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# The use of antidepressant drugs in pregnant women with epilepsy: *A study from the Australian Pregnancy Register.*

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**Running title:** “Antidepressants in epileptic pregnant women”

**Key words:** Antiepileptic drugs, depression, anxiety, congenital malformations, birth defects, seizure control.

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**SUMMARY**

**Objective:** To study interactions between first-trimester exposure to antidepressant drugs (ADD) and antiepileptic drugs (AED), and a history of clinical depression and/or anxiety, on pregnancy outcomes and seizure control in pregnant women with epilepsy (WWE).

**Methods:** We examined data from the Australian Pregnancy Register of Antiepileptic Drugs in Pregnancy, collected from 1999 to 2016. The register is an observational, prospective database, of which this study retrospectively analysed a cohort. Amongst the AED exposed outcomes, comparisons were made among three exposure groups: (1) pregnancy outcomes with first-trimester exposure to ADDs; (2) those with mothers diagnosed with depression and/or anxiety but were not medicating with an ADD; and (3) those with mothers who were not diagnosed with depression and/or anxiety and were not medicating with ADD. Prevalence data was analysed using Fisher's exact test.

**Results:** A total 2124 pregnancy outcomes were included in the analysis. 1954 outcomes were exposed to AEDs in utero, whilst 170 were unexposed. Within the group of WWE

taking AEDs, there was no significant difference in the prevalence of malformations in infants additionally exposed to ADDs (10.2%, 95% CI 3.9-16.6), compared to individuals in the non-ADD medicated depression and/or anxiety group (7.7%, 95% CI 1.2-14.2), or those without depression or anxiety (6.9%, 95% CI 5.7-8.1;  $p=0.45$ ). The malformation rates in pregnancy outcomes unexposed to AEDs were also similar in the above groups ( $p=0.27$ ). In WWE medicated with AEDs and ADDs, the frequency of convulsive seizures ( $p=0.78$ ), or non-convulsive seizures ( $p=0.45$ ) throughout pregnancy, did not differ across comparative groups.

**Significance:** Co-medicating with ADDs in WWE taking AEDs does not appear to confer a significant added teratogenic risk, nor does it affect seizure control.

### **KEY WORDS**

Antiepileptic drugs, depression, anxiety, congenital malformations, birth defects, seizure control.

### **KEY POINT BOX**

- Out of 2081 women, 159 (7.6%) reported clinical depression and/or anxiety, of which, 94 (59.1%) were medicating with an antidepressant drug.
- Co-medicating with ADDs and AEDs does not appear to increase teratogenic risk or affect occurrence of convulsive and non-convulsive seizures.
- Non-medicating with ADDs for depression and/or anxiety did not appear to affect the teratogenic or seizure risk during pregnancy.
- Adequately powered, larger studies are required to confirm these preliminary findings.

### **INTRODUCTION**

Women with epilepsy (WWE) comprise of up to 0.7% of all pregnancies.<sup>1</sup> Although a few WWE can discontinue AEDs prior to conception, most will require continued use during pregnancy to achieve seizure control.<sup>2</sup> It is widely accepted that first-trimester exposure to AEDs increases the risk of congenital malformations (CMs) from the background risk.<sup>3</sup> Psychiatric conditions are commonly comorbid with epilepsy, affecting up to a third of

patients.<sup>4</sup> Depression is the most common of these, with many population-based studies reporting a prevalence over 20%.<sup>5</sup>

Antidepressant (ADD) medication treatment in pregnant women has been steadily increasing over the last twenty years, despite with their use being questioned as potentially increasing the risk of CMs.<sup>6,7</sup> Despite this, the combined foetal risk of medicating with both AEDs and ADDs in WWE has not been addressed in the scientific literature. Furthermore, there has been a longstanding concern amongst clinicians that certain ADDs may decrease the seizure threshold, where approximately half of women with epilepsy have at least one seizure during pregnancy.<sup>8-11</sup> Whether ADD use during pregnancy could be associated with worse seizure control, is also an important clinical question that has not been addressed in previous studies. Therefore, we designed this study to investigate the use of ADD treatment during pregnancy, utilizing data from the Australian Pregnancy Register of Antiepileptic Drugs.

