

# Erythema nodosum associated with pregnancy and oral contraceptives

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## Summary

Erythema nodosum recurred in a woman during each of her four pregnancies and every time she was started on oral contraceptives. The lesions always disappeared in the fifth month of gestation or when contraceptives were withdrawn. Erythema nodosum is mediated by immune mechanisms, and both pregnancy and oral contraceptive use can interfere with the immune system. The concentrations of oestrogen and progesterone or the ratio between them may be critical to the development of erythema nodosum. The observation that the lesions spontaneously resolved in the fifth month of pregnancy supports this hypothesis.

## Introduction

Erythema nodosum is a rare complication of oral contraceptive use<sup>1</sup>; in other women it is sometimes associated with pregnancy.<sup>2</sup> We describe here a young woman in whom repeated pregnancies and oral contraceptive use were regularly complicated by erythema nodosum.

## Case report

A 33-year-old multipara was admitted in February 1975 to the rheumatic diseases unit of the University of Pisa for painful skin eruptions on both knees and ankles.

She had no history of rheumatic or allergic disorders. At the age of 28, in the second month of her first pregnancy, she had noted skin lesions on her legs which were diagnosed as erythema nodosum and which spontaneously resolved three months later. Two successive pregnancies, when she was 31 and 32, were complicated by typical lesions of erythema nodosum, which again appeared at the second month of gestation and cleared by the fifth month. In February 1974, two months after she had started taking oral contraceptives containing DL-norgestrel 0.25 mg and ethinyloestradiol 0.05 mg, the patient complained of chest pain and became feverish: left fibrinous pleurisy was diagnosed, and the symptoms promptly resolved after antibiotic treatment. Five weeks later, another patch of erythema nodosum appeared on her feet. Contraceptives were discontinued and the erythema nodosum cleared in a month with systemic and local steroid treatment. She restarted the same contraceptive in July 1974, but four months later she developed similar multiple skin lesions on her legs. This time, however, local and oral corticosteroids, non-steroidal anti-inflammatory drugs, and antibiotics were ineffective, and three months later the patient was referred to our service.

Physical examination showed nothing abnormal except many

painful erythematopapular eruptions on both calves and ankles and on the right thigh. These were typical of erythema nodosum, and the clinical diagnosis was subsequently confirmed by a skin biopsy. Laboratory investigations showed an erythrocyte sedimentation rate (ESR)(Westergren) of 85 mm in one hour; raised seromucous levels (0.1 g/l); an antistreptolysin O titre of 400 units; and proteinuria of 64 g/l, with 46% albumin, 4%  $\alpha_1$ -globulin, 15%  $\alpha_2$ -globulin, 14%  $\beta_1$ -globulin, 8%  $\beta_2$ -globulin, and 13%  $\gamma$ -globulin. While blood levels of IgM and IgG were normal or slightly raised (2.5 g/l and 13 g/l), IgA levels were considerably increased (8.0 g/l). The patient had a mild normochromic anaemia (red blood count  $3.4 \pm 10^{12}/l$  ( $3\,400\,000/mm^3$ ), haemoglobin 9.3 g/dl, serum iron  $11.1\,\mu\text{mol/l}$  ( $62\,\mu\text{g}/100\,\text{ml}$ )) with a white cell count of  $6 \times 10^9/l$  ( $6000/mm^3$ ) and a normal differential count. Urine analysis showed proteinuria (1+) with growth of Gram-negative bacteria on the first specimen, followed by four negative results. A tuberculin test gave positive results (++) at 24 and 48 hours. C reactive protein; LE preparation; antinuclear antibodies; latex fixation; blood urea nitrogen; serum creatinine, urea, enzymes, cholesterol, urate, calcium, and glucose concentrations; creatinine clearance; prothrombin time; glucose tolerance; electrocardiogram; chest radiograph; and intravenous pyelogram were all normal.

On admission, oral contraceptives and all other medications were stopped and the symptoms promptly resolved. Eight days later the ESR dropped to 21 mm in one hour, serum iron rose to  $32.5\,\mu\text{mol/l}$  ( $183\,\mu\text{g}/100\,\text{ml}$ ), and two weeks later the patient was discharged well.

In July 1975, when she was not taking oral contraceptives, the patient noticed the onset of erythema nodosum; a pregnancy test was positive. The lesions spontaneously disappeared in the fifth month, when the pregnancy was terminated. In December 1975 she again started to take the same oral contraceptive: three weeks later erythema nodosum appeared. This cleared a month later, when the contraceptive was stopped. She has been well ever since.

## Discussion

In this patient erythema nodosum either followed administration of oral contraceptives or appeared regularly between the second and fifth month of pregnancy. The symptoms spontaneously resolved, however, in the second half of the pregnancy. Erythema nodosum is considered to be a lesion mediated by immune mechanisms which develops in response to a variety of antigenic stimuli. Several observations have linked erythema nodosum with the use of oral contraceptives<sup>1,2</sup> and have attributed it to hypersensitivity to the constituent hormones, either oestrogens or progestogens.<sup>1</sup> In our patient, however, a drug reaction could be ruled out, because erythema nodosum resulted not only from the use of anovulatory agents but also from pregnancy.

