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Pregnancy and Leprosy: The Consequences of Alterations of Cell-mediated and Humoral Immunity During Pregnancy and Lactation[1]

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Leprosy has at least three properties which make it of particular immunological interest:

a) It is an exceedingly chronic disease. *Mycobacterium leprae*, the infecting organisms, have division times of about 12 days ([58]). Thus the incubation period is about 2–10 years ([42]). Moreover, because of slow progression of the disease, the period from first appearance of symptoms to initiation of treatment can be several years.
b) *M. leprae* are almost nontoxic. Patients with active leprosy can show a bacteremia of 10^5 AFB per ml and remain physically healthy ([16]). The clinical manifestations of the disease are largely the result of the host response to the infection.
c) The host parasite relationship in leprosy is often unstable, and variations in both cell-mediated (CMI) and humoral immune responses to *M. leprae* can cause clinical manifestations (called reactions) which are not directly related to the bacteriological progress or regression of the disease.

Cell-mediated immunity underlies the immune response in leprosy. The organisms are killed within macrophages activated by lymphocyte products generated in the immune response to the bacilli. The delayed hypersensitivity inflammatory reactions found in leprosy are a manifestation of the cell-mediated response and involve a local accumulation of mononuclear cells. The wide spectrum of leprosy seen clinically and histologically is due to the level of cell-mediated immunity and/or delayed hypersensitivity (DH) possessed by the individual patient. In tuberculoid leprosy where the CMI is high there are few skin lesions and relatively few bacilli, most of which are found in nerves. In lepromatous leprosy, where the patient's CMI is low, there are multiple skin lesions and the body tissues may harbour as many as 10^{11} bacilli ([57]). Between the two polar forms of tuberculoid (TT) leprosy and lepromatous (LL) leprosy there is the immunologically unstable borderline zone: borderline tuberculoid (BT), borderline (BB), and borderline lepromatous (BL) ([52]).

Reactions in leprosy are clinical phenomena caused by alterations in the immune status of the patient. There are two main types of reaction: Type 1 lepra reaction, which is an example of Coombs and Gell Type 4 reaction ([24]) and Type 2 lepra reaction, or erythema nodosum leprosum, which is an example of Coombs and Gell Type 3 reaction ([75]). Type 1 lepra reaction is attributed to factors which alter the patient's DH with a shift along the classification scale ([49]). Increase in DH will tend to cause upgrading or shift towards the tuberculoid end of the leprosy scale (reversal reaction), which may involve either skin or nerve lesions. Decrease in CMI or downgrading is only occasionally associated with a Type 1 reaction, although frequently with worsening of the patient's leprosy and increase of the bacillary load.

It is evident that many of the damaging

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complications of leprosy are caused by an unstable host-parasite relationship related to changes in the host's immune response potential. Diminished CMI can cause increased bacillary multiplication, progress of leprosy and downgrading of classification. Type 1 reactions can cause neuritis, nerve damage and permanent deformity. Type 2 reactions can cause both nerve damage and systemic illness. Although the trigger mechanisms of reactions are not as yet understood, conditions causing general diminution (or increase) of CMI may initiate reactions. Pregnancy is such a condition.

During the course of pregnancy, parturition, the puerperium and lactation, there are profound changes in the immunological status of the mother. Little information, however, is available on the effect of pregnancy on leprosy except from retrospective studies. A collaborative study was therefore established to investigate prospectively clinical and immunological aspects of the effects of a) the mother's pregnancy and lactation on her leprosy; b) the mother's leprosy on her pregnancy and lactation; and c) the mother's leprosy on her child from birth up to the age of two years. The study was carried out at the Addis Ababa Leprosy Hospital in Ethiopia by the Medical Research Council Leprosy Project and the Armauer Hansen Research Institute between December 1975 and May 1978. This paper presents the results of the clinical observations on the effect of the mother's pregnancy and first 12 months of lactation on her leprosy.

