Introduction

Epilepsy is the most common serious chronic neurological condition, with a prevalence of between 4 and 10 people per 1000. Most of those affected, including women of childbearing age, will require long term treatment with antiepileptic drugs (AEDs) to prevent seizures. Although the interactions between epilepsy and pregnancy are multiple, it is the potential effect of AEDs on the developing foetus that raises most concern.

It is widely accepted that prenatal exposure to AEDs increases the risk of a major congenital malformation (MCM) from the background risk of 1–2% to 4–9%. (1)

The first report that antiepileptic drugs (AEDs) may have teratogenic effects dates back over 40 years. Since that time, evidence has been accumulated demonstrating that AEDs are associated with an increased risk of congenital malformations and may have long-term effects on intellectual development during childhood. (2) Epilepsy provides one of the most objective models of this precarious balancing act, as lower serum concentrations of the AEDs often have immediate and measurable consequences of seizure worsening, and higher serum concentrations often results in identifiable side effects. (3)

Valproate (VPA) has demonstrated the highest teratogenic potential among the first generation AEDs like Carbamazepine (CBZ), VPA, Phenytoin (PHT) and Oxcarbazepine (OXC). Therefore, the trend is to prefer the use of second-generation AEDs in fertile women, a trend confirmed by a recent analysis of AEDs prescription patterns in a nation-wide population: Lamotrigine (LTG), Gabapentin (GBP) and Topiramate (TPM). (2)

The desire to avoid VPA has led to a wider use of second-generation AEDs in fertile women, particularly the novel broad spectrum drugs in women with generalized epilepsies. New drugs devoid of interactions with hormonal contraceptives are also preferred in fertile women. This trend is confirmed by a recent survey of AED prescription patterns in Norwegian patients with epilepsy. (4) The purpose of this article is to provide a review of the safety and risk associated with prenatal exposure to antiepileptic therapy, to describe the main malformation patterns associated with the various.

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MAJOR CONGENITAL MALFORMATION

Major congenital malformations (MCM) are defined as an abnormality of an essential anatomic structure present at birth that interferes significantly with function and/or requires major intervention. The MCMs most commonly associated with AED exposure include congenital heart disease, cleft lip/palate, urogenital defects, and neural tube defects(5).

Table 1 shows the MCM rate by type of AED exposure. The MCM rate was significantly higher in polytherapy than with monotherapy exposures (crude OR=1.63 (p=0.010); OR adjusted for age at birth, parity, family history of MCM, folic acid exposure, sex of infant=1.83 (p=0.002)).

**Monotherapy**

Table 2 shows MCM details for monotherapy exposures with over 25 outcomes. The MCM rate was significantly less for carbamazepine than for valproate.

There was a trend towards fewer MCMs for lamotrigine compared with valproate exposed pregnancies (unadjusted OR=0.517 (p=0.015); however, when adjusted for age at birth, parity, family history of MCM, folic acid exposure, and sex of infant, statistical significance was lost (OR=0.589 (p=0.064)). Two infants exposed to topiramate (35 exposures) had an MCM (one case of cleft lip and palate, one case of hypospadias) and one infant exposed to gabapentin had a ventricular septal defect. No MCMs were recorded from any other monotherapy exposures (levetiracetam (25), ethosuximide (12), clonazepam (9), vigabatrin (6), oxcarbazepine (7), and piracetam (1)).

**Polytherapy**

There were 126 different combinations among the 770 cases exposed to AEDs in polytherapy. The MCM rates for the 388, 430, and 304 cases exposed, respectively, to carbamazepine, lamotrigine, and valproate as part of a polytherapy combination were 4.1% (95% CI, 2.5% to 6.7%), 4.8% (3.1% to 7.3%), and 9.0% (6.3% to 12.8%). For polytherapy combinations, those containing valproate in any combination had a significantly higher risk of MCM than polytherapy combinations not containing valproate (OR=2.49 (1.31 to 4.70)). (1)
Considering the most commonly used polytherapy combinations, the MCM rate for pregnancies exposed to carbamazepine and valproate (n=62) was 8.8% (3.8% to 18.9%) and for pregnancies exposed to valproate and lamotrigine (n=141) it was 9.6% (5.7% to 15.7%). No MCMs were recorded in pregnancies exposed to carbamazepine and lamotrigine (n=118) (MCM rate 0.0% (0.0% to 3.3%)).(1).

