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SPECIAL REPORT

Epilepsy-pregnancy registries: An update

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Abstract

This report is the first comprehensive update on the activities of existing epilepsy-pregnancy registries since 2010. The primary aim of these registries, which were initiated by independent international research groups some 25 years ago, has been to assess the risk of major congenital malformations (MCMs) in offspring exposed in utero to different antiseizure medications (ASMs). Progress reports are provided here from the five original registries (the International Registry of Antiepileptic Drugs and Pregnancy EURAP, the North American Antiepileptic Drug Pregnancy Registry, the UK and Ireland Epilepsy and Pregnancy Register, the Kerala Registry of Epilepsy and Pregnancy, and the Raoul Wallenberg Australian Pregnancy Register of Antiepileptic Drugs) plus the more recently initiated West China Registry. Since their inception, the registries have published a wealth of data revealing important differences in risks across the most frequently used ASM treatments, thereby facilitating rational management of women with epilepsy who are of childbearing potential. Although the number of pregnancies enrolled in the different registries has more than doubled since the 2010 report, many questions remain. These include outcomes following prenatal exposure to most of the newer ASMs or different ASM combinations, as well as associations with specific MCMs rather than MCMs as a collective. All the registries, therefore, remain active and continue to enroll pregnancies. Administrative health care databases have been utilized more recently for the assessment of MCM risks and other adverse pregnancy outcomes associated with in utero exposure to ASMs. Although these can provide population-based complementary information, they cannot replace the specific epilepsy-pregnancy registries with their more detailed validated individual information. Given the multiple newer ASMs that are increasingly used and the continuing multiple knowledge gaps for the older ASMs, epilepsy-pregnancy registries will continue to play an important role in the future.

For affiliations refer to page 56.

KEYWORDS
antiseizure medications, congenital malformations, epilepsy, pregnancy, registries, teratogenicity

1 | INTRODUCTION

In the late 1990s, several independent international research groups established prospective epilepsy-pregnancy registries with the overarching aim of enrolling large numbers of pregnancies to facilitate comparison of the teratogenic risks associated with exposure to different antiseizure medications (ASMs) during pregnancy. Some registries also aimed to compare these risks with those associated with ASMs prescribed for indications other than epilepsy, or with the risks of malformations in women with epilepsy not taking ASMs. These initiatives were prompted by the introduction of a number of new ASMs with unknown teratogenic potential, and the emerging, yet still limited, understanding of the risks associated with older ASMs.[1] In 2008, after approximately a decade of operation of these registries, the International League Against Epilepsy (ILAE) convened a workshop where the three largest independent registries—namely, the UK Epilepsy and Pregnancy Register (subsequently renamed "UK and Ireland Epilepsy and Pregnancy Register" [UK&IEPR]),[2] the North American Antiepileptic Drug Pregnancy Registry (NAAPR),[3] and the International Registry of Antiepileptic Drugs and Pregnancy (EURAP)[4]—gathered to exchange experiences, discuss methodological issues, harmonization efforts, and potential collaborations. The workshop resulted in a publication that also included information on two other major registries, the Kerala Registry of Epilepsy and Pregnancy (KREP)[5] and the Australian Pregnancy Register of Antiepileptic Drugs (subsequently renamed "Raoul Wallenberg Australian Pregnancy Register of Antiepileptic Drugs" [APR]).[1,6] Although all registries focused on major congenital malformations (MCMs) in the offspring as the primary outcome of interest, variations existed in enrollment methods, exposure definitions, follow-up duration, outcome criteria, and comparison groups.[1] The workshop concluded that the presence of distinct registries, rather than data pooling, could serve as an advantage, enabling validation or contradiction of observations across studies. Differences in methodology across registries also hampered data pooling.

Some 25 years after the launch of these registries, and 15 years after the workshop, these registries are still active, and a new one has been established in West China.[7]

Key points

- This report updates a 2010 report on the activities of the major epilepsy-pregnancy registries.
- There are now six registries, five longstanding (International Registry of Antiepileptic Drugs and Pregnancy EURAP, the North American Antiepileptic Drug Pregnancy Registry [NAAPR], the UK and Ireland Epilepsy and Pregnancy Register [UK&IEPR], the Kerala Registry of Epilepsy and Pregnancy [KREP], and the Raoul Wallenberg Australian Pregnancy Register of Antiepileptic Drugs [APR]), and a more recent one (West China Registry).
- These registries have advanced the understanding of differences in teratogenic risks across antiseizure medications (ASMs) as well as other adverse pregnancy outcomes.
- All registries remain active and represent critical resources to address important unanswered questions related to the management of epilepsy in pregnancy.