## **METHODS**

The Australian Pregnancy Register (APR) of Antiepileptic Drugs in Pregnancy has been prospectively collecting observational data concerning the pregnancies and fetal outcomes in WWE since 1999.<sup>12</sup> The APR is a voluntary, Australia-wide, telephone interview based register. The register requires written informed consent and has ethics committee approval from the Melbourne Health Human Research and Ethics Committee. For this study, a retrospective analysis comparing in WWE the rate of CMs and the occurrence of seizures, and the relationship of these to co-medication with ADD and a history of depression, was performed on women enrolled from the register's inception in 1999 until 2016. The register also enrolls women taking AEDs for reasons other than epilepsy, but these women who represent approximately 1% of participants were excluded in this analysis.

During the period of participation of WWE in the Register, four interviews were conducted: (1) on recruitment (usually in the first or second trimester); (2) seven months of pregnancy; (3) within the post-natal month; and (4) at the end of the post-natal year. Details regarding the pregnancy outcomes were obtained in the third interview, and repeated, in case of any changes, in the fourth interview. CMs were classified per the Birth Defects Registry of Victoria.<sup>13</sup> Women were asked for occurrence of seizures at each of the interviews, however for the purposes of effective comparison, only binary seizure outcomes were analysed (i.e.

whether seizures occurred, or did not occur during pregnancy). As seizures were self-reported, there was no reliable method to discern between true epileptic seizures and non-epileptic events.

After excluding women who did not have epilepsy, two exposure types were first determined; WWE who were medicating with at least one AED and WWE who were *not* under medical treatment of their epilepsy at the time they became pregnant. These two groups were further sub-categorised based on three additional exposure types in each of the AED treated and AED untreated groups: (1) mothers treated with ADDs; (2) mothers with depression and/or anxiety but were not medicated with ADDs; and (3) mothers without depression and/or anxiety who were not medicated with ADDs.

The APR routinely asks women about whether have comorbid medical and psychiatric illnesses, including depression, and for all medications taken in addition to AEDs. Dosage information was recorded if volunteered, but as this information was incomplete in many women, this was excluded in our analyses.

There are many reasons for medicating with ADDs. Although this study centres around depression and anxiety, we recognise that obsessive-compulsive disorder, pain and migraines can be other potential reasons for medication with ADDs.<sup>14</sup> For the purposes of effective comparison, women must have had a diagnosis of depression and/or anxiety to be considered. Five women had a diagnosis of bipolar disorder and were on ADDs, these women were also included.<sup>14</sup>

The following AEDs were included in this study: carbamazepine, clonazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbitone, phenytoin, sodium valproate, tiagabine, topiramate, trileptal and vigabatrin. For the assessment of ADDs the following medications were included: (1) selective serotonin reuptake inhibitors (SSRIs) consisting of citalopram, escitalopram, fluoxetine, fluvoxamine and paroxetine; (2) selective norepinephrine reuptake inhibitors (SNRIs) consisting of desvenlafaxine, duloxetine and venlafaxine; (3) tricyclic antidepressants (TCAs) consisting of amitriptyline, dosulepin and doxepin; and (4) other atypical ADDs consisting of moclobemide, quetiapine and mirtazapine.

## STATISTICAL METHODS

Statistical analyses were performed with STATA 12 (StataCorp, College Station, TX, USA). Characteristics of the study population was expressed as counts (with percentages) and medians (with interquartile ranges). Comparisons between groups were performed using the Kruskal-Wallis one-way analysis of variance for continuous data, and the Fisher's exact test for categorical data. A two-tailed  $p$  value of  $<0.05$  was considered statistically significant on all tests performed.

## RESULTS

When the data for this study was analysed, 2081 women with epilepsy had completed their pregnancies on the APR, including 43 twin pregnancies, resulting in a total of 2124 pregnancy outcomes. 1592 (76.5%) women were between the ages of 21 and 34 and 449 (21.6%) were over the age of 35 (Table 1). 1647 (79.1%) women were employed at enrolment and 1653 (79.4%) belonged to households with an income greater than \$50,000.

