Antiepileptic drug pregnancy registries: do the latest findings concur?

The risk of antiepileptic drug (AED) exposure to the developing fetus is of global concern. Every year, 25,000 children are born to women with epilepsy (WWE) in the USA alone. Most pregnant WWE require AEDs and, therefore, scientifically derived evidence from large studies is essential to help determine the best management. AED pregnancy registries were initiated in the early 1990s to assess pregnancy outcomes in WWE, with the aims of obtaining accurate information about AED-related teratogenesis and evaluating the risks of the newer AEDs in a timely manner. The registries have had varied methodologies, which has been, in part, dictated by the healthcare system in which they are used. Countries with nationalized healthcare systems permit population-based data gathering, whereas in areas where medical care is privatized, a more focused prospective approach is taken. Furthermore, pharmaceutical companies have supported several registries aimed at determining the risk of exposure to a single compound. Therefore, each registry has different rules for enrollment, inclusion/exclusion criteria, length and detail of follow-up, and predetermined publication criteria. Owing to these differences and because a few subjects enroll in more than one registry, the registries do not lend themselves to a meta-analytic approach. This article will summarize the major concurrent and differing findings of the current registries from the perspective of their direct impact on managing WWE during pregnancy. We will discuss registries based in the USA, UK, Australia, Finland, Sweden and from the European and International Registry of AEDs in Pregnancy (EURAP).

KEYWORDS: antiepileptic drug ■ epilepsy ■ major congenital malformation ■ pregnancy ■ registry ■ seizure ■ teratogenicity ■ valproate ■ women with epilepsy

Leticia Tornes[1] & Cynthia L Harden†[1]

[1]University of Miami Miller School of Medicine, 1120 NW 14th Street, Suite 1324, Miami, FL 33136, USA
†Author for correspondence:
Tel.: +1 305 243 7713
Fax: +1 305 243 8108
charden@med.miami.edu

Registry versus clinical trial

The main goal of pregnancy registries includes the rapid identification of signals of increased teratogenic risk as quickly as possible, which is especially important for newly available antiepileptic drugs (AEDs) [1–3]. When the association between an increased risk and an AED is found in a registry, the cause can be further explored in a case–control study or aspects of the risk can be studied in a clinical trial. In general, registry data are considered to be less accurate than data from clinical trials because the enrollment criteria in a registry study may be more subject to bias and variability, whereas the enrollment criteria can be refined and strictly controlled for case–control studies or clinical trials. On the other hand, risks discovered in a clinical trial can be evaluated for their importance in a larger population by surveying for them in a registry.

Seizure control

■ Australian Pregnancy Registry

In 2008, the Australian registry published a report on seizure control during pregnancy for women with epilepsy (WWE) on AEDs [4]. The investigators compared seizures during pregnancy with seizure occurrence in the year prior to pregnancy, determined by the patient's retrospective recall and confirmed by the medical practitioner (see characteristics of registries in Table 1). At the time of the report, 1002 pregnancies were analyzed, of these, 841 were AED exposed. Of the 841, 418 (49.7%) were associated with seizures during the pregnancy and half of the seizure-affected pregnancies included generalized tonic–clonic seizures. Seizure occurrence during pregnancy was 22-times more likely to be associated with seizures during labor than if the pregnancy was seizure free.

Primary generalized epilepsies were associated with a decreased risk of seizures during pregnancy compared with partial epilepsies, whereas polytherapy was associated with an increased risk of seizures. Only 19.8% of the 450 patients that had no seizures during the year prior to pregnancy had seizures during pregnancy (implying that 80% remained seizure free). The risk of seizures during pregnancy was 24.9% with at least 1 year without seizures, 22.8% with 2 years, 20.5% with 3 years and 20% with 4 years or more. Therefore, the authors concluded that after 1 year of seizure freedom, there was no advantage to delaying pregnancy in order to avoid seizure occurrence during pregnancy [4].

part of future medicine fsg

Table 1. Summary of study design, methodologies, outcomes and major contributions of five pregnancy registries.

