ISSN: 2576-2842

Opinion Article

Journal of Gynecology & Reproductive Medicine

Blastocystosis And Iron Deficiency Anemia in Pregnant Women. A Call to Deep in A Little-Known Association

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Submitted: 04 Nov 2021; **Accepted:** 30 Nov 2021 **Published:** 15 Dec 2021

Citation: *Luis Fonte, Yamilé Aleaga, Yisel Hernandez , Maria Ginori, Gissel Garcia, Enrique J Calderon and Yaxsier de Armas (2021) Blastocystosis And Iron Deficiency Anemia in Pregnant Women. A Call to Deep in A Little-Known Association. J Gynecol Reprod Med, 5(2): 200-204.*

Abstract

During the last twenty-five years, in parallel with the demonstration of a rapid increase of the global prevalence of blastocystosis, it has been documented the association between this parasitic infection and iron deficiency anemia in general population. More recently, it has been evidenced the high prevalence of blastocystosis in pregnant women and its association with iron deficiency anemia. Herein, we revise the most recent progress in the understanding of this association, the possible mechanisms that support it, including the Blastocystis subtypes involved, and its clinical consequences and public health significance. Taken in consideration the adverse impacts of anemia on the health of mothers and progeny, an adequate prevention and control of this parasitism during pregnancy may be mandatory. At the same time, and looking the problem from a more holistic multi-disease-based perspective, the current initiatives to improve the prevention and control of intestinal parasitism in endemic areas may include in their communication strategies actions to inform, both at academic and community levels, about the possible adverse effects of blastocystosis on pregnancy evolution.

Keywords: Intestinal Parasites, *Blastocystis* sp., Blastocystosis, Pregnancy, Iron Deficiency Anemia, Prevention and Control.

Introduction

Infections by parasites, as occur with other groups of pathogens, are frequent in pregnant women [1-3]. From a biological perspective, those infections constitute adverse consequences of two interacting physiological processes that take place in the woman during pregnancy: the modulation of her immune responses and the occurrence of changes in her microbiota, both necessary for the healthy development of the fetus [1, 4].

Numerous studies on the prevalence of parasitism in pregnant women have been carried out in recent years, mainly in countries of Africa, Asia and Latin America [3]. However, the methodological differences in the performance of those studies (for example, in the number of fecal samples collected per participating individual and in the types of diagnostic tests used in each work) have made difficult to interpret and compare their results. Roughly speaking, the analysis of the available information has permitted the identification of the parasites most frequently found during pregnancy: among helminths *Schistosoma mansoni*, *Ascaris lumbricoides, Trichuris trichiura* and hookworms; and among protozoa, *Plasmodium* sp., *Entamoeba histolytica* and *Blastocystis* sp. [1-3].

In the revised literature, the number of studies that specifically reported the presence of *Blastocystis* sp. in pregnant women is not ample. El Deeb et al. found the parasite in 26.5% of gravid women of urban areas of Menoufia, Egypt [5]. Espinosa et al., working on pregnant women who lived in low socioeconomic residential areas in Bogota, Colombia, reported a prevalence of *Blastocystis* sp. infection of 25% [6]. Malatyali et al. observed the protozoon in the feces of 14% of pregnant women living in rural areas of Muğla, Turkey [7]. Likewise, in a recent study of 135 pregnant women who lived in urban areas in Havana, Cuba, we found that 39 of them (28.9%) were infected with *Blastocystis* sp. [8].

Blastocystis sp. is a cosmopolitan intestinal parasite with significant morphological variability and genetic heterogeneity, which was defined for the first time as a distinct organism in 1911 by Alexeieff, who named it *Blastocystis enterocola* [9]. In 1912, Brumpt proposed the name *Blastocystis hominis* for the organism isolated from human fecal material, and this was the term employed during long time until its low species specificity was recognized limiting the name to *Blastocystis* species [10-12]. This eukaryote is classified under the group Stramenopiles, which mostly comprises unicellular flagellated or ciliated free-living organisms [13]. Nevertheless, *Blastocystis* sp. is an obligate anaerobic protist transmitted via the fecal-oral route [12].