In light of this ongoing activity, a roundtable discussion was convened with representatives from the six major epilepsy pregnancy registries on December 2, 2023. This report aims to provide an update on the accomplishments of these registries, their current activities, and their envisioned roles in the future.

2 | UPDATES FROM INDIVIDUAL PREGNANCY REGISTRIES

Table 1 provides a summary of the individual characteristics of the six major epilepsy-pregnancy registries, whereas Table 2 details the prevalence of MCMs associated with the most common ASM monotherapy exposures across the registries. Although the primary objectives align across these registries, as highlighted in the 2008 workshop, some significant divergences also exist. Below we provide brief updates on the evolution, major accomplishments—particularly those post-2010—and future plans of each registry.

TABLE 1 Characteristics of the six major epilepsy-pregnancy registries.

	EURAP	NAAPR	UK&IEPR	APR	KREP	West China Registry
Launched, year	1999	1996	1996	1999	1998	2012
Catchment area	47 Countries, world-wide	US and Canada	UK and Ireland	Australia	Kerala (India)	China
Inclusion criteria	ASM exposure at time of conception	ASM exposure during pregnancy (exposure during first trimester considered for teratogenicity)	ASM exposure during first trimester	ASM exposure at time of conception	ASM exposure at time of conception	WWE planning a pregnancy
Methods for enrollment	Through network of reporting physicians	Pregnant women self-enroll, sometimes on advice of their treating clinician	Pregnant women with epilepsy self-enroll, sometimes on advice of their treating clinician, epilepsy nurses, or midwives. Enrollment is also from reporting physicians and epilepsy nurses	Pregnant women register on advice of their treating clinician or lay organization, or may also be self-referred	WWE referred by their treating clinicians at the preconception period or during pregnancy	WWE planning a pregnancy register on advice of their treating clinician, or may also be self-referred
Main outcome of interest	Major congenital malformations	Major congenital malformations	Major congenital malformations From 2023, neurodevelopmental/ cognitive outcomes	Major congenital malformations	Major congenital malformations Cognitive outcomes at 1, 6, 12 and 18 years.	Adverse child outcomes including major congenital malformations, preterm birth, low birth weight and neurodevelopmental delay
Time window of assessment	Within 12 months after birth	Within 12 weeks after birth	Three months after birth From 2023, through and beyond childhood	Within 12 months after birth	Within 12 months after birth	Within 12 months after birth
Comparator/control	Internal comparison between ASMs	Internal comparison between ASMs as well as a control group of women not taking ASMs, and an external comparison group of 206 244 pregnancies	Internal comparison between ASM exposures, as well as a control group of women not on ASMs	Internal comparison between ASMs as well as a control group of women with epilepsy not on ASMs	Internal comparison between ASMs as well as a small group of women with epilepsy not on ASMs	Internal comparison between ASMs as well as a control group of women with epilepsy not on ASMs
Currently enrolled pregnancies (as of December 2, 2023), n	29 938	14 832	12 272	2899	3078	1763
Current activity	Active, open for expansion	Active	Active	Active	Active, open for expansion	Active, open for expansion
Website	eurapinternational.org	www.aedpregnancyregistry.com	www.epilepsyandpregnancy.co.uk	apr.org.au	n/a	n/a

Abbreviations: APR, Raoul Wallenberg Australian Pregnancy Register of Antiepileptic Drugs; ASM, antiseizure medication; EURAP, International Registry of Antiepileptic Drugs and Pregnancy; KREP, Kerala Registry for Epilepsy and Pregnancy; NAAPR, North American AED Pregnancy Registry; n/a, not available; UK&IEPR, UK and Ireland Epilepsy and Pregnancy Register; WWE, women with epilepsy.

TABLE 2 Prevalence (%) and 95% confidence intervals of major congenital malformations (pregnancies with malformations/exposed pregnancies) for eight different monotherapies, across the six major epilepsy-pregnancy registries.

