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CASE REPORT

Visceral Leishmaniasis During Pregnancy: A Case Report

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Abstract
Visceral leishmaniasis is a life-threatening disease endemic in tropical and subtropical regions and in the Mediterranean basin. Two species (*Leishmania infantum/chagasi* and *Leishmania donovani*) with different host reservoirs are responsible for visceral disease. The infection is usually transmitted by phlebotomine sandflies, whereas vertical and blood transfusion transmission is rarely observed. We report a 35-year-old Italian pregnant woman in the 26th gestational week presenting with progressive fatigue, intermittent fever, and pancytopenia who finally was diagnosed with visceral leishmaniasis. She had treatment with liposomal amphotericin B and delivered at week 38 a baby small for gestational age. The newborn had a positive *Leishmania* serology that turned negative at 6 months of age.

Background
Visceral leishmaniasis (VL) is an endemic disease found in tropical and subtropical regions and the Mediterranean basin, including Italy. VL can be classified as zoonotic (caused by *Leishmania infantum/chagasi*) or anthroponotic (caused by *Leishmania donovani*) according to the different reservoir host. The infection is usually transmitted by phlebotomine sandflies but can also occur as a consequence of blood transfusion or vertical transmission. VL during pregnancy is a rare condition, although probably underreported. A systematic literature review (from 1926 to 2020) reported 451 cases of VL in pregnant women with the disease being diagnosed during pregnancy in 398 cases (88.2%) (1).

Objectives
To describe a case of VL in a 35-year-old Italian woman presenting with pancytopenia in the 26th week of pregnancy and to raise awareness among Western physicians about this rare occurrence among pregnant women.

Case Report
A 35-year-old Italian woman living in Milan (Italy) presented in June 2022 in the 26th week of pregnancy for the onset of pancytopenia (hemoglobin 7.6 g/dL, leukocytes 2620/µL, platelets 77 000/µL). She had had a previous pregnancy 1 year before with spontaneous abortion at 6 weeks of gestation. Her medical history was notable for a mild infection by SARS-CoV-2 in July 2021. She had no history of traveling abroad, but in the previous years she had visited many Italian regions (Apulia, Sardinia, Marche, and Abruzzi). She referred the onset of progressively more severe asthenia from April 2022 and 3 episodes of mild fever (37.5 °C) in May 2022 with spontaneous resolution. Her body weight increased 1.5 kg during pregnancy. Initial serologic work-up showed negative results for HIV-1, *Toxoplasma gondii*, and parvovirus B19 infections, and it was consistent with previous infection by Epstein–Barr virus, rubella virus, and cytomegalovirus (IgM negative, IgG positive). Fecal occult blood test results were negative, serum iron was 49 µg/dL, ferritin 147 µg/L, and transferrin saturation 7%. Anticardiolipin antibodies and extractable nuclear antigen test results were negative, whereas antinuclear antibody results were positive (1:320). Protein electrophoresis showed hypoalbuminemia, the polyclonal increase of gamma globulin, and revealed the presence of 2 monoclonal bands,

Table 1. **Anti-*Leishmania* Drugs and Their Possible Use During Pregnancy**

Drug	FDA category	Comments
Amphotericin B deoxycholate	B	1 mg/kg/day for 20 days; important nephrotoxicity and side effects during infusion (high fever, chills, thrombophlebitis)
Liposomal amphotericin B	B	3 mg/kg/day for 7–10 administrations. In one study treatment extended to up to 12 doses to achieve cure*
Miltefosine	D	Contraindicated in pregnancy (embryotoxic and teratogenic)
Paromomycin	No category assigned	No data available for the use during pregnancy. Concern about possible renal and auditory damage for the fetus
Pentamidine isethionate	C	Contraindicated during the first trimester of pregnancy
Pentavalent antimony (meglumine antimoniate, sodium stibogluconate)	C	Pentavalent antimonial drugs can induce spontaneous abortion, miscarriages, preterm deliveries, and hepatic encephalopathy in the mother† Used almost exclusively in Africa

FDA = Food and Drug Administration.
*Pekelharing et al (6).
†Mueller et al (14) and Adam et al (15).