Variable	NAAEDPR	UK	Australia	EURAP	Finland
Size (n)	>7000	>7000	>1500	>14,000	–
Study design	Prospective/retrospective	Prospective	Prospective/retrospective	Prospective/retrospective	Prospective/retrospective
Enrollment setting	USA and Canada	UK and Ireland	Australia	International (42 countries)	Finland
Methods for enrollment	Self-enrollment by the pregnant woman	Self-enrollment (50%), referral by physicians and nurses	Self-enrollment by eligible women	Through a network of reporting physicians	Population-based nationwide Finnish registers of AED exposure and birth defects
Maternal inclusion criteria	Women taking AEDs for any reason during pregnancy (~10% on AEDs for other reasons)	All WWE, regardless of AED exposure in the first trimester	Pregnant WWE with/without AED in the first trimester Women on AEDs for other indications in the first trimester	Pregnancies with AED exposure at time of conception	Children born after maternal diagnosis of epilepsy
Maternal exclusion criteria	Those switching AEDs in first trimester	Prenatal tests with abnormality before referral Loss of pregnancy with abnormality prior to referral Change of AED in the first trimester Start of AED postconception	NA	Change of AED in the first trimester Outcome unclassifiable	Pregnancies leading to abortion not included
Criteria for prospective	'Pure' prospective enrolled before results from prenatal screening	Enrollment before pregnancy outcome is known	Prospective enrolled before screening results known	Enrolled before outcome is known and within week 16 of gestation	Drug exposure recorded prospectively by the Social Insurance Institute of Finland
AEDs exposure	AED dose, regimen, brand	AED dose, regimen, dose change	AED dose, regimen	AED dose, regimen	AED dose, regimen
AED drug levels	Not systematically recorded	Not recorded	Not recorded	Not recorded	Not recorded
Other risk factors	Smoking, alcohol, other medications, other diseases	Demographics, seizure type/frequency, family history, among others	Demographics, epilepsy, seizure type/frequency, family history, among others	Demographics, epilepsy, seizure type/frequency, family history, among others	Maternal age, number of prior pregnancies
Data collection and methods for follow-up	Three contacts, telephone interviews, supplemented by medical records in 60% of women that grant consent	Two contacts with the patient's physician	Four telephone interviews with patient, supplemented by contact with the physician	Four to five contacts, mainly personal visits with reporting physician supplemented by medical records	Finnish Birth Registry, Social Insurance Institute of Finland and abstracted medical records
Diagnosis of epilepsy	Self-report, records from neurologist of enrollee	Patient's physician	Patient's physician	Patient's physician	Patient's physician

AED: Antiepileptic drug; EURAP: European and International Registry of AEDs in Pregnancy; ICD: International classification of diseases; MCM: Major congenital malformation; NA: Not applicable; NAAEDPR: North American AED Pregnancy Registry; WWE: Women with epilepsy.
Adapted from [1].

Table 1. Summary of study design, methodologies, outcomes and major contributions of five pregnancy registries (cont.).

Variable	NAAEDPR	UK	Australia	EURAP	Finland
Fetal exclusion criteria	Genetic/chromosomal, minor anomalies, positional deformations	Genetic/chromosomal, minor anomalies analyzed separate from major malformations	Genetic/chromosomal abnormalities analyzed separately	Genetic/chromosomal abnormalities analyzed separately Same as those with screening before enrollment	Still births
Assessment	Review of medical records by teratologist, direct communication with mother/physician when needed	Abnormal outcomes classified by one clinical geneticist based on medical records	Based on review of medical records	Central classification by blind teratologists based on reports from physicians	Review of medical records
Time window of assessment	Malformations detected within the first 5 days of life and at a postpartum call at 8–12 weeks of age	Within 3 months after birth	Within 12 months after birth	Within 12 months after birth	Unclear
Classification of outcome	Major malformations	Major malformations; using EUROCAT	Major malformations (birth defects as defined by the Victorian Birth Register)	Major malformations according to predefined criteria	Main categories of malformations as defined by ICD-9
Data analysis comparator/ control population	External comparison group AEDs for nonepilepsy Internal unexposed control group is being recruited	Internal comparison between different AED groups and untreated epilepsy	Untreated WWE AEDs for nonepilepsy Internal comparison between different AEDs	Internal comparison between different AED treatments	Untreated WWE
Confounding factors	Information collected on several factors	Information collected on several factors Adjustments for age at delivery, parity of mother, family history of MCM, periconceptional folic acid exposure and sex of infant	Information collected on several factors	Information collected on several factors to be included in multivariate analysis	Information on maternal age and number of prior pregnancy

AED: Antiepileptic drug; EURAP: European and International Registry of AEDs in Pregnancy; ICD: International classification of diseases; MCM: Major congenital malformation; NA: Not applicable; NAAEDPR: North American AED Pregnancy Registry; WWE: Women with epilepsy.
Adapted from [1].