ASM	EURAP[8] Prevalence, 95% CI (MCM/exposed)	NAAPR[9] Prevalence, 95% CI (MCM/exposed)	UK&IEPR[2,10–12] Prevalence, 95% CI (MCM/exposed)	APR[13] Prevalence, 95% CI (MCM/exposed)	KREP[14] Prevalence, 95% CI (MCM/exposed)	West China Registry[15] Prevalence, 95% CI (MCM/exposed)
Carbamazepine	5.4, 4.5–6.4 (121/2255)	2.8, 2.0–4.0 (32/1132)	2.6, 1.9–3.5 (43/1657)[10]	5.9, 3.8–8.6 (24/409)	4.7, 2.8–6.6 (23/490)	9.7, 2.0–25.7 (3/31)
Lamotrigine	3.1, 2.5–3.7 (110/3584)	2.1, 1.6–2.8 (52/2461)	2.3, 1.8–3.1 (49/2098)[10]	4.9, 3.0–7.5 (20/406)	2.0, −1.8–5.9 (1/50)	.0, .0–9.2 (0/38)
Levetiracetam	2.5, 1.8–3.5 (33/1325)	2.0, 1.4–3.0 (26/1283)	.7, .2–2.5 (2/304)[11]	3.6, 1.2–8.2 (5/139)	4.7, .7–8.8 (5/106)	.0, .0–3.4 (0/107)
Oxcarbazepine	2.9, 1.7–5.0 (13/443)	1.5, .56–3.7 (5/327)	n/a	5.3, .13–26.0 (1/19)	7.0, 1.1–13.0 (5/71)	4.5, .6–15.5 (2/44)
Phenobarbital	6.2, 4.1–9.3 (21/338)	6.0, 3.3–10.5 (12/200)	n/a	n/a	5.8, 1.9–9.8 (8/137)	n/a
Phenytoin	6.3, 3.4–11.6 (9/142)	2.8, 1.5–5.0 (12/423)	3.7, 1.3–10.2 (3/82)[2]	2.3, .06–12.0 (1/44)	5.9, 1.7–10.1 (7/119)	n/a
Topiramate	4.9, 2.7–8.8 (10/204)	5.1, 3.4–7.5 (26/510)	4.3, 1.7–13.3 (3/70)[12]	1.8, .05–9.72 (1/55)	n/a	n/a
Valproate	9.9, 8.5–11.5 (153/1549)	9.2, 6.4–12.9 (31/337)	6.7, 5.5–8.3 (82/1220)[10]	14.8, 10.9–19.45 (43/290)	7.9, 5.1–10.8 (27/341)	6.4, .8–21.4 (2/31)

Abbreviations: APR, Raoul Wallenberg Australian Pregnancy Register of Antiepileptic Drugs; ASM, antiseizure medication; CI, confidence interval; EURAP, International Registry of Antiepileptic Drugs and Pregnancy; KREP, Kerala Registry for Epilepsy and Pregnancy; NAAPR, North American AED Pregnancy Registry; n/a, not available or <10 exposures; UK&IEPR, UK and Ireland Epilepsy and Pregnancy Register.

2.1 | International Registry of Antiepileptic Drugs and Pregnancy (EURAP)

Established in 1999, EURAP initially included selected European countries. Since then, EURAP has gradually expanded to include more centers and countries, now encompassing 47 countries across Europe, Asia, Oceania, Latin America, and Africa. EURAP collaborates with the APR, KREP, and UK&IEPR, and more recently the West China Registry. Specifically, EURAP receives selected pregnancies fulfilling EURAP criteria from these four registries. With enrollment of about 30 000 pregnancies, EURAP stands as the largest among the epilepsy-pregnancy registries. Altogether, the contributions from other registers comprise 11% of all pregnancies in EURAP.[8] Although the fundamental methodology remains unchanged since inception, the reporting system has evolved to allow physicians within the EURAP network to submit reports directly to the central registry using an online system. Women using ASMs at conception, regardless of indication, may qualify for inclusion, with epilepsy currently accounting for 99% of indications. For enrollments occurring in the first trimester of gestation, data are collected at every trimester, at birth, and 1 year after birth.[16]

In a series of publications EURAP has reported on the prevalence of MCMs after exposure to monotherapy with the eight most frequently used ASMs.[8,16,17] The highest MCM prevalence was seen in pregnancies exposed to valproic acid, whereas the lowest risks were observed with levetiracetam, lamotrigine, and oxcarbazepine in monotherapy. Carbamazepine, phenytoin, topiramate, and phenobarbital were associated with intermediate risks. Dose dependency of the MCM risk was demonstrated for carbamazepine, phenobarbital, and valproic acid. Contrary to earlier analyses, the most recent, larger EURAP analysis did not find dose dependency of the MCM risk for lamotrigine.[8] In addition, EURAP has reported a significant decline in the prevalence of MCMs over time (from 6.1% to 3.7%) in parallel with a decrease in the use of valproic acid and carbamazepine, and increase in the use of lamotrigine and levetiracetam.[8,18]