1912 (91.9%) women were medicating with at least one AED whilst 169 (8.1%) were not medically treated for their epilepsy at the time they became pregnant. 1371 (71.7%) women on AED therapy required only one AED, but 541 (28.3%) were taking two or more AEDs. Amongst the AED medicated women, 203 (10.6%) reported tobacco use during pregnancy, 315 (16.5%) consumed alcohol, and 1821 (95.2%) were supplementing with folic acid prior to conception and in the first-trimester. Amongst the WWE who were not treated with an AED, 10 (5.9%) reported tobacco use throughout pregnancy, 32 (18.9%) consumed alcohol, and 150 (88.8%) were supplementing with folic acid.

159 (7.6%) women reported clinical depression and/or anxiety, of which, 94 (59.1%) were medicating with an ADD (Table 2). 57 (65.5%) women medicated with an ADD were on SSRI monotherapy, 13 (14.9%) were on SNRI monotherapy and five (5.7%) were on ADD polytherapy or medicating with an ADD combined with an antipsychotic (Table 5). A diagnosis of depression and/or anxiety (both treated and untreated with ADDs) did not impact the rates of cigarette smoking and alcohol use (Table 1). In women treated with AEDs, those with untreated depression and/or anxiety were twice as likely (11.3%) to not use folic acid supplementation than those who were taking an ADD (4.6%).

In pregnancy outcomes exposed to AEDs, those additionally exposed to ADDs had a CM rate (10.2%, 95% CI 3.9-16.6) which was comparable to the control groups (7.7%, 95% CI 1.2-14.2 and 6.9%, 95% CI 5.7-8.1; Table 2). Of pregnancy outcomes that were not exposed to AEDs but exposed to ADDs, one (14.3%, 95% CI 0-40.2) CM was seen, compared with 0% and 2.5% (95% CI 0.1-4.9) in the comparison groups (Table 3). Live births without defects and the baby's median birth weights were statistically similar across the comparison groups, for both AED exposed and unexposed women. Spontaneous abortions and still births were not statistically analysed due to insufficient numbers in the depressed and/or anxious group.

The malformation rate in pregnancy outcomes with mothers who did not have depression and/or anxiety was almost three times (6.9%, 95% CI 5.7-8.1) greater in those exposed to AEDs than those unexposed (2.5%, 95% CI 0.1-4.9;  $p=0.02$ ). Similarly, in pregnancy outcomes without exposure to depression and/or anxiety but who had AED treatment, there were 55 (3.1%) spontaneous abortions, compared to zero outcomes in the same exposure group but without AED treatment ( $p=0.01$ ).

Overall, medicating with ADDs in WWE, who were both treated and untreated with AEDs, was not associated with significantly different frequencies of convulsive or non-convulsive seizures (Table 4). ADD and AED treated women had a significantly greater frequency of non-convulsive seizures than the comparison groups at only one time point, seven months to delivery. The number of women who had at least one seizure at each of the telephone interview time intervals was similar for both AED treated and untreated women, across all comparison groups (Table 4). Four (4.6%) and nine (10.3%) women who were treated with AEDs and ADDs respectively, had sustained convulsive and non-convulsive seizures throughout pregnancy.

Specific ADDs were not associated with any adverse pregnancy outcomes and birth weight (Table 5). Sertraline was the most popular SSRI (44%) and the most popular ADD overall, with 25 (28.7%) WWE taking this ADD during their pregnancy. Three CMs occurred to women taking sertraline, four with citalopram and escitalopram respectively, and two with other atypical ADDs. The frequency of seizures during pregnancy was not associated with any specific ADD. One statistically significant result was found for non-convulsive seizures from seven months to delivery, for atypical ADDs.

## DISCUSSION

Our findings from the APR suggest that among women with epilepsy, including those treated and untreated with AEDs, having depression and/or anxiety with or without treatment with ADDs *does not appear* to increase teratogenicity for the foetus, or affect the occurrence of seizures during pregnancy. To our knowledge, this is the first study to evaluate the teratogenicity of ADDs in WWE, and the association with seizure control, two clinically important issues.

