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Letters to the editor

## Can benfluorex induce congenital malformations?

### *Le benfluorex peut-il être responsable de malformations congénitales ?*

*Keywords:* Benfluorex; Amphetamine; Pregnancy; EFEMERIS; Malformation

*Mots clés :* Benfluorex ; Amphétamine ; Grossesse ; EFEMERIS ; Malformation

Benfluorex (marketed as Mediator) is an anorectic agent that has been available in France since 1976 as an adjuvant drug for diabetic patients who are overweight. In November 2009, the drug was withdrawn due to reports of several cases of heart valve disease. The reasons for benfluorex withdrawal were fully presented and discussed in the media, and a letter was sent by the French Health Products Safety Agency (*Agence française de sécurité sanitaire des produits de santé* [Afssaps]) to patients who had taken benfluorex, asking them to consult with their physician to look for any potential valvular disease. Several women who had taken benfluorex before or during pregnancy had already questioned the Midi-Pyrénées Centre of Pharmacovigilance to find out whether benfluorex intake could be associated with malformations (mainly cardiovascular) in the newborn.

As no clinical data have yet been published on benfluorex and pregnancy, we performed a nested case-control study based on EFEMERIS, a French prescription database including pregnant women [1]. EFEMERIS is a database of all prescribed and delivered drugs during pregnancy [data from the Health Insurance Service (*Caisse primaire d'Assurance maladie*) of Haute-Garonne], and their outcomes (data from the Maternal and Infant Protection Service and the Antenatal Diagnostic Centre). At the time of the present study, 40,355 women who had delivered between 1 July 2004 and 30 June 2008 in Haute-Garonne, and were registered in the French Health Insurance Service, were found in the EFEMERIS database. Benfluorex prescriptions taken during organogenesis were compared between children with (943 cases) and children without (39,412 controls) congenital anomalies.

During the 4-year study period, 59 of the women registered in EFEMERIS had at least one prescription for benfluorex during pregnancy: 52 during the first 2 months; six during the second trimester; and one during the third trimester. Seven women only had an associated prescription for a hypoglycaemic medication. In the group with congenital anomalies (cases), two babies (0.2%) had been exposed to benfluorex during the first 2 months of pregnancy versus 50 (0.1%) among the controls (OR: 1.7 [0.4–6.9], $P = 0.5$ after adjusting for the mother's age and maternal diabetes mellitus). Malformations in benfluorex-exposed babies included one urinary tract malformation and one heart defect (ventricular septal defect). In these two cases, there was no associated prescription of drugs known to be teratogenic.

Benfluorex is a fenfluramine derivative, and several animal studies have reported an increased risk of malformations after exposure in utero to amphetamine derivatives. Experimental studies in mice have shown an increase in cleft palate at high doses [2], as well as heart, skeletal and eye defects [3]. Methamphetamine also induces cleft palate, exencephaly and eye defects in mice, head anomalies in rabbits [4] and eye defects in rats [5]. Several case reports have associated amphetamine exposure during pregnancy with various malformations, such as cardiac anomalies, exencephaly, limb reduction and cataracts. In addition, a retrospective epidemiological study found an association between cardiovascular malformations and exposure in utero to amphetamine during organogenesis [6]. However, other studies have not confirmed these data [7–9] and, in any case, a too-limited number of subjects were included.

In fact, the present study has also failed to show any significant association between teratogenic risk and benfluorex exposure during early pregnancy. However, as benfluorex intake only involved around one out of 775 pregnant women in the EFEMERIS database, the dataset would have only been able to detect at least a five-fold increase in teratogenic risk. Thus, given the data on amphetamines in pregnancy, it would be of interest to perform further studies involving a larger number of exposed women by extending the observation period.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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