PATIENTS AND METHODS

One hundred forty-seven women were studied during 156 pregnancies. There were 114 women with leprosy (119 pregnancies) and 33 healthy women (healthy controls: HC, with 37 pregnancies). The women with leprosy were classified initially, on entry to the study, as follows using the scale of Ridley and Jopling ([52]): cured tuberculoid and borderline tuberculoid leprosy (TT and BT/"cured"), 25 women (25 pregnancies); active tuberculoid and borderline tuberculoid leprosy (TT and BT/"active"), 17 women (18 pregnancies); borderline lepromatous leprosy (BL), 40 women (41 pregnancies); and lepromatous leprosy (LL), 32 women (35 pregnancies).

Eighty-two patients were receiving dapsone monotherapy (50 mg–100 mg daily); 26 patients (1 BL, the rest BT or TT) were believed to be cured and had stopped treatment. Six patients (2 BL, 4 LL) had developed dapsone-resistant leprosy and were receiving clofazimine (4 patients all LL, 5 pregnancies) or rifampin plus thiambutosine and dapsone (2 patients, both BL).

The patients were all Ethiopian women from the low socio-economic class, most of whom lived in the villages adjacent to the Addis Ababa Leprosy Hospital. The patients were first seen when they presented themselves at the hospital's antenatal clinic. Selection of patients was based on their willingness to participate in the study, to deliver their babies in the hospital rather than at home, and to be seen with their babies for regular assessment, including blood tests, for a period of up to two years during lactation.

The patients' hospital case records were examined and data were abstracted regarding leprosy status (clinical relapse, slit skin smear results and biopsy reports) and frequency and type of reaction prior to admission to the study. Particular attention was paid to the three-month period immediately preceding pregnancy; this was expected to provide a base line figure for the frequency of complications in Ethiopian women of childbearing age.

Assessment of the patients' leprosy was made during pregnancy and after delivery at six monthly intervals whenever possible. The assessment included full examination, clinical drawings, slit skin smears, biopsies for histology and mouse foot pad inoculation ([47]), sensory skin testing ([34]) and voluntary muscle testing ([25]). Full details are reported elsewhere. ([17])

i) **Worsening of the patient's leprosy status** is defined as one or more of the following: conversion from negative to positive or rise in bacillary concentration and proportion of solid stained (presumed viable) bacilli in slit skin smears; appearance of new lesions, extension of existing lesions, erythema of tuberculoid lesions (with no histological evidence of reaction) or increased activity of the lesion as diagnosed histopathologically.

ii) Type 1 lepra reaction was diagnosed by the occurrence of one or more of the following: erythema and edema (sometimes with ulceration) of skin lesions; tender enlargement of nerves with or without loss of nerve function and often of abrupt onset; loss of nerve function without tender nerves in patients with tuberculoid or borderline leprosy ([46]) ("silent neuritis"); tenosynovitis, especially of the extensor tendons over the back of the wrist ([76]); or histopathologically ([5]).

iii) Type 2 lepra reaction was diagnosed by the occurrence of one or more of the following: the appearance in the skin of crops of shiny, painful red nodules, either superficial or deep, and lasting from 3–5 days (these were frequently accompanied by a systemic upset with fever, malaise, lymphadenopathy and tender, enlarged peripheral nerves); iridocyclitis; dactylitis; or histopathologically ([51]).

RESULTS

i) Worsening of the patient's leprosy status

Table 1 and Figure 1(i) show the number of cases and timing of the worsening of the leprosy status in the women in the study by three-month intervals from three months prior to conception to 12 months postpartum. Two of the 155 women (one LL, one BL) had shown increased activity of slit skin smears prior to conception. By comparison 55 (35.5%) showed worsening of their leprosy status in association with pregnancy or the first 12 months of lactation. In 43 of the 55 women the deterioration occurred during the second half of pregnancy or the first three months of lactation, most commonly (31 cases) during the third trimester.

