

A Review on Strongyloidiasis in Pregnant Women

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Abstract: Strongyloidiasis is a parasitic infection distributed worldwide, with an estimated 614 million people infected. Strongyloidiasis usually presents asymptotically or with aspecific and mild clinical symptoms, mainly cutaneous, respiratory, or gastrointestinal. Disseminated disease and hyperinfection syndrome are the most serious complications, have a high mortality rate, usually occur in immunosuppressed patients, and are particularly associated with the use of corticosteroids. Strongyloidiasis is the most neglected of the neglected diseases, and its occurrence in pregnancy has been neglected and understudied. In this review, we focus on the effects of strongyloidiasis during pregnancy and highlight the knowledge shortage and the need for more research on the subject. There are few studies addressing strongyloidiasis prevalence during pregnancy and hyperinfection incidence during pregnancy is practically unknown, with only isolated case reports published. Although data are scarce, the infection has been associated with developmental disabilities and anemia during pregnancy, while hyperinfection may cause both maternal and neonatal death. Data on the best screening and diagnostic strategies during pregnancy are lacking. There is insufficient evidence on ivermectin safety in pregnancy, complicating treatment recommendations.

Keywords: strongyloides, pregnancy, hyperinfection, anemia, stillbirth

Background

Strongyloides stercoralis is an intestinal helminth that causes a parasitic infection in humans called strongyloidiasis. This nematode has a worldwide distribution, but it is more frequent in tropical and subtropical areas. However, it may also be present in mild countries with favorable conditions.¹ Within these regions, exposure to infection is strongly associated with poor sanitary and living conditions, and thus certain vulnerable populations (such as refugees or occupationally soil-exposed groups) are at especially high risk of strongyloidiasis. Strongyloidiasis is thus primarily determined by the socioeconomic status of communities, rather than geographic or climatic conditions, and should no longer be referred to as a “tropical” disease, but rather a disease of disadvantage.²

It is estimated that at least 613.9 (95% CI 313.1–910.1) million people are infected worldwide.^{3,4} A recent systematic review estimated a pooled seroprevalence of 12.2% (95% CI 9%–15.9%) in migrants from endemic areas residing in nonendemic areas,⁵ while a similar study in Spain yielded a *Strongyloides* seroprevalence of 14% among migrants from endemic areas.⁶

Strongyloidiasis usually presents asymptotically or with aspecific and mild clinical symptoms related to skin penetration (rash, urticaria, larva currens), migration through the body (cough, sore throat, pulmonary infiltrates), and presence of the adult helminth in the intestine (abdominal pain, diarrhea, nausea, or vomiting, among others).¹ Disseminated disease and hyperinfection syndrome are the most serious

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complications of the infection, and they mostly occur in immunosuppressed patients and are particularly associated with the use of corticosteroids.⁷ However, many other conditions causing immunosuppression (such as leukemia or transplant, immunosuppressive agents, hypogammaglobulinemia, malnutrition) have also been associated with a severe form of the disease, with a reported mortality up to 62% in the case of disseminated disease.⁸ Other less immunosuppressant states, such as alcoholism and liver cirrhosis, have also been associated with disseminated disease.⁹ Severe cases have also been reported in pregnant women, another condition with altered immunostatus.¹⁰ There are many knowns and unknowns (Table 1) regarding *S. stercoralis* infection during pregnancy.

Diagnosis of strongyloidiasis has improved thanks to enhanced microscopy-based direct techniques, such as agar-plate culture or the Baermann method, but their

sensitivity remains low due to the intermittent larval excretion and a low parasitic burden.⁷ Due to its accuracy, simplicity, and reproducibility, serology is today the most widespread technique used.⁷ However, serological tests may be less specific in endemic regions, due to cross reactivity with other helminthic diseases, although increasing the serology cutoff may overcome this issue.¹¹ Sensitivity and specificity in pregnant women is unclear.

