

## **The association of pregnancy and leprosy**

### **II. Pregnancy in dapsone-resistant leprosy**

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*Summary* Sixty-seven women with lepromatous leprosy were studied during 70 pregnancies and followed up during lactation; 6 patients were already dapsone resistant and an additional 4 were receiving dapsone 100 mg daily under trial conditions for suspected dapsone resistance. During the study 28 patients including the 4 already suspected of having dapsone resistance relapsed with probable dapsone resistance. While failure in patient compliance was thought to be important in some cases, recurrent pregnancies, by providing periods of physiological suppression of cell-mediated immunity, could well be the factor in causing the progression of dapsone resistance among women.

### **Introduction**

Dapsone-resistant leprosy has become a major problem in Ethiopia. The incidence among patients with lepromatous leprosy in the Addis Ababa area in the period 1973–77 was about 3% per annum<sup>1</sup> and a high prevalence of primary dapsone resistance has also been reported.<sup>2</sup>

The factors contributing to the development of drug-resistant leprosy are probably much the same as those in tuberculosis. Inadequate dosage, irregular treatment and above all prolonged monotherapy all played a part in the causation of the Ethiopian epidemic of dapsone-resistant leprosy. However, it is possible that other factors, such as the immunosuppression associated with

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pregnancy, could play a part in determining the time at which incipient dapsone-resistant leprosy becomes clinically manifest.

Even in untreated lepromatous leprosy host factors are present which make some contribution towards controlling the infection. Thus, it is almost universally observed that such patients have only some 10% of solidly staining, presumed viable bacilli, the remainder are for the most part fragmented and non-viable, and therefore some host mechanism must be responsible for this process. Such a host factor must either prolong the generation time or (more likely) slow down the increase in bacillary load by killing a considerable proportion of bacilli without assistance by chemotherapy. If this control were lessened, for example as part of the process of immunosuppression during pregnancy, it could be expected that relapse or deterioration of untreated patients would be associated with pregnancy. Similarly, a subpopulation of dapsone resistant *Mycobacterium leprae* might be expected to show a rapid increase in numbers under these conditions, even if a patient were receiving monotherapy with dapsone.

This paper reports the results of a prospective study of the effects of pregnancy on lepromatous leprosy.

### **Patients and methods**

The patients were all Ethiopian women of the low socio-economic class who lived in the villages surrounding the Addis Ababa Leprosy Hospital. There were 67 women (35 classified as having borderline lepromatous leprosy, BL and 32 with lepromatous leprosy, LL)<sup>3</sup> studied throughout 70 pregnancies. They were all receiving outpatient treatment for leprosy and were first seen and taken into this study when they presented themselves at the Hospital Antenatal Clinic. Selection of patients was based on their willingness to participate in the study, to deliver their babies in hospital rather than at home and to be seen with their babies for regular assessment including blood tests for a period of up to 2 years during lactation. Intake of patients was staggered over 12 months.

Assessment of leprosy was made during pregnancy and after delivery at 6-month intervals whenever possible. This included inspection of skin lesions, clinical drawings, palpation of nerves and regional lymph nodes, slit skin smears and biopsies; full details are recorded elsewhere.<sup>4</sup> When a patient was suspected of having developed dapsone-resistant leprosy, a biopsy of an active skin lesion, with a positive morphological index (MI), was taken and tested for dapsone resistance in all 11 cases by the mouse foot-pad technique.<sup>5, 6</sup>

Resistance to dapsone was defined as multiplication of *M. leprae* in mouse foot pads at a concentration of dapsone 0.0001% or more in the diet.<sup>6</sup>

## Results

Sixty-seven patients were included in the study (35 were BL, 32 LL); 3 of them were followed through 2 pregnancies. At the start of the study 6 patients were already diagnosed as dapsone resistant, and were taking clofazimine or rifampicin plus thiacetazone and dapsone. An additional 4 patients were suspected of dapsone resistance, and were receiving dapsone 100 mg daily under trial conditions with the maximum possible supervision and frequent assessments. Thus the initial prevalence of proven and suspected dapsone-resistant leprosy was 10/70, 14%; that is, much the same as the general prevalence among lepromatous patients at that time. The remaining patients were receiving dapsone 100 mg daily under routine outpatient clinic supervision.

During the course of the study an additional 24 patients showed clinical and/or bacteriological or histological deterioration despite apparently continuing to take dapsone, and were therefore considered to have prima-facie evidence of dapsone-resistant leprosy. In the majority of cases the diagnosis was clinical; the patients showed new active skin nodules, in which the BI and MI were raised. However, nearly half of the patients (10/24) gave indications of relapse on routine skin smears and/or biopsies before new skin lesions became evident, and an additional 3 cases showed definite relapse on smears/biopsies when there was only minimal clinical evidence of relapse. A striking feature of clinical relapse in these patients was the rapidity of development and increase in number of skin lesions after routine smears gave indications of relapse. The most rapid deterioration occurred toward the end of pregnancy when 7/24 women showed marked clinical deterioration during a 3-month period including part or all of the third trimestre. An additional 5 patients showed moderately rapid deterioration starting in the third trimestre and extending into the first 6 months of lactation.