In 19 cases the deterioration was transient with increased activity (in skin lesions, slit skin smears or biopsy) most often in the third trimester, which disappeared during lactation. However, in the remaining 36 cases (23% of those studied) the deterioration was significant and progressive.

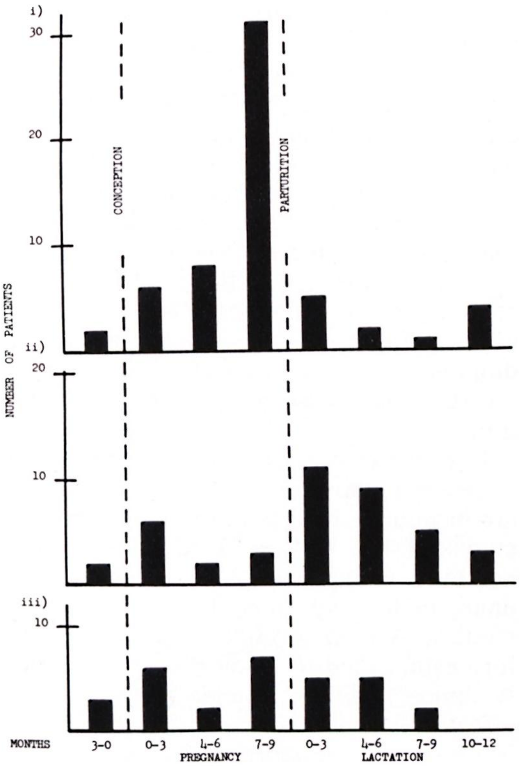

FIG. 1. Time of first occurrence of complications of leprosy prior to conception and during pregnancy and lactation.
(i) Worsening of leprosy status
(ii) Type 1 lepra reaction
(iii) Type 2 lepra reaction

ii) Type 1 lepra reaction

The number of patients who were diagnosed as having type 1 lepra reaction and the timing of the first episode in relation to pregnancy/lactation is shown in Table 2 and Figure 1(ii). Two women developed the reactions shortly after a previous pregnancy and within three months of the pregnancy under study. After an initial increase in the numbers of women with reaction in the first trimester, the number of new cases dropped during the second and third trimesters and then increased sharply after delivery, decreasing only gradually within the first year of lactation. Type 1 lepra reaction often continued for many months. Figure 2(i) shows the number of patients who showed evidence of reaction in each three-month period, and demonstrates the magni-

TABLE 1. *Number of patients showing worsening of leprosy status.*

Initial classification of leprosy status	No. of women studied	No. of pregnancies studied	No. of patients with worsening of leprosy status: 3 months preceding pregnancy	Pregnancy: 1st trimester	Pregnancy: 2nd trimester	Pregnancy: 3rd trimester	Lactation: 0–3 months	Lactation: 4–6 months	Lactation: 7–9 months	Lactation: 10–12 months	Total
Healthy controls	33	37	—	—	—	1 (as BT)[a]	1 (as BL)	—	—	—	2
TT and BT "cured"	25	25	—	1 (as BT)	1 (as BT)	5 (2 as BT) (3 as BL)	—	—	—	1 (as BT)	8
TT and BT "active"	17	18	—	—	—	5	—	1	1	—	7 (5)
BL	40	41	1	3	3	7	3	1	—	—	18 (5)
LL	32	35	1[b]	2	4	13	1	—	—	1	22 (9)
Total	147	156	2	6 (2)	8 (2)	31 (13)	5 (1)	2 (1)	1	2	57 (19)

[a] Figures in parentheses ( ) indicate the number of patients with transient worsening of leprosy status.
[b] Further deterioration at 13 months postpartum.