The EURAP database has also been used to study other outcomes associated with different ASMs, such as seizure control and status epilepticus during pregnancy,[19] the increased risk of deterioration in seizure control associated with withdrawal of valproic acid in early pregnancy,[20] the lack of deterioration in seizure control over time despite changes in ASM selection,[18] and the apparent lack of protective effect of folate supplementation on MCM prevalence.[8,17]

EURAP continues to enroll pregnancies and to welcome new participants, with the collaboration with the West China Registry being the most recent example. In addition to the obvious need to obtain more pregnancies to assess the safety of newer ASMs, EURAP intends to assess the most frequently used ASM duotherapies, pregnancies outcomes in specific epilepsy syndromes, and outcomes other than MCMs, such as growth parameters.

2.2 | North American Antiepileptic Drug Pregnancy Registry (NAAPR)

The NAAPR enrolls pregnant women prescribed ASMs for any indication. The proportion of participants with a diagnosis of epilepsy ranges from 78% to 100% depending on the medication. Methods of recruitment have not changed since the NAAPR was established, except for the computerization of data capture tools, questionnaire expansion (e.g., generics, devices, ketogenic diet), the technology of communications, and the use of social media to improve awareness and enrollment. Women self-enroll by calling a toll-free telephone number or can enter their contact information on the NAAPR website, which will result in them being called by a Clinical Research Coordinator from the Registry. Women are interviewed at enrollment, 7 months of gestation, and 8–12 weeks after the expected date of delivery. Interviews include questions on ASMs, seizures during pregnancy, demographics, habits, family history, and prenatal testing. Postnatally the mother is asked about the birth/health status of the infant, and to sign and return a medical record release form.

Enrollment is considered "pure prospective" if subjects enroll before prenatal screening tests or an ultrasound after 15 weeks of gestation. With respect to evaluation of teratogenicity, women are considered exposed if they used ASMs during the first four lunar months after the last menstrual period. For other outcomes, exposures later in pregnancy are considered. The primary outcome of interest are MCMs; secondary outcomes include maternal seizures during pregnancy, gestational age at birth, and birthweight for gestational age.

The primary reference group have been women exposed to lamotrigine because it has been the most common ASM in the Registry. The rationale for the active reference group is twofold. First, this comparison responds to the most clinically relevant question: which ASM is safest? Second, it minimizes confounding by indication. A secondary internal reference consists of ASM-unexposed pregnant women without epilepsy who had been recruited since 2003, among friends and relatives of ASM-exposed participants and followed with the same methodology. To estimate the expected risk of specific malformations, the NAAPR also uses a population-based external reference

group[21] of 206 244 infants born at Brigham and Women's Hospital in Boston and captured by a surveillance system that used the same criteria for outcome definition.

The NAAPR has reported on the teratogenicity of specific ASMs taken as monotherapy[22] and polytherapy.[23] The finding of an association between topiramate and oral clefts[22] was used by regulatory agencies to inform the pregnancy label. Other findings include a lower risk of seizures during pregnancy associated with valproate[22] and a higher risk of low birthweight associated with topiramate.[24,25] In addition, investigators had methodologic contributions to the design of other pregnancy registries.[26] Future plans include generating more precise information on the safety of the newer ASMs, specific ASM polytherapies, and non-pharmacological therapies used for the treatment of epilepsy during pregnancy.

2.3 | UK and Ireland Epilepsy and Pregnancy Register (UK&IEPR)

The UK&IEPR was established in 1996. Initially collecting data from the UK, it subsequently merged with the Ireland Epilepsy and Pregnancy Register. This prospective, observational, registration and follow-up study was set up to provide information on the comparative MCM risks across ASMs used in pregnancy. Data collection has traditionally been at enrollment and at 3 months after birth, but follow-up has recently been extended beyond this time point (see subsequent text).

Since 2008, the UK&IEPR has published on the teratogenic risks with individual ASMs, including those used less frequently in pregnancy such as zonisamide, as well as on the overall risks for polytherapy exposures and for ASM-unexposed pregnancies.[10,27] The UK&IEPR has also reported on the effects of dose and formulations, the risks of MCM recurrence, and the effect of folic acid supplementation.[28] In keeping with experiences elsewhere, the Register has reported changing trends in ASM-prescribing patterns in women with epilepsy, observing declining MCM rates.[29]

