

Birth defects following maternal exposure to ergotamine, beta blockers, and caffeine

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SUMMARY Ergotamine exposure during pregnancy has been suggested to cause birth defects which have a vascular disruptive aetiology. The present case provides additional support for the possible adverse fetal effects of exposure to ergotamine, caffeine, and propranolol during the first four months of pregnancy. At birth the infant showed evidence of early arrested cerebral maturation and paraplegia. The nature of these defects suggests a primary vascular disruptive aetiology. We hypothesise that ergotamine, acting either alone or in synergy with propranolol and caffeine, produced fetal vasoconstriction resulting in tissue ischaemia and subsequent malformation. This case raises the possibility that fetal malformation may result from concomitant use of multiple vasoconstrictive agents during pregnancy.

It is now accepted that a variety of anomalies such as limb reduction defects, porencephalic cysts, microcephaly, intestinal atresia, and paraplegia can result from vascular disruptive phenomena in utero.¹ The types of congenital defects depend on the fetal vessels involved and the duration, timing, and mechanism of injury.^{1,2} Vascular injury with subsequent tissue anoxia can result from a number of mechanisms such as thromboembolic phenomena in a monozygotic twin survivor after death of a co-twin in utero, maternal hypotension/hypertension, uterine artery occlusion, and vasculitis.¹⁻⁴

Vasoconstrictive agents also have been implicated as causes of birth defects with a vascular disruptive aetiology. For example, ergotamine has been suggested as a possible cause of intestinal atresia.⁵ Indirectly, ergotamine has been implicated as one cause of Poland sequence following its use as an abortifacient.⁶ The present case report provides further support for the hypothesis that birth defects may result from vascular occlusion caused by ergotamine therapy during pregnancy. The potentiating effect of concomitant exposure to multiple vasoconstrictive agents is suggested.

Case report

The infant, a Caucasian female (fig 1), was born at

term after spontaneous onset of labour. She was the product of the first pregnancy of a young, non-consanguineous couple with an unremarkable family history. However, the mother had been treated for

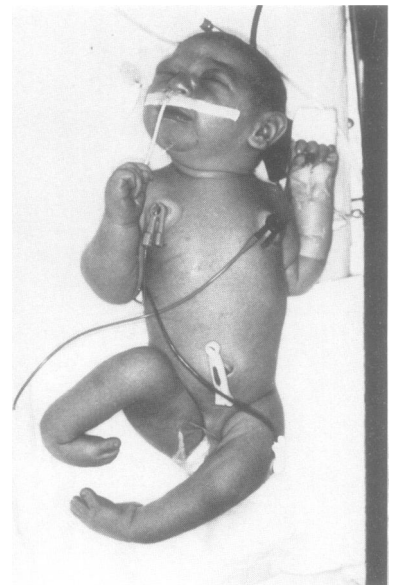


FIG 1 *Infant in newborn period. Note microcephaly and underdeveloped, contracted lower limbs.*

migraine and pregnancy was complicated by severe migraine headaches which were treated with a variety of medications including ergotamine and caffeine, taken in the form of 'cafergot' suppositories, and propranolol (table). There was no history of smoking, alcohol or other drug intake, decreased fetal movements, vaginal bleeding, toxæmia, or hypotension.

The infant was a breech presentation. Birth weight was 2860 g and length was approximately 46 cm (compromised by lower limb contractures). She was clinically microcephalic with a head circumference of 31 cm and the anterior fontanelle was almost closed. There were no facial dysmorphic features and the baby's upper trunk and arms were normally developed. The movements and tone were normal in the upper limbs and the reflexes were brisk.

However, the infant was paraplegic with underdeveloped and hypotonic lower limbs. The anal, knee, and ankle reflexes were absent. Sensation was absent up to the level of the knees and it was variably absent on the thighs. The findings suggested a spinal cord abnormality and it was estimated to be in the upper lumbar region. Both hips were dislocated and there was a marked equinovarus deformity bilaterally.

INVESTIGATIONS

Radiographs of the lower limbs revealed osteoporosis and fractures of the femora and tibiae. In contrast, the bone density in the arms was normal. The spine was also normal with no evidence of dysraphism. An electromyographic study was normal in the biceps, but in the lower limbs sensory action potentials were absent and only very minimal motor action potentials were recorded. The findings were consistent with a spinal cord lesion or myelodysplasia. However, a CT scan of the cord failed to reveal a structural abnormality. A CT scan of the head showed a small brain with lissencephaly, a primitive Sylvian fissure, and ventriculomegaly. The corpus callosum and falx were present (fig 2a, b).