**Types of Malformations**

The types of malformations caused by AEDs are, Preterm birth, Cleft lip/palate, Club foot, Hypospadias, Inguinal hernia, Undescended testes. The types of malformations recorded for individual monotherapy exposures are shown in table 3.

**Dose response**

The mean daily dose of AED was not different for cases with and without an MCM for either carbamazepine (respectively, 657.5 mg and 611.7 mg; p=0.56) or valproate (1053.5 mg and 936.0; p=0.153).

For lamotrigine the mean daily dose was significantly higher for those with an MCM than for those without an MCM (respectively, 352.4 mg and 250.6 mg; p=0.005).

The MCM rates by exposure to carbamazepine, valproate, and lamotrigine as a function of dose are shown in table 4 and illustrated in fig 2.

**New Data on Commonly Prescribed AEDs Across Neuropsychiatric Disorders**

**Topiramate**

In TPM-exposed pregnancies, the rate of all malformations is 4.2% -- 4.9%, with an increase in MCMs (mostly oral cleft and hypospadias); prenatal exposure to TPM has been associated with an elevated frequency of small size for gestational age newborns. (2)

**Levetiracetam**

The UK and Ireland Epilepsy and Pregnancy Registers combined results for first trimester exposure to LEV with outcome data for 304 monotherapy pregnancies and 367 polytherapy pregnancies [7]. The MCM rate in the LEV monotherapy group was 0.7% (95% CI 0.19–2.51) and in the polytherapy group was 5.56% (95% CI 3.54–8.56).

The NAAPR reported on 450 first trimester LEV monotherapy exposures, and the MCM rate was 2.4% (95% CI 1.2–4.3) [1].

**Oxcarbazepine**

No adverse effects are reported in the new born of OXC-treated mothers [8,9]. In a study, MCMs at birth were found in 11 of 393 (2.8%) children exposed to OXC, a rate that was not significantly higher than non-exposed infants. A recent innovative study had shown that the encapsulation of OXC into nanoparticles may offer promise for treating pregnant women with epilepsy by improving brain delivery and limiting the transplacental permeability of AEDs.

The physical properties of the developed nanoparticles were evaluated. In this work, the authors have encapsulated OXC into biodegradable and biocompatible nanoparticles to reduce the placental transfer of the drug, maintaining the passage of the blood–brain barrier.(3)

**Gabapentin**

Although gabapentin is widely prescribed for a variety of neuropsychiatric disorders, sparse data are available on its risk during pregnancy. The NAAPR did report a MCM rate of 0.7% with fairly wide 95% CIs (0.02–3.80), given that only 145 pregnancies were captured [5]. A prospective cohort study of the teratogen information services and pharmacovigilance centres in Canada, Europe, and Korea reported on 223 gabapentin-exposed women and 223 controls [10]. Rates of MCMs were similar in the 2 groups, (4.1 % in the gabapentin group), but the gabapentin group had higher rates of preterm births, low birth weight, and neonatal complications; 38% were admitted to the neonatal intensive care unit or special care nursery versus only 2% in the control group. The indications for the gabapentin prescriptions were epilepsy (34%), pain (43%), and psychiatric conditions (22%).

**Zonisamide**

The teratogenic effects of Zonisamide (ZNS) were reported in one study with 26 children exposed to ZNS in utero. Malformations were found in two cases where ZNS was combined with first-generation AEDs, but not in the four cases treated with monotherapy.(2).

**Neurodevelopmental effects**

In utero exposure to VPA has been identified as a risk factor for cognitive impairment in children. Cognitive functions in the offspring have recently been compared for VPA, CBZ, phenytoin and LTG in an on-going prospective, observational multicentre study. Exposure to VPA during pregnancy was associated with the poorest cognitive results at 3 years of age, compared with the global IQs of their mothers, whereas offspring and maternal IQs correlated well for the other drugs.(11)
**DISCUSSION**

**Based on the review of the results, the following things are analyzed:**

1. The 1st generation drugs are known to have major complications causing various congenital malformations like Neural tube defects, Hydrops, Facial clefts, cardiac, skeletal, GIT and GIT defects in pregnant women under AED therapy.

