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Pregnancy with epilepsy: obstetric and neonatal outcome of a controlled study

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Abstract

Purpose—to determine the influence of epilepsy and its treatment on pregnancy and its outcome.

Design—controlled, observational study.

Setting—National Health Service maternity hospitals in Liverpool and Manchester regions.

Population—277 women with epilepsy (WWE) and 315 control women.

Methods—WWE were recruited from antenatal clinics. Controls were matched for age and parity but not gestational age. Information was obtained by interview and from clinical records. Main Outcome Measures: obstetric complications, mode of delivery, condition of newborn.

Results—Distribution of epilepsy syndromes was similar to previous surveys. Most WWE (67%) received monotherapy with carbamazepine, sodium valproate or lamotrigine. Half WWE had no seizures during pregnancy but 34% had tonic clonic seizures. Seizure related injuries were infrequent. Pregnancies with obstetric complications were increased in women with treated epilepsy (WWTE 45%, controls 33%; p = 0.01). Most had normal vaginal delivery (WWTE 63%, controls 61%; p = 0.65). Low birth weight was not increased (WWTE 6.2%, controls 5.2%; p = 0.69). There were more major congenital malformations (MCM) (WWTE 6.6%, controls 2.1%; p = 0.02) and fetal/infant deaths (WWTE 2.2%, controls 0.3%; p = 0.09). Amongst monotherapies MCM prevalence was highest with valproate (11.3%; p = 0.005). Lamotrigine (5.4%; p = 0.23) and carbamazepine (3.0%; p = 0.65) were closer to controls (2.1%). There was no association between MCM and dose of folic acid preconception.

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**See the appendix for a complete list of Group members

Statement of conflict of interest

G.A. Baker, R. Bromley, J. Clayton-Smith, U. Kini and G. Mawer have each given expert testimony on fetal anticonvulsant syndrome. G.A.B. has received educational grants from Sanofi Aventis to support this research. The remaining Authors have no conflicts of interest to disclose.

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Conclusion—MCM were more prevalent in the babies of WWTE particularly amongst those receiving sodium valproate.

Keywords

Epilepsy; Antiepileptic drugs; Pregnancy outcome; Teratogenicity

1. Introduction

Women with epilepsy (WWE), who are considering pregnancy, may have concerns about worsening of seizures, obstetric complications, abnormal delivery and malformations in their children. Previous research has shown that most WWE experience no increase in seizures during pregnancy.[1-7] Several authors[8-11] have found increased prevalence of specific complications including vaginal bleeding, anaemia, vomiting, urinary infection, hypertension and breech presentation. Others concluded that most WWE have uncomplicated pregnancies.[3, 4, 6] Increased caesarean section rate,[2, 8] pre-term delivery and low birth weight[4, 9, 10] have been reported.

There is a 2-3 fold increase in major congenital malformations (MCM) in babies of WWE treated with a single antiepileptic drug (AED) during pregnancy.[12] Higher rates have been reported with sodium valproate.[6, 13 - 17] A review[18] of several studies found increased stillbirth and neonatal death in pregnancy with epilepsy but this was not replicated in two recent studies.[2, 11] Increased maternal mortality during and soon after pregnancy is also recognised.[4, 19]

This paper reports on the pregnancies, deliveries and immediate outcomes in a study of WWE. Unlike many previous studies it utilises a control group of women without epilepsy recruited specifically for the purpose. The number of women recruited also allows for important statistical and clinical differences to be observed.

2. Methods

This was an observational study. The investigators played no part in clinical management. WWE were recruited from antenatal clinics at 11 National Health Service (NHS) hospitals within Merseyside and Greater Manchester between 2000 and 2006. Midwives in the antenatal clinics approached each woman, who gave a history of epilepsy, whatever her stage of gestation. An information sheet was provided with a verbal explanation of the project. The research nurse then made contact by phone, gave more detail, posted the consent form and arranged to meet the WWE as soon as possible. All consenting WWE were followed up but those with chronic medical conditions predisposing to abnormality in the child and those with an earlier pregnancy in the study are not included in this report.

The longer-term objective of this 6-year study is to monitor a cohort of children born to WWE and a corresponding cohort of children born to mothers without epilepsy. By comparing the physical and cognitive development of the two groups it is hoped to assess the impact of in utero exposure to different AED. Using the Differential Ability Scale as the primary outcome measure and seeking 80% power at a 95% confidence level to detect a difference of 1.5 SD, it was estimated that 45 children were required in each monotherapy group. To allow for fetal deaths and withdrawals the recruitment target became a minimum of 50 pregnancies in each monotherapy group.

WWE receiving monotherapy with carbamazepine (CBZ), lamotrigine (LTG) or valproate (VPA) were also invited to join an NIH funded, multi-centre study (Neurodevelopmental Effects of Antiepileptic Drugs; NEAD) which compares outcomes with different AED. Some

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results from children of these women have been published previously.[6, 20, 21] The NEAD study excludes women on polytherapy and does not incorporate a control group of women without epilepsy.

Women without epilepsy were recruited from the same NHS hospital antenatal clinics. The research nurse after interviewing each WWE searched through the records of healthy women, who attended the clinic on the same day or a few days later. The aim was to find a woman control, who matched each WWE for age (within a five-year band), for parity, for residential district (postal code) and employment. Since the WWE and the healthy woman controls were attending the same clinic at about the same time it was assumed that there would be no systematic difference in gestational age. This assumption proved to be incorrect.

