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ABSTRACT

Background: Epilepsy is a common neurological condition characterized by recurrent seizures affecting 1–2% of the population. Women with epilepsy (WWE) are assumed to account for 0.3–0.7% of all pregnancies in developed countries. Antiepileptic drug (AED) therapy is generally sustained in pregnancy, in order to control seizures that can harm the foetus and mother. The use of AEDs during pregnancy is of concern because of the potential complications to the mother (during pregnancy and delivery) as well as to the foetus (major congenital malformations) and the newborn (adverse effects on cognitive development).

Objective: The aim of this review is to critically summarise the literature on the effects of drug use for the treatment of epilepsy on mother and foetus/newborn, and to study the ethical considerations related to childbearing for WWE to provide an update of current knowledge in the field.

Methods: A systematic literature review was performed following the PICOS approach. PubMed and Scopus were searched for articles providing primary estimates of the clinical impact of drug use on mother and foetus/newborn, as well as ethical issues around childbearing for WWE.

Results: The review included 51 studies that met the inclusion criteria. On average, 78.1% of treated WWE were treated on monotherapy, whereas the remaining 23.6.% on polytherapy. Among monotherapy regimes the most frequently used AEDs were valproate, carbamazepine, lamotrigine, phenytoine, phenobarbital and oxcarbazepine. Average rates of adverse pregnancy outcomes (obstetric, delivery and neonatal complications) in women with treated epilepsy (WWTE) were higher than in women with untreated epilepsy (WWUTE) and, within the WWTE, rates were higher with polytherapy than monotherapy. Generally, traditional AEDs were more teratogenic than the newer generation of drugs.

Conclusions: Although pregnant women should limit any therapeutic drug intake, drug therapy in epilepsy during pregnancy is often unavoidable. The use of AEDs during pregnancy is of concern due to the associated adverse effects, especially related to the teratogenicity of drugs. Further research is still needed to enhance the understanding of the teratogenic risks attributable to individual AEDs, particularly the new generation of drugs which seem less teratogenic than traditional AEDs. A better understanding of the influence of

AEDs on pregnancy outcome is crucial for developing initiatives aimed at preventing adverse outcomes.

Keywords: epilepsy, pregnancy, pharmaceutical therapy

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Abbreviations

AED	anti-epileptic drug
CBZ	carbamazepine
CLB	clobazam
CM	congenital malformation
CZP	clonazepam
DZP	diazepam
ESM	ethosuximide
GBP	gabapentin
LBW	low birth weight
LTG	lamotrigine
LVT	levetiracetam
MCM	major congenital malformation
OXC	oxcarbazepine
PHB	phenobarbital
PHT	phenytoine
PICO	participants, interventions, comparators, outcomes, and study design
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PRM	pirimidone
QALY	quality adjusted life year
SGA	small for gestational age
TPM	topiramate
VGB	vigabatrin
VPA	valproate (valproic acid)
WWE	women with epilepsy
WWTE	women with treated epilepsy
WWUTE	women with untreated epilepsy

1. Background

With more women getting pregnant later in life and prevalence of chronic diseases on the rise, the number of pregnant women with chronic diseases is increasing. Therefore, there is a pressing need to understand the effects of drug treatment during pregnancy. Since the thalidomide tragedy more than 50 years ago, it has been widely accepted that pregnant women should avoid all but essential therapeutic drug intake. Nevertheless, the need to control epileptic seizures makes drug use in pregnancy often essential.

1.1. About the disease

Epilepsy is a common neurological problem. It is defined as a disorder of the brain function characterized by the periodic and unpredictable occurrence of seizures . Epilepsy can be classified in different types: primary generalised and focal/partial with or without secondary generalisation. Primary general seizures can be divided into absence, myoclonic, atonic, or tonic-clonic (Wyllie 2001). Epilepsy is one of the most frequently studied maternal diseases during pregnancy (Tompson et al, 1997; Aminoff 2004). Pregnancy of a woman with epilepsy (WWE) is a high-risk pregnancy due to a more frequent occurrence of complications and a higher risk for congenital malformations (CMs) and postnatal developmental anomalies than observed in the general population (Oguni and Osawa, 2004).

Epilepsy affects 1–2% of the population (Mcauley et al, 2012) with an annual incidence varying between 40 and 80 per 100,000 worldwide (Wallace et al, 1998). Although epilepsy affects men and women equally, there are many gender-specific health issues in epilepsy (Kobau et al, 2008). Issues unique to women include choice of AED in women of childbearing age, teratogenicity, breastfeeding, hormonal influences on seizures and contraceptive drug interactions (Pennell and Thompson, 2009). These issues can be challenging for the WWE as well as for her healthcare provider (Morrell et al, 2004).

Epidemiological investigations indicate that 0.3 to 0.4% of the general population of women have epilepsy and between 0,3% and 0,7% of all pregnancies are in WWE (Viinikainen et al, 2006). However, the proportion of women using AEDs in pregnancy may be even higher, considering the widespread and growing use of AEDs for pain and psychiatric conditions (Spina and Perugi, 2004).

1.2. Management of the disease

Most WWE can, with careful planning of pregnancy and management of delivery, expect a normal pregnancy outcome (Widnes et al, 2012). AEDs are the mainstay of treatment for patients with epilepsy (Mcauley et al, 2012), and is generally sustained during pregnancy in order to control seizures that can harm both the mother and the foetus (NICE, 2012). However, the use of AEDs during pregnancy is of concern to physicians because of the adverse outcomes that may affect the mother (during pregnancy and delivery) and particularly the foetus (i.e. congenital malformations) and the newborn (i.e. cognitive development).

Thus, treatment of epilepsy during pregnancy must balance the risks associated with foetal AED exposure against the harm of uncontrolled seizures associated with epilepsy (Nadebaum et al, 2011). The dilemma remains on how to achieve optimal therapeutic results (seizure control) by choosing effective AEDs in an adequate dosage with the lowest teratogenic risk according to today's evidence. Pharmacokinetic changes associated with pregnancy can decrease the serum concentration of several AEDs. Therapeutic drug monitoring is recommended for pregnant women using these drugs and dose escalation is commonly required in order to maintain a therapeutic serum concentration. Consequently, dose reduction after birth is necessary (Sethi et al , 2010).

In the last decade of the 20th century, more than 10 new AEDs were introduced to the market including lamotrigine (LTG), levetiracetam (LVT), topiramate (TPM), oxcarbazepine (OXC), and gabapentin (GBP), often referred to as 'second generation AEDs'. These new drugs have been added to the traditional agents such as phenobarbital (PHB), phenytoin (PHT), valproate (VPA), and carbamazepine (CBZ), also referred as 'older generation AEDs', some of which have been available since the 1940s. The new AEDs possess some novel characteristics, fuelling expectations that they may be more suitable for managing difficult-to-treat epilepsy syndromes, more easily tolerable than the older agents, and undergo fewer interactions. Their favourable pharmacokinetic profiles may render them suitable for use in polytherapy and in special situations such as in pregnant WWE (Perrucca et al 2001). However, there are also the important issues of the possible teratogenic effects of these newer AEDs when taken in pregnancy, how they compare with the older generation of AEDs in this regard, and whether

such effects may extend to both the physical and the cognitive development of the infant (Beghi et al, 2004).

