Highlights

- Less than 50% of women with epilepsy (WWE) were reviewed by services pre-conception
- Only two thirds were reviewed during pregnancy, majority in second/third trimester
- Almost 60% of WWE had poor adherence to their anti-seizure medication (ASM)
- Routine health data can identify pregnant WWE, enabling timely access to services
- Accessing prescribing data can improve ASM adherence in WWE during pregnancy

Abstract

Purpose: To evaluate service access for women with epilepsy (WWE) during pregnancy; to determine seizure frequency and rates of adherence to anti-seizure medication (ASM).

Methods: Between June 2019-June 2020, pregnant WWE within NHS Greater Glasgow and Clyde health-board were identified from the National Obstetric Register. A manual review of electronic patient records was undertaken to ensure diagnostic accuracy, determine contact with epilepsy services and documented seizures. Medication dispensing records were obtained six months before and six months after midwifery booking and measures of ASM adherence calculated.

Results: Between June 2019-June 2020, 4592 women were registered with a pregnancy. Eighty-five (1.9%) were identified as having active epilepsy (generalised- 40/85 (47.0%), focal- 35/85 (41.2%), unclassified- 10/85 (11.8%)).

Preconceptually, 42/85 WWE (49.4%) had input from epilepsy services. Only 59/85 (69.4%) were reviewed during pregnancy (First trimester- 21/59 (35.6%), Second trimester- 25/59 (42.4%) and Third trimester- 13/59 (22.0%)).

Seizure occurrence was documented in 37/85 WWE (43.5%) during the antenatal/postnatal period.

71/85 WWE (83.5%) were prescribed ASM. Poor adherence was noted in 50/85 (58.9%) and a documented seizure recorded in 26/50 (52.0%) of these women.

Conclusion: Too many WWE do not receive input from epilepsy services during pregnancy, leaving some with poor ASM adherence and continued seizures. We aim to use "near-live" obstetric and dispensing data to facilitate early identification of WWE, promoting timely access to epilepsy specialists. This will also provide an opportunity to address concerns regarding ASM safety and allow medication dose changes to be considered.

Keywords: epilepsy, pregnant, antiseizure medication, adherence, compliance

Delivery of care, seizure control and medication adherence in women with epilepsy during pregnancy

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1. Introduction

Epilepsy is one of the most common neurological disorders affecting an estimated 50 million people worldwide,[1] 15 million of whom are women of childbearing age.[2] Two to 5 per 1000 babies annually are born to women with epilepsy (WWE).[3, 4] Epilepsy is associated with poorer maternal outcomes and the mortality rate is consistently higher in WWE during pregnancy in comparison to those without.[5,6] The most recent confidential enquiry from MMBRACE-UK identified epilepsy-related death as an important cause of mortality during pregnancy between 2016 and 2018.[7] Perhaps more significantly, fatalities from sudden unexpected death in epilepsy (SUDEP) has almost tripled in comparison to the observed mortality rate between 2013 and 2015. The latest report also concluded that, in the majority of cases, better care and attention to anti-seizure medication (ASM) management could have potentially improved outcomes. A key recommendation was that a clear pathway for early referral of WWE who become pregnant should be established, allowing women timely access to epilepsy services.

Publication in the UK of the Cumberlege report "First Do No Harm" has brought the potential risk of ASM exposure to the attention of both the scientific and mainstream media.[8] For some women, there may be a resulting perceived difficult choice between adequate seizure control and the potential adverse foetal effects caused by ASM.[9] This has led to fears that women may elect to abruptly stop ASM when they find out they are pregnant.[10] Poor medication adherence in epilepsy has consistently been associated with increased rates of hospital admissions and mortality.[11] Thus, the importance of ASM adherence during pregnancy cannot be overstated.

women with epilepsy (WWE); anti-seizure medication (ASM); NHS Greater Glasgow and Clyde (NHSGGC); medication possession ration (MPR); community health index (CHI) number; Scottish Index of Multiple Deprivation (SIMD)

