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Australian Pregnancy Registry of Women Taking Antiepileptic Drugs

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Established in 1999, the Australian Registry enrolls women with epilepsy treated with antiepileptic drugs (AEDs), untreated women with epilepsy, and those taking AEDs for other indications. It is a centralized observational study, with ethical committee approval and patient consent. Data from patients fulfilling the criteria for enrollment also are fed into the EURAP database, coordinated by the center in Milan by Professor Dina Battino, supervised by a Board (T. Tomson, Chair). Four telephone interviews are conducted. Patients are enrolled prospectively as well as retrospectively. To date, 830 women have contacted the Registry; 630 have been enrolled, and 565 pregnancies reached completion, including 10 sets of twins.

Live births with no defect composed 89%; live births with defect, 5%; spontaneous abortions, 3%; and stillbirths, induced abortion with defect, and lost to follow-up, 1% each. The reason for AED intake was predominantly for epilepsy (542 of 555 women). Folic acid intake before conception was noted in 378, and no folate in 187. Truly prospective enrollment (before any tests for malformation) comprised 233, with prospective, 252; and retrospective, 80 patients. Primary generalized epilepsy was present in 253 women, partial in 266, the remainder were unclassified. Drug therapy outcomes were related to valproate (VPA) in monotherapy, with a statistically significant increase over untreated patients in incidence of malformations on monotherapy treated (16.1%), and combined groups treated with monotherapy and polytherapy (15.1%) over untreated. patients (2.5%: $p < 0.05$). On further analysis, it became striking that this increase in VPA-treated patients was related to VPA dose, Doses >1,100 mg/day were associated with a high risk ($p < 000.1$), whereas at less than this dose, in monotherapy, no drug to date has been shown to be a statistically significantly increased risk factor for fetal malformations. Lamotrigine (LTG) was not associated with a single defect in monotherapy (61 patients); carbamazepine (CBZ) and phenytoin (PHT) were similarly not significantly different from the results in untreated patients, at this stage, noting the small numbers available. In total, 165 patients were taking VPA (mono- and polytherapy), 209 taking CBZ, 129 taking LTG, and 38 taking PHT. Categories of malformations comprised neurologic (12), cardiac (11), craniofacial (seven), skeletal (15), and genitourinary (15). The results of self-reporting on medication changes and additions and documentation available on seizure control were analyzed, in relation to various time periods during pregnancy and in terms of auras, partial episodes, and convulsive seizures.

Results indicate that all seizure types were observed statistically more frequently when patients were taking LTG than when taking VPA. This improved seizure control with VPA was noted at all interviews, of which the first is of most interest. Incidence of convulsive seizures was 5.3% with VPA and 21.3% with LTG. χ^2 analysis showed the risk of increased seizures with LTG to be $p < 0.0029$. Selection bias and small numbers may confound this issue. CBZ was not significantly different from VPA, but significantly more protective than LTG at the second and third interviews. Two fetuses were lost, one as a result of status epilepticus after cessation of VPA, and the second as a result of prolonged seizures with LTG. Seizure control did not appear to be related to teratogenicity but did contribute to fetal loss.

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