Considered primarily a commensal of the digestive system of its respective host, the pathogenic character of *Blastocystis* sp. has been the subject of intense debate over the last three decades [12,14]. The finding of this protozoon in the feces of asymptomatic individuals has been one of the arguments against the acceptance of its pathogenicity [14-15]. However, the accumulation of phenotypic and genotypic evidence allows to assume that the taxonomic category *Blastocystis* sp. designates a group of morphologically indistinguishable microorganisms, genetically divisible into subgroups (subtypes), which, depending on the relationship they establish with their respective hosts, may show different degrees of pathogenicity [12, 16-18]. Seventeen morphologically indistinguishable subtypes have been identified based on an analysis of a small subunit rDNA (SSU rRNA) gene sequence among *Blastocystis* sp. isolated from humans and other animals. Those numbered from 1 to 9, and 12, have been found in human feces and the first four have been related to different clinical forms of this parasitism [19]. Different *Blastocystis* sp. subtypes exhibit different growth rates, drug susceptibilities, host ranges, and other distinctive biological features [12, 20-22]. It has been suggested that these differences could influence on the gut microbiota. Moreover, it has been considered that microbiota composition, in relation to *Blastocystis* sp., may be dependent on the organism's subtype identity [17,23].

The prevalence of blastocystosis, an entity scarcely reported at the end of the past century, has increased rapidly during recent years [24]. The growing number of findings argued in favor of the pathogenicity of *Blastocystis* sp., which has led to pay more attention to its detection, has contributed notably to that increment [12,14-15,21]. On the other hand, the development of nucleic acid-based procedures has led to significant advances in molecular characterization and detection of *Blastocystis* sp. Those advances, included the optimization of more sensible PCR assays, have allowed a more accurate diagnosis of blastocystosis and a better understanding of its clinical significance. Nowadays, *Blastocystis* sp. is considered the most prevalent intestinal human protozoan worldwide [12,25].

Originally, the infection by *Blastocystis* sp. was associated with unspecific symptoms of the gastrointestinal system [26]. More recently, blastocystosis has been linked with others disorders: irritable bowel syndrome, inflammatory bowel disease, urticaria, Steven Johnson's syndrome, and iron deficiency anemia (IDA), among others [27-31]. Herein, we revise the most recent progress in the understanding of the reported association of blastocistosis and IDA, the mechanisms that support it, including the *Blastocystis* subtypes involved, and its possible clinical consequences and public health significance.

Blastocystosis, Iron Deficiency Anemia and Pregnancy

During the last twenty-five years, some works with different designs and target populations have been arguing in favor of an association between human *Blastocystis* infection and anemia. In 2003, Cheng et al., studying the hematological effects of blastocystosis on foreign workers in Taiwan, found that infected individuals had significantly lower hemoglobin level, hematocrit and total leukocyte counts than non-infected persons [32]. In 2008, Yavasoglu et al. reported for the first-time higher frequency of *Blastocystis* sp. infection in patients with IDA than in control group [31]. Four years later, El Deeb et al. found that *Blastocystis* sp. infection was a contributing risk factor for the development of IDA in pregnant women [5]. They observed that the frequency of infection by *Blastocystis* sp. was significantly higher in pregnant women with IDA (40%) than in non-anemic pregnant controls (6.3%). Almost immediately, and working on general population, El Deeb and Khodeer encountered that the prevalence of the parasite was significantly higher in a group of individuals with IDA (54.2%) when compared to a control group (17.3%) [33]. In 2019, with the objective of knowing the prevalence of blastocistosis and its possible association with IDA, we studied several parasitological and hematological variables in expectant women of Havana City [8]. We encountered that the proportion of pregnant women suffering from IDA was significantly higher in the group of gravid women parasitized by *Blastocystis* sp. (41.0%) than do non-parasitized women (19.8%) [8].