Through the development of close collaborations with other institutions, the UK&IEPR has contributed to determining the safety of different ASMs, such as valproate, levetiracetam, and topiramate, on postnatal neurodevelopment and other behavioral outcomes.[30–32] In a larger collaborative study, which included UK&IEPR participants, no impact on cognition, language, or motor scores, up to 2 years of age, were found in infants exposed to lamotrigine and levetiracetam.[33]

Over the last number of years and in conjunction with the University of Manchester, the UK&IEPR has been focused increasingly on routinely including neurodevelopmental outcomes and other aspects of child health. As one of the pilot sites of the Lifetime Framework, part of the EU Innovative Medicines Initiative ConcePTION Study,[34] the UK side of the UK&IEPR has extended follow-up of infants exposed to ASMs. At a series of time-points, up to 2 years initially, in addition to continuing the collection of information on MCMs, the Registry now collects neurodevelopmental outcome data and data on breastfeeding exposure and other child health outcomes. Data are collected from women recruited and their health care professionals, via health questionnaires and the third edition of the parentally completed Ages and Stages Questionnaire (ASQ-3). Both pre- and post-natal data are aligned to a common data model, permitting data to be combined with other sites across Europe. This approach aims to provide a feasible and sensitive approach to screening large populations of pregnancies exposed to ASMs for developmental signals. These can then be replicated in comprehensive, blinded neuropsychological assessments, with the opportunity to follow up into early school years and beyond.

2.4 | Kerala Registry for Epilepsy and Pregnancy (KREP)

KREP is a prospective, observational, single-center registry located in the Kerala State in South India. It was established in 1998. Women with epilepsy are referred by general practitioners, gynecologists, and neurologists. All referrals are evaluated by two or more epileptologists, and the diagnosis of epilepsy is confirmed before registration. Women have six visits or telephone contacts with the Registry: (1) for preconception care; (2) for pregnancy reporting in the first trimester; (3) for screening of MCMs; (4) for review of seizure control (at 24–32 weeks); (5) newborn physical examination, echocardiography, and ultrasonography (3 months after delivery); and (6) infant developmental assessment (at least at 1 year post-delivery).[35] At the 3-month post-delivery follow-up, the attending obstetrician and neonatologist are sent a form via email to detail information regarding peripartum status and neonatal examination.

Since the 2008 workshop, KREP has reported that: women with epilepsy have increased risks of infertility;[36] about 50% of women with epilepsy experience seizures during pregnancy[37]; women who experience seizures in the month prior to pregnancy have a 15-fold higher risk of seizures during pregnancy compared to those who are seizure-free in the same month[38]; women with epilepsy have increased risk of certain pregnancy complications, such as spontaneous abortion and pre-eclampsia, compared to others[37]; the overall MCM rate associated with ASM use in pregnancy is 7.4% (6.4% with monotherapy

and 9.9% with polytherapy) with most ASMs showing a dose-dependent increase in fetal malformation[39]; the negative impact of prenatal ASM exposure is noted on cognitive development and education levels achieved[40,41]; and women with drug-resistant focal epilepsy who opt for epilepsy surgery before pregnancy can expect better seizure control and reduced ASM burden during pregnancy compared to those who continue on ASM treatment alone.[42] It is noteworthy that in KREP the most commonly prescribed ASMs (as monotherapy or in combination therapy) are carbamazepine, valproate, phenobarbitone, and phenytoin, potentially contributing to some of the specific findings.

The scope of the work carried out by KREP is expected to expand to MCM risks with newer ASMs, MCM risks with polytherapy regimens including older vs newer ASMs, long-term cognitive trajectories of children of women with epilepsy, fertility and pregnancy outcomes in women with epilepsy who undergo epilepsy surgery, psychosocial wellbeing of women with epilepsy including incidence of postpartum depression, and genetic and epigenetic factors implicated in MCM risks.

2.5 | Raoul Wallenberg Australian Pregnancy Register of Antiepileptic Drugs (APR)

The APR is an ongoing observational study established in 1999 to assess the risk of MCMs associated with in utero exposure to different ASMs. It comprises pregnancy data from three groups: (a) women with epilepsy on ASMs; (b) women on ASMs for indications other than epilepsy; and (c) women with epilepsy not on ASMs. The recruitment methodology has not changed since the inception of the APR, with enrollment usually initiated by the woman's physician using an online form or a toll-free number. Women may also be self-referred or register on advice by lay organizations. Most women are enrolled during their pregnancy, but enrollment is permitted up to 1 year post-delivery. For prospective pregnancies, there are four interviews: at enrollment (before antenatal investigations for possible birth defects); at 7 months of gestation; within 6 weeks of delivery; and at 1 year after delivery. The APR has collected data on almost 2900 pregnancies from all over Australia and has contributed with prospective pregnancies to EURAP since 2000.