The teratogenicity of prenatal AED exposure is widely known. Exposure carries an inherent risk for major CMs of around 4 to 9%, compared with the background risk of 1% to 2%.<sup>15-18</sup> Of the AEDs, valproic acid is the most well documented teratogen. A meta-analysis which collated 59 studies concerning 65,533 WWE, found an overall risk of 10.73% for MCMs with valproic acid use.<sup>2</sup> These findings accorded with our study where there was an increased malformation rate of almost three-fold in pregnancies exposed to AEDs, compared to those who were not.

On the other hand, the literature on malformation risks of ADDs has been more equivocal. SSRIs are the most common class of ADDs prescribed in developed countries such as Australia, with a prevalence of 80%.<sup>19</sup> Some studies have found no appreciable association of SSRI use during pregnancy with malformation rates,<sup>20-23</sup> whilst others demonstrate the contrary<sup>24, 25</sup>. Of the SSRIs examined in the literature, fluoxetine and paroxetine have been the most noteworthy. In 2005, the Food and Drug Administration (FDA) issued an advisory indicating first-trimester exposure to paroxetine may increase the risk for cardiac defects.<sup>26</sup> Since then, several studies have found significant associations between paroxetine and cardiac CMs,<sup>21, 22, 24, 25, 27, 28</sup> however there are inconsistencies.<sup>23, 29, 30</sup> Similarly, numerous studies have found no association between fluoxetine and CMs,<sup>22, 23, 28, 31, 32</sup> while others again demonstrated contradictory results.<sup>30, 33</sup>

No previous study has examined the risk of taking ADDs in WWE, nor the interaction with AEDs on this risk. This study did not find a significant increased risk of CMs by co-medicating with ADDs, in addition to that of taking an AED. Likewise, there was no significant increased risk of the women having a history of depression and/or anxiety. There was a small absolute increase in the incidence of CMs in women taking ADDs and AEDs

compared to individuals in the non-ADD medicated depression and/or anxiety group and to those without depression or anxiety who were also taking AEDs. It is therefore possible, that a small increased risk was missed due to lack of power, and this argues for the importance of future large-scale studies examining this important issue. Additionally, this study only had three pregnancy outcomes who were exposed to ADDs but not AEDs, and thus a statistically relevant observation about the effects of ADDs alone is not possible.

Despite a longstanding concern amongst clinicians that prescribing ADDs in people with epilepsy may adversely affect seizures control, evidence indicates that the risk of seizures from medicating with SSRIs is low (0.0%-0.4%), and not clearly greater than the incidence of first seizures in the general population (0.07-0.09%).<sup>8, 34</sup> Most women in developed countries with depression are treated with an SSRI drug, as was the experience in this study population. WWE taking ADDs only had statistically more non-convulsive seizures than those not taking ADDs during the last two months of pregnancy. This could be attributed to the fact that during this time, five women belonging to the atypical ADD group, which includes TCAs, had non-convulsive seizures. Furthermore, the seizure occurrence in this time interval was minimal for the other classes of ADDs. TCAs taken at therapeutic doses are thought to have a higher risk (0.4% to 1-2%) of precipitating seizures.<sup>34</sup> In one study, poor seizure control was found to be a risk factor for depression and anxiety.<sup>35</sup> Unfortunately, this study did not assess for a proportional relationship.

Our study not only compared women exposed to ADDs to those without the relevant psychiatric illness, but also to those with non-medicated depression and/or anxiety. Symptomatic depression has risks to the foetus including low birth weight, small for gestational age, preterm delivery, foetal irritability, less activity and attentiveness and fewer facial expressions as well as maternal risks of self-injury, suicide, inadequate self-care and poor compliance with prenatal care.<sup>36-39</sup> Assessing the direct effect of depression and/or anxiety is difficult, as shown by the relative scantiness in data assessing for the teratogenicity of ADDs. There are many reasons for depressed or anxious women not using ADDs. Women could be avoiding taking ADDs due to potential teratogenic properties, have milder affective symptoms, or could be utilizing non-pharmacological management strategies. However, like other studies examining the teratogenicity of ADDs, untreated depression in this study was not associated with CMs.<sup>21, 23, 28</sup> This study also found no association of a history of depression and/or anxiety with birth weight and maternal seizure control.

