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The role of ethnicity on pregnancy outcomes in women with epilepsy: The need for specific research

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Summary

The role of ethnicity on pregnancy outcomes of women with epilepsy (WWE) has received little specific research, and is important to guide management. The aim of this paper is to identify and describe current knowledge of ethnicity for WWE giving birth. Literature searches were performed with following terms: ethnic/race combined with epilepsy/seizure, antiepileptic drug (AED), or/and pregnancy, and combined them with congenital malformation, birth outcome or pregnancy complication, with English language restriction in PUBMED, EMBASE, and Web of Science. Both primary studies and review articles were included. Ethnicity disparities exist in specific congenital malformations, pregnancy complications, and birth outcomes among the general population. There is also ethnicity related diversity of AEDs disposition. Information on ethnicity is rarely considered in studies about pregnant WWE. The association between ethnicity and pregnancy outcomes of WWE remains to be elucidated. The lack of data relating to ethnicity in pregnancy studies among WWE needs addressing. Knowledge of potential effects of ethnicity on pregnancy outcomes in WWE while help inform better clinical care around the world.

Key words: Congenital Malformations, Obstetric Complications, Birth Outcomes, AEDs disposition, Race

Introduction

Epilepsy is one of the most common neurological disorders. During pregnancy, most women with epilepsy (WWE) requiring ongoing medical treatment with anti-epileptic drugs (AEDs). WWE, especially those treated with AEDs, are reported to face an increased risk of adverse pregnancy outcomes compared to the general population^{1;2}.

Intrauterine exposure to certain AEDs has been associated with specific congenital malformations, neurodevelopmental problems and low birth weight^{3;4}. Advances in our understanding of the increased risks associated with exposure to AED therapy

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during pregnancy has highlighted the need for individualized treatment and appropriate provision of care. Information about some other potential risk factors, in particular as ethnicity, however, has seldom been reported.

Ethnicity refers to a person's ancestry, ethnic identity, and cultural diversity, and is influenced by both genetic and environmental factors⁵. It is well documented from different studies that there are some ethnicity disparities in the rates of illness, treatment response, and clinical features in terms of disorders such as hypertension, diabetes and cancer^{6; 7}. Furthermore, ethnicity disparities exist in specific congenital malformations, pregnancy complications, and birth outcomes among the general population. This may help physicians provide appropriate interventions to patients with different ethnic backgrounds. Whether ethnicity plays a role in pregnancy outcomes of WWE needs to be examined in order to guide management. The aim of this paper is to systematically review the literature to identify and describe current knowledge of ethnicity for WWE giving birth.

Ethnicity disparities in pregnancy outcomes among general populations

1. Congenital Malformations (CMs)

CMs, or birth defects, are the leading cause of infant morbidity and mortality. It is estimated that approximately 3% of all births are affected by major CMs⁸. A population-based long-term study in the United States found that American Indians/Alaskan Natives face significantly higher risks for seven conditions, including anotia or microtia, cleft lip, trisomy 18, encephalocele, and limb deficiency. Cubans and Asians, especially Chinese and Asian Indians, had either lower or similar rates of these defects compared with Europeans⁹. Other studies on birth defects providing data on ethnic variation also suggest the existence of racial disparities in children with selected CMs^{10; 11}.

2. Pregnancy complications/maternal outcomes

Maternal ethnic background has been found to be an important contributor to pregnancy outcomes and complications in the general population.

2. 1. Vaginal bleeding and Preeclampsia. A nation-wide study in Finland¹² found that bleeding was one of the most often recorded events for pregnant women of African origin, followed by women of Finnish origin. Asians¹³ and Native Americans¹⁴ were found to be more likely to have postpartum hemorrhage compared to Europeans. Likewise, ethnicity related distributive differences of preeclampsia exist. Pregnant women of African¹⁵ ancestry are at a higher risk of preeclampsia. Women with Asian background, however, are less likely to have preeclampsia¹⁶. Women of non-European origin were reported to have a higher risk of recurrence than European women¹⁷.

