Visceral Leishmaniasis in pregnancy and vertical transmission: A systematic literature review on the therapeutic orphans

Prabin Dahal1,2*, Sauman Singh-Phulgena1,2, Brittany J Maguire1,2, Eli Harriss3, Koert Ritmeijer4, Fabiana Alves5, Philippe J Guerin1,2, Piero L Olliaro2

1Infectious Diseases Data Observatory (IDDO), Oxford, UK
2Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK
3The Knowledge Centre, Bodleian Health Care Libraries, University of Oxford, Oxford, UK
4Médecins Sans Frontières, Amsterdam, Netherlands
5Drugs for Neglected Diseases initiative, Geneva, Switzerland

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Email addresses:
PD prabin.dahal@iddo.org
SSP sauman.singh@iddo.org
BJM brittany.maguire@iddo.org
EH eli.harriss@bodleian.ox.ac.uk
KR koert.ritmeijer@amsterdam.msf.org
FA falves@dndi.org
PJG philippe.guerin@iddo.org
PLO piero.olliaro@ndm.ox.ac.uk

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*Correspondence to:
prabin.dahal@iddo.org

Infectious Diseases Data Observatory (IDDO), Oxford, UK
Abstract

Background: Reports on the occurrence and outcome of Visceral Leishmaniasis (VL) in pregnant women is rare in published literature. The occurrence of VL in pregnancy is not systematically captured and cases are rarely followed-up to detect consequences of infection and treatment on the mother and foetus.

Methods: A review of all published literature was undertaken to identify cases of VL infections during pregnancy by searching the following database: Ovid MEDLINE®; Ovid Embase; Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials; World Health Organization Global Index Medicus: LILACS (Americas); IMSEAR (South-East Asia); IMEMR (Eastern Mediterranean); WPRIM (Western Pacific); ClinicalTrials.gov; and the WHO International Clinical Trials Registry Platform. Selection criteria included any clinical reports describing the disease in pregnancy or vertical transmission of the disease in humans. Articles meeting pre-specified inclusion criteria and non-primary research articles such as textbook, chapters, letters, retrospective case description, or reports of accidental inclusion in trials were also considered.

Results: We screened 272 publications and identified a total of 70 records (1926–2020) describing 447 VL cases in pregnant women. The disease was detected during pregnancy in 394 (88.1%), retrospectively confirmed after giving birth in 52 (11.6%), and the time of identification was not clear in 1 (0.2%). Of the 394 mothers whose infection was identified during pregnancy, 344 (89.1%) received a treatment, 3 (0.8%) were untreated, and the treatment status was not clear in the remaining 47 (12.2%). Of 344 mothers, Liposomal Amphotericin B (L-AmB) was administered in 202 (58.7%) and pentavalent antimony (PA) in 92 (26.7%). Outcomes were reported in 176 mothers treated L-AmB with 4 (2.3%) reports of maternal deaths, 5 (2.8%) miscarriages, and 2 (1.1%) foetal death/stillbirth. For PA, outcomes were reported in 87 mothers of whom 4 (4.6%) died, 24 (27.6%) had spontaneous abortion, 2 (2.3%) had miscarriages. A total of 26 cases of confirmed, probable or suspected cases of vertical transmission were identified and the median time to detection was 6 months (range: 0–18 months).

Conclusions: Outcomes of VL treatment during pregnancy is rarely reported and under-researched. When it is reported, information is often incomplete and it is difficult to derive generalisable information on outcomes for mothers and babies, although reported data favours the usage of liposomal amphotericin B for the treatment of VL in pregnant women.
Author summary

Visceral Leishmaniasis (VL) is a neglected tropical disease with an estimated incidence of 50,000 to 90,000 cases in 2019. Women who are susceptible to becoming pregnant or those who are pregnant and lactating are regularly excluded from clinical studies of VL. A specific concern of public health relevance is the little knowledge of the consequences of VL and its treatment on the mother and the foetus. We did a systematic review of all published literature with an overarching aim of identifying cases of VL in pregnancy and assess the risk-benefit balance of antileishmanial therapies to the mother and the child. We identified a total of 70 records (1926–2020) describing 447 VL cases in pregnant women. In 394 mothers, infection was identified during pregnancy of whom 202 received Liposomal Amphotericin B (L-AmB) and 92 received pentavalent antimony (PA). Reports of maternal deaths, abortion, and miscarriages were proportionally lower among those who received L-AmB compared to PA regimens. A total of 26 cases of confirmed, probable or suspected cases of vertical transmission were identified and the median time to detection was 6 months (range: 0–18 months). Our review brings together scattered observations of VL in pregnant women in the clinical literature and clearly highlights that the disease in pregnancy is under-reported and under-studied. Our findings indicate that L-AmB should be the preferred treatment for VL during pregnancy.
Introduction

Visceral Leishmaniasis (VL) is a neglected tropical disease caused by *Leishmania* sp. parasites transmitted by female sandflies. The disease is endemic in parts of South Asia, East Africa, South America and the Mediterranean region with an estimated 50,000 to 90,000 cases in 2019 [1]. A specific concern of public health relevance is the little knowledge of the clinical aspects of VL and treatment outcomes in pregnant and lactating women [2].

In pregnancy, VL diagnosis relies essentially on symptoms and serology as parasite detection by splenic aspiration is not recommended because of the risk for the foetus. More severe anaemia and increased requirements for blood transfusion have been reported for pregnant women infected with VL [2]. Case management must take into account the consequences of the disease and the therapeutic intervention on the mother-foetus pair [3]. Of note, except amphotericin B, all other available drugs are either contraindicated or subjected to restricted use in pregnant and lactating women and in women of child-bearing age (Table 1) [4–6]. Further complexities arise from potential vertical transmission of the disease either congenitally (maternal–foetal transmission *in utero*) or through transplacental infection as a result of blood exchange during labour. While vertical transmission of VL is well-studied and established in animal studies, reports in humans are sporadic with observations of clinical manifestation several months post-partum [7–10]. Such vertical transmission can induce *in utero* death or can be potentially deleterious to the foetus and infant [6,9,11].

The regulatory restrictions and limited evidence on safety of antileishmanial chemotherapeutics on the mother-foetus pair meant that historically clinicians had to rely on personal experience or limited published case-reports to make a decision. This led to some clinicians delaying the treatment of pregnant women until after delivery, especially
when the case was detected closer to the due date [12,13]. Others had treated them when
the adjudicated risk of VL to the mother outweighed the risk posed by the drug to the
mother-foetus pair [14]. Similar delays in treatment of pregnant mothers has also been
reported in post kala-azar dermal leishmaniasis (PKDL) [15,16]. Currently liposomal
amphotericin B (L-AmB) remains the preferred regimen for the treatment in pregnancy
(Table 1). However, pregnant and lactating women are regularly excluded from clinical
studies [17] and are considered “therapeutic orphans” [18]. In studies that enrol females of
childbearing age, counselling measures are usually set in place to inform the patients
regarding the potential teratogenic harms of study drugs and either adoption of suitable
contraception methods or observance of abstinence is mandatory (for example in
miltefosine trials) [17]. In regular clinical practice and non-clinical trial settings, pregnancy
tests and counselling however, might not be done routinely. A study conducted in South
Asia found that only one in every six doctors ruled out pregnancy before prescribing
miltefosine [19].

Finally, there is a lack of active pregnancy registries for most of the antileishmanial drugs
expect for miltefosine. In the context of Impavo® (Profounda Inc.), the commercial name of
miltefosine registered to the US medicines regulatory agency (US Food Drug
Administration), a pregnancy registry was established to fulfil post marketing requirements
[20,21]. The recruitment of pregnant women as part of the observational study started in
2015 and the study is expected to be completed in 2026, and is estimated to recruit 0–1
patients per year over the 10 year study period, hence unlikely to generate a large volume
of new safety data [20]. There are no other active pregnancy registries on exposures to VL
treatments from which to derive information on consequences on gestation, mother,
foetus, and the newborn. Therefore, to understand the risks and benefits of treatment to
the mother and the child, one must turn to the published literature.