This study was not without limitations. The telephone questionnaire used in the APR was not primarily designed to collect detailed information regarding psychiatric comorbidities nor were medical records routinely requested. As such, if women responded positively to having depression and/or anxiety, this binary data was recorded and no further questions were asked regarding the nature of the illness, including how it was diagnosed or the severity. Out of 2081 women enrolled in the study, only 94 (4.5%) were on ADDs, which is comparable to one Australian study (4.6%) looking at antidepressant use in pregnancy but is approximately half of the rate found in one large observational study involving over one million pregnant women in the United States.<sup>19, 40</sup> This discrepancy could be explained by varying prescription standards between countries or as one study found, WWE are less likely to be prescribed ADDs when compared to pregnant women without epilepsy.<sup>35</sup> Similarly, only 3.1% of pregnant women had depression listed on their admission record in one study (compared with 7.6% in our study), and they also found 80% of women were dispensed an ADD without a relevant psychiatric comorbidity listed.<sup>40</sup> The difference in the prevalence of depression and/or anxiety could be explained by women in our study over-reporting because they were self-diagnosing based on symptoms or unsure of a diagnosis. Furthermore, data on ADD dosage and changes in dosage throughout pregnancy were incomplete. Although this study was mainly concerned with first-trimester exposure of ADDs, changing dosages during pregnancy could have led to medical interpretations regarding efficacy of treatment and severity of the psychiatric illness. Women with severe symptoms being compared to those with milder symptoms. For example, a diagnosis of depression may be interpreted as major depressive disorder (MDD) but could be confused with dysthymia, a milder and longer lasting form of depression. One study identified a significant relationship between CMs and congenital heart defects *only* when paroxetine was taken at dosages exceeding 25mg/day.<sup>21</sup> As such, defining dosage relationships in this study was not possible.

## **CONCLUSION**

The data reported here represents the first to specifically address the risk for CMs and seizures from co-medicating with ADDs in WWE. Although this study was limited by statistical power, the results indicate that taking AEDs does not appear to confer major teratogenic risk nor does it affect seizure control. This data should be helpful for clinicians

treating and counselling WWE who have depression and/or anxiety, for which an ADD may be indicated. Future research addressing these clinically important questions with a larger cohort of individuals, is warranted to confirm these findings. This would require a collaborative effort from several ongoing prospective database-linked studies and population studies.

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### **DISCLOSURE OF CONFLICTS OF INTEREST**

None of the authors has any conflict of interest to disclose.

### **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.

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**TABLES**

Table 1. Demographic information of women with epilepsy (WWE) with and without antiepileptic drug (AED) treatment, exposed to antidepressant drugs (ADD) and non-medicated depression (DEP) and/or anxiety (ANX).

