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Cigarette smoking in pregnancy and fetal hyperviscosity

A leading article in the *BMJ* listed cigarette smoking during pregnancy as a major cause of fetal intrauterine growth retardation.¹ This effect has been attributed to chronic hypoxia caused by a reduction in placental blood flow due to the vasoconstrictor effects of nicotine and decreased oxygen availability consequent on raised concentrations of carboxyhaemoglobin in fetal and maternal blood.² In non-pregnant adults cigarette smoking is associated with increased blood viscosity and arterial insufficiency affecting many organs.³ This study investigates the effects of maternal cigarette smoking on fetal blood viscosity and its major determinants to see if there might be a relation between the intrauterine growth retardation associated with cigarette smoking and fetal hyperviscosity.

Patients, methods, and results

Blood was collected from the umbilical vein at birth in 40 infants born to mothers who had smoked more than 20 cigarettes a day throughout pregnancy and from 40 matched non-smoking controls. Blood and plasma viscosity, packed cell volume, plasma fibrinogen concentration, and erythrocyte deformability were measured by standard techniques⁴ and statistical comparison of the differences in means between the two groups made using Student's *t* test. The table gives the results. Cigarette smoking was associated with a

Haemorheological profiles of infants born to smoking and non-smoking mothers. Values are means (SD)

	Non-smokers	Smokers	Statistical comparison
No of subjects	40	40	
Gestational age (weeks)	39.4 (0.6)	38.7 (0.8)	NS
Birth weight (g)	3215 (210)	2897 (252)	p < 0.01
Packed cell volume	0.50 (0.03)	0.56 (0.04)	p < 0.01
Plasma fibrinogen (g/l)	1.8 (0.7)	1.7 (0.7)	NS
Plasma viscosity (mPa s)	1.5 (0.3)	1.5 (0.4)	NS
Whole blood viscosity (mPa s)	16.3 (2.2)	20.7 (2.8)	p < 0.01
Erythrocyte deformability index	0.79 (0.01)	0.65 (0.11)	p < 0.02

NS = Not significant.

Conversion: SI to traditional units—Viscosity of plasma and whole blood: 1 mPa s = 1 cP.

30% increase in fetal blood viscosity, this rise being compounded of a 12% increase in packed cell volume and an 18% fall in erythrocyte deformability. Neither plasma viscosity nor plasma fibrinogen values were altered.

The mean birth weight was 318 g lower in infants born to smoking mothers.

Comment

Maternal cigarette smoking in pregnancy results in changes in fetal blood viscosity and its major determinants similar to those described in non-pregnant adult smokers.³ When adult smokers become pregnant the large physiological variations in blood viscosity factors obscure the effects of smoking in maternal blood⁵ but not so in the fetus. In the extensive capillary microcirculation of the fetal placental villi, raised blood viscosity and reduced erythrocyte deformability would be apt to reduce blood flow significantly in accordance with Poiseuille's law. Reduced intravillous perfusion would combine with reduced intervillous blood flow on the maternal side of the placenta, owing to the effects of nicotine, and with the already reduced oxygen availability in both maternal and fetal blood, to cause fetal hypoxia stimulating fetal erythropoiesis with a further increase in blood viscosity leading to a vicious circle of decreasing flow and further hypoxia. This study indicates a new pathogenic pathway for the deleterious effects of maternal cigarette smoking on fetal growth and development in pregnancy.

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Plasmodium malaria resistant to chloroquine in a Zambian living in Zambia

Recently, chloroquine resistant *Plasmodium falciparum* has been acquired in east Africa by white visitors.^{1 2} We have carried out more than 25 successful in vitro macrotests, 15 in vitro microtests using capillary blood specimens, and 130 in vivo tests on the susceptibility of *P. falciparum* in Zambia to chloroquine and to the new antimalarial drug mefloquine.³⁻⁵ In the in vivo tests the patients were observed in an environment free of mosquitoes for 28-63 days after they developed malaria. Our results showed that *P. falciparum* in Zambia is generally sensitive to standard doses of chloroquine or mefloquine. Here, however, we report perhaps the first proved case of chloroquine resistant *P. falciparum* in an African living in Africa.