2. 2. Cesarean Delivery. Complications of labour including failure to progress, fetal distress, and fetal malpresentation¹⁸ were reported to be responsible for cesarean delivery, which is associated with a higher cost than vaginal delivery and a higher risk of postpartum readmission^{19; 20}. Other risk factors include a history of previous Cesarean-section, age older than 35 years²¹, higher parity²², presence of certain chronic diseases²³, and ethnicity²⁴. African, Hispanic²⁵, and Asian²⁶ women were found to have higher odds of cesarean delivery compared with European women even after taking potential confounders into account. Women with the diagnosis of epilepsy seem to have a higher risk of caesarean delivery^{1; 27} relative to control groups.

2. 3. Maternal mortality. A Report from the UK demonstrated the prevalence of overall maternal mortality to be 11.39 per 100,000 births²⁸. The maternal mortality

rate among African women was estimated to be four times higher than that of Caucasian women. Disparity in the availability to professional maternal care among different ethnic groups was one of the key findings in this report.

3. Birth outcomes

3. 1. Growth deficit. Weight gain is usually recognized as an important indicator of fetal health. An infant with a birth weight of less than 2500 g, regardless of gestational age, is defined as a low birth weight (LBW) infant. The small for gestational age (SGA) infant is an infant who does not achieve a weight threshold or percentile for a specific gestational age. In the general population, newborns of ethnic minority women were more often of LBW and SGA compared with infants of women of European origin²⁹. This has been observed for a long time and it has been regarded as a physiological phenomenon. Practical race-specific fetal growth standards have been established in US³⁰. Some reports strongly suggest, however, that racial differences in birth weight for gestational age more pathological than physiological³¹⁻³³, and the variability of ethnicity-related birth weight becomes small, when it involves women at low risk.

3. 2. Perinatal mortality/ still birth. Perinatal mortality rates vary in different ethnic groups. A population-based report found the fetal mortality rate of Native American women in United States was more than twice the rate of both Caucasian and Asian women³⁴. In Australia, a significant difference in the stillbirth rate has been defined by maternal country of birth, and women from South Asia have an increased risk of stillbirth³⁵.

3. 3. Preterm birth. Preterm delivery is a major cause of neonatal mortality. African

origin has been demonstrated to be one of the risk factors for spontaneous preterm births in the general population. Different trends of premature birth have been demonstrated among Pacific, Maori, and European/other women in New Zealand.

Ethnic disparities in AEDs disposition and treatment response: underlying biologic mechanisms

Recent advances in the understanding of the molecular basis of epilepsy has thrown light on mechanisms in individual variability of pharmacotherapy, where genetic polymorphisms are involved. This might enable us to identify more preconception related and pregnancy related risk factors associated with adverse pregnancy outcomes in WWE.

AEDs are a series of drugs with extensive pharmacokinetic variability between and within individuals. As one of the host factors, ethnicity has an effect on both AED metabolism and clinical response. The prevalence of certain alleles associated with pharmacokinetics of AEDs varies among populations. Differences in the distribution of polymorphisms usually reflect the way genetic differences exist among ethnic groups³⁶.

The main route of metabolism for many of the AED is through the cytochrome P450 system (CYP), with various CYP isoenzymes. CYP2C9 contributes to about 20% of total CYP content³⁷, which has at least five natural variants all identifying poor metabolizers compared with the wild type³⁸. The allelic frequencies of these variants vary from different ethnic groups. The CYP2C9*2 variant and homozygous of CYP2C9*3 are common in Africans and Europeans, while rare in East Asians³⁷⁻³⁹, suggesting that the metabolism of CYP2C9 related AEDs, such as phenytoin, primidone, and valproate⁴⁰, is slower in Europeans and Africans than in Asians, which may lead to higher serum concentrations of such AEDs. Whereas, the CYP2C9*4

variant is found exclusively in Japanese, and CYP2C9*5 and 6 are found exclusively in African-Americans⁴¹. Fetal malformations are hypothesized to be associated with peak blood concentration of AEDs in WWE, and so ethnic variations in the rate and nature of AED metabolism could influence the incidence of AED-associated CM.

Pronounced ethnic variation related differences have also been defined for CYP2C19, an important enzyme catalyzing the metabolism of clobazam, lacosamide, diazepam, valproate, phenytoin, and phenobarbital^{40; 42}. The two common defective alleles are CYP2C19*2 and CYP2C19*3. Asian population are at a higher risk with about 35% of allele frequency⁴³, twice as high in comparison with the population of African or European origin.