The most comprehensive reviews on VL in pregnant women were conducted in the mid
2000s [9,22]. We therefore conducted a systematic review of all published literature with an
overarching aim of identifying cases of VL in pregnancy. The specific objectives were to
assess the risk-benefit balance of antileishmanial therapies to the mother and the child and
to identify the cases of vertical transmission. The review was not limited by language or any
interventions.
### Table 1: Antileishmanial usage during pregnancy

| Drug                      | Indication                                                                 | FDA Category (reviewed in [23, 24]) |
|---------------------------|----------------------------------------------------------------------------|-------------------------------------|
| Pentavalent antimonials:  |                                                                             |                                     |
| Pentostam                | “Although no effects on the foetus have been reported, Pentostam should be  | C                                    |
| (Sodium Stibogluconate)  | withheld during pregnancy unless the potential benefits to the patient    | (Risks cannot be ruled out)         |
|                           | outweigh the possible risk to the foetus. Children should not be breast-fed |                                     |
|                           | by mothers receiving Pentostam”                                             |                                     |
|                           | – Source: The EMC [25]                                                     |                                     |
|                           | “Pentavalent antimonials are less safe in pregnancy, as they can result in  |                                     |
|                           | spontaneous abortion, preterm deliveries and hepatic encephalopathy in    |                                     |
|                           | the mother and vertical transmission”                                       |                                     |
|                           | – Source: WHO-2010 [26]                                                    |                                     |
| Amphotericin B deoxycholate | “Animal reproduction studies have failed to demonstrate a risk to the foetus | B                                    |
|                           | and there are no adequate and well-controlled studies in pregnant women.” | (No evidence of risk in studies)     |
|                           | “Amphotericin B deoxycholate and lipid formulations are the best           |                                     |
|                           | therapeutic options for visceral leishmaniasis. No abortions or vertical   |                                     |
|                           | transmission have been reported in mothers treated with liposomal           |                                     |
|                           | amphotericin”                                                               |                                     |
|                           | – Source : WHO-2010 [26]                                                   |                                     |
| Liposomal amphotericin B  | “Animal studies do not indicate direct or indirect harmful effects with    | B                                    |
| (AmBisome)                | respect to reproductive toxicity. The safety of AmBisome in pregnant women | (No evidence of risk in studies)     |
|                           | has not been established. Systemic fungal infections have been successfully |                                     |
|                           | treated in pregnant women with conventional amphotericin B without obvious  |                                     |
|                           | effect on the foetus, but the number of cases reported is insufficient to   |                                     |
|                           | draw any conclusions on the safety of AmBisome in pregnancy. AmBisome should |                                     |
|                           | be used during pregnancy if the possible benefits to be derived outweigh   |                                     |
|                           | the potential risks to the mother and foetus. It is unknown whether AmBisome |                                     |
|                           | is excreted in human breast milk. A decision on whether to breastfeed while  |                                     |
|                           | receiving AmBisome should take into account the potential risk to the child|                                     |
|                           | as well as the benefit of breast feeding for the child and the benefit of   |                                     |
|                           | AmBisome therapy for the mother”                                            |                                     |
|                           | – Source: The EMC [27]                                                     |                                     |
|                           | “Amphotericin B deoxycholate and lipid formulations are the best            |                                     |
|                           | therapeutic options for visceral leishmaniasis. No abortions or vertical   |                                     |
|                           | transmission have been reported in mothers treated with liposomal           |                                     |
|                           | amphotericin”                                                               |                                     |
|                           | – Source : The WHO-2010 [26]                                               |                                     |
|                           | This is the first line therapy for treatment against pregnancy in Kenya,    |                                     |
|                           | Ethiopia, Somalia, Sudan, South Sudan, Uganda, and Brazil                    |                                     |
|                           | – Source : The WHO [28]                                                    |                                     |
| Pentamidine               | Contraindicated during the first trimester of pregnancy                     | C                                    |
|                           | – Source : WHO-2010 [26]                                                   | (Risks cannot be ruled out)         |
| Drug Name            | Note                                                                                                                                                                                                 |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Miltefosine (Impavid) | Contraindicated in pregnancy: “Impavid may cause foetal harm. Foetal death and teratogenicity occurred in animals administered miltefosine at doses lower than the recommended human dose. Do not administer IMPAVIDO to pregnant women. Obtain a serum or urine pregnancy test in females of reproductive potential prior to prescribing IMPAVIDO. Females of reproductive potential should be advised to use effective contraception during IMPAVIDO therapy and for 5 months after therapy. “
|                     | – Source: The US FDA Impavid prescribing information [29]                                                                                                                                              |
|                     | “Miltefosine is potentially embryotoxic and teratogenic and should not be used during pregnancy. Women of child-bearing age should be tested for pregnancy before treatment and use effective contraception for 3 months after treatment.”
|                     | – Source: WHO-2010 [26]                                                                                                                                                                             |

| Paromomycin (aminosidine) | “Otoxicity in the foetus is the main concern. Insufficient data are available on the use of paromomycin in pregnant women”
|                         | – Source: WHO-2010 [26]
|                         | “Paromomycin crosses the placenta and can cause renal and auditory damage in the unborn child. Paromomycin is excreted in breast milk and adverse effects in the breastfed infant cannot be excluded.”
|                         | – Source: National guidelines of Kenya-2017 [30]  |

| Risk Category | D (Positive evidence or risk) | No category assigned |
Material and Methods

Literature search

A review of all published literature was undertaken on 26th of March 2020 to identify records describing VL in pregnant women or any reports of vertical transmission of the disease in humans by searching the following clinical databases: Ovid MEDLINE®; Ovid Embase; Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials; World Health Organization Global Index Medicus: LILACS (Americas); IMSEAR (South-East Asia); IMEMR (Eastern Mediterranean); WPRIM (Western Pacific); ClinicalTrials.gov; and the WHO International Clinical Trials Registry Platform (ICTRP). The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic-Reviews and Meta-Analyses (PRISMA) guidelines (S1 Text)[31]. In addition, full text screening of the publications indexed in the Infectious Diseases Data Observatory (IDDO) clinical trials library was carried out to identify any description of VL in pregnant women [32]. The references of all included publications were further checked to identify any relevant articles. This review is not registered and the protocol describing the search strategy including database search strings, search dates and eligibility criteria for screening is presented in supplemental file (S2 Text).

Study screening

Study screening was carried out in two stages to identify the studies fulfilling the inclusion and exclusion criteria (S2 Text): title and abstract screening (stage I) and then full-text screening (stage II). As reports on VL in pregnancy are sparse, articles meeting minimal inclusion criteria and non-primary research articles such as opinion pieces, clinical guidelines, textbooks, chapters, correspondences, reports of accidental inclusion in trials, or
case reports of unplanned pregnancies during the study follow-up were also considered for comprehensiveness. No restrictions were applied regarding study design, follow-up duration, sample size, region, or the treatment regimen for eligibility of inclusion in this review. Title and abstracts were screened in the first stage, followed by screening the full-texts. Articles that were not in English language (Spanish, Portuguese, Korean, and German) were evaluated using google translation (https://translate.google.co.uk/).

The articles were screened against eligibility criteria by a single reviewer (PD). A second reviewer was consulted (SSP) when the first reviewer couldn’t reliably assess the eligibility. The first reviewer (PD) extracted data from all the eligible records and it was verified by the second reviewer (SSP) (who was not blinded) on all publications included in the review. Any discrepancy in the extracted information was flagged by the second reviewer and the differences were resolved through consensus. Screening and data extraction was carried out on a prospectively designed Excel database.

Data extraction

The following bibliographic information were extracted: study title, name of the first author, year of publication, name of the study site and country. The following maternal and child characteristics were extracted: age of the mother, period of gestation (or trimester), treatment administered including drug dosage, follow-up duration, the outcome of the treatment for mother (cured, relapsed, death), and foetal outcomes (abortion, stillbirth, premature birth, healthy born, vertical transmission).

Definitions

The records were classified as: case report/case series, prospective cohort or retrospective cohort studies. Records describing one or a small group of patients included as a part of prospective (or retrospective) studies in which VL in pregnancy was not of primary focus.
were considered as case report/case series. Similarly, studies that described a cohort of pregnant women without selection of a non-pregnant comparator group were also considered as case series. Countries were classified into sub-regions according to United Nations designation of geographical regions [33].

Data analysis
Since majority of the studies included were either case reports or case series, analysis of data was restricted to presentation of descriptive statistics and meta-analysis was not carried out. Descriptive summaries were presented for the characteristics of the studies included in the review, maternal characteristics (trimester, gestational age), treatment regimen including dosage and duration, clinical outcomes on the mother and the child. Graphics were generated using R software [34].