Antenatal and obstetric care outside the NHS is rare in the UK particularly for WWE but even within the NHS, WWE and healthy women follow different patterns of antenatal care. Both groups usually present themselves to their General Medical Practitioner for health care during the pregnancy but thereafter the management is different. A pregnant WWE is typically referred directly for hospital-led antenatal care, whereas a potential 'control' woman with no medical history is typically referred to the community mid-wife service often based in the local medical practice. Thus hospital midwives often meet WWE during the first trimester or early in the second, whereas they commonly meet women without epilepsy first at the 19-21 week scan. This phenomenon has created within this study a systematic difference between WWE and women controls with respect to gestational age at recruitment.

There was no payment to women for study visits to hospital beyond expenses for travel and refreshments. Nevertheless, it was expected that a high proportion of WWE would take part. Acceptance amongst control women was expected to be about 50%. Research nurses therefore approached two potential control subjects for each WWE.

At her first meeting with each newly recruited subject the research nurse took a personal and medical history in accordance with the prospectively designed Patient Basic and Control Basic Record Forms. Questions covered education, occupation, welfare benefits and lifestyle issues such as use of tobacco and alcohol. Previous miscarriages and terminations were recorded but the reasons for termination were not ascertained. The Patient Basic Forms also covered seizure history and details of the clinical units and physicians involved in the investigation and treatment of the epilepsy. An epilepsy specialist (G.M.) confirmed seizure type, syndrome diagnosis, current seizure frequency and antiepileptic medication. Information from the patient was supplemented from clinical records.

The epilepsy syndrome was classified as symptomatic/cryptogenic focal (localisation-related) or idiopathic generalised (IGE). When uncertain whether tonic clonic seizures were primary or secondarily generalised, the epilepsy was unclassified. Seizures were recorded as tonic clonic or non-convulsive (simple/complex partial, myoclonic, absence). Frequency was ascertained from the patient and an observer, if available, since not all WWE kept seizure diaries. Seizure-related injuries and hospital admissions were noted. Seizures after delivery were not recorded.

Details of each pregnancy were recorded in prospectively designed Patient and Control Pregnancy & Delivery Record Forms. These were filled in partly at a meeting with the research nurse during later pregnancy, often on the day of an ultrasound scan. The remainder was filled in after delivery, if possible before discharge from the maternity unit. Failing this the information was obtained by phone. The forms covered AED medication, the timing of dosage changes, nutritional supplements, presence of specific complications of pregnancy, investigations, attendance for ultrasound scans, the delivery and the immediate outcome. The occurrence of seizures, injuries and emergency admissions were recorded on the Patient Forms.

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Obstetric records were studied for details of complications, reports of ultrasound scans, fetal presentation and mode of delivery.

Condition at birth (Apgar score, neonatal problems, need for special care, birth weight) was recorded on the First Paediatric Assessment Form. Congenital abnormalities were identified from reports of fetal scans and paediatric medical examination of the baby before discharge. Length, occipito-frontal circumference and details of physical examination were recorded. Some congenital abnormalities were not identified until later during follow up, which is continuing up to 6 years. These have also been included. Major malformations (MCM) were distinguished from minor anomalies using Eurocat instructions for the Surveillance of Congenital Abnormalities.[22] MCM in babies with chromosome abnormalities were not included in the analysis of possible adverse effects of AED.

The study was conceived and designed as a prospective study. The content of the Basic Form however related mainly to the previous medical history and was clearly retrospective. The content of the Pregnancy & Delivery Form was mixed. The data on pre-conceptual dosage of AED and folate related to the time before recruitment and was retrospective. Data on mode of delivery was prospective. The point of transition between the recording of past history and of events as they happened depended on the date of recruitment. Since a substantial proportion of WWE and most women controls were recruited in the second and third trimester, the term prospective has not been applied to the early results of this 6 year long study.

Physical examination and cognitive function assessments of each child were repeated at 1-2 years, 3 and 6 years. Details of the examinations, test batteries and Record Forms are beyond the scope of the present report.

The WWE were divided into two groups 1) those with ‘treated epilepsy’ (WWTE), who were taking AED to prevent seizures and 2) those with ‘untreated epilepsy’ (WWUTE), who were taking no AED. The treated group was expected to have a poorer outcome in terms of complications and MCM. Its results have been presented separately to avoid bias towards a good outcome arising from inclusion of the untreated group that was expected to resemble the control group. A similar approach was adopted by Viinikainen et al[7].

Differences between groups were expressed as Odds Ratios (OR) with 95% Confidence Intervals (CI). Explicit p values were derived from Chi^2 test, or Fisher’s exact test for small samples. Unpaired t-test was used to compare continuous variables. Mann Whitney U test was used to compare variables not normally distributed. When repeated tests were applied to related features (obstetric complications) the effect of a multiple test correction (Bonferroni) was noted. Discriminant analysis (Wilks lambda) was used to identify and rank variables that were significant discriminators for MCM. Subject variables were converted to binary form for this analysis to ensure the samples were from multivariate normal populations and had equal variance-covariance matrices (Box’s M). Thus, for example, maternal age was recorded as below or above the study population mean, and gestational age at recruitment was recorded as early (up to 20 weeks, before anomaly scan) or late (more than 20 weeks, after anomaly scan). Because WWE and women controls were not matched for gestational age, particular attention has been given to the influence of this variable. Tests were accessed through Confidence Interval Analysis for Windows and SPSS version 16 for Windows. Missing data below 10% was ignored.

3. Results

WWE (277) were recruited between 7 and 38 weeks gestation with 169 (61%) in the first 20 weeks and 108 (39%) thereafter. The distribution was uni-modal with the peak frequency of enrolment between 9 and 16 weeks. Women controls (315) were recruited between 8 and 39

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weeks with 101 (32%) in the first 20 weeks and 214 (68%) thereafter. The distribution was bi-modal with one peak between 19 and 22 weeks and a second between 26 and 33 weeks. Acceptance rates amongst WWE and control women were estimated as 80% and 60% respectively. Three years into the study 84 872 women had given birth in the participating hospitals and from that population 231 pregnant WWE had been recruited (2.72 per thousand). The number of WWE receiving CBZ monotherapy was well above the target and subsequent recruitment was narrowed to those receiving VPA or LTG. Three WWE were excluded from this report because of neurofibromatosis, tuberous sclerosis and heroin addiction.