Usually pregnant women are excluded from clinical trial programmes (Koren et al, 1998), and consequently the safety of medicine use during pregnancy and its impact on the risk of CMs cannot be fully assessed until the drug has been marketed. Pregnancy registries have been set up in various countries over the past two decades to obtain data and to monitor the safety of a new product on the market. In particular, registries aim to detect any increase in the risk of major congenital malformations (MCMs), defined as life threatening conditions that require major surgery or result in the child having a considerable disability.

1.3. Ethical issues around WWE

The foetal-maternal relationship, it has been argued, is full of smaller or larger conflicts (Lappé 1975). However, the ethical dilemma arises when the needs of the foetus intervenes with the needs of the mother in such a way that forces us to make decisions that may potentially affect the physical well-being of the mother or the foetus. Such a dilemma is relevant in the treatment of epilepsy during pregnancy where meeting the mother's physical needs may compromise the physical well-being of the foetus and increase the risk of developing abnormalities, while ceasing the epilepsy treatment may jeopardise the mother's health, as well as the health of the foetus. Knowing these risks raises the ethical question of whether to continue the treatment, or whether WWE should conceive at all (Lappé 1975). Under these circumstances, who is to be considered "the patient"? Whose needs are to be given priority? These questions are unlikely to be solved until we have better knowledge about the impact on mother and foetus and about the ethical weights to be given to the rights and obligations of all parties involved (Lappé 1975).

Against this background, this review was conducted to gauge the level of understanding of the impact of drug use during pregnancy in WWE in order to develop better informed guidelines for disease management during pregnancy. The objectives were threefold: a) to explore the evidence of drug use during pregnancy in WWE and the likely impact of the drug on mother, the foetus and the newborn, b) to investigate the ethical considerations related to childbearing and the management of the disease and the pregnancy, c) to explore the economic implications of drug use during pregnancy for WWE. The article is structured as

follows. First, the methodology employed is presented. Second, an overview of the results is provided. Finally, a discussion is given, followed by some concluding remarks.

2. Methods

A systematic literature review on the use of drug treatment for epilepsy during pregnancy and the effects on mother, foetus and newborn was conducted in September 2013. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009) was followed for identification, screening, eligibility and inclusion of articles in the review.

2.1. Search strategy

Searches were performed for papers published between January 2000 and June 2013 in relevant databases (PubMed and Scopus). Reference lists in the papers meeting the articles included in the review were searched to identify further eligible papers. Search terms and their combinations are set out in Table 1. Databases were searched using the primary term "epilepsy" in combination with pregnancy or pregnant (column 2 in Table 1) and one term associated with drug treatment (column 3 of Table 1).

Table 1. Search terms

Column 1	***Column 2 Combined with (individually)***	***Column 3 Combined with (individually)***
epilepsy	pregnancy	"drug use"
	pregnant	"medication use"
		drugs
		medication(s)
		treatment
		therapy
		Pharmacotherapy
		"pharmaceutical use"
		management

Study eligibility was determined by two reviewers based on abstracts of publications and full papers when necessary. Articles were considered eligible if they met the inclusion criteria set out in the PICOS framework as described in table 2. The primary endpoint of the review was any clinical outcome for mother, foetus and newborn due to drug use for the treatment of

epilepsy. Further, ethical considerations regarding the use of medication during pregnancy or the choice to become pregnant or complete the pregnancy were examined. Finally, any data on socioeconomic impact and costs of treating WWE were taken into account. Only studies that presented primary data and only studies in English were considered eligible. Due to the absence of pregnant woman in RCT trials, it was anticipated that no such study design would be retrieved from the search. Consequently, cohort studies, case reports and registry studies were considered for inclusion in the review. Although case reports are prone to bias (Doherty 1994), these studies were expected to enable the identification of relevant information on ethical considerations concerning drug use in pregnancy.

Table 2. Inclusion criteria

P	Population	Pregnant woman diagnosed with epilepsy before pregnancy
I	Intervention/ treatment	Any drug intervention or combination of drug interventions or lack of drug intervention given for the treatment of epilepsy
C	Comparator	N/A
O	Outcome	Any clinical outcome for mother, foetus and newborn (younger than 28 days), ethical considerations, and costs
S	Study design	Cohort studies, controlled trials, studies based on registry data, case studies, surveys/interviews

Studies examining different diseases during pregnancy with no disaggregated data for WWE were excluded. This applied also to studies in which part of the sample of pregnant women were treated with AEDs for diseases other than epilepsy (e.g. bipolar disorders), even if in a small percentage. Additionally, studies with no clear specification of whether the entire sample included (pregnant women under AED treatment) was composed of WWE were also excluded. Reported outcomes for children born to WWE older than 28 days, including cognitive and psychomotor outcomes were not considered in the review.

2.2. Data Extraction and Analysis

The review included articles using both quantitative and qualitative research methods. Therefore, an aggregative synthesis (Dixon-Woods et al 2006) was undertaken in which data was extracted and summarised into an excel spreadsheet using predefined categories. The data collected for each article included (a) information about the study (study design, study

objective, country of origin, year of data collection, sample size); (b) interventions (treatment regimens studied); (c) clinical outcomes (disease-related outcomes, birth outcomes, foetal complications); (d) further endpoints (ethical considerations and costs). With regard to case reports, these were analysed to assess the ethical considerations around pregnant WWE as case reports often provide anecdotal evidence and allow for a more holistic description of the patient, providing non-clinical information. In particular, the question of interest for this paper was whether there was any evidence that the chronic disease had implications for the way in which the woman, their partners and their doctors made decisions about family planning (i.e. decisions about whether or not to become pregnant based on their chronic condition and the risks involved for mother and the baby). For this reason, case reports identified in the data base searches were screened for information about ethical issues and included if they provided information on the ethics of pregnancy in WWE.

2.3. Limitations

This review is not without limitations. First, papers failing to meet the criteria of disaggregated data and specificity of epilepsy in the study sample may have led to the exclusion of data relevant for the review. However, the authors believe that not applying strict criteria could have led to inaccurate estimates of the outcomes of interest. Second, some data on complications were excluded from the comparative analysis because they employed a format which was not comparable with the majority of studies. In particular, the majority of the studies reported certain outcomes as rates of abnormal outcomes (i.e. LBW, SGA, pre-term, etc) whereas in some studies these were reported simply as absolute values (i.e. average birth weight, birth size, gestational age, etc). Third, different studies used slightly different criteria to define certain outcomes, making the comparability of the same complications somewhat inaccurate. For example, the outcome pre-term birth was mostly defined as a birth occurring at gestational age <37 weeks (Kulaga et al, 2011; Lin et al, 2009; Veiby et al, 2009; Viinikainen et al, 2006), whereas in other studies this was defined as a birth occurring before 32 (Borthen et al, 2009), 34 (Borthen et al, 2010) and 36 (Mawer et al, 2010) weeks. Finally, the influence of confounding variables such as type or severity of epilepsy, socioeconomic status, smoking condition, family history of birth defects maternal IQ/ability, and gestational age at birth on the occurrence of pregnancy complications was not assessed However, not all studies reported on confounders and when they did, most of them had not have sufficient statistical power to quantify the association between risk factors and adverse pregnancy

outcomes. Therefore, it is still debatable whether the higher risks of adverse outcomes are associated with epilepsy itself (genetic predisposition or adverse effect of seizures), AEDs, other factors (i.e. lifestyle) or their interaction. However, it has been showed that pregnant women with a history of epilepsy, but without AED treatment during pregnancy had no higher risk for CMs (Holmes et al, 2001), confirming the teratogenic role of AEDs, although untreated women are expected to be affected with less severe epilepsy (Fried et al, 2004).