Assessment of risk of bias
The risk of bias in case report/case series was assessed using a checklist proposed in Murad-2018 [35]. The following domain were assessed: patient selection, ascertainment of exposure, outcome assessment, adequacy of follow-up, and reporting of results. A single case report was considered to be at a high risk of selection bias whereas a series of cases selected based on an audit of complete records over a study period was considered to be at a low risk of selection bias. Bias in ascertainment of exposure was considered to be high if the diagnosis of VL was based solely on clinical features. For cohort studies (prospective or retrospective), risk of bias was assessed using The Newcastle-Ottawa scale. Two authors (PD, SSP) independently assessed the risk of bias in the studies included.
Results

We identified 395 records from the literature searches up until 26th of March 2020, of which 272 were unique after removing duplicate entries. Of the 272 unique records, 99 were excluded at title and abstract screening stage (Fig 1) leaving 173 records for full-text assessment of which 53 met the eligibility criteria for inclusion in the review (Fig 1). An additional 17 records were identified by searching the references of the eligible records and through personal communication. A total of 70 records published from 1926 through 2020 were included in this review of which were 69 were case-reports or case-series and 1 was a retrospective cohort study with non-pregnant patient as a comparative group (Table 2). Further details on the studies included in this review are presented in supplemental files (S1 Data, S2 Data).

Spatial distribution

A total of 21 (30.0%) records were from Europe, 21 (30.0%) from Southern Asia, 13 (18.6%) from South America, 8 (11.4%) from Northern America, 5 (7.1%) from Eastern Africa, and 1 (1.4%) record each were from Eastern and Western Asia. There were 16 records from India (22.8%), 13 (18.6%) from Brazil, 8 (11.4%) from Sudan, and further breakdown by country is presented in Fig 2 (left panel). There were 62 (88.6%) records in English language, 7 (10.0%) in Portuguese, and 1 (1.4%) in French. The 70 records included in this review described 447 cases of VL in pregnant women, of whom 159 (35.6%) were from Sudan, 113 (25.3%) from...
South Sudan, 80 (17.9%) from India, 23 (5.1%) from Bangladesh, 20 (4.5%) from Brazil, 12
(2.7%) from Italy, 10 (2.2%) from Uganda, and the rest of the breakdown is presented in Fig
2 (right panel).

**Fig 2: Number of records and patients by country of origin**

**Treatment regimens**

Of the 447 pregnant mothers identified, the disease was detected during pregnancy in 394
(88.1%), retrospectively confirmed after giving birth in 52 (11.6%), and the time of
identification was not clear in one (0.2%). Ten (2.2%) were suspected of having carried the
infection during their pregnancy, of whom 6 were cases of sub-clinical persistence of the
parasites without the mother ever suffering from the disease previously. One case of
oligosymptomatic mother was identified in Brazil [36] (Table 2). Of the 394 mothers whose
infection was identified during pregnancy, 344 (89.1%) received a treatment, 3 (0.8%) were
untreated, and the treatment status was not clear in the remaining 47 (12.2%) (Table 2).

Description of characteristics and outcomes among 344 mothers who were treated and 3
untreated mothers are presented next.

**Liposomal Amphotericin B (n=202)**

There were 5 (2.5%) mothers treated in the first trimester, 8 (4.0%) in second trimester, 9
(4.5%) in third trimester, and the time in pregnancy was not clear in 180 (89.1%). Survival
status was not reported or was unclear in 26 (12.9%) mothers and from the remaining 176
mothers, a total of four (2.3%) maternal deaths were reported. There were a total of 5
(2.9%) miscarriages (trimester not clear), 1 (0.6%) foetal death (from a mother in 1st
trimester), 1 (0.6%) stillbirth (trimester not clear), and 1 (0.6%) premature birth (trimester
not clear). Three cases of vertical transmission were identified [37–39]: one was detected immediately after vaginal birth (the baby was treated with L-AmB and recovered successfully), another at 11 months after birth (treatment information not available), and for the third case, vertical transmission was suspected at 8 months after birth (treated with sodium stibogluconate 20 mg/kg IV for 20 days and discharged) (Table 3).

**Pentavalent antimony (n=92)**

There were 20 (21.7%) mothers in the first trimester, 45 (48.9%) in the second, 22 (23.9%) in the third, and the time in pregnancy was not clear in 5 (5.4%). Survival status was available on 87 (94.6%) mothers of whom 4 (4.6%, 4/87) died due to hepatic encephalopathy [40]. There were 24 (27.6%) abortions (or spontaneous abortions) [13,41], 2 (2.3%) miscarriages, 2 (2.3%) pre-term births [40,42], and 1 (1.1%) mother required splenectomy after delivery due to poor recovery [43]. One of the babies died due to myelomeningocele 3 hours after birth [40], another died one day after being born [44], another died due to VL at 2 months [40], and one was born with Down’s syndrome to a 47 years old mother [40]. There were 3 cases of vertical transmission identified [45–47], detected at 6, 7, and 12 months after birth. All three of them were treated with PA; 1 baby died (who was born with signs of intra-uterine growth retardation and was diagnosed with vertical VL at 7 months) and the other two survived (Table 3).

**Amphotericin B deoxycholate (n=20)**

Of the 20 mothers treated with amphotericin B deoxycholate, 3 (15.0%) were in their first trimester, 6 (30.0%) in the second, 3 (15.0%) in the third, and the trimester was not clear in 8 (40.0%). There was one (5.0%) maternal death after 7 days of treatment due to haemorrhagic complications occurring after delivery (the mother was in 28.7 ± 7.8 weeks of
pregnancy—exact time not available) [48]. The remaining 19 mothers were discharged alive. The delivery of babies was described as normal for 18 mothers, haemorrhagic complication occurred in a mother after delivery (as described earlier) [48], and the information was not reported on 1. There was no evidence of vertical transmission of the disease in 12 (60.0%) babies in whom the information was reported. Nineteen of the children were alive and the survival status for 1 was missing.

**Pentavalent antimony plus paromomycin (aminosidine) (n=11)**

Eleven pregnant mothers were treated with sodium stibogluconate plus aminosidine (paromomycin) [14,49]. Information regarding trimester, maternal survival status, or vertical transmission were not available. One spontaneous abortion was reported [49].

**Liposomal amphotericin B plus pentavalent antimony (n=4)**

Four mothers were treated with the combination regimen [50], of whom two in the second trimester and two in their third. L-AmB was administered at 3–7 mg/kg daily on days 1, 6, 11 and 16 (or on days 1, 2, 3, 4, 10 and 15), followed by 20 mg/kg sodium stibogluconate intramuscularly once daily for 30 days. All four mothers were discharged alive. At discharge, one mother delivered a healthy baby and the remaining three were still pregnant – no follow-up data was available.

**Paromomycin (aminosidine) (n=3)**

Three pregnant mothers were treated with paromomycin administered by deep gluteal intramuscular injection once daily for 21 consecutive days [51]. The delivery was described as normal for all three with normal healthy babies at birth and all three mothers were alive.
Unclear drug name (n=12)

Two publications described one case each without reporting the name of the drug administered [52,53]. In an article, the number of mothers (n=10) allocated to each drug arm (pentavalent antimony or amphotericin B deoxycholate) was not clear [54]. Two (16.7%) of the mothers were in their third trimester and the status was unknown for the remaining 10 (83.3%). There were two (16.7%) maternal deaths [54] and two cases of vertical transmission [52,53]. The first one was identified at 8 months after birth and another at 6 weeks after birth (the baby died after 3 days). Both babies were administered treatment upon detection of VL.

Untreated (n=3)

Three cases of VL identified during pregnancy were untreated [12,55,56]. Treatment was deferred until after delivery due to safety concerns in one study [12]; there were signs of intra-uterine growth retardation requiring emergency C-section, and both mother and the child were alive. The second mother was not treated due to lack of adequate hospital resources [55]; the baby born to the mother died after 2 months due to malnutrition with no evidence of vertical transmission. In the third case, VL was diagnosed but the mother died after giving birth and before treatment could be administered [56]; the baby also died and foetal part placenta examination revealed presence of Leishman Donovan bodies by PCR indicating vertical transmission.