2. Compared to first generation Anti-epileptic drugs, the second generation Anti-epileptic drugs are concluded to be safer and less riskier in the patients with epilepsy during pregnancy.

3. Valproate has a higher rate of MCMs in pregnant women in comparison with other 1st generation AEDs, so Valproate should be avoided in pregnancy along with other 1st generation AEDs.

4. Also VPA is known to have poor verbal IQ, performance IQ, and Full Scale IQ in children born to those women with Valproate therapy during pregnancy.

5. Monotherapy of AEDs has less risk of ADR in pregnancy rather than Polytherapy and Polytherapy with Valproate should be avoided must. Zonisamide and Oxcarbazepine are the safest among all AEDs during pregnancy and its use is to be encouraged.

**Pregnancy changes the pharmacokinetics of AEDs**

Recently, several pharmacokinetic studies have identified and characterized factors which may alter AED pharmacokinetics during pregnancy:

Renal blood flow and glomerular filtration rate increase by as much as 50–80% during pregnancy. Serum concentrations of AEDs and/or their metabolites that are predominantly eliminated via the kidneys may be reduced accordingly. This effect starts shortly after conception with persistence throughout the second trimester and with some reduction in the last few weeks of pregnancy[13-15]

Hormonal changes, that is, increased oestrogen levels, lead to accelerated drug glucuronidation. This effect seems to increase gradually throughout the first and second trimester, with little change during the last trimester [16]. In addition, the activity of some CY P450 enzymes is increased [15];

Reduced serum albumin concentrations may affect AED protein binding and, thus, total plasma clearance; increased plasma volume and/or increased total body water may increase the volume of distribution, and thus lead to reduced AED serum concentrations.

**Safety Measures**

**Therapeutic Drug Monitoring** in maintaining seizure control during pregnancy,

**Establishing Individual AED Target Concentrations and monitoring them**

The findings reported by EURAP that the dose at conception is important for all AEDs studied [17], suggest that a woman’s preconception dose should be scrutinized prior to pregnancy and reduced if possible based upon her seizure history and personal characteristics. It is helpful to measure baseline serum concentration in the non-pregnant state, and use that for guidance if she has good seizure control without side effects, and if it is thought that her dose cannot be lowered further. However, if she is on a concomitant hormonal contraceptive that includes an oestrogen, then her dose can often be adjusted lower when the hormonal contraceptive is stopped if she is on LTG, VPA, and probably OXC.LTG clearance is increased not only in pregnancy with the endogenous rise in sex steroid hormones, but clearance is also approximately 2-fold higher with exogenous administration of oestrogens via combined oral contraceptive pills and other contraceptives that contains oestrogens (e.g., patch, vaginal ring) [18-22]. Similar but more modest effects have been shown for VPA [23]; VPA concentrations were 25% lower in the VPA plus combined oral contraceptive group than the VPA alone group. It is likely OXC also has enhanced clearance with exogenous oestrogens given the glucuronidation pathway of elimination.

Prenatal exposure to antiepileptic therapy may also be to determine effects on neurological and cognitive development.

Where possible, Valproate should be avoided in women of childbearing potential and newer AEDs should be used.

**CONCLUSION**

During pregnancy, monthly AED levels should be obtained for therapeutic drug monitoring to maintain the non-pregnant individual target concentration for most AEDs studied with the possible exception of CBZ; AEDs should be adjusted back to preconception doses or slightly higher over 2 weeks to 3 months, depending on the AED. These same evolving concepts and principles can be applied to women on AEDs for other neuropsychiatric indications that require chronic, daily dosing and principles can be applied to women on AEDs for other neuropsychiatric indications that require chronic, daily dosing during pregnancy and postpartum. However the use of AEDs such as Zonisamide (ZNS) and microencapsulated Oxcarbazepine (OXC) is highly beneficial in pregnancy.

**Reference**


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