Thus neither oestrogens nor progestogens directly cause erythema nodosum, but they may create a fertile background for its generation by other antigens.<sup>1</sup> There is evidence to support this hypothesis. In a large clinical survey of adults erythema nodosum was more common among women, regardless of the underlying disease. Pregnant women and those using anovulatory agents had particularly high incidences. The incidence of erythema nodosum increased sharply in women after puberty and decreased after the age of 40.<sup>2</sup>

On the other hand, current evidence indicates that pregnancy and oral contraceptives may interfere with the immune system in various ways. It is well known that pregnancy can influence the course of human collagen disease, usually by lowering the disease activity. Oral contraceptives may induce rheumatic

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complaints or serological abnormalities (patients have rheumatoid factor, antinuclear antibodies, LE cells, C reactive protein, and increased IgM levels).<sup>3</sup> In-vitro studies have shown that the lymphocyte response to mitogens is depressed in both pregnant women and those taking oral contraceptives,<sup>4</sup> while a combination of oestrogens and progesterone increases the Arthus phenomenon in experimental animals.<sup>5</sup>

Our observation that erythema nodosum spontaneously cleared in the second half of pregnancy suggests that a given concentration of either sex hormones or an optimal ratio between them may be critical to the development of the cutaneous lesions.

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SHORT REPORTS

Epilepsy and drowning in childhood

Though injuries sustained during epileptic attacks have been well documented, reports on epilepsy-related immersion accidents are few. Thus the Brisbane Drowning Study<sup>1</sup> provided an opportunity to assess the risk in epileptic children. Details of 111 consecutive freshwater accidents in children were included, with an analysis of causes. In addition all 24 cases of saltwater drowning in children in Southern Queensland over the same period were analysed. Data on a further 14 cases occurring in 1970 and 1976 were also available. Necropsy was performed on all drowned victims.

Altogether eight cases (5.4%) occurred as a result of convulsive seizure—three in bathtubs, two in swimming pools, and three in the sea (see table). Out of 76 consecutive childhood drownings, 2 (2.6%) were caused by epileptiform seizures, both in bathtubs.

Case reports

Case 3—A 9-year-old girl who suffered severe uncontrolled grand-mal seizures after a head injury at 18 months and was receiving phenytoin and carbamazepine had attended swimming classes weekly in the summer for seven years. She had a seizure in the water and was rescued from the bottom

of the pool by the instructor (immersion time 1–3 minutes). She responded well to mouth-to-mouth resuscitation and spent five days in hospital.

Case 8—A 15-year-old mentally normal girl who had not had a seizure for several years was staying at the home of a sponsor in a student-exchange scheme. She was not taking anticonvulsants. While kneeling over a bath washing her hair under the running tap she had a seizure and slumped into the water. A flannel stopped the water escaping and, she was found drowned after about 20 minutes.

Comment

Epileptic children who swim are four times more likely to drown than normal children, but the absolute risk remains low. When properly supervised there is no evidence that such children are likely to drown or suffer brain damage from anoxia. Although some 400 epileptic children were at risk from drowning each year in Brisbane during the seven-year study, no epilepsy-induced pool or sea deaths occurred. This illustrates the confidence with which such children may be encouraged to swim. No epilepsy-induced immersion occurred in a child with controlled epilepsy who had an adequate blood concentration of anticonvulsants. Seizures occurring in the bathtub, however, may be life-threatening.<sup>2</sup>

The role of trigger mechanisms in epilepsy-induced drownings remains unresolved. Hot baths trigger one form of somatosensory-

Details of eight consecutive immersion accidents in epileptic children

Case No	Age	Sex	Pre-accident state	Immersion site	Depth of water	Activity at time of seizure leading to accident	Rescuer	Immersion time	Outcome
1	11 mnth	M	Normal infant. Two febrile convulsions in preceding days	Family bath-tub	23 cm	Child left in bath by mother	Mother	4–6 min	Drowned
2	2 yr 8 mnth	M	Normal child. Feverish and ill on day of accident	Family bath tub	15 cm	Child left in bath by mother	Mother	2–5 min	Severe spastic quadriplegia and amentia. Child institutionalised
3	9 yr 3 mnth	F	Mentally retarded with poorly controlled (1 fit/month) post-traumatic epilepsy Pre-immersion IQ 55	Municipal swimming baths	2 m	Supervised swimming class with other children	Swimming instructor	1–3 min	No apparent clinical intellectual sequelae. Post-immersion IQ 53
4	10 yr 3 mnth	M	Mentally retarded with poorly controlled post-traumatic grand-mal epilepsy	Sea	1 m	Swimming with mother and sibs	Mother	1 min	No apparent neurological or intellectual sequelae
5	12 yr 9 mnth	M	Mentally retarded with tuberosus sclerosis and poorly controlled grand-mal epilepsy	Private swimming pool	2 m	Swimming with friends and parents	Bystander	1–3 min	No change from baseline neurological signs
6	13 yr 3 mnth	M	Poorly controlled epileptic. Normal intellect	Sea	1–2 m	Swimming with family	Father	1 min	Complete recovery within 2 days
7	14 yr 4 mnth	M	Gross mental retardation after measles encephalitis. Poorly controlled epileptic	Surf	1 m	Swimming with parents	Father	1 min	No change in intellect
8	15 yr 1 mnth	F	Mentally normal. Well controlled idiopathic grand-mal epilepsy	Bathtub	38 cm	Washing hair, kneeling over bath	Sponsor	10–20 min	Drowned. Did not respond to resuscitation