In terms of treatment, ivermectin is currently the drug of choice.¹² The optimal dosage schedule for ivermectin has recently been demonstrated to be one dose for uncomplicated chronic strongyloidiasis.¹³ A recent systematic review and meta-analysis has however raised concern about the scarcity of safety data on ivermectin in pregnant women.¹⁴

During pregnancy, a certain immunosuppression has been postulated, although it remains unclear how this affects clinical aspects and evolution of the infection and how *S. stercoralis* affects the immune system of the mother and the fetus.

In this review, we focus on the effects of strongyloidiasis during pregnancy and highlight the knowledge shortage and the need for more research on the subject.

Table 1 Summary of knowns and unknowns regarding *Strongyloides stercoralis* infection during pregnancy

	What is known	What is unknown
Prevalence	Few studies exist. Seems to mirror that of the general population. Higher in rural areas.	Very little data to draw firm and solid conclusions.
Diagnostic methods	Most frequent is single stool evaluation with a concentration method.	Sensitivity and specificity of serology, which is the optimal diagnostic technique. Need for combination techniques.
Effect on the mother	Cases of severe strongyloidiasis have been described.	Risk of the pregnancy per se as a trigger of hyperinfection is unknown.
Effect on the fetus	Developmental issues have been described, as well as low birth weight.	Causality has not been established, only association.
Treatment	Ivermectin is the treatment of choice outside pregnancy and should be offered to pregnant women with severe presentations.	There is not much safety data on the use of ivermectin during pregnancy. Benefit:risk ratio for treating nonsevere cases in pregnant women not at risk of immunosuppression needed.

Prevalence of Infection in Pregnant Women

There have been few studies to address the prevalence of *Strongyloides* spp. infection in pregnant women. In one study conducted in rural Peru, the estimated prevalence ranged from 10% with stool-based techniques to 33% with serological methods.¹⁵ In other studies from Venezuela and Kenya, prevalence was 0–9.2%, but only stool-based diagnostic methods were used.^{16,17} A recent systematic review found a mean prevalence of 12.3%, with a median of 6% and higher prevalence in rural areas.¹⁸ Regional variation, pregnancy trimester, and diagnostic methods used may explain most of this variability. Also, the Venezuelan study excluded malnourished pregnant women. Most studies use spot feces sampling and direct microscopy evaluation after a concentration method has been performed. However, when *Strongyloides* charcoal culture is performed, the prevalence seems to be higher.^{15,19} In an Australian study, there were implementation issues leading to only 60 of 86 women being screened by serology, and seroprevalence of 3.3% was reported.²⁰

Diagnosis of Strongyloidiasis in Pregnant Women

Serology has been proposed as a possibly useful tool for the screening of strongyloidiasis in pregnancy, but there are some caveats. Diagnostic accuracy in immunosuppressed

patients is not clear and seems to be lower.²¹ In this subgroup, a combination of techniques has been recommended.²²

In pregnant women who have little immunosuppression, serology accuracy has not been well studied. To the best of our knowledge, there has been only one study to evaluate the sensitivity and specificity of serology in pregnant women. Ortiz-Martínez et al evaluated the prevalence of *Strongyloides* infection among pregnant women using different techniques.¹⁵ They found serology to have sensitivity of 61.3% and specificity of 69.6%, clearly below the general population,⁷ raising concern as to its applicability in pregnant women. However, the choice of gold standard is questionable, and the optical density cutoff chosen for serology positivity was not reported. Also, the study did not provide data to estimate sensitivity in the general population, which prevents drawing conclusions on the accuracy of serology in pregnant women. In addition, serology is the gold standard for detecting many other parasitic infections (eg, Chagas diseases or toxoplasmosis, among others) without concerns about potentially decreased sensitivity of the techniques.^{23,24}

Information on the accuracy of *Strongyloides* diagnostic tools in pregnancy is very scarce. A well-designed comparative study of different strongyloidiasis diagnostic techniques in pregnant women is much needed.