It was not possible to perform mouse foot-pad tests for dapsone resistance in all cases. In some cases, because of shortage of mice, foot-pad tests were only done with DDS in low dietary concentrations. There were 4 'technical failures' on account of delays in the biopsied material reaching the laboratory; in these cases repeat biopsies were not carried out as alternative dual therapy had been instituted on account of rapid deterioration during pregnancy. Four of the 6 patients, already designated as DDS resistant, had this confirmed by mouse tests prior to their present pregnancies. Results of the 7 patients tested successfully *during* the study are shown in Table 1. Three of these (Nos. 1, 2 and 7) were from the 4 patients suspected of being DDS resistant, but improving on dapsone 100 mg daily monotherapy under trial conditions prior to pregnancy; the remaining 4 were from the 24 patients relapsing for the first time during pregnancy. Of the patients whose detailed results are known 11/11 were resistant at 0.0001% DDS in diet, 6/8 were resistant at 0.001% DDS in diet and 6/6 were sensitive at 0.01% DDS in diet. None of the patients tested was proved dapsone sensitive.

**Table 1.** Results of mouse foot-pad assessment of dapsone sensitivity

	No. of Patients	Patient No.	Concentration of DDS in Mouse Diet			Conclusion
			0.01%	0.001%	0.0001%	
			Human Equivalent Dose			
			100 mg	10 mg	1 mg	
Tested during study	7	1	ND	+	+	R
		2	0	+	+	R
		3	0	+	+	R
		4	0	+	+	R
		5	0	ND	+	R
		6	0	0	+	R
		7	0	0	+	R

ND = Not done.

R = Resistant.

+

0 = No growth of bacilli.

The timing of relapse is shown in Table 2. Half the patients (14/28) relapsed clinically in the third trimestre (in some cases a rising BI was detected earlier in the pregnancy) and most of the remainder within 6 months after delivery.

In addition to these patients, all 4 patients already suspected of dapsone resistance and being treated under trial conditions showed further deterioration during this study (3 in the third trimestre or lactation, 1 at the end of the first trimestre).

The complaint of 'rheumatism' was commonly associated with relapse, it preceded relapse in about half the patients, and was almost always a complaint at the time of relapse. ENL and neuritis preceded relapse in about half the patients (but were not uncommon in smear positive cases who did not relapse). At the time when relapse became clinically evident ENL was observed in half (14/28) of the patients. ENL was much more common than might be expected in BL patients, being recorded during pregnancy in 25% (9/36) of them: ENL was seen more frequently in BL patients who relapsed (33%: 5/15) than in BL patients who did not relapse (19%: 4/21).

Three BL patients downgraded to LL in association with relapse due to probable dapsone resistance; 2 downgraded during the third trimestre of pregnancy, 1 at 6 months postpartum. The diagnosis was made on histological grounds. The 2 patients who downgraded during pregnancy at the time of clinical relapse, together with another patient (initially classified LL) who had also relapsed during the third trimestre of pregnancy, all upgraded during lactation (1 to BL, 1 to BB/BL and 1 to BB/BT). The upgrading reaction was associated with new nerve enlargement or frank neuritis in all 3 cases and was confirmed by histology. The upgrading reaction was most marked at 6 months postpartum when all 3 women were still lactating and amenorrhoeic. In addition, and as reported elsewhere,<sup>4</sup> 3 patients downgraded to polar lepromatous

**Table 2.** Timing of clinical relapse due to probable dapsone resistance

Classification of mother's leprosy	BL	LL	Total
No. of pregnancies studied	34	34	70
No. of relapses	15	13	28
Timing of clinical relapse:			
Pregnancy trimestre – first	2	–	2
– second	1	2	3
– third	8	6	14
Lactation (3-month periods) 0–3	2	2	4
4–6	1	1	2
7–9	–	–	–
10–12	1	1	2
13–15	–	–	–
16–18	–	–	–
19–21	–	1	1
22–24	–	–	–

leprosy (LL<sub>p</sub>)<sup>7</sup> showing for the first time, the histological features of LL<sub>p</sub> during late pregnancy or the puerperium in association with relapse.

During the course of the study it became evident that there was an unexpectedly high incidence of probable dapsone-resistant leprosy associated with pregnancy. Therefore, case records of women already diagnosed as suffering from dapsone-resistant leprosy were reviewed, and the patients interviewed. An obstetrical history was obtained from 42 patients; 36 of them had had children after starting anti-leprosy treatment, of whom 31 first noticed new relapse nodules during pregnancy or soon after delivery or after a spontaneous abortion. Only 5 relapsed independently of pregnancy. The patients themselves were well aware that pregnancy had made their leprosy worse.