Maternal demographic information		WWE with AED treatment (n=1912)			WWE without AED treatment (n=169)		
		ADD treated (n=87)	Non-medicated DEP/ANX (n=62)	No DEP/ANX (n=1763)	ADD treated (n=7)	Non-medicated DEP/ANX (n=3)	No DEP/ANX (n=159)
Age	≤20	2 (2.3)	2 (3.2)	34 (19.3)	0 (0)	0 (0)	1 (0.6)
	21-34	64 (73.6)	48 (77.4)	1350 (76.6)	6 (85.7)	3 (100)	121 (76.1)
	≥35	21 (24.1)	12 (19.4)	378 (21.4)	1 (14.3)	0 (0)	37 (23.3)
	Missing values	0(0)	0(0)	1 (0.1)	0 (0)	0 (0)	0 (0)
Employment	Unemployed	29 (30)	13 (21)	349 (19.8)	1 (14.3)	1 (33.3)	22 (13.8)
	Part-time	17 (19.5)	21 (33.9)	472 (26.8)	5 (71.4)	2 (66.7)	49 (30.8)
	Full-time	40 (46)	27 (43.5)	927 (52.6)	1 (14.3)	0 (0)	86 (54.1)
	Missing values	1 (1.1)	1 (1.6)	15 (0.9)	0 (0)	0 (0)	2 (1.3)
Household Income	<50,000	26 (29.9)	13 (21)	358 (20.3)	1 (14.3)	1 (33.3)	21 (13.2)
	>50,000	61 (70.1)	49 (79)	1398 (79.3)	6 (85.7)	2 (66.7)	137 (86.2)
	Missing values	0 (0)	0 (0)	7 (4)	0 (0)	0 (0)	1 (0.6)
Parity	0	37 (42.5)	20 (32.3)	774 (43.9)	3 (42.9)	2 (66.7)	73 (45.9)
	1	24 (27.6)	20 (32.3)	571 (32.4)	4 (57.1)	0 (0)	55 (34.6)
	2	8 (9.2)	4 (6.5)	180 (10.2)	0 (0)	0 (0)	14 (8.8)
	>2	8 (9.2)	5 (8.1)	59 (3.3)	0 (0)	0 (0)	3 (1.9)
	Missing values	10 (11.5)	13 (21)	179 (10.2)	0 (0)	1 (33.3)	14 (8.8)
Number of AEDs	1	65 (74.7)	46 (74.2)	1260 (71.5)			
	2	16 (18.4)	11 (17.7)	415 (23.5)			
	>2	6 (6.9)	5 (8.1)	88 (5)			
Cigarette smoking	0	69 (79.3)	46 (74.2)	1377 (78.1)	6 (85.7)	2 (66.7)	132 (83)
	Ex-smoker	5 (5.7)	5 (8.1)	207 (11.7)	1 (14.3)	0 (0)	18 (11.3)
	1-10/week	0 (0)	0 (0)	2 (0.1)	0 (0)	0 (0)	0 (0)

	<b>1-10/Day</b>	11 (12.6)	6 (9.7)	111 (6.3)	0 (0)	1 (33.3)	8 (5)
	<b>11-20/Day</b>	1 (1.1)	3 (4.8)	49 (2.8)	0 (0)	0 (0)	0 (0)
	<b>21-30/Day</b>	0 (0)	2 (3.2)	14 (0.8)	0 (0)	0 (0)	1 (0.6)
	<b>&gt;30/Day</b>	1 (1.1)	0 (0)	3 (0.2)	0 (0)	0 (0)	0 (0)
<b>Alcohol use</b>	<b>No</b>	73 (83.9)	51 (82.3)	1473 (83.6)	7 (100)	3 (100)	127 (79.9)
	<b>Yes</b>	14 (16.1)	11 (17.7)	290 (16.4)	0 (0)	0 (0)	32 (20.1)
<b>Folic acid use</b>	<b>No</b>	4 (4.6)	7 (11.3)	78 (4.4)	0 (0)	2 (66.7)	16 (10.1)
	<b>Yes</b>	83 (95.4)	55 (88.7)	1683 (95.5)	7 (100)	1 (33.3)	142 (89.3)
	<b>Missing values</b>	0 (0)	0 (0)	2 (0.1)	0 (0)	0 (0)	1 (0.6)

Table 2. Pregnancy outcomes in women with epilepsy (WWE) treated with AEDs.

<b>Pregnancy Outcome</b>	<b>Pregnancy outcomes with AED exposure (n=1954)</b>			<i>p</i> value
	<b>ADD treated (n=88)</b>	<b>Non-medicated DEP/ANX (n=65)</b>	<b>No DEP/ANX (n=1801)</b>	
<b>Congenital Malformation, no. (%), 95% CI)</b>	9 (10.2%, 3.9-16.6)	5 (7.7%, 1.2-14.2)	124 (6.9%, 5.7-8.1)	0.45 <sup>a</sup>
<b>Spontaneous abortion, no. (%)</b>	1 (1.1)	1 (1.5)	55 (3.1)	-
<b>Still birth, no. (%)</b>	1 (1.1)	1 (1.5)	16 (0.9)	-
<b>Induced maternal indication, no. (%)</b>	0 (0)	1 (1.5)	2 (0.1)	-
<b>Live birth without defects, no. (%)</b>	77 (87.5)	57 (87.7)	1604 (89.1)	-
<b>Birth weight (g), median ± IQR</b>	3226±284	3280±830	3355±689	0.25 <sup>b</sup>