One hundred and eight (39%) of the WWE also actively participated in the NEAD study.[6, 20, 21] The first of the NEAD reports focussed on serious adverse outcomes (MCM and fetal death) in the offspring of WWTE on monotherapy. Four of the babies with MCM reported here were described in that report. [6] These are identified by the footnote[b] in Table 5. No other information from this study has been published earlier.

WWE (mean 27.4 years) were a little younger than control women (mean 28.7 years), difference 1.3 (95% CI 0.41 – 2.25; p = 0.005). There was no difference in parity between WWE (0:1:2:3 or more = 143:90:23:22) and controls (174:94:34:13) (Chi^2 5.27, degrees of freedom 3; p = 0.15).

3.1. Epilepsy and AED usage

Half of the WWE had no seizures during their pregnancy. This proportion remained high (46%) even if WWUTE were excluded. Fourteen per cent had non-convulsive seizures only but a third experienced tonic clonic seizures (see Table 1). The most frequent syndrome diagnosis was symptomatic/cryptogenic focal epilepsy. Amongst those with IGE, 1 in 5 women had juvenile myoclonic epilepsy.

Thirty-four women attended hospital in seizure-related emergencies. These women were all experiencing tonic clonic seizures. Most were allowed home after a few hours observation, which included fetal monitoring. Ten were observed overnight and two for several days. Four women were observed overnight on 2 or more occasions. One woman needed suture of a head wound. None were in convulsive status.

There were 46 WWUTE (17%) who took no AED before or during pregnancy (see Table 1). Their syndrome diagnoses were focal (17), idiopathic generalised (15) and unclassified (14). Twenty-three had been free from seizures for more than 2 years and 10 for more than 10 years. Seven continued to experience non-convulsive seizures (absences 2, simple or complex partial 5). Twelve had a history of infrequent tonic clonic seizures; of these only one had such seizures during the pregnancy.

Most WWE (67%) received one AED only. CBZ (range 100 – 1 600 mg/day; median 600) was prescribed mainly when the epilepsy was focal (see Table 1). VPA (range 200 – 3 000 mg/day; median 900) was prescribed mainly for WWE with IGE. LTG (range 50 – 800 mg/day; median 200) was prescribed equally for WWE with either diagnosis.

Polytherapy (two or more AED) was prescribed for 46 WWE (17%). In 26 this included VPA giving a total of 83 WWE prescribed VPA as mono- or poly-therapy. Thirty-nine of these were prescribed 1 000 mg/day or more.

Ninety-seven WWE (35%) had drug treatment changes during pregnancy. Forty women on monotherapy had their AED dose raised; fifteen had their dose lowered and in 14 the AED was stopped. Fifteen women on polytherapy had treatment increased and 7 had treatment reduced. Five had one AED substituted for another and one woman had her three AEDs withdrawn.

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Most (32/40) of those in whom monotherapy was increased had experienced seizures (23 convulsive) during the pregnancy.

The number of women in the different treatment groups, who had one or more tonic clonic seizures, is shown in Table 1. In general fewer women had convulsive seizures during the second half of pregnancy (21 weeks to term) than in the first 20 weeks. This did not apply to those on LTG or to those on polytherapy.

Before conception a folic acid supplement at high dose (4 or 5 mg/day) was taken by 91 WWE (32.9%). In the remainder the dose was the standard nutritional daily requirement of 0.4 mg (9.0%), none (55.6%) or unknown (2.5%).

3.2 Obstetric complications and mode of delivery

Pregnancies with obstetric complications were more frequent in WWTE but no single complication was increased significantly (see Table 2). WWUTE (30.4%)(14/46) resembled controls ($p = 0.87$). The higher frequency of vaginal bleeding in WWTE (15.7%, controls 9.6%; $p = 0.05$) was not significant after Bonferroni correction for multiple tests (p value for significance 0.01). Most bleeding (70-80%) occurred in the first half of pregnancy. Ante-partum haemorrhage was reported twice in WWTE and in controls.

Vaginal bleeding was most prevalent in the WWTE who received polytherapy (21.7%, 10/46, controls 9.6%, 30/311; $p = 0.02$). The frequencies with VPA (19.3%, 11/57; $p = 0.04$) and CBZ (17.6%, 13/74; $p = 0.06$) were similar. The frequencies with LTG (2.5%, 1/39) and other monotherapies (7.1%, 1/14) were low. The frequency of vaginal bleeding was higher in women recruited later (after 20 weeks gestation) than in women recruited later; this applied both to WWTE (late 20.0%, early 12.9%; $p = 0.19$) and to women controls (late 10.3%, early 8.2%; $p = 0.68$). In neither case was the difference significant.

There was no significant increase in other complications in the WWTE. Raised maternal alpha-fetoprotein, oligo-/poly-hydramnios, cholestasis, gestational diabetes and prolonged rupture of membranes, were each infrequent (<2%) and not amenable to confidence interval analysis. Probabilities of differences ranged from $p = 1.00$ for poly-hydramnios to $p = 0.24$ for prolonged rupture of membranes (Fisher's exact test).

Most WWTE (62.8%) and controls (60.5%) had normal vaginal deliveries (see Table 2). Women with untreated epilepsy were similar (68.9%) (31/45). There were no significant differences in abnormal deliveries between WWTE and controls. Most of the babies presenting by the breech in each group were delivered by caesarean section.