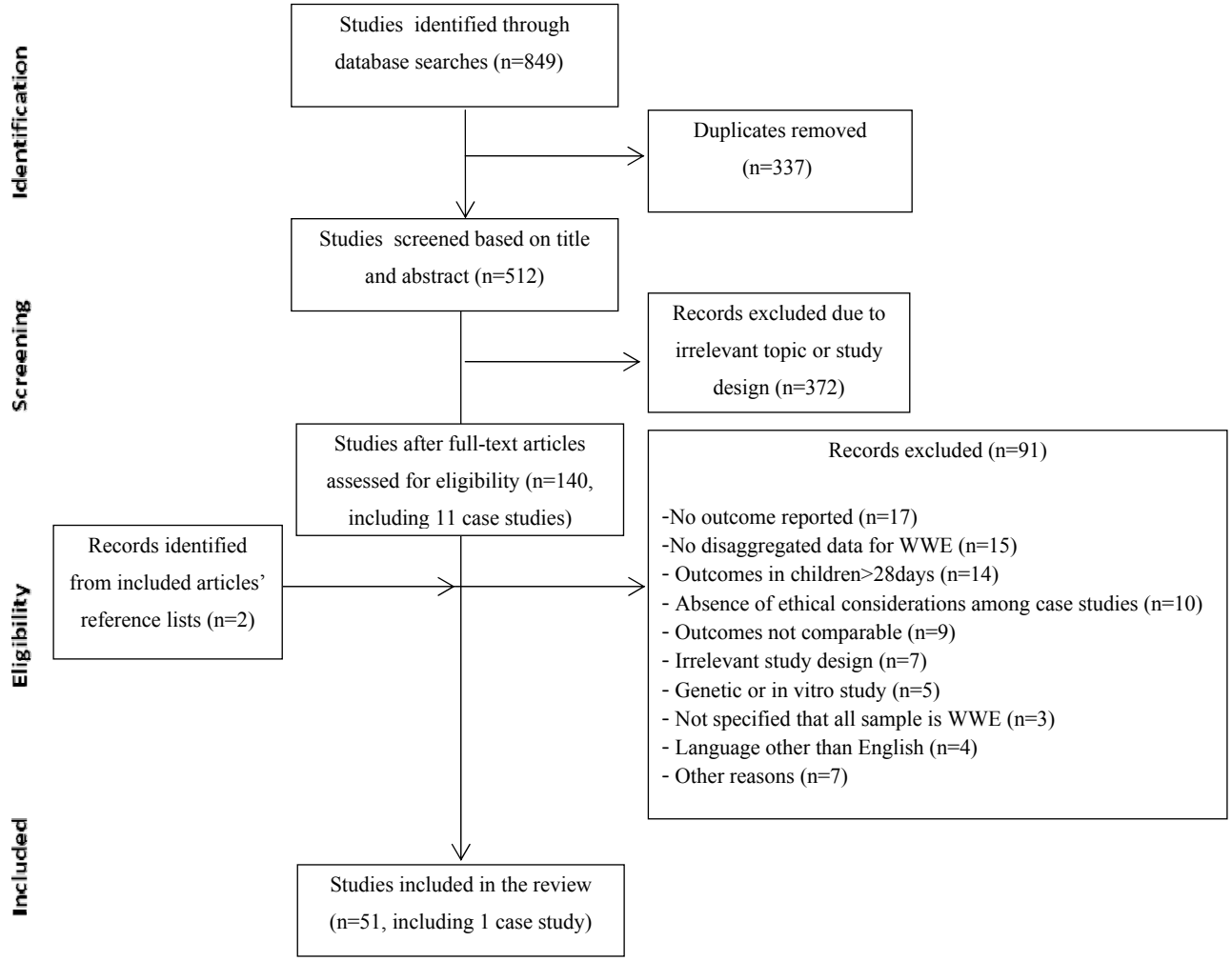
3. Results

3.1. Search yields

The flow of articles in the study selection process of the review is depicted in

Figure 1. In total, 849 articles were identified from Pubmed and SCOPUS. After duplicates were removed (n=337), the remaining studies (n=512) were first reviewed in terms of title and abstract to gauge their suitability following the inclusion and exclusion criteria presented in table 2 and 3. At this point, 372 studies were excluded. 91 additional studies were further excluded after full-text assessment. The main reasons for exclusion were: no adverse pregnancy outcomes reported (n=17), lack of disaggregated data for the epileptic sub-population in studies examining more diseases (n=15), outcomes in children older than 28 days (n=14), absence of ethical consideration among the case studies (n=10), outcomes not comparable with the majority of the studies (n=9), irrelevant study design (n=7), genetic or in vitro studies (n=5), lack of specification of whether the entire sample was epileptic (n=3), and language other than English (n=3). Finally, 51 studies, including 2 articles identified from the included articles' reference lists were included in the review. All but one studies analysed (n=50) were cohort studies, mostly based on registries. These were compared based on the adverse pregnancy outcomes, including obstetric, delivery and neonatal complications. The remaining study was a case report.

Figure 1 Flow chart of the articles selection process for the review



3.2. Antiepileptic treatment

In 9 studies the entire sample of WWTE were on monotherapy, whereas in the remaining 41 studies some WWTE were on monotherapy and others on polytherapy regimes (Table 3). On average, 78.4% of WWTE were on monotherapy whereas the remaining 21.6% were on polytherapy, with a distribution between the two regimes ranging from 33.3% and 66.7% (Hunt et al, 2006), to 93.3% and 6.7% (Lakshmi et al, 2008), for monotherapy and polytherapy respectively. In monotherapy regimes the most frequently used AEDs were

VPA, CBZ, LTG, PHT, PHB and OXC. On average, within monotherapy regimes, 41.6% of WWE were treated with CBZ, ranging from 5.4% (Lin et al, 2009) to 79.1% (Burja et al, 2006), 26.5% with VPA, ranging from 5.6% (Wide et al, 2000) to 43.3% (Lin et al, 2009), 30.3% with LTG, ranging from 6.8% (Artama et al, 2013) to 35% (Sabers et al, 2004), 5.7%

Table 3. Proportion of pregnancies of WWTE either in monotherapy or polytherapy regimes and proportion of women treated with specific AEDs within those treated with monotherapy regimes.