Immunopathophysiology of *Strongyloides* Infection and Pregnancy

Chronic strongyloidiasis has been associated with T_H2 immunoresponse. $CD4^+$ T cells can differentiate mainly into two different T-helper cell types: T_H1 and T_H2 . T_H1 cells activate a cytotoxic response through cytokines (IFN γ , TNF α , IL12). T_H2 cells activate the humoral immunoresponse system and the secretion of IL4 and IL5. IL4 ultimately stimulates IgE production, and IL5 signals eosinophils. Therefore, *Strongyloides* infection is capable of downregulating host immunity, protecting them from being eliminated and also minimizing severe pathology in the host. However, the immunological mechanisms manifesting in severe forms of the infection in immunosuppressed patients, particularly those on steroids, are poorly understood.²⁵ During pregnancy, the classical view is that the T_H1 response is downregulated, whereas the T_H2 response predominates, as it occurs in chronic infection. However, several studies have challenged this view as overly simplistic, and immunology of pregnancy is viewed more as a result of a complex interplay of

signals between the maternal immune system and the fetal-placental immune system.²⁶ In general, the T-helper response is diminished during pregnancy, as well as other elements of the adaptive immunoresponse. On the other hand, there is evidence on the exacerbation of the innate immunoresponse of natural killer cells, monocytes, and plasmacytoid dendritic cells.^{27,28} Immunological changes are dynamic over time during pregnancy, with three different phases. During the first trimester, the implantation and placentation resemble an “open wound” and there is a need for a strong inflammatory response.²⁹ The blastocyst must break through several structures in order to implant, so an inflammatory environment is required to secure adequate repair of the uterine epithelium and the removal of cellular debris. Therefore, the first trimester is a proinflammatory phase. In the second trimester of pregnancy, an anti-inflammatory state is more predominant, and during the third trimester, a new inflammatory process is needed to induce labor. This chronological evolution of immunology during pregnancy was captured recently in a model defining the immunological clockwork of the immune system during pregnancy.³⁰ Therefore, as there are different periods, it could be expected that the larval burden may vary throughout the pregnancy, as well as symptoms, risk of hyperinfection, and the possibility of detecting larvae in feces.

S. stercoralis is a helminth that is canonically controlled by a T_H2 immunological response. Nevertheless, eradication of migrating L_3 larvae is mediated predominantly not only by eosinophils but also by neutrophils.³¹ Efficient expulsion of the helminth from the intestine is mediated by basophils and mast cells. This is an innate response triggered by IL33 and dependent on ILC2, IL9, and mast cells.³² Patients infected with *Strongyloides* spp. show little intestinal inflammation, suggesting that *Strongyloides* does not activate the IL33 pathway in humans intensely. However, there is a marked reduction in the number of dividing macrophages and replicating enterocytes compared with controls.³³

Obstetric Complications

Pregnant women are especially susceptible to certain parasitic infections, such as malaria. Being pregnant is a risk factor of severe malaria, and associations with maternal anemia, stillbirth, and low birth weight (LBW) are well established.³⁴ Evidence from other helminth infections suggest that they are also associated with obstetric complications like stillbirth, abortion, intrauterine growth

retardation, and LBW.³⁵ The underlying mechanisms of these associations is unclear, as so far treatment of helminths during pregnancy has not shown benefits in terms of fetal outcomes.³⁶ Therefore, it is possible that the associations found are more a reflection of underlying social conditions than a direct effect of helminths. Nevertheless, data on the specific effects of strongyloidiasis are even more scarce. There have been case reports of stillbirth due to *Strongyloides* hyperinfection in pregnant women.¹⁰ However, beyond those cases reported, the impact of *Strongyloides* on stillbirth is unclear. Other studies have found that strongyloidiasis increases the odds of LBW. A study from Tanzania found an association of strongyloidiasis with 5.97 (95% CI 1.23–28.98) times the adjusted relative odds of LBW.³⁷ Another study from Thailand found an OR of 2.59 (95% CI 1.09–6.16), and³⁸ a study from Ghana found an OR of 2.1 (95% CI 0.97–4.49, $p=0.05$) for LBW, small for gestational age, or preterm delivery.³⁹ However, all these were cross-sectional studies, and despite adjusting for confounders, causality could not be demonstrated. Evidence from other helminth infections suggests this possible association as well, pointing out that the most important factor to correct is the mother's anemia.⁴⁰ However, of five studies that searched for an association between *Strongyloides* and maternal anemia, only one found helminth infections to be a predictor of maternal anemia, but helminths were considered as a whole and no differential effect of *Strongyloides* could be found.¹⁸

Developmental Complications

Some reports have addressed the long-term impact on height and weight of *Strongyloides* infection in children,^{18,41} showing decreased, although not always statistically significant, weight for height or weight for age Z-scores. However, from these reports it can be interpreted that malnutrition is a driving force behind the findings, but it cannot be concluded whether *Strongyloides* drives malnutrition or malnutrition facilitates *Strongyloides* infestation.

