

## LETTERS TO THE EDITOR

### Fluconazole teratogenicity

A 38-year-old-primigravida presented in the 12th week of pregnancy asking for prenatal diagnosis by CVS. There was no history of congenital malformations or consanguinity. She had taken 150 mg of fluconazole in a simple oral dose about the date of conception for vaginal candidiasis. The karyotypes in both the cytotrophoblast and mesenchymal core of the villi were normal: 46,XY. A routine ultrasound scan at the 32nd week revealed an occipital encephalocoele, severe hypoplasia of the cervical vertebrae and a large cisterna magna because most of the cerebellum was in the encephalocoele. A caesarean section was performed at the 39th week. The male infant had an encephalocoele and postnatal echocardiography revealed that both the pulmonary artery and the aorta emerged from the right ventricle, and he had dextrocardia. He died at seven days and anatomopathological studies were not performed.

Recently (Aleck and Bartley, 1997) a report was published of a baby born to a mother treated with 400 g/day of fluconazole from before conception until the fourth or fifth week of pregnancy. The boy presented with a constellation of malformations that included exophthalmus, a large pear-shaped nose, dysplastic ears and radio-humeral synostosis, resembling Antley–Bixler syndrome (Hassel and Butler, 1994). The boy's phenotype was similar to three previously reported patients with *in utero* exposure to fluconazole (Lee *et al.*, 1992; Pursley *et al.*, 1996).

Although the report of Aleck and Bartley (1997) mentioned two studies (Inman *et al.*, 1994; Mastroiacovo *et al.*, no reference found) of a total of 286 women who had taken a simple dose of fluconazole at or around conception without

having a baby with congenital malformations, the author pointed out '... it is still unclear whether low dose exposure is below a threshold for teratogenicity in all pregnancies' and recommended a large epidemiological study including women who had taken fluconazole shortly before conception. Our patient showed a different phenotype compared with Antley–Bixler syndrome (Hassel and Butler, 1994) and the other fluconazole exposed infants. Nevertheless all these patients had ossification defects and two of the four patients had cardiac defects. The aim of this letter is to contribute another case of a malformed newborn in a mother taking fluconazole. We cannot draw conclusions from such a small number of cases but we agree with Aleck and Bartley (1997) on the necessity of an epidemiological study of pregnancies in which a single dose of fluconazole had been taken periconceptionally.

We think that this is a significant problem, given that fluconazole is a very effective drug for the treatment of vaginal candidiasis and because of the general assumption that the first two weeks after conception are a safe period for teratogens.

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## Polyhydramnios as a first prenatal symptom of non-ketotic hyperglycinaemia

Polyhydramnios is widely recognized as being a non-specific indicator of fetal disease of which interference with decreased fetal swallowing due to fetal cerebral dysfunction may be one potential mechanism. In the following case report, we present a neonate with non-ketotic hyperglycinaemia (NKH) (Hamosh *et al.*, 1995), in which severe CNS damage commenced *in utero* and led to decreased fetal swallowing followed by the occurrence of polyhydramnios.

In a 30-year-old woman polyhydramnios was detected by sonography at 31 weeks of gestation. Previous sonographic examinations during pregnancy showed a normal amount of amniotic fluid. Amniocentesis was not carried out due to the advanced state of pregnancy. The polyhydramnios remained unchanged during subsequent sonography checks during the following weeks. Fetal movements appeared to be normal. A male infant weighing 2980 g, Apgar score 7/9 was delivered spontaneously at 39 weeks of gestation. General muscular hypotonia was observed immediately after delivery and on day 2 of life the infant was transferred to our NICU due to muscular hypotonia and insufficient sucking. On admission, there were pathological neurological reflexes, virtually permanent hiccups, and respiratory insufficiency required mechanical ventilation. The initial metabolic values led to the diagnosis of NKH: glycine concentrations were highly elevated in plasma: 1310  $\mu\text{mol/l}$  (normal 56–308) and in the cerebrospinal fluid (198  $\mu\text{mol/l}$ , normal 2.9–10.4) and the CSF/plasma ratio was pathognomonically high as well (0.15, normal 0.012–0.040).

Non-ketotic hyperglycinaemia is a rare autosomal recessive disease caused by a defect of the glycine cleavage system leading to accumulation of large amounts of glycine in body fluids. The onset of classic NKH is in the first days of life with hypotonia, hiccups, multifocal myoclonus and stupor and a characteristic EEG with burst suppression pattern. The outcome is very poor and most patients die in the first year of life; those who survive manifest severe psychomotor retardation. Glycine is structurally the simplest of amino acids and plays a major role in neurotransmission; being predominantly inhibitory in the spinal cord and mediating excitatory neurotransmission in the cerebral cortex and other regions of the forebrain during early brain development, associated with the N-methyl-D-aspartate (NMDA) glutamate receptor. In the immature prenatal brain the NMDA receptor channel is especially active, which may be the reason of the deleterious effect of glycine on the brain and neurological functions. Fetal cerebral dysfunction is part of the differential diagnosis of polyhydramnios, the pathogenetic mechanism appearing on the one hand to involve direct central neuronal damage (Volpe, 1995) and on the other, qualitatively altered fetal movements (Visser *et al.*, 1985) and reduced breathing movements (Prechtl, 1989).

A literature survey of NKH has not revealed any publications in which polyhydramnios has been described as the first symptom.

Since CNS damage commences *in utero* due to glycine toxicity resulting from NKH, the occurrence of polyhydramnios may be the first symptom