Author	Number of pregnancies of WWTE	Regime (%)		Women treated with specific AEDs in monotherapy regimes (%)														
		M	P	VPA	CBZ	LTG	PHT	OXC	PHB	GBP	TPM	CLB	CZP	DZP	LVT	VGB	PRM	ESM
Almgren et al 2009	2426	90.5	9.5	20.9	50	14	6.2	0.4	0.5	2.3	0.3		3.2		0.2	1	0.3	0.3
Artama et al 2005	857	87.2	12.8	21.4	65.4													
Artama et al 2013	3051	83.7	16.3	27.6	42.2	6.8	1	20.7					0.5		0.5			
Barqawi 2005	32	50	50		100													
Borthen et al 2009	942	86	14	22	46	25												
Borthen et al 2010	942	88.8	11.1	25.7	46.4	27.8												
Borthen et al 2011	116	76.7	23.3	16.4	24.1	25.8												
Bromfield et al 2008	259	100	0	100														
Burja et al 2006	37	64.9	35.1	8.3	79.1				4.2					4.2			4.2	
Cassina et al 2013	385	77.1	22.9	17.5	34.3	8.8			22.6								1	
Chang et al 2007	39	71.8	28.2		33.3													
Charlton et al 2011	3186	77.5	22.5															
El-Taweel et al 2009	30	80	20															
Endo et al 2004	30	76.7	22.3	17.4	34.8				43.5				4.3					
Eroğlu et al 2008	84	100	0	16	49		14		5									
EURAP Study Group	1736	78.7	21.3	25.2	36.4	17.4	3.2	3	8.6									
Hunt et al 2006	117	33.3	66.7												100			
Hunt et al 2008	203	34.5	65.5															
Hvas et al. 2000	106	84	16	16	51		1	10				1	21					
Kaaja et al 2003	733	80	20	10.3	61.1		20.9	1.5	0.8				2.2				1	0.3
Kaaja et al 2010	662	78.7	21.3		72.2		24.4	1.3	0.9								1.1	
katz et al 2001	100	69	21															
Kochen et al 2011	94	65.9	34.1	32.2	48.3													
Kulaga et al, 2011	307	70.7	29.3															

Lakshmi et al 2008	30	93.3	6.7		50		25		25									
Laskowska et al 2001	36	75	25															
Lin et al 2009	166	100		43.3	5.4		46.5		4.8									
Mawer et al 2010	231	80.1	19.1	30.8	40	21.6												
Mawhinney et al 2012	1109	100	0	100														
Mawhinney et al, 2013	671	45.3	54.7												100			
Meador et al 2006	323	100	0	20.7	33	29.4	16.8											
Meischenguiser et al	114	72.8	27.2	25.3	19.3		1.2	42.1	6			2.4	3.6					
Miškov et al 2009	23	100				100												
Morrow et al 2006	3368	77.1	22.9	29	36.4	26.2	3.32			1.2	1.1				0.9			
Reiff-Eldridge et al	149	100				100												
Richmond et al 2003	335	77	23															
Sabers et al 2004	138	74	26	20	12	35		25					9			7		
Sabers et al 2009	42	100				100												
Tennis et al 2002	389	50.3	49.7			100												
Thomas et al 2001	23	87.5	12.5															
Thomas et al 2008	387	67.5	32.5	27.1	42.7		11.8		16.4				0.7					
Tomson et al 2011	24061	100		22.2	30.9	28.2			4.8									
Vajda et al 2003	291	69.7	30.3															
Vajda et al 2007	875	73.1	26.9	25.6	36	22.5	4.8			1.7	2.3		3.2		0.8			
Vajda et al 2012	1178	72.9	27.1	25	35	27	4				3.6		2.3		2.6			
Veiby et al, 2009	961	86	14	22	46	25												
Viinikainen et al 2006	127	82	18	26.9	69.2		1.9	1.9										
Wide et al 2000	87	83	17	5.6	54.9		31						5.6				2.8	
Average		**78.4**	**21.6**	**26,5**	**41,6**	**30,3**	**5,7**	**8,9**	**10,2**	**1,7**	**1,4**	**1,7**	**2,3**	**4,2**	**0,8**	**1,3**	**0,7**	**0,3**

M= monotherapy; P=polytherapy; VPA=valproate (valproic acid); CBZ=carbamazepine; LTG=lamotrigine; PHT=phenytoine; OXC=oxcarbazepine; PHB= Phenobarbital; GBP=gabapentin; TPM=topiramate; CLB=clobazam; CZP=clonazepam; DZP=diazepame; LVT=levetiracetam; VGB=vigabatrin; PRM=pirimidone; ESM=Ethosuximide.

with PHT, ranging from 1% (Artama et al, 2013) to 46.5% (Lin et al, 2009), 8.9% with OXC, ranging from 0.4% (Almgren et al, 2009) to 42.1% (Meischenguiser et al, 2004), and 10.2% with PHB, ranging from 0.5% (Almgren et al, 2009) to 43.5% (Endo et al, 2004). Details of regimes of AED therapy and distribution of specific AEDs in monotherapy regimes are presented in Table 3.

3.3. Adverse pregnancy outcomes

With regard to adverse pregnancy outcomes these were broadly grouped in those affecting the mother and those affecting the foetus and newborn (El-Taweel et al 2009).

Table 4). The former were further classified in outcomes during pregnancy, referred to as obstetric outcomes (i.e. vaginal bleeding) and outcomes during delivery, including abnormal modes of delivery (i.e. caesarean section). The latter category included the adverse birth outcomes, also referred to as neonatal outcomes. With regard to obstetric complications, the most frequently reported were preeclampsia, gestational hypertension, vaginal bleeding during pregnancy , still birth and spontaneous abortion. Other obstetric outcomes have been reported only by few studies, such as anemia, placenta previa, intrauterine growth retardation (IUGR), hydramnios, postpartum hemorrhage, urinary infection and breech presentation. Among the delivery complications, caesarean section was often reported whereas rates of assisted deliveries (both vacuum and forceps assisted deliveries) and induction of labour have been less frequently reported. In addition, with regard to adverse outcomes related to epilepsy increased rates of seizure frequency during pregnancy have been reported. The most frequently reported neonatal outcomes in infants born to WWE were low birth weight (LBW), small for gestational age (SGA), abnormal Apgar score (<7 after 5 minutes), pre term birth and, particularly, CMs, including MCMs. Rates of other neonatal complications have also been reported less consistently, such as small head circumference (SHC), foetal distress, admission to intensive care unit (ICU) and withdrawal symptoms.

3.3.1. Adverse pregnancy outcomes in WWTE

Among obstetric outcomes in WWTE (including both monotherapy and polytherapy regimes), the average rates of complications were 7.0% for pre-eclampsia, ranging from 6.5%

(Borthen et al, 2009) to 12.9% (Borthen et al, 2011), 3.7% for gestational hypertension, ranging from 2.8% (Borthen et al, 2009 and Veiby et al, 2009) to 8.7% (Mawer et al, 2010), 4.1% for vaginal bleeding during pregnancy, ranging from 1.5% (Veiby et al, 2009) to 18.1% (Borthen et al, 2011), 4.6% for spontaneous abortions ranging from 3.4% (Vajda et al 2007) and 8.5% (Kochen et al 2011) and 4.2% for still birth, ranging from 0% (Viinikainen et al 2006 and Lakshmi et al 2008) to 9.5% (Artama et al 2013). With regard to mode of delivery, the average rate of caesarean section in WWE treated with AED was 20.9%, ranging from 5.7% (Saleh et al, 2008) and 46.2% (Eroğlu et al, 2008). As for seizure control, seizure frequency increased in 16.8% of WWE, ranging from 5% (Viinikainen et al, 2006) to 50% (El-Taweel et al 2009).