European & International Registry of AEDs in Pregnancy

In 2006, the European and International Registry of AEDs in Pregnancy (EURAP) group published a report on seizure control in pregnancy [5]. They followed almost 2000 patients prospectively during pregnancy and used seizure frequency in the first trimester as the baseline comparator. The study included 1956 pregnancies and, of those, 1013 (58.3%) were seizure free and 723 (41.6%) had seizures. EURAP reported that 60 (3.5%) patients had seizures during delivery and the only factor significantly associated with this was the occurrence of seizures earlier in pregnancy, which increased the risk of seizures during delivery by a factor of five. EURAP also found that partial seizures were twice as likely to occur during pregnancy than generalized seizures (odds ratio [OR]: 2.11; 95% CI: 1.72–2.58) with 503 out of 736 (68.3%) of those with generalized seizures remaining seizure free during pregnancy compared with 451 out of 913 (49.4%) of those with partial seizures. Similarly, EURAP reported localization-related epilepsy to be associated with a greater risk of occurrence for all seizures (OR: 2.5; 95% CI: 1.7–3.9).

Furthermore, the investigators found that polytherapy was independently associated with an increased risk of occurrence of all seizures (OR: 9.0; 95% CI: 5.6–14.8) and convulsive seizures (OR: 4.2; 95% CI: 2.5–7.0). Finally, they reported oxcarbazepine (OXC) monotherapy had a greater occurrence of convulsive seizures (OR: 5.4; 95% CI: 1.6–17.1). The EURAP study is one of few that reported on status epilepticus; the occurrence rate was low, present in 36 (1.8%) pregnancies and, of these, 12 out of 36 were convulsive. No risk factors for status were identified.

Teratogenesis

The risks of major congenital malformations (MCMs), in association with first trimester AED exposure is discussed later, divided into specific AED's per registry. The definition of MCMs used in this article refer to structural abnormalities with surgical, medical or cosmetic importance [6].

Valproate

Australian Pregnancy Registry

The Australian Pregnancy Registry of AEDs was started in 1999 and it recruits were informed, consenting WWE being treated with AEDs, those with epilepsy not on treatment and those on AEDs for other indications [4]. Patients are recruited by medical practitioners, other patients, nurses or from advertisements, and enroll voluntarily [4]. All patient contact is via phone, and this occurs at 28 weeks gestation, 4 weeks postpartum and 1 year after birth [4].

In the first comprehensive report regarding valproate (VPA), 555 pregnancy outcomes were analyzed. Within a group of WWE taking AEDs, out of the multiple factors analyzed, only VPA monotherapy at doses greater than 1100 mg/day in the first trimester were associated with an increased risk of MCM (OR: 7.3; $p < 0.0001$) [7]. The rate of MCMs was not increased with VPA monotherapy daily doses lower than 1100 mg/day when comparing outcomes to unexposed fetuses. The authors also reported that those patients with primary generalized epilepsy were more likely to have infants with MCMs; however, these patients were also more likely to be on VPA. After multivariate analysis, it was confirmed that MCMs are secondary to the VPA use. In summary, the Australian registry found a high incidence of MCMs in those patients on VPA, regardless of whether they received mono- or polytherapy.

UK Epilepsy & Pregnancy Register

The UK registry was established in 1996 and enrolls a large proportion of eligible pregnancies (~25–33%) from the UK and Ireland [3,8]. It is a prospective, observational study in which data collection occurs at enrollment and then at 3 months postdelivery. The major report from this registry included 4414 enrollments, of whom, 3607 had full outcomes, making it one of the largest, prospective and population-representative studies. Of the 3607 pregnancies, 2598 (72.0%) had been exposed to monotherapy, 770 (21.3%) to polytherapy and 239 (6.7%) were reported to have epilepsy but were not on treatment [8].

The UK Pregnancy Register reported that 96% of infants exposed to any AED or combination of AEDs *in utero* had MCMs [8]. However, the rate of MCMs in the VPA monotherapy-exposed pregnancies was the highest of any AED as monotherapy at 44 out of 715 (6.2%); 95% CI: 4.6–8.1. The OR for VPA-exposed patients was 2.78 (95% CI: 1.62–4.76) compared with carbamazepine (CBZ), which was the AED with the lowest rate of MCMs at 2.2% (20 out of 900).

A prospective, observational, multicenter trial of children exposed to either VPA, CBZ, phenytoin or lamotrigine (LTG) *in utero* who underwent cognitive evaluation at 3 years of age, showed a remarkable adverse effect of VPA on IQ [9]. Children exposed to VPA had an IQ score 6–9 points lower than those exposed to other AEDs, and the association was dose dependent.