It is very difficult to measure medication adherence reliably within routine clinical practice. Clinicians often underestimate the extent of poor adherence in their patients.[12, 13, 14] Several direct and indirect methods have been proposed for adherence measurement[15] but there is no consensus on a "gold standard".[16, 17] There have been very few studies that have focused specifically on ASM adherence in pregnant WWE; these have mainly used self-reporting questionnaires.[18, 19, 20] Higher quality methods such as calculating a medication possession ratio (MPR) through prescription refill monitoring have been used in patients with epilepsy to assess ASM adherence, [21, 22, 23] but rarely used to infer adherence during pregnancy.

Reaching out early to WWE, both during preconception and throughout the antenatal and postnatal period, allows women to be fully informed of the benefits and risks of ASM, medication dose changes to be considered in a timely manner, and is likely to improve the care and outcomes of WWE during pregnancy.[24 25, 26]

By accessing routinely collected health data from Scottish National databases, we aimed to identify WWE during pregnancy, provide a comprehensive overview of access and engagement with specialist epilepsy services, and calculate a surrogate marker of adherence to ASM.

2. Methods

Each individual registered with a primary care practice in Scotland has a unique ten-digit community health index (CHI) number. This CHI number allows linkage of health-related datasets providing a unique electronic resource of information on patient aspects such as outpatient clinic attendances, hospital admissions and community medication dispensing.

Pregnant WWE registered with the regional health board of NHS Greater Glasgow and Clyde (NHSGGC) were identified via the National Obstetric Register (Badgernet) between June 2019 and June 2020. Women were included if they were receiving ASM or had more than one unprovoked seizure in the previous 10-year period.

A retrospective manual review of electronic patient records was undertaken by the first author (AA) to ensure a robust clinical diagnosis, obtain additional clinical information and to identify the following key variables:

1. Input from epilepsy services within 12 months prior to conception and during the antenatal period.
2. Seizure frequency within 12 months prior to conception and during the antenatal and six-week postnatal period.

In cases where there was diagnostic uncertainty, both senior authors (JPL/CH) reviewed the case and came to a consesus agreement.

Medication dispensing records for WWE were obtained from the National Prescribing Information System (PIS). Adherence to ASM was expressed as an MPR and assessed

during two distinct time periods: six months leading up to and six months following a patient's first 'booking' antenatal appointment with her midwife (defined as the adherence period of interest). MPR was calculated by taking the number of days within the six-month observation window and dividing by the number of days in the observation window, then subtracting this value from one; this value was then represented as a percentage. In line with other studies,[11] poor adherence was defined as an MPR of less than 80%.

Socioeconomic status based on home postcode for each patient was also measured using Scottish Index of Multiple Deprivation (SIMD).[27] Deprivation categories are classified into pentiles; each pentile containing 20% of Scotland's population: pentile 1= most deprived and pentile 5=least deprived.

This study received local research ethics committee approval.

3. Results

3.1 Demographics

Between June 2019-June 2020, 4592 women were registered with a pregnancy within NHSGGC. 119/4592 (2.6%) were registered as having a previous or current history of epilepsy. Thirty-four of these women were excluded from the study due to an alternative diagnosis (n=19), having inactive epilepsy (n=10), no digital case notes available (n=3) and being a resident from another health board (n=2). The remaining 85 women were considered as having a diagnosis of active epilepsy, equating to 1.9% of all pregnancies within NHSGGC during this year.

Basic demographic features including epilepsy classification of these women are summarised in Table 1.

3.2 Delivery of Care- Contact with Epilepsy Services

A review by epilepsy services during the preconception period occurred in 42/85 WWE (49.4%).

A review by epilepsy services during the antenatal period occurred in 59/85 WWE (69.4%), 21/59 (35.6%) of whom were seen in the first trimester, 25/59 (42.4%) in the second and 13/59 (22.0%) in the third.