CYP3A4 is another member of cytochrome P450 system, contributing to metabolism of several kinds of AEDs including clobazam, clonazepam, ethosuximide, tiagabine, and zonisamide^{40; 42}. The frequency of its defective allele, CYP3A4*1B has been reported to be much higher in the population of African origin, low in Europeans, and absent in Chinese and Japanese subjects^{44; 45}. Whether different frequencies among various ethnic populations in CYP3A4 genes contribute to altered metabolism of the CYP3A4 substrate AEDs needs further research.

Pharmacokinetic diversity is a major determinant of differences in response to AED treatment, which is mainly determined by genetic or ethnic origin. There may be of associations between pharmacokinetic variability and susceptibility to an increased risk for AED associated birth defects. Such information will allow physicians to make better judgments about the risk- benefit ratios of these treatments for individual pregnant WWE.

Ethnicity in the current pregnancy research initiatives of WWE

Findings from several studies have confirmed approximately a three times greater risk

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of CMs in children exposed to AEDs in utero compared to children of mothers not taking AEDs⁴⁶. Malformation rates across studies vary for the same AED in monotherapy due to differences in study populations, methodology, and criteria. Meanwhile, rates of CMs vary according to different drugs involved (Table 1). It appears that some specific types of malformations are associated with particular AED exposures. A higher risk of neural tube defects is reported in children exposed to valproate⁴⁷. Topiramate exposure is found to be associated with a ten times increased risk of cleft lip⁴⁸. Rates of cardiac malformations are distinctly higher in children after exposure to barbiturates⁴⁹ (Table 2). Dose-dependent teratogenic effects of other AEDs have also been demonstrated⁵⁰. Information regarding ethnicity is rarely described in these studies making it hard to tell if ethnicity play a role in the differences, but most subjects in these registers were Caucasian. Whether the prevalence of CMs differs among ethnic groups or whether specific ethnic groups are more vulnerable to specific type of birth defects needs further investigation. Large number of pregnancies are needed to adequately investigate these issues.

Higher risk of bleeding during pregnancy has been observed in WWE^{1; 51}. Increased odds of post-partum haemorrhage have also been reported³, but not in all studies^{27; 52}. AED use during pregnancy is thought to be associated with both of these conditions^{1; 3}. Ethnic information was not explicitly involved, although most of them were population-based studies with a large sample size.

Several early^{51; 53} and recent^{1; 54} studies found an increased risk of preeclampsia in pregnant WWE, which may be associated with AED utilization^{54; 55}. Ethnic information is limited among WWE on this issue. Mark Yerby and colleagues presented information about ethnicity in their cohort study⁵³, but they did not explore further the effects of ethnicity on pregnancy complications among WWE.

Infants of WWE have an increased risk of LBW infants in the neonatal period^{51; 53}.

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Compared to non-epilepsy controls, AED intrauterine exposed infants were more likely to be of LBW or SGA⁵⁴. When women receiving AEDs were excluded⁵⁶, women with seizures during pregnancy were found to be at a significantly higher risk of having neonates of LBW and SGA compared with women without chronic disease. Both epilepsy and AEDs have effects on fetal growth. No ethnic information is available in the above mentioned research studies.

Associations between ethnicity and maternal death in WWE were hard to investigate, given the small number of epilepsy-related deaths being considered. Regarding perinatal deaths, a study from Norway found that the rates of perinatal mortality and stillbirth in infants of WWE were similar to controls⁵⁴. Other researchers also failed to find any differences in perinatal death between infants with maternal epilepsy and without maternal epilepsy^{57; 58}. Among them, ethnicity was considered as a confounding factor in one study⁵⁷, where reproductive outcomes remained similar after adjusting for ethnicity and other factors. It is hard to draw a conclusion whether ethnicity plays a role or not from this study.

The risk of preterm delivery has been reported to be almost increased twofold in WWE^{54; 58-61}, but this was not reported in all studies²⁷. Prematurity is obviously increased in AED-exposed infants, especially in those with polytherapy treatment⁵⁴.