3.3 Newborn

Gestational age at birth (range 29 – 42 weeks: mode 40) was similar in the babies of WWTE and controls ($p = 0.14$; Mann Whitney U test) and the difference in mean birth weights was small (WWTE 3.32 kg, controls 3.42 kg ; difference – 0.10 kg, 95% CI –(0.001 – 0.20) $p = 0.05$). There were no significant differences (see Table 3) in the frequencies of pre-term or low birth weight babies, those with birth weights at or below the 9th centile, or those admitted for special care. The babies of WWUTE did not differ from controls with respect to gestational age at birth ($p = 0.19$) or birth weight ($p = 0.72$).

3.4 Major malformations and deaths

The prevalence of MCM amongst babies of WWTE (6.6%) was greater than amongst control babies (2.1%) (see Table 4). The highest prevalence (16.7%) was in babies exposed to VPA within polytherapy. This was followed by VPA as monotherapy (11.3%). When all babies

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exposed to VPA (as mono- or poly-therapy) were excluded, the MCM amongst those exposed to other AEDs fell to 3.0%, which did not differ from the level in control babies. The babies of WWUTE (AED none) did not differ from controls.

The prevalence of MCM in offspring exposed to higher doses of VPA (> 1000 mg/day) as monotherapy was 16.0% (4/25) compared with 7.1% (2/28) at doses below 1000 mg/day but the difference was not significant (p = 0.40; Fisher's Exact test). The prevalence of MCM after exposure to LTG (5.4%, 2/37) was higher than that after CBZ (3.0%, 2/66) but neither differed significantly from the control level of 2.1% (see Table 4). Babies of WWTE, who had taken high dose folic acid pre-conception, had MCM prevalence of 6.25% (5/80) compared with 6.29% (9/143) (OR 0.99, CI 0.32 –3.07; p = 1.00) in babies, whose mothers had taken the lower dose or none.

Individual malformations are listed with pre-conception doses of AED and/or folic acid in Table 5. Three MCM were detected well after birth. The atrial septal defect (Table 5) was diagnosed and corrected by surgery in the second year; during surgery a diaphragmatic defect was found and repaired. The clubfoot was detected at pre-natal scan but not diagnosed as a major malformation until early treatments had failed and surgical correction became necessary. Hydronephrosis in the child of a WWE on no AED was detected at two years during investigation for recurrent urinary tract infection.

The baby with spina bifida (Table 5, column 1) had hypospadias and radial ray defects in addition to a sacral meningomyelocele. Four babies with MCM (3 WWTE, 1 control) had chromosome abnormalities and were not included in the comparisons of outcome between different AED.

In the WWTE 6 of 18 MCM were identified on ultrasound scan before birth (see Table 5). Four of these were routine and two were extra scans. Only 1 in 8 of the cardiovascular MCM was detected by ultrasound. In the control women 3 of 7 MCM were detected by routine scans. One pregnancy only in the WWTE was terminated. This was because of intense maternal anxiety about possible adverse effects of exposure to VPA. The mother's decision was not based on the result of a scan.

In the search for features that discriminate for MCM, 21 variables were considered. These included maternal age, multi-parity, gestational age at recruitment, family history of MCM, employment, complicated pregnancy, convulsive seizures, AED (CBZ, VPA or LTG), treatment change, high dose folate pre-conception, alcohol and smoking.

Stepwise discriminant analysis, applied to the total subject population (WWE and Controls), identified a solution set of significant discriminators in order of decreasing importance with respect to MCM; these were treatment with VPA (standardised discriminant coefficient (SDC) = 0.69), complicated pregnancy (SDC = 0.60), convulsive seizures (SDC = 0.43), multi-parity (SDC=0.42). These were included in the solution set of discriminators by an F to enter >= 3.84. All other variables had an F to enter of less than 3.84 and were thus excluded from the solution set. Gestational age at recruitment was not a significant discriminator and when entered into a single step discriminant equation with the solution set variables, its SDC was 0.04 compared to 0.69 for VPA. The values of SDC quoted above were obtained from the discriminant function using the solution set of variables and gestational age. The discriminant function using only the solution set variables gave slightly larger values to the SDC, for example, VPA (SDC= 0.70).

Five pregnancies in WWTE (5/226 = 2.2%) ended in death, one by termination (referred to above), two by stillbirth, one by cot death in the first week and one from heart failure during the first year. In two cases the in utero exposure was to VPA and in three to CBZ . In the control

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group there was one stillbirth (1/310 = 0.3%; p = 0.09, Fisher's exact test). In the untreated epilepsy group there was one late miscarriage giving 6 deaths in the offspring of WWE as a whole (6/272 = 2.2%, p = 0.05). There were 2 maternal deaths during the early infancy of the child, one seizure-related amongst WWE and one road traffic accident amongst controls.

4. Discussion

All the women recruited into this study had already begun to attend NHS clinics for their antenatal care. The WWE were not under the care of the investigators but were identified by NHS midwives in their routine work. They introduced them to the study and invited them to meet the research nurses. This inclusive approach is believed to have yielded a broad population of pregnant WWE that does not exclude those with less organised lives, who have failed to access specialist epilepsy services. The proportion of 2.7 WWE recruited per thousand recorded births was less than the widely accepted population prevalence of 3 - 5 WWE per thousand pregnancies.[23] Nevertheless the proportion recruited was considered large enough to be representative of the whole.

The broad spread of gestational age at recruitment does however mean that a variable amount of information about the pregnancy was obtained by retrospection. Equally the later recruitment of women controls means that differences due to gestational age at recruitment could be confounded with differences due to treated epilepsy.