Of the 26/85 WWE (30.0%) not reviewed during the antenatal period, seven women were referred to epilepsy services: three had an antenatal review organised but did not attend; one had a miscarriage before a planned antenatal review; two had review after the postnatal period; and one had no anticipated review.

Demographics	**Proportion of Total Cohort (n=85)**
Age Group	
17-20yrs	7 (8.2%)
21-25yrs	9 (10.6%)
26-30yrs	24 (28.2%)
31-35yrs	23 (27.1%)
36-40yrs	19 (22.4%)
41-43yrs	3 (3.5%)
Mean Age at Booking (Range)	30.3yrs (17-43yrs)
Socioeconomic Status	
SIMD 1	36 (42.4%)
SIMD 2	17 (20.0%)
SIMD 3	9 (10.6%)
SIMD 4	15 (17.6%)
SIMD 5	8 (9.4%)
Epilepsy Classification	
Generalised	40 (47.0%)
Focal	35 (41.2%)
Unclassified	10 (11.8%)

Table 1. Clinical demographics. *Total number of women with epilepsy n=85. Scottish Index of Multiple Deprivation (SIMD) categories: pentile 1= most deprived and pentile 5=least deprived.*

3.3 Seizure Frequency

At least one documented seizure during the preconception period was noted in 36/85 WWE (42.4%), twenty-four of whom also had a seizure during the antenatal period (66.7%).

Overall, 37/85 WWE (43.5%) had a documented seizure during the ante/postnatal period.

Four WWE had a seizure during labour, two of whom required emergency Caesarean Section. 3/4 (75.0%) of these WWE had previous poor seizure control during their pregnancy, as well as within one year prior to conception.

3.4 Folic Acid

Eighteen out of 85 WWE (21.2%) were on high-dose (five milligrams) folic acid during the preconception period (all of whom were older than 25 years of age), and forty-seven out of 85 WWE (55.3%) were on high-dose folic acid at “booking”.

3. 5 Adherence to ASM

i) WWE on prescribed ASM

During the adherence period of interest, 71/85 WWE (83.5%) had a prescription for at least one ASM. Sixty-seven out of these 71 women were prescribed at least one ASM during the entirety of the study period, i.e. both pre- and post-booking; three women were started on their first ASM post-booking and one had their only ASM stopped pre-booking as per medical advice.

Forty-five out of 67 WWE (67.2%) were on monotherapy with the same ASM throughout the study period. Of the 22/67 WWE (32.8%) on polytherapy, ASM remained unchanged for

15/22 during the study period: 13 women on two AEDs and two women on three AEDs. Four WWE required additional adjuvant therapy and three WWE rationalisation of polytherapy.

Overall, a total number of 84 ASM treatments amongst the 67 women were prescribed throughout the entirety of the 12-month study period. The frequency of ASM use is summarised in Table 2.

ASM	**Proportion of Total Number of Treatments**
Lamotrigine	29 (34.5%)
Levetiracetam	28 (33.3%)
Carbamazepine	8 (9.5%)
Sodium valproate	6 (7.1%)
Topiramate	3 (3.6%)
Zonisamide	3 (3.6%)
Brivaracetam	2 (2.4%)
Lacosamide	2 (2.4%)
Clonazepam	1 (1.2%)
Clobazam	1 (1.2%)
Ethosuxamide	1 (1.2%)

Table 2. Frequency of prescribed anti-seizure medication. *A total number of 84 prescribed anti-seizure medication (ASM) treatments were generated* from 67 women with epilepsy. *ASM prescriptions stopped at any time during the study period as per medical advice or started post-booking are not included here.*

Table 3 summarises the adherence of WWE to prescribed ASM treatments six months leading up to and six months following their first antenatal booking appointment date with their midwife.