Since the 2008 workshop, the APR has been productive from a scientific point of view with >50 peer-reviewed publications, not infrequently identifying "signals" that were later confirmed by larger studies such as the finding that the teratogenic risk associated with ASM polytherapy is related to the nature of the medications or doses combined rather than polytherapy per se.[43] Different analyses of the APR have documented a change in patterns of ASM prescriptions in pregnancy over time, including a progressive decline in the maternal daily dosage at conception and use of valproate, a gradual reduction in the use of carbamazepine, an initial increase followed by plateauing in the use of lamotrigine, an initial increase and then drop in the use of topiramate, and a gradual increase in the use of levetiracetam.[44,45] Overall, these changes have been paralleled by a reduction in severe MCMs, such as spina bifida.[44,45]

The APR has also investigated outcomes other than MCMs, including seizure control during pregnancy,[46] neurodevelopmental outcomes of offspring exposed to ASMs in utero,[47] the role of de novo genetic mutations in the occurrence of ASM-associated MCMs,[48] and the economic impacts of the APR from both societal and health care system perspectives.[49]

Future plans for the APR include assessing MCM risks associated with specific ASM polytherapies and further investigating the genetic underpinnings of ASM-associated anatomic and behavioral teratogenicity.

2.6 | West China Registry

The West China Registry is a prospective, hospital-based study for women with epilepsy of childbearing age, which was established in 2012 at the West China Hospital, Sichuan University. It expanded to include the Sichuan province in 2015 and became a nationwide multicenter study in 2021, now comprising 172 centers from 22 provinces and 7 municipalities and autonomous regions across China. The Registry is supported by national and provincial government funding. Women with epilepsy of childbearing age are recruited before pregnancy, and are followed through pregnancy, delivery, and up to 1 year post-delivery. Each pregnant woman undergoes five assessments. Three are conducted at 3-month intervals during pregnancy up to delivery, with collection of information on seizures, ASMs, obstetric complications, and anxiety/depression and, since 2017, blood samples. The other two assessments are conducted postnatally at 6-month intervals up to 1 year post-delivery, where neurodevelopmental screening of the offspring is performed.

The West China Registry has summarized pregnancy characteristics in China, showing higher rates of cesarean section and ASM discontinuations during pregnancy compared to Western countries.[7] It also found that a higher risk of neurodevelopmental delay in offspring born to women who had status epilepticus in pregnancy.[15] Other salient findings from the Registry include the identification of clinical and genetic risk factors for polycystic ovary

syndrome in women with epilepsy[50]; the increased risk of preterm birth, low birthweight, and neurodevelopmental delay with prenatal valproate exposure and the increased the risk of preterm birth and low birthweight with ASM polytherapy[15]; higher rates of Apgar scores ≤7 among infants born to mothers who underwent epilepsy surgery before pregnancy compared to those who did not, a result that require replication from larger studies[7]; and the suggestion of possibly higher risk of adverse fetal outcomes associated with new-onset epilepsy in the first trimester of gestation compared to its occurrence later in pregnancy.[15]

In November 2023, the West China Registry joined EURAP, contributing valuable data from the Chinese population. In the future, the Registry plans to conduct long-term outcome studies, investigating the effect of seizure control and ASM use during pregnancy on neurodevelopmental and behavioral outcomes of offspring of at least 8 years of age.

3 | WHAT WE STILL NEED TO LEARN

Despite major contributions from the pregnancy registries and other sources, many questions remain unanswered.[51] Table 3 underscores the inadequate data on the teratogenic risks associated with newer antiseizure ASMs like brivaracetam, cannabidiol, cenobamate, fenfluramine, lacosamide, perampanel, and zonisamide, which preclude drawing definitive conclusions even if data across all registries were to be combined. Moreover, up to now, most reports have been on ASM monotherapy exposure. There is an obvious need for continued activities by epilepsy-pregnancy registries to fill knowledge gaps regarding newer ASMs. In addition, the interactive effects of polytherapy need delineation, as animal studies have shown that some combinations may produce synergistic effects on the immature brain.[52]

So far, most registries have reported the prevalence of MCMs as a composite primary outcome. They have rarely considered associations with specific MCMs, which may differ across different ASMs.[8,53] This is an important limitation, not least given the wide range in impact of different MCMs on quality of life (e.g., hypospadias vs neural tube defects). In this regard, the NAAPR found cleft palate alone to be more specific to carbamazepine exposure than topiramate exposure, which in turn seems to be associated with cleft lip and palate.[54] Because sample sizes to study specific MCMs are larger than those required for MCMs as whole (irrespective of type), continued recruitment of additional pregnancies is crucial to enable investigation of associations between individual ASMs and specific MCMs. This is also important to facilitate

TABLE 3 Number of pregnancies exposed to some of the newer ASMs, along with those resulting in major congenital malformations (MCMs), across the six major epilepsy-pregnancy registries.