### Discussion

Emergence of dapsone-resistant leprosy occurs more frequently when the dosage of dapsone is low or irregular; thus it will be associated with poor-patient compliance in taking dapsone regularly. Studies in Ethiopia have indicated that outpatients swallow approximately half the dapsone issued to them.<sup>8</sup> This is the usual finding in such studies, though figures as high as 89% have been reported.<sup>9</sup>

In the study we are reporting, less than 10% of women stated they had stopped taking dapsone for a few weeks during the first trimestre on account of emesis gravidarum. They all stated they had resumed treatment during the second trimestre. The rest of the women said they never stopped taking dapsone. Furthermore, it appeared to be generally believed that dapsone (unlike some other drugs) would not harm the foetus. The degree of patient–

doctor contact was high, and we considered it probable that the women took treatment regularly. However, from the results of the mouse foot-pad tests (Table 1) there is evidence that patients 2–7 could not have been taking dapsone regularly or fairly regularly, otherwise the lower level of dapsone-resistant mutants would have been killed. The failure of compliance demonstrated by these patients is disturbing. Nevertheless, it follows the pattern of other diseases; attempts to improve compliance by educating diabetic, hypertensive or tuberculosis patients about the importance of regular treatment have all failed.<sup>10</sup>

In Ethiopia, where dapsone resistance has become a major problem, dapsone resistance at a concentration of dapsone 0.0001% in the diet is referred to as low-grade resistance and has been shown to respond, for a period of up to 4 years, to treatment with dapsone 100 mg daily.<sup>11</sup> But as these patients harbour a number of more highly resistant dapsone mutants<sup>12</sup> in time resistance to higher dosage of dapsone emerges in a stepwise fashion.<sup>11, 12</sup> This is in contrast with the single-step emergence of resistance to rifampicin.<sup>13</sup> Recurrent pregnancies by providing periods of physiological suppression of CMI could well be a factor in contributing to the progression of dapsone resistance among women.

The suppression of CMI during pregnancy is also probably responsible for the extremely rapid deterioration observed during the third trimestre of pregnancy – 3 to 6 months for half of our patients compared with 12 months for clinical relapse in a male patient under closely controlled conditions.<sup>14</sup> Downgrading and upgrading in association with relapse, occurring during pregnancy and lactation respectively is further evidence of the increased immunological instability associated with pregnancy.

The association of pregnancy and the emergence of dapsone-resistant leprosy is clear from the obstetrical histories of women already diagnosed as having developed dapsone-resistant leprosy. It is fully confirmed by this prospective study. Indeed, the difficulty is not to establish the relationship but to account for the excessively high incidence in the trial patients during the study period. Possible sources of error include:

- (1) Selection of patients. Although to the best of our knowledge no special selection of patients occurred, it is possible that patients who were already feeling that all was not well regarding their leprosy opted to be in the study, thus applying some degree of self-selection.
- (2) Overdiagnosis of relapse. This is not a serious possibility. The clinical and laboratory findings supported each other in most cases, as most of the patients showing (at first) only laboratory evidence of relapse, had relapsed clinically by the end of the study.
- (3) Overdiagnosis of resistance. This again is unlikely. Four of the 6 patients already dapsone resistant (following relapse in a previous pregnancy) and

7 patients in the present study were tested by mouse foot pad tests and none showed dapsone-sensitive bacilli.

- (4) One possibility is that in the early stages of emergence of dapsone-resistant leprosy the clinical signs are labile, and that relapse lesions might resolve between pregnancies, the condition progressing in a stepwise fashion. The relatively short period of this study prevents any definite conclusion but when last seen only 3 of the patients suspected of dapsone-resistant leprosy, but not tested in mice, were still improving on dapsone monotherapy.

### *Practical applications*

There are 3 important areas of application of these findings to the practical management of women with lepromatous leprosy.

- (1) The possibility of giving supplementary chemotherapy in effective dosage during pregnancy and lactation might be considered: this would aim both to prevent the emergence of dapsone-resistant leprosy and also to lessen the risk of infecting the baby before and after delivery. Clofazimine (in the dosage of 100 mg at least 3 times a week) for 1 year starting at the beginning of the second trimestre would probably be the most suitable drug for the purpose, and would have the additional advantage of possibly reducing the amount of ENL occurring during pregnancy and lactation.
- (2) There is a clear risk that pregnancy will make leprosy worse; patients frequently develop ENL and neuritis, which could be damaging even in the absence of dapsone resistance. It would be reasonable to advise women with lepromatous leprosy to limit the size of their families by whatever means are locally acceptable. However, it should be remembered that the role of exogenous oestrogens (such as are found in the contraceptive 'pill') in the causation of relapse is as yet unknown, and use of oral contraceptives should be carefully monitored. Personal interviews with patients who had suffered relapse or reaction in association with pregnancy not only revealed that the patients were aware of the adverse effect of pregnancy on leprosy, but in addition many patients volunteered the information that they wished for no more than 1 or 2 children at most.
- (3) Should any of the children of women with dapsone-resistant leprosy develop leprosy at an early age, it is highly likely that they will have dapsone-resistant leprosy – and hence would require alternative therapy.

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