Adherence Pre-booking/Post-booking	**Number of WWE (% of total n=67)**
Good/Good	32 (47.8%)
Good/Poor	2 (3.0%)
Poor/Poor	26 (38.8%)
Poor/Good	7 (10.4%)

Table 3. Anti-seizure medication adherence pattern during the 12-month study period six months pre and post-booking. *Total number of women with epilepsy (WWE) on prescribed anti-seizure medication (ASM) during the total duration of the study n=67. If WWE on polytherapy had poor adherence to at least one of their ASM, they were considered here as being poorly adherent in general. Poor adherence was defined as an MPR of less than 80%.*

ii) WWE not on prescribed ASM

Fourteen out of 85 WWE (16.5%) had no prescription for ASM during the study period. Eleven had stopped their ASM without medical advice. Three women elected not to start ASM. As all these WWE actively chose not to be on medication, they were considered to be poorly adherent throughout the 12-month study period, with an MPR of zero.

Of these 14 WWE, five had generalised, five focal, and four unclassified epilepsy. Only 3/14 (21.4%) of these women were reviewed by epilepsy services prior to conception

and 4/14 (28.6%) during the antenatal period. Three out of 14 WWE (21.4%) had at least one documented seizure during the preconception period and 2/14 (14.3%) at least one documented seizure during pregnancy.

iii) Summary of Poor Adherence

Overall, 50/85 WWE (58.9%) had a period of poor adherence to at least one of their ASM during the 12-month study period. Forty-seven out of 85 WWE (55.3%) had poor adherence to at least one of their ASM six months leading up to booking and 44/85 WWE (51.8%) had poor adherence to at least one of their ASM six months following booking.

iv) Seizures During Periods of Poor Adherence

Overall, seizures were documented in 26/50 (52.0%) of WWE during a period of poor adherence throughout the study period.

A review by epilepsy services took place in 26/50 WWE (52%) with poor adherence during the preconception period and 30/50 (60.0%) during pregnancy.

Demographics and several other clinical factors associated with poor ASM adherence are shown in Table 4. Although there was a trend noted in a number of variables, none of these reached the accepted level of statistical significance.

Demographics/Clinical Factors	Poor Adherence		Odds ratio (95%CI)
	Yes	No	
Age			
17-30 (n=40)	26 (65.0%)	14 (35.0%)	-
31-43 (n=45)	24 (53.3%)	21 (46.7%)	1.61 (0.67-3.95)
Epilepsy Classification			
Generalised	21 (50.0%)	21 (50.0%)	-
Focal	22 (66.7%)	11(33.3%)	0.51 (0.19-1.30)
Unclassified	7 (70.0%)	3 (30.0%)	0.45(0.08-1.90)
SIMD			
1	24 (66.7%)	12 (33.3%)	-
2	7 (41.2%)	10 (58.8%)	2.78 (0.85-9.69)
3+	19 (59.4%)	13 (40.6%)	1.36 (0.50-3.74)
Documented seizure prior to conception			
Yes	20 (55.6%)	16 (44.4%)	-
No	30 (61.2%)	19 (38.8%)	0.79 (0.32 – 1.92)
Documented seizure during pregnancy			
Yes	20 (57.1%)	15 (42.9%)	-
No	30 (60.0%)	20 (40.0%)	0.89 (0.37-2.17)
Contact with epilepsy services prior to conception			
Yes	26 (61.9%)	16 (38.1%)	-
No	24 (55.8%)	19 (44.2%)	1.28 (0.54-3.10)
Contact with epilepsy services during pregnancy			
Yes	31 (52.5%)	28 (47.5%)	-
No	19 (73.1%)	7 (26.9%)	0.42 (0.14-1.11)
Type of ASM therapy			
Polytherapy	15 (68.2%)	7 (31.8%)	-
Monotherapy	21 (43.7%)	27 (56.3%)	2.69(0.94-8.32)
None	14 (93.3%)	1 (6.7%)	0.17(0.01-1.22)