One study found that helminth infection during pregnancy was associated with poor cognitive and gross motor functions at 12 months of age, even after adjusting for gravidity, maternal education, family possession, child sex, and HOME score.⁴² In this study, *Strongyloides* was found among the intestinal helminths assessed, but was not the only one.

Risk of Disseminated Disease

Few case reports have been found in the medical literature on *Strongyloides* hyperinfection in pregnancy.^{10,43–45} In two of the cases reported, both the mother and the fetus died. In the other two, both recovered successfully. Three cases were migrants from endemic areas living in high-income countries. However, there is no hard evidence on the increased risk of severe strongyloidiasis during pregnancy, as there have not been prospective studies on maternal and fetal outcomes of infected pregnant women. Nonetheless, pregnant women may well be affected by severe strongyloidiasis through two mechanisms: pregnancy-induced immunosuppression and chronic nutritional deficiencies. It could well be that severe hyperinfection cases in pregnancy are occurring inadvertently in poor rural areas, where maternal deaths are not systematically studied. Moreover, drugs used during pregnancy like corticosteroids for preterm labour could potentially trigger a severe outcome.^{10,44} Therefore, it is advisable to proceed with caution when prescribing steroids in populations with high endemicity of strongyloidiasis or migrants from these areas. A recent study suggested that presumptive treatment is cost-effective in migrants from endemic areas at risk of being immunosuppressed.⁴⁶ In our opinion, in pregnant women coming from endemic areas, current uncertainty about ivermectin safety in pregnancy precludes the use of widespread presumptive treatment. However, what would be desirable is to screen childbearing-age women for strongyloidiasis and treat them before pregnancy.

Treatment of Strongyloidiasis During Pregnancy

The drug of choice for the treatment of strongyloidiasis is ivermectin.¹² The optimal dosage schedule of ivermectin has recently been demonstrated to be one dose for uncomplicated chronic strongyloidiasis.¹³

A recent systematic review and meta-analysis has raised concern about the scarcity of safety data for ivermectin in pregnant women,¹⁴ highlighting an important knowledge gap in this subgroup of patients. The few data available and analyzed did not point toward any obvious adverse effects; however, the low number of cases analyzed and the low quality of the evidence does not allow a firm conclusion on safety.¹⁴ An open data repository of inadvertent ivermectin drug exposure during pregnancy has been proposed as a strategy to mitigate this lack of

knowledge.¹⁴ A randomized clinical trial has also been advocated for.^{47,48}

Ivermectin is an FDA class C drug, meaning that:

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.⁴⁹

For the treatment of severe cases of strongyloidiasis during pregnancy, we believe that benefits outweigh the risks and ivermectin should be used. In cases where immunosuppressant drugs are used, such as corticosteroids for preterm labour, and *Strongyloidiasis* cannot be ruled out, presumptive treatment could be an option after discussing with the woman the benefits and risks of that strategy. Screening for strongyloidiasis and treating only those pregnant women screening positive and at risk of immunosuppression could avoid unnecessary ivermectin exposure, but availability of the results in time is a limiting issue in most settings.