<sup>a</sup>Fisher's Exact test<sup>b</sup>Kruskal-Wallis one-way non-parametric test

IQR = inter quartile range

Table 3. Pregnancy outcomes in women with epilepsy (WWE) without AED exposure

Pregnancy Outcome	Pregnancy outcomes <i>without</i> AED exposure (n=170)			p value
	ADD treated (n=7)	Non-medicated DEP/ANX (n=3)	No DEP/ANX (n=160)	
<b>Congenital Malformation, no. (%), 95% CI</b>	1 (14.3%, 0-40.2)	0 (0)	4 (2.5%, 0.1-4.9)	0.27 <sup>a</sup>
<b>Spontaneous abortion, no. (%)</b>	0 (0)	0 (0)	0 (0)	-
<b>Still birth, no. (%)</b>	0 (0)	0 (0)	1 (0.6)	-
<b>Induced maternal indication, no. (%)</b>	0 (0)	0 (0)	0 (0)	-
<b>Live birth without defects, no. (%)</b>	6 (85.7)	3 (100)	155 (97)	-
<b>Birth weight (g), median ± IQR</b>	3585±495	3410*	3460±620	0.53 <sup>b</sup>

<sup>a</sup>Fisher's Exact test

<sup>b</sup>Kruskal-Wallis one-way non-parametric test

IQR = inter quartile range

Table 4. Women with epilepsy (WWE) who had seizure occurrence during pregnancy by seizure type and time period.

Seizure Type	WWE with AED treatment (n=1912)				WWE without AED treatment (n=169)				
	ADD treated (n=87)	Non- medicated DEP/ANX (n=62)	No DEP/ANX (n=1763)	<i>p</i> value <sup>a</sup>	ADD treated (n=7)	Non- medicated DEP/ANX (n=3)	No DEP/ANX (n=159)	<i>p</i> value <sup>a</sup>	
Convulsive Seizures <i>no.</i> (%)	12 months before LMP <i>no.</i> (%)	26 (29.9)	16 (25.8)	545 (30.9)	0.77	2 (28.6)	1 (33.3)	44 (27.7)	1.00
	LMP to enrolment	16 (18.4)	9 (14.5)	245 (13.9)	0.88	0 (0)	0 (0)	34 (21.4)	0.41
	Enrolment to 7 months	12 (13.8)	9 (14.5)	219 (12.4)	0.77	1 (14.3)	0 (0)	29 (18.2)	1.00
	7 months to delivery	7 (8.0)	5 (8.1)	130 (7.4)	0.88	0 (0)	1 (33.3)	12 (7.5)	0.29
Non- convulsive seizures <i>no.</i> (%)	12 months before LMP	26 (29.9)	12 (19.4)	405 (23)	0.44	2 (28.6)	1 (33.3)	31 (19.5)	0.52
	LMP to enrolment	23 (26.4)	10 (16.1)	323 (18.3)	0.15	2 (28.6)	1 (33.3)	28 (17.6)	0.38

<b>Enrolment to 7 months</b>	19 (21.8)	10 (16.1)	309 (17.5)	0.55	1 (14.3)	0 (0)	24 (15.1)	1.00
<b>7 months to delivery</b>	14 (16.1)	6 (9.7)	203 (11.5)	<b>&lt;0.001</b>	1 (14.3)	0 (0)	14 (8.8)	0.62

<sup>a</sup>Fisher's Exact test

Table 5. Women with epilepsy (WWE) who had seizure occurrence during pregnancy.