It is possible that some pregnant women, who were potential subjects for this study, had terminations for fetal abnormalities found on ultrasound scan (19 - 21 weeks) and were therefore no longer available for recruitment. This would lead to underestimation of major congenital malformations (MCM) in WWE but more particularly in controls, since the proportion of women recruited after 20 weeks was greater in the control group.

The incidence of termination of pregnancy for fetal malformation in pregnant women without epilepsy has been reported as 0.16% (3 terminations in 2,206 pregnancies[20]). It is unlikely therefore that any women had been removed by earlier termination from the group of 214 control subjects recruited after 20 weeks gestation in this study. The possibility cannot be excluded however.

There were no known terminations for malformation in this study even in the nine cases (Table 5, footnote [a]) where MCM were detected by prenatal ultrasound. All the MCM amongst controls were found in women who had entered the study after 20 weeks. The observed prevalence of MCM in the offspring of controls (2.1%, Table 4) accords well with the incidence of births with congenital malformations in healthy women obtained by meta-analysis of 16 published studies (2.28%; CI 1.46 – 3.10).[20] The authors are therefore satisfied that underestimation of MCM in control pregnancies is unlikely to have occurred.

The distribution of epilepsy syndromes in this study (see Table 1) was very similar to that found by Gaily et al (2004).[24] Half the WWE (52%) had no seizures during the pregnancy. This is consistent with recent studies, which give the proportion of WWE seizure-free throughout pregnancy as 30 – 80%.[2 -7] Seizure-related trauma was uncommon and there was no evidence of resulting harm to the fetus.

Most WWE (66.5%) received one AED only. Whilst broadly in line with accepted guidelines[25, 26] this is lower than the monotherapy rate (70 - 90%) reported in recent studies.[7, 16, 27] The main drugs taken, CBZ, VPA and LTG, match those reported by the UK Epilepsy and Pregnancy Register.[16] The large number of WWE with changes in AED treatment during pregnancy (35%) was unexpected and no one cause is known. It is suspected that in some cases AED doses were reduced before conception and increased during pregnancy when seizures

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recurred. Avoidance, if possible, of VPA doses above 1 000 mg/day has been recommended.[25] Fourteen WWE on VPA monotherapy received doses above 1 000 mg/day. Four of these women had no tonic clonic seizures during pregnancy and may therefore have been suitable for dose reduction before conception.

It was expected that the WWUTE (17%), who remained largely seizure-free, would have the same outcome to pregnancy as the control group. This has proved to be so. There were no significant differences with respect to pregnancy complications, mode of delivery, gestational age and weight at birth or prevalence of MCM. To avoid bias towards a good outcome the results from the women with treated epilepsy (WWTE) have been presented separately.

In obstetric terms the similarities between WWTE and controls were more impressive than the differences. Pregnancy without complication culminating in a normal vaginal delivery was the most common sequence in each. There was however a significant increase in pregnancies with complications in WWTE compared with controls. This was attributable mainly to the increase in vaginal bleeding. This increase failed to attain significance after correction for multiple tests but it has also been found in other studies.[9, 10] We have not found the reported increases in urinary infection,[10] hypertension,[9, 11] breech presentation,[8] caesarean section[2, 8] or pre-term delivery.[4, 9, 10] We found no increase in babies that were unusually small.[2, 7, 28]

The impressive differences between WWTE and controls related to the serious adverse outcomes of MCM and death. The 6.6% prevalence of MCM amongst all recorded live births in WWTE (Table 4) was consistent with the 7.1% (CI 5.6-8.5) obtained by meta-analysis of 79 published studies.[20] The level of agreement suggests that underestimation of MCM arising from the extension of recruitment beyond 20 weeks gestation is unlikely. There were no terminations for MCM. The strongest discriminator for MCM was exposure to VPA. This is consistent with other reports.[6, 13 - 17, 29] The mortality amongst the offspring of WWTE was also higher but there was no particular association between a fatal outcome and exposure to VPA. Increased perinatal mortality has been reported previously.[18]

Cardiovascular MCMs were relatively frequent in the babies of WWTE but the proportion detected by pre-natal ultrasound was low. There may be a case for an extra scan in WWTE at a later stage of gestation, when the heart can be visualised in more detail.

A third of WWTE took high dose folic acid before conception but this was not associated with a lower prevalence of MCM. This is consistent with results from the UK Epilepsy and Pregnancy Register.[30] Folic acid supplementation, mainly at high dose, did however reduce spontaneous miscarriage in WWE receiving VPA.[31]

There have been few controlled studies with the newer AEDs in pregnancy. The outcome in WWTE on LTG monotherapy was therefore of particular interest. The prevalence of MCM did not differ significantly from the level in controls (Table 4) but confidence in this observation is limited by the modest group size. The number of WWTE taking LTG was less than planned but the observed prevalence of MCM corresponded with that reported for doses above 200 mg/day by the UK Epilepsy and Pregnancy Register.[16]

Our results have implications for pre-conceptual counselling. In patients with focal epilepsy CBZ and VPA have comparable efficacy.[32] The available evidence would encourage a woman receiving VPA for focal epilepsy to change to CBZ before conception. The choice for a woman with IGE is less clear. Both VPA and LTG are effective against IGE[33] although VPA proved more efficacious than LTG in a recent randomised controlled trial[34] and other studies have shown LTG to be less effective particularly against absence and myoclonic seizures.[33, 35, 36] Leaving aside newer AEDs, with which there is not yet sufficient pregnancy experience, she

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might choose to stay on VPA at a reduced dose or to change to LTG. Either of these changes could allow seizures to recur.

The authors recognise the need for prospective studies of sufficient size, and with a matched control group, that focus not only on the immediate outcome of pregnancy but also on the development of the child in the longer term. Our retrospective studies have suggested that cognitive development can be impaired.[38], 39 This paper relates to the first phase of a prospective study in which the later development of the children is being monitored into the school years and will be reported on in subsequent papers.