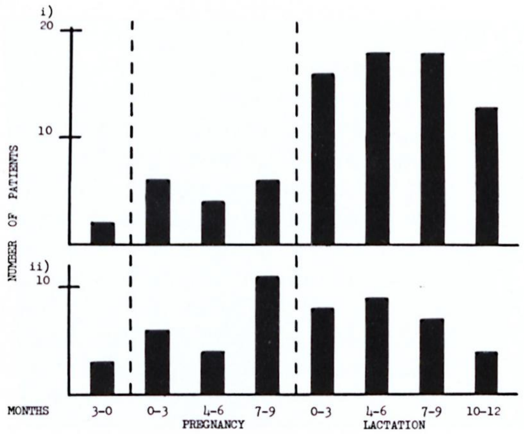

FIG. 2. Time of occurrence of all episodes of lepra reactions prior to conception and during pregnancy and lactation.
(i) Type 1 lepra reaction
(ii) Type 2 lepra reaction

tude of the problem during lactation. It should be noted, however, that this figure includes patients with "silent neuritis"; this is probably caused by Type 1 lepra reaction, but histological proof of the etiology has not as yet been obtained ([18]).

Site of reaction. Reaction in skin, or skin and nerve, was a feature of pregnancy and early lactation (especially with regard to the first occurrence). Reaction in nerve alone was a marked feature of lactation and occurred in only two patients during the second half of pregnancy (Table 3). Where Type 1 lepra reaction occurred in skin during late lactation it was always in association with worsening of the patient's leprosy status.

Downgrading and upgrading. These were diagnosed histologically in all cases. Downgrading from BL to LL occurred in five patients. In 3 the phenomenon was observed during the third trimester, in 1 immediately postpartum, and in 1 at six months postpartum in association with worsening of the leprosy status. Upgrading reaction was observed in six patients after delivery, in four of whom there was concomitant clinical evidence of reaction in skin or nerve.

iii) Type 2 lepra reaction

The number of patients diagnosed as having Type 2 lepra reaction and the timing of the first episode in relation to

TABLE 2. *Incidence of Type 1 and Type 2 lepra reaction according to classification of leprosy.*

Final classification of leprosy[a]	No. of patients[a]	No. of pregnancies studied[a]	No. of patients developing reactions		
			Type 1 lepra reaction	Type 2 lepra reaction	Type 1 and Type 2 reaction concurrently
TT and BT "cured" and "active"	40	41	11 (27%)	0	0
BL	44	45	19 (42%)	10 (22%)	3 (7%)
LL	32	35	10 (29%)	18 (51%)	2 (6%)

[a] The initial classification and grouping of patients has been revised to include new cases (previously healthy controls) and relapse cases (previously TT and BT "cured") under appropriate classifications.

pregnancy/lactation are shown in Table 2 and Figure 1(iii), respectively. Three women had reaction during the three months preceding the pregnancy under investigation; in two cases the reaction followed a previous pregnancy. There was a rise in incidence of reaction throughout pregnancy and the first six months of lactation. Figure 2(ii) shows the timing of the recurrent episodes of Type 2 lepra reaction; most of them occurred during the third trimester and the first nine months of lactation.

Mixed reactions. Type 1 and Type 2 reactions occurred concurrently in five patients, all of whom were upgrading during lactation. One patient had previously downgraded during pregnancy. In four cases there was also some evidence of worsening of the leprosy status.

DISCUSSION

In certain diseases natural remission occurs with the advance of pregnancy followed by deterioration after delivery. Such diseases include rheumatoid arthritis ([27, 28, 44]), ulcerative colitis ([15]), and sarcoidosis ([59]). Systemic lupus erythematosus frequently presents for the first time immediately postpartum ([56]), as does rheumatoid arthritis ([44]). Transient hypothyroidism and transient hyperthyroidism have been observed following delivery of patients with Hashimoto's and Graves' disease, respectively ([1, 2]). In poliomyelitis ([41]), tuberculosis ([48, 72]), and leprosy ([26, 53]) the disease has been shown to become overt or to progress rapidly during pregnancy, especially the third trimester and immediately postpartum. The high fatality and unusual severity of viral hepatitis in malnourished women

TABLE 3. *Number of patients developing Type 1 lepra reaction in pregnancy and lactation—site of reaction.*

