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BRIEF REPORT

# Cutaneous Leishmaniasis: Case Series on Pregnancy Outcome

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We report the pregnancy outcomes of 6 women with cutaneous leishmaniasis; 5 of these women received topical antileishmenial therapy during gestation with paromomycin plus methylbenzethonium chloride combination ointment and/or sodium stibogluconate intralesional injections. No teratogenic effects were reported. Furthermore, no vertical transmission was observed.

**Keywords.** cutaneous leishmaniasis; paromomycin plus methylbenzethonium chloride; pregnancy; sodium stibogluconate; vertical transmission.

Leishmaniasis, a neglected tropical disease, is a major public health concern in many tropical and subtropical countries. It affects ~12 million people worldwide with an annual incidence of 2 million cases [1]. The most common form of occurrence is cutaneous leishmaniasis (CL), with an estimate of 1–1.5 million CL cases per year [1]. CL is endemic in the Middle East and is making a resurgence in Israel, with 4.4 cases per 100 000 people in 2012, compared with 0.4 cases per 100 000 people in 2001. In 2018, the incidence declined to ~3 per 100 000 people [2].

Current recommendations for the treatment of uncomplicated cutaneous leishmaniasis are local therapy with heat or cryotherapy and pharmacological treatments such as intralesional injections of pentavalent antimonials, as well as topical paromomycin [3]. Methylbenzethonium chloride (MBCL) is a quaternary ammonium salt that exhibits antileishmanial activity in high concentrations [4]. It is often used synergistically with the aminoglycoside antibiotic paromomycin (PR) in a combination of 15% PR/12% MBCL ointment. Although not FDA approved, this therapeutic duo has been used in Israel and Latin America for >20 years and demonstrates high efficacy with good cure rates, especially against *Leishmania major* [5, 6]. Even though the aforementioned pharmacotherapy has been used for a few decades, little is known about its safety in pregnancy. Consequently, clear treatment guidelines for CL in pregnancy are lacking.

In addition, the vertical transmission of the *Leishmania* parasite in the context of CL is an open question. To date, no transplacental CL transmission has been reported in humans. However, congenital visceral leishmaniasis transmission has been suspected and described in the literature [7]. As for animal models, CL transmission has been observed in mice [8], and a hamster model suggested the congenital transmission of both cutaneous and visceral leishmaniasis [9].

## METHODS

The Israeli Teratology Information Service (TIS) database was searched for contacts regarding leishmaniasis from January 2000 until the end of March 2019. The characteristics of the inquiries were analyzed, and women who called the TIS about leishmaniasis in pregnancy were contacted by telephone for follow-up using a structured questionnaire. Pregnancies were ascertained prospectively (unknown pregnancy outcome and no prenatal pathology diagnosed at time of first contact). The following information was recorded at the initial contact: maternal demographics, medical and obstetric histories, and exposure details (dose, duration, and timing in pregnancy, additional exposures). Each neonate in Israel undergoes at least 2 physical examinations before being discharged from the hospital. All neonates in the present study were delivered in hospitals. Follow-up was conducted after the expected date of delivery to obtain details on the pregnancy outcome, gestational age at delivery, birth weight, congenital anomalies, and neonatal complications. In addition, all exposures were ascertained. Major anomalies were defined as structural abnormalities in offspring that have serious medical, surgical, or cosmetic consequences. Gestational age was defined from the last menstrual period.

### Patient Consent Statement

Verbal consent to participate in the study was given by the woman. The study protocol was approved by the ethics committee of Israel Ministry of Health.

## RESULTS

From a total of 36 inquiries, the distribution of the call types was as follows: 2 were counseled regarding paternal leishmaniasis, 4 were planning a pregnancy, 9 sought information on lactation, and 21 women were pregnant. The first 2 cases were imported from South America, while the others were acquired

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in Israel. Two of the pregnant women asked about indirect contact with the disease in their nephew or dog. Many women had multiple lesions and reported concurrent CL in their partners or children. Pregnancy outcome was successfully obtained in 6 women, 5 of whom were treated with antileishmanial drugs indicated for CL. These cases are presented in the following text and are summarized in Table 1.

#### Case 1

Case 1 was a 31-year-old woman with hypothyroidism, treated with 150 μg of levothryoxin daily. She had a single lesion on her leg at week 20; leishamnia diagnosis was confirmed by a sample taken from the lesion. Treatment with PR/MBCL ointment was considered, but was not given due to pregnancy. She had an uncomplicated delivery at week 40 of a male newborn, 3650 g with a small hemangioma on his thigh. He had jaundice and was readmitted on day 7 of life for 24 hours of phototherapy.

The patient reported that the healing process resulted in a scar.

#### Case 2

Case 2 was a 46-year-old woman with gestational diabetes had 1 single leishmanial lesion near the eye, which was treated with both PR/MBCL ointment and intralesional sodium stibogluconate injections from weeks 16 and 20, respectively.