5. Conclusions

Amongst the women with epilepsy a third had convulsive seizures but these did not increase as pregnancy advanced. Overnight stay in hospital was uncommon and physical injury was rare. Pregnancies with complications were more common but most women had a normal delivery.

Major congenital malformations were increased, particularly when the fetus had been exposed to valproate. Fetal/infant deaths were increased. They were not particularly associated with exposure to any one antiepileptic drug.

Appendix

Liverpool and Manchester Neurodevelopment Group. Alder Hey Children's Hospital, Liverpool, UK: Alan Fryer, MD, Rachel Kneen, MD; Liverpool University, UK: Gus Baker, PhD, Rebecca Bromley, BSc, Pete Dixon, PhD , Joanne Eatock, BA, Alison Gummery, BSc, Rebekah Shallcross, BSc; St Mary's Hospital, Manchester UK: Siddharth Banka, MRCP(Ch), Maria Briggs, RGN, Deirdre Cilliers MD, Jill Clayton-Smith, MD, Helen Coyle, MPhil, Usha Kini, MD, Mila Kuzmyshcheva, BS, Kathryn Leask, MBChB, Sam Lucas, PhD, George Mawer, FRCP(E), PhD, Audrey Smith, MD; Walton Centre for Neurology and Neurosurgery, Liverpool, UK: David Chadwick, MD, Loretta Kerr, Kate O'Hanlon, RGN, Lynne Owen, EPTA, Gilla Veling-Warnke, MD, Lynne Wyatt, BSc.

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Statistical Analysis

Conducted by S.B. Lucas, PhD, Former Director, Faculty of Medicine Computational Group, University of Manchester, Manchester UK.

Details of Ethics Approval

Full ethics committee approval for the study was obtained from the NW Main Research Ethics Committee in 1999 (Reference Code MREC 99/8/15) and from the Local Research Ethics Committees covering the 11 NHS maternity hospitals in the Manchester and Liverpool regions from where the women with epilepsy and the women controls were recruited.

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References

1. Delgado-Escueta AV, Janz D. Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy. Neurology 1992;42:149–160. [PubMed: 1574171]
2. Olafsson E, Hallgrimsson JT, Hauser WA, Ludvigsson P, Gudmundsson G. Pregnancies of women with epilepsy: a population-based study in Iceland. Epilepsia 1998;39:887–892. [PubMed: 9701382]
3. Al Bunyan M, Abo-Talib Z. Outcome of pregnancies in epileptic women: a study in Saudi Arabia. Seizure 1999;8:26–29. [PubMed: 10091844]
4. Fairgrieve SD, Jackson M, Jonas P, Walshaw D, White K, Montgomery TL, Burn J, Lynch SA. Population based, prospective study of the care of women with epilepsy in pregnancy. British Medical Journal 2000;321:674–675. [PubMed: 10987772]
5. EURAP. Seizure control and treatment in pregnancy: Observations from the EURAP epilepsy and pregnancy registry. Neurology 2006;66:354–360. [PubMed: 16382034]
6. Meador KJ, Baker GA, Finnell RH, Kalayjian LA, Liporace JD, Loring DW, et al. NEAD Study Group. In utero antiepileptic drug exposure: fetal death and malformations. Neurology 2006;67:407–412. [PubMed: 16894099]
7. Viinikrainen K, Heinonen S, Eriksson K, Kalviainen R. Community-based, prospective controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. Epilepsia 2006;47:186–192. [PubMed: 16417548]
8. Robertson IG. Breech presentation associated with anticonvulsant drugs. Journal of Obstetrics and Gynaecology 1984;4:174–177.
9. Wilhelm J, Morris D, Hotham N. Epilepsy and pregnancy – a review of 98 pregnancies. Australian and New Zealand Journal of Obstetrics and Gynaecology 1990;30:290–295. [PubMed: 2082882]
10. Laskowska M, Leszczynska-Gorzelak B, Oleszczuk J. Pregnancy in women with epilepsy. Gynecologic and Obstetric Investigation 2001;51:99–102. [PubMed: 11223702]
11. Richmond JR, Krishnamoorthy P, Andermann E, Benjamin A. Epilepsy and pregnancy: an obstetric perspective. American Journal of Obstetrics and Gynecology 2004;190:371–379. [PubMed: 14981376]
12. Iheanacho, I., editor. Drug and Therapeutics Bulletin. Vol. 43. 2005. Anti-epileptics, pregnancy and the child; p. 13-16.
13. Canger R, Battino D, Canevini MP, Fumarola C, Guidolin L, Vignoli A, et al. Malformations in offspring of women with epilepsy: a prospective study. Epilepsia 1999;40:1231–1236. [PubMed: 10487185]
14. Vajda FJ, O'Brien TJ, Hitchcock A, Graham J, Lander C. The Australian registry of antiepileptic drugs in pregnancy: experience after 30 months. Journal of Clinical Neuroscience 2003;10:543–549. [PubMed: 12948456]
15. Vajda FJ, O'Brien TJ, Hitchcock A, Graham J, Cook M, Lander C, et al. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of antiepileptic drugs in pregnancy. Journal of Clinical Neuroscience 2004;11:854–858. [PubMed: 15519862]
16. Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. Journal of Neurology Neurosurgery and Psychiatry 2006;77:193–198.
17. Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB. Antiepileptic Drug Register. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology 2005;64:961–965. [PubMed: 15781808]
18. Teramo, K.; Hiilesmaa, VK. Pregnancy and fetal complications in epileptic pregnancies: review of the literature. In: Janz, D.; Dam, M.; Richens, A.; Bossi, L.; Helge, H.; Schmidt, D., editors. Epilepsy, Pregnancy, and the Child. New York: Raven Press; 1982. p. 53-59.
19. CEMACH. Why Mothers Die (2000-2002). London: CEMACH; 2004. Report of confidential enquiries into maternal and child health in the United Kingdom; p. 187-188.