	3 months preceding pregnancy	Pregnancy (trimester) 1	2	3	Lactation (months) 0–3	4–6	7–9	10–12	Total patients	Total episodes
Skin only		1	2 (1)[a]	2 (1)	2 (2)	2 (1)	2 (2)	1 (1)	4	12
Skin and nerve		1	1 (1)	2 (1)	3 (1)	1	1 (1)	1 (1)	6	10
Nerve only	2	4	1	2 (1)	11 (2)	14 (8)	14 (10)	11 (8)	28	59
Upgrading[b]						1	1		2	2
Total	2	6	4 (2)	6 (3)	16 (5)	18 (9)	18 (13)	13 (10)	40	83

[a] Figures in parentheses ( ) denote the number of patients developing recurrent episodes of Type 1 reaction.
[b] Upgrading was diagnosed histologically with no clinical evidence of Type 1 reaction.

during late pregnancy is well known ([8]). Possible explanations for these observations have been:

a) **Raised hormone levels during pregnancy.** Increased levels of free cortisol and 17-hydroxycorticosteroid explain the remissions of rheumatoid arthritis and ulcerative colitis ([15,56]). Increase in endogenous corticosterone causing suppression of host resistance may in part explain the exacerbation of tuberculosis and leprosy during pregnancy. In mouse experiments no change was observed in the rate of multiplication of *M. leprae*, but a higher count of viable bacilli was achieved in foot pads of mice fed on a diet containing hydrocortisone ([58]). Similar results have been obtained in experiments using *M. tuberculosis* ([5]).

   Treatment with stilbestrol and thyroid hormones has been considered a factor in the sudden appearance of skin lesions of leprosy ([32,68]) (W. H. Jopling, 1979, personal communication). Conversely, treatment with drugs which have anti-thyroid activity has been successful in murine leprosy ([36]).

b) **Metabolic disturbances.** General malnutrition and protein deficiency are probable etiological factors in leprosy ([31,60]) and have been reported as common in pregnant women in Ethiopia ([22]). The rapid worsening of leprosy and disappearance of reactions under conditions of near starvation has been recorded ([55]). It is likely that depression of CMI associated with severe malnutrition ([11]) is responsible for these phenomena.

c) **Alteration in CMI during pregnancy.** Recent publications have reported varying results regarding alterations in CMI during pregnancy ([6,10,14,21,29,30,43,61,70]). Some of the differences in results are due to variations in methodology, concentrations of lymphocytes in tissue culture, use of autologous plasma rather than standard serum and choice and dosage of mitogens and/or antigens used. Since these tests are all carried out *in vitro* and isolated from the intact immune system, the results may bear little resemblance to what really happens *in vivo*. It is generally agreed that there is some suppression of CMI probably due to serum factor(s). Cell-mediated suppressor mechanisms, however, may also be involved ([62]), in particular causing an impaired response to PPD which reverts to normal shortly after delivery.

Attempts to explain this suppression of CMI in terms of endocrine levels have been made by assessing the *in vitro* response to phytohemagglutinin and other mitogens in women taking contraceptive pills, with conflicting results ([3,20]). However, the immunosuppressive properties of pregnancy associated α-macroglobulin (PAM) which rises dramatically in pregnancy and then drops to insignificant levels within six to nine weeks postpartum has been demonstrated ([63,64]). PAM has been identified on the surface of peripheral leukocytes in both pregnant women and in women taking oral contraceptives, and is present in some women until six months postpartum. Estrogen has been shown to trigger the rise in levels of PAM (later renamed pregnancy associated α-glycoprotein: PAG) both in women taking oral contraceptives and in men taking stilbestrol for prostatic carcinoma ([66]). It is likely that the estrogen-induced immunoregulation is mediated through the thymus ([67]). While PAM (PAG) was shown to modify cellular transformation most when elective stimulators of T cells were used, the exact role of PAM (PAG) in the impairment of the immune response in pregnancy has not been ascertained since other factors are known to be involved. In leprosy in particular it is very likely that plasma from pregnant leprosy patients contains increased suppressive factors, since plasma from mothers with leprosy had a greater inhibitory effect on their babies' lymphocyte transformation than plasma from healthy mothers ([7]).