Table 4. Demographics and other clinical factors associated with poor anti-seizure medication adherence. *Total number of women with epilepsy (WWE) n=85. Women with poor adherence to at least one of their anti-seizure medication (ASM) either pre or post-booking are included here, as well as the 14 WWE who did not have an ASM prescription during the study period, as they had either previously stopped ASM against medical advice or did not wish to start. The three WWE started on their first ASM post-booking are included in those who are on monotherapy. The one WWE who had her only ASM stopped pre-booking is included in those that were on no treatment. Scottish Index of Multiple Deprivation (SIMD) categories: pentile 1= most deprived and pentile 5=least deprived.*

v) Sodium Valproate Use During Pregnancy

At the time of conception, seven out of 85 WWE (8.2%) were prescribed valproate (four were on polytherapy). All these women had generalised epilepsy. Five out of these seven women (71.4%) had preconceptual counselling within a year of conception and four (57.1%) antenatal review by epilepsy services.

Following conception, two of the seven WWE stopped valproate without medical advice despite having poor seizure control within a year prior to conception and had no review by epilepsy services during pregnancy. One woman stopped valproate following conception on advice from their epilepsy clinician despite having poor seizure control during preconception. Of the four WWE who remained on valproate throughout pregnancy, one had poorly controlled seizures despite polytherapy; one did not wish to stop valproate despite medical advice to do so; and the other two women did not receive input from epilepsy services during pregnancy. Two of these four women who continued on valproate had a period of poor adherence to this ASM pre- and post-booking.

3.6 Foetal Loss During Pregnancy

Foetal loss was noted in three WWE; two before 23 weeks gestation and one after. None of these women had contact with epilepsy services prior to conception nor during the antenatal period. One woman with generalised epilepsy on Lamotrigine had a loss at 12+1 weeks; she was seizure-free preconception and during pregnancy with good ASM adherence pre- and post-booking. One woman with unclassified epilepsy on Lamotrigine had a loss at 23+5 weeks; she was also seizure-free preconception and during pregnancy but had poor adherence pre- and post-booking. One woman with unclassified epilepsy prescribed valproate had a miscarriage at an unknown week of gestation; her seizures were poorly controlled and she had poor adherence.

4. Discussion

A large proportion of WWE are not routinely reached by specialist epilepsy services prior to conception nor in a timely manner during pregnancy. Only two thirds of women were reviewed during the antenatal period, the majority during the second and third trimester. Additionally, the observed level of poor adherence in WWE during pregnancy is of concern. Overall, almost 60% of women had a period of poor adherence during the study period. It is entirely plausible that some of the excessive mortality in WWE during pregnancy highlighted in previous studies[5, 6, 7] reflects poor ASM adherence and thus, is potentially reversible.

As far as we are aware, this is the first study to use MPR as an objective measure of adherence in WWE during pregnancy. Previous studies in pregnant WWE report rates of good adherence to ASM ranging from to 37.7%[18] to 98%.[19] Both studies used self-reported measures of adherence and thus, are less robust than more objective measures used here. One other study has considered objective measures of adherence in pregnancy using hair analysis[10] but this method is not considered sufficiently sensitive to detect brief or minor cessations of ASM.

The relatively small number of women included within this study prevents us reaching a definitive conclusion regarding risk factors for poor ASM adherence. A trend towards poor adherence was noted in a number of clinical and demographic factors but further work using a larger cohort is pending to explore this in greater details.

Given the study design, we were unable to consider trends in adherence over time. It would be of interest to evaluate longitudinal trends in ASM adherence following the Medicines and Healthcare Products Regulatory Agency (MHRA) recommendations concerning the use of

ASM in pregnancy.[28] Although the recommendations are to be commended, there are concerns that misinformation or "clumsy" application may risk worsening adherence due to misunderstanding about the balance between medication risk (teratogenicity and/or developmental delay) and adequate seizure control.

Previous studies have identified that the most important predictor of seizure control during pregnancy is the occurrence of seizures before pregnancy when on the same ASM treatment.[29,30] Although this study did not specifically address this issue, it was noted that a large proportion of women experienced at least one seizure during both the preconception and antenatal period.

