of this UR is the rigorous electronic search strategy. Through this review, we were able to highlight the importance of prevention in reducing both maternofetal and neonatal mortality and morbidity.

Limitations

Three of nine SRs included, exhibited bias with respect to food consumption, socioeconomic status and dietary habit related to demography and six of the SRs did not demonstrate bias. In general, the heterogeneity of the methodology included in the SRs and their subsequent results were poorly reported. Such heterogeneity could have been due to the differing validity of reported diagnoses and outcomes, such as miscarriage, which may have led to under- or over-estimation in the reported statistics. The included reviews did not provide a full list of exclusion criteria and failed to justify why they excluded papers from the original searches. Finally, there was a shortage of well-conducted SRs, which is why we decided to include reviews which had at least one search in an international database.

Proposal for future approach

Food safety and education are key to minimizing the future risks of listeriosis in pregnancy [1, 7, 8, 11, 15, 23]. Screening pregnant women, who are exposed or who are symptomatic, for the presence of anti-LLO bodies may help prevention or detection in pregnancy and minimize the risk of complications. When there is a suspicion of listeriosis in an asymptomatic pregnant woman, commencement of antibiotic therapy could be preventive. If a pregnant woman presents with mild symptoms, blood culture, fetal surveillance and antibiotic therapy provide better control of the disease. When a pregnant woman has severe infection and presents with symptoms that confirm listeriosis, blood culture should be performed, and IV antibiotic therapy initiated. Future diagnostics might include ear and umbilical swabs, DNA hybridization and serological testing for anti-listeriolysin antibodies, as is already used in certain hospitals [5, 8, 11].

The epidemiological data yield different results and can affect the reported outcome and prevention of listeriosis. There are several gaps in our knowledge, which should be considered and would benefit from future research. It would be more precise to include cases that are not detected or registered in low, medium, or high-income countries. Only four countries have provided clinical guidelines for the prevention and treatment of listeriosis (Ireland, USA, Canada, and Australia), the most recent being from 2017 [8].

CONCLUSIONS

Available data about listeriosis during pregnancy and the neonate are of moderate to high quality. *L. monocytogenes* is an unusual pathogen due to the intracellular nature of its cycle, which may explain the ready ease of transplacental passage. Listeriosis in pregnancy is 13 to 20 times more common in pregnant women compared to the general population. This UR on listeriosis in pregnancy emphasizes the importance of its prevention during pregnancy. Furthermore, it underlines the importance of educating pregnant women, particularly vulnerable subgroups to raise their awareness. The UR demonstrates that the most likely reason for listeriosis during pregnancy is a lack of knowledge and information. Too little information and knowledge is available about which food to avoid, and caution with respect to preparation and consumption of certain products like hot-dogs, unpasteurized milk, soft cheeses, and refrigerated smoked

seafood and fruits and vegetables. Care should be taken to prevent cross contamination of foods.

Pregnant women with co-morbidities are at increased risk due to compromised cell-mediated immunity. Maternal illness is usually mild compared to fetal illness that can be devastating. Fetal and neonatal mortality are potentially preventable with early diagnosis and intervention. Maternal and neonatal treatments are a combination of IV antibiotics with a variable one-two week's duration.

Author Contributions:

CAP, KSK and JSJ made substantial contributions to conception and design. IBH applied the screening algorithm in the searching and revised the manuscript. AMA and IFK carried out the work, they were reviewers in the SR, extracted data information and drafted the first version of the manuscript. CAP was a third reviewer. CAP, KSK, JSJ and RFL, revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

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Informed Consent Statement:

Patient consent was waived because the Umbrella Review relies on retrieval and synthesis of data from existing Systematic Reviews and Meta-analysis.

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Conflicts of Interest:

The authors have no conflict of interest to declare.

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Table 1: AMSTAR-2 checklist items

Author, Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Craig et al, 2019[7]	Yes	PY	No	Yes	Yes	No	No	Yes	PY	Yes	No	No	Yes	Yes	No	Yes
Wadhwa et al, 2017[23]	Yes	No	No	No	No	No	No	PY	No	No	No	No	No	No	No	Yes
Pucci et al, 2017[8]	Yes	No	No	No	No	No	No	Yes	No	No	No	Yes	No	Yes	No	Yes
Madjunkov et al, 2017[1]	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
De Luca et al, 2015[15]	Yes	PY	No	Yes	No	No	No	PY	No	No	No	No	No	Yes	No	Yes
Noordhout et al, 2015[18]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No	No
Feng et al, 2013[21]	Yes	Yes	No	Yes	No	Yes	No	Yes	PY	Yes	No	No	Yes	Yes	No	No
Lamont et al, 2011[11]	Yes	No	No	Yes	No	No	No	PY	No	Yes	No	No	No	Yes	No	No
Mylonakys et al, 2002[22]	No	PY	No	PY	No	No	No	Yes	No	No	No	No	No	Yes	No	No

PY: Partial Yes; 1. Did the research questions and inclusion criteria for the review include the components of PICO?; 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?; 3. Did the review authors explain their selection of the study designs for inclusion in the review?; 4. Did the review authors use a comprehensive literature search strategy?; 5. Did the review authors perform study selection in duplicate?; 6. Did the review authors perform data extraction in duplicate?; 7. Did the review authors provide a list of excluded studies and justify the exclusions?; 8. Did the review authors describe the included studies in adequate detail?; 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?; 10. Did the review authors report on the sources of funding for the studies included in the review?; 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?; 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?; 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?; 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? 15. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?; 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Figure 1: Flow chart