The presence of immune complexes during normal pregnancy is controversial ([23,39]). The discrepancies in results may be due to differences in methodology, and the role of immune complexes in human pregnancy remains unknown ([38]).

The diseases mentioned above show a pattern of amelioration during pregnancy and rebound deterioration postpartum. Leprosy, however, shows what may be called a biphasic adverse effect, with deterioration of the leprosy status during pregnancy and prolonged Type 1 lepra reaction following delivery. While various factors as mentioned may influence the patient's leprosy status, we feel that the most likely explanation for this biphasic effect is suppression of the mother's CMI during pregnancy and recovery of CMI postpartum.

i) Worsening of the patient's leprosy status

Previous reports indicate that pregnancy is apt to precipitate the appearance of overt leprosy ([13, 26, 37, 53, 69]). Our results fully confirm this. Six percent (2/33) of the "control" patients developed leprosy during the study, and 32% (8/25) of the apparently cured cases relapsed.

It has also been shown previously that pregnancy is associated with the exacerbation of existing leprosy ([13, 26, 33, 35, 37, 54, 69]). The results of this study confirm this; 20% of the patients receiving treatment showed transient worsening of their leprosy during the study period despite apparently effective chemotherapy.

A novel and hitherto unrecorded finding was the high proportion of patients (38% of those receiving treatment) who showed significant and apparently progressive deterioration almost certainly caused by the emergence of dapsone-resistant leprosy (proven in all seven cases where mouse foot pad tests were undertaken). This high figure may be related to the high proportion of new cases in Ethiopia (about 50%) showing primary low-grade dapsone resistance ([45]). The immunosuppression of pregnancy may well afford the opportunity for drug-resistant bacilli to multiply and cause overt disease unusually rapidly. These findings have been fully reported elsewhere ([19]).

The phenomenon of downgrading was observed particularly during pregnancy and might be expected in any condition where CMI is suppressed. Within the LL group a number of patients showed a shift from subpolar lepromatous leprosy (LL_s) to polar lepromatous leprosy (LL_p) ([50]) in association with exacerbation of the infection.

ii) Type 1 lepra reaction

Since this is usually due to an increase in CMI or DH it is not surprising that it occurs immediately after delivery and our study confirmed the findings of others ([12, 33, 53]). However, the classical appearance of reversal reaction with erythema and edema of skin lesions was not a prominent feature in our patients, except in those who also relapsed with active leprosy or who had very recently started treatment. The picture described by Rose and McDougall ([53]) may reflect the natural evolution of the disease in untreated patients. We did, however, observe that reaction in skin or skin and nerve was a feature of pregnancy and early lactation; whereas reaction in nerve alone was a feature of the lactation period. This may reflect predominant exposure of the surface antigens of actively multiplying *M. leprae* during pregnancy and relatively increased uncovering of cytoplasmic antigens postpartum ([4]), if postpartum recovery of CMI leads to bacillary destruction. Reversal reaction was sometimes unusual in that it was seen coincidentally with Type 2 lepra reaction.

While the peak incidence of new cases of Type 1 lepra reaction occurred immediately after delivery, new and recurrent episodes also occurred late in lactation, suggesting that residual Schwann cells in the nerve trunks contained small numbers of bacilli which previously went unrecognized ([74]), but with recovery of CMI were recognized and attacked. Alternatively, late reaction may be caused by the release of sensitized lymphocytes which can be trapped in the spleen for prolonged periods ([9]).

iii) Type 2 lepra reaction

Our observations confirmed other reports of an increase in Type 2 lepra reaction during pregnancy ([33, 40, 71]) and during lactation ([33, 37]). The reaction was associated with exacerbation of leprosy and occurred throughout pregnancy with a peak in the third trimester [Fig. 2(ii)], gradually decreasing during the first year of lactation. The incidence is higher than would be expected in non-pregnant patients on treatment, particularly in the

BL group, and is probably associated with the suppression of CMI, increased multiplication of bacilli and hence increased antigen load, and a tendency to shift towards the lepromatous pole ([73]).