There is consensus that seizure control and ASM use during any potential future pregnancies should form an important part of pre-conceptual counselling of women of reproductive potential.[26] Preconception planning has been shown to be associated with improved seizure control[25], greater ASM adherence during pregnancy[25], monotherapy treatment[25], and the use of ASM other than valproate.[24,25] A major challenge to planning epilepsy care is the significant proportion of unplanned pregnancies; approximately 56-65% of pregnancies in WWE in the UK and US were unplanned.[18, 31] This may account for why a significant proportion of women in this study were not seen prior to conception. Given this finding, we suggest issues around pregnancy should be discussed early and regularly at routine epilepsy review consultations with WWE of reproductive potential, in order avoid missing opportunities to improve pregnancy outcomes.

Prescribing of ASM in WWE during pregnancy was in-line with the current UK MHRA advice.[28] A small but significant number of women were receiving valproate. Interestingly, most women on valproate stopped, (or showed poor adherence), without medical advice,

when they found out they were pregnant. It is important for clinicians to counsel WWE on the dangers of stopping ASM abruptly after conception without the support of specialist services. Annual contact with specialist services, currently recommended as part of the MHRA guidance within the UK, provides an opportunity for further education regarding ASM management in the context of pregnancy.

This study has many strengths: the data reflects a representative, prospective sample of WWE from a single centre. Previous studies more usually identified women from epilepsy pregnancy registers, introducing the potential for selection bias. In addition, manual review of electronic patient records ensured that those included in the study had a robust clinical diagnosis verified by a clinician. Due to availability of a centralised database, MPR could also be calculated from prescription refills. This can be considered to be a strong objective surrogate measure of adherence. Although we cannot exclude the possibility that women may collect a prescription but decide not to take their ASM, we at least are confident that those who did not collect a prescription would be unable to access ASM from an alternative source. Lastly, the method of calculating MPR was 'expanded' beyond the study period. This enabled the researcher to take in account the potential for 'stockpiling' of ASM prior to the study observation period and increased the accuracy of adherence calculation.

Regarding this study's limitations, relatively small numbers of WWE were registered with a pregnancy in the largest health board in Scotland, limiting statistical power. The lack of access to primary care records may have understimated seizure frequency, particularly in those women not in contact with specialist epilepsy services. Information on additional potential co-founders such as ethnicity, age at first seizure, history of mental health disorder or learning difficulty, current ASM dose and baseline serum ASM level would have been desirable but were not available.

In addition, the methodology of the current study is such that ASM dose changes and routine drug monitoring levels during pregnancy were not available. It is well recognised that ASM levels may fall in pregnancy due to altered pharmacokinetics.[34] ASM dose changes, routine ASM level monitoring and seizure control will be assessed in future studies**.** Future developments using routine health data will also allow early access to specialist services, enabling clinicians to obtain routine drug level monitoring in a timely manner and ensure that any falls in ASM levels can be most efficiently counteracted.[35]

5. Conclusion

By using routine health datasets we have demonstrated that services as delivered are not fully meeting the needs of WWE during pregnancy. To address this issue, we have incorporated obstetric and dispensing data onto a "near-live" interactive informatics platform. This allows the prospective identification of pregnant WWE at the point of booking, allowing specialist epilepsy services to reach out to women in a timely manner and enabling clinicians to evaluate ASM adherence. Early review of WWE facilitates identification of poor adherence and allows health care professionals the opportunity to address any concerns or misperceptions about ASM safety. By alleviating fears and emphasising the importance of good ASM adherence for the health of both themselves and their baby, we hope to improve outcomes of WWE during pregnancy.

With the support of the Scottish Government, we hope to replicate this work in a number of additional health boards.

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CA Heath: In the last 3 years CH has received Speakers' Honoraria and Advisory Board payments from UCB Pharmaceutical, Eisai and Arvelle

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