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20. Meador KJ, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: A systematic review and met-analysis of published pregnancy registries and cohorts. Epilepsy Research 2008;81:1–13. [PubMed: 18565732]
21. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. New England Journal of Medicine 2009;360:1597–1605. [PubMed: 19369666]
22. EUROCAT. Central Registry. Instructions for the Registration and Surveillance of Congenital Anomalies. 2005. www.eurocat.ulster.ac.uk
23. Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: Management issues for women with epilepsy (summary statement) Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2005;51:944–948.
24. Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M, Matila R, Kotila M, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 2004;62:28–32. [PubMed: 14718692]
25. Wallace, H.; Shorvon, SD.; Hopkins, A.; O'Donoghue, M. Guideline Development Group. Adults with poorly controlled epilepsy. London: Royal College of Physicians; 1997. Contraception and pregnancy; p. 19-23.
26. Crawford P, Appleton R, Betts T, Duncan J, Guthrie E, Morrow J. The Women with Epilepsy Guidelines Development Group. Best practice guidelines for the management of women with epilepsy. Seizure 1999;8:201–217. [PubMed: 10452918]
27. Wide K, Winbladh B, Kallen B. Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid: a nation-wide population-based register study. Acta Paediatrica 2004;93:174–176. [PubMed: 15046269]
28. Hvas CL, Henriksen TB, Ostergaard JR, Dam M. Epilepsy and pregnancy: effect of antiepileptic drugs and lifestyle on birth weight. British Journal of Obstetrics and Gynaecology 2000;107:896–902. [PubMed: 10901562]
29. Bromfield EB, Dworetzky BA, Wyszynski DF, Smith CR, Baldwin EJ, Holmes LB. Valproate tetatogenicity and epilepsy syndrome. Epilepsia 2008;49:2122–2124. [PubMed: 18557775]
30. Morrow JI, Hunt SJ, Russell AJ, Smithson WH, Parsons L, Robertson I, et al. Folic acid use and major congenital malformations in offspring of women with epilepsy. A prospective study from the UK Epilepsy and Pregnancy Register. Journal of Neurology Neurosurgery and Psychiatry 2009;80:506–511.
31. Pittschieler S, Brezinka C, Jahn B, Trinka E, Unterberger I, Dobesberger J, et al. Spontaneous abortion and the prophylactic effect of folic acid supplementation in epileptic women undergoing antiepileptic therapy. J Neurology 2008;255:1926–1931.
32. Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalised tonic clonic seizures. New England Journal of Medicine 1992;327:765–771. [PubMed: 1298221]
33. Nicolson A, Appleton RE, Chadwick DW, Smith DF. The relationship between treatment with valproate, lamotrigine, and topiramate and the prognosis of the idiopathic generalised epilepsies. Journal of Neurology Neurosurgery and Psychiatry 2004;75:75–79.
34. Marson AG, Al Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of valproate, lamotrigine or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet 2007;369:1016–1026. [PubMed: 17382828]
35. Coppola G, Auricchio G, Federico R, Carotenuto M, Pascotto A. Lamotrigine versus valproic acid as first line monotherapy in newly diagnosed typical absence seizures: an open label, randomised parallel group study. Epilepsia 2004;45:1049–53. [PubMed: 15329068]
36. Mohanraj R, Brodie MJ. Outcomes of newly diagnosed idiopathic generalised epilepsy syndromes in a non-paediatric setting. Acta Neurol Scand 2007;115:204–8. [PubMed: 17295717]
37. Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, et al. The longer term outcome of children born to mothers with epilepsy. Journal of Neurology Neurosurgery and Psychiatry 2004;75:1575–83.
38. Vinten J, Adab N, Kini U, Gorry J, Gregg J, Baker GA. Neuropsychological effects of exposure to anticonvulsant medication in utero. Neurology 2005;64:949–954. [PubMed: 15781806]

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Table 1

Clinical features of pregnant women with epilepsy (WWE)

	WWE	%
Seizures during pregnancy		
- none	144	52.0
- non-convulsive only	38	13.7
- tonic clonic (TC) [a]	94	33.9
- data missing	1	0.4
Total	277	100.0

Antiepileptic drug treatment			Epilepsy syndrome			WWE with TC[a] seizures	
	n	%	focal	IGE	unclass.	0 –20wk	21wk – term
None	46	16.6	17	15	14	0	1
Monotherapy	185	66.8	92	66	27	56	42
carbamazepine	74	26.7	55	6	13	20	12
valproate	57	20.6	9	40	8	21	15
lamotrigine	40	14.4	17	17	6	11	12
other	14	5.1	11	3	0	4	3
Polytherapy	46	16.6	30	13	3	20	24
Total	277	100	139	94	44	76	67

[a] women with epilepsy, who had one or more tonic clonic (TC) seizures during the pregnancy, with or without non-convulsive seizures;

n = number of women, IGE = idiopathic generalised epilepsy, unclass. = unclassified, wk = weeks, other = gabapentin, oxazepam, phenytoin, topiramate or vigabatrin

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Table 2

Obstetric complications and mode of delivery in women with treated epilepsy (WWTE) and control women