This study highlights the risks to which leprosy patients are exposed when they become pregnant. Their disease may relapse or deteriorate, and they are liable to develop reactions or neuritis for many months after delivery. Moreover, there may be reluctance to use either additional chemotherapy or corticosteroids during pregnancy and lactation; thus the medical management of these patients is made more difficult. There is clearly a place for health education in this situation. Patients should be made aware of the risks they undergo and encouraged to plan their pregnancies to take place only when their leprosy is fully controlled by chemotherapy. Careful medical supervision during and after pregnancy should, however, reduce the consequences (if not the incidence) of leprosy complications associated with pregnancy. Awareness on the part of the obstetrician of potential leprosy problems may play a critical part in their early recognition and correct management.

SUMMARY

One hundred fourteen Ethiopian women with leprosy and 33 healthy women without leprosy were studied prospectively throughout 119 and 37 pregnancies, respectively, and followed up during lactation. Fifty-five women showed worsening of their leprosy status; in 31 (56%) this was observed during the third trimester of pregnancy. Forty women were diagnosed as having Type 1 lepra reaction; in 20 (50%) the first occurrence was during the first six months of lactation. Twenty-eight women had Type 2 lepra reaction, which in 19 (68%) first occurred during the third trimester of pregnancy or the first six months of lactation. These adverse effects of pregnancy on leprosy are thought to be associated with suppression of maternal cell-mediated immunity during gestation and recovery postpartum. Implications for the obstetrician, physician and leprosy health worker are discussed.

RESUMEN

Se hizo un estudio prospectivo de 114 mujeres con lepra y de 33 mujeres sanas a través de 119 y 37 embarazos, respectivamente. El estudio se continuó hasta la lactancia. Cincuenta y cinco mujeres mostraron un agravamiento de su enfermedad; en 31 mujeres (56%) ésto se observó durante el tercer trimestre del embarazo. Cuarenta mujeres presentaron reacciones leprosas del Tipo 1; en 20 de ellas la primer aparición de reacción leprosa ocurrió durante los primeros 6 meses de la lactancia. Veintiocho mujeres tuvieron reacción leprosa del Tipo 2 la cual, en 19 (68%) apareció durante el tercer trimestre del embarazo o durante los primeros 6 meses de lactancia.

Se piensa que estos efectos adversos del embarazo en lepra están asociados con supresión de la inmunidad celular materna durante la gestación y durante la recuperación post-parto. Se discuten las implicaciones para el obstetra, el médico y el leprólogo.

RÉSUMÉ

On a mené une étude prospective de la grossesse et de la lactation chez cent quartorze femmes éthipiennes souffrant de lèpre (119 grossesses) et chez trente-trois femmes témoins indemnes de lèpre (37 grossesses). Chez cinquante-cinq femmes malades, on a observé une détérioration de la situation de la maladie. Chez 31 d'entre elles (56%) cette détérioration a été observée au cours du troisième trimestre de la grossesse. Une réaction lépreuse de Type 1 a été diagnostiquée chez quarante femmes; chez 20 (50%), le premier épisode se situait au cours des six premiers mois de la lactation. Une réaction lépreuse de Type 2 a été notée chez vingt-huit femmes, dont 19 (68%) ont présenté le premier épisode au cours du troisième trimestre de la grossesse ou durant les six premiers mois de la lactation. On estime que les effets adverses qu'exerce la grossesse sur la lèpre sont associés à une suppression de l'immunité à médiation cellulaire chez la mère au cours de la grossesse et du post-partum. Les implications pour l'obstétricien, le médecin et le travailleur de lèpre sont discutées.

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