Table 4. Classification of adverse pregnancy outcomes of interest for the study

<table>
<tr><th>Mother</th><th>Foetus/newborn</th></tr>
<tr><td>Obstetric and delivery
• Vaginal bleeding
• Preeclampsia
• Gestational hypertension
• Spontaneous abortion
• Still birth
• Caesarean section</td><td rowspan="2">• Low birth weight (LBW)
• Low gestational age (LGA)
• Abnormal Apgar score
• Congenital malformation (CM)
o Major (MCM)
o Minor (mCM)</td></tr>
<tr><td>Epilepsy related
• Increased seizure frequency</td></tr>
</table>

Among neonatal outcomes in infants born to WWE in both monotherapy and polytherapy AED regimes, the average rates of complications were 6.6% for LBW, ranging from 4% (Sabers et al, 2004) to 86.7% (Lakshmi et al,2008), 4.8% for SGA, ranging from 0% (Wide et al 2000) to 20.0% (Hvas et al, 2000), 4.9% for abnormal Apgar score, ranging from 2.6% (Borthen et al, 2010) to 7% (Kaaja et al 2003), and 6.7% for pre-term birth, ranging from 1.9% (Saleh et al, 2008) to 10.7% (Veiby et al, 2009). The average rate of CMs (without distinction between major and minor malformations) was 6.9%, ranging from 3.1% (Sabers et al, 2004) and 25% (Barqawi et al, 2005). More specifically, the average rate of MCMs was 6.4%, ranging from 0.8% (Kaaja et al 2003) to 10.6% (Kochen et al, 2011). Rates of the most

Table 5. Rates (%) of the most frequently reported obstetric, delivery and neonatal complications in WWTE (in M and P).

Author	Sample		Increased seizure frequency rates(%)	Obstetric and delivery complication rates (%) (*)						Neonatal complication rates (%) (*)					
	Number of pregnancies	Number of newborns		Preeclampsia	Gestational hypertension	Vaginal bleeding	Cesarean section	Spontaneous abortion	Still birth	LBW	SGA	Abnormal Apgar score	PREterm	CMs	MCMs
Artama et al 2005		1411													4.6
Artama et al 2013	3051	3067					19.2		9.5	4.7	2.4	5.6	5.5		
Barqawi et al 2005		32												25	
Borthen et al 2009	942	942		6.5	2.8	2.3							4.9		
Borthen et al 2010	942	942					21.1					2.6			
Borthen et al 2011	116	116		12.9	7.8	18.1	32.8					3.4	5.2	6.9	
Burja et al 2006		37									8.6				4.3
Cassina et al 2013	385	337						7.8	0.5	4.8	2.9		7		7.7
Chang et al 2007	39	27					44.44						7.41	3.7	
El-Taweel et al 2009	30		50												
Endo et al 2004		30													2.9
Eroğlu et al 2008	84	80	19.04				46.2							10	
EURAP Study Group	1736		17.3												
Hvas et al. 2000		104								9	20		8		5
Kaaja et al 2003	733	740							0.8			7			0.8
katz et al 2001		93													1.1
Kochen et al 2011	94	94	17					8.5	2.3						10.6
Lakshmi et al 2008	30	30					6.7		0	86.7			3.3		
Mawer et al 2010	231	218			8.7	15.6	25.1			5.9			8.3		6.6
Mawhinney et al, 2013	671	626						5.51	0.6					8.34	3.3
Meischenguiser et al		114												14	7
Reiff-Eldridge et al		121												6.5	
Sabers et al 2004		128								4				3.1	
Saleh et al 2008	53	53					5.7						1.9		3.8

Thomas et al 2001		23												12.5	
Thomas et al 2008		388													36
Vajda et al 2004		371												6.7	
Vajda et al 2007	875	825						3.4	1					3.9	
Veiby et al, 2009	961	961		6.8	2.8	1.5	21.5		1	9.6	10	2.7	10.7	5.3	3.3
Viinikainen et al 2006	127	127	5						0	5.5	17.3	3.2	3.9		4.8
Wide et al 2000	87	84	12.6								0		6		
Average			**16.8**	**7.0**	**3.7**	**4.1**	**20.9**	**4.6**	**4.2**	**6.6**	**4,8**	**4.9**	**6.7**	**6.9**	**6.4**

LBW= low birth weight; SGA= small for gestational age; CMs= congenital malformations; MCMs= major congenital malformations (*) Rates of obstetric and delivery complications are calculated against the number of pregnancies. Rates of neonatal complications are calculated against the number of newborns.

Table 6. Rates (%) of the most frequently reported obstetric, delivery and neonatal complications in WWE treated with AEDs in M regimes.

Author	Sample		Increased seizure frequency rates (%)	Obstetric and delivery complication rates (%)(*)					Neonatal complication rates (%) (*)					
	Number of pregnancies	Number of newborns		Gestational hypertension	Vaginal bleeding	Cesarean section	Spontaneous abortion	Still birth	LBW	SGA	Abnormal Apgar score	PRE term	CMs	MCMs
Artama et al 2005		1230												4.2
Artama et al 2013	2254	2567				17.7		9.4	4.3	2	5.5	5.3		
Bromfield et al 2008		259											11	
Cassina et al 2013		260												6.2
Chang et al 2007	28	28					7.8							
Charlton et al 2011		2468												3.7
El-Taweel et al 2009	24		37.5											
Hunt et al 2006	39	35				23.1	5.1	2.6	10.2			11.4	0	0
Hunt et al 2008	70	61				24.4	8.6	0					12.9	4.8
Kulaga et al, 2011	217	123					2.8	0	8.2	18.2		10		9.9
Laskowska et al 2001		27											3.7	
Lin et al 2009		166							7.2	21.7		8.4		
Mawer et al 2010		159												5.9
Mawhinney et al 2012	1109	1044					3.7	1.1						6.7
Mawhinney et al,	304	286					4.93	0.66					5.24	0.70
Meador et al 2006	323	333						2.7					6.6	
Miškov et al 2009		23					4.3	4.3			4.3		0	0
Morrow et al 2006		2468												3.7
Richmond et al 2003	258	258		11.2	11.6	22.1		1.2				10		6.2
Sabers et al 2009	42		19											

Tennis et al 2002	195	168						0.6						1.8
Thomas et al 2008		261											6.5	
Tomson et al 2011	4540	4424						1.5					4.6	
Vajda et al 2012	859	859											8.61	
Average			**22**	**11.2**	**11.6**	**19.3**	**4.1**	**3.4**	**5.3**	**8.6**	**5.5**	**6.7**	**5.6**	**4.3**

LBW= low birth weight; SGA= small for gestational age; CMs= congenital malformations; MCMs= major congenital malformations (*) Rates of obstetric and delivery complications are calculated against the number of pregnancies. Rates of neonatal complications are calculated against the number of newborns

Table 7. Rates (%) of the most frequently reported obstetric, delivery and neonatal complications in WWE treated with AEDs in P regimes.

Author	Sample		Increased seizure frequency rates (%)	Obstetric and delivery complication rates (%) (*)						Neonatal complication rates (%) (*)					
	Number of pregnancies	Number of newborns		Preeclampsia	Gestational hypertension	Vaginal bleeding	Cesarean section	Spontaneous abortion	Still birth	LBW	SGA	Abnormal Apgar score	PRE term	CMs	MCMs
Artama et al		181													7.2
Artama et al	797	500					26.9		10	6.6	4.2	6.4	6.4		
Borthen et al	105	105					29.5					1.7			
Borthen et al	27	27		11.1		25.9	29.6								7.4
Cassina et al		77													12.8
Charlton et al		718													6
El-Taweel et	6		100												
Hunt et al	78	74					74.3	2.6		12.9			24.3	10.7	4
Hunt et al	133	111					25.6	9	1.5					19.8	11.2
Kulaga et al,	90	41						4.4	2.4	7.1	11.9		9.5		19
Laskowska et		9												11.1	
Mawer et al		39													9.3
Mawhinney et	367	340						5.99	0.54					11.99	5.56
Morrow et al		718													6
Richmond et	77	77			11.7	11.7	26		1.3				8.2		9.1
Tennis et al		166													6
Thomas et al		127												10.3	
Veiby et al,	132	132							0.8	15.2	17.4	3.1	17.6	8.3	6.1
Average			**100**	**11.1**	**11.7**	**15.4**	**30**	**6.0**	**5.5**	**8.8**	**9.0**	**5.3**	**10.7**	**11.5**	**6.7**

LBW= low birth weight; SGA= small for gestational age; CMs= congenital malformations; MCMs= major congenital malformations

(*) Rates of obstetric and delivery complications are calculated against the number of pregnancies. Rates of neonatal complications are calculated against the number of newborns

frequently reported obstetric, delivery and neonatal complications in WWE treated with AEDs are reported in Table 5. The same outcomes in WWE treated with AEDs either in monotherapy or polytherapy are presented respectively in

Table 6 and

Table 7.