Furthermore, the children's IQs were significantly related to maternal IQs among children exposed to CBZ, LTG or phenytoin, but not among those exposed to VPA. This finding provides additional evidence for the broad teratogenic effect of VPA, and identifies the kind of information that must be obtained in a clinical study versus a pregnancy registry.

North America AED Pregnancy Registry

The North America AED Pregnancy Registry (NAAEDPR) was established in 1997 and enrolls pregnancies from the USA and Canada. Recruitment is through self-enrollment and the women must call a toll-free number to register [3]. Subjects are interviewed at enrollment, at 7 months gestation and at 8–12 weeks postdelivery.

In 2005, Wyszynki *et al.* published data from the NAAEDPR on the occurrence of major malformations in infants whose mothers were receiving VPA monotherapy [10]. The VPA-exposed group (n = 149) was compared with both an internal and external group. The internal group (n = 1048) included women in the registry that were exposed to a monotherapy AED other than VPA, and this group had an MCM prevalence of 2.9% (95% CI: 2.0–4.1%). The external group consisted of newborns in the Active Malformations Surveillance Program at Brigham and had a prevalence of 1.62% of nongenetic major malformations.

Of the 149 VPA-exposed infants, 16 (10.7%) had MCMs (95% CI: 6.3–16.9%). Therefore, there was a fourfold increased risk of MCMs with VPA exposure compared with all other AEDs (OR: 4.0; 95% CI: 2.1–7.4; $p < 0.001$). Furthermore, there was a sevenfold increased risk of MCMs with VPA exposure compared with external healthy controls (OR: 7.3; 95% CI: 4.4–12.2; $p < 0.001$) [10].

Finland National Medical Birth Registry

The Finnish registry is a nationwide, population-based registry. It uses the drug prescription database and the national medical birth registry to identify all women with AED exposure during pregnancy [11]. The investigators have reported on WWE on treatment versus untreated WWE. The 561 untreated patients had 939 births and the 857 treated patients had 1411 births. Most of the treated patients were on monotherapy (n = 1231) and, of these, 263 included on VPA monotherapy. The most common malformations were anomalies of the cardiovascular system (n = 16), cleft lip and palate (n = 9), anomalies of the genital organs (n = 18), musculoskeletal abnormalities (n = 11) and other abnormalities of the limbs (n = 17). Furthermore, six children were born with spina bifida [10].

Overall, when comparing the rate of fetal malformations in offspring of WWE not receiving AEDs to the general Finnish population, there was no significant difference. However, within the group of WWE, the risk of MCMs was higher for those on AEDs (65 out of 1411; 4.6%) than for mothers not on AEDs (26 out of 939; 2.8%); half of the MCMs were born to mothers taking VPA (37 out of 65; 57%). The risk of MCMs with VPA monotherapy was 11% (28 out of 263), which was four-times that of untreated WWE (OR: 4.18; 95% CI: 2.13–7.57). The investigators also found a relationship between dose and MCM risk with VPA; at doses greater than 1500 mg/day the risk was threefold compared with doses less than 1500 mg/day, with the caveat that even at less than 1500 mg/day, the risk is still markedly increased at four-times the MCM occurrence compared with untreated WWE. Importantly, there was no increased risk for any other AEDs in this registry [11].

Swedish Medical Birth Registry

The Swedish Medical Birth Registry has contained information on drug use reported by women during pregnancy since 1994 as well as an international classification of diseases coding information for congenital malformations [12]. This registry is population based and can be linked to other healthcare registries in Sweden; in this case, the drug information was linked to the Hospital Discharge Registry and the Swedish Register of Congenital Malformations. A total of 1398 AED-exposed infants were compared with an estimated 582,656 total infants in the registry. The risk of MCMs was doubled in the AED-exposed group compared with controls (OR: 1.86; 95% CI: 1.42–2.44); however, VPA monotherapy was associated with an absolute risk of 10% (26 out of 268) and again emerged as having a higher risk than CBZ monotherapy, with an OR of 2.51 (95% CI: 1.43–4.68) [11].

Lamotrigine

Australian Pregnancy Registry

In 2006, the Australian registry reported that no malformations occured in those exposed to LTG; however, there were only 65 outcomes available [7]. Notably, women taking LTG needed more dose adjustments for breakthrough seizures than those on VPA. This was likely to be secondary to accelerated LTG metabolism and increased clearance

caused by elevated reproductive hormones during pregnancy. Therefore, it is necessary to monitor plasma levels and increase LTG dose accordingly to ensure appropriate seizure control. Hence, it may be possible that the registry's discoveries of less fetal MCMs in the LTG-exposed group is secondary to lower plasma levels.