Case report

A 26 year old Zambian staff nurse developed clinical malaria, which was confirmed microscopically to be due to asexual *P. falciparum*, one month after she had moved to a village 1000 km north east of Ndola. She was treated on 10 June 1982 with two doses of 200 mg chloroquine intramuscularly at an interval of eight hours. She refused a further injection of chloroquine the next day and instead took 600 mg amodiaquine by mouth. Her clinical condition improved for four days, during which time she returned to Ndola. For the next 10 days she felt slightly unwell with fever and headache in the evenings; blood slides at the end of that time again showed asexual *P. falciparum* (11.37 × 10⁹ parasites/l blood).

An in vitro macrotest was set up for both chloroquine and mefloquine on 24 June. The test was repeated five days after she had been given a total dose of 1.55 g (25.8 mg/kg) chloroquine base by mouth over three days. Venous blood samples taken on days 3 and 4 showed plasma chloroquine concentrations of 2.89 and 2.97 μmol/l on day 3 and 3.35 μmol/l on day 4. These concentrations were more than adequate to produce a radical cure of an infection sensitive to chloroquine—that is, one in which maturation of schizonts is completely inhibited by a concentration of 1.0-1.25 μmol/l—and so this confirmed resistance. Results of daily blood smears after administration of chloroquine were: 0.66 × 10⁹ asexual parasites/l on day 3, 0.42 × 10⁹/l on day 4, 2.55 × 10⁹/l on days 5 and 6, and 4.35 × 10⁹/l on day 7. Because

she did not respond satisfactorily to oral chloroquine, on day 7 (2 July) she was given a free combination of pyrimethamine 75 mg and sulfadoxine 1500 mg. On day 8 the parasite density had fallen to $0.18 \times 10^9/l$. Subsequent blood smears taken until day 63 remained negative for *P. falciparum* trophozoites.

Comment

The results of the two in vitro macrotests showed that schizonts formed up to the last chloroquine concentration tested of $3.0 \mu\text{mol/l}$; schizont formation was completely inhibited at a mefloquine concentration of $0.25 \mu\text{mol/l}$. Thus the strain of *P. falciparum* was resistant to chloroquine but sensitive to mefloquine. The in vivo results show that this was a case of type II resistance (World Health Organisation classification), successfully treated with a combination of pyrimethamine and sulfadoxine.

Detailed results of our work on the sensitivity of *P. falciparum* to chloroquine and mefloquine in Zambia will be published later. The chloroquine resistant strain is in continuous culture, and further work is being done on it.

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Idiopathic hypoparathyroidism associated with stable untreated myelofibrosis

Idiopathic hypoparathyroidism is rare and characteristically occurs in young people in association with other endocrine conditions.¹ An acute form has been described in elderly patients,² but more recently hypocalcaemia and hypoparathyroidism have been recognised in association with chemotherapy for both haematological malignancies³ and solid tumours.⁴ The chemotherapy has been the presumed cause, but the neoplasm itself may predispose to hypoparathyroidism.

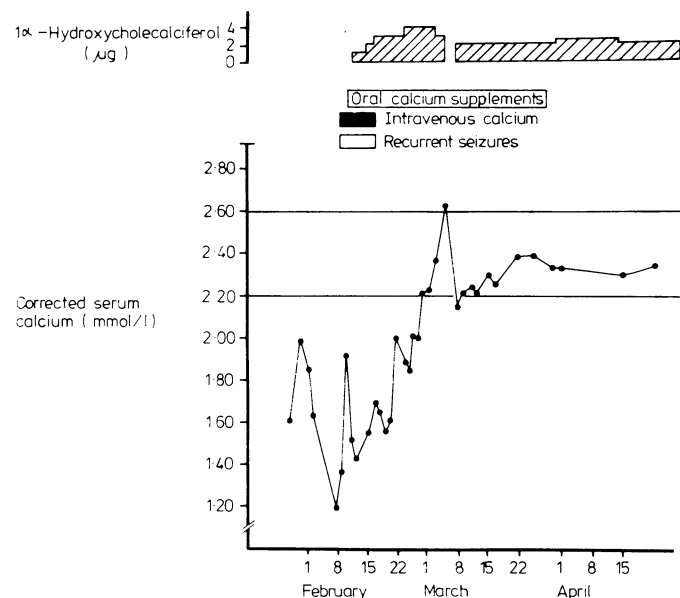
We describe a patient with untreated myelofibrosis who developed hypoparathyroidism associated with profound hypocalcaemia and recurrent major convulsions.