A study conducted among WWE on fetal antiepileptic drug exposure and cognitive outcomes had provided some information about the background of maternal ethnicity. An association between AED therapy during pregnancy and ethnicity was noted, reflecting underlying different AED treatment patterns among pregnant WWE depending on ethnicity. These studies did not provide data about any association between fetal IQ scores and ethnic background⁶².

Ethnicity is rarely considered in research about pregnancy outcomes of WWE. The numbers of participants of non-Caucasian ethnicity are small in the current AED

pregnancy registries^{2; 62-64}. Data from the Australian Pregnancy Register showed that the ethnic group distribution in the registry was not comparable to the census involving the entire Australian population, and participants from minority ethnic group were much fewer than the expected number based on demographics of the general population⁶³. Less access to pregnancy registers and cultural reluctance for participation of subjects from minority ethnic groups may be the cause for the difference. Fortunately, proportion of participants from ethnic minorities has grown over time, especially that from the Asian population in Australia⁶⁵. Ethnic background of participants has also been noted in the US-UK NEADs study, which is focused on neurodevelopment of children with maternal epilepsy⁶², but no research on pregnancy outcomes of WWE has specifically focused on the influence of ethnicity.

Caution when use ethnicity as a variable in research

The effects of migration on pregnancy outcomes should be taken into account⁶⁶. Some studies show a negative association between migration and pregnancy outcomes, such as maternal mortality⁶⁷, fatal growth retardation, and assisted delivery⁶⁸. The explanations for these findings are usually related to maternal health behaviour, language barriers, reasons for migration, and social factors. Other studies have revealed an equally or more favorable pregnancy outcomes in migrating groups compared to the groups from the host-country⁶⁹. Explanations are postulated to be a 'healthy immigrant effect', where- by younger and healthier women have greater chances to migrate. Caution is required in arriving at conclusions from research addressing ethnicity which does not account for these confounding factors.

Given population diversity, ethnicity is mostly self-classified and there are many different terms used for groups. For instance, the populations of "White" is categorized as White, European, or Caucasian in different studies. People are

allocated to ethnic groups according to different criteria^{70; 71}. The lack of a unified classification for ethnicity makes it hard to compare results among different studies.

Ethnicity is often used ambiguously with race in most published studies, though race is thought to be biologically determined, while ethnicity is determined by both biogeographical and cultural ancestry⁷¹. Ethnicity should not be arbitrarily explained as a predictor of biological differences. The variation of reproductive outcomes among different ethnic groups is widely affected by genetic factors, social position, economic status, health care conception, and psychological condition⁷². Research in human genetics has found that there is a wide genetic variation within or between human groups which are defined in terms of geography, language, and culture⁷³. These genetic factors are likely modulated by a host of environmental factors. Ultimately, we need to understand the underlying genetic factors and environmental modulating factors that affect pregnancy outcomes in WWE.

The lack of details about ethnicity in pregnancy studies among WWE needs more critical attention. There are many biological, environmental and social reasons to lead us to believe ethnicity could affect the outcomes of pregnancies in WWE taking AEDs. It is therefore critical that future research specifically investigates if potential associations exist, so that more precise and better evidence-based care can be offered to pregnant WWE of different ethnicities, and not just extrapolate from data largely derived from Caucasian women in Western countries.

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Disclosure of Conflict of Interest

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Ethical Publication Statement

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.

Key point box

- Ethnicity disparities exist in specific congenital malformations, pregnancy complications, and birth outcomes in the general population.
- There is also ethnicity related diversity of AEDs disposition.
- The lack of details of ethnicity in pregnancy studies among WWE needs more critical attention.
- The association between ethnicity and pregnancy outcomes of WWE remains to be elucidated.