UK Epilepsy & Pregnancy Register

In the UK registry, LTG exposure was associated with the occurrence of MCMs in 3.2% (21 out of 647) and this finding was not significantly increased compared with the control group of 227 untreated WWE (relative risk: 0.92; 95% CI: 0.41–2.05). Furthermore, a dose–malformation relationship was reported in this study, with an increased risk associated with first trimester doses greater than 200 mg/day [8].

North American AED Pregnancy Register

In 2008, the NAAEDPR reported 16 cases of isolated cleft palate and/or cleft lip in newborns of 684 women on LTG monotherapy (proportion 2.3%; 95% CI: 1.7–4.3) [13]. Of the 16 patients, five had oral clefts, three had isolated cleft palates and one had an isolated cleft lip. The rate among the LTG-exposed infants showed a 10.4-fold increase (95% CI: 4.3–24.9) when compared with 206,224 unexposed infants from the Brigham and Women's Hospital in Boston, USA. A major weakness of this finding is that the occurrence of orofacial clefts is racially and population associated; therefore, the increased rate in this self-referred study group may be a chance finding.

Furthermore, this finding was refuted in a population-based case–control study with malformed controls using the EUROCAT congenital anomaly registers [14]. The investigators reported no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations associated with LTG monotherapy and that the distribution of other nonchromosomal malformation types with LTG exposure was similar to non-AED-exposed fetuses.

International LTG Pregnancy Registry

The International LTG Pregnancy Registry enrolled patients between September 1992 and March 2010. This registry was carried out in order to detect an early signal of LTG-associated teratogenic risks. The full executive summary is available online [101]. Patients were referred by healthcare professionals throughout the world and there was also a comparator group. Only pregnancies with unknown outcomes at the time of enrollment were included. In total, 2444 pregnancy outcomes were assessed, not including 972 cases or (28.5%), which were not available for follow-up.

The registry reported that MCMs occurred in 35 out of 1558 first trimester monotherapy exposures, or 2.2% (95% CI 1.6–3.1%). However, there was a significant adverse effect of VPA on the malformation rate; MCMs occurred in 16 out of 150 exposed to polytherapy with VPA during the first trimester (10.7%; 95% CI: 6.4–17.0%), while MCMs occurred in only 12 out of 430 for polytherapy without VPA in the first trimester (2.8%; 95% CI: 1.5–5.0%). There was no specific pattern of structural malformations found in this registry. Furthermore, there was no dose–malformation relationship found, in contrast to the dose relationship reported in the UK Epilepsy and Pregnancy Register.

Carbamazepine

UK Epilepsy & Pregnancy Register

In the UK registry, CBZ exposure was associated with a 2.2% occurrence of MCMs (20 out of 900) and this finding was not significantly increased over the control group of 227 untreated WWE (relative risk 0.63; 95% CI: 0.28–1.41) [8].

Finland National Medical Birth Registry

In the Finland registry, there were 32 MCMs out of 805 (4%) in the CBZ monotherapy-exposure group (95% CI: 2.8–5.5), and investigators found no increased risk with CBZ compared with the general population [11].

Swedish Medical Birth Registry

In the Swedish registry, there were 28 MCMs out of 703 (3.9%) in the CBZ monotherapy-exposure group for a rate of 3.9% (95% CI: 2.8–5.6) [12].

Phenobarbital

The only registry information on phenobarbital is from the NAAEDPR in 2004, in which five MCMs were found in 77 monotherapy exposures at a rate of 6.5% (95% CI: 2.1–14.5) and, compared with the general control population, phenobarbital had a relative risk of 4.2 (95% CI: 1.5–9.4) [15]. Cardiac defects comprised the majority of the MCMs.

Oxcarbazepine

There is little systematic information regarding OXC, but the initial information appears encouraging; the Swedish Medical Birth

Registry included 99 exposures to OXC monotherapy and one MCM, which was urogenital, occurred among these [12].

Topiramate

The UK Pregnancy Registry published the only systematic information on topiramate (TPM) in 2008 [16]. Of the 70 monotherapy TPM-exposed pregnancies, three had MCMs (4%; 95% CI: 1.5–11.8). The average daily dose of TPM monotherapy in those with MCM was 400 mg/day, compared with 238 mg/day in the unaffected group [15].

Overall, the UK Registry found that the rate of oral clefts was 11-times the background rate in those infants exposed to TPM. However, it is worth noting that there was a small sample size [16].