The infant's lymphocyte chromosomes were normal (46,XX, Giemsa banded) and antibody titres (toxoplasma, rubella, cytomegalovirus, and herpes simplex) in both mother and baby were not raised. Urine and cerebrospinal fluid viral cultures were also negative. The placenta and membranes were examined in detail and were unremarkable with no

TABLE Medications taken during pregnancy.

		Dose	Gestation (wk)
Acetaminophen	325 mg	6-20/day	0-16
Cocaine	8 mg		
Propranolol	40 mg	2/day	0-20
Ergotamine	2 mg	1-4/week	0-14
Caffeine	100 mg		
L. Belladonna alk	0.25 mg		
Pentobarbital	60 mg		
Dimenhydrinate	75 mg	0-3/week	0-12

The information in this table was provided retrospectively by the mother. She appeared to be an accurate historian and was sure of the date of conception. Both 'cafergot' and propranolol were prescribed by her physician.

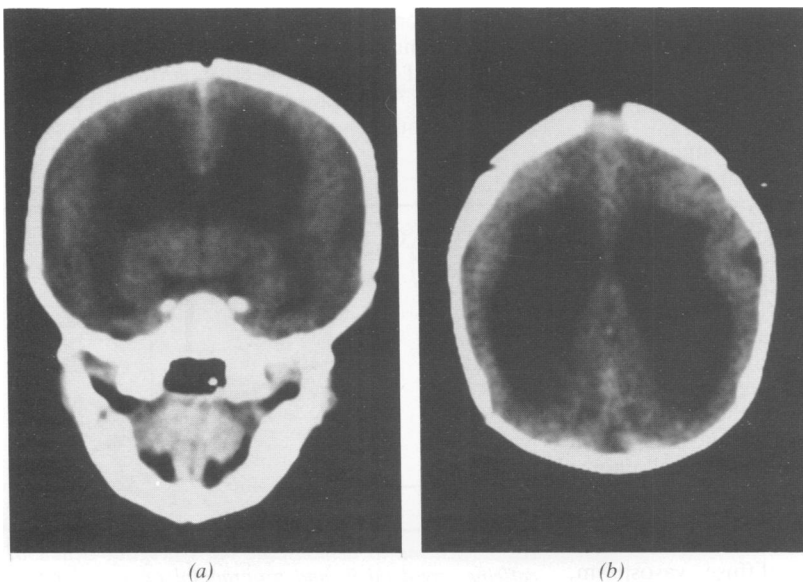


FIG 2 CT scans in newborn period. Coronal section (a) shows presence of falx and 'bat-wing' dilatation of lateral ventricles, a sign commonly associated with early arrest of cerebral development. Note in section (b) lack of sulci and gyri except for a shallow Sylvian fissure.

evidence of a twin pregnancy and no areas of infarction. The cord was 42 cm in length and had three vessels which were patent at all levels sectioned.

Discussion

The co-occurrence of the brain abnormality and cord lesion in this infant could be accounted for by a vascular disruptive mechanism, such as in utero hypoperfusion of the fetal cerebral and spinal vessels.⁷ The brain CT scan findings are compatible with the arrest of cerebral development early in the second trimester of pregnancy. Presence of the corpus callosum and falx suggest that the insult occurred later than 10 to 13 weeks of gestation.^{8,9} The infant's spinal cord lesion could have occurred either as a result of an acute disruption of blood supply or from chronic hypoperfusion with consequent ischaemia in one of the spinal cord watershed areas. These watershed regions are most vulnerable to vascular deprivation because they are the most distal regions perfused by a given arterial supply.¹⁰ One such area, L1, is compatible with the neurological findings in this infant.