Reference

1. Borthen I, Eide MG, Daltveit AK, et al. Obstetric outcome in women with epilepsy: a hospital-based, retrospective study. *Bjog* 2011;118:956-965.
2. Meador KJ, Baker GA, Browning N, et al. Effects of fetal antiepileptic drug exposure: outcomes at age 4.5 years. *Neurology* 2012;78:1207-1214.
3. Borthen I, Eide MG, Daltveit AK, et al. Delivery outcome of women with epilepsy: a population-based cohort study. *Bjog* 2010;117:1537-1543.
4. Hernandez-Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012;78:1692-1699.
5. Xie HG, Kim RB, Wood AJ, et al. Molecular basis of ethnic differences in drug disposition and response. *Annu Rev Pharmacol Toxicol* 2001;41:815-850.
6. Cox RH, Carpenter JP, Bruce FA, et al. Characteristics of low-income African-American and Caucasian adults that are important in self-management of type 2 diabetes. *J Community Health* 2004;29:155-170.
7. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-2572.
8. Honein MA, Paulozzi LJ, Cragan JD, et al. Evaluation of selected characteristics of pregnancy drug registries. *Teratology* 1999;60:356-364.
9. Canfield MA, Mai CT, Wang Y, et al. The association between race/ethnicity and major birth defects in the United States, 1999-2007. *Am J Public Health* 2014;104:e14-23.
10. Saad AN, Parina RP, Tokin C, et al. Incidence of oral clefts among different ethnicities in the state of California. *Ann Plast Surg* 2014;72 Suppl 1:S81-83.
11. Kim K, Wang Y, Kirby RS, et al. Prevalence and trends of selected congenital malformations in New York State, 1983 to 2007. *Birth Defects Res A Clin Mol*

Teratol 2013;97:619-627.

12. Malin M, Gissler M. Maternal care and birth outcomes among ethnic minority women in Finland. *BMC Public Health* 2009;9:84.
13. Grobman WA, Bailit JL, Rice MM, et al. Racial and ethnic disparities in maternal morbidity and obstetric care. *Obstet Gynecol* 2015;125:1460-1467.
14. Chalouhi SE, Tarutis J, Barros G, et al. Risk of postpartum hemorrhage among Native American women. *Int J Gynaecol Obstet* 2015;131:269-272.
15. Pare E, Parry S, McElrath TF, et al. Clinical risk factors for preeclampsia in the 21st century. *Obstet Gynecol* 2014;124:763-770.
16. Caughey AB, Stotland NE, Washington AE, et al. Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: predictors of preeclampsia. *Obstet Gynecol* 2005;106:156-161.
17. Boghossian NS, Yeung E, Mendola P, et al. Risk factors differ between recurrent and incident preeclampsia: a hospital-based cohort study. *Ann Epidemiol* 2014;24:871-877e873.
18. Boyle A, Reddy UM, Landy HJ, et al. Primary cesarean delivery in the United States. *Obstet Gynecol* 2013;122:33-40.
19. Ann Arbor MI THA. The cost of having a baby in the United States., 2013. Available at: <http://transform.childbirthconnection.org/reports/cost/>. Accessed 7 June, 2017.
20. Eugene D, Barger M, Cabral HJ, et al. Maternal Outcomes Associated With Planned Primary Cesarean Births Compared With Planned Vaginal Births. *Obstetrics & Gynecology* 2007;109:669-677.
21. Witt WP, Wisk LE, Cheng ER, et al. Determinants of cesarean delivery in the US: a lifecourse approach. *Matern Child Health J* 2015;19:84-93.
22. MacDorman MF, Menacker F, Declercq E. Cesarean birth in the United States:

- epidemiology, trends, and outcomes. *Clin Perinatol* 2008;35:293-307, v.
23. Linton A, Peterson MR. Effect of preexisting chronic disease on primary cesarean delivery rates by race for births in U.S. military hospitals, 1999-2002. *Birth* 2004;31:165-175.
24. Sebastiao YV, Womack L, Vamos CA, et al. Hospital variation in cesarean delivery rates: contribution of individual and hospital factors in Florida. *Am J Obstet Gynecol* 2016;214:123.e121-123.e118.
25. Edmonds JK, Hawkins SS, Cohen BB. The influence of detailed maternal ethnicity on cesarean delivery: findings from the U.S. birth certificate in the State of Massachusetts. *Birth* 2014;41:290-298.
26. Edmonds JK, Yehezkel R, Liao X, et al. Racial and ethnic differences in primary, unscheduled cesarean deliveries among low-risk primiparous women at an academic medical center: a retrospective cohort study. *BMC Pregnancy Childbirth* 2013;13:168.
27. Katz O, Levy A, Wiznitzer A, et al. Pregnancy and perinatal outcome in epileptic women: a population-based study. *J Matern Fetal Neonatal Med* 2006;19:21-25.
28. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *Bjog* 2011;118 Suppl 1:1-203.
29. Kelly Y, Panico L, Bartley M, et al. Why does birthweight vary among ethnic groups in the UK? Findings from the Millennium Cohort Study. *J Public Health (Oxf)* 2009;31:131-137.
30. Joseph KS, Wilkins R, Dodds L, et al. Customized birth weight for gestational age standards: Perinatal mortality patterns are consistent with separate standards