Levetiracetam

The UK Pregnancy Registry published the only systematic review of levetiracetam in 2006 [17]. Of the 117 exposures, 39 of which were monotherapy, three MCMs occurred, but all three were exposed to polytherapy. Therefore, this finding does not provide insight into the specific risk of levetiracetum and further results, including from the UCB Pregnancy Registry are anticipated.

Polytherapy versus monotherapy

Although AED polytherapy may pose a greater risk for MCMs than monotherapy, evidence is emerging that VPA drives much of the increase risk in polytherapy.

UK Epilepsy & Pregnancy Register

The UK registry found that polytherapy was associated with higher risk of MCMs than monotherapy (6.0 vs 3.7%) [8]. The UK Epilepsy and Pregnancy Register also found that, for polytherapy combinations, those containing VPA in any combination had a significantly higher risk of MCM than those without VPA (OR: 2.49; 95% CI: 1.31–4.70) [8].

Finland National Medical Birth Registry

In one report, MCMs occurred in 52 out of 1231 births (4.2%) for patients on monotherapy and in 13 out of 180 births (7.2%) for those on polytherapy. The Finnish registry also reported that the use of VPA significantly increases the risk of MCMs, whether it is used as a mono- or poly-therapy [11]. Most importantly, they found that mothers on polytherapy regimens that did not include VPA, such as CBZ, OXC, phenytoin or other AEDs, did not have an increase in malformations when compared with untreated WWE [11].

Folic acid

In 1965, Hibbard and Smithells described that a lack of folate or disturbed folate metabolism was more often positive in women carrying a fetus with neural tube defects than in controls [18]. Later, randomized controlled trials, controlled trials and noncontrolled intervention studies demonstrated that giving patients folic acid supplementation before or early in pregnancy reduced the incidence of primary and recurrent neural-tube defects and other congenital abnormalities [19]. Therefore, folic acid supplementation during pregnancy is recommended to the general population to reduce the frequency of neural-tube defects and other MCMs. Some of the AEDs, including CBZ, phenobarbital, phenytoin and primidone, are known to influence folic acid absorption and, therefore, it is recommended that WWE take folate to counteract these known antifolate effects.

Australian Pregnancy Registry

The incidence of MCMs was not statistically significant between those exposed to folate and those who were not [7].

UK

In the UK registry, 88.3% of the 4680 pregnant women were on folic acid by the time of registration. Of these women on folic acid, 41.3% had begun it preconceptually. For the 4680 registrations, 3.4% (95% CI: 3.0–4.0) MCMs were identified [20]. Surprisingly, the OR for having an MCM was 1.76 (95% CI: 1.25–2.56) when folic acid was started preconceptually compared with those pregnancies in which folic acid was begun after conception or not at all [20]. Owing to the increase in risk, the investigators concluded that one may not be able to extrapolate studies from the general population to WWE and that the increased risk of MCM in this group occurs through different mechanisms to folic acid metabolism.

Other outcomes: small for gestational age from Taiwan's Birth Certificate Registry

One study linked two nationwide, population-based data sets: Taiwan's birth certificate registry and the Taiwan National Health Insurance Research dataset [21]. The investigators evaluated WWE not taking AEDs who had single births between 2001 and 2003. The number of WWE not taking AEDs was 850 out of 1016 eligible candidates; making this a very unique group in which the outcome is not confounded

by the possible effect of AED exposure. The WWE were further stratified into two groups for analysis: women who did and did not have seizures during pregnancy. The investigators found that the risk of being small for gestational age increased significantly (OR 1.34: 95% CI: 1.01–1.84) when women had seizures during pregnancy compared with WWE who did not have seizures during pregnancy. This is one of the few studies of WWE to document a risk of having seizures during pregnancy versus being seizure free, and is not confounded by AED use.

Conclusion

This article demonstrates that the current pregnancy registries do not differ in their findings, in that many show an increased risk of MCMs with VPA, and a lesser risk with LTG and CBZ, with more information needed about TMP, levetiracetum and OXC. VPA also contributes to much of the risk of AED polytherapy. The differences in registry findings may also be minimized by the inclusion of the same subjects in some registries, in particular, the LTG registry and a geographic registry; furthermore, the EURAP and the Australian registry are known to have some overlapping subjects.

Even the counterintuitive finding of no risk reduction with folic acid supplementation was found in two geographically distinct registries. The lower overall rates of MCMs in the UK registry may be related to their methodology of excluding WWE who have known fetal abnormalities. However, the increased rate of orofacial clefts in the NAAEDPR was not supported by EUROCAT data, and this may reflect selection bias in the NAAEDPR.

Future perspective

It is hoped that the current registries will provide data on dose relationships with MCMs; however, future registries should aim to provide information on AED levels and pregnancy outcomes. Ideally, pregnancy registries will provide further insight into associations between outcomes and AED exposure, but will also look at associations between characteristics of WWE and their partners, and their genetically imparted vulnerability to AED and epilepsy-related pregnancy risks. Optimistically, we will be able to use data from the registries in order to complete translational research into the mechanisms that cause MCMs. There would be investigations on free radicals, antifolate antibodies and the mechanisms that cause MCM in only a fraction of those exposed. The mechanism by which AEDs cause malformations is unknown. Some proposed mechanisms underlying teratogenicity of AEDs include folate, ischemia, neuronal suppression, AED-induced neuronal apoptosis and reactive intermediates, such as epoxides and free radicals. Risk of AED exposure on the nervous system of the human fetus is largely unknown, but animal studies that demonstrate AED-induced neuronal apoptosis in immature brain tissue are raising concern.

Currently, the registries have different methodologies, making it challenging to use data across studies to compare outcomes. Ideally, a more global standard in methodologies for the pregnancy registries would make this comparison more feasible.

Features of an ideal registry are:

- The registry would be population based, and would record prospective data accurately and with prolonged follow-up for the child after birth. The registry would collect the time of exposure, schedule, duration, dose and the levels of the AEDs;
- The registry would collect more detailed data on the mother and father, including age, medical history, family history of miscarriages or malformations, social history, ethnicity, employment, educational level and, for the mother, parity with outcomes of previous pregnancies;
- The type of epilepsy and seizure frequency during pregnancy would be included. Other medical conditions and medications other than AEDs would also be collected, including supplements, such as folate and other prenatal vitamins;
- Follow-up would be for at least 1 year, including an examination of the infant, as in Australia and EURAP, preferably for longer to assess cognitive development. The duration of follow-up has to be taken into consideration; although more outcomes will be captured with a long follow-up, there will be more subjects lost to follow-up.

In summary, there must be a balance between a comprehensive approach, which may limit the number of pregnancies that will be enrolled, and a more simplistic 'user-friendly' evaluation system that will enroll more pregnancies. The cost of such a complete registry would be high and, therefore, would need to be supported by global resources and multiple stake-holders.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Seizure control

- The pregnancy registries are remarkably concurrent and do not disagree in their major findings. The variability of their findings is readily explained by differing methodologies.
- Approximately 80% of women with epilepsy who are seizure free in the year before pregnancy will likely remain seizure free during pregnancy.
- Localization-related epilepsies versus primary generalized epilepsies are associated with an increased risk of seizures during pregnancy.
- Antiepileptic drug (AED) polytherapy is also associated with an increased risk of seizures during pregnancy.
- Seizures during pregnancy are associated with an increased risk of seizures during labor and delivery.

Teratogenesis

- Four pregnancy registries found an increased risk of major congenital malformations (MCMs) when valproate (VPA) was administered in the first trimester, with rates ranging from 6.2 to 11.0%.
- Two registries showed that VPA exposure carries a 2.5-fold greater risk of MCMs than carbamazepine.
- Two registries showed a relationship between increased VPA dose during pregnancy and the risk of MCMs in exposed infants, with a marked increase in risk with doses greater than 1100 mg/day.
- There appears to be a low rate of MCMs with lamotrigine exposure, at 2.7–3.2% in large studies.
- The dose–malformation effect and the association with orofacial clefts with lamotrigine is not consistent between registries and these associations are not clear.
- There appears to be a low rate of MCMs with carbamazepine exposure, at 2.2–4.0% in large studies.
- Emerging information suggests that the risk of MCMs with topiramate, oxcarbazepine and levetiracetum is lower than that with VPA, but larger studies are needed. There is likely to be an increased risk of cardiac MCMs with phenobarbital.
- AED polytherapy may have a higher risk than monotherapy for MCMs; however, it appears that VPA use contributes to most of the increased risk.

Folic acid

- There is little evidence that folic acid supplementation provides increased risk reduction for MCM occurrence for the offspring of women with epilepsy taking AEDs during pregnancy; however, it is established that folic acid reduces birth defects in the general population.

Other outcomes: small for gestational age from Taiwan's Birth Certificate Registry

- Seizures during pregnancy for women with epilepsy may be independently associated with small for gestational age outcomes.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Meador KJ, Pennell PB, Harden CL *et al.*: Pregnancy registries in epilepsy: a consensus statement in health outcomes. *Neurology* 71(14), 1109–1117 (2008).

2 Tomson T, Battino D, French J *et al.*: Antiepileptic drug exposure and major congenital malformations: the role of pregnancy registries. *Epilepsy Behav.* 11(3), 277–282 (2007).

▪ **Summarizes the main methodologies and findings of the registries.**

3 Tomson T, Battino D, Craig J *et al.*: Pregnancy registries: differences, similarities, and possible harmonization. *Epilepsia* 51(5), 909–915 (2010).

4 Vajda FJE, Hitchcock A, Graham J, O'Brien T, Lander C, Eadie M: Seizure control in antiepileptic drug-treated pregnancy. *Epilepsia* 49(1), 172–175 (2008).

5 The EURAP Study Group: Seizure control and treatment in pregnancy: observations from the EURAP pregnancy registry. *Neurology* 66(3), 354–360 (2006).

6 Holmes LB, Harvey EA, Coull BA *et al.*: The teratogenicity of anticonvulsant drugs. *N. Eng. J. Med.* 344(15), 1132–1138 (2001).

7 Vajda FJE, Hitchcock A, Graham J *et al.*: Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur. J. Neurol.* 13(6), 645–654 (2006).

▪ **Reported that those with lamotrigine exposure had no major congenital malformations (MCMs), and that there was a dose effect of valproate.**

8 Morrow J, Russell A, Guthrie E *et al.*: Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J. Neurol. Neurosurg. Psychiatr.* 77(2), 193–198 (2006).

▪▪ **Summarizes class I data on MCMs, including carbamazepine, valproate and lamotrigine.**

9 Meador KJ, Baker GA, Browning N *et al.*; NEAD Study Group: Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N. Engl. J. Med.* 360(16), 1597–605 (2009).

10 Wyszynski DF, Nambiasan M, Surve T, Alsdorf RM, Smith CR, Holmes LB: Increased rate of major malformation in offspring exposed to valproate during pregnancy. *Neurology* (64), 961–965 (2005).

11 Artama M, Auvinen A, Raudaskoski T, Isojarvi I, Isojarvi J: Antiepileptic drug use in women with epilepsy and congenital malformations in offspring. *Neurology* 64(6), 1874–1878 (2005).

12 Wide K, Winbladh B, Kallen B: Major malformations in infants exposed to antiepileptic drugs *in utero*, with emphasis on carbamazepine and valproic acid: a nation wide, population-based register study. *Acta. Paediatr.* 93(2), 174–176 (2004).

▪▪ **A population-based study with a summary of MCMs on valproate and carbamazepine.**

13 Holmes LB, Baldwin EJ, Smith CR *et al.*: Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 70(22), 2152–2158 (2008).

14 Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LT; EUROCAT Antiepileptic Drug Working Group: Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations. *Neurology* 71(10), 714–722 (2008).

15 Holme LB, Wyszynski DF, Lieberman E: The AED (antiepileptic drug) pregnancy registry – A 6-year experience. *Arch. Neurol.* 61(5), 673–678 (2004).

▪ **Only publication to focus on the MCMs associated with phenobarbital.**

16 Hunt S, Russell A, Smithson WH *et al.*: Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregancy Register. *Neurology* 71(4), 272–276 (2008).

17 Hunt S, Craig J, Russell A *et al.*: Levetiracetam in pregnancy: preliminary experience from UK epilepsy and pregnancy register. *Neurology* 67, 1876–1879 (2006).

18 Hibbard E, Smithells R: Folic acid metabolism and human embryopathy. *Lancet* 285(7398), 1254 (1965).

19 Czeizel AE: Periconceptional folic acid and multivitamin supplementation for the prevention of neural tube defects and other congenital abnormalities. *Birth Defects Res. A Clin. Mol. Teratol.* 85(4), 260–268 (2009).

20 Morrow JI, Hunt SJ, Russell AJ: Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register. *J. Neurol. Neurosurg. Psychiatry* 80(5), 506–511 (2009).

21 Chen YH, Chiou HY, Lin HC, Lin HL: Affect of seizures during gestation on pregnant outcomes in women with epilepsy. *Arch. Neurol*. 66(8), 979–984 (2009).

▪ **An interesting paper that discusses the outcome of infants born to mothers with frequent seizures.**

Website

101 GlaxoSmithKline Pregnancy Registries http://pregnancyregistry.gsk.com