characterized as IgG kappa (FLK 68.8 mg/L and FLL 45.5 mg/L, ratio 1.51). An abdominal ultrasound scan revealed splenomegaly with spleen longitudinal diameter of 15 cm. *Leishmania* Western blot (Wb) assay was positive and *Leishmania* DNA on peripheral blood was also positive by polymerase chain reaction (PCR). Given the high sensitivity and specificity of peripheral blood *Leishmania* PCR in the diagnosis of VL, bone marrow aspiration was not performed to confirm the diagnosis (2). After counseling, liposomal amphotericin B (L-AmB) was started at a dose of 3 mg/kg/day for 5 days, followed by 2 more doses on days 14 and 21 according to the Food and Drug Administration–approved regimen. *Leishmania* DNA PCR turned negative 10 days after starting L-AmB, with a concurrent improvement in laboratory values (Hb 9.6 g/dL, leukocytes 8879/μL, PLTs 311 000/μL). At week 30 of gestational age, an ultrasound scan showed normal fetal growth (with an estimated fetal weight of 1656 g) with normal umbilical artery Doppler indices and without ultrasound signs of fetal infection. The woman delivered with vacuum extractor in another hospital at week 38+5 due to premature rupture of membranes. The neonate body weight was 2.7 kg (small for gestational age) with an Apgar score of 8 and 10 at first and fifth minute. The newborn had no signs or symptoms of VL, with laboratory findings within normal range, along with normal cerebral and abdominal ultrasound. At the time of birth *Leishmania* Wb was positive with negative *Leishmania* DNA PCR on blood cord and peripheral blood. During the follow-up, peripheral blood *Leishmania* DNA was persistently negative (checked at 2 and 6 months of age) and *Leishmania* Wb turned negative at 6 months. At the last follow-up at the age of 16 months, he was healthy and also the mother had no relapse of the disease.

Discussion

VL is a neglected tropical disease endemic also in 9 European countries, including Italy. The infection can run as an asymptomatic infection for a long time and develops into disease under suppression of cell-mediated immunity. VL during pregnancy is an apparently rare infection, with only 451 cases reported in a review of the literature encompassing 94 years (1).

The case we describe here was diagnosed during the second trimester of pregnancy, in line with what has been reported for most cases by Dahal and colleagues (87/212, 41%) (1). Cases of VL during pregnancy were diagnosed mainly in sub-Saharan Africa (285, 63.2%), the Indian subcontinent (107, 23.2%), and Brazil (20, 4.4%) (1). However, it is worth noting that Italy is the European country with the greatest number of diagnoses reported (13, including our own). The Th-2–predominant response beneficial for maintenance of pregnancy favors the persistence of *Leishmania* infection, increasing the risk for congenital transmission (3). Indeed, a permissive immune response during pregnancy might allow placental invasion by *Leishmania* parasites, which in turn is responsible for villous vessels thrombosis and trophoblastic degeneration (4, 5). Vertical transmission of *Leishmania* spp. can occur either in utero (transplacentally) or during labor through mother-to-child blood exchange. The main complications of VL described during pregnancy are severe anemia, miscarriage, and premature delivery with low birth weight of neonates and postpartum hemorrhage (6). Figueirò-Filho and coworkers (7) suggested that the diagnosis of VL during pregnancy should be based on epidemiologic clues (origin of the patient, proximity to sick dogs, contact with sandflies), clinical aspects (fever, weight loss, adynamia, hepatosplenomegaly, hemorrhage, decline of general condition) and nonspecific laboratory examination findings (pancytopenia, inversion of albumin/globulin ratio) as well as specific subsidiary examinations findings (serologic and parasitologic). However, because of the rarity of this condition in Europe, with only 25 cases described in the literature up to 2021, the correct diagnosis might be delayed. The main symptoms in our patient were fatigue associated with pancytopenia; fever was mild and resolved spontaneously. Among cases reported in Europe, fever was absent only in 2 cases (8–10). In the systematic literature review by Dahal and colleagues (1), the diagnosis of VL was retrospectively confirmed after delivery in 52 women (11.5%). Confirmation of VL diagnosis by bone marrow biopsy or splenic aspirate might be difficult during pregnancy, and a positive rK39 antigen or peripheral blood *Leishmania* DNA PCR provides a reliable diagnosis, as described in our patient.

As far as the vertical transmission of leishmaniasis is concerned, since the first description in 1926, only 26 cases of confirmed, probable, or suspected cases of congenital leishmaniasis have been reported (1, 11). In our case the newborn was small for gestational age with positive *Leishmania* serology at birth but showed negative peripheral blood *Leishmania* PCR and his serology turned negative at the age of 6 months. At 16 months, he was in good health without any signs or symptoms of VL, a reassuring issue since in the review of Dahal and colleagues (1), 12 cases of vertically transmitted VL were identified after 6 months from birth. Beyond our case, we are aware of only another single report in which *Leishmania* PCR was used for monitoring the newborn to exclude or confirm the diagnosis of VL (12).

Treatment of VL during pregnancy is essential for the survival of both mother and child and to reduce the risk for vertical transmission (1, 6, 13). L-AmB (category B in pregnancy) seems to be highly efficacious and safe compared with other drugs (i.e., pentavalent antimony, amphotericin B deoxycholate, and pentamidine isethionate), although there is no available guideline indicating the more appropriate schedule during pregnancy (1, 5) (Table 1). A study conducted in South Sudan showed a 100% cure rate without relapses at 6-month follow-up with a total dose of 30 mg/kg for 10 consecutive days (4). Mortality rate during treatment among women with VL in pregnancy has been reported to be as low as 1.8% when L-AmB was used and as high as 18% when sodium stibogluconate was used in 2 Sudanese studies (6, 12). Moreover, treatment with sodium stibogluconate was associated with high rates (57%) of first- and second-trimester miscarriages in one study (14) and death of the mothers for hepatic encephalopathy in another study (15).