for males and females but not for blacks and whites. *BMC Pregnancy Childbirth* 2005;5:3.

31. Kramer MS, Ananth CV, Platt RW, et al. US Black vs White disparities in foetal growth: physiological or pathological? *Int J Epidemiol* 2006;35:1187-1195.
 32. Villar J, Papageorghiou AT, Pang R, et al. The likeness of fetal growth and newborn size across non-isolated populations in the INTERGROWTH-21st Project: the Fetal Growth Longitudinal Study and Newborn Cross-Sectional Study. *Lancet Diabetes Endocrinol* 2014;2:781-792.
 33. Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 2014;384:857-868.
 34. MacDorman MF, Gregory EC. Fetal and Perinatal Mortality: United States, 2013. *Natl Vital Stat Rep* 2015;64:1-24.
 35. Drysdale H, Ranasinha S, Kendall A, et al. Ethnicity and the risk of late-pregnancy stillbirth. *Med J Aust* 2012;197:278-281.
 36. Wood AJ. Racial differences in the response to drugs--pointers to genetic differences. *N Engl J Med* 2001;344:1394-1396.
 37. Inoue K, Yamazaki H, Imiya K, et al. Relationship between CYP2C9 and 2C19 genotypes and tolbutamide methyl hydroxylation and S-mephenytoin 4'-hydroxylation activities in livers of Japanese and Caucasian populations. *Pharmacogenetics* 1997;7:103-113.
 38. Aynacioglu AS, Brockmoller J, Bauer S, et al. Frequency of cytochrome P450 CYP2C9 variants in a Turkish population and functional relevance for phenytoin. *Br J Clin Pharmacol* 1999;48:409-415.
 39. Aithal GP, Day CP, Kesteven PJ, et al. Association of polymorphisms in the
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- cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet* 1999;353:717-719.
40. Pennell PB. Antiepileptic drug pharmacokinetics during pregnancy and lactation. *Neurology* 2003;61:S35-42.
41. Schwarz UI. Clinical relevance of genetic polymorphisms in the human CYP2C9 gene. *Eur J Clin Invest* 2003;33 Suppl 2:23-30.
42. Johannessen SI, Landmark CJ. Antiepileptic drug interactions - principles and clinical implications. *Curr Neuroparmacol* 2010;8:254-267.
43. Kosaki K, Tamura K, Sato R, et al. A major influence of CYP2C19 genotype on the steady-state concentration of N-desmethyloclobazam. *Brain Dev* 2004;26:530-534.
44. Tayeb MT, Clark C, Ameyaw MM, et al. CYP3A4 promoter variant in Saudi, Ghanaian and Scottish Caucasian populations. *Pharmacogenetics* 2000;10:753-756.
45. Sata F, Sapone A, Elizondo G, et al. CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12: evidence for an allelic variant with altered catalytic activity. *Clin Pharmacol Ther* 2000;67:48-56.
46. Meador K, Reynolds MW, Crean S, et al. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res* 2008;81:1-13.
47. Lindhout D, Meinardi H. Spina bifida and in-utero exposure to valproate. *Lancet* 1984;2:396.
48. Holmes SHDRMLB. Comparative Safety of Topiramate During Pregnancy. *Pharmacoepidemiol Drug Saf* 2010;19:s124-s125.
49. Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. *Lancet Neurol* 2012;11:803-813.

50. Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* 2011;10:609-617.
51. Bjerkedal T, Bahna SL. The course and outcome of pregnancy in women with epilepsy. *Acta Obstet Gynecol Scand* 1973;52:245-248.
52. Olafsson E, Hallgrimsson JT, Hauser WA, et al. Pregnancies of women with epilepsy: a population-based study in Iceland. *Epilepsia* 1998;39:887-892.
53. Yerby M, Koepsell T, Daling J. Pregnancy complications and outcomes in a cohort of women with epilepsy. *Epilepsia* 1985;26:631-635.
54. Veiby G, Daltveit AK, Engelsen BA, et al. Pregnancy, delivery, and outcome for the child in maternal epilepsy. *Epilepsia* 2009;50:2130-2139.
55. Pilo C, Wide K, Winbladh B. Pregnancy, delivery, and neonatal complications after treatment with antiepileptic drugs. *Acta Obstet Gynecol Scand* 2006;85:643-646.
56. Chen YH, Chiou HY, Lin HC, et al. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. *Arch Neurol* 2009;66:979-984.
57. McPherson JA, Harper LM, Odibo AO, et al. Maternal seizure disorder and risk of adverse pregnancy outcomes. *Am J Obstet Gynecol* 2013;208:378.e371-378.e375.
58. Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. *Lancet* 2015;386:1845-1852.
59. Thomas SV, Sindhu K, Ajaykumar B, et al. Maternal and obstetric outcome of women with epilepsy. *Seizure* 2009;18:163-166.
60. Borthen I, Eide MG, Veiby G, et al. Complications during pregnancy in women with epilepsy: population-based cohort study. *Bjog* 2009;116:1736-1742.

61. Razaz N, Tomson T, Wikstrom AK, et al. Association Between Pregnancy and Perinatal Outcomes Among Women With Epilepsy. *JAMA Neurol* 2017.
62. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013;12:244-252.
63. Vajda FJ, O'Brien T, Hitchcock A, et al. The Australian antiepileptic drug in pregnancy register: aspects of data collection and analysis. *J Clin Neurosci* 2007;14:936-942.
64. Meador KJ, Baker GA, Browning N, et al. Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. *JAMA Pediatr* 2014;168:729-736.
65. Vajda FJ, O'Brien TJ, Graham J, et al. The Australian Register of antiepileptic drugs in pregnancy: changes over time in the epileptic population. *J Clin Neurosci* 2014;21:1478-1482.
66. Gagnon AJ, Zimbeck M, Zeitlin J, et al. Migration to western industrialised countries and perinatal health: a systematic review. *Soc Sci Med* 2009;69:934-946.
67. Yoong W, Wagley A, Fong C, et al. Obstetric performance of ethnic Kosovo Albanian asylum seekers in London: a case-control study. *J Obstet Gynaecol* 2004;24:510-512.
68. Ibison JM. Ethnicity and mode of delivery in 'low-risk' first-time mothers, East London, 1988-1997. *Eur J Obstet Gynecol Reprod Biol* 2005;118:199-205.
69. Rizzo N, Ciardelli V, Gandolfi Colleoni G, et al. Delivery and immigration: the experience of an Italian hospital. *Eur J Obstet Gynecol Reprod Biol* 2004;116:170-172.
70. U.S. Census Bureau: Definition of Race Categories Used in the 2010 Census.

Available at: https://www.census.gov/quickfacts/meta/long_RHI225215.htm.

71. Australian standard classification of cultural and ethnic groups (ASCCEG), The Australian Bureau of Statistics (ABS), BARGO: 11. 30am (Canberra time) 7 Jul 2005. In Editor (Ed)^(Eds) Book Australian standard classification of cultural and ethnic groups (ASCCEG), The Australian Bureau of Statistics (ABS), BARGO: 11. 30am (Canberra time) 7 Jul 2005.
72. Nazroo JY. The structuring of ethnic inequalities in health: economic position, racial discrimination, and racism. *Am J Public Health* 2003;93:277-284.
73. Rosenberg NA, Pritchard JK, Weber JL, et al. Genetic structure of human populations. *Science* 2002;298:2381-2385.
74. Meador KJ, Baker GA, Finnell RH, et al. In utero antiepileptic drug exposure: fetal death and malformations. *Neurology* 2006;67:407-412.
75. Artama M, Auvinen A, Raudaskoski T, et al. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. *Neurology* 2005;64:1874-1878.
76. Cunnington MC, Weil JG, Messenheimer JA, et al. Final results from 18 years of the International Lamotrigine Pregnancy Registry. *Neurology* 2011;76:1817-1823.
77. Campbell E, Kennedy F, Russell A, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neurosurg Psychiatry* 2014;85:1029-1034.
78. Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* 2011;10:609-617.
79. Vajda FJ, O'Brien TJ, Lander CM, et al. The teratogenicity of the newer

antiepileptic drugs - an update. *Acta Neurol Scand* 2014;130:234-238.