It is significant that the infant in this report was exposed to ergotamine, caffeine, and propranolol during the first 14 to 20 weeks of gestation. Propranolol and caffeine are known to cross the placental barrier and will produce pharmacological effects in the fetus.¹¹ Ergotamine has also been shown to cross the placenta in small quantities.¹² No other predisposing cause for the birth defects could be identified. Specifically, there was no history of either acute or chronic maternal hypotension and, to the best of our knowledge, the other drugs ingested (table) have not been associated with birth defects comparable to those in this infant.¹³

The ergot alkaloids, including ergotamine, have a wide range of effects upon vascular regulation at levels ranging from the central nervous system to the vessel wall.¹⁴ These agents have documented pharmacological effects on multiple receptors including alpha adrenergic, cholinergic, and serotonergic sites. Ergotamine has been used for some time in the therapy of migraine although the precise mechanisms by which ergotamine results in overall pressor effects have not been defined. Nevertheless, physiological studies have consistently shown a specific pattern of vascular responsiveness and the potent vasoconstrictive power of ergotamine is well known from the gangrene and multiple organ infarction seen with therapeutic and accidental ergotism.¹⁵ Therapeutic benefit can be derived from the drug at doses which do not induce diffuse vasospasm,

suggesting that there is some specificity of action on cerebral vasculature.¹⁶

Caffeine also presents a complex pharmacological picture. In general, caffeine is a smooth muscle relaxant and vasodilator. However, it appears to exert a constrictor effect on human cerebral vasculature.¹⁷⁻¹⁹ Thus, it is reasonable to speculate that the synergistic effect of caffeine and ergotamine could result in a more pronounced vasoconstriction of the cerebral vessels. This effect is shown in dogs where dihydroergotamine alone does not cause cerebral vasoconstriction but is a potent vasoconstrictor in the presence of caffeine.²⁰ It is possible that caffeine may enhance the apparent specificity for cerebral vessels by acting as a vasodilator in other vascular beds.

Propranolol, the prototypical beta adrenergic blocker, acts as a vasoconstrictor in most or all vascular beds by interfering with the vasodilating effects of peripheral beta receptors. This effect is usually masked by decreased cardiac contractility which results in a net fall in blood pressure. Poor peripheral circulation is often noted as a side effect of propranolol therapy and on rare occasions beta blockade has resulted in peripheral ischaemia with gangrene.²¹ In the presence of beta blockade, the unbalanced alpha-like activity of ergotamine might be expected to result in more severe vasoconstriction. For example, two patients who received a combination of a beta blocker and ergotamine developed severe peripheral ischaemia.²² It would appear that the concomitant use of ergotamine, caffeine, and propranolol might increase the risk for severe vasoconstrictive complications (fig 3).

Case reports provide the initial suggestion that a specific agent may be teratogenic and may stimulate initiation of small prospective series of exposed pregnancies.²³ Obviously, the true teratogenic risk of the various vasoconstrictive agents can only be

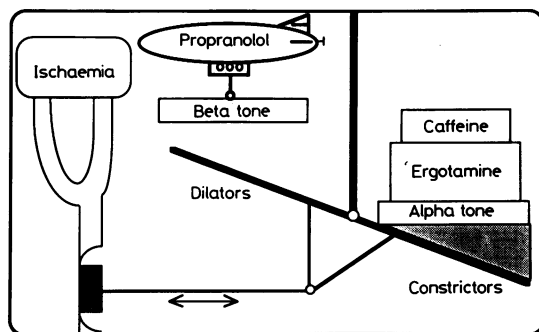


FIG 3 Schema to demonstrate the synergistic action of caffeine, ergotamine, and propranolol on vascular tone.

estimated by population studies, but such data would be difficult to obtain because of the known oxytocic effect of ergot derivatives. To date, studies on offspring of women treated for migraine have not shown an increased risk of congenital malformations.^{24 25} However, the number of subjects in these studies is small so that the effect of a weak or inconsistent teratogen, or the result of multiple drug interaction, could be missed. The Collaborative Perinatal Project²⁴ reported on 25 exposures to ergotamine and 32 exposures to other ergot derivatives. The relative risk of malformation was 1.24 and 1.45 respectively. A retrospective study of the association between maternal migraine and malformations in offspring²⁵ showed that 70% of women had taken ergot alkaloids at some time in the past, but no data regarding exposure during pregnancy were obtained. Thus, the actual number of exposed women and severity of exposure are unknown.

The present case suggests the need for caution in the use of combined vasoconstrictive agents for the treatment of migraine during pregnancy. Therapy with ergotamine combined with caffeine or beta blocking agents or both may place the fetus at increased risk for malformations with a vaso-occlusive aetiology.

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