3.3.2. Adverse pregnancy outcomes in WWUE

Among untreated WWUE, the average rates of obstetric complications were 5.3% for preeclampsia, ranging from 5% (Borthen et al, 2009) to 12.4% (Veiby et al, 2009), 2.0% for gestational hypertension, ranging from 1.7% (Veiby et al, 2009) to 13.6% (Richmond et al 2003), 1.4% for vaginal bleeding during pregnancy, ranging from 0.7% (Veiby et al, 2009) to 15.2% (Richmond et al 2003), and 3.1% for still birth (foetal death), ranging from 0% (Richmond et al 2003) to 5.6% (Artama et al 2013). With regard to spontaneous abortions (miscarriage) the reported rate was 0% in the 2 studies which reported this outcome in untreated WWE (Kulaga et al, 2011 and Vajda et al, 2007). Among the delivery outcomes, the average rate of caesarean section was 18.4%, ranging from 14.6% (Borthen et al 2011) to 27.3% (Richmond et al 2003). Seizure control in WWUTE was not reported.

Among the neonatal outcomes of infants born to untreated WWE, the average rates were 5.8% for LBW, ranging from 3.6% (Artama et al 2013) to 10.5% (Kulaga et al, 2011), 8.3% for SGA, ranging from 2.3% (Artama et al 2013) to 16.1% (Lin et al 2009), 1.9% for abnormal Apgar score, ranging from 1.6% (Borthen et al 2010) to 2.2% (Borthen et al 2011), and 6.1% for pre-term birth, ranging from 3.5% (Borthen et al 2009) to 15.8% (Kulaga et al, 2011). The average rate of CMs (both major and minor malformations) was 4.7% ranging from 0% (Hvas et al, 2000; Laskowska et al, 2001; Sabers et al, 2004) to 5.2% (Vajda et al 2012). More specifically, the average rate of MCMs was 2.8%, ranging from 0% (Viinikainen et al 2006) to 20% (Kulaga et al, 2011). Rates of the most frequently reported obstetric, delivery and neonatal complications in WWUTE are reported in Table 8.

Table 8. Rates (%) of the most frequently reported obstetric, delivery and neonatal complications in untreated WWE.

Author	Sample		Obstetric and delivery complication rates (%) (*)						Neonatal complication rates (%)(*)					
	Number of pregnancies	Number of newborns	Preeclampsia	Gestational hypertension	Vaginal bleeding	Cesarean section	Spontaneous abortion	Still birth	LBW	SGA	Abnormal Apgar score	PRE term	CMs	MCMs
Artama et al 2005		939												2.8
Artama et al 2013	1793	1800				18.4		5.6	3.6	2.3		4.7		
Borthen et al 2009	1863	1863	5.2	1.8	1.5							3.5		
Borthen et al 2010	1863	1863				18.1					1.6			
Borthen et al 2011		89	12.4	4.5	4.5	14.6					2.2	5.6	4.5	
Burja et al 2006		32								1.4				
Charlton et al 2011		227												3.5
Hvas et al. 2000		87							5	16		6	0	
Kaaja et al 2003	237	239						1.3			4.6			0.8
katz et al 2001		10												1
Kulaga et al, 2011	42	20					0	2.4	10.5	5.3		15.8		20
Laskowska et al		5											0	
Lin et al 2009		1016							8.3	16.1		7.3		
Mawer et al 2010		40												2.4
Morrow et al 2006		227												3.5
Richmond et al	66	66		13.6	15.2	27.3		0				15.4		4.6
Sabers et al 2004		9											0	
Thomas et al 2008		74											8	
Vajda et al 2003		23											4.3	
Vajda et al 2004		32											3.1	
Vajda et al 2007	83	79					0	1					3.6	
Vajda et al 2012		139											5.2	
Veiby et al, 2009	1900	1900	5	1.7	0.7	18.7		1.1	6.6	9.5	1.9	8.9	4.7	2.6
Viinikainen et al		52												0
Average			**5.3**	**2.0**	**1.4**	**18.4**	**0**	**3.1**	**5.8**	**8.3**	**1.9**	**6.1**	**4.7**	**2.8**

LBW= low birth weight; SGA= small for gestational age; CMs= congenital malformations; MCMs= major congenital malformations (*) Rates of obstetric and delivery complications are calculated against the number of pregnancies. Rates of neonatal complications are calculated against the number of newborns

3.3.3. Comparison of adverse pregnancy outcomes between WWTE and WWUTE

Average rates of adverse pregnancy complications in WWTE were constantly higher than rates in WWUTE. With regard to obstetric and delivery complications, the differences between average rates between WWTE and WWUTE ranged from less than 2% such as in the cases of preeclampsia (7.0% VS 5.3%), gestational hypertension (3.7% VS 2.0%) and still birth (4.2 VS 3.1%) to higher differences such as in the cases of vaginal bleeding (4.1% VS 1.4%), cesarean section (20.9% VS 18.4%) and spontaneous abortion (4.6% VS 0%). With regard to neonatal complications, only SGA was higher in WWUTE (8.3%) in comparison to WWTE (4.8%). For the remaining neonatal outcomes, average rates in WWTE were always higher than in WWUTE, with differences ranging from less than 2% such as in the cases of pre term rate (6.7% versus 6.1%) and LBW (6.6% VS 5.8%) to higher differences such as in the cases of abnormal Apgar Score (4.9% VS 1.9 and CMs (6.9% VS 4.7%), including the MCMs (6.4 % versus 2.8%).

3.3.4. Comparison of adverse pregnancy outcomes between WWTE on polytherapy and WWTE on monotherapy regimes

Among the treated population of WWTE, average rates of pregnancy complications in WWTE on polytherapy were higher than those in WWTE on monotherapy. With regard to obstetric and delivery complications, the differences between average rates in WWE treated on polytherapy and those on monotherapy ranged from less than 2% such as in the cases of gestational hypertension (11.7 % VS 11.2%), spontaneous abortion (6.0 % VS 4.1%) and still birth (5.5 VS 3.4) to higher differences such as in the cases of cesarean section (30% VS 19.3%). With regard to neonatal complications only the rate of abnormal Apgar score was higher in newborns to WWUTE (5.5%) in comparison to newborns to WWTE (5.3%). For the remaining neonatal outcomes, average rates of complications in newborns of WWTE were always higher than in newborns to WWUTE, with differences ranging from less than 2% such as in the case of small for gestational age (9.0% VS 8.6%) to higher differences such as in the cases of LBW (8.8% VS 5.3%), pre term rate (10.7% VS 6.7%) and CMs (11.5% VS 5.6%), including the MCMs (6.7% versus 4.3%).