80. Thomas SV, Jose M, Divakaran S, et al. Malformation risk of antiepileptic drug exposure during pregnancy in women with epilepsy: Results from a pregnancy registry in South India. *Epilepsia* 2017;58:274-281.

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Table 1. Rates (%) of major congenital malformation with AED monotherapy exposures vary among different populations.

Studies	Methods	Participants	Maternal ethnic distributions	AEDs monotherapy exposed							
				VPA	CBZ	PB	PHT	LTG	LEV	OXC	TPM
Neurodevelopmental Effects of Antiepileptic Drugs ⁷⁴	A multicenter prospective study	323 women on AED monotherapy	80% Caucasian 10% Hispanic 4% black 5% other	17.4	4.5	-	7.1	1.0	-	-	-
Finish Medical Birth Register ⁷⁵	A population-based study	939 AED-unexposed and 1411 exposed births	Not available (All Finish citizens)	10.7	2.7	-	2.6	-	-	1.0	-
International Lamotrigine Pregnancy Registry ⁷⁶	A multicenter study	2,444 LTG-exposed pregnancies	Not available (geographic region: 65.1% data from USA; each >1.5% from Poland, United Kingdom, Germany, Sweden, and Denmark)	-	-	-	-	2.2	-	-	-
North American AED Pregnancy Registry ⁴	A hospital-based study	4,899 women on AED monotherapy and 442 unexposed women	Around 90% Caucasian	9.3	3.0	5.5	2.9	2.0	2.4	2.2	4.2
UK and Ireland	A prospective	5206 pregnancies	Not available	6.7	2.6	-	-	2.3	-	-	-

Epilepsy and study on AEDs																			
Pregnancy Register ⁷⁷				monotherapy															
European and A multicenter	5366	women on	Not available (geographic	9.7	5.6	7.4	5.8	2.9	-	-	-								
International prospective	AEDs	monotherapy	region: 1% data from																
Registry of study			Americas; 86% Europe; 3%																
Antiepileptic Drugs			Southeast Asia; 10%																
and Pregnancy ⁷⁸			Western Pacific)																
Australian A nationwide	1725	pregnancies	Not available	13.8	5.5	0	2.4	4.6	2.4	5.9	2.4								
Pregnancy Registry study																			
⁷⁹																			
Kerala Registry of A prospective	1665	pregnancies	Non-European descent	9.0	5.4	5.4	5.66	2.6	3.33	7.32	-								
Epilepsy and single-center																			
Pregnancy ⁸⁰		registry																	

AEDs=antiepileptic drugs; VPA=valproate; CBZ=carbamazepine; PB=phenobarbitone; PHT=phenytoin; LTG=lamotrigine; LEV=levetiracetam; OXC=oxcarbazepine; TPM=topiramate; WWE=women with epilepsy

Table 2. Rates (%) of some specific major congenital malformations vary among different AEDs ^{4; 76-78}

Major congenital anomaly	AEDs monotherapy exposed			
	VPA	CBZ	LTG	PB
Cardiovascular	1.1-2.5	0.3-1.6	0.2-0.6	0.3-2.5
Hypospadias	1.2-3.1	0.2-0.6	0-0.5	0.5-1.0
NTD	1.1-1.2	0.2-0.4	0.1-0.2	0-0.5
Oro-facial defects	0.4-1.2	0.2-0.5	0.1-0.5	2.0

AEDs=antiepileptic drugs; VPA=valproate; CBZ=carbamazepine; PB=phenobarbitone; LTG=lamotrigine

NTD=Neuro Tube Defects

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