

Adverse Reactions Following Pregnancy in Patients with Borderline (Dimorphous) Leprosy

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Following pregnancy, adverse reactions are described in 7 patients suffering from borderline (dimorphous) leprosy. The reactions in most cases were sudden and severe; nerve damage often occurred within the space of a day or so, with resultant paralysis and anaesthesia. Some of these patients were seen in remote areas, and on clinical signs alone it was not possible to distinguish between immunologically beneficial (upgrading, reversal), and immunologically detrimental (downgrading) reactions. However, their spontaneous occurrence following pregnancy and the fact that cell-mediated (not humoral) immune factors are known to be involved in this type of reaction, raise the possibility that they may have been precipitated by a return of cell-mediated competence following pregnancy. These reactions frequently cause tissue damage, and this is most important in peripheral nerves; their pathogenesis is as yet poorly understood. The possible significance of their occurrence in or following the puerperium is discussed in relation to recent research on depression of cell-mediated immune responses in pregnancy, and in women taking the contraceptive pill.

Introduction

Since the earliest days of observation in clinical medicine and obstetrics, attention has been drawn to the adverse influence of pregnancy and labour on a wide range of diseases, notable among them heart disease and phthisis. In the field of leprosy, it is well known that the disease may be precipitated or made worse during pregnancy (Lawson, 1967), but has no obvious effect on the pregnancy itself (Ryrie, 1938). In the widespread, symmetrical form of leprosy termed lepromatous, where cell-mediated responses are totally lacking, reactions during or shortly after pregnancy commonly take the form of an immune-complex disease in which Erythema Nodosum Leprosum (ENL) may be prominent in the skin; these have a high incidence in females with lepromatous leprosy, and the clinical findings and treatment are already well documented. Far less understood however, are the unpredictable and often rapidly damaging reactions associated with borderline (dimorphous, intermediate) forms of leprosy. This type of leprosy

is the most commonly encountered in clinical practice between the tuberculoid and lepromatous poles; its wide range of skin and nerve manifestations, together with the histopathology, have been fully described (Ridley and Jopling, 1966), giving a valuable classification according to immunity. Two basic forms of reaction in borderline leprosy have been described (Ridley, 1969). Downgrading reactions occur in untreated patients and are associated with a decline in cell-mediated immune competence. Upgrading (syn. reversal) reactions occur usually—though not invariably—under the influence of drug treatment, as the patient regains capacity to produce hypersensitivity at the main sites of bacillary deposition (Turk and Bryceson, 1971), following a reduction in the bacillary load. Both forms of reaction cause swelling and inflammation in dermal and neural lesions, and although this may be controllable (for instance by steroids), in practice these adverse reactions continue to account for a high percentage of all nerve damage in a disease which itself heads the world list for disabling sensory-motor neuropathies. The numerous other factors which may apparently precipitate these cell-mediated reactions in borderline leprosy are listed in standard works (Cochrane and Davey, 1964; Trautman and Enna, 1970; Jopling, 1971; Bryceson and Pfaltzgraff, 1973). The present paper describes a small group of patients from widely differing countries who were not on drug treatment at the time of reaction and in whom a recent pregnancy appeared to have been the most likely precipitating factor. The possible implications of this are discussed in the light of recent work on depressed cell-mediated immunity in pregnancy (Purtilo *et al.*, 1972; Finn *et al.*, 1972; Kasakura, 1971; Fabris, 1973; St Hill *et al.*, 1973) and in women taking oral contraceptives (Barnes *et al.*, 1974).

Case Reports

Case 1 (L.T.) aged 40, Guyana. A woman of African descent was seen four months after her 11th pregnancy ended in stillbirth. She gave a history of red marks on her nose for three months, first seen about one month after delivery and increasing in size and redness. Red swollen spots had recently appeared on the backs of her hands. Examination revealed a well-nourished woman whose entire body was covered by raised pink plaques, some of them slightly oedematous, and mainly well-demarcated from surrounding normal skin. The most striking feature was a single brilliant red, oedematous plaque occupying the entire right side of the face, including the eyelids and extending over the midline to cover the nose. No enlarged nerves were found, neither were there any palpable branches approaching the plaques, but the larger lesions showed diminished sensation to light touch.