ASM monotherapy	EURAP MCM/exposed, *n*	NAAPR MCM/exposed, *n*	UK&IEPR[a] MCM/exposed, *n*	APR[a] MCM/exposed, *n*	KREP[a] MCM/exposed, *n*	West China Registry[a] MCM/exposed, *n*
Brivaracetam	0/2	0/15	0/0	0/0	0/0	0/0
Cannabidiol	0/0	0/0	0/0	0/0	0/0	0/0
Cenobamate	0/0	0/2	0/0	0/0	0/0	0/0
Eslicarbazepine acetate	0/7	0/10	0/1	0/0	0/0	0/0
Fenfluramine	0/0	0/0	0/0	0/0	0/0	0/0
Lacosamide	0/31	0/93	0/5	0/2	0/6	0/5
Perampanel	0/0	0/5	0/0	0/3	0/2	0/3
Zonisamide	1/29	3/240	0/25	0/6[b]	0/3	0/0

Abbreviations: APR, Raoul Wallenberg Australian Pregnancy Register of Antiepileptic Drugs; ASM, antiseizure medication; EURAP, International Registry of Antiepileptic Drugs and Pregnancy; KREP, Kerala Registry for Epilepsy and Pregnancy; MCM/exposed, number of pregnancies exposed to a specific ASM monotherapy resulting in a MCM/overall number of pregnancies exposed to the same specific ASM monotherapy; NAAPR, North American AED Pregnancy Registry; n/a, not available; UK&IEPR, UK and Ireland Epilepsy and Pregnancy Register.

[a]To avoid duplication, pregnancies also reported to EURAP are not provided in this column.

[b]One of the pregnancies exposed to zonisamide monotherapy in the APR was a twin pregnancy.

analyses of potential interactions between ASM exposure and different co-variates (e.g., outcome of previous pregnancies, family history of MCMs, epilepsy type, and seizure control).

Other important issues that could be addressed with larger cohorts include the impact of ASM withdrawals or switches during pregnancy, as well as refining the assessment of potential dose dependency of MCM risks with the less frequently used ASMs.

4 | OTHER SOURCES OF INFORMATION

While recognizing the value of animal studies, which can guide human studies and provide major insights into biological underpinnings,[55,56] this section focuses on sources of human data other than pregnancy registries.

In recent years, administrative health care databases (i.e., electronic health records, National or Regional Health Registers, and insurance claims databases) have been utilized for the assessment of MCM risks and other adverse pregnancy outcomes associated with in utero exposure to ASMs, with investigators from pregnancy registries among the major contributors.[57–64] In particular, existing nationwide databases in the Nordic countries offer opportunities to conduct population-based studies, which can be an advantage compared to the specific epilepsy-pregnancy registries that rely on assessment of more or less selected cohorts. Further advantages are access to unexposed control populations, the size of the cohorts, opportunities for long-term follow-up (even beyond school-age) through linkage to other relevant registers, and reduced costs. Limitations, in comparison with the epilepsy-pregnancy registries, include lack of reliable information on the mothers' epilepsy type, no information on seizure control, reliance on maternal-filled prescriptions to measure ASM exposure (which does not necessarily correspond to actual ASM intake), less detailed information on ASM doses during pregnancy and on many potential confounders (e.g., family history of MCMs), and less meticulous assessment of the offspring, as the outcome relies on International Classification of Diseases (ICD) codes and procedures in the databases. Hence, these two types of cohort studies provide complementary information.

