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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

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 factors[5]. 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 CMs[8]. 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 Europeans[9]. 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 Finland[12] found that bleeding was one of the most often recorded events for pregnant women of African origin, followed by women of Finnish origin. Asians[13] and Native Americans[14] were found to be more likely to have postpartum hemorrhage compared to Europeans. Likewise, ethnicity related distributive differences of preeclampsia exist. Pregnant women of African[15] ancestry are at a higher risk of preeclampsia. Women with Asian background, however, are less likely to have preeclampsia[16]. Women of non-European origin ware reported to have a higher risk of recurrence than European women[17].

2. 2. Cesarean Delivery. Complications of labour including failure to progress, fetal distress, and fetal malpresentation[18] 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 years [21], higher parity [22], presence of certain chronic diseases [23], and ethnicity[24]. African, Hispanic[25], and Asian[26] 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 births[28]. 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 origin[29]. 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 US[30]. Some reports strongly suggest, however, that racial differences in birth weight for gestational age more pathological than physiological[31-33], 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 rate**s** 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 women[34]. 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 stillbirth[35].

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 groups[36].

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 content[37] , which has at least five natural variants all identifying poor metabolizers compared with the wild type[38]. 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 Asians [37-39], suggesting that the metabolism of CYP2C9 related AEDs, such as phenytoin, primidone, and valproate[40], 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-Americans[41]. Fetal malformations are hypothesized to be associated with peak blood concentration of AEDs in WWE, and so ethic 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 frequency[43], 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

of CMs in children exposed to AEDs in utero compared to children of mothers not taking AEDs[46]. 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 valproate[47]. Topiramate exposure is found to be associated with a ten times increased risk of cleft lip [48]. Rates of cardiac malformations are distinctly higher in children after exposure to barbiturates[49] (Table 2). Dose-dependent teratogenic effects of other AEDs have also been demonstrated[50]. 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 reported[3], 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 study[53], 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].

Compared to non-epilepsy controls, AED intrauterine exposed infants were more likely to be of LBW or SGA[54]. When women receiving AEDs were excluded[56], 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 controls[54]. 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 study[57], 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 studies [27]. Prematurity is obviously increased in AED-exposed infants, especially in those with polytherapy treatment[54].

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 background[62].

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 population[63]. 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 Australia[65]. Ethnic background of participants has also been noted in the US-UK NEADs study, which is focused on neurodevelopment of children with maternal epilepsy[62], 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 account[66]. Some studies show a negative association between migration and pregnancy outcomes, such as maternal mortality[67], fatal growth retardation, and assisted delivery [68]. 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-country[69]. 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 ancestry[71]. 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 condition [72]. 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 culture[73]. 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.

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

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