Case 2 (S.S.F.) aged 32, Guyana. A patient of Indian descent was seen three months after the birth of her 3rd child, with a history of exacerbation of pre-existing skin lesions from about two weeks post-partum. Examination revealed a well-nourished woman with longstanding, bilateral foot-drop. Her limbs were covered by bright pink plaques—larger and more numerous on the right side of the body; they ranged in size from 2 in diameter on the dorsum of the hands to enormous, annular lesions covering thighs and knees. The lateral surface of the right leg was almost covered by a single, dry, hairless, hypopigmented macule. However, the most striking feature was a single, bright pink and grossly oedematous plaque that almost covered her face, involving more of the right side than the left and making it impossible to test accurately for lagophthalmos until a

later date. Superficial nerves were enlarged, especially the lateral popliteals; the majority of plaques showed diminished sensation to cotton wool and there was marked loss of sensation over the right thumb and index finger.

Case 3 (B.F.) aged 20, Guyana. A patient of Indian descent was seen two months after the birth of her first baby with a history of pale spots on the body that turned bright red shortly after delivery. She also complained of painful, swollen hands and feet especially during the night and early morning. Examination revealed many, large pink plaques symmetrically disposed on the whole body and maximal over limbs, with margins well marked out from normal skin but not raised. The face was covered by large, red, oedematous plaques, ears were red and swollen and there was early bilateral lagophthalmos. There was no wrist or foot drop but the right foot and ankle were swollen and there was marked "spindling" of thumb, index and middle fingers. Superficial nerves were enlarged and there was diminished sensation to touch over most of the large lesions, the facial lesions and the fingers. Complete right foot drop occurred some days later, but this resolved with treatment, as did the lagophthalmos.

Case 4 (M.C.) aged 22, Zambian. First pregnancy. Three weeks after delivery of full-term normal child, the patient presented with multiple raised skin lesions on trunk, limbs and face, with pain and tenderness of left ulnar, right popliteal and right posterior tibial nerves. The larger skin lesions were erythematous and shiny, showed a tendency to superficial necrosis, and those in proximity to enlarged peripheral nerves were anaesthetic to light touch. A biopsy of a typical skin lesion showed epithelioid cells, considerable numbers of lymphocytes and moderate numbers of acid-fast bacilli, over 95% of which were fragmented. There was oedema in the granuloma and also in the adjacent tissue.

Case 5 (J.Z.) aged 17, Zambian. First pregnancy. Twenty-six days after delivery of a full-term normal child, the entire left side of the face became swollen, red, shiny, painful and tender; the left eye closed. She reported to a general medical clinic and was treated with penicillin for erysipelas, and later with anti-histamines on suspicion of a bee sting. As the swelling subsided slightly, complete paralysis of the left facial nerve was apparent, and she was admitted to a leprosarium, where steroids produced dramatic reduction in the swelling, but no effect on the nerve paralysis, which was permanent.

Case 6 (N.C.) aged 17, Zambian. Five weeks after the delivery of a stillborn eight months foetus, the patient noted tingling along the ulnar border of the left arm and hand, with similar tingling on the dorsum of the right foot, and a tendency to foot-drop on that side. These increased in severity and the left ulnar nerve became intensely painful and tender. Two weeks later scattered raised red lesions were noted on the skin of the left arm, right side of the chest and the face. Examination at that time showed a clinical picture typical of BT (Borderline-Tuberculoid) leprosy in reaction, with tenderness and swelling of both ulnar nerves and a complete left foot-drop. The latter proved permanent, and during the next year she developed anaesthesia and claw-hand deformity due to bilateral ulnar nerve damage. A biopsy taken two years previously had shown groups of epithelioid cells focalised by lymphocytes, with fairly numerous giant cells, and very occasional acid-fast bacilli on searching numerous oil-immersion fields. She had at that time been put onto Dapsone treatment, but defaulted almost at once, and could not be traced.