Problem	WWTE N = 231			Control women N = 315			Odds Ratio	Confidence Interval	
	y	n	dm	y	n	dm	OR	95% CI	p
Complications									
Any	104	126	1	103	208	4	1.67	1.18 – 2.38	0.01
Vaginal bleeding	36	194	1	30	281	4	1.74	1.04 – 2.92	0.05[a]
Urinary infection	24	206	1	35	276	4	0.92	0.53 – 1.59	0.78
Hypertension	20	210	1	21	290	4	1.32	0.70 – 2.49	0.42
Breech presentation	18	204	9	16	293	6	1.62	0.81 – 3.24	0.21
Fetal distress	11	211	9	10	299	6	1.56	0.65 – 3.74	0.37
Multiple pregnancy	5	225	1	1	310	4	6.89		0.09 [b]
Mode of delivery									
Normal	140	83	8 [c]	187	122	6 [d]	1.10	0.77 – 1.57	0.65
Caesarean section	58	165	8	76	233	6	1.08	0.73 – 1.60	0.76
Vacuum assisted	16	207	8	20	289	6	1.12	0.57 – 2.21	0.86
Forceps assisted	8	215	8	22	287	6	0.49	0.21 – 1.11	0.09
Vaginal breech	1	222	8	4	305	6	0.34		0.41[a]

y = yes, n = no, dm = data missing, p = probability.

[a] 0.01 required for significance after Bonferroni correction for multiple comparisons

[b] Fisher's exact test

[c] 8 mode of delivery 'unknown' = 3 fetal deaths + 5 lost to follow up

[d] 6 mode of delivery 'unknown' = 1 fetal death + 5 lost to follow up

Data from 2nd twin excluded.

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Table 3

Pre-term deliveries and related features in babies of women with treated epilepsy (WWTE) and babies of women with no history of epilepsy (controls)

Problem	WWTE babies			Control babies			Odds Ratio	Confidence Interval	
	y	n	dm	y	n	dm	OR	95% CI	p
Pre-term delivery (< 36 wks)	18	194	6	16	289	3	1.68	0.83 – 3.37	0.15
Low birth weight (< 2.5 kg)	13	197	8	15	275	18	1.21	0.56 – 2.60	0.69
Birth weight centile (< 9th)	14	196	8	15	275	18	1.31	0.65 – 2.73	0.56
Admitted to SCBU 17	23	188	7	23	264	21	1.40	0.77 – 2.58	0.28
Total recorded live births		218			308				

y = yes, n = no, dm = data missing, p = probability, SCBU = special care baby unit

Data from twin pairs was excluded

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Table 4

Prevalence of major congenital malformations in babies of women with treated epilepsy (WWTE) on different anti-epileptic drugs (AED), and women with untreated epilepsy (WWUTE) on no AED, compared with controls

Treatment	Major malformations					Odds Ratio	Confidence Interval	
	y	n	dm	total	%	OR	95% CI	p
Controls	6	279	30	315	2.1	-		
WWTE	14	198	19	231	6.6	3.29	1.24 – 8.70	0.02
AED								
none	1	40	5	46	2.4	1.16		1.00[a]
monotherapy	10	159	16	185	5.9	2.92	1.04 – 8.20	0.06
polytherapy	4	39	3	46	9.3	4.77	1.29 – 17.65	0.03
Mono								
CBZ	2	64	8	74	3.0	1.45	0.23 – 7.37	0.65
VPA	6	47	4	57	11.3	5.94	1.84 – 19.19	0.01
LTG	2	35	3	40	5.4	2.66	0.52 – 13.68	0.23
other[b]	0	13	1	14	0.0	-		
Poly								
no VPA	0	19	1	20	0.0	-		
with VPA	4	20	2	26	16.7	9.30	2.43 – 35.66	0.004
All AED								
no VPA	4	131	13	148	3.0	1.42	0.39 – 5.12	0.73
with VPA	10	67	6	83	13.0	6.94	2.44 – 16.20	0.001

[a] Fisher's exact test,

[b] other monotherapies, gabapentin 2, oxazepam 1, phenytoin 7, topiramate 3, vigabatrin 1;

y = yes, n = no, dm = data missing (including major malformation in association with chromosome abnormality), % = 100y/(y + n), CBZ carbamazepine, LTG lamotrigine, VPA sodium valproate

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Table 5

Major congenital malformations, pre-conceptual antiepileptic drug (AED) & folate doses, in babies of women with treated epilepsy (WWTE) and of controls

Babies of WWTE				Babies of control women	
Malformation	**AED1 mg**	**AED2 mg**	**folate mg**	**Malformation**	**folate mg**
spina bifida [a, b]	VPA 2000	VGT 2000		spina bifida	
cerebellar defect [a]	LTG 150			pulmonary cyst [a]	
coarctation of aorta [c]	VPA 1200			polycystic kidney [a]	0.4
coarctation of aorta	VPA 1000			hydronephrosis	
atrial septal defect [c]	VPA 700		5.0	hypospadias	
ventricular septal def.	VPA 1000		5.0	hip dysplasia	
ventricular septal def. [a]	VPA 600	PHT 350			
ventricular septal def.	VPA 2000	LTG 50	0.4		
cleft lip and palate [a]	CBZ 600				
hydronephrosis [a, c]	VPA 900				
hypospadias [c]	CBZ 400				
extra digit	VPA 1000		5.0		
radial ray defect	VPA 600	LTG 400	5.0		
club foot [a]	LTG 100				
with chromosome def.					
atrial septal defect[d]	-			brain cyst[a, e]	
Fallot's tetralogy[f]	CBZ 100		5.0		
parathyroid agenesis[f]	LEV 2000	TPM 150			

[a] detected by ultrasound,

[b] child also had hypospadias & radial ray defect,

[c] reported previously in multi-centre NEAD study[6],

[d] Downs,

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[e] Edwards,

[f] Di George syndrome;

CBZ carbamazepine, LTG lamotrigine, LEV levetiracetam, PHT phenytoin, TPM topiramate, VPA valproate, VGT vigabatrin.