The genetic heterogeneity that characterizes *Blastocystis* sp., which greatly influences the relationship it establishes with its hosts, has

motivated the study of the association between microorganism subtypes and clinical manifestations, approach that has headed the researches on this parasite during the beginning of the present century. In 2013, in correspondence with that contemporary trend, El Deeb et al. explored the possible association of the infection by *Blastocystis* sp. subtypes with the development of IDA [33]. The PCR amplification of isolates of the protozoon from IDA patients and non-anemic controls using subtype-specific sequenced-tagged site primers encountered that subtype 3 was the most frequent, followed by subtype 1. However, both subtypes had similar frequency in both groups. Thus, this work didn´t find association between a particular genotype and the occurrence of IDA. In 2020, Deng et al., in a study carried out in individuals randomly selected in rural areas of Yunnan province, China, found that subtype 1 infection was associated with anemia [24]. In the same year, Malatyali et al. investigated the subtype distribution of *Blastocystis* sp. in pregnant women of rural areas of Muğla, Turkey. They found that *Blastocystis* sp. subtype 3 was the predominant genotype, independence of pregnant clinical manifestations [7]. That finding is in accordance with the reported *Blastocystis* sp. subtype distribution in other study populations (patients with cancer, ulcerative colitis, and irritable bowel syndrome); which *Blastocystis* sp. subtype 3 was the predominant genotype [34]. Nevertheless, and taking into account the variability of *Blastocystis* sp. subtypes composition in diverse epidemiological contexts and the differences in the designs of the previously mentioned studies, additional genotype researches are necessary to confirm, or discard, any association of infection by a *Blastocystis* sp. subtypes and IDA in pregnant women.

Unfortunately, the mechanisms by which infection with *Blastocystis* sp. would cause IDA are still little known. Some factors, or combination of them, may be at play:

1. *Blastocystis* sp., as other intestinal parasites, competes with the host for critical nutritional elements and energy sources [35].
2. A decrease in the efficiency of absorption of iron and other micronutrients, as a consequence of the infection by the protozoon, has been reported by some authors [36].
3. An increased intestinal permeability due to damage to the intestinal wall, with the corresponding loss of nutrients, was demonstrated in individuals infected by *Blastocystis* sp. [37].
4. At least, two papers have reported the occurrence of rectal bleeding in patients of blastocystosis [11, 32]. On the other hand, and opining from a more inclusive perspective, all analysis on those possible mechanisms should take into account that pregnant women are particularly vulnerable to the development of IDA due to their exponential rise of iron requirements, necessary to support the expanding of the maternal erythrocyte component and the growth of the fetal-placental unit [38-39].

The global prevalence of IDA in pregnant women is estimated to be approximately 38%, and it is higher in low-income countries [40]. In these areas several entities frequently coexist in some way associated with the development of IDA, such as malnutrition and other parasitic infections (*Ascaris lumbricoides, Trichuris trichiura* and the hookworms*, Necator americanus* and *Ancylostoma duodenale*). IDA can impair maternal and fetal outcomes: in the mother, it is associated with reduced physical and cognitive performances, increased risk of infection and hospitalization, preterm delivery, poor labor and severe hemorrhagic phenomena; for the fetus, IDA may result in growth retardation and low birth weight, among others adverse consequences [39-43]. In extreme cases, the impairments can lead to the death of the mother or the fetus, or both [42].

Considering the high global prevalence of anemia in pregnant women and its serious consequences for the health of mothers and progeny, the World Health Organization (WHO) has recognized anemia, mainly that produced by iron deficiency, a world sanitary problem [44]. For the prophylaxis of IDA, WHO promotes daily iron supplementation during pregnancy for women who live in areas with a high prevalence of iron deficiency [45]. However, there is poor evidence about the efficacy of that practice in the reduction of the global iron deficiency prevalence and, consequently, in the reduction of maternal and fetal adversities [46-47]. In that scenery, the prevention and control of the entities linked to the development of IDA, possibly including parasite infection such as blastocystosis, emerge necessary actions for avoiding those complications.

Conclusions

Recently, it has been evidenced the high prevalence of *Blastocystis* infection in pregnant women and its association with IDA. Unfortunately, the mechanisms supporting that association remain poorly understood. Taken in consideration the adverse impacts of anemia on the health of mothers and progeny, an adequate prevention and control of this parasitism during pregnancy may be necessary. At the same time, and looking the problem from a more holistic multi-disease-based perspective, the current initiatives to improve the prevention and control of intestinal parasitism in endemic areas may include in their communication strategies actions to inform, both at academic and community levels, about the possible adverse effects of blastocystosis on pregnancy evolution.

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