In conclusion, VL in pregnancy should be suspected in all women presenting with pancytopenia who live or are coming from endemic countries. Treatment is always warranted, even in paucisymptomatic cases, and L-AmB should be used. Finally, as stated by Dahal and colleagues (1) in their systematic review of the literature, limited evidence exists regarding the best practices for management of VL in pregnancy because of the lack of high-quality studies. Our case report complies with the checklist items suggested for reporting purposes (1).

References

1. Dahal P, Singh-Phulgenda S, Maguire BJ, et al. Visceral leishmaniasis in pregnancy and vertical transmission: a systematic literature review on the therapeutic orphans. PLoS Negl Trop Dis. 2021;15:e0009650. [PMID: 34375339] doi:10.1371/journal.pntd.0009650
2. Antinori S, Calattini S, Longhi E, et al. Clinical use of polymerase chain reaction on peripheral blood and bone marrow samples for the diagnosis and monitoring of visceral leishmaniasis in HIV-infected and HIV-uninfected patients: a single-center, 8-year experience in Italy and review of the literature. Clin Infect Dis. 2007;44:1602-10. [PMID: 17516404] doi:10.1086/518167
3. Berger BA, Bartlett AH, Saravia NG, et al. Pathophysiology of *Leishmania* infection during pregnancy. Trends Parasitol. 2017;33:935-45. [PMID: 28988681] doi:10.1016/j.pt.2017.08.012
4. Eltoum IA, Zijlstra EE, Ali MS, et al. Congenital kala-azar and leishmaniasis in the placenta. Am J Trop Med Hyg. 1992;46:57-62. [PMID: 1536385] doi:10.4269/ajtmh.1992.46.57
5. Baergen R. Infectious diseases. In: Manual of Pathology of Human Placenta. New York: Springer; 2011:281-319.
6. Pekelharing JE, Gatluak F, Harrison T, et al. Outcomes of visceral leishmaniasis in pregnancy: a retrospective cohort study from South Sudan. PLoS Negl Trop Dis. 2020;14:e0007992. [PMID: 31978116] doi:10.1371/journal.pntd.0007992
7. Figueirò-Filho EA, Duarte G, El-Beitune P, et al. Visceral leishmaniasis (kala azar) and pregnancy. Infect Dis Obstet Gynecol. 2004;12:31-40. [PMID: 15460194] doi:10.1080/1064744042000210384
8. Pagliano P, Carannante N, Rossi M, et al. Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. J Antimicrob Chemother. 2005;55:229-33. [PMID: 15649998] doi:10.1093/jac/dkh538
9. Dereure J, Than HD, Lavabre-Bertrand T, et al. Visceral leishmaniasis. Persistence of parasites in lymph nodes after clinical cure. J Infect. 2003;47:77-81. [PMID: 12850167] doi:10.1016/s0163-4453(03)00002-1
10. Panagopoulos P, Mitsopoulos V, Papadopoulos A, et al. Visceral leishmaniasis during pregnancy: a rare case report from Greece. PLoS Negl Trop Dis. 2017;11:e005134. [PMID: 28207741] doi:10.1371/journal.pntd.0005134
11. Low GC, Cooke WE. A congenital infection of kala azar. Lancet. 1926;208:1209-11.
12. Argy N, Lariven S, Rideau A, et al. Congenital leishmaniasis in a newborn infant whose mother was coinfected with leishmaniasis and HIV. J Pediatr Infect Dis Soc. 2020;9:277-80. [PMID: 31589299] doi:10.1093/jpids/piz055
13. Adam GK, Omar SM, Ahmed MA, et al. Cross-sectional study of the case-fatality rate among patients with visceral leishmaniasis infections during pregnancy in Sudan. Int J Gynaecol Obstet. 2018;140:119-20. [PMID: 28960291] doi:10.1002/ijgo.12332
14. Mueller M, Balasegaram M, Koummuki Y, et al. A comparison of liposomal amphotericin B with sodium stibogluconate for the treatment of visceral leishmaniasis in pregnancy in Sudan. J Antimicrob Chemother. 2006;58:811-5. [PMID: 16916865] doi:10.1093/jac/dkl342
15. Adam GK, Abdulla MA, Ahmed AA, et al. Maternal and perinatal outcomes of visceral leishmaniasis (kala-azar) treated with sodium stibogluconate in eastern Sudan. Int J Gynaecol Obstet. 2009;107:208-10. [PMID: 19766208] doi:10.1016/j.ijgo.2009.08.002