Seizure Type	WWE with AED treatment (n=1912)				WWE without AED treatment (n=169)			
	ADD treated (n=87)	Non- medicated DEPR/ANX (n=62)	No DEPR/ANX (n=1763)	<i>p</i> value <sup>a</sup>	ADD treated (n=7)	Non- medicated DEPR/ANX (n=3)	No DEPR/ANX (n=159)	<i>p</i> value <sup>a</sup>
<b>Convulsive no. (%)</b>	4 (4.6)	2 (3.2)	57 (3.2)	0.78	0 (0)	0 (0)	4 (2.5)	1.00
<b>Non-convulsive no. (%)</b>	9 (10.3)	4 (6.5)	122 (6.9)	0.45	1 (14.3)	0 (0)	7 (4.4)	0.39

<sup>a</sup>Fisher's Exact test

Table 6. Specific antidepressants drug (ADD) associations with pregnancy outcomes and seizure control in women with epilepsy (WWE) who are treated with antiepileptic drugs (AEDs).

Pregnancy Outcome & Seizures Activity	WWE exposed to ADD and AEDs (n=87)								<i>p</i> value <sup>a</sup>
	SSRI Monotherapy (n=57)					SNRI Monotherapy (n=13)	Others (n=12)	Polytherapy (n=5)	
	Sertraline (n=25)	Paroxetine (n=7)	Fluoxetine (n=5)	Citalopram & Escitalopram (n=20)	Fluvoxamine (n=1)	Venlafaxine & Desvenlafaxine	TCA, MAO, Antipsychotics & Mirtazapine		
<b>Congenital Malformation</b>	3 (12)	0 (0)	0 (0)	4 (19)	0 (0)	0 (0)	2 (16.7)	0 (0)	0.67
<b>Spontaneous abortion</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20)	-
<b>Still birth</b>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.7)	0 (0)	0 (0)	-
<b>Live birth</b>	22 (88)	7 (100)	5 (100)	17* (81)	1 (100)	12 (92.3)	10 (83.3)	4 (80)	-

without defects									
<b>Birth weight (g), median <math>\pm</math> IQR</b>	3350 $\pm$ 808	3010 $\pm$ 670	2790 $\pm$ 497	3087 $\pm$ 286	3310*	3530 $\pm$ 561	3360 $\pm$ 950	3717.5 $\pm$ 749	0.09 <sup>b</sup>
<b>Convulsive seizures 12 months before LMP no. (%)</b>	5 (20)	3 (42.9)	2 (40)	9 (45)	0 (0)	4 (30.8)	3 (25)	0 (0)	0.45
<b>Convulsive seizures from LMP to enrolment</b>	2 (8)	2 (28.6)	1 (20)	5 (25)	0 (0)	3 (23.1)	3 (25)	0 (0)	0.60
<b>Convulsive seizures from enrolment to 7 months</b>	2 (8)	2 (28.6)	2 (40)	2 (10)	0 (0)	0 (0)	4 (33.3)	0 (0)	0.07
<b>Convulsive seizures from 7 months to delivery</b>	1 (4)	2 (28.6)	1 (20)	1 (5)	0 (0)	0 (0)	2 (16.7)	0 (0)	0.20
<b>Non-convulsive seizures 12 months before LMP no. (%)</b>	5 (20)	3 (42.9)	1 (20)	6 (30)	0 (0)	1 (7.7)	7 (58.3)	3 (60)	0.07
<b>Non-convulsive seizures from LMP to enrolment</b>	5 (20)	3 (42.9)	0 (0)	4 (20)	0 (0)	2 (15.4)	6 (50.0)	3 (60)	0.13
<b>Non-convulsive seizures from enrolment to 7 months</b>	3 (12)	3 (42.9)	1 (20)	4 (20)	0 (0)	1 (7.7)	4 (33.3)	3 (60)	0.14
<b>Non-convulsive seizures from 7 months to delivery</b>	1 (4)	2 (28.6)	1 (20)	3 (15)	0 (0)	0 (0)	5 (41.7)	2 (40)	<b>0.02</b>

<sup>a</sup>Fisher's Exact test

<sup>b</sup>Kruskal-Wallis one-way non-parametric test

IQR = inter quartile range

\*One individual was medicating with Citalopram/Escitalopram had a twin pregnancy, and thus the total pregnancy outcomes add to 21 not 20.