Confirmed/probable/suspected vertical transmission

We identified a total of 26 cases of confirmed, probable or suspected cases of vertical transmission (Table 3). The median time to detect vertically transmitted VL was 6 months (range: 0–18 months). Eleven children were born to mothers in whom the disease status
was confirmed during their pregnancy (3 were treated with L-AmB, 3 were treated with PA, the drug name was not clear in 2, 1 was untreated and the treatment status was not clear in remaining 2). Histopathological examination of the placenta confirmed the vertical transmission of the disease in two cases [47,56] and this was not reported for the remaining cases. Treatment status was described in 18 children, of whom 11 received pentavalent antimony, 6 received L-AmB and 1 received amphotericin b deoxycholate. Two of the children died (one received pentavalent antimony and the drug name was not clear in the other).

Risk of bias assessment

Of the 69 case reports/case series, 48 (69.6%) were considered to be at a high risk of bias in patient selection, 9 (13.0%) were at high risk of exposure (confirmed VL status) ascertainment bias, 12 (17.4%) were at high risk of outcome ascertainment bias, 13 (18.8%) at high risk of incomplete reporting bias, and 14 (20.3%) studies were at a high risk of bias due to inadequate follow-up (See S1 Table). One retrospective cohort study with a comparative group of non-pregnant patient group was considered of high quality.
Table 2: Description of reported 447 cases of VL in pregnant or lactating women