Treatment of nonsevere cases during pregnancy in women not receiving immunosuppressants is unclear, and the benefits and risks are difficult to evaluate, as the risk of developing hyperinfection and adverse pregnancy outcome due to ivermectin have not been appropriately established. Although fetus adverse effects in animals have been seen with doses that were toxic to the mother and 60–200 times above the human therapeutic target,⁵⁰ the CDC does not recommend presumptive treatment in healthy pregnant women coming from endemic areas.⁵¹ For those confirmed cases of *Strongyloides* infection in pregnant women not receiving immunosuppressants, there is no clear recommendation. Other second-line regimens for the treatment of strongyloidiasis include albendazole. Despite being classified as an FDA class C drug (reference), it seems to have a more established safety profile (although with less efficacy), and could be considered.⁵² We believe that if treatment during pregnancy is to be offered to nonsevere not-at-risk women, their choice should be considered after a thorough discussion on treatment benefits and risks. Close follow-up and prompt treatment only if needed is also an approach to be considered.

Both ivermectin and albendazole should be avoided during the first trimester. Due to its lower efficacy, if albendazole is given during pregnancy, treatment with ivermectin after delivery may be considered.

Discussion

There is not much evidence on the interaction between strongyloidiasis and pregnancy. Strongyloidiasis prevalence in pregnant women seems to be similar to the general population from the area in question. However, in most studies, the most frequent diagnostic method reported was the single stool direct microscopic examination with or without a concentration procedure. This is a technique that is far from optimal, and thus the burden of strongyloidiasis in pregnant women is probably underreported and underestimated. Studies using culture techniques have yielded higher prevalence of *Strongyloides* infection. There are very limited data on the use of serology during pregnancy. Difficulties in compliance with testing protocols using serology have been reported.²⁰ There is a clear need to include reliable serological tests in further studies of *Strongyloides* prevalence in pregnant women. Worldwide, health-care providers would benefit from more accurate prevalence data to appropriately manage strongyloidiasis in pregnant women and women of child-bearing age. We believe that prevalence and thus health effects of strongyloidiasis in pregnancy are most probably underestimated in the current literature.

Studies looking at the effects of strongyloidiasis on pregnant women and their offspring are scarce. Strongyloidiasis has been found to be associated with some adverse obstetric outcomes and infant developmental outcomes. However, the causality of these outcomes has not been established as malnutrition, and other conditions (such as HIV infection and poverty) are confounding factors. Therefore, we cannot determine whether *S. stercoralis* infection in the mother is an independent risk factor of LBW, small for gestational age, intrauterine growth retardation, or preterm delivery.

The most concerning adverse outcome of strongyloidiasis during pregnancy is the risk of hyperinfection. Fatal cases have been reported in the literature. Although there is no strong evidence for any treatment recommendations in pregnant women, for severe strongyloidiasis we believe the use of ivermectin outweighs the risks. For pregnant women not on immunosuppressants, close follow-up and prompt treatment if needed seems a reasonable strategy.

In pregnant women that are going to receive immunosuppressants, screening and treatment of positive cases or presumptive treatment are options to consider and discuss with the mother after a thorough evaluation of the specific risks and benefits of every individual case.

We believe there are enough arguments to support increased screening and treatment of strongyloidiasis in pregnant women to confer the best-possible outcomes for them and their children. However, ivermectin efficacy and safety in pregnancy should be urgently evaluated through well-designed studies.

As this is a narrative review with no systematic research strategy for the literature, bias may be of concern. However, the review is very comprehensive and our conclusions are in line with other similar but systematic reports, indicating a high degree of consistency.^{18,36} The main limitation of this review is the scarcity of reports on different issues associated with strongyloidiasis in pregnant women. Many open questions remain, and studies are warranted to assess the optimal diagnostic method for *Strongyloides* infection in pregnant women, the impact of *Strongyloides* infection on maternal and newborn outcomes, if there are long-term effects on child growth and development, if pregnancy itself is a risk factor of the development of *Strongyloides* hyperinfection, and what the effectiveness and safety of ivermectin treatment in pregnant women is.

In conclusion, we strongly believe that pregnant women should be protected through research and not from research. Well-designed studies directed to evaluate all these questions regarding the interaction between *Strongyloides* and pregnancy are urgently needed. Furthermore, evidence-based protocols of *Strongyloides* screening and treatment before, during, and after pregnancy should be developed and implemented, both in developed and developing countries. We need to provide evidence-based care to the thus far neglected pregnant women with *Strongyloides* infection.

Disclosure

The authors report no conflicts of interest for this work.

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