3.4. Ethical considerations and economic implications

11 case studies describing cases of pregnant WWE on drug treatment were identified, of which only one study discussed the ethical dilemma of childbearing for WWE (Šepić-Grahovac et al. 2010). The article stated that pregnant WWE must be treated in a specific way in order to address medical as well as bioethical issues. The report describes a 17 year old girl with epilepsy caused by a brain tumour who experienced an unplanned pregnancy. After consulting the patient, her partner and parents regarding the risks involved, it was decided to continue the pregnancy with a multidisciplinary approach including neurological, neurosurgical, gynaecological and clinical pharmacological consultations. Drug doses of PHB and CBZ were reduced to 50mg per day and 400mg per day respectively and folic acid (5mg daily) was included. After intensive monitoring and no epileptic seizure, a healthy baby was delivered through caesarean section, simultaneously with a neurosurgical tumour removal. The patient's recovery was good. Three years later, the patient became pregnant again, this time with a planned pregnancy and hence treatment doses were adjusted beforehand.

No cost data, either direct or indirect, were found in any of the studies included in the review.

4. Discussion

4.1. Adverse clinical outcomes

The rates of adverse pregnancy outcomes varied depending on whether the women had epilepsy and whether they were treated or not. Rates also varied according to the therapy regime of AEDs (whether monotherapy or polytherapy), the particular AED chosen and the dosage.

4.1.1. WWE compared to non-epileptic women

The majority of the studies reported an increased risk of pregnancy and delivery complications in WWE compared to non-epileptic women, with an even greater risk in WWE treated with AEDs (Artama et al, 2013; Borthen et al, 2010). Two studies did not find any

increased risk for obstetric and neonatal complications in WWE in comparison to the general population (Saleh et al, 2008 and katz et al, 2001). Similarly, Thomas and colleagues found that the majority of WWE had safe pregnancy and childbirth without any aggravation of epilepsy (Thomas et al, 2008).

4.1.2. WWTE compared to WWUTE

As shown in the results, average rates of adverse pregnancy complications in WWTE were constantly higher than rates in untreated WWUTE. Some of the studies directly compared the effects of AED therapy between WWTE and WWUTE, confirming higher rates of adverse pregnancy, delivery and birth complications in WWTE compared to WWUTE (Borthen et al 2011, Veiby et al, 2009, Cassina et al 2013, Artama et al 2013, Burja et al 2006). Only few studies seemed to indicate an opposite trend. For example, a study reported an increased risk of adverse pregnancy outcomes for WWE who do not receive AED during pregnancy, but none for WWTE (Lin et al 2009). Similarly, Kaaja and colleagues assessed the risk of bleeding in the neonate born to WWE taking enzyme-inducing AEDs in pregnancy, concluding that neonatal bleeding was not associated with exposure to enzyme-inducing AED (Kaaja et al 2010). In addition, analysing the teratogenic effect of AEDs, Lakshmi and colleagues found no adverse neonatal outcomes other than LBW (Lakshmi et al 2008).

4.1.3. Monotherapy compared to polytherapy

As also shown in the results, average rates of adverse pregnancy outcomes in WWTE on polytherapy were higher compared to those of WWTE on monotherapy. Some of the studies comparing treatment regimens confirmed higher rates of adverse outcomes, particularly CMs, in polytherapy compared to monotherapy. For example, Morrow and colleagues reported rates of MCMs almost double in polytherapy (6%) compared to monotherapy (3.7%) (Morrow et al 2006). Another study found a similar increase of risk of CMs with polytherapy (10.3%) compared to monotherapy (6.5%) (Thomas et al 2008). Hunt and colleagues found a higher risk of MCMs with TPM in polytherapy (11.2%) compared to monotherapy (4.8%) (Hunt et al 2008), while Mawhinney and colleagues found similar results for LVT (Mawhinney et al, 2013). Another study found that the rate of MCMs increased in proportion to the number of AEDs prescribed (Richmond et al 2003). Similarly, Almgreen and

colleagues found a significant increase in the occurrence of microcephaly after any AED treatment in polytherapy, but not after monotherapy regimes.

4.1.4. Specific AEDs

Some studies compared specific AEDs to each other, all of which found a lower teratogenic potential for the newer AEDs compared to the traditional ones, particularly VPA. For example, a study from Argentina found that the newer AEDs (e.g. OXC) have a lower teratogenic risk than traditional AEDs (e.g. VPA), with most CMs being observed following exposure to PHB, VPA, and CBZ (Meischenguiser et al, 2004). Vajda and colleagues also concluded that new AEDs appear no more teratogenic than traditional drugs in monotherapy, and among the traditional AEDs, VPA was found to be the most teratogenic (Vajda et al, 2012). For example, in a controlled observational study from UK, MCM prevalence was highest with VPA in monotherapy (11.3%), whereas rates with LTG (5.4%) and CBZ (3.0%) were closer to controls (2.1%) (Mawer et al, 2010). Vajda and colleagues found comparable results, with the incidence of CM being higher for VPA (16.7%) compared to PHT (10.5%), LTG (7.7%) and CBZ (3.3%)(Vajda et al, 2003). Slightly lower rates of MCMs were found by Charlton and colleagues, but still with a similar pattern (6.2% for VPA compared to 2.2% for CBZ and 3.2% for LTG) (Charlton et al, 2011). Similarly, a Finnish study found an increased risk of CMs only in patients using VPA during pregnancy, whereas the risk for CMs was not elevated in offspring of mothers using CBZ, OXC, or PHT (either as monotherapy or polytherapy without VPA) (Artama et al, 2005). Higher risk of CMs with VPA was also confirmed in to studies by Thomas and colleagues (Thomas et al 2001; Thomas et al 2008).

A higher teratogenic potential was also confirmed for traditional AEDs, particularly VPA, when used in polytherapy regimes. Lower rates of CMs were found for LVT in association with LTG (1.7%) than in association with traditional AEDs such as VPA (6.9%) or CBZ (9.3%) (Mawhinney et al, 2013). A similar result was also found by Tennis and colleagues where the frequency of MCMs after exposures to LTG-VPA was higher than after exposure to LTG in monotherapy or LTG in polytherapy without VPA (Tennis et al, 2002). Further, in another study an increased risk of MCMs was demonstrated only for exposure to VPA both in monotherapy and polytherapy regimes (Veiby et al, 2009). Finally, along with MCMs, a

higher rate of foetal death was observed in pregnancies with in utero VPA exposure compared to the other AEDs (Meador et al 2006).

Among traditional AEDs, CBZ was found to be associated with the lowest risk of MCMs (Morrow et al 2006). This result was also confirmed in a Turkish study where despite an increased risk of CMs for all the four main traditional AEDs (CBZ, PHT, VPA, PHB), CBZ seemed to be the safest agent in monotherapy regimes (Eroglu et al 2008). Conversely, a Slovenian study found a particularly significant connection between CBZ therapy during pregnancy and cerebral haemorrhage in the neonates (Burja et al 2006).

With particular regard to LTG, this was found to be relatively safe, with CM rates (2.0%) lower than for OXC (5%) and VPA (6.7%) (Sabers et al 2004). Similarly, a prospective Croatian study found that pregnant women on LTG monotherapy were relatively safe (Miškov et al 2009).