Case report

A 77 year old woman with stable chronic renal failure, serum creatinine concentration $200-230 \mu\text{mol/l}$ ($2.3-2.6 \text{ mg/100 ml}$), and a six year history of myelofibrosis was admitted to hospital for routine blood transfusion. Her myeloproliferative state had been managed conservatively, and she had not received either chemotherapy or radiotherapy. On admission, apart from obvious anaemia, her condition was satisfactory but she had multiple

painful gouty tophi in both hands. Biochemical investigation confirmed her usual degree of renal impairment but showed hyperuricaemia, the plasma urate concentration being 0.83 mmol/l (14 mg/100 ml) (normal $0.12-0.45 \text{ mmol/l}$ ($2.0-7.6 \text{ mg/100 ml}$)). She was mildly hypocalcaemic, with serum calcium concentration (corrected for albumin) 2.06 mmol/l (8 mg/100 ml). Despite her poor renal function serum phosphate concentration and alkaline phosphatase activity were normal. Haemoglobin concentration was 6.4 g/dl . Three units of packed cells were transfused and allopurinol 100 mg/day started. Her initial progress was satisfactory, and she was discharged home, taking allopurinol, after five days.

She was admitted six days later (8 February; figure) after a major convulsion at home associated with blurred vision and mental confusion. She was drowsy and confused, and Trousseau's and Chvostek's signs were present. Serum biochemistry showed no appreciable change in renal function, but she had profound hypocalcaemia: corrected calcium concentration was 1.16 mmol/l (4.6 mg/100 ml), phosphate concentration 2.09 mmol/l (6.5 mg/100 ml), and alkaline phosphatase activity 58 IU/l , while the serum magnesium concentration, also corrected for albumin, was 0.7 mmol/l (1.7 mg/100 ml) (normal $0.7-1.1 \text{ mmol/l}$ ($1.7-2.7 \text{ mg/100 ml}$)). She had recurrent major convulsions, which were successfully treated with repeated injections of intravenous calcium gluconate ($10\% \text{ w/v}$). No parathyroid hormone was detectable by radioimmunoassay.



Corrected serum calcium concentration and forms of replacement treatment given.

Conversion: SI to traditional units—Calcium: $1 \text{ mmol/l} \approx 4 \text{ mg/100 ml}$.

100 ml), and alkaline phosphatase activity 58 IU/l , while the serum magnesium concentration, also corrected for albumin, was 0.7 mmol/l (1.7 mg/100 ml) (normal $0.7-1.1 \text{ mmol/l}$ ($1.7-2.7 \text{ mg/100 ml}$)). She had recurrent major convulsions, which were successfully treated with repeated injections of intravenous calcium gluconate ($10\% \text{ w/v}$). No parathyroid hormone was detectable by radioimmunoassay.

Over the next eight days she needed large quantities of intravenous calcium (figure) and was also given oral calcium supplements. In addition, oral 1α -hydroxycholecalciferol $1 \mu\text{g}$ daily was started. Her general condition improved, and the corrected serum calcium concentration rose to 2.14 mmol/l (8.6 mg/100 ml). The dose of 1α -hydroxycholecalciferol was stabilised at $2 \mu\text{g}$ daily, at which point the corrected serum calcium concentration was 2.22 mmol/l (8.9 mg/100 ml). Her mental state had returned to normal, and she had no further convulsions.

Another predominant symptom was diarrhoea. Stool cultures and tests for malabsorption yielded negative results, as did barium studies of the alimentary tract. Diarrhoea is a recognised feature of hypocalcaemia⁵ and in this case resolved when the serum calcium concentration was restored to normal.

At discharge from hospital she had no symptoms and was taking $2 \mu\text{g}$ 1α -hydroxycholecalciferol daily and a normal diet without calcium supplements. Her corrected serum calcium concentration was 2.28 mmol/l (9.1 mg/100 ml).

Comment

This patient suffered recurrent major convulsions associated with hypocalcaemia, which was subsequently corrected by oral 1α -hydroxycholecalciferol. The aetiology of her hypoparathyroidism was unclear. An age related decline in parathyroid function may occur, and this patient and two other cases² may represent extreme examples. Acute idiopathic hypoparathyroidism has been reported in patients with leukaemia treated with cytotoxic agents³ and in patients with breast cancer treated with chemotherapy.⁴ Our patient had never received any chemotherapeutic agents. Freedman *et al*³ postulated that low