| Author-year          | Country | Time of detection/description | Number of mother(s) | Trimester | Description of maternal treatment                                                                 | Pregnancy outcome              |
|----------------------|---------|--------------------------------|--------------------|-----------|--------------------------------------------------------------------------------------------------|--------------------------------|
| Low and Cooke-1926   | UK      | During pregnancy               | 1                  | 3         | Urea Stibamine                                                                                   | Normal delivery                |
| Hindle-1928          | China   | Retrospectively suspected      | 1                  | Not applicable (retrospective)                  | No information                                                                      | No description                 |
| Hindle-1928          | China   | Retrospectively suspected      | 1                  | Not applicable (retrospective)                  | No information                                                                      | No description                 |
| Banerji-1955         | India   | During pregnancy               | 1                  | 2         | Treated with 10 IV Urea Stibamine                                                                | Remission of fever             |
| el-Saaran-1979       | UAE     | During pregnancy               | 1                  | 2         | Pentostam: 6 ml IV daily for ten days, at intervals of ten days to a total of 180 ml             | Did not recover; Splenectomy performed after birth |
| Rees-1984            | Kenya   | During pregnancy               | 1                  | No information                                  | Pentostam                                                                            | No information                 |
| Blanc-1984           | France  | Retrospectively identified     | 1                  | Not applicable (retrospective)                  | Treatment with N-methylgluca mine (antimony) for 10 days                          | Normal delivery                |
| Badarao-1986         | Brazil  | During pregnancy               | 1                  | 3         | Untreated (posthumous diagnosis)                                                                 | Mother died 5 weeks later      |
| Mittal-1987          | Indian  | During pregnancy               | 1                  | 3         | Drug name not stated                                                                             | Normal term delivery           |
| Nyakundi-1988        | Sudan   | During pregnancy               | 1                  | Not clear                                        | Unclear                                                                              | Premature birth at 6 months of gestation |
| Yadav-1989           | India   | Retrospectively identified     | 1                  | 2         | Not treated (herbal medicine were given)                                                         | Normal and uneventful delivery |
| Elamin & Omer 1992   | Sudan   | During pregnancy               | 1                  | 3         | Drug name not stated                                                                             | Normal delivery                |
| Eltoum-1992          | Sudan   | During pregnancy               | 1                  | 2         | SSG: 10 mg/kg/daily for 30 days                                                                  | Normal delivery                |
| Eltoum-1992          | Sudan   | During pregnancy               | 1                  | 2         | Not clear                                                                                       | Abortion of a female foetus    |
| Seaman-1993          | Sudan   | During pregnancy               | 3                  | Not clear                                        | SSG 20 mg/kg/day for 30 days                                                       | No information                 |
| Study        | Country   | Time Period | Duration | Treatment Details                                                                 | Outcome          |
|--------------|-----------|-------------|----------|----------------------------------------------------------------------------------|------------------|
| Seaman-1993[14] | Sudan     | During pregnancy | 3        | Not clear                                                                        | SSG + Aminosidine (20 mg/kg/day SSG for 17 days + 15 mg/kg of Aminosidine for 17 days) | No information  |
| Thakur-1993 [86] | India    | During pregnancy | 1        | 2                                                                                | Amphotericin B (1 mg/kg body weight daily starting with 0.5 mg/kg body weight till a total dose of 20 mg/kg) | Normal delivery |
| Thakur-1993 [63] | India    | During pregnancy | 1        | 2                                                                                | Amphotericin B (1 mg/kg body weight daily starting with 0.5 mg/kg body weight till a total dose of 20 mg/kg) | Normal delivery |
| Thakur-1993 [63] | India    | During pregnancy | 1        | 2                                                                                | Amphotericin B (1 mg/kg body weight daily starting with 0.5 mg/kg body weight till a total dose of 20 mg/kg) | Normal delivery |
| Thakur-1993 [63] | India    | During pregnancy | 1        | 2                                                                                | Amphotericin B (1 mg/kg body weight daily starting with 0.5 mg/kg body weight till a total dose of 20 mg/kg) | Normal delivery |
| Giri-1993 [64] | India    | During pregnancy | 1        | 2                                                                                | Amphotericin B | Normal term delivery |
| Gradoni-1994 [65] | Italy    | During pregnancy | 1        | 2                                                                                | L-Amb total dose of 18 mg/kg | Normal delivery |
| Gradoni-1994 [65] | Italy    | Retrospectively identified (treated after delivery) | 1        | Not applicable (retrospective)                                                    | Untreated (diagnosed after birth); treated with 18 mg/kg/day PA after birth | Normal delivery |
| Jeronimo-1994 [66] | Brazil   | During pregnancy | 1        | No information                                                                   | Meglumine antimoniate (20 mg/kg/day for 20 days) | No information |
| Utili-1995 [8]  | Italy     | During pregnancy | 1        | 2                                                                                | Meglumine antimoniate (12 mg/kg for 20 days) | Normal term birth (patient delivered a baby weighing 4.2 kg at 41 weeks of pregnancy) |
| Sharma-1996 [67] | India    | Retrospectively identified | 1        | Not applicable (retrospective)                                                    | Untreated | Normal delivery |
| Thakur-1998 [91] | India    | During pregnancy | 1        | No information                                                                   | Amphotericin B deoxycholate (total dose 20 mg/kg) | Normal delivery |
| Study          | Country | Study Phase | Gestational Age | Treatment | Outcome                  |
|---------------|---------|-------------|-----------------|-----------|--------------------------|
| Thakur-1998   | India   | During pregnancy | 1               | No information | Amphotericin B deoxycholate (total dose 20 mg/kg) | Normal delivery |
| Thakur-1999   | India   | During pregnancy | 1               | No information | Amphotericin B (total dose 20 mg/kg) | Normal delivery |
| Thakur-1999   | India   | During pregnancy | 1               | No information | Amphotericin B (total dose 20 mg/kg) | Normal delivery |
| Thakur-1999   | India   | During pregnancy | 1               | No information | Amphotericin B (total dose 20 mg/kg) | Normal delivery |
| Meinecke-1999 | Germany | Retrospectively identified | 1               | Not applicable (retrospective) | Untreated (retrospective identification) | Complicated pregnancy with febrile gastroenteritis; birth weight was 3,720 g |
| Viana-2001    | Brazil  | Retrospectively identified | 2               | Not applicable (retrospective) | Untreated (retrospective identification) | One preterm birth |
| Kumar-2001    | India   | During pregnancy | 1               | 3          | Untreated (treatment deferred until birth) | Intrauterine growth retardation; small for gestational age; Emergency C-section required |
| Dereeure-2003 | France  | During pregnancy (routine check-up) | 1               | 2          | L-AmB (3 mg/kg daily for five days; a 6th injection 10 days later) | Normal term birth |
| Caldea-2003   | Brazil  | During pregnancy | 1               | 1          | Amphotericin B (1mg/kg for 14 days) | Normal term birth |
| Silveria-2003 | Brazil  | During pregnancy | 1               | 2          | Meglumine antimoniate (850mg/day for 20 days) | Premature birth |
| Pagliano-2003 | Italy   | During pregnancy | 2               | No information | L-AmB | Normal delivery |
| Kumar-2004    | Iran    | Retrospectively identified (after death of mother-child) | 1               | 3          | Untreated (posthumous diagnosis) | Death |
| Pagliano-2005 | Italy   | During pregnancy | 1               | Not clear | L-AmB (3 mg/kg at days 1–5 & 3 mg/kg at day 10) | Healthy term birth |
| Pagliano-2005 | Italy   | During pregnancy | 1               | Not clear | L-AmB (3 mg/kg at days 1–5 & 3 mg/kg at day 10) | Healthy term birth |
| Pagliano-2005 | Italy   | During pregnancy | 1               | Not clear | L-AmB (3 mg/kg at days 1–5 & 3 mg/kg at day 10) | Healthy term birth |
| Pagliano-2005 | Italy   | During pregnancy | 1               | Not clear | L-AmB (3 mg/kg at days 1–5 & 3 mg/kg at day 10) | Healthy term birth |
| Author          | Country   | Timeframe          | Cases | Details                                                                 | Outcome                                                                 |
|-----------------|-----------|--------------------|-------|-------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Pagliano-2005   | Italy     | During pregnancy   | 1     | Not clear                                                               | L-AmB (3 mg/kg at days 1–5 & 3 mg/kg at day 10)                         | Healthy term birth                                                      |
| Figueiró Filho-2005 | Brazil   | During pregnancy   | 1     | 3                                                                       | L-AmB (1 mg/kg/day for 21 days)                                        | Normal birth at 38 weeks with baby weighing 2.995 g                    |
| Mueller-2006    | Sudan     | During pregnancy   | 23    | 11 in first; 8 in second; 4 in third                                   | SSG: 20 mg/kg for 30 days                                               | 13 spontaneous abortion during days 13 to 30 of SSG; 1 spontaneous abortion prior to treatment; 1 healthy baby born; remaining 8 still pregnant at discharge |
| Mueller-2006    | Sudan     | During pregnancy   | 4     | 2 in second; and 2 in third                                           | L-AmB + SSG (AmBisome 3–7 mg/kg daily on days 1, 6, 11 and 16 or on days 1,2,3,4,10, and 15), followed by 20 mg/kg SSG IM once daily for 30d | 1 healthy baby born; Remaining 3 were still pregnant at discharge       |
| Mueller-2006    | Sudan     | During pregnancy   | 12    | 2 in first; 6 in second; 4 in third                                   | L-AmB (AmBisome 3–7 mg/kg daily on days 1, 6, 11 and 16 (or on days 1,2,3,4,10, and 15) | Premature birth (n=1); Two healthy babies; Remaining 9 still pregnant at discharge |
| Boehme-2006     | Germany   | Possibly before pregnancy | 1 | Not applicable (retrospective)                                      | No treatment given (retrospective speculation)                         | Spontaneous birth at 39 weeks of gestation and healthy baby delivered |
| Mueller-2007    | Sudan     | During pregnancy   | 5     | No information                                                          | AmBisome: Six doses of 2.5–8.2 mg/kg on days 1, 2, 3, 5, 10, 15          | No information                                                         |
| Viera-2007      | Brazil    | During pregnancy   | 1     | 3                                                                       | Untreated                                                               | Baby died 2 months after birth                                         |
| Topno-2008      | India     | During pregnancy   | 1     | 2                                                                       | Amphotericin B (15 infusions of 1 mg/kg)                                 | Normal term birth                                                      |
| Topno-2008      | India     | During pregnancy   | 1     | 2                                                                       | Amphotericin B (15 infusions of 1 mg/kg)                                 | Normal term birth                                                      |
| Topno-2008      | India     | During pregnancy   | 1     | 3                                                                       | Amphotericin B (15 infusions of 1 mg/kg)                                 | Normal term birth                                                      |
| Topno-2008      | India     | During pregnancy   | 1     | 3                                                                       | Amphotericin B (15 infusions of 1 mg/kg)                                 | Normal term birth                                                      |
| Figueiró Filho-2008 | Brazil   | During pregnancy   | 1     | -                                                                      | Amphotericin B deoxycholate (1 mg/kg/day for 20 days)                    | One maternal death after 7 days of treatment due to haemorrhagic complications occurring after delivery |
| Study          | Country    | Intervention                          | Dose and Duration | Outcome                                                                 |
|---------------|------------|---------------------------------------|-------------------|-------------------------------------------------------------------------|
| Figueiró Filho-2008 [48] | Brazil     | During pregnancy                      | 1                 | Untreated during pregnancy (Diagnosed after birth and given SSG: 20 mg/kg/day for 20 days) No information |
| Figueiró Filho-2008 [48] | Brazil     | During pregnancy                      | 1                 | L-AmB (3 mg/kg/day for 20 days)                                     No information |
| Figueiró Filho-2008 [48] | Brazil     | Retrospectively confirmed             | 1                 | -                                                                      | No information |
| Lorenzi-2008 [80]         | UK         | Retrospectively identified            | 1                 | Miscarriage                                                            | |
| Adam-2009 [40]            | Sudan      | During pregnancy                      | 42                | SSG: 20 mg/kg SSG once daily IM for 30 days                            | Miscarriage in first trimester (n=2); death due to hepatic encephalopathy (n=4); Preterm birth (n=2) |
| Muller-2009 [54]          | Uganda     | During pregnancy                      | 10                | PA or amphotericin B deoxycholate                                     | 2 maternal deaths |
| Papa-Georgiou-2010 [37]    | Greece     | Confirmed few days before labour      | 1                 | L-AmB (4 mg/kg on 6 consecutive days and repeated doses at days 14 and 21) | No information |
| Miah-2010 [13]            | Bangladesh | During pregnancy                      | 11                | SAG (20 mg/kg for 30 days)                                            | Abortion (n=11) |
| Miah-2010 [13]            | Bangladesh | During pregnancy                      | 5                 | SAG (20 mg/kg for 30 days)                                            | Good outcome (n=5) |
| Zinchuk and Nadraga-2010  [38] | Ukraine | During pregnancy                      | 1                 | L-AmB (3 mg/kg days 1–5 followed by a single dose 3 mg/kg on day 10)   | Delivery by elective C-section at 38 weeks of gestation; baby Birth weight of 2900g |
| Sinha-2010 [81]           | India      | During pregnancy                      | 3                 | L-AmB (5 mg/kg on days 0, 1, 4, and 9)                                | Not described (successful treatment) |
| Haque-2010 [82]           | Bangladesh | Retrospectively identified            | 1                 | -                                                                      | Vertical transmission identified at 15 days of birth |
| Ritmeijer-2011 [83]       | Ethiopia   | During pregnancy                      | 1                 | L-AmB (6 infusions of 5 mg/kg)                                         | Good response to treatment |
| Ritmeijer-2011 [83]       | Ethiopia   | During pregnancy                      | 1                 | L-AmB (6 infusions of 5 mg/kg)                                         | Good response to treatment |
| Study          | Location | Time of Diagnosis | Incidence | Treatment                                      | Outcome                                      |
|---------------|----------|------------------|-----------|-----------------------------------------------|----------------------------------------------|
| Sinha-2011    | India    | During pregnancy | 3         | Paromomycin (11 mg/kg/day for 21 days)         | Normal delivery                              |
| Pilaca-2011   | Albania  | Retrospectively identified | 1         | Untreated [After giving birth: Glucantime for 28 days. The baby was not fed by his mother’s breast. PA given as L-AmB was not available] | Preterm birth                                |
| Damodaran-2012 | UK       | Retrospectively identified | 1         | Untreated during pregnancy (diagnosed after birth); After diagnosis L-AmB (total dose of 20 mg/kg over 5 days) | Vertical transmission (Suspected) at 15 months |
| Lima-2013     | Brazil   | During pregnancy | 1         | L-AmB                                         | No information                               |
| Lima-2013     | Brazil   | Retrospectively identified | 1         | Untreated (diagnosed after birth); Amphotericin b deoxycholate 1 mg/kg followed by IV L-AmB 3mg/kg/day | Acute foetal distress requiring section delivery; Extremely premature birth (1,170g) |
| Mescouto-Borges-2013 | Brazil | Retrospectively identified | 1         | Untreated (diagnosed after birth); IV L-AmB given at 3 mg/kg/day for 7d | Acute foetal distress requiring section delivery; Premature birth |
| Milsovic-2013  | Serbia   | Retrospectively identified | 1         | Untreated (diagnosed after birth)             | Normal vaginal delivery                       |
| Salih-2014    | Sudan    | During pregnancy | 23        | L-AmB (30 mg/kg divided into 10 IV infusions of 3 mg/kg) | No information                               |
| Burza-2014    | India    | During pregnancy | 49        | Ambisome                                      | No information                               |
| Bode-2014     | Germany  | Not clear         | 1         | No information                                | Vertical transmission at 8 months            |
| Llamazares-2014 | Spain  | Retrospectively identified | 1         | -                                              | Normal delivery                              |
| Study Year | Country | Pregnancy Week | Study Design | L-AmB Dose | Prognosis |
|------------|---------|----------------|--------------|------------|-----------|
| Rahman-2014 [92] | Bangladesh | During pregnancy | 1 | No information | L-AmB | Stillbirth baby |
| Colomba-2015 [93] | Italy | Retrospectively identified (After 4 days of giving birth) | 1 | After delivery | Untreated (treated with L-AmB 3 mg/kg/day on days 1-5 and on day 10) | No information |
| Pawar-2015 [94] | India | During pregnancy | 1 | 2 | Amphotericin B deoxycholate (later switched to liposomal preparation to minimise nephrotoxicity) | Full term normal vaginal delivery at 38 weeks of gestation |
| Kumar-2015 [95] | India | Retrospectively identified (After 5 months of delivery) | 1 | 3 | Untreated | Normal vaginal birth |
| Almada-silva-2015 [96] | Brazil | During pregnancy | 1 | 1 | L-AmB | Foetal death |
| Basher and Nath-2017 [56] | Bangladesh | During pregnancy | 5 | No information | One untreated; One was treated with L-AmB | Untreated mother died |
| Kimutai-2017 [49] (personal communication with Dr Alves) | East Africa | During pregnancy | 8 | No information | SSG+PM | Spontaneous abortion (n=1) |
| Panagopoulos-2017 [97] | Greece | During pregnancy | 1 | 3 | L-AmB (3 mg/kg/day for 5 days and on days 14 and 21) | Normal term birth |
| Adam-2018 [98] | Sudan | During pregnancy | 45 | Mostly 3rd | No information | 8 maternal death (6 in prenatal and 2 in postnatal); 37 survived; 30 were full term; 6 pre-term birth; 2 spontaneous abortion; 1 stillbirth |
| Goyal-2018 [99] (personal communication With Dr Alves) | India | During pregnancy | 2 | No information | Single dose AmBisome (10 mg/kg) | No complications |
| Russo-2018 [100] | Italy | Retrospectively identified | 1 | - | - | Vertical transmission |
| Cunha-2019 [101] | Brazil | During pregnancy | 1 | 3 | L-AmB (3 mg/kg for 7 days) | Normal term birth without complications |
| Argy-2019 [39] | Brazil | During pregnancy | 1 | 3 | L-AmB | Vertical transmission at birth |
| Parise-2019 [102] | France | Retrospectively identified | 1 | - | - | Maternal death |
| Retrospectively identified (two weeks post-partum) | During pregnancy | Identified |
|--------------------------------------------------|-----------------|------------|
| L-AmB (30 mg/kg in 6 doses)                        | L-AmB = Liposomal amphotericin B; PA = pentavalent antimony; SSG = sodium stibogluconate; SAG = Sodium antimonyl glycolate; IV = intravenous; MI = intramuscular; | L-AmB (30 mg/kg in 6 doses) |

PM = Paromomycin
### Table 3: Details of 26 reported cases of confirmed, probable, or suspected vertical VL

| Study                  | Location | Case description                                                                                                                                                                                                 |
|------------------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Low and Cooke-1926 [45]| UK       | A retrospective description of a child born to a mother who contracted the disease during pregnancy while residing in India and had given birth in the UK.                                                            |
| Hindle-1928 [57]       | China    | A four months' old baby whose spleen puncture confirmed presence of Leishmania parasites. “The main interest of this case lies in the fact that it could not possibly have been exposed to the bites of sandflies, as their season ended approximately two months before the child was born. Although the mother showed no obvious signs of disease it is difficult of explanation except on the hypothesis of congenital transmission. Low and Cooke (1926) recorded a case of Indian Kala Azar in a child born in England, and there can be no doubt that in this patient the infection was derived from the mother who was also infected.” |
| Hindle-1928 [57]       | China    | “Dr Marshall Hertig kindly informed me of a similar case at Hsii-Chowfu in which the patient, a five months old child, was successfully treated for Kala Azar at the local mission hospital. This infant also, from the date of its birth, could never have been exposed to the bites of sandflies.” |
| Banerji-1955 [46]      | India    | Mother contracted kala-azar in the fifth month of pregnancy and suspected vertical transmission occurred when the child was 6 months old.                                                                 |
| Blanc and Robert-1984 [59]| France  | Mother with a subclinical infection during pregnancy with the disease detected within a month after delivery. The child had a confirmed VL and was the first case reported in the hospital. The child never left the hospital and never came in contact of dogs thus suggesting that congenital /vertical transmission was the likely mode of transmission. |
| Mittal-1987 [52]       | India    | “An 11-month-old male infant admitted with symptoms that were later confirmed as VL. The baby’s mother had also suffered from kala-azar while carrying this child. As the baby and his mother did not leave New Delhi, India, where the case was related, either during or after the delivery and the vector found in New Delhi was not competent to transmit leishmaniasis, the infant could not have been infected by the bite of a sandfly. It therefore seems most likely that he was congenitally exposed to kala-azar.” |
| Study                      | Country | Description                                                                                                                                 |
|---------------------------|---------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Nyakundi-1988 [61]         | Kenya   | “We recently treated a 4 months old male infant born prematurely on 18 June 1986, after 6 months gestation to a then febrile para 6+3 mother diagnosed as having had kala-azar during pregnancy. Mother and infant were admitted to the Clinical Research Centre, Kenya Medical Research Institute, on 20 October-1986; when kala-azar was confirmed in the mother. This infant with congenital kala-azar was only the fourth and youngest patient with this disease ever reported in the world medical literature. The mode of infection in the baby could be (a) direct transmission from mother to offspring, (b) acquired in hospital, (c) acquired at the time of birth from perineal haemorrhages with swallowing of maternal blood or secretions or through the cord or skin abrasions, or (d) acquired congenitally from the mother through the placenta. Only the last of these possible modes of transmission is likely in view of the poor health of the infant from the 6th day of life, the mother’s bad obstetric history, the hospital’s high altitude which makes it unsuitable for sandfly transmission, and because the period that elapsed from birth to the appearance of symptoms was compatible with a congenital infection.” |
| Yadav-1989 [62]           | India   | An 11-month male infant was admitted with kala-azar. The mother suffered from the disease during pregnancy. The mother from Bihar migrated to Delhi during first trimester. She showed signs of disease during sixth month of pregnancy. The most likely mode of infection was in utero transmission of the disease. |
| Eltoum-1992 [47]          | Sudan   | During an epidemic of visceral leishmaniasis in the Sudan, two cases of congenital kala-azar were seen. The first child, whose mother had contracted kala-azar in southern Sudan, was born in Khartoum, where no transmission of leishmaniasis is currently occurring. At seven months, the child had fever, lymphadenopathy, and hepatosplenomegaly; leishmania parasites were detected in the bone marrow. The child died and an autopsy showed leishmania parasites in all tissues including the lungs, kidneys, and thymus. |
| Eltoum-1992 [47]          | Sudan   | In the second case, parasites were found in the placenta of a five-month-old foetus.                                                            |
| Elamin & Omer-1992 [53]  | Sudan   | A case of visceral leishmaniasis in a 6-week-old infant from southern Sudan who most likely got the infection through transplacental transmission. This is the first reported case of congenital kala-azar in Africa and the seventh in the global medical literature. |
| Sharma-1996 [67]          | India   | “Thus, in all possibility, it was a case of congenital kala-azar acquired transplacental by the baby from a mother having subclinical kala-azar.” The infection was possibly active when the child was 4 months of age and it was detected when the child was 18 months. |
| Meinecke-1999 [70]        | Germany | Because the child had never left Germany, nonvector transmission was suspected and household contacts were examined. His mother was the only one who had a positive antibody titre against Leishmania donovani complex. She had travelled several times to endemic Mediterranean areas (Portugal, Malta, and Corse) before giving birth to the boy. But she had never been symptomatic for visceral leishmaniasis. Her bone marrow, spleen, and liver biopsy results... |
Boehme-2006 [77] Germany We describe a case of VL in a German infant, who never had been to a VL endemic area. Most likely, the parasite was congenitally transmitted from the asymptomatic mother to her child.

Papageorgiou 2010 [37] Greece We report the first case of congenital disease described in Greece. The mother of the infant was hospitalised a few days before labour because of anaemia and hepatosplenomegaly, and titres for Leishmania antibodies were positive. A bone marrow aspirate showed no evidence of malignancy, except from a slight decrease of myelopoiesis, erythropoiesis and thrombopoiesis. However, the promastigote form of Leishmania was found, and the refore, diagnosis of leishmaniasis was confirmed.

Haque-2010 [82] Bangladesh The first report of vertical transmission of VL in Bangladesh

Zinchuk and Nadraga 2010 [38] Ukraine An 8-month-old boy was diagnosed with visceral leishmaniasis in Ukraine, a non-endemic area. His mother had been treated for visceral leishmaniasis at 28–32 weeks gestation whilst working in Alicante, Spain and delivered her infant at 38 weeks gestation by elective caesarean section in Ukraine. It is presumed that the infant’s infection was as a result of vertical transmission.

Pilaca-2011 [84] Albania Leishmania amastigotes were detected in bone marrow biopsy of the mother. Two days later, premature birth was simulated. After 2-3 months of the birth the baby was not well. After admitted to hospital, baby resulted positive for VL. He was treated with Glucantime and was cured after a scheme of two 14-day cycles with good outcome.

Damodaran-2012 [85] UK “A 15 month-old girl, family from East Timor, referred from primary care with weight-loss and a non-healing skin ulcer. She appeared undernourished with pallor, pyrexia and hepatosplenomegaly. FBC showed pancytopenia. Bone marrow examination confirmed Leishmaniasis. Her mother had inanition Leishmaniasis. The child was born in United Kingdom with no history of foreign travel and responded well to treatment with Ambisome”

Mescouto-Borges-2013 [86] Brazil We report two human cases of congenitally transmitted visceral Leishmaniasis in two patients who developed symptoms during pregnancy. The diagnosis was made by visual examination of Leishmania parasites in bone marrow aspirates of the mothers and by detecting parasite DNA in bone marrow samples of the new-born children using polymerase chain reaction.

Bode-2014 [90] Germany “One infant girl (P8) had only been in an endemic area (Spain) in utero. Vertical transmission resulting in congenital visceral leishmaniasis must be assumed, as the mother, who remained clinically asymptomatic, was serologically positive. Diagnosis of visceral leishmaniasis was delayed for more than 3 weeks”. The girl had never been abroad after birth and the mother had positive Leishmania serology after a trip to Spain during pregnancy.
| Author       | Country    | Details                                                                                                                                 |
|--------------|------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Kumar-2015   | India      | It was presumed that the infant's infection was a result of vertical transmission. In our case we can presume that the mother might be having subclinical infection and has transmitted the disease to the offspring. |
| Basher and Nath-2017 | Bangladesh | “One term mother died before starting treatment after the birth of a death baby due to pregnancy & disease complication. Foetal part placenta was collected; found PCR positive for LD body. Kala azar in the mother may have been the cause of the foetal wastage” |
| Russo-2018   | Italy      | “Here we present a 6-month-old girl with parents from Southern Italy. Our case of vertically transmitted Leishmaniasis highlights the importance of recognizing infectious etiologies.” |
| Argy-2019    | France     | Few intracellular Leishmania amastigotes were found during the microscopic examination of the placenta confirmed by positive PCR results. Sequential PCR follow-up of VL in the HIV-positive pregnant woman and her newborn supports our hypothesis that the transmission of VL in this neonate occurred transplacentally. |

338 *An article from Sudan (Adam 2009 [40]) described a case of a 2 months baby with parasites detected in lymph node. The article did not mention whether this could be a case of vertical transmission.*

341 *In Nyakundi-1988[61], three cases of vertically transmitted VL in clinical literature were identified: Low and Cooke-1926[45]; Banerji-1955[46] and Napier-1946[103]. The first two reports are included in this table whereas we have decided not to include the last report as a case of vertical transmission as the original article could not be retrieved and case details couldn’t be verified. The following description appears in Napier-1946 [103]: “Even in India kala-azar occurs among infants; we reported a case of an infant of less than eight months with well-developed kala-azar of about four months’ duration”. While it is clear that VL was identified when the infant was of four months old, there is no further description of the case [103]. The brief description in Napier-1946[103] matches an earlier publication (Napier and Das Gupta-1928 [104]) in which the plausibility of vertical transmission was ruled out: “As the mother showed no sign of the disease at all it is extremely unlikely that the child was suffering from the disease at birth.*
Discussion

The occurrence and effects of VL during pregnancy is under-researched and poorly understood as evidenced by having identified only 70 publications describing a total of 447 cases of VL in pregnancy in the past 90 years.

The small case volume reported in the literature could have several explanations. In the first place, there is an apparent imbalance in caseloads with predominance of the disease among males; ascribed to biological or behavioural causes [3,17,63,105–107]. Pentavalent antimony is contraindicated in pregnancy and was the first line therapy before the development of Liposomal amphotericin B (L-AmB) – this might have traditionally dissuaded physicians from treating VL during pregnancy and leaning towards postponing the treatment until after delivery unless treatment is absolutely warranted [12]. However, this situation might have changed recently as liposomal amphotericin B has no contraindication during pregnancy and is the treatment of choice. It has also been postulated that early pregnancies are missed due to spontaneous abortion caused by VL [63]. Women with childbearing potential or those who are already pregnant are systematically excluded from VL clinical studies and only a third of the patients enrolled in clinical trials are females [17]. For example, of the 158 studies indexed (to date) in the IDDO systematic library of VL clinical trials, 52 studies presented details from screening logs of patients (33,455 patients were screened; 17,572 patients were excluded including 32 pregnant women, and 15,883 included) [See S1 Data] [32]. Assuming all those screened for eligibility indeed had the disease, this would give an estimated 0.096% (likely an underestimate) of the total cases of VL to be pregnant women. If there are 100,000 cases per year, this translates to a minimum of 96 cases of the disease in pregnancy per year. It is clear that the likely size of the problem
is much bigger than what can be estimated from available reports. For example, during Jan
2016–Jul 2019 in Lankien, Jonglei state, South Sudan, out of 4,448 cases of VL diagnosed,
39% occurred in women of childbearing age, and 13% of the women (2.5% of all cases) were
pregnant [2]. It is also likely that the clustering in space and time of reported cases (more
than half of all cases in this review were from studies in Sudan or South Sudan after 2005) is
more a result of local interest into the subject matter than a true reflection of disease
burden.

There was also geographical disparity in the treatment regimens used, reflecting
heterogeneity in treatment practices. Only half of the patients received amphotericin B
regimens in studies conducted in Africa compared to more than two-thirds of the patients
from Asia. There was a total of 11 maternal deaths; four (4.6%, 4/87) occurred in those
treated with pentavalent antimony-based regimens, 4 (4/176; 2.3%) among those treated
with L-AmB, 1 (1/20, 5.0%) with amphotericin b deoxycholate, and the drug name used for
the treatment was not clear in 2 (16.7%, 2/12) cases. Spontaneous abortion following PA
regimen was observed in just over a quarter of the mothers (24/88, 27.3%) while there were
a total of 5 (2.9%) miscarriages and 1 (0.6%) foetal death following L-AmB regimen. Taken
together, these results support the use of liposomal amphotericin B for the treatment of VL
during pregnancy.

Our review identified 26 cases of vertically transmitted VL with a median time of detection
of 6 months (range: 0–18 months). This suggests that children born to mothers with VL
during pregnancy require a longer post-treatment follow-up than the standard 6-months
follow-up duration among non-pregnant patients to monitor the well-being of the maternal-
foetal pair. The underlying mechanism of the onset of clinical leishmaniasis among neonates
and infants born to a successfully-treated mother during pregnancy (2.4% overall) is currently not clear; it has been ascribed to imbalances in immune-mechanism modulated by T cell responses (Th1/Th2) [10] or by parasites entering a state of dormancy in the lymph nodes [72].

Our review has identified limitations in reports of VL in pregnancy. Complete information was often not available on treatment administered and on efficacy and safety outcomes for the mother and baby. For 12% of the mothers, it could not be ascertained whether they had received any treatment or not. Majority of the studies were considered to be a high risk of bias for patient selection while some retrospective studies were at high risk of bias for ascertainment of exposure domain as VL diagnosis was purely based on clinical signs and symptoms or suspicion. This suggests that existing practices for management of VL in pregnancy is guided by limited evidence generated from case reports and small case series. High quality studies (such as Pekelharing-2020 [2]) is warranted for generation of a robust evidence regarding safety and efficacy of antileishmanial agents during pregnancy. There was also a lack of standardised reporting as information was missing on several critical parameters such as trimester status, time on detection of VL, and therapeutic outcomes of the mother and the child. Taken together, these findings highlight the need to improve and harmonise the reporting of VL in pregnant women. We have outlined a minimum checklist of items that might be useful for reporting purposes (Box 1).

As conducting randomised controlled trials during pregnancy poses ethical challenges, it is important to maximise currently available information from observational studies and case reports to gauge the potential safety of the therapies in pregnant women. Data from mothers who become pregnant after completion of therapy but within the follow-up period
enrolled in trials might provide further resource, especially on the reproductive consequences of the treatment (Table 4). The recently proposed safe ethical framework for the recruitment of women susceptible to and becoming pregnant is an important development towards filling the existing knowledge gap [18]. Like for many NTDs, there is currently an absence of a comprehensive pregnancy-specific registry for exposures to antileishmanials, with the exception of the one dedicated for miltefosine [108]. Therefore, creating an open registry where all these cases are indexed and continually updated would help in better characterisation of the safety aspects of the drugs. Finally, the Infectious Diseases Data Observatory (IDDO) data platform, that is currently standardising individual participant data from several VL clinical studies, offers a unique resource to explore host, parasite, and drug dynamics affecting the safety and efficacy in pregnant populations [109].

**Conclusions**

In conclusion, this review brings together scattered observations on VL in pregnant women and the cases of vertically transmitted VL reported in the clinical literature. Available reports clearly underestimate the scale of the problem. Existing therapeutic guidelines regarding the usage of drugs in pregnancy is guided by limited evidence generated from case reports and small case series. Our review suggests that liposomal amphotericin B should be the preferred treatment for VL during pregnancy.
### Table 4: Description of patients enrolled in clinical trials who became pregnant after completion of treatment

| Study                  | Number of patients | Treatment received at enrolment | Pregnancy and outcome description |
|------------------------|--------------------|---------------------------------|-----------------------------------|
| Bhattacharya-2007 [110]| 2                  | Miltefosine                      | "Despite extensive counselling for contraception, 2 cases of pregnancy were reported, with the conception date close to the exposure period. One patient became pregnant 2 weeks after the end of treatment, and the other became pregnant at 3 months after the end of the treatment period. Two healthy babies were delivered at gestational weeks of 39 and 40, without any birth anomaly" |
| Sinha-2011 [51]       | 1                  | Paromomycin                      | One female patient became pregnant more than 1 month after completing treatment. The offspring was born alive and determined to be normal/healthy just after birth. |
| Mondal-2014 [111]     | 4                  | Liposomal Amphotericin B (Single dose) | Four female participants became pregnant within months after treatment and in one the pregnancy was completed with delivery of a term normal birth after 6 months of follow-up. The other three pregnant women were clinically healthy during the last follow-up visit. |
| Jamil-2015 [112]      | 1                  | Paromomycin                      | Pregnancy was reported in one female during the follow-up period. The offspring was born healthy, and a hearing test conducted on the infant at 1.5 months of age confirmed reaction to sound. An otoscopy and oto-acoustic emission test to determine function of the middle and inner ear was conducted at 3 months of age and confirmed normal hearing function. |
| Pandey-2016 [113]     | 15                 | Miltefosine                      | All the female patients were suggested not to become pregnant within 6 months of treatment. However, 15 patients became pregnant within 6 months of follow-up (after 2 months of treatment completion). All these patients became pregnant 2 months after end of treatment. All of them were followed up till 1 year and all had full-term normal pregnancy with no congenital anomalies. |
Box 1: Proposed minimum variable recording and reporting for studies or case reports for VL in pregnancy

Adapted from Saito-2017 [114]

| Domain                          | Checklist Item                                      |
|--------------------------------|-----------------------------------------------------|
| Maternal history               | Parity                                               |
|                                | Gravidity                                            |
|                                | Maternal history of the disease                      |
|                                | History of travelling to endemic regions             |
|                                | Any previous treatment of the disease                |
|                                | Comorbidities (HIV, malaria, TB etc.)                |
| Maternal characteristics       | Age                                                  |
|                                | Weight                                               |
|                                | Nutritional status                                   |
|                                | Trimester                                            |
|                                | Gestational age                                      |
| Maternal clinical signs and symptoms | History of illness (duration of fever)               |
|                                | Hepatomegaly status                                  |
|                                | Splenomegaly                                         |
| Diagnostics                    | Diagnostic method used (PCR, ELISA, rk39DAT, IFA)    |
|                                | Sample analysed (blood, bone marrow aspirates, splenic aspirates etc) |
|                                | Method of confirmation of disease status             |
|                                | Parasite species (L. donovani, L. infantum)          |
| Treatment details              | Dose, duration, frequency including mode of administration |
|                                | Concomitant medication status (antipyretics, antimalarial etc) |
| Delivery characteristics | Mode of delivery (C-section, natural) |
|---------------------------|--------------------------------------|
| Trauma during delivery    |                                      |
| APGAR score               |                                      |
| Examination of placenta   |                                      |
| Birth status (still birth, abortion, healthy birth) | |
| Any birth-related complications |  |
**Declarations**

**Authors’ contributions**

- Conceptualization: PD, PJG, PLO
- Data Curation: PD, SSP
- Formal Analysis: PD, SSP, PJG, PLO
- Funding Acquisition: PJG
- Investigation: PD, SSP, PJG, PLO
- Methodology: PD, SSP, EH, BJM
- Project Administration: PD, PLO
- Resources: PJG, PLO
- Software: PD
- Supervision: PJG, PLO
- Validation: PD, SSP, PJG, PLO
- Visualization: PD
- Writing – Original Draft Preparation: PD, PLO
- Writing – Review & Editing: PD, SSP, BJM, EH, KR, FA, PJG, PLO

**Availability of data and material**

The database(s) supporting the conclusions of this article are available within the tables and figures presented within the manuscript along with the supplemental files (S1 Data, S2 Data).

**List of supplemental files**

- S1 Text: PRISMA checklist
- S2 Text: Search details
- S1 Data: Screening list
- S2 Data: Study data
- S1 Table: Risk of bias assessment
Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

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Competing interests

None

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Fig 2: Number of records and patients by country of origin

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Box 1: Proposed minimum variable recording and reporting for studies or case reports for VL in pregnancy
Total number of records identified through database search as of 26th March 2020 (n = 395)

Duplicate records (n = 123)

Exclusion after title and abstract screening (n = 99)
- 40 articles in non-humans
- 32 articles in lab/diagnostics/entomological surveys
- 20 articles not in VL
- 2 articles not found for abstract screening
- 2 review articles with no description of new cases
- 2 articles described qualitative surveys
- 1 article excluded pregnant women

Records eligible for title and abstract screening after deduplication (n = 272)

Exclusion after reviewing full text (n = 120)
- 50 articles not in pregnancy or no description of pregnant women
- 28 full text articles not available
- 29 review articles describing previously published cases
- 4 conference abstracts later fully published
- 2 articles not in non-VL
- 2 articles describing ongoing study
- 1 article not in human
- 1 article excluded pregnant women
- 1 article described immunology
- 1 article from Iran; not able to translate
- 1 article had no clear description

Records eligible for full text screening (n = 173)

Full text articles included (n = 53)

Total number of records included in the final review (n = 70)

Additional articles identified by searching the references of the included articles and from other sources (n = 17)