A male infant, weight 3000 g, was delivered at week 37 and 3 days without complication; epidural anesthesia was not performed due to concern for leishmania.

The neonate had perinatal jaundice; no congenital malformations were detected.

An elevated scar was left near the patient's eye.

#### Case 3

Case 3 was a 31-year-old woman with no underlying diseases who had 3 leishmanial lesions on her leg. A 10-day treatment with PR/MBCL ointment was completed 6 months before pregnancy. She was then treated with intralesional sodium stibogluconate injections, the third of which was administered 11 days after conception.

A healthy female newborn was delivered at week 39 and 6 days without complications, weight 3400 g.

Congenital malformations were not detected.

#### Case 4

Case 4 was a 28-year-old woman who had 10 lesions on the forehead, hand, arm, and leg. From the fifth gestational week, she was treated with PR/MBCL for 10 months with positive results: some lesions healed completely, while others left very small scars.

She delivered a healthy 3600-g male newborn at week 42 and 2 days with no congenital malformations.

#### Case 5

Case 5 was a 35-year-old healthy patient who had 2 lesions treated with intralesional sodium stibogluconate until week 5 of pregnancy.

She delivered a male infant at week 40 and 1 day, weight 3780 g.

The offspring was born with genetic oculocutaneous albinism, nystagmus, and abnormal vision, which later required special education.

#### Case 6

Case 6 was a 35-year-old generally healthy woman who presented with 2 lesions on the nose and arm at around gestational week 26.

Initially, before *Leishmania* was diagnosed, she was treated with intravenous cefazolin, which transiently decreased the inflammatory response. Later, *L. major* species was confirmed via

**Table 1. Description and Outcome of Cutaneous Leishmaniasis Cases in Pregnancy**

| Case Number | Maternal Age, y | Number of Lesions | Treatment | Lesion Outcome | Pregnancy Outcome (Sex, Gestational Age at Delivery, Birth Weight, Anomalies) |
|---|---|---|---|---|---|
| 1 | 31 | Single | None | Cured with a scar | Male, week 40, 3650, small hemangioma on thigh |
| 2 | 46 | Single | PR/MBCL ointment, intralesional sodium stibogluconate | Cured with an elevated scar near the patient's eye | Male, week 37 + 3, 3000, none |
| 3 | 31 | 3 | PR/MBCL ointment 6 mo before pregnancy, intralesional sodium stibogluconate | Cured | Female, week 39 + 6, 3400, none |
| 4 | 28 | 10 | PR/MBCL ointment | Some lesions healed completely; the others left very small scars | Male, week 42 + 2 3600, none |
| 5 | 35 | 2 | Intralesional sodium stibogluconate | Cured | Male, week 40 + 1, 3780, genetic oculocutaneous albinism, nystagmus, and abnormal vision |
| 6 | 35 | 2 | PR/MBCL ointment after delivery: laser and sodium stibogluconate solution applied topically | Improvement | Female, week 40 + 1, 3700, none |

Abbreviation: PR/MBCL, paromomycin/methylbenzethonium chloride.

polymerase chain reaction; she was then treated with PR/MBCL ointment daily for 2 days, which was discontinued due to the development of facial edema.

Intralesional sodium stibogluconate was considered, but was not given due to her pregnancy and anticipated intolerable local pain in the nose.

She delivered a healthy female infant at week 40 and 1 day, weight 3700 g, with no congenital malformations.

After delivery, experimental treatment with laser and sodium stibogluconate solution applied topically was given monthly. At the time of follow-up, the treatment was still ongoing, with improvement.

In addition, she received an oral course of cephalexin after the first treatment.

In all 6 cases, there was no evidence of vertical transmission.

## DISCUSSION

CL is endemic in Israel, and new infections have been on the rise in the last 2 decades. CL during pregnancy is often characterized by exuberant larger lesions [10]; in addition to the cosmetic consequences, this condition might throw the immune T-cell response out of balance [9, 11], which could theoretically increase the risk for fetal complications, such as preterm births and stillbirths [10]. Limited systemic absorption of paromomycin, 12%, is anticipated after topical administration [12].

## CONCLUSIONS

This case series provides preliminary outcome data on CL in pregnancy. In the small case series detailed above, local therapy with PR and MBCL ointment and sodium stibogluconate intralesional injections were not associated with teratogenic or fetotoxic effects. However, the small sample size calls for caution in the interpretation of results.

Large studies that include a control group with sample size that allows sufficient calculated power are needed before conclusions regarding the safety of local antileishmanial agents during pregnancy and the possibility of vertical transmission can be drawn. This work was prompted by the lack of knowledge on the treatment of CL in pregnancy in general, and the safety of PR/MBCL use during pregnancy in particular, as currently no data exist on MBCL use during gestation.

We hope that our findings will enhance awareness and encourage more research on this topic.


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