Case 7 (I.R.) aged 24, Peru. Para 8, all living children. Half way through her ninth pregnancy this South American Indian patient developed vague macules on

the face and trunk, which faded and virtually disappeared as she went towards full term. Delivery and lactation were uneventful, but eight weeks later she was seen and examined in a remote area of the country (without any possible access to dispensary or drugs), with raised erythematous lesions on the face, trunk and limbs, anaesthesia and paralysis in the distribution of the ulnar nerve on the right, and right facial paralysis. According to the patient and her relatives, all features had developed rapidly over a period of only 24 hours. No follow-up was possible, but at the time of examination ulnar and facial nerve paralyses appeared to be total.

Discussion

The long recognized adverse effect of pregnancy and labour on a wide range of diseases has generally been ascribed to the physical burden of a gravid uterus on such organs as heart or lungs, or to the physical exertion of labour itself. But it is clear from the literature that many other factors may be involved. Some of these were revealed in the first reports (Hench, 1934, 1938) on remissions in rheumatoid arthritis during pregnancy and jaundice. The effect of pregnancy on various forms of arthritis and some other diseases has more recently been reviewed (Hill and Holley, 1972), and attention drawn to the relapse which occurs in rheumatoid arthritis, usually in the first month following delivery. Indeed a closer examination of published work on the effect of "pregnancy and labour" on various diseases reveals that in many of them deterioration is most marked not in pregnancy or labour, but in the puerperium. This is probably true for multiple sclerosis (Scheinberg, 1967), myasthenia gravis and systemic lupus erythematosus (Harvey, 1967). In the case of tuberculosis, at least one comprehensive review (Rich, 1951) throws considerable doubt on the notion that pregnancy itself is deleterious, while emphasising the number of new cases which arise "close on the heels of labour" or in the year following it.

In the field of leprosy there are remarkably few studies on the influence of pregnancy and labour on the course of disease. In the lepromatous form, its adverse effects have been reviewed by King and Marks (1958), and other writers (Hardas *et al.*, 1972; Tajiri, 1936) have described clinical findings in gynaecology and obstetrics generally. In an important account of the subject, Lawson (1967) draws attention to the fact that exacerbation of leprosy occurs more often during the first six months following, than it does during pregnancy, and he describes reactive, oedematous erysipeloid swellings of the face similar to those noted in our present patients with borderline (dimorphous) disease. Clinically it is usually impossible to distinguish between reactions in patients with borderline leprosy which are on the one hand immunologically beneficial (upgrading, reversal), and on the other detrimental (downgrading). However, the spontaneous occurrence of reactions in this series following pregnancy, and without the influence of drug treatment, alerts one to the possibility that a recovery of cell-mediated competence may have taken place following its depression in pregnancy. Evidence for this depression is now increasingly well documented and has been reviewed in the human (St Hill *et al.*, 1973), and in the mouse (Fabris, 1973). Although the evidence for any effect on the clinical course of leprosy by the contraceptive pill is as yet conflicting (Walter, 1968; Warren, 1969), recent work (Barnes *et al.*, 1974) shows that oral contraceptives produce immunological abnormality, including depression of phytohaemagglutinin-induced lymphocyte transformation.

While it may be that hormonal factors are not solely or mainly responsible for such changes (Sljivic, 1973), the use of oral contraceptives—or their sudden discontinuation—should now be closely watched in women with active borderline (dimorphous) leprosy.

Although lepromatous patients present serious reactional problems of their own, and require many years, probably a lifetime of treatment, the continuing problem of neuropathic damage in this disease lies in the borderline (dimorphous) range. In women with this form of leprosy, it is possible that *Mycob. leprae* might greatly multiply during pregnancy, but without clinical manifestations, tissue damage only occurring in the puerperium or later, as cell-mediated immunity is restored (Godal, 1973). In practice, many patients present with widespread, established anaesthesia and paralysis, and under field conditions in endemic areas it is often difficult to treat them effectively. Precipitating factors are not well defined. It is more than likely that valuable information on the aetiology, mechanism and treatment of these reactions in leprosy would result from the application of modern hormonal and immunological techniques to the menarché, menopause, pregnancy—and the puerperium.

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