4.1.5. Dosages

Some studies also assessed the impact of different dosages on the teratogenic effect of AEDs, concluding that the risk of MCMs is influenced not only by type of AED, but also by dose. For example, Tomson and colleagues noted the lowest rates of CM with daily doses of LTG less than 300 mg and daily doses of less than 400 mg. Also, compared with LTG monotherapy at doses less than 300 mg per day, risks of CM were higher with VPA and PHB at all investigated doses, and with CBZ at doses greater than 400 mg per day (Tomson et al, 2011). Similarly, another study from UK found that exposure to 1000mg a day or more of VPA was associated with almost double the risk of MCM compared with daily doses below 1000 mg daily (Mawhinney et al, 2012). Additional studies also confirmed the dose-related increased risk of CM associated with VPA (Vajda et al, 2007; Bromfield et al, 2008). In addition to choose the correct dosage, adherence to the prescribed AED regimen is also important to achieve the goal of reducing the seizure burden in patients with epilepsy. A recent article has shown that decreased AED adherence is associated with more than a three-fold increase in mortality (Faught et al, 2008). Periods of non-adherence in patients with epilepsy were also associated with more emergency department visits, hospital admissions, injuries, and fractures. The issue of AED adherence is especially important in pregnant

WWE, as seizures during pregnancy can cause harm to mother and baby (Mcauley et al, 2012).

4.2. Ethical and economic considerations

Little is known about the ethical considerations related to pregnancy in WWE. The reviewed case study (Šepić-Grahovac et al, 2010) illustrated that the decision about continuing the pregnancy influenced the intensive monitoring and treatment adjustments, and stressed the need for thorough discussion with the patient so that she could make an informed decision. The authors emphasised the need to strengthen pregnancy counselling for WWE as this is likely to result in planned rather than unplanned pregnancies.

Information needs for pregnant WWE has been discussed elsewhere, and reviewed systematically by McGrath and colleagues (McGrath et al, 2013), who found that while the woman are aware of the risks involved, they have limited knowledge. The authors indicated that preconception counselling for WWE was insufficient and led to uninformed decision making about pregnancy (McGrath et al. 2013). In a cross-sectional study of 1444 WWE aged 19 to 44 years on information needs, 87% of the woman who considered getting pregnant wanted more information about the risks to the foetus (Crawford and Hudson 2003). Similar conclusions were drawn from a Korean study, which highlighted the importance of education and pregnancy counselling to WWE in reproductive ages (Lee et al, 2013). Lee and colleagues interviewed 186 WWE aged 20 to 45 years old about the influence of pregnancy-related knowledge and risk perception on reproductive decision making. They found that more than 50% of the woman said they would discontinue drug treatment during a future pregnancy, and 25% of the woman stated that they would have fewer children because of their chronic disease. The decision to discontinue treatment was associated with low levels of pregnancy-related knowledge and knowledge of the risks, and the decision to have fewer children was associated with an exaggerated perception of the child's risk to develop epilepsy (Lee et al, 2013).

The reviewed literature provided no information on the economic aspects of drug use during pregnancy with specific regard to WWE. The literature was therefore explored to gather information on this area. Only few studies focused on economics of epilepsy and epilepsy treatment. In particular, a recent economic evaluation of AED treatment was performed in the Netherlands to estimate the impact of teratogenicity on the costs per quality adjusted life year

(QALY) (Jentink et al, 2012). CBZ, LTG and VPA were compared in terms of cost and effectiveness. According to the results, the incremental cost-effectiveness of LTG vs CBZ and of LTG vs VPA was estimated at €175,534 and €13,370 per QALY, respectively, making CBZ and LTG cost-effective treatment options compared to VPA when focusing on teratogenicity. Another cost-effectiveness analysis comparing newer and older AEDs was performed in the UK (Wilby et al, 2005). The analysis concluded that newer AEDs, used as monotherapy, may be cost-effective for the treatment of patients who have experienced adverse events with older AEDs, who have failed to respond to the older drugs, or where such drugs are contraindicated. In addition, newer AEDs used as adjunctive therapy might be cost-effective compared with the continuing current treatment alone at a threshold willingness to pay per QALY greater than 20,000. Finally, another study conducted in the Netherlands assessed the economic burden of side-effects due to AEDs from a societal perspective (de Kinderen et al, 2013). Based on data from 203 patients, the total societal costs of common side-effects of AEDs in 2012 were estimated to be €20,751 per patient per year, including health care costs, patient and family costs and additional costs such as productivity losses.

5. Conclusion

In conclusion, pregnancy in WWE is a high-risk condition due to the higher risk of adverse outcomes such as CMs. Although it is widely accepted that pregnant women should limit any therapeutic drug intake, drug treatment in epilepsy is often essential to control epileptic seizures which can be harmful both for the mother and the foetus. On the other side, the use of AEDs during pregnancy is of concern due to the associated adverse effects, especially the teratogenic effects. Thus, treatment of epilepsy during pregnancy must balance the risks associated with foetal AED exposure against the harm of uncontrolled seizures associated with epilepsy. This is a challenging task since it is still unclear whether the increased complications in pregnancy in WWE are due to the use of AEDs or the epilepsy itself.

The results of this review confirmed higher rates of pregnancy complications for WWTE compared to WWUTE and, among the treated ones, AED polytherapy exhibited higher overall adverse outcomes than monotherapy. Also, across AEDs, traditional AEDs showed higher teratogenic potential compared to the new generation AEDs. In particular, VPA was associated with the highest risk of CMs in a dose-effect relationship, with higher doses of

VPA associated with a significantly greater risk than with lower doses or with other AEDs. These results highlight the need to limit, where possible, the dose of VPA in pregnancy. Despite the well-known adverse effects associated with AEDs, most WWE can expect a normal pregnancy outcome with careful planning of pregnancy and management of delivery, especially when prescribed newer generation AEDs .

Information should be an essential part of the physician-patient relationship, and should aim to address the ethical considerations regarding epilepsy and childbearing. Pregnant women, including those with epilepsy, must be informed about teratogenic risks of medicines. The risk of CMs in children exposed to AED should be communicated as part of the routine informed consent process for WWE who are prescribed AEDs and are of childbearing age. Understanding the impact of prenatal AED exposure, both in terms of birth outcomes and longer-term developmental effects, is vital for women and their physicians to make well-informed decisions about AED use during pregnancy.

The establishment of several large international pregnancy registers in the last decade has greatly improved our understanding of immediate birth outcomes following prenatal AED exposure. However, further research is needed to determine the exact teratogenic risks attributable to each individual AED, particularly the new ones, and to delineate the mechanisms underlying AED-induced teratogenesis. A better understanding of the influence of AEDs on pregnancy is crucial for developing initiatives aimed at preventing adverse outcomes.

Key messages:

- Treated WWE have higher rates of pregnancy complications compared to untreated WWE. AED in polytherapy is associated with higher risks than AED in monotherapy.
- Newer AEDs seem to have less teratogenic potential compared to the traditional AEDs.
- Among AEDs, VPA is the most teratogenic. The use of VPA should be limited, where possible during pregnancy.
- There is a dose-related increased risk of CMs associated with AEDs.
- Pregnant WWE should receive more information regarding the potential risks of the AEDs in order to make well-informed decisions about AED use during pregnancy.
- Adherence to the prescribed AED regimen is key to reduce the seizure burden in patients with epilepsy.
- Further research is needed to determine the exact teratogenic risks attributable to each individual AED, particularly to newer drugs.

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