Although national database studies have made significant contributions by confirming increased MCM risks associated with exposure to valproate[57,62] and topiramate,[59,63] specific epilepsy-pregnancy registries remain pivotal for these outcomes due to their aforementioned advantages. Database studies, on the other hand, provide an approach for the investigation of clinical disorders, including neurodevelopmental, psychiatric and somatic disorders, which complements the work of observational studies, assuming that the outcomes of interest are captured by the ICD codes in the databases.[64–67]

More specific neurodevelopmental outcomes, such as different cognitive domains (e.g., intelligence quotient, executive function, language), require a different approach with individual follow-up and meticulous assessments. This is accomplished in prospective, smaller-scale, observational, cohort studies such as the NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) and MONEAD (Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs) studies.[68–70]

In addition to the independent epilepsy-pregnancy registries, some pharmaceutical companies have set up their own prospective registries to collect data on the manufacturers' own products.[71,72] The results of such registries are difficult to interpret because they are restricted to the company's own product and lack comparators. Spontaneous reports to pharmacovigilance databases of market authorization holders of ASMs[73,74] have similar limitations as well as the risk of reporting bias. Hence, although these sources can be useful to generate signals, they do not provide information on comparative teratogenic risks with different ASMs and cannot replace the independent pregnancy registries.

A further source of information on the risk of specific MCMs with in utero exposure to ASMs are case–control surveillance studies.[75] Here, cases with specific MCMs are compared to controls without MCMs or with other MCM types with respect to different exposures, including ASMs. These studies rely on interviews of mothers of offspring with or without MCMs, which are conducted post-delivery (typically within 6 months after delivery) to collect pre-pregnancy and pregnancy data, including exposure information. As such, a notable limitation is the potential recall bias.

5 | FUTURE PLANS FOR THE PREGNANCY REGISTRIES

Since the workshop in 2008, there have been changes to the epilepsy-pregnancy registries' landscape, with the emergence of a new registry (West China Registry) and the change in the main focus for another registry (UK&IEPR). Nevertheless, registries remain a reality, providing important contributions to advance the management of epilepsy in pregnancy and, in most cases, continuing to enroll new pregnancies aiming to address some of the still unanswered questions. Although the general conclusion of the 2008 workshop was reaffirmed in that there are inherent advantages in maintaining individual registry independence, opportunities for collaboration between registries

were discussed and ideas put forward. Examples where collaborations across registries could be explored are the assessments of rare exposures, including specific ASM combinations and even non-pharmacological therapies, for example, vagus nerve stimulation (VNS) and dietary therapies. Registry independence can also be leveraged to address current knowledge gaps. For example, given that regional differences exist in ASM prescribing patterns, comparisons between registries can provide important insights into specific outcomes, for example, seizure control in pregnancy, neonatal complications, postnatal neurodevelopment, and ASM exposure via breastfeeding. Individual registries can provide the framework for new lines of investigations, such as the assessment of neuroimaging, neurophysiological, or genetic biomarkers of pregnancy outcomes. Other aspects that were discussed included how enrollment of pregnancies could be enhanced in the future and the need to consider expanding register activities to regions that currently are poorly represented, such as countries in Africa.

In conclusion, the various epilepsy-pregnancy registries have made major contributions during their more than 25 years of function. Given the multiple newer ASMs that are now being increasingly used in clinical practice and the continuing multiple knowledge gaps for the older ASMs, these registries will continue to play an important role also in the future provided that appropriate and sustainable funding can be secured.

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CONFLICT OF INTEREST STATEMENT

P.P. has received speaker honoraria or consultancy fees to his institution from Chiesi, Eisai, LivaNova, Novartis, Sun Pharma, Supernus, and UCB Pharma. He is on the board of EURAP-International Registry of Antiepileptic Drugs and Pregnancy, a non-profit organization that has received financial support from Accord, Angelini, Bial, EcuPharma, Eisai, Glenmark, GW Pharma, GlaxoSmithKline, Sanofi, SF Group, Teva, UCB, and Zentiva. He is an Associate Editor for *Epilepsia Open*.

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J.C. has received honoraria from UCB-Pharma, Glaxo Smith Kline, Janssen-Cilag, Sanofi-Synthelabo, Pfizer, and Eisai to attend advisory boards, present lectures/tutorials, and to attend conferences and received donations from UCB-Pharma, Glaxo Smith Kline, Janssen-Cilag, Sanofi-Synthelabo, Pfizer, and Eisai to fund research.

L.B.H. is the Director of the North American AED (antiepileptic drug) Pregnancy Registry. This Registry is based in the Department of Pediatrics of the Massachusetts General Hospital (MGH) in Boston, MA. In this department, he is the Emeritus Chief of the Medical Genetics and Metabolism Unit; the department is known as Mass General for Children. This is a teaching hospital of the Harvard Medical School, where he is a Professor of Pediatrics. Part of his salary is provided by funds provided by contracts with several manufacturers of AEDs, which are Sponsors and Contributors to Hospital in support of the Registry. The corporate institution of which